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Cardiovascular magnetic resonance: Diagnostic utility and specific considerations in the pediatric population

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Abstract

Cardiovascular magnetic resonance is a non-invasive imaging modality which is emerging as important tool for the investigation and management of pediatric cardiovascular disease. In this review we describe the key technical and practical differences between scanning children and adults, and highlight some important considerations that must be taken into account for this patient population. Using case examples commonly seen in clinical practice, we discuss the important clinical applications of cardiovascular magnetic resonance, and briefly highlight key future developments in this field.

Key words: Cardiology; Pediatrics; Imaging; Diagnosis; Cardiovascular magnetic resonance

Core tip: Cardiovascular magnetic resonance is playing an increasingly important role in the investigation and management of pediatric cardiovascular disease. However, imaging this patient population brings its own unique set of challenges. This article describes some of the key differences between scanning children and adults, discusses the important clinical applications of cardiovascular magnetic resonance in pediatrics, and highlights some of the key future developments in this field.

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INTRODUCTION

Cardiovascular magnetic resonance (CMR) is a non-invasive imaging technique that uses magnetic resonance imaging (MRI) to provide clear delineation of cardiovascular anatomy, detailed tissue characterization, and a comprehensive evaluation of cardiac function. In recent decades there has been a significant increase in use of CMR for a variety of purposes in both congenital and acquired heart disease in children.

Overall, the basic sequences and imaging strategies used in children are similar to those used in adults. Adolescents with normal intellectual and emotional development can usually be successfully imaged using adult techniques[1]. However, younger children may not be able to comply with breath-holding during image acquisition and their faster heart and respiratory rates provide technological challenges. Additionally, their anatomy is smaller and, in cases of congenital heart disease, often unique and complex. Pediatric imaging is therefore more demanding in terms of sequence optimization and each scan requires an individualized approach[2,3].

Despite these challenges, CMR remains a useful tool to assist with investigation and management of a wide range of cardiovascular pathology in children. It can be used for diagnostic and screening purposes to define anatomy and assess function, to monitor disease progression as part of serial follow-up, and to plan and evaluate the outcomes of surgery and other therapeutic interventions. This article provides an overview of the main applications of CMR in children and discusses some of the specific considerations for this patient population.

HOW DOES CMR WORK?

CMR uses magnetic fields and radiofrequency energy to produce tomographic images of the human body. It is based on the phenomenon of "nuclear magnetic resonance" - the ability of some atomic nuclei to selectively absorb then later re-emit radiofrequency energy. The emitted energy can then be captured and transformed into an image. Only nuclei with an odd number of protons and neutrons (thus possessing a "net magnetic moment") are capable of exhibiting this phenomenon[4]. Several examples of such nuclei are present in biological tissues[5], however the hydrogen (^{1}H) atom is the primary choice for clinical imaging due to its abundance in water and fat.

Under normal conditions, hydrogen nuclei in tissues behave as tiny bar magnets randomly oriented in space such that the net magnetization of the tissue is zero. When placed in a strong magnetic field (created by the large superconducting magnet of the scanner), the nuclei align in the direction of the magnetic field creating a net tissue magnetization oriented along the axis of the scanner. The nuclei spin (precess) around the direction of the magnetic field at a frequency specific to the magnetic field strength[4]. The field strengths of clinical scanners can vary from 0.15 to 7 tesla (T) although CMR is typically performed at 1.5 T, approximately 20000 times the magnetic field strength of the earth[6].

External radiofrequency transmitter coils are used to apply radiofrequency energy to the tissue at a specific "resonance" frequency. Hydrogen nuclei absorb this energy and flip their orientation within the magnetic field, going from a stable low energy state to an unstable high energy state. When the radiofrequency transmission ceases, the nuclei relax back to the lower energy state and re-emit the absorbed energy, which is detected by a receiver coil as radiofrequency signals. The signals are electronically amplified by a computer and the intensity of each signal is plotted on a grey-scale in order to build up a cross-sectional image of the tissue. The resulting image is a representation of the spatially-resolved signals[4,5].

In order to localize the part of the tissue from which these emitted radiofrequency signals originate, gradient coils driven by pulses of electricity are used to produce small field gradients in multiple planes within the wider magnetic field of the scanner magnet. These gradients cause a predictable variation in both the magnetic field strength and resonant frequency in different parts of the patient. By varying the times at which gradient fields are switched on and off in relation to the application of the radiofrequency pulses, then analyzing the properties of the emitted signal (in terms of frequency and phase), the computer is able to reconstruct an image of the patient[6].

The hydrogen nucleus relaxes back to the lower energy state by two main processes: Longitudinal relaxation with relaxation time T1, and transverse relaxation with relaxation time T2[7]. The relative proportions of T1 and T2 relaxation times vary between different tissues. By altering the timing of radiofrequency pulses, strength of the gradient fields, and through use of contrast agents and magnetization preparation pulses (such as inversion recovery, saturation recovery, fat-suppression and blood-nulling sequences), the differences in T1 and T2 values between tissues can be exploited to enable detailed tissue characterization, producing images that highlight the tissue of interest[8].

CMR *VS* OTHER IMAGING MODALITIES IN PEDIATRICS

Echocardiography is the mainstay of cardiovascular imaging in children. It is cheap, quick, accessible, non-invasive and particularly informative in neonates and infants for whom it is possible to achieve good acoustic windows. However, it is operator dependent and provides only limited views of extra-cardiac vascular

structures[9,10]. Cardiac catheterization provides useful hemodynamic information and permits concurrent therapeutic intervention. However, it is invasive with rare but potentially fatal complications, involves exposure to ionizing radiation and is dependent on the use of iodine-based contrast agents[11-13]. CMR on the other hand, is non-invasive and radiation-free. This is particularly relevant to children, for whom the risk of risk of radiation-induced malignancy is significantly higher than in adults[14]. Thus CMR is amenable to being used for serial assessments, such as pre- and post-procedure or for ongoing follow-up to monitor disease progression. CMR reduces the requirement for invasive study in certain cases and enables the assessment of anatomy and function where echocardiographic views are sub-optimal. Non-contrast imaging provides excellent soft tissue contrast resolution permitting detailed tissue characterization, and superior structural and functional information, including the determination of extra-cardiac anatomy and hemodynamic parameters[15].

However, CMR scanners are rarely mobile and availability is limited compared to echocardiography. Even in a centre that offers conventional MRI, CMR requires significant software, training and expertise[16]. The data acquisition time is long, typically 20-50 min depending on what information is required, and the space within the magnet is limited. It can be claustrophobic, and for children unable to co-operate with the scanning procedure, general anesthesia may be required. It is also less suitable for clinically unstable patients requiring intensive monitoring, and in the event of a cardiopulmonary arrest, the patient must be removed from the magnet environment of the CMR scanner before advanced life support can commence. All monitoring equipment used during a CMR scan must be MRI compatible, requiring a switch to compatible pumps before the patient enters the scanner.

Computerized tomography (CT) is often used as an alternative to CMR - it permits acquisition of a high resolution data set in a much shorter time period and is therefore useful for children and unstable patients unable to tolerate a lengthy CMR scan. In the pediatric population, it is considered superior to CMR when evaluating airway anatomy in cases of vascular rings, when assessing pulmonary vasculature (particularly in thromboembolic disease of the pulmonary arteries, where breath-holding capability is often compromised), and when determining the presence or absence of any major aorto-pulmonary collateral arteries (MAPCAs)[17,18]. CT can also be used as an alternative where CMR is contraindicated due to the presence of implanted devices, foreign bodies or claustrophobia. However, it is less detailed in terms of tissue characterization and exposes patients to high doses of ionizing radiation - particularly in the case of serial imaging where the cumulative radiation dose is significant[19].

Despite its shortcomings, CMR remains a versatile tool with distinct advantages over other modalities. However, outcomes are most successful when it is used in conjunction with other imaging technologies in a directed manner to obtain an answer to a specific clinical question.

BASIC CMR PULSE SEQUENCES

CMR pulse sequences represent the co-ordinated actions of turning on and off the gradient coils and transmitted radiofrequency pulses in order to highlight specific features of the tissue being imaged[15]. The basic principles of these sequences are similar for adult and pediatric CMR. As with adult imaging, sequences used in the pediatric setting must be carefully selected in order to best answer the clinical question. However, in children specific adaptations must be made in order to accommodate the smaller patient size (demanding a higher spatial resolution), and faster heart rates (demanding a higher temporal resolution)[20]. Also, in cases of congenital heart disease where the anatomy is complex, a more individualized approach to the scan is required[2].

Spin echo

Spin echo pulse sequences produce images that are acquired during one fixed point of the cardiac cycle (Figure 1A and B). They are static images in which blood appears black and the surrounding stationary tissue appears in shades of grey[16]. These images are useful for providing anatomical information[21] and they permit excellent tissue characterization (particularly when magnetization preparation pulses are used), achieving good visualization of pathology for conditions such as myocarditis, pericarditis, cardiomyopathies, vasculitis and cardiac tumours[22]. Acquisition time is long, and although faster variants exist, they result in poorer spatial and temporal resolution[20].

Gradient echo cine

Gradient echo cine imaging enables the generation of short "movies" depicting motion of the heart throughout the cardiac cycle. This is achieved by dividing the cardiac cycle into multiple segments (frames) to produce a series of 2D images that can then be laced together into a cinematic display. Blood appears bright and the resulting "cines" are useful for assessing the dynamic function of the heart - such as blood flow, valvular function, ventricular volumes, ventricular mass, ejection fraction and motion of the ventricular walls. CMR volume measurements are considered more accurate and reproducible compared to echocardiographic measurements[15,23,24], and normal values for both atrial and ventricular volumes have been widely published in children[25-28] with studies demonstrating good reproducibility[29].

Gradient echo cine imaging can be performed using a standard spoiled gradient echo pulse sequence, or the more recent steady state free precession sequence (SSFP) (Figure 1C and D). SSFP has generally surpassed the use of spoiled gradient echo for cine imaging as it is faster and provides superior contrast between blood

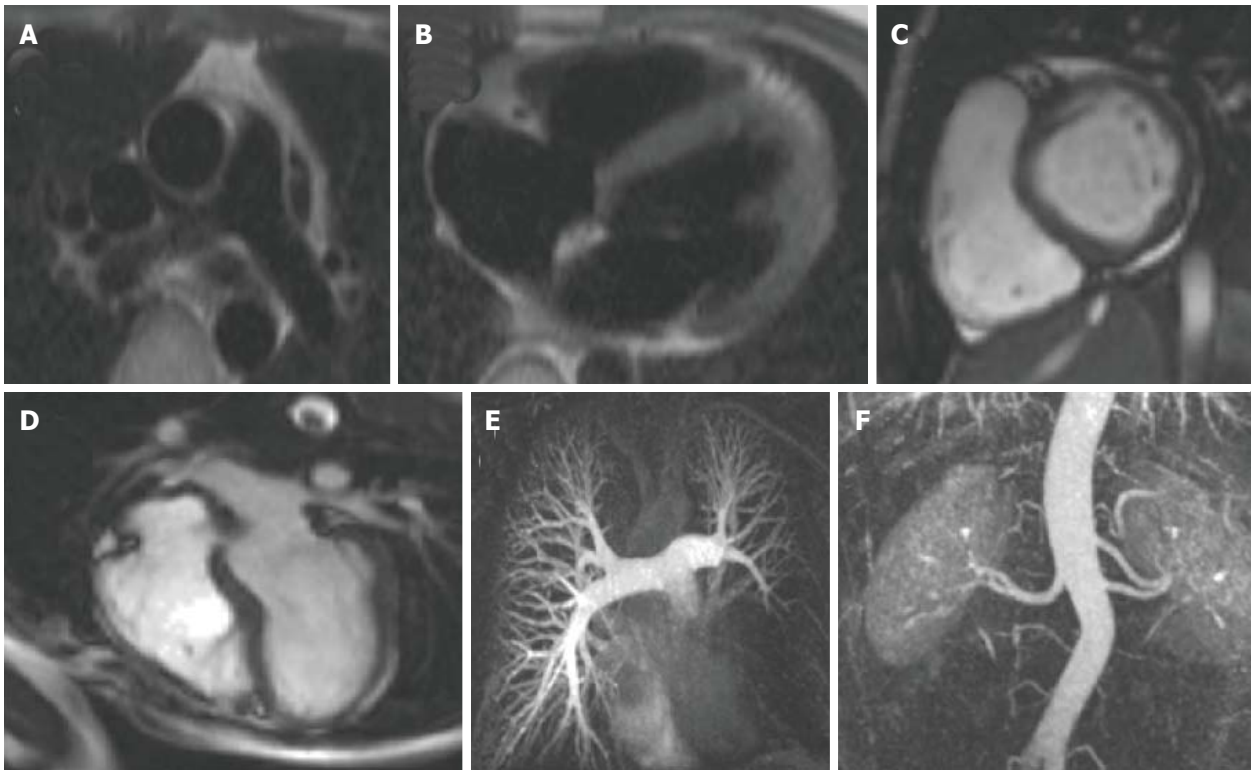

Figure 1 Examples of images produced by individual cardiovascular magnetic resonance pulse sequences. A and B are black blood spin echo images showing the ascending and descending aorta at the main pulmonary artery level A and the 4 cardiac chambers B; C and D are bright blood SSFP cine images showing short axis and 4 chamber views respectively, while E and F are examples of 3D contrast-enhanced MRA; E is a contrast-enhanced MRA of the pulmonary tree in a patient with a large sarcoma. There is no opacification of the arterial supply of the left lower lobe, indicating complete occlusion of the lower branch of the left pulmonary artery; F is a contrast-enhanced MRA of the descending aorta for assessment of renal anatomy, demonstrating an accessory renal artery to left kidney (a common normal variant). SSFP: Steady state free precession; MRA: Magnetic resonance angiography.

and myocardium[20]. It can also be adapted for 3D imaging, enabling acquisition of a high resolution 3D anatomical dataset of the heart and thoracic vasculature without the requirement for intravenous contrast[30-32]. However, SSFP is more prone to artefact when there is inhomogeneity in the magnetic field[20], so both types of sequence still form the basis of multiple cardiac imaging applications. Spoiled gradient echo sequences are still widely used for late gadolinium enhancement (LGE) imaging to detect myocardial fibrosis, 3D contrast-enhanced magnetic resonance angiography (MRA), velocity encoded phase contrast imaging for assessment of *in-vivo* blood flow, and first-pass perfusion imaging for evaluation of myocardial perfusion.

LGE imaging: Gadolinium-based contrast agents (GBCAs) distribute in greater volumes in fibrosed myocardium and demonstrate slower washout times compared to normal myocardium. Using spoiled gradient echo sequences, it is possible to demonstrate the abnormal deposition of contrast late after contrast injection as focal regions of fibrosis become hyperenhanced[16]. Validation studies have strongly correlated the finding of LGE with the presence and extent of myocardial fibrosis[33,34]. In children, LGE is typically seen along areas of reconstruction post-surgically following repair of congenital cardiac lesions[35-38]. The presence of LGE is known to be associated with arrhythmias and poorer ventricular function and studies in adults have demonstrated that it is associated with a poorer prognosis in dilated cardiomyopathy[39], hypertrophic cardiomyopathy[40,41] and valvular heart disease[42].

3D contrast-enhanced MRA: Running a spoiled gradient echo pulse sequence during administration of intravenous GBCAs enables detailed, high resolution vascular imaging (Figure 1E and F). Gadolinium reduces the T1 relaxation time of blood, enhancing the contrast between blood and the surrounding tissue[43]. By varying the time delay between contrast administration and the pulse sequence, it is possible to alter the portion of the thoracic vasculature imaged. In this manner, clear images of the aorta and its branches, the pulmonary vessels, systemic veins, collateral vessels and any shunts, conduits or vascular grafts can be obtained[44-49]. The collected data can be formatted to generate 2D slices in any orientation, or volume-rendered into a 3D image, often negating the requirement for invasive diagnostic catheterization.

Velocity encoded phase contrast imaging: When hydrogen nuclei (such as in blood) flow through specially designed magnetic field gradients, the signal they emit accumulates a phase shift relative to the signal from the surrounding tissue that is proportional to their velocity. Velocity encoded phase contrast sequences capture

data encoding this velocity information in addition to data encoding information about the surrounding tissue. Software can then be used to obtain measurements of flow rates within individual vessels by contouring the vessel in a cross-sectional plane and calculating volume of blood passing through the plane as a product of velocity and cross-sectional area[50-52]. Using this technique, it is possible to assess flow in large and small arteries and the systemic and pulmonary veins. It is also possible to quantify cardiac output and intra- and extra-cardiac shunts, measure pressure gradients across areas of stenosis and calculate valvular regurgitant fractions[53-56].

First-pass perfusion imaging: Performed using spoiled gradient echo or SSFP sequences, this technique involves the administration of a GBCA followed by dynamic imaging of the passage of contrast through the myocardium in order to detect zones of decreased perfusion[57]. Normally perfused myocardium gives a bright signal and areas of poor perfusion appear darker. Images are typically acquired both at rest and under pharmacological stress (induced *via* administration of a coronary artery vasodilator such as adenosine) in order to accentuate the difference between the perfusion of myocardium supplied by normal coronary arteries compared to myocardium supplied by abnormal vessels[16,20]. Examples of uses in children include the investigation of chest pain, congenital heart disease with anomalous coronary artery origins, post-surgery involving coronary artery re-implantation and in acquired abnormalities of the coronaries such as aneurysms in Kawasaki disease[17,58-60]. CMR offers distinct advantages compared to the traditional nuclear perfusion imaging in terms of improved spatial resolution and lack of ionizing radiation[61-64]. Dobutamine instead of adenosine is also used for stress imaging in certain circumstances[65,66].

SPECIFIC CONSIDERATIONS IN CHILDREN

In addition to the technological challenges with regards to performing CMR in children, there are a number of specific practical considerations to take into account. These include the strategies employed in order to minimize both generalized and cardio-respiratory motion artefact (both accentuated in children due their reduced ability to co-operate with the scanning procedure, and their elevated heart rate and respiratory rate in comparison with adult patients), the equipment used, and some of the additional preparation steps that can be taken with children in order to facilitate the scanning process.

In terms of generalized motion artefact, older children (typically greater than 7 years of age) with normal development are often capable of lying still and following instructions such that adequate quality images can be obtained. However, for neonates, infants, younger children and patients with developmental delay, specific strategies must be employed in order to minimize motion artefact. Approaches will vary depending on the age of the child, their clinical condition, and the expertise and resources available. For infants less than 6 mo, it may be possible to perform the scan during natural sleep after feeding[67], however early awakening will likely compromise the scan. Deep sedation using sedative medications is an option[68], but is avoided where possible due to risks of hypoventilation and aspiration. Thus, for children unable to breath-hold, the preferred approach is endotracheal intubation and mechanical ventilation under general anesthesia (GA). CMR under GA is resource intensive, requiring a pediatric anesthetist with cardiac experience and CMR compatible equipment. It is also challenging since intensive monitoring is required despite limited access to the child during the scan. However, with trained personnel, good communication and a comprehensive emergency plan in place, it has an excellent safety profile[69-71]. Additionally, it presents the opportunity to perform other invasive investigations during a single GA, for example trans-oesophageal echocardiography and endoscopic procedures. However, the decision for a child to undergo CMR under GA is not taken lightly and is usually made in discussion with the wider multi-disciplinary team. There should be careful consideration of the age and maturity of the child, the parents' perception of the child's ability to co-operate with a non-GA procedure, their clinical condition, relevant past experiences, the length of the scanning protocol, the risks of anesthesia and the benefits of the scan in terms of diagnosis and patient management[2,72].

In order to minimize the effect of cardio-respiratory motion on image quality, specific strategies are employed. For cardiac motion, the techniques used are broadly similar for adults and children. To obtain images of acceptable quality, CMR data is acquired over multiple heart beats, synchronizing the data acquisition to a particular time point in the cardiac cycle. MRI compatible electrodes and leads are applied to the patient's chest and specific software detects the ECG trace, synchronizing the CMR pulse sequence (and thus data acquisition) to the R wave. In this manner, with each cardiac cycle there is a new repetition of the pulse sequence. Images can be obtained either at a single time point in the cardiac cycle for still imaging, or at multiple time points for cine imaging and the resulting images can are laced together in a cinematic display. Two main ECG synchronization techniques exist: Prospective triggering and retrospective gating. Typically for still imaging using spin echo sequences, prospective triggering is used, whereas for cine imaging using gradient echo sequences, either technique can be used[6,73]. For respiratory motion, most pulse sequences enable data acquisition to be completed within a single breath-hold, thus older children can be taught to breath-hold with practice. Breath-holding can also be achieved under general anesthetic, with the anesthetist strategically pausing the ventilator at specific times. In sedated infants and small children, breathing tends to be shallow and regular so a technique

Table 1 Tips for a successful pediatric cardiovascular magnetic resonance scan

Before the scan
Begin preparation for the scan well in advance of the appointment
If multiple children from the same family require scans (such as when screening for hereditary conditions), where possible arrange for all children to be scanned at a similar time (ideally on the same day) so they can prepare together
Discuss the procedure with the child in an age-appropriate manner and provide parents with a detailed description of the procedure so they can be of assistance
Play therapists can help prepare the child by talking them through pictures of the scan, and using dummy scanners to practice lying still and breath-holding
Arranging a pre-scan visit to the CMR department and allowing the child to see the scanner before their scheduled appointment may help reduce anxiety
Perform a full metal screen on parents so that they can demonstrate going into the scanner if the child is anxious, and so that they can remain in the room for the duration of the scan to reassure the child if necessary
Some modern scanners have MRI compatible audio-visual equipment, where this is available allow the child to pre-select their own music or movie to play during the scan (ideally bringing a favourite one from home) – this may help them tolerate longer scanning times
Within reason, allocate a lengthier appointment for the scan to give the child time to get accustomed to the magnet, coils, ear protection and breath-holding instructions
During the scan
Be patient and flexible
Minimize the time the child must spend in the scanner by only running sequences that will directly answer the relevant clinical questions
Run the most essential sequences first bearing in mind that the child may not tolerate the whole scan
For a breath-holding child, use short sequences only as they may struggle with a long breath-hold
An inspiratory breath-hold is easier for a child to understand and achieve compared to an end-expiratory breath-hold
For stress perfusion studies provide the child with a stress ball that can be repeatedly squeezed during administration of the stress agent to minimize side effects (61)
After the scan
Praise and reward the child with stickers and certificates even if the scan was not entirely successful, bearing in mind that for many conditions repeat scanning may be required in future so all attempts to alleviate bad experiences should be made

employing multiple signal averages can be used to average out respiratory motion artefact at the expense of reduced spatial resolution. Alternatively, respiratory gating strategies can be employed to synchronize data acquisition to the respiratory cycle such as using a navigator beam to track the motion of the diaphragm and gating data acquisition to a point in end expiration when the diaphragm is relatively still[73,74].

For pediatric CMR, the use of smaller coils placed directly on top of or underneath the child significantly improves image quality. Adolescent children can be imaged using a standard adult surface coil, while for younger children, infants and neonates, better image quality can be obtained with a smaller surface coil. Specific pediatric coils are commercially available for imaging the brain and spine, and while pediatric thoracic coils are becoming increasingly available, often adult coils designed for other applications (such as adult orthopedic extremity coils) are used for this purpose[75].

On a practical level, better outcomes are achieved with children when there is thorough planning and preparation prior to the scan. Some practical considerations and tips for achieving a successful outcome are described in Table 1.

CMR SAFETY CONSIDERATIONS

It is essential that all patients and any accompanying persons (such as parents) undergo thorough screening for the presence any implanted medical devices or foreign bodies - these include pacemakers, implantable defibrillators, neurostimulators, stents, cerebro-spinal fluid shunts, cerebrovascular clips and coils, cochlear implants, orthopedic devices, shrapnel, bullets and metal fragments[76]. Where the history is unreliable, plain radiographs can be used to aid the screening process. The strong magnetic fields of the scanner may disrupt the function of some electrically, magnetically or mechanically activated devices, and ferromagnetic objects risk becoming dislodged during the scan causing local tissue damage[77]. Many modern devices are designed to be MRI compatible - they may cause artefact but are not ferromagnetic and will not overheat or fail in the presence of the magnetic field. Older devices, on the other hand, are less likely to be MRI compatible, therefore it is essential to thoroughly check the safety information for each specific device and follow all recommendations made by the manufacturer.

The use of GBCAs can also raise issues. Although the incidence of complications relating to the use of these agents is low, children are susceptible to all the adverse effects experienced by adults. These include feelings of coldness or warmth on injection, nausea, vomiting, headache, paresthesia, dizziness, itching, extravasation of contrast agent and allergic reactions ranging from a simple rash to anaphylaxis[78-80]. A serious complication of GBCAs is nephrogenic systemic fibrosis (NSF), a progressive, incurable and often fatal condition that involves widespread fibrosis of the skin, subcutaneous tissue, joints, skeletal muscles, and organs such as the eyes, lungs, heart and liver. It typically occurs in the context of renal dysfunction when GFR is less than 30 mL/min per 1.73 m^2, additional risk factors include the requirement for renal replacement therapy, concurrent hepatic disease and a pro-inflammatory state[81,82]. NSF is exceedingly rare, and even more so in children compared to adults[83]. This is surprising given the immature renal function of

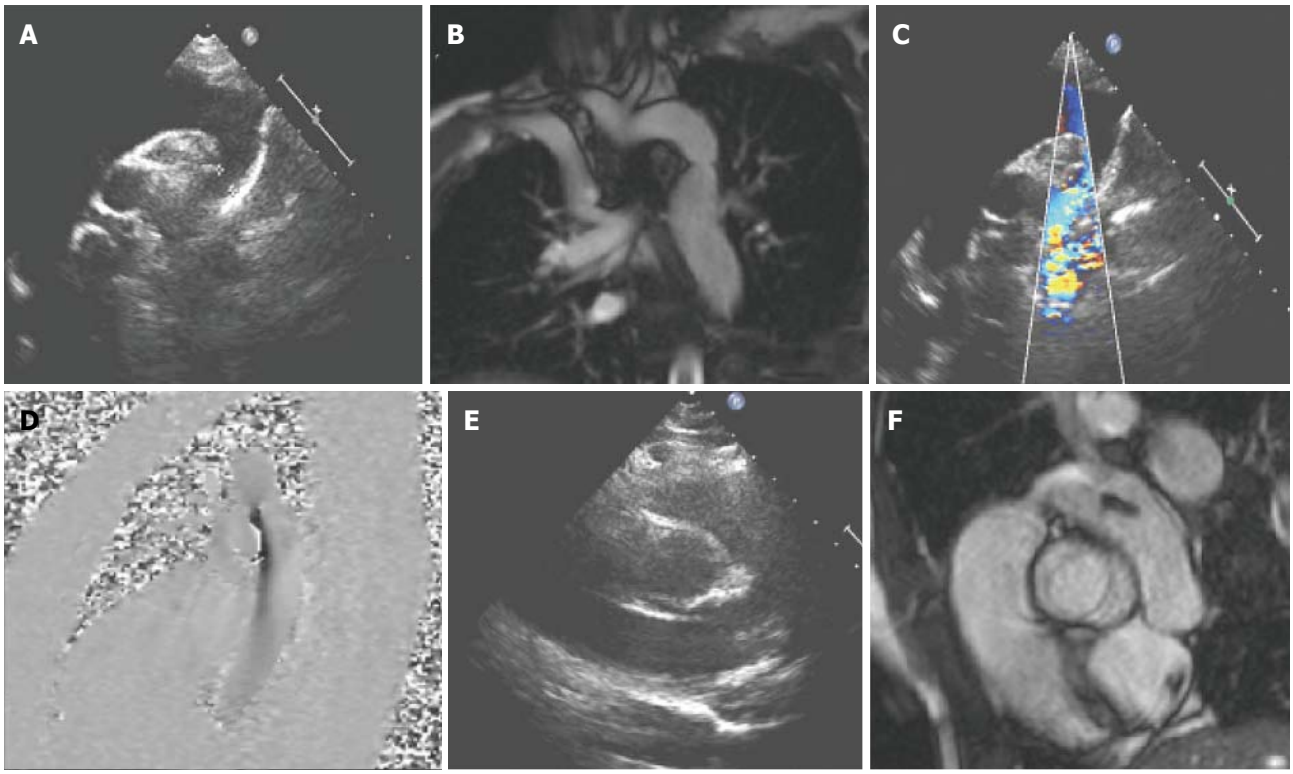

Figure 2 A 17-year-old girl with coarctation of the descending aorta, imaged by transthoracic echocardiography (A,C,E) and cardiovascular magnetic resonance (B,D,F). Imaging of the aortic arch using TTE can be challenging, depending on the suprasternal image quality A and especially in older children with poorer acoustic windows. CMR allows accurate measurement of the dimensions of the area of stenosis B and assessment of the remainder of the thoracic aorta and head and neck vessels. Flow velocity mapping D, similar to Doppler echocardiography C is used to measure peak velocity through the stenosed area and assess for a diastolic tail. In this case, the bicuspid aortic valve was not well visualised on TTE E but was clearly seen on CMR F. CMR: Cardiovascular magnetic resonance; TTE: Transthoracic echocardiography.

neonates and infants. Nevertheless, all patients should be screened for risk factors and renal function should be checked before GBCAs are administered[84]. If renal dysfunction is identified, local or national guidelines should be consulted and steps should be taken to minimize relevant risk factors with contrast-enhanced scanning only proceeding after careful consideration of the risks and benefits[85]. In light of this screening process, and the introduction of safer agents bound to a cyclic chelate[83], the incidence of GBCA-related NSF has fallen significantly in recent years[86].

Additional CMR safety considerations, especially with relation to neonates and infants, include the use of ear protection in order to prevent hearing damage from the acoustic noise of the scanner[87], and the requirement for close monitoring of body temperature. Scanning rooms are deliberately kept cool to reduce overheating of the electrical equipment however local heating of the coils in close proximity to the patient can still occur. Thus, small children, infants and neonates with reduced ability to control their body temperature are at risk of both hypothermia and hyperthermia during CMR[88].

CLINICAL APPLICATIONS IN CHILDREN

Disease of the aorta

Conditions amenable to assessment with CMR include coarctation, interrupted aortic arch, vascular rings and congenital connective tissue diseases[2]. Echocardiography is usually sufficient for diagnostic purposes for these conditions in neonates and infants, however CMR can be a useful adjunct in older children with poor acoustic windows, especially with regards to planning surgical or catheter intervention (Figure 2). CMR is also used first-line for post-intervention follow-up[89-91]. The use of black blood sequences along with contrast-enhanced 3D MRA and non-contrast 3D SSFP allows delineation of arch geometry and morphology, evaluation of the presence of collaterals, the site and size of areas of stenosis, the extent of any aneurysm formation, and characterization of coarctation stents[92-97]. SSFP cine sequences are also useful for assessing aortic valve morphology (often bicuspid), and left ventricular function. Velocity encoded phase contrast imaging can be used to quantify collateral flow[98]. CMR can also be used for monitoring aortic dimensions, aortic root dilation and aortic regurgitation in cases of connective tissue disease such as Marfan's in order determine optimum time for intervention[99,100].

Conotruncal anomalies

For tetralogy of Fallot (ToF) CMR is usually only performed pre-operatively if there are associated situs and aortic arch anomalies, however it is the preferred tool for the post-operative serial follow-up of these patients[101]. Pulmonary regurgitation, right ventricular outflow tract (RVOT) obstruction and pulmonary artery stenosis are common

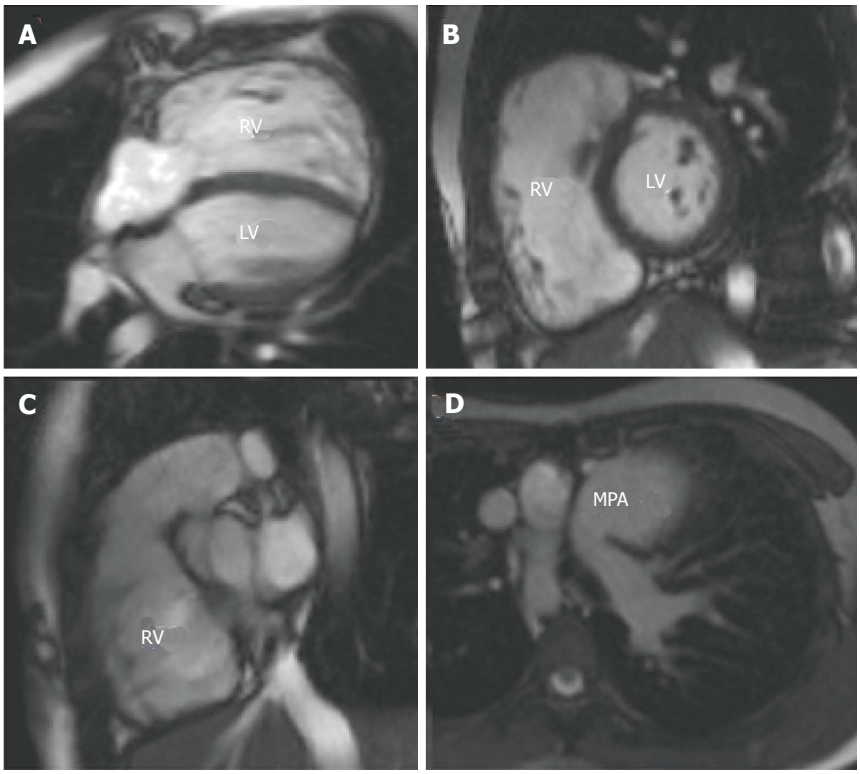

Figure 3 A 10-year-old girl with tetralogy of Fallot repaired at 1 year of age. She had a 1 year history of increasing exertional breathlessness and reduced exercise capacity. Her CMR showed near-free pulmonary regurgitation with a dilated right ventricle and a reduced right ventricular ejection fraction. In view of these findings, she was offered a pulmonary valve replacement. A shows a 4 chamber SSFP cine image; B a short axis through the mid ventricle; C a right ventricular outflow tract view and D a transverse section through the thorax at main pulmonary artery level showing the dilated main pulmonary artery. RV: Right ventricle; LV: Left ventricle; MPA: Main pulmonary artery; SSFP: Steady state free precession; CMR: Cardiovascular magnetic resonance.

post-operatively and lead to right ventricular volume and pressure overload. This is initially well tolerated in childhood and adolescence, but may ultimately cause right ventricular dysfunction, arrhythmias and premature death[102,103]. Intervention is required in most cases, either with a surgical pulmonary valve replacement or percutaneous pulmonary valve implantation (PPVI) and the decision about when to intervene is controversial[104]. CMR can assist the decision making process[105,106]. LGE CMR contributes to risk stratification of these patients, SSFP cines enable accurate right ventricular volumetric and functional analysis (Figure 3), and velocity encoded phase contrast sequences can be used for flow assessment in relation to the pulmonary regurgitation and stenosis. Contrast-enhanced 3D MRA and 3D SSFP can also be used to delineate RVOT anatomy for intervention planning[107]. Similarly, with transposition of the great arteries (TGA), echocardiography is usually sufficient to define anatomy pre-operatively and the predominant role of CMR is for the investigation of late post-operative complications. These will vary depending on the corrective procedure performed, however for the most commonly performed arterial switch operation (ASO), complications include RVOT stenosis, supravalvular pulmonary artery stenosis, branch pulmonary artery stenosis, coronary ostial stenosis, dilatation of the neo-aortic root and neo-aortic valve regurgitation[108-110]. Spin echo, gradient echo and phase contrast sequences are used for assessment of anatomy, stenosis and valvular function and 3D MRA and 3D SSFP and first-pass perfusion sequences are useful for assessing the patency of the re-implanted coronary arteries[111-113].

Complex congenital heart disease

CMR is considered the first-line imaging modality for complex congenital heart disease (CHD) as it achieves superior delineation of anatomy and enables a concurrent hemodynamic assessment[2,101]. Specific congenital anomalies amenable to assessment with CMR include viscero-atrial situs anomalies, abnormal atrio-ventricular and/or ventriculo-arterial connections, septal defects, outflow tract malformations, abnormal extra-cardiac thoracic vessels and any associated tracheo-bronchial anomalies. CMR can also play a key role in the staged palliation of univentricular hearts[114]. Initially, it can help determine the approach required particularly in borderline cases where there is debate over whether to perform a single ventricular or bi-ventricular repair[115], and subsequently CMR can be used in conjunction with echocardiography and catheterization to perform an anatomical and functional assessment at each stage of the palliation process for evaluating outcomes and planning subsequent interventions[116-119].

Assessment of valvular disease, pulmonary vessels and shunts

Although echocardiography remains the gold-standard modality for valvular morphological assessment, CMR can play a complementary role when acoustic windows are poor. SSFP cine imaging can be used to determine the functional consequences of valvular lesions, particularly in terms of the effect on ventricular volumes and myocardial mass, and velocity encoded phase contrast imaging permits visualization and quantification of regurgitant and stenotic jets[15]. In terms of the pulmonary vasculature, contrast-enhanced 3D MRA and 3D SSFP sequences provide good visualization of the morphology and dimensions of the pulmonary arteries and veins, revealing anomalous connections and areas of stenosis, and

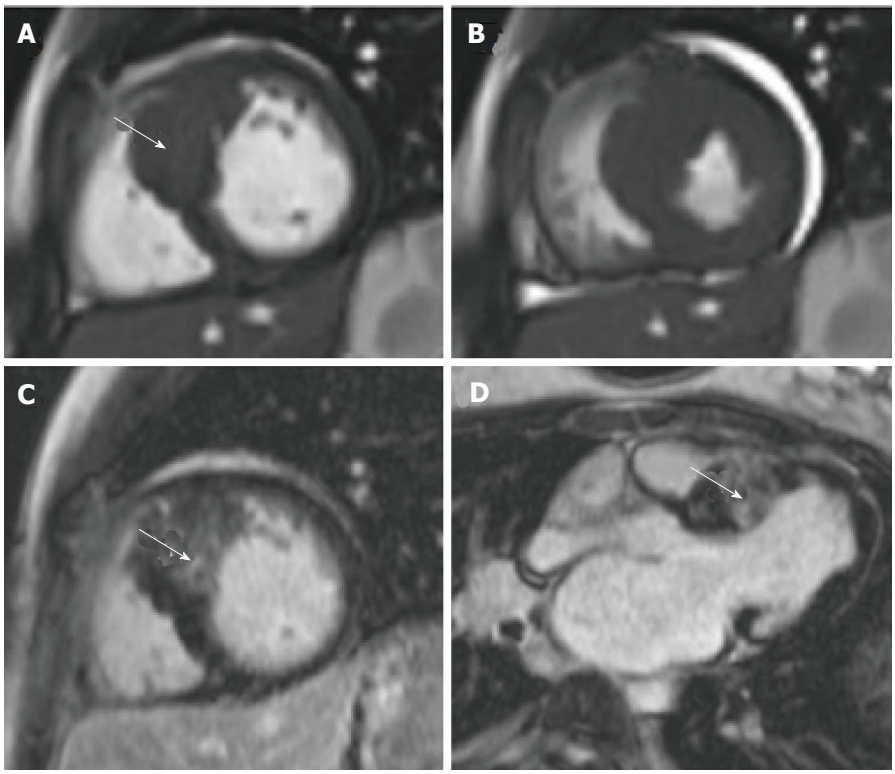

Figure 4 A new diagnosis of hypertrophic cardiomyopathy in a 12-year-old girl who presented as an out of hospital arrest with documented ventricular fibrillation. A shows a short axis view of the left ventricle at end systole at basal level. There is asymmetrical septal hypertrophy (arrowed) with a maximal wall thickness of 26 mm; B shows the same ventricular position in end systole; C and D are late gadolinium enhancement images demonstrating extensive patchy fibrosis of the hypertrophied septum (arrowed).

velocity encoded phase contrast cines enable quantitative measurements of blood flow within these vessels[2]. CMR also permits evaluation cardiac shunts in terms of their location, flow direction, magnitude and functional consequences such as volume loading of any of the cardiac chambers whilst providing detailed anatomical information. Shunt quantification is performed using velocity encoded phase contrast cines to assess the ratio of pulmonary (Qp) to systemic flow (Qs), and this important hemodynamic parameter is often used as a determining factor when planning surgical or interventional management[120].

Assessment of coronary arteries

Imaging the coronary vessels is challenging due to small vessel size and an increased susceptibility to cardio-respiratory motion artefact. Indications for coronary artery imaging in children include presence of congenital anomalous coronary arteries, vasculitis (in particular Kawasaki disease), before any surgery or interventional procedure close to the proximal course of the coronary arteries, and post-operatively for procedures involving transfer and re-implantation of the coronary arteries[2]. Although cardiac catheterization is considered gold standard for assessment of the coronary arteries, 3D SSFP CMR sequences can being increasingly used for this purpose[121-125]. First-pass perfusion and LGE imaging are also useful for the assessment of myocardial viability in the context of coronary artery pathology, and cine imaging can provide information about the functional consequences of myocardial ischemia where this is suspected.

Cardiomyopathy

CMR permits detailed *in vivo* myocardial tissue characterization and therefore can play a key role in the diagnosis, risk-stratification and ongoing management of these patients[126]. Dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) are the most commonly encountered cardiomyopathies in children[127]. In DCM, the extent of both left and right ventricular dilation can be easily visualized and quantified using CMR. LGE imaging can help distinguish between DCM of ischemic and non-ischemic etiology[126], and SSFP cine sequences can be used to provide valuable information about global ventricular function especially in terms of contractility, relaxation impairment and wall motion anomalies. DCM in children is also known to be associated with anomalous coronary arteries, the presence of which can be determined using CMR[121]. Where myocarditis is suspected, spin echo sequences are useful in revealing the extent of inflammatory change[128]. Since left ventricular hypertrophy is generally considered an independent risk factor for cardiac events[129], accurate assessment of the magnitude and distribution of hypertrophy is essential in order to appropriately risk stratify and manage affected patients. Echocardiography is the most commonly used modality for the diagnosis and follow-up of HCM, however it has been shown that CMR can detect hypertrophy missed by echocardiography[130,131]. Ventricular mass and function in HCM can also be well characterized using CMR (Figure 4) and it has been demonstrated that with LGE imaging in HCM, the extent of myocardial fibrosis is closely correlated with the development of left ventricular dilatation and failure, and the risk of sudden cardiac death[40,132,133]. Where myocardial hypertrophy is related to a metabolic defect such as in Pompe's disease or Fabry's disease, CMR can play a useful role in the diagnosis of these conditions and in monitoring response to enzyme replacement therapies[134,135]. CMR

can also be used in the assessment of iron overload cardiomyopathy. This predominantly affects children with inherited severe anemias such as thalassemia and sickle cell disease, where the excess iron load from regular blood transfusions deposits in the tissues of organs such as the heart and liver. In the myocardium, this causes fibrosis, systolic impairment ultimately cardiac failure. The measurement of T2*, a CMR relaxation parameter derived from local magnetic field inhomogeneities[6], has been shown to accurately reflect tissue iron load[136,137], thus CMR can be used as a means of evaluating the requirement for and response to chelation regimens[138-140].

Cardiac tumours

The most common cardiac tumours in children are benign fibromas or rhabdomyomas. Malignant secondaries from leukemia, lymphoma, neuroblastoma and nephroblastoma are rare, and malignant primaries, typically cardiac sarcomas, are rarer still[141]. Using spin echo, SSFP cine, first-pass perfusion and LGE sequences it is possible to assess the size, site and malignant potential of the tumour through detailed tissue characterization, and assess hemodynamic relevance in terms of how any obstructive mass effects may impair myocardial or valvular function[142-144].

FUTURE DIRECTIONS

Technological advances in CMR hardware and software are continually occurring, resulting in faster sequences with shorter acquisition times, and improved image quality with greater spatial and temporal resolution. Such advances have permitted the development of real-time imaging, involving rapid and continuous data acquisition with nearly instantaneous image reconstruction and a reduced requirement for cardio-respiratory motion compensation - which is particularly advantageous in pediatrics[145-147]. Real-time imaging has also paved the way for the growing field of interventional CMR, whereby CMR performed using open magnets can be used to guide cardiac catheterization procedures, thus avoiding exposure to ionizing radiation[148]. However, although the concept of purely CMR guided interventional procedures is promising, a number of obstacles still exist that prevent it translating into routine clinical practice[149-151]. Thus, interventional CMR in current practice falls into the realm of hybrid CMR/X-ray cardiac catheter (XMR) laboratories. In these laboratories both modalities are present in the same room and the patient can be rapidly moved between them during the imaging process permitting cross-modality image integration. Additional emerging techniques include time-resolved 3D MRA permitting direct visualization of complex flow dynamics in vessels[152] and time-resolved 3D (4D) velocity encoded phase contrast imaging allowing quantification of flow parameters in multiple planes[153]. Higher field strength 3T scanners also exist that yield a higher signal-to-noise ratio and better spatial resolution. This is particularly beneficial when imaging small children. However, these scanners have their own limitations and are not yet compatible with all CMR sequences[154].

CONCLUSION

CMR is emerging as helpful imaging tool in pediatric cardiology and is becoming increasingly available for a wide range of range of both congenital and acquired cardiac disease. Its non-invasiveness and lack of exposure to ionizing radiation are particular advantages with regards to the pediatric population, and CMR is well tolerated in children of all ages with an excellent safety profile when performed in specialist centres by experienced personnel. Outcomes are most successful when scans are undertaken using an individualized approach specifically tailored to the clinical question. In these circumstances, CMR is capable of providing detailed anatomical and functional information, and it is well suited to serial imaging for long-term follow-up and as a means of planning and evaluating surgical and interventional management. In light of all the technological developments currently taking place in the field of CMR, it will be interesting to see what the future holds for this modality in the world of pediatric cardiology.

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REVIEW

Synthetic cannabinoids 2015: An update for pediatricians in clinical practice

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Abstract

Synthetic cannabinoids are a group of substances in the world of designer drugs that have become increasingly popular over the past few years. Synthetic cannabinoids are a chemically diverse group of compounds functionally similar to THC. Since first appearing on the world market a few years ago these compounds have evolved rapidly. Newer more potent analogues have been developed. Identifying youth who abuse these substances can be difficult. Newer forms of consumption have also evolved. These products are now manufactured in products that look like natural cannabis resin and in liquid cartridges used in electronic cigarettes. Synthetic cannabinoids appear to be associated with potentially dangerous health effects that are more severe than that of marijuana. Some synthetic cannabinoid compounds have been associated with serious physical consequences, such as, seizures, myocardial infarction and renal damage. In addition, psychoactive effects, such as aggression, confusion, anxiety and psychosis have also been reported. The diagnosis remains primarily clinical with toxicological confirmation difficult due to manufacturers constantly developing new analogues to avoid detection. Pediatricians are urged to familiarize themselves with these drugs and the typical presentations of patients who use them.

Key words: Synthetic; Cannabinoids; Youth; Children; Adolescents

Core tip: Synthetic cannabinoids are a group of substances that are typically much more potent than natural cannabis. These substances have been increasingly abused by youth over the past few years. A number of published reports have emerged documenting the serious health consequences associated with use of these products. Seizures, myocardial infarction and renal damage are some of the significant physical consequences associated with their use. With current limitations of toxicological analyses pediatricians are urged to familiarize themselves with these drugs and the typical presentations of patients who use them.

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INTRODUCTION

Synthetic cannabinoids (SCs), also known as cannabimimetics, were originally synthesized in the 1960's, but emerged as recreational drugs in Europe in about 2004. They became popular as a recreational drug in Germany in 2008, and have been increasingly available worldwide since then[1-3]. Over 130 different synthetic cannabinoids have been detected in recent years. Most of these substances appear to be manufactured in China. After being shipped in powder form to Europe, the chemicals are typically added to plant material, packaged for sale as "legal high" products and often misleadingly labelled "not for human consumption".

SCs are usually smoked. Recently several countries have also reported finding the substances in products that look like cannabis resin either in branded "legal high" products or simply misrepresented as cannabis resin on the illicit market. This development is likely to be a response to the popularity of cannabis resin in many countries. Another recent development has been the manufacturing of synthetic cannabinoids in the liquid cartridges used in electronic cigarettes. The use of SCs in electronic cigarettes likely reflects manufacturers' opportunistically taking advantage of the recent popularity of "vaping" among young people. Synthetic cannabinoids have also been detected in mixtures containing other psychoactive substances such as stimulants, hallucinogens and sedatives and in a small number of cases, they have been detected in what are sold as ecstasy tablets[4].

Users often perceive these preparations as a natural way of getting high that is also legal and undetectable. The preparations are far from natural: They consist of unknown mixtures of plant products that are sprayed with a liquid form of the SCs, containing many unidentified chemical structures[5]. New preparations are constantly being synthesized, leading to the difficulties developing reliable methods of detection. Several identified forms of synthetic cannabinoids have been banned, and are therefore illegal, but newly synthesized SCs are designed to circumvent any laws or regulations that ban them[6].

SCs are sold commercially under a variety of names, such as Mr. Nice Guy, Green Buddha, Blonde, Summit, Standard, Blaze, Red Dawn X, Citron, Green Giant, Smacked, Wicked-X, AK-47, Spice, Special K, K2, Kronic, Barely Legal, and Fake Weed[7]. The cost of synthetic marijuana preparations is comparable to the cost of cannabis. These drugs have become increasingly popular among adolescents and young adults[8]. SCs are the second-most widely used illicit drug in high school seniors in the United States. In a 2012 national survey of 8th, 10th and 12th grade students, 4.4% of the 8th graders, 8.8% of the 10th graders and 11.3% of the 12th graders admitted using synthetic marijuana. The rise in use of SCs among younger individuals is particularly alarming. Among 8th graders SCs are the third highest category of illicit drug being used after marijuana and inhalants[9]. A nationally representative sample of nearly 12000 high school seniors revealed 10% of students reported using SCs in the previous 12 mo, and 3.2% reported "frequent use" (at least 6 times) in the previous 12 mo. Females were significantly less likely than males to use SCs in this study. The odds of using SCs was significantly increased if the teenagers endorsed a history of using alcohol, cannabis, or cigarettes and was directly related to the number of evenings per week the teenagers went out "for fun". The strongest correlation was with a history of cannabis use. Indeed, only 0.5% of non-marijuana users in this study reported the use of SCs[10]. Correlates from this important study of high school seniors can be used by pediatricians in the evaluation of youth who are suspected of using SCs.

In a study of college students, eight to 14% of participants in the study reported the use of SCs, starting at an average age of 18 years[11]. The attractiveness of these SCs for young people include the lack of readily available methods of detection, the perception that these drugs are legal or "harmless," and availability in shops that sell paraphernalia for marijuana and tobacco users (head shops), in gas stations or convenience stores, or sometimes over the internet. Studies have demonstrated that the motivation for use of these products were not only to "get high" but also to avoid detection[12,13]. Those individuals who have used both marijuana and SCs describe a "better high" from the natural cannabinoids (fewer negative subjective mood experiences), but may gravitate toward SCs for the reasons described above, especially the difficulties in detection with routine urine toxicology screenings. In a study of patients admitted to outpatient treatment for SC use, those who were on probation reported the main reason for using SC instead of marijuana was to avoid detection[14].

In a recent study of 5947 athletes in the United States, 4.5% tested positive for SCs (using specialized detection methods unavailable in routine urine toxicology screening). This rate is much higher than the rate found in earlier studies of athletes, making it imperative for physicians to be aware of the possibility of synthetic cannabinoid use in this population. While the ages of the athletes in this study were not specified, pediatricians should be aware of the possibility of synthetic cannabinoid use in middle school, high school, and college athletes[15].

Young people may perceive these "natural" preparations of SCs as safe. On the contrary, many instances of dangerous reactions to the SCs have been reported. These include seizures, kidney failure, rhabdomyolysis, aggression and psychosis. Calls to poison control centers regarding human exposures to synthetic marijuana have increased.

Poison control centers have already registered 4377 calls in the first 6 mo of 2015 compared with 3680 for the entire year of 2014[16]. In 2010, more than 11000 emergency department (ED) visits in the United States involved a synthetic cannabinoid: Three-fourths of these visits involved young patients aged 12 to 29[17]. The following year the number of ED visits involving SCs increased significantly, totaling 28531. Pediatricians should be aware that the number of ED visits involving SCs for patients aged 12 to 17 years doubled from 3780 visits in 2010 to 8212 visits in 2011. Males accounted for nearly 80% of ED visits, but a threefold increase in synthetic cannabinoid-related ED visits for females has been observed[18]. While it is true that youth who use SCs also frequently use other substances[10,13,14,19,20], only one third of the synthetic cannabinoid-related emergency department visits revealed use of other substances at the time of the encounter[18]. These statistics should serve to highlight the frequency and severity of ED presentations of synthetic cannabinoid-related visits in the pediatric population.

Many clinicians are unaware of the prevalence and severity of physical and psychoactive symptoms, and the potentially serious consequences related to the use of SCs. A study of clinically active emergency physicians at a large, urban emergency department revealed that knowledge of SCs came mostly from nonmedical sources, and that most emergency physicians have only a general familiarity with SCs[21]. Because of the prevalence of the use of SCs in adolescents, and the potential serious consequences of their use, it is imperative that pediatricians and other physicians become educated in the identification, evaluation, and treatment of youth who are using these substances. We will present information below on the identification and evaluation of young patients in the emergency department setting and outpatient office setting who may be using SCs.

PHARMACOLOGY

Cannabinoids may be classified as phytocannabinoids, endocannabinoids, or SCs, based on their origin. THC is the phytocannabinoid found in cannabis plants, and is responsible for the "high" associated with smoking natural cannabis or marijuana. Endocannabinoids are endogenous molecules involved in nervous system and immune system function. SCs are a chemically diverse group of molecules functionally similar to THC. Cannabinoids exert their effects on the nervous system *via* the CB1 receptor, found in the brain and peripheral nervous system. Within the brain, CB1 receptors are located in the cerebral cortex, basal ganglia, and hippocampus. The desired effect, or "high" associated with smoking marijuana or SCs occurs when THC or SCs bind to the CB1 receptor in the brain. SCs are a full agonist at this receptor; THC is a partial agonist. Accordingly, SCs can bind to the CB1 receptor with an affinity up to one hundred times as great as THC[22,23].

Interestingly, synthetic cannabinoid preparations do not contain cannabidiol, a substance found in marijuana that has anxiolytic and antipsychotic properties. In addition to their higher affinity for the CB1 receptor, SCs also have a longer half-life than naturally-occurring cannabinoids[24]. The potentially longer duration impacts both the desired effects and the adverse psychoactive and physical effects of SCs. The absence of cannabidiol, together with a higher affinity for CB1 receptors and longer half-life compared to marijuana, may account for the increased potential of SCs to produce adverse psychiatric and physical symptoms[25].

SCs are metabolized in the liver *via* conjugation and oxidation pathways. The complex pharmacokinetics are poorly understood, but it is clear that active metabolites exist, and that cytochrome P450 pathways can be involved in adverse drug-drug interactions in patients who mix SCs with prescription medications[26].

CLINICAL EFFECTS

Acute effects of synthetic cannabinoid use typically last from 30 to 120 min but symptoms may last until the next day ("Hangover" feelings). Users report effects can be similar to cannabis use with the "rush" being similar to the one from cannabis, but shorter and more intense[13,27]. Frequently, users report other effects not typical of cannabis use that are more serious in nature[13,27-29]. Reactions are generally reported to be experienced on a sliding scale of intensity. Users mention inexperience with SC use leading to excessive dosing and type/generation or potency of SCs as influencing factors[30]. A systematic review was conducted of literature regarding synthetic cannabinoid use in Medline, PubMed, review of abstracts from professional meetings and conferences and government reports and alerts. Our knowledge base of the clinical effects regarding SCs has grown over the past few years but many of the publications reviewed lacked toxicological confirmation. To date there are no randomized controlled studies on the clinical effects of SCs. Most of our current knowledge is based on case series and reports, admissions to emergency services, reports to poison control centers and internet forums.

The adverse effects associated with SCs appear related to both the intrinsic properties of the substances and to the way the products are produced. There have been numerous reports of non-fatal intoxications and a smaller number of deaths associated with their use. Some of these compounds are very potent; the potential for toxic effects is high, even for the experienced user. The process by which synthetic cannabinoid products are manufactured has been associated with uneven distribution of the substances within the herbal material, which may result in some products containing doses that are higher than intended[4].

Synthetic cannabinoid use has been associated with both physical and psychoactive effects.

Physical effects

Cardiovascular: The most common cardiovascular

side effects are tachycardia and elevated blood pressure. Individuals can also present with palpitations, chest discomfort or tightness, or dysrhythmias[14,27-29,31-42]. Zimmermann *et al*[43] reported on two persons who presented with ischemic stroke after the use of synthetic cannabinoids. More serious cardiovascular consequences of SC use have also been noted. Several studies have documented chest pain, and cardiac ischemia after SC use[28,29,35,40,44-54]. Evidence that SC use is associated with myocardial infarction also exists[55,56]. Anecdotal reports describe two adolescents who died in the United States after ingestion of a SC product called "K2", one due to a coronary ischemic event[57]. At least four case reports now exist of pediatric patients who have been diagnosed with myocardial infarction (MI) associated with smoking SCs[58,59].

Gastrointestinal: Gastrointestinal effects, such as nausea, vomiting, and gagging, are also common after consumption of SC products[14,25,28,29,35,42,44,46,47,51,60,61]. SC use can also induce "cotton" mouth or xerostomia typical of marijuana use[13,31,35,36,46,60,62].

Neurological: A number of motor neurological effects of SCs have been reported including tremors, ataxia, fasciculations, hypertonicity, hyperflexion, and hyperextension[24,37-39,45-48,62]. Musshoff *et al*[63] and the study[64] describe several case examples of youngsters who displayed impairment of fine motor skills associated with difficulty operating a motor vehicle. Sensory changes, such as numbness, have been reported[14,47]. Other neurological symptoms associated with SC use include headaches[37,44,52] and dizziness[37,51].

There are several instances of SC use being associated with more serious neurological effects such as seizures[28,29,34,35,40,47,59,64-67], loss of consciousness[51] and coma[47,59].

Renal: Over the past two years acute kidney injury has been added to the list of toxicities associated with use of SCs. Recently, over 20 cases of acute renal failure with associated acute tubular necrosis after SC use have been reported[68-72]. While the precise cause of renal damage in these patients is unclear, one specific synthetic cannabinoid may be implicated[68,69].

Metabolic: Similar to marijuana, SC products have been reported to stimulate appetite[13,14,27-29,46,59]. However, Buser *et al*[73] discovered in a large global sample that users of SCs reported having less appetite-stimulating properties than marijuana. SCs can also induce other metabolic effects, such as hypokalemia, hyperglycemia, acidosis[25,28,29,36] and diaphoresis[37,44,48].

Ophthalmologic: Conjunctival injection or redness of the eyes, typical of marijuana use has also been frequently observed after SC use. Other ocular effects include pupillary changes, such as miosis and mydriasis, blurry vision and light sensitivity[25,31,35-37,40,44,51].

Pulmonary: A handful of case reports have emerged describing respiratory symptoms and complications after SC use. Hyperventilation[37,40,52], apnea[51], alveolar infiltrates[74,75] and pneumonia have been reported[76].

Other physical effects: Other physical symptoms reported with SC use include hyperthermia, rhabdomyolysis, symptoms suggestive of anticholinergic effects, and tinnitus[27-29,44,61]. Insomnia[14,77], hair loss and unspecified "skin problems"[14] have also been reported.

Psychoactive effects

Cognitive: The most common cognitive effects of SC use are impairments in attention, concentration and memory[13,27,51,52,63]. Difficulty thinking clearly (not associated with psychosis)[43] and confusion have also been reported[4,36,37,40,41,43,44,50,78].

Affective: Although synthetic cannabinoid users frequently experience euphoria with use of these products, negative emotions are also commonly reported. Anxiety and panic are frequently associated with SC use[13,37,40,48,77,79,80]. Since panic symptoms frequently accompany palpitations, it can be difficult to differentiate to what extent these symptoms are due to anxiety. To a lesser extent, irritability is less frequently reported by users[13,44,81].

Speech: Dysarthric[37], pressured[37], slowed[37,48] and disorganized speech[51] as well as inappropriate laughter[27,40], have been observed with and reported by SC users.

Behavioral: Restlessness[13,37] and agitation during acute intoxication has been described in several scientific reports[32,37,40,41,44,46,47,52,79]. Reports of users of SCs exhibiting violent and aggressive behavior have dominated the lay and scientific literature. Many of the subjects displayed symptoms consistent with psychosis and altered mental status[8,37,77,79,82,83].

Psychosis and perceptual distortions: Researchers have increasingly described the mental status changes associated with SC use and intoxication. Perceptual changes such as, "alteration of perception"[31] and seeing "things not actually there"[13,37] have been described. Psychotic symptoms, such as hallucinations, disorganization of thoughts and delusions in subjects with and without a previous history of psychosis have been reported[14,27-29,32,35,39,40,46-48,80,84-86].

Suicide: Non-fatal, self-mutilatory behaviors secondary to SC use appear rare, with just two cases described in the literature[52,87]. Multiple reports connecting SC use and suicidal behaviors can be found in the media and throughout the internet[88,89]. Our review of the scientific literature discovered ten subjects in six different studies describing suicidal ideation[40,52,77,80,90].

Tolerance, dependence and withdrawal: Case series

and reports have indicated that use of SCs can produce effects beyond acute intoxication, with tolerance and withdrawal symptoms described following prolonged use. These preliminary reports suggest dependency may be associated with chronic SC use. A few reports indicating dependence are noted throughout the literature. Banerji *et al*[44], Nacca *et al*[91] and Rominger *et al*[92] each described one to two person case reports of persons exhibiting significant craving and acute withdrawal, presumably due to prolonged synthetic cannabinoid use. Bozkurt *et al*[14] examined one hundred fifty-eight patients enrolled in an outpatient substance abuse clinic. Seventy percent of these individuals had unsuccessful attempts to stop SC usage and/or symptoms of dependence. At the present state of knowledge it appears that the withdrawal syndrome from synthetic cannabimimetics is similar to but more severe than that from marijuana[14,92].

EVALUATION

In an emergency department (ED) setting, adolescent or young adult patients often present in a state of acute intoxication with SCs (either alone, or in combination with other substances)[93]. Physical consequences of SC intoxication can affect any system of the body. The pediatrician should always be aware of the potential serious medical sequelae of SC intoxication, such as myocardial infarction, seizures and acute kidney injury. In light of current limitations of toxicological testing in the emergency department, a diagnosis requires a high index of suspicion and knowledge of the typical history of users and possible symptoms. Evaluation of the patient should therefore include a thorough medical history, physical examination with documentation of vital signs, and laboratory studies to evaluate kidney function, electrolytes, and hepatic function. An EKG is recommended, and other cardiac testing as appropriate depending on the clinical presentation (including serial cardiac enzymes if chest pain is present)[94].

Acute intoxication with SCs can produce alterations in mental status, behavioral disturbances, changes in mood and affect, and psychotic symptoms. In an acute emergency setting a typical presentation may include confusion, hallucinations, anxiety and panic, agitation and aggression as well as suicidal behaviors. Evaluation of the youngster should include a mental status examination, with particular attention to the suicide risk assessment, and also an assessment of the risk of aggressive behavior toward others[37]. Given the fact that the patient may present with confusion or agitation, gathering collateral information from other informants such as family members or friends is important. Obtaining information about pre-existing psychiatric conditions will help guide the treatment of the patient. Information from paramedics or others who transport the youngster to the ED about the possible ingestion of substances, a history of substance use or the presence of drug paraphernalia, may be very helpful.

The clinician must suspect intoxication with SCs in any young person who presents with the sudden onset of otherwise unexplained psychosis. Psychotic symptoms frequently include paranoid thoughts, disorganized thoughts, flat or inappropriate affect, visual misperceptions, and auditory and/or visual hallucinations. Psychotic symptoms may represent the direct effects of the SCs, *vs* exacerbation of a pre-existing psychotic disorder such as schizophrenia. Patients may sometimes present to the ED in a state of withdrawal from SCs, with symptoms of insomnia, anxiety, nausea, and lack of appetite[91]. Since SCs are not detectable in routine urine toxicology screening, the pediatrician should be familiar with the characteristic symptoms and signs of intoxication and have a high index of suspicion to help make the diagnosis of SC intoxication. Alcohol and drug use are not rare in teenagers. Seventy percent of 12th graders in the United States are reported to have at least tried alcohol. Marijuana is by far the most widely used illicit drug used by youth in the United States. The most commonly used illicit drugs by 12th graders (lifetime) include marijuana (45%), ecstasy (7.2%) and cocaine (4.9)[9]. Synthetic cannabinoid intoxication should be strongly suspected in an adolescent who is known to use other substances such as marijuana and/or alcohol, is in a setting where he or she is undergoing periodic urine toxicology screening, and presents to the ED with the characteristic symptoms and signs of synthetic cannabinoid intoxication described here[95]. Urine toxicology screening may be helpful in that a positive screening test for marijuana, together with the characteristic presentation, greatly increases the likelihood of synthetic cannabinoid use/intoxication[14,20,34].

Adolescents rarely present to the pediatrician's office in a state of acute SC intoxication. In the office setting, the diagnosis of SC use is based more on the clinical history than on the mental status examination. Some persistent symptoms and signs resulting from SC use can, however, be identified on examination in the pediatrician's office. These include fatigue, persistent psychotic symptoms, and conjunctival injection[95]. Routine urine toxicology screening in the office setting may be helpful in identifying other substances the patient may be using, such as marijuana. If the diagnosis of SC use is made in the outpatient setting, laboratory screening for liver function and kidney function, as well as an evaluation of cardiac function, would be appropriate.

Some general principles involved in the evaluation and diagnosis apply in both the ED and office settings. The discovery of paraphernalia used in the consumption of SC products (pipes, rolling papers, electronic cigarettes) increases the likelihood that the patient is using these substances[4]. There is no characteristic odor of SCs, but the presence of the characteristic odor of marijuana may be present in a youngster who is using both substances. Manufacturers are constantly producing new synthetic cannabinoid compounds. Toxicological exams that screen for routine drugs of abuse may not detect most synthetic cannabinoid compounds. Unfortunately, many clinical laboratories do not routinely test for these recreational drugs because of financial

Table 1 Symptoms and history supportive of synthetic cannabinoid use

Synthetic cannabinoid use should be strongly suspected if a youngster presents with
A history of marijuana or other drug use
Symptoms and signs consistent with cannabis use
Unexplained sudden onset of psychotic symptoms
Unexplained sudden-onset renal, neurological, and/or cardiovascular problems is in a situation in which his or her urine is being routinely monitored for illicit substance use has had negative routine urine toxicology screens

constraints, analytical capabilities, and time limitations. Long turnaround times for the sophisticated laboratory examinations necessary to detect SCs greatly diminish the usefulness of these tests in the acute ED setting. The newest SC compounds on the street are chemically different than the earlier generation compounds. For this reason many SC compounds are invisible to older designer drug screens and traditional drug tests. This diversity of new products make detection by emerging enzyme-linked immunosorbent assay (ELISA) tests difficult. If possible, healthcare professionals are urged to utilize a laboratory experienced in testing for emerging drugs that uses comprehensive mass spectrometry testing[40,96-98].

Synthetic cannabinoid use should be strongly suspected if a youngster presents with: (1) a history of marijuana or other drug use; (2) symptoms and signs consistent with cannabis use; (3) otherwise unexplained sudden onset of psychotic symptoms; (4) otherwise unexplained sudden-onset renal, neurological, and/or cardiovascular problems; (5) is in a situation in which his or her urine is being routinely monitored for illicit substance use; and/or (6) has had negative routine urine toxicology screens (Table 1).

TREATMENT

A thorough clinical history, knowledge of clinical effects of synthetic cannabinoids and high index of suspicion are necessary for the diagnosis. Interventions for acute intoxication with all designer drugs target the presenting symptoms. No medications are currently available to treat synthetic cannabinoid intoxication per se. Symptoms of SC intoxication may be self-limited and resolve spontaneously, generally within 4-14 h[28,29]. In EDs, intravenous hydration, electrolyte replenishment and monitoring may suffice for youngsters who present with mild to moderate signs and symptoms of intoxication. Treatment of any particular renal (*e.g.,* acute tubular necrosis), neurological (*e.g.,* seizures) or cardiovascular (*e.g.,* cardiac ischemia) morbidities should be implemented promptly. Patients who present with symptoms of anxiety, panic, agitation, and arousal after SC exposure may benefit from a benzodiazepine. Lorazepam administered intravenously or intramuscularly, is the benzodiazepine most often utilized by practitioners[28,29,37,58,99]. An antipsychotic medication may be indicated when a patient presents with symptoms of psychosis, particularly when the psychosis is associated with behavioral disturbances (*e.g.,* agitation, aggression); the patient has a history of a psychotic disorder; or the psychotic symptoms do not appear to be remitting spontaneously or with supportive measures[28,29,99].

Our review of the literature did not identify any studies that have addressed formal treatment of SC use. Synthetic cannabinoids can be more psychologically addictive than marijuana. Outpatient services are a viable option for less severe cases, especially if synthetic cannabinoids are the only drugs being used and the youngster is displaying little or no symptoms of withdrawal. Inpatient or residential treatment centers offer intensive care that can help youth get through the early stages of withdrawal in a prompt manner. The length of inpatient or residential synthetic cannabinoids treatment depends on the severity of the use and/or addiction, whether the youngster is also abusing other substances and varies from patient to patient.

Because substance abuse and addiction are multidimensional and disrupt so many aspects of a person's life, treatment is complex. Parents and other family members should be engaged to ensure appropriate linkage and follow-up with a qualified substance abuse professional and/or program. Intensive therapy helps the youngster apply new behavioral skills to daily life. Effective substance use treatments are typically comprehensive and incorporate various components, each targeting a particular aspect of the illness.

CONCLUSION

Synthetic cannabinoids are a group of substances in the world of designer drugs that present potentially dangerous health effects. These compounds have evolved rapidly since first appearing on the world market a few years ago. Identifying youth who abuse these drugs can be difficult. Since the safety profile of synthetic cannabinoid compounds is largely unknown, the ability to perform human studies to determine their effects presents an ethical challenge. As more research continue to emerge our understanding of both the extent of use and the associated harms will continue to develop. Our review of the literature suggests that synthetic cannabinoids may have adverse effects that are more severe than that of marijuana. In addition to the psychoactive effects, some SC compounds have been associated with more serious physical consequences, such as, seizures, myocardial infarction and renal damage. Clinicians are urged to familiarize themselves with these drugs and the typical presentations of patients who use them. Synthetic cannabinoid use should be strongly suspected if a youngster presents

with a history of marijuana use, symptoms and signs consistent with cannabis use, unexplained sudden onset of mental status changes and/or renal, neurological, or cardiovascular problems, and is in a situation in which his or her urine is being routinely monitored for illicit substance use.

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REVIEW

Novel insights in the management of sickle cell disease in childhood

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Abstract

Sickle cell disease (SCD) is a life-threatening genetic disorder characterized by chronic hemolytic anemia, vascular injury and multiorgan dysfunctions. Over the last few decades, there have been significant improvements in SCD management in Western countries, especially in pediatric population. An early onset of prophylaxis with Penicillin and a proper treatment of the infections have increased the overall survival in childhood. Nevertheless, management of painful episodes and prevention of organ damage are still challenging and more efforts are needed to better understand the mechanisms behind the development of chronic organ damages. Hydroxyurea (Hydroxycarbamide, HU), the only medication approved as a disease-modifying agent by the United States Food and Drug Administration and the European Medicines Agency, is usually under-used, especially in developing countries. Currently, hematopoietic stem-cell transplantation is considered the only curative option, although its use is limited by lack of donors and transplant-related toxicity. SCD symptoms are similar in children and adults, but complications and systemic organ damages increase with age, leading to early mortality worldwide. Experts in comprehensive care of young patients with SCD, especially those approaching the transition age to adulthood, are missing, leading people to rely on urgent care, increasing health care utilization costs and inappropriate treatments. It would be important to establish programs of comprehensive healthcare for patients with SCD from birth to adulthood, to improve their quality and expectancy of life.

Key words: Clinical management; Hydroxyurea; Sickle cell disease; Children; Hematopoietic stem-cell transplantation

Core tip: The correct management of sickle cell disease (SCD) requires a comprehensive medical care. Both a wider use of hydroxyurea and an early treatment of pain in children are needed to improve long-term outcomes. Moreover, we report in details the possibility offered by hematopoietic stem cell transplantation as a future curative option for SCD patients.

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INTRODUCTION

Sickle cell disease (SCD) is an inherited red blood cell disorder, characterized by chronic haemolysis, vaso-occlusive complications and progressive multi-organ damage, with a major impact on patients' life expectancy and quality of life[1,2]. The incidence is estimated as more than 300000 new cases worldwide per year, mostly from sub-Saharan Africa, Arabian Peninsula and India[3]. Migration of affected populations from their native countries makes SCD a global disease.

SCD results from a single-point mutation (replacement of glutamic acid with valine in position 6) on the β-globin subunit of hemoglobin, creating the sickle hemoglobin (HbS)[4]. Homozygous (HbSS) patients inherit two copies of the HbS mutation and present clinical symptoms and complications of the disease while heterozygous carries (HbAS) do not exhibit clinical manifestations except in extremely rare cases.

Other sickle-related hemoglobinopathies occur when HbS is inherited in heterozygosis with other β globin chain mutation (HbSC) or quantitative defects in β-globin production (HbSβ^0 and HbSβ^+ thalassemia). HbSS and HbSβ^0 patients have the most severe clinical course, while patients with HbSC and HbSβ^+ have milder phenotypes[5]. Hypoxia, acidity and cellular dehydration influence the polymerization of HbS within erythrocytes and their deformation into the characteristic sickle shape.

Interaction between vascular endothelium and sickle red blood cells leads to episodic microvascular occlusion, with consequent tissue ischemia and further reperfusion; these processes are characterized by severe vascular and inflammatory stress due to increased expression of vascular oxidase, inflammatory cytokines and adhesion molecules[6].

Severe SCD-related complications may begin during early infancy, but thanks to the current multidisciplinary care, almost all SCD children have a chance to achieve adulthood. The improvement in survival rate results from important interventions including newborn screening, prophylaxis with penicillin, immunization against Heamophilus influenzae type B and Streptococcus pneumoniae, advances in supportive care and increased use of disease modifying treatments.

The aim of the review is to provide an overview of SCD management in childhood, focusing on common complications, current standard treatments, implementation of neonatal screening and comprehensive care programs.

NEWBORN SCREENING AND INFECTIONS PROPHYLAXIS

Bacterial infection is the primary cause of death in childhood; infants and children younger than 3 years of age are at risk of mortality and morbidity from sepsis.

In the 1970s, SCD had a very poor prognosis with high mortality in the first 5 years of life[7]. More recently, the mortality rate has been significantly reduced, and the number of children with SCD able to achieve adulthood is continuously growing[8-11]. The main cornerstones that have influenced SCD prognosis improvement are the introduction of neonatal screening and the antibacterial prophylaxis. In fact, neonatal screening leads to precocious identification of SCD subjects and provides the opportunity for early initiation of antibiotic prophylaxis, coupled with early immunization against *Streptococcus pneumoniae* and *Haemophilus influenzae*. Thirty years ago the PROPS Study showed the effectiveness of daily penicillin prophylaxis (starting before two months of age at 125 mg twice/day *per os*) in reducing incidence of pneumococcal infections in children with SCD[12]. A recent review confirmed that prophylactic penicillin significantly reduces the risk of pneumococcal infections in children with homozygous SCD, and is associated with minimal adverse reactions. However, further clinical trials are needed to determine the ideal age to safely discontinue penicillin[13].

Unfortunately, neonatal screening programs are still insufficient: Each newborn affected by SCD should rapidly achieve a definitive diagnosis and appropriate intervention[14] to avoid complications and reach the optimal development.

The implementation of newborn screening programs in Western countries (especially in Europe) is recommended by WHO and European Community, seen the large diffusion of a wide spectrum of hemoglobinopathies, caused by high migration rate from Middle East, South East Asia and malaria-endemic countries.

VASO-OCCLUSIVE CRISIS AND PAIN MANAGEMENT

Painful vaso-occlusive crisis (VOC) is the most common debilitating manifestation of SCD and the first cause of hospitalization for both children and adults[15]. Patients with SCD averagely refer pain more than the half of the days of the year[16] and approximately 60% of them have at least one episode of severe pain per year. Subjects with highest pain rates have an increased risk of early death compared to those with the lowest rates[17]. The sites more affected are extremities, chest and back although first episodes, that may occur as early as 6 mo of age, often present as dactylitis. For healthcare professionals, pain management in SCD is challenging and often complicated by the subjective nature of pain and the lack of standard care[18]. The treatment of painful VOC consists of non-opioid and opioid analgesics and intravenous hydration[19,20]. Early opioids administration, within 30-60 min from pain onset, improves VOC outcomes together with the use of an adequate starting dose, and frequent repeat doses until pain is reduced[21]. Parenteral administrations should be scheduled according

to an individualized protocol agreed by patients and clinicians or, when not available, guided by an institutional SCD-specific protocol[22].

The management of VOC has not significantly changed during the last decades. Recent studies about novel agents including inhaled nitric oxide and purified poloxamer-188, have demonstrated little benefits[23,24]. Among other emerging treatments for the management of vaso-occlusive events, pan-selectin inhibitor (GMI-1070)[25], anti-platelet therapies (*e.g.,* prasugrel), antioxidants (*e.g.,* N-acetyl cysteine), and anti-inflammatory medications (*e.g.,* regadenoson) have been tested in early-phase clinical trials and may represent future therapeutic opportunities[26].

Patients with SCD and acute pain crises may be wrongly identified as those with drug seeking or addiction. SCD patients are not drug- but care-seekers, seen the lack of psychosocial support, poor coping skills and inappropriate therapeutic expectations[27].

ABDOMINAL AND GENITO-URINARY COMPLICATIONS

Children with SCD often present vaso-occlusive pain as abdominal pain. The differential diagnosis of abdominal pain is broad in any child, and more complicated in patients with SCD. The most urgent cause of abdominal pain is splenic sequestration. It is defined as an acute enlargement of the spleen with a drop in hemoglobin of at least 2 g/dL from baseline associated with normal or increased reticulocyte count. In severe cases it may result in hypovolemic shock and death[28]. Early transfusion can be life saving, the starting volume is usually 5 mL/kg. Splenic sequestration can occur as early as 3 mo of age but is rarely seen beyond the age of 6 years. Hepatic sequestration is rare, caused by the obstruction of hepatic sinusoidal blood flow and characterized by painful hepatomegaly, anemia and reticulocytosis. Severe abdominal pain in patients with sickle cell disease often unresponsive to analgesia and associated with intestinal ileus and acute ischemic colitis is "Girdle syndrome" owing the circumferential distribution of pain.

Even if early implementation of supportive therapy may prevent irreversible ischemic damage to the gut, some authors have reported abdominal perforation requiring emergency surgery. Although most of these cases have been reported in adult patients, this syndrome should be considered in pediatric patients with abdominal pain.

Other more common causes of abdominal pain to be considered in children with SCD are: Cholelithiasis due to gallstones derived by unconjugated bilirubin and constipation. In children with SCD urinary tract impairment is frequent and include: Renal infarction, urinary tract infections/pyelonephritis[29].

A typical complication that occurs in male with SCD is priapism defined as unwanted painful erection of the penis. It can occur as young as 3 years of age and 90% of males with HbSS will have at least one episode by 20 years. Usually at the onset of priapism urinate, drink water, take a warm shower promote detumescence. Oral analgesic for pain and pseudoephedrine can be given at home and usually terminates priapism. Prolonged episode (> 4 h) represent a urological emergency[28,30].

ACUTE CHEST SYNDROME

Acute chest syndrome (ACS), an acute illness characterized by fever and/or respiratory symptoms associated to pulmonary infiltrate on chest X-ray[31], is a life-threatening complication of SCD with at least one episode during life in 30% of patients[32,33].

ACS usually originates from a lung injury due to pulmonary infection, fat embolism and/or pulmonary infarction. Consequently, alveolar oxygenation tension falls causing the HbS polymerization[34] and the ischemia-reperfusion process in lung vessels leads to the respiratory impairment[35].

Infective triggers are more common in children than adults and are frequently associated with viral infections especially in patients under 10 years of age. Multicenter studies, in particular in United States, demonstrate that the most common virus isolated is the respiratory syncytial virus while the most common bacteria are the Chlamydia pneumoniae in adults and the Mycoplasma pneumoniae in children[34].

Symptoms vary depending on age. Young patients often present with fever, cough and wheezing while adults show more painful episodes and impaired clinical conditions due to severe hypoxia, higher requirement for transfusion and higher mortality.

The optimal management of ACS requires an aggressive and comprehensive approach. Vital signs (pulse rate, systemic blood pressure, respiratory rate), oxygen saturation, frequent assessment of symptoms, should be monitored at least every four hours. Chest X-ray, full blood count, basic biochemistry tests, blood cultures, infectious respiratory disease testing, and blood group and screen are also needed. Oxygen administration or more aggressive respiratory supports, as Bi-level positive airway pressure or mechanical ventilation, should be used to maintain $SpO_2 \geqslant 95\%$, while intravenous fluids and opioids should be carefully managed to avoid risks of acute pulmonary edema and alveolar hypoventilation.

Other therapeutic tools include: Incentive spirometry, chest physiotherapy, antibiotic, and for those patients with progressive hypoxia or clinical deterioration, simple or exchanged red blood cell transfusion[36,37].

Although it is not confirmed by randomized controlled trials, it has been reported that blood transfusion can produce rapid improvements in clinical and radiological parameters in ACS[34,38]. Both "top up" and exchange transfusions increase oxygenation but exchange blood transfusion may have additional benefits in terms of reduction of circulating sickle cells and it is more indicated in patients with severe disease or with higher hemoglobin

concentration (> 90 g/L)[36].

It is important to bear in mind that approximately 50% of ACS occurs in patients hospitalized for other causes such as VOC or surgical intervention. This percentage could be reduced by incentive spirometry during hospitalization or by preoperative transfusion[22]. ACS consequences are scarring, pulmonary fibrosis and chronic sickle lung disease: Prevention of infections with antibiotic prophylaxis, administration of annual influenza vaccination, and avoidance of smoking may decrease the risk of ACS. Furthermore, children recovered from an episode of ACS should be offered therapy with hydroxyurea[39], at least to those with homozygous sickle cell anemia.

NEUROLOGICAL IMPAIRMENT

Neurological complications in SCD include silent cerebral infarct, stroke, and intracranial bleeding. Sickle cell anemia (SCA; HbSS and HbSβ^0) is associated with a high prevalence (4.01%) and incidence (0.61/100 patient years) of cerebrovascular accidents[40] and is higher still in the absence of primary prevention. Overt stroke has been reported in about 10% of children with HbSS with a peak incidence between 2 and 5 years of age[41]. Prior transient ischemic attack, low steady-state hemoglobin concentration, recent episode of ACS, and elevated systolic blood pressure are considered risk factors for ischemic stroke. Despite limited available evidences to guide best practice in the acute management of ischemic stroke in SCD, initial supportive strategies including co-operation of a multidisciplinary team of specialists (hematologist, neurologist, neuroradiologist, and transfusion medicine specialist) and exchange transfusions are recommended[42]. The risk of stroke recurrence, in the absence of secondary preventative measures, has been reported to be as high as 60%-90%. Chronic transfusions are currently considered the standard for care of secondary stroke prevention. Moreover, the use of Hydroxyurea, although not as effective as regular blood transfusions, represents a reasonable therapeutic alternative and recently it has also been showed that hematopoietic stem-cell transplantation (HSCT) reduces rate of stroke recurrency when compared with regular blood transfusions in the following five years[43-46].

Children with HbSS and HbSβ^0 should be routinely monitored by Transcranial Doppler (TCD) from the age of 2 until 16[47,48]. The STOP trial (Stroke Prevention Trial in Sickle Cell Anemia) showed that an abnormal TCD flow velocity exceeding 200 cm/s is associated with a 40% increased risk of stroke within 3 years. In patients with abnormal velocity, the introduction of regular transfusions resulted in a reduction in stroke incidence by almost 95%[49]. Although long-term transfusions have major long-term side effects, the STOP 2 trial showed that cessation of transfusions after the normalization of TCD resulted in a recurrence of abnormal blood flow velocity on TCD and increased risk of stroke[50]. The role of hydroxyurea for prevention of primary and secondary stroke has also been investigated. An ongoing phase III trial, TWiTCH (Transcranial Doppler with Transfusions Changing to Hydroxyurea) (ClinicalTrials.gov identifier number NCT01425307) intends to compare hydroxyurea *vs* transfusions for pediatric patients with SCA and abnormally high TCD velocities, who currently receive chronic transfusions to reduce the risk of primary stroke. The SWiTCH study (Stroke with Transfusions Changing to Hydroxyurea) was designed to compare alternative therapy of hydroxyurea and phlebotomy with standard therapy (transfusions and iron chelation) for the prevention of secondary stroke. However, this study was stopped, as alternative therapy was associated with a higher stroke rate[51]. Lifelong transfusion remains the standard of care for secondary stroke prevention, and in those with high flow velocity on TCD (primary prevention)[37]. However, hydroxyurea is a reasonable alternative in patients with complications of transfusions, with poor compliance, or in countries with limited blood supplies.

Silent cerebral infarcts

Silent cerebral infarcts (SCI) are characterized by an abnormal brain MRI in the absence of history or physical findings of an overt stroke. SCI occur in approximately one-quarter of the children with SCA before six years of age and in one-third of those younger than fourteen. Risk factors include male sex, lower baseline hemoglobin concentration, higher baseline systolic blood pressure and previous seizures[52]. While overt strokes are typically located in both cortex and white matter, SCI usually occur in deep white matter of the frontal, parietal lobes or, less frequently, in basal ganglia, thalamus and temporal lobes[53]. Children with SCI have lower cognitive test scores compared with the general population, and have additional specific functional impairment, impacting such executive functions as selective attention, card sorting, working memory and processing speed, visual motor speed and coordination, vocabulary, visual memory and abstract reasoning and verbal comprehension[54-59]. Children with SCD and SCI have twice the chance of academic difficulties than those without SCI[60]. The presence of SCI is a risk factor for additional neurologic injury, with a higher risk of both clinical stroke (14-fold), and progressive silent infarction. It has been showed that approximately 25% of children with SCI, have new and/or enlarging lesions on follow-up MRI scan[53,61]. Despite the high prevalence of SCI in patients with SCD, no established therapy is available for primary or secondary prevention. The STOP Trial showed that the presence of SCI in the setting of an abnormal TCD measurement is associated with increased risk of stroke compared to those with no SCI (52% *vs* 21%). In the same group of patients the stroke risk decreased with blood transfusion therapy compared to those with only elevated TCD measurement (0% *vs* 5%, respectively)[49]. These results provided the preliminary evidence suggesting that regular blood transfusion therapy may be effective in

preventing neurologic injury. At the end of STOP2 study, when children with elevated TCD measurements were randomized to continue or stop transfusions, 8% of those who continued transfusions developed new brain MRI lesions compared with the 28% of those who stopped[50]. Similarly, the SIT trial showed that children with SCA had a relative risk reduction of infarcts recurrence of 58%, if they were receiving regular blood transfusions. The optimal timing to detect SCI is still unclear but most data support commencing MRI from around 5 years or school entry[62]. Developmental delay or declining school performance may be the only clinical signs of SCI and therefore in this instance an early neurocognitive evaluation should be offered in patients with SCD.

DISEASE-MODIFYING AGENTS

Hydroxyurea (HU) is an inhibitor of ribonucleotide reductase that increases fetal hemoglobin (HbF) in red blood cells, rising cellular size and deformability. HU also impairs leukocytes and reticulocytes production and the expression of adhesion molecules, reducing vascular occlusion. In addition, when metabolized, HU releases nitric oxide, contributing to local vasodilation[63,64]. HU is the only medication approved for treatment of SCD by the United States Food and Drug administration (1998) and by the European Medicines Agency (2007)[65]. A multicenter, randomized, double-blind, placebo-controlled clinical trial in infants from 9-18 mo of age with SCA (BABY-HUG) demonstrated that treatment with HU was associated with statistically significant lower rates of initial and recurrent episode of pain, dactylitis, ACS, and hospitalization compared to placebo group[66]. Similar results have been also showed by the Multicenter Study of Hydroxyurea, with positive effects of HU on painful vaso-occlusive events at all ages[67]. HU treatment seems to be associated with decreased mortality[68,69] and it is generally well tolerated in both children and infants, with no influence on growth and development[70]. Leukopenia, neutropenia and thrombocytopenia are the most frequently reported side effects, but they are generally mild and reversible with discontinuation or with dose decreasing[66,71]. However, several concerns about the HU long-term side effects have been expressed especially in pediatric population. Even though HU does not appear to increase the risk of malignancy in SCD patients[63], potential effects on fertility and teratogenicity have been described[72-75]. Considering the benefit of HU in preventing end organ damage and improving survival, it seems reasonable to recommend hydroxyurea to SCD patients with HbSS or HbSβ^0 genotypes, regardless of their disease severity. Recently, it was suggested to offer HU therapy in children starting at 9 mo of age, including those who are asymptomatic[22]. When considering the use of hydroxyurea for patients with SCD, it is important to balance its well-established benefits with its hypothetical long-term side effects, in particular in asymptomatic children[37].

HEMATOPOIETIC STEM CELL TRANSPLANTATION AND GENE-THERAPY

Despite the development of supportive care including HU and transfusion programs, hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for patients affected by severe SCD. The first successful pediatric HSCT was performed in 1984[76], and since there, several hundreds of patients with SCD have been transplanted, mainly from an HLA-identical sibling donor. Results of major clinical studies on allogeneic HSCT from an HLA-identical sibling donor in children with SCD, in the past decade, reported an overall survival rate (OS) greater than 90% and an event-free survival rate (EFS) greater than 80%[44,46,77-81]. Recent studies on HLA-identical sibling HSCT are summarized in Table 1[82-87]. Of interest, 37/38 subjects, treated with HU before HSCT survived free of SCD, with an estimate EFS of 8-year, significantly higher compared to those who did not receive hydroxyurea before HSCT ($P < 0.001$)[85]. HSCT from matched-sibling related donor offer the best outcomes of transplantation and it seems to be curative in 90%-95% of pediatric recipients with severe SCD following a conventional conditioning regimen[88]. Transplants outcomes are best in young people (< 16 years) before long-term transfusions become necessary, in absence of comorbidities and organ damages[46]. With the achievement of such survival rates, the risk of transplant related morbidity has become a major concern and clinical focus has recently shifted to the minimization of the regimen-related toxicity. A recent Italian study[89] showed that a conditioning regimen with treosulfan/thiotepa/fludarabine for HLA-matched sibling and unrelated donor HSCT was well tolerated with no case of grade Ⅲ and Ⅳ regimen-related toxicity. The 7-year OS and DFS for the whole cohort were 100% and 93%, respectively.

Umbilical cord blood (UCB)-derived hematopoietic stem cells in pediatric patients with hematological disorders are increasing as alternative source of hematopoietic stem cells, seen the safe technique of hematopoietic collection, the low risk of viral contamination of the graft and the reduced incidence and severity of acute and chronic graft *vs* host disease (GVHD)[90,91]. A recent update of HLA-identical sibling UCB transplantation compared marrow and UCB transplants outcomes of 485 recipient cases with thalassemia major and SCD. The overall 6-year DFS in 160 patients with SCD was 92% ± 2%: 90% ± 5% in 30 patients after UCB transplantation and 92% ± 2% in 130 patients after bone marrow transplantation. None of the patients developed chronic extensive GVHD and none died of GVHD after UCB transplantation[92]. UCB and marrow from HLA-identical donors might be used interchangeably, and UCB from a sibling donor appears to be useful in terms of lower risk of acute and chronic GVHD. For patients with no HLA-identical sibling donor hematopoietic

Table 1 Recent series of human leukocyte antigen-identical transplant for sickle cell disease in children

Ref.	Conditioning regimen	*n*	Age range in years	Deaths	Follow-up (yr)	Outcome
Krishnamurti *et al*[82]	BU, Flu, eATG, total lymphoid irradiation	7	6-18	None	2-8.5	All patients alive EFS 86%
McPherson *et al*[83]	BU, CY, ATG	25	3.3-17.4	1	0.1-10	OS and DFS 96% (median survivor follow-4.9 yr)
Lucarelli *et al*[84]	BU, CY, rATG ± Flu	40	2-17	3	1-10	5-yr OS and DFS 91%
Dedeken *et al*[85]	BU, CY, ± rATG, ± HU	50	1.7-15.3	2	0.4-21.3	8-yr EFS 85.6% and OS 94.1%
Bhatia *et al*[86]	BU, Flu, Alem	18	2.3-20.2	None	0.4-7.5	2-yr EFS and OS both 100%
Soni *et al*[87]	BU, CY, rATG	15	1.5-18	None	0.9-7.5	3-yr EFS and OS both 100%

ATG: Antithymocyte globulin; BU: Busulfan; CY: Cyclophosphamide; DFS: Disease free survival; eATG: Equine antithymocyte globulin; EFS: Event free survival; Flu: Fludarabine; HU: Hydroxyurea; OS: Overall survival; rATG: Rabbit antithymocyte globulin; Alem: Alemtuzumab.

cells from an HLA-mismatched related donor could help. The Johns Hopkins group in 2012 reported the largest study of HLA haploidentical bone marrow transplantation in severe SCD. In this pilot investigation, 14 recipients of haploidentical HSCT were treated and all had prompt recovery after HSCT, although 6 of these patients developed graft rejection, all were alive with a median follow-up of 711 d[93]. Despite promising data, allo-HSCT is underutilized[94]. The main barrier is the limited availability of suitable donor. It has been estimated that only 14% of those patients with SCD have a suitable HLA-identical sibling donor and that only 19% have a very well matched unrelated marrow donor in the volunteer registry[95,96]. Nevertheless, conventional treatment itself is a high-risk of mortality procedure and of treatment-related morbidity, due to GVHD, infertility and gonadal failure[88]. Considering all the allogenic HSCT limitations, the gene therapy using autologous stem cells can potentially cure SCD, and could overcome the problems of lack of available donors and immunologic side effects. Inherited hematopoietic disorders are potentially targetable, because hematopoietic stem cells can be readily isolated from bone marrow or mobilized from peripheral blood, manipulated *ex vivo*, and transplanted back using current tools and knowledge of bone marrow transplant technology. Gene therapy has exploited the ability of retrovirus vectors, which are equipped with the machinery to reverse, to transcribe their RNA into complementary DNA and integrate this latter into the host cell genome to deliver therapeutic genes into cells. Seen the success in β-thalassemia gene therapy, similar studies on SCD are started. Both γ-globinbased and modified β-globin-based vectors have been developed for SCD gene therapy[97]. There are still no data available, but clinical trials using lentiviral vectors have begun in France (NCT02151526) and in United States (NCT02140554, NCT02186418, NCT02247843)[98]. The development of gene therapy technologies holds the promise of genetic correction of future hemoglobinopathies.

TRANSITION FROM PEDIATRIC TO ADULT HEALTHCARE

Management programs for pediatric patients with SCD in Western world areas include acute care, routine prevention, monitoring and treatment of complications[99]. The management of SCD in adult patients is more complex, because of the additional co-morbidities, increased multi-organ involvement, chronic pain and psychosocial and socioeconomic factors. Although an increasing number of children with SCD are achieving adulthood, there has not been a corresponding increase in medical experts trained to treat older patients, delaying transition from adolescent to adult care[100]. Epidemiological studies indicate that SCD-related mortality and morbidity are increased in young adults and most patients feel that they are not ready for transition to adult healthcare[101]. These data supported by findings of a recent study of the Dallas Newborn Cohort show that SCD patients are at greatest risk of mortality when they are transition-aged. In this cohort, seven of the most recent patients died were aged 18 years or older, and six of these patients had recently transitioned out of the pediatric care[8]. With no adult SCD care providers, patients become dependent of acute care services and do not receive the necessary coordinated multi-disciplinary care[102]. Identification of a designated adult SCD provider and enhanced early education of all pediatric SCD patients regarding the need to continue comprehensive care in the adult setting is imperative for a successful transition from pediatric to adult care.

CONCLUSION

Sickle cell disease is a global health problem that affects more than 300000 newborns per year, predominantly in sub Saharan Africa. In this area, mortality is estimated to be more than 50% by the age of 5 years for those with homozygous hemoglobin S. With the implementation of neonatal screening programs and new therapeutic approaches, SCD related morbidity in childhood is decreasing, raising the number of patients achieving adulthood. Currently, there are few pharmacological treatments available for SCD, while promising disease-modifying agents, as HU, are still significantly under-utilized. Moreover, the use of curative options as HSCT, is limited because of the lack of matching donors and some concerns regarding long-term toxicity. Although

comprehensive management programs for SCD pediatric patients have started in the last years in United States and Europe, an improvement in transition age care, to reduce early mortality in young adults and hospital costs, is needed.

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REVIEW

Retinopathy of prematurity: Past, present and future

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Abstract

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina occurring principally in new born preterm infants. It is an avoidable cause of childhood blindness. With the increase in the survival of preterm babies, ROP has become the leading cause of preventable childhood blindness throughout the world. A simple screening test done within a few weeks after birth by an ophthalmologist can avoid this preventable blindness. Although screening guidelines and protocols are strictly followed in the developed nations, it lacks in developing economies like India and China, which have the highest number of preterm deliveries in the world. The burden of this blindness in these countries is set to increase tremendously in the future, if corrective steps are not taken immediately. ROP first emerged in 1940s and 1950s, when it was called retrolental fibroplasia. Several epidemics of this disease were and are still occurring in different regions of the world and since then a lot of research has been done on this disease. However, till date very few comprehensive review articles covering all the aspects of ROP are published. This review highlights the past, present and future strategies in managing this disease. It would help the pediatricians to update their current knowledge on ROP.

Key words: Retinopathy of prematurity; Retrolental fibroplasia; Screening guidelines; Oxygen; Classification; Epidemics; Anti vascular endothelial growth factor; Vitrectomy; Laser; Future trends

Core tip: Although literature is full of various articles on retinopathy of prematurity (ROP), there are very few comprehensive review articles on this disease. This article covers ROP from 1940s and 1950s when seen as retrolental fibroplasia, to the current screening and treatment guidelines to the future trends. Our objective is to consolidate the literature on this disease, which will benefit the pediatricians.

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INTRODUCTION

Retinopathy of prematurity (ROP) used to be called as retrolental fibroplasia (RLF) in 1940s. RLF was the term first coined in the year 1942 by Terry[1] and was defined as a progressive disorder seen exclusively in premature infants of low birth weight, where in a fibrous tissue is formed behind the lens, resulting in blindness and severe visual impairment. When it was first described this disease was not commonly seen, and hence had little interest but 10 years later it became a major problem to all paediatricians and ophthalmologists. It now affects thousands of children worldwide[2].

STUDY METHODS

Literature search in PubMed was conducted covering the period 1940-2015 with regards to retinopathy of prematurity, retrolental fibroplasia, classification, treatment, laser, anti vascular endothelial growth factor and recent advances[3-81].

PAST

Role of oxygen - the cause or the treatment

Many studies were conducted worldwide since 1951 to determine the exact mechanism of this disorder. Ophthalmic literature of the past reveals, anoxia in premature babies to be the prime causative factor for the development of RLF and hence in 1952 was called as anoxic retinopathy. A study by Szewczyk[3] revealed that this was the response of immature neural tissue to anoxia. He explained the mechanism would probably be due to low oxygen tension in the fetal blood of premature which causes retinal vessels to dilate initially, and still when the demand is not satisfied it leads to edema, transudation and haemorrhages. Campbell[4] first brought to notice the development of RLF in infants undergoing intensive oxygen therapy. A clinicopathologic study at the Women's hospital Melbourne, Australia by Ryan[5] between 1948 and 1950 revealed 23 cases of RLF. It was noted that no case of RLF was reported prior to the introduction of an oxygen cot. The nursing staffs were giving oxygen liberally to all babies with this oxygen cot and hence there was increase in the incidence. Later on, from October 1950, oxygen was restricted to only babies with cyanosis and since then a fall in number of RLF was seen. With this study it was understood that, the normal human fetus is in a state of cyanosis, because pure arterial blood is not carried by any of the arteries. Since high oxygen concentrations are toxic to adults, similarly normal concentration is toxic to immature tissues. Hence it was concluded that RLF can be prevented by giving oxygen only to those premature babies who require it.

It was observed that anoxia might occur at the cellular level during oxygen therapy even though the environmental oxygen and the blood oxygen levels are increased. This paradoxical situation, which was called as "hypoxic-anoxia" will occur as a result of inactivation of oxidative enzymes from prolonged exposure to high oxygen levels.

Equal importance was also given to the rate of withdrawal from oxygen since it was noted that it minimizes the retinal damage induced by hyperoxia. A controlled nursery study by Bedrossian *et al*[6] reported a significantly higher incidence of RLF in infants who were rapidly withdrawn from an atmosphere of continuous oxygen as compared with a group where oxygen was gradually reduced.

Hence, it became necessary to monitor the oxygen and prior to the availability of arterial oxygen tension to measure, ophthalmoscopic monitoring of retinal vessel caliber was done. The following guidelines for oxygen therapy were recommended: (1) Oxygen should be given to premature infants proved to be hypoxic or strongly suspected; (2) When high concentrations of oxygen are required for significant periods, in addition to measuring the incubator oxygen level, arterial oxygen tension monitoring should also be done; (3) Ophthalmoscopic monitoring of retinal vasoconstriction should be done at regular intervals, and when marked constriction is detected, prompt reduction in the concentration of administered oxygen may prevent retinal damage; and (4) Even for a full term infant, retina is incompletely vascularised temporally, hence oxygen therapy should be cautiously administered and limited to specific indication only.

Pathogenesis

The effect of oxygen on the retina on the immature vasculature was described in two stages: (1) Primary stage or vasoconstrictive phase: This occurs during exposure to hyperoxia and there is also suppression of the normal anterior ward vascularisation of the retina. This mechanism of vasoconstrictive and obliterative effect of oxygen is seen predominantly in the developing retinal vessels. This inturn leads to suppression of vascular endothelial growth factor; and (2) Secondary stage or vasoproliferative phase: This occurs during the shifting from oxygen to room air, and involves dilatation and tortuosity of the existing larger vessels with neovascularisation and proliferation of new vessels into the vitreous. This is mainly due to the sudden surge in vascular endothelial growth factor levels.

Laboratory findings

In the 1950's the kitten model was used in most experiments as its immature retinal vessels showed selective response to oxygen[7,8]. Smith *et al*[9] in the year 1994 demonstrated a good, easily replicable and measurable mouse model of oxygen induced retinopathy. One week old C57BL/6J mice were put in 75% oxygen chambers for 5 d and then brought back to normal atmospheric air. Vascular pattern was assessed using a fluorescein-dextran perfusion method.

The abnormal neovascularization was measured by counting the nuclei of new vessels extending from the retina into the vitreous in 6 μ sagittal cross section[9]. Fluorescein-dextran angiography highlighted the entire retinal vasculature, including the neovascularization. Hyperoxia induced new vessels occurred at the junction between vascularised and avascular retina in the mid periphery[9]. Retinal neovascularisation was seen between day 17 and day 21, postnatally. Thus from this study it was concluded that, neovascularisation was seen after loss of patent vessels in the central retina with hyperoxia exposure. A shift from hyperoxia to room air causes relative ischemia in the non-perfused retina and the development of neovascularisation was seen at the interface of perfused and non-perfused retina.

Epidemics in ROP

A variation in number of cases was seen in different era and in different countries. This was termed as epidemics in ROP. What actually triggered the beginning of first epidemic was unmonitored oxygen supplementation in the late 1940's and 1950's in Europe and North America[10,11]. After this incident, overuse of oxygen was stopped and careful administration of oxygen was recommended. Second epidemic was faced by the developed countries, in premature and low birth weight babies (< 1000 g at birth)[12]. India and the other developing countries come under the third epidemic which is characterized by severe ROP in bigger premature babies[13]. The reason again being lack of proper neonatal care and improper oxygen administration. Hence there is a need for strict guidelines of oxygen administration and monitoring and neonatologist play a major role in this aspect.

PRESENT

Classification

A committee for ROP classification was formed in 1984, which proposed an international classification of ROP (ICROP) by dividing the retina into three zones, extending from posterior to anterior retina and describing the extent of ROP in clock-hours of involvement[14]. However with the advances in retinal imaging techniques, a revised ICROP classification was put forth which described the zones better[15].

Zones

Three concentric zones, centered on the retina define the antero-posterior location of retinopathy.

Zone Ⅰ: With optic disc as the center, and twice the distance from the disc to fovea, the circle formed is zone I. Using a 25 or 28 diopter (D)-condensing lens, when the nasal edge of the optic disc is kept at one edge, the temporal field of view is zone Ⅰ extent.

Zone Ⅱ: It starts from the edge of zone Ⅰ and extends till the ora serrata nasally, with a corresponding area temporally.

Zone Ⅲ: Zone Ⅲ is the remaining crescent of retina temporally.

Extent of retinopathy

The extent of the ROP is documented by the number of clock hours involved. For the observer examining each eye, the temporal side of the right eye is 9 o'clock and that of the left eye is 3 o'clock and *vice versa*.

Stages of ROP

It denotes the degree of vascular changes. There are five stages.

Stage 1 - demarcation line: A demarcation line is seen between the vascular and avascular retina. It is a thin structure that lies in the plane of the retina (Figure 1A).

Stage 2 - ridge: The demarcation line grows to occupy a volume and has a height and width to form a ridge above the plane of retina (Figure 1B). Small tufts of new vessels also called as "popcorn" vessels may be seen posterior to the ridge.

Stage 3 - ridge with extra retinal fibrovascular proliferation: In this stage extraretinal fibrovascular tissue is seen arising from the ridge into the vitreous (Figure 1C). It may be continuous or non-continuous and is posterior to the ridge.

Stage 4 - subtotal retinal detachment: Here a partial detachment of the retina is seen which may be exudative or tractional. It is sub divided into the following: (1) Partial retinal detachment not involving the fovea (stage 4A) (Figure 1D); and (2) Partial retinal detachment involving the fovea (stage 4B) (Figure 2A).

Stage 5 - total retinal detachment: Here a total retinal detachment is seen as child usually presents with leukocoria (white pupillary reflex) (Figure 2B).

Plus disease: It is an indicator of severity of the disease and is defined as venous dilation and arterial tortuosity of the posterior pole vessels (Figure 2C).

Pre-plus disease: It is defined as posterior pole vascular dilation and tortuosity which is more than normal but less than plus disease.

Aggressive posterior ROP: This refers to an uncommon, rapidly progressive, form of ROP previously referred to as "rush disease". It is characterized by a posterior location, severe plus disease, and flat intraretinal neovascularization (Figure 2D). It can progress very fast to stage 5 ROP and blindness, if not intervened early. The flat neovascularization can be quite subtle and can easily confuse less experienced

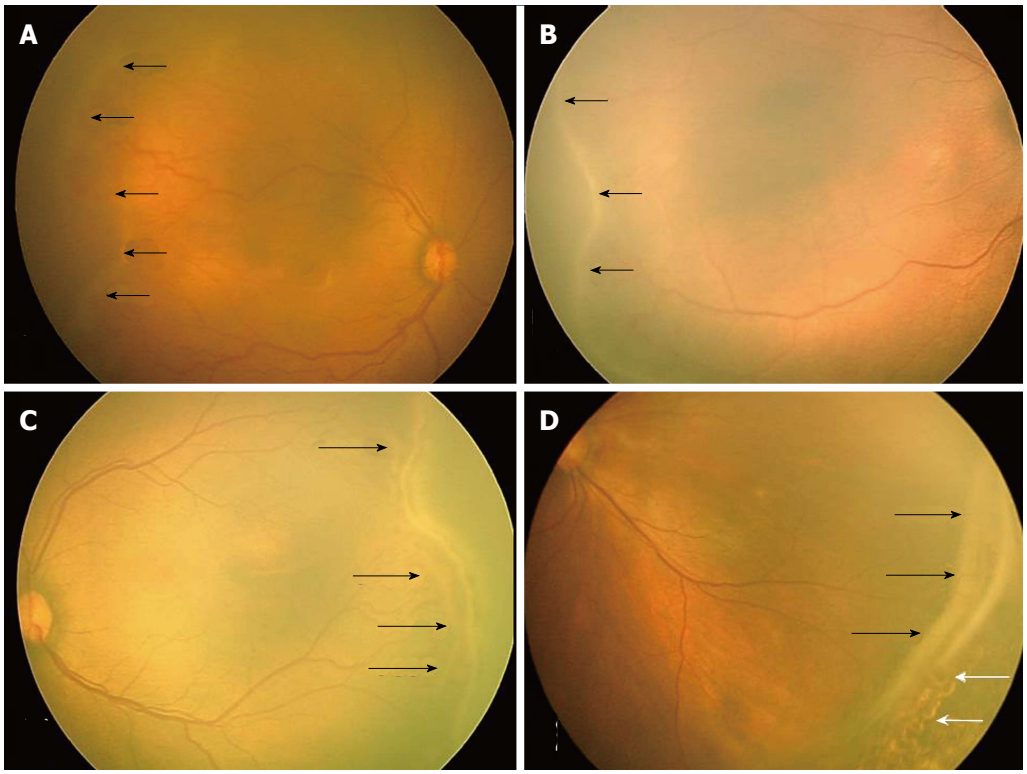

Figure 1 RetCam fundus images showing retinopathy of prematurity stages 1, 2, 3 and 4A. A: Fundus image of right eye showing stage 1 ROP with demarcation line (black arrows); B: Fundus image of right eye showing stage 2 ROP with ridge (black arrows); C: Fundus image of left eye showing stage 3 extra retinal fibrovascular proliferation (black arrows); D: Fundus picture of left eye showing stage 4A partial retinal detachment not involving the fovea (black arrows). Laser scars are shown with white arrows. ROP: Retinopathy of prematurity.

examiners.

Screening for ROP - present concept

Worldwide ROP is amongst the leading causes for childhood blindness[16]. Early detection and timely intervention to reduce this burden of blindness, makes screening an important aspect of ROP.

Screening is a process of identifying disease in the apparently normal subjects who are at risk by applying simple, safe, repeatable, sensitive and valid tests for disease detection. Due to lack of gold standard tests for ROP, the screening process may also be referred as "case detection initiative"[16]. The neonatal care for each country needs to be understood as ROP is diverse in presentation owing to the geographic variations, available infrastructure and altered temporal development of retinopathy in different locations in the retina[17]. Screening ultimately aims at reducing the incidence of ROP, prompt case detection and optimal treatment for ROP, thereby reducing the severity and overall burden of childhood blindness.

Eighty percent of infants with birth weight less than 1500 g born in the United Kingdom survive and the incidence of stage 3 ROP of approximately 8% to 10% has been reported[18]. Thus all babies having gestational age $\leqslant$ 31 wk or $\leqslant$ 1500 g are screened in United Kingdom[18]. American guidelines given by the American Academy of Pediatrics state that, infants with a birth weight $\leqslant$ 1500 g or gestational age of $\leqslant$ 30 wk and selected infants with a birth weight between 1500 and 2000 g or gestational age of more than 30 wk with an unstable clinical course, should be screened for ROP[19].

In many developing economies, larger babies with a birth weight between 1500 and 2000 g may also develop ROP[20]. Hence in counties like India, a birth weight $\leqslant$ 1750 g and/or gestational age of $\leqslant$ 34 wk may be used as a cut-off for ROP screening. Bigger babies with a gestational age of 34 to 36 wk gestation or a birth weight between 1750 and 2000 g should also be screened if child has a stormy neonatal course[20]. New Zealand has reported a reduced incidence in ROP due to progress in the screening and clinical management and recommends screening criteria of < 31 wk' gestation or < 1250 g to be sufficient[21]. Other risk factors for ROP include severe respiratory distress syndrome, anemia, neonatal sepsis, thrombocytopenia, multiple blood transfusions and apnea. If these risk factors are not seriously taken into consideration, affected infants may inadvertently get excluded and hence careful review for risk factors should be taken by the pediatrician.

ROP screening should start by 31 wk postconceptional age or 4 wk after birth, whichever is later[22]. In developing countries some babies may develop early aggressive posterior (AP)-ROP[23,24]. Thus, in developing countries, to enable early identification and treatment of AP-ROP, infants < 28 wk or < 1200 g birth weight should be screened relatively earlier at 2-3 wk of age[25].

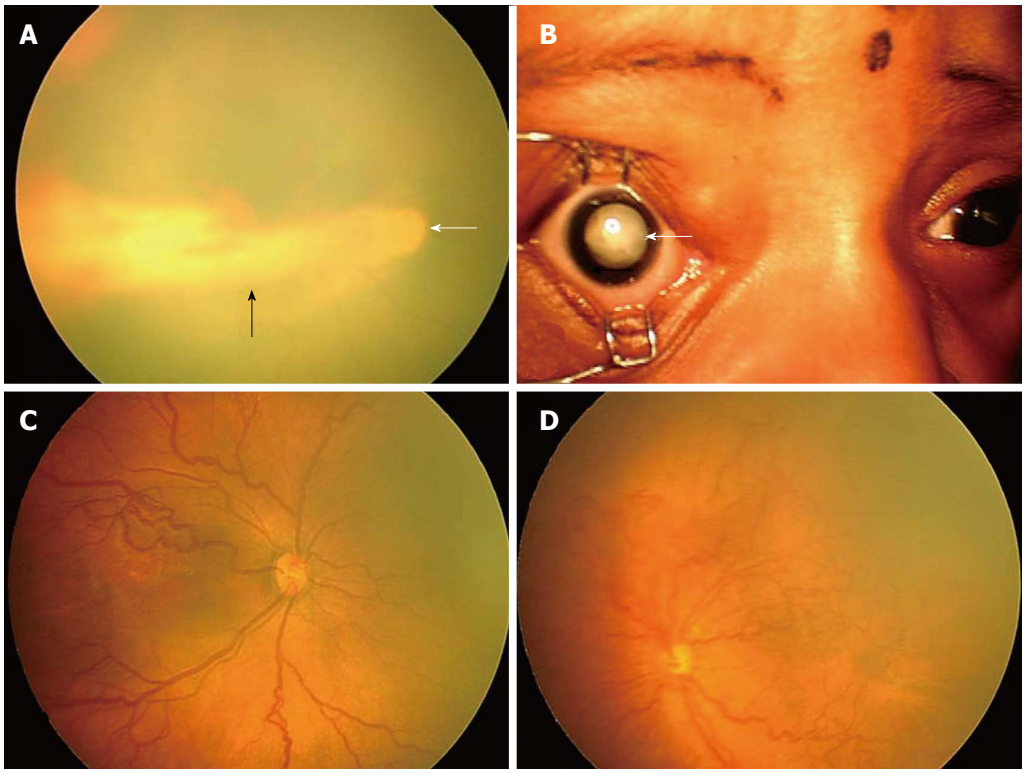

Figure 2 RetCam fundus images showing retinopathy of prematurity stages 4B, 5, plus disease and aggressive posterior-retinopathy of prematurity. A: Fundus picture of right eye showing stage 4B partial retinal detachment involving the fovea (black arrow). Optic disc is shown with a white arrow; B: Anterior segment picture of right eye showing stage 5 ROP with total retinal detachment (white arrow); C: Fundus picture of right eye showing dilated and tortuous vessels suggestive of plus disease; D: Fundus picture of left eye showing aggressive posterior ROP. ROP: Retinopathy of prematurity.

Examination technique: The examination technique traditionally involves two steps namely the dilatation of pupil and indirect ophthalmoscopy preferably with a 28D lens. It is preferred to perform pupillary dilatation 45 min prior to commencement of the screening. Dilating drops used are a mixture of cyclopentolate (0.5%) and phenylephrine (2.5%) drops to be applied two to three times about 10-15 min apart. Alternatively, tropicamide (0.4%) may be used instead of cyclopentolate. Diluted cyclopentolate may also be used to reduce probable systemic adverse effects. Use of atropine is to be avoided. The neonatal nurse should be instructed to wife any excess drops from the eye lid to prevent systemic absorption and complications like tachycardia and hyperthermia. If the pupil is resistant to dilatation, it may indicate presence of persistent iris vessels (tunica vasculosa lentis) and must be confirmed by the ophthalmologist before applying more drops.

The United Kingdom guidelines do not mandate use of eye speculum (*e.g.*, Barraquer, Sauer, Alfonso specula) and scleral depression (*e.g.*, Flynn depressor) with topical anaesthesia. However, meticulous examination, warrants its use.

Present screening tools: ROP screening today follows a telemedicine approach which refers to use of information technology between participants who are geographically separated and offers a possible solution to screening challenges and aids effective management. There are no reports requiring on-site diagnostic examination by an ophthalmologist even if images have not appropriately identified severe retinopathy[26,27]. Retinal examination of infants at risk for ROP using the RetCam digital camera system using wide angle lens with interchangeable high magnification lenses allows photographic documentation permitting remote interpretation of images and is increasingly being used for telemedicine world over[28-31]. But this telescreening is advisable only in places where no ophthalmologist is available for bed side screening, as a recent review showed that digital imaging screening cannot replace indirect ophthalmoscopy[32].

Predictive factors for ROP progression which include postnatal weight gain, serum insulin-like growth factor 1 (IGF-1) levels, and quantifiable vessel changes in the retina can reliably be isolated and used to indicate presence or absence of disease. The Weight, IGF-1 levels, Neonatal, ROP (WINROP) study[33] carried out weekly measurements of IGF-1 levels and weekly weight from birth until 36 wk. WINROP correctly identified all infants with a low risk ROP and those requiring laser treatments for proliferative ROP on the basis of predictive factors.

The rapid advances in technologies and increasing knowledge about disease and genetics along with the growing need for efficient, effective, and timely ROP evaluations may completely transform the present diagnostic

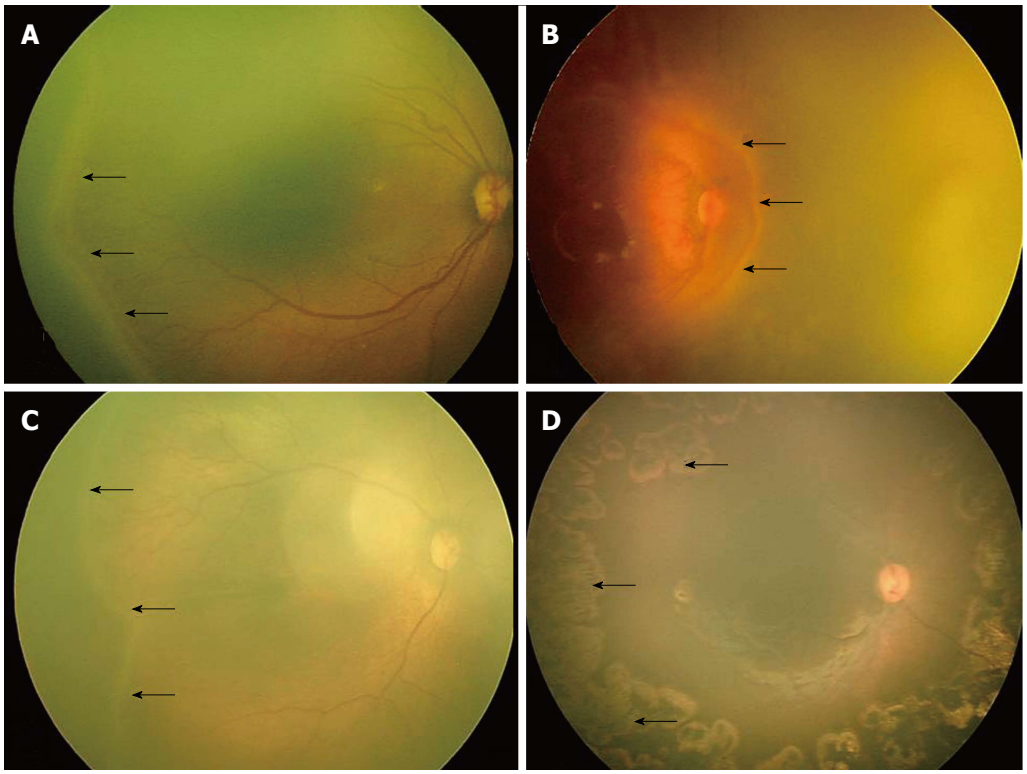

Figure 3 RetCam fundus images showing threshold, type 1, type 2 retinopathy of prematurity and post laser regressed retinopathy of prematurity. A: Fundus image of right eye showing "threshold ROP" (black arrows); B: Fundus image of right eye showing stage 3 ROP in zone 1 (black arrows) with plus disease suggestive of "type 1 ROP"; C: Fundus image of right eye showing stage 2 ROP in zone 2 (black arrows) without plus disease suggestive of "type 2 ROP"; D: Fundus picture of right eye showing laser scars (black arrows). ROP: Retinopathy of prematurity.

approach in near future.

Treatment for ROP - present concept

Although the ICROP classification gave a detailed classification of ROP, it never recommended when to treat ROP. Following are the treatment stages of ROP.

Threshold ROP: The cryotherapy for retinopathy of prematurity (CRYO-ROP) study[34] stated that treatment should be imparted to eyes with threshold disease, defined as stage 3 ROP in zone Ⅰ or Ⅱ, having five contiguous or eight discontiguous clock hours with plus disease (Figure 3A). This was the previous "cut off" for treatment.

Pre-threshold ROP: The early treatment for retinopathy of prematurity (ETROP) study[35] redefined these guidelines. They defined the actively treatable and observational types of pre-threshold ROP as "type 1" (high-risk prethreshold ROP) and "type 2" ROP respectively. "Type 1 ROP" is defined as: (1) Any stage of ROP in zone Ⅰ with plus disease (Figure 3B); or (2) Stage 3 in zone Ⅰ without plus; or (3) Stages 2 or 3 in zone Ⅱ with plus disease. These are the modified guidelines for treatment. "Type 2 ROP" is defined as stages 1 or 2 in zone Ⅰ (Figure 3C) without plus, or stage 3 in zone Ⅱ without plus. These can be observed and watched at one week or less follow-up. Cases having stages 1 or 2 in zone Ⅱ require two weekly follow up, while stages 1 or 2 in zone Ⅲ require three weekly follow-up[19].

Treatment modalities

Cryotherapy: This involves treatment of the avascular retina using of a cryoprobe in order to reduce unfavorable outcomes of ROP like retinal folds and retinal detachment. Cryotherapy however is stressful for the babies, requires general anesthesia and creates lot of periocular inflammation. It is therefore no more the treatment of choice.

Indirect laser photocoagulation: Laser photocoagulation of the peripheral retina using indirect delivery system has proved to be the gold standard, time tested and successful means of treatment since many years[33,36,37]. Laser photocoagulation using infra red diode laser forms a portable mode of treatment and can be performed in the nursery by skilled professionals (Figure 3D). The biggest advantage is that it can be done under topical anesthesia. However many institutions prefer general anesthesia for patient comfort. Laser ablation covers the relatively hypoxic retina into anoxic, thereby reducing stimulus for new vessel formation and disease progression. The ETROP study from its six years analysis confirmed that eyes with type 1 ROP benefited from laser treatment at high risk pre threshold stage[38]. This failure rate of 9.6%, was better than the results shown by the CRYO-ROP study.

Cryotherapy or laser photocoagulation, ablation has its own demerits and causes destruction of the retina

amounting to significant visual field loss. Pharmacologic therapy is thus ushering a new era of ROP management.

Anti-vascular endothelial growth factors drugs: Anti-vascular endothelial growth factor (VEGF) drugs directly block the effects of VEGF, and a single intravitreal injection is less time consuming and less expensive as compared to lasers. Exceptionally successful results with anti-VEGF drugs in adult retinal vascular diseases led to its trial in paediatric retinopathy as a monotherapy as well as in combination with lasers. Intravitreal bevacizumab as an initial mono therapy was reported to cause regression of type 1 ROP in 88% cases with 9% requiring additional laser treatment and 1% requiring additional injection[39]. The BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of ROP) study[40] is the only randomised trial done comparing anti-VEGF *vs* conventional laser. It suggested superiority of anti-VEGF treatment over conventional laser therapy for stage 3+ ROP in zone Ⅰ. Superiority in severe ROP in zone Ⅱ could not be established due to inadequate sample size. Safety is a major concern with use of anti-VEGF drugs in paediatric age group and this study could not prove it because of a short follow up. Recent studies also shown that that systemic VEGF levels remain suppressed for 8 wk after intravitreous bevacizumab injection[41].

Regarding the best approach, laser treatment is still the gold standard and anti-VEGF therapy should be tried only in selected cases.

Surgical management is reserved for advanced stages of ROP (stages 4 and 5). The stage of ROP and features specific to each eyes guide the choice of surgical technique. It is shown that best anatomical and visual outcome can be attained if surgical intervention is done at 4A ROP as it halts progression to worse stages[42]. The surgical options available for stage 4 ROP are lens sparing vitrectomy or scleral buckling. For stage 5, vitrectomy with lensectomy or open sky vitrectomy can be performed. Visual outcome for stages 4B and 5 is very poor and can lead to permanent visual impairment[42].

Periodic follow up and the burden of visual morbidity then become the prime concerns after the retinopathy is adequately treated. Visual rehabilitation can be achieved only through an integrated coordination between the pediatricians, ophthalmologists, paramedicals and parents. With the advances in screening tools, it may be hoped that occurrence of severe retinopathy or severe visual morbidity from ROP may be reduced in future.

FUTURE

Future trends in screening of ROP

Newer predictor of ROP: Timely screening of ROP is crucial for early management and improved outcomes. Current screening guidelines use only two most important risk factors gestational age and birth weight, and not the post-natal factors. However only approximately 10% of the premature babies screened need treatment[43]. Various neonatal scoring systems such as clinical risk index for babies, scores for neonatal acute physiology (SNAP), and SNAP-perinatal extension-Ⅱ have also been attempted to predict ROP, but none showed sufficient power to predict severe ROP[44]. Thus there is a need for improvement of the current screening protocols by developing new better predictors to reduce the number of ROP screening examinations[44].

Low weight gain proportion: Currently, low weight gain by six weeks of life after premature birth is being accepted as a risk factor for causing ROP. Proportion of the weight gain is defined as the weight at 6 wk of life minus the birth weight divided by the birth weight. Low weight gain proportion, *i.e.*, weight gain less than 50% of the birth weight in the first 6 wk of life is being considered superior to birth weight and gestational age alone as predictors for severe ROP[45,46]. In order to develop an efficient clinical prediction model, Binenbaum *et al*[47] found that a birth weight-gestational age-weight gain model could reduce the need for examinations by 30% in a high-risk cohort, while still identifying all infants requiring laser therapy.

WINROP algorithm: A surveillance algorithm WINROP was developed by Löfqvist *et al*[33] to detect infants at risk for developing severe ROP. WINROP is based on the weekly measurement of body weight and serum IGF-1 level from birth until postconceptional age of 36 wk. In their first prospective study, which included 50 preterm infants, the WINROP algorithm could identify all preterm babies diagnosed with severe ROP later. Since then WINROP algorithm has been validated in different cohorts of many countries with sensitivity ranging from 85% to 100%[48-51]. These studies have validated WINROP algorithm as a useful ROP screening tool that can be used to focus care on those at high risk for ROP. Currently, WINROP is being tested in a large multi-center multinational trial to validate it as universal screening tool.

ROPScore: ROPScore is based on birth weight, gestational age, weight gain and blood transfusions from birth to 6th week of life and use of oxygen. Eckert *et al*[44] initially analyzed 16 variables and established this score after linear regression. The study with 474 patients, and the area under the receiver operating characteristic curve for the score were 0.77 and 0.88 to predict any stage and severe ROP respectively. They concluded ROPScore as a promising tool which maybe more predictable than birth weight and gestational age in predicting the occurrence of ROP in very low birth weight preterm infants. Also, the score is easy enough to be routinely used by ophthalmologists or the nursing staff during screening for ROP.

IGF-1: Apart from use of IGF-1 in WINROP algorithm, the usefulness of IGF-1 level was evaluated in a prospective study by Pérez-Muñuzuri *et al*[52] They studied 74 premature newborn babies and concluded that determination of IGF-1 serum levels in the 3rd week post-partum, is a good prognostic tool to identify babies that are at a high risk of

developing ROP.

Plasma soluble E-selectin: Elevated plasma soluble E-selectin (sE-selectin) levels have been found to have an association with ROP and have been reported as independent risk predictor for ROP by Pieh *et al*[53]. They concluded that a score based on the gestational age of the preterm child and sE-selectin plasma levels would improve prediction of ROP. Increase of 10 ng/mL increases the ROP risk by 1.6 fold. For this purpose, plasma concentrations should be assessed 2 to 3 wk after birth, in premature infants.

Thus in the future, new screening tools would be developed with a hope to reduce the burden of ROP screening on the ophthalmologist and also reduce these stressful examinations on the preterm babies. Further studies are needed to validate the usefulness of these predictors. Once validated, these post-natal variables can be used successfully for early prediction of severe ROP.

Telescreening: Timely referral by pediatricians and meticulous examination by an experienced ophthalmologist is the gold standard for ROP screening. Digital retinal imaging is emerging as an important tool for ROP screening. Non-ophthalmologists like the neonatal nurses and technicians are being trained to use these digital imaging devices effectively. Pediatric ophthalmologists' services can be extended to the remote areas by electronic transfer of the images captured by these paramedical staffs[54]. Daniel *et al*[55] validated that remote evaluation of the digital retinal images by trained technicians taken by them can reduce referral warranted ROP. The result of these studies suggest that telescreening provides future strategies for outreach ROP screening and will allow access of diagnostic expertise to underserved areas in developing as well as developed countries[56].

Optical coherence tomography: It is an imaging tool which gives cross sectional images of the retina and has been extensively used in adults. Although it is not widely used in ROP, this technology is already providing new insights at a cellular and subcellular level into normal retinal development, the acute ROP process, and its long-term sequelae[57].

Newer therapeutic modalities for ROP

Anti-VEGF, systemic propranolol, IGF-1 replacement, granulocyte colony stimulating factor, Jun kinase inhibitor and omega-3 polyunsaturated fatty acid supplementation are the newer preventive strategies being evaluated through insights into the molecular pathogenesis of ROP in animal studies[58]. Newer emerging therapeutic options have the potential to complement current therapies and improve treatment outcomes. However, any new therapeutic option must be thoroughly evaluated before existing treatment paradigms can be modified, as these newer agents are mostly systemically administered and may have unknown widespread side effects.

Anti-VEGF: Recently various anti-VEGF agents are being evaluated as promising treatment modality for various stages of ROP. Bevacizumab is the most widely used anti-VEGF for treatment of acute ROP since 2007, and evidences from case reports and small studies suggest that intravitreal bevacizumab monotherapy may be a viable first-line treatment for select cases of ROP[58]. Other anti-VEGF agents are also being evaluated as adjunctive or alternate therapy. A recent study showed that administration of intravitreal pegaptanib along with laser is useful therapy with stable regression of ROP in 90% of eyes compared to 61% of only laser treated eyes[59]. Recently one prospective nonrandomized interventional case series study has evaluated 1-year outcomes of intravitreal aflibercept injection in 26 eyes with type 1 prethreshold ROP and found favorable anatomical and visual outcome in 96% and 80% eyes[60]. The efficacy of ranibizumab and bevacizumab for the regression of ROP have been compared and found similar in retrospective studies. However, high myopia was more prevalent in the bevacizumab-treated eyes, while reactivation rate was significantly higher following treatment with ranibizumab, probably due to shorter half-life[61,62]. Lutty *et al*[63] studied the effect of VEGF trap on normal retinal vascular development and oxygen-induced retinopathy in dog and concluded that it inhibits the retinal neovascularisation, however dose selection is an important variable as higher doses also inhibit vasculogenesis or retinal revascularization.

In future, intravitreal anti-VEGF injection may become the first choice treatment replacing laser therapy for zone I stage 3 ROP or cases with media opacity, if efficacy and safety are validated. Also anti-VEGF can be considered as an adjunctive therapy in patients treated with laser photocoagulation or vitrectomy.

Propranolol: Reports of use of systemic propranolol for an effective treatment of infantile hemangioma resulted in exploration of anti-angiogenic role of propranolol in ROP. A study on oxygen-induced retinopathy in a mouse model showed that propranolol decreases VEGF overproduction in the hypoxic retina. In addition, beta-AR blockade has no effect on VEGF levels in the heart, brain or lungs, as VEGF expression is these organs is independent of hypoxia[64]. Based on these findings, the safety and efficacy of propranolol in newborns with ROP (PROP-ROP) study[65], was conducted. It evaluated safety and efficacy of oral propranolol given to preterm newborns infants having early stages of ROP. In this study, 26 preterm babies with stage 2 ROP treated with oral propranolol (0.25 or 0.5 mg/kg per 6 h) showed less progression to stage 3 or stage 3 plus and a 100% relative reduction of risk for progression to stage 4. However serious adverse effects like bradycardia and hypotension were observed in about 20% of infants treated with propranolol, and the study was halted due to increased mortality in the treatment arm[65]. Recently, an experimental study reported failure of propranolol treatment to suppress retinopathy development in mice[66]. Thus, the safety of oral

propranolol to the vulnerable premature infants is uncertain, and further studies including animal as well as prospective clinical trial are needed.

IGF: IGF plays an important role in fetal development during pregnancy. The levels IGF-1 rise significantly during the 3rd trimester of pregnancy, and it controls VEGF-mediated vascular growth in the retina[67]. However, IGF-1 levels fall rapidly after preterm birth, and prolonged period of low IGF-1 in preterm children have been reported to be associated with development of ROP. Conversely, normal vessel development occurs, if the IGF-1 levels are sufficient after birth[68]. Recent studies have shown that intravenous administration of recombinant IGF-1 (rhIGF-1) with its binding protein 3 (rhIGFBP-3) to premature infants increases the serum concentrations of IGF-1 and IGFBP-3, and is found to be safe[69,70]. Can *et al*[71] studied the effect of early aggressive parenteral nutrition (APN) *vs* conservative nutrition and found that IGF-1 levels were higher in the APN group.

Granulocyte colony stimulating factor: The potential role of granulocyte colony stimulating factor (G-CSF), a biologic cytokine commonly used to increase leukocyte count in neutropenic patients, is currently being evaluated to prevent ROP[72]. In a retrospective review of 213 neonates who received G-CSF for non-ophthalmic indications, Bhola *et al*[73] studied 50 infants with birth weight < 1500 g and gestational age < 32 wk. Only 10% of the infants who received G-CSF required laser compared to 18.6% in the control group. However the observed difference was not statistically significant. Another retrospective study determined the vitreous level of 27 types of cytokines in eyes with ROP, and levels of 6 cytokines including G-CSF were found significantly higher ($P < 0.05$) in eyes with ROP compared to the control group[74]. Recently, in an animal study of oxygen-induced retinopathy, G-CSF significantly reduced the vascular obliteration ($P < 0.01$) and neovascular tissue formation ($P < 0.01$) mainly by increasing levels of IGF-1[75]. The results of these studies suggest a potential role of G-CSF in ROP prevention, however further studies are needed to establish the same, and to determine the dose required, side effects and safety.

Omega-3 polyunsaturated fatty acids: Like IGF-1, omega-3 and 6 polyunsaturated fatty acids (PUFAs) are non-oxygen-regulated angiogenic factors, which are transferred from mother to the fetus in the third trimester of pregnancy. Consequently, premature newborns lack the maternal supply of PUFAs[72]. The mouse model studies of ROP have shown that omega-3 PUFA supplementation as well as an increased retinal omega-3 and omega-6 PUFA ratio result in a protective effect against pathologic retinal neovascularisation[76,77]. The protective action of omega-3 PUFA is considered to be mediated through the suppression of tumor necrosis factor-alpha[78]. These lipids supplementation can be provided through total parenteral nutrition in premature infants, and this may be an interesting therapeutic approach for ROP prevention. However, larger studies are required to establish the safety and efficacy of omega-3 PUFA supplementation therapy in premature babies.

Gene therapy: Association of mutations and polymorphism of various genes (*e.g., Norrin*, *Frizzled 4*, *Lrp5*) with severity of ROP or failure of treatment has been investigated in a number of small studies[79]. A recent study performed about the genetic and environmental influences on ROP in 257 infants including 38 monozygotic twins, 66 dizygotic twins, and 153 simple births found the heritability of ROP to be 0.73[80]. Interestingly, Good *et al*[81] demonstrated in a rat model of ROP that local gene transfer into retinal blood vessels was possible using recombinant viruses carrying genes of interest. They also found that adenovirus vector was specific to the inner retinal blood vessels and does not appear in deeper neural retina, when compared to other vectors like retroviruses and herpes virus[81]. Though no significant association between genetic abnormality and ROP has been reported till now, targeting the expression and regulation of various cytokines and growth factors involved in the pathogenesis of ROP by gene therapy appears as a promising future treatment method to restore an anti-angiogenic state[72].

Medico legal implications

Screening for ROP needs to be initiated timely after birth to prevent blindness. It is the responsibility of the caring pediatrician to initiate screening by referring to an ophthalmologist and it is the responsibility of the ophthalmologist to do correct screening and treatment. This has immense medico legal implications because if a child goes blind due to missed or late screening then the pediatrician and the ophthalmologist are at a very high risk of getting into a law suit[82,83].

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MINIREVIEWS

Sublingual immunotherapy for pediatric allergic rhinitis: The clinical evidence

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Abstract

Allergic rhinitis affect 10%-20% of pediatric population and it is caused by the IgE-sensitization to environmental allergens, most importantly grass pollens and house dust mites. Allergic rhinitis can influence patient's daily activity severely and may precede the development of asthma, especially if it is not diagnosed and treated correctly. In addition to subcutaneous immunotherapy, sublingual immunotherapy (SLIT) represents the only treatment being potentially able to cure allergic respiratory diseases, by modulating the immune system activity. This review clearly summarizes and analyzes the available randomized, double-blinded, placebo-controlled trials, which aimed at evaluating the effectiveness and the safety of grass pollen and house dust mite SLIT for the specific treatment of pediatric allergic rhinitis. Our analysis demonstrates the good evidence supporting the efficacy of SLIT for allergic rhinitis to grass pollens in children, whereas trials regarding pediatric allergic rhinitis to house dust mites present lower quality, although several studies supported its usefulness.

Key words: Allergic rhinitis; Grass pollen allergy; House dust mite allergy; Sublingual immunotherapy

Core tip: This manuscript aims at describing objectively the current evidences of sublingual immunotherapy (SLIT) for the treatment of pollen and house dust mite allergic rhinitis in children, based upon the available randomized, double-blinded, placebo-controlled trials. All these studies have been directly analyzed by the authors and have been summarized in this manuscript, in order to be readily available to the reader. We concluded that there is a good evidence of efficacy for grass pollen SLIT, while the benefit seems to be weaker for house dust mite SLIT, in the specific setting of pediatric allergic rhinitis.

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BACKGROUND

Rhinitis is the term indicating the inflammatory disease of nasal mucosa and, clinically, is defined by the onset of two or more of the following symptoms: Nasal discharge, sneezing, nasal itching and congestion.

If these symptoms last longer than 10 d, the rhinitis is defined as chronic. Chronic rhinitis can persist weeks and even months or can have a recurrent trend. While acute rhinitis are usually caused by transient viral illnesses, infectious agents are not the main etiology of chronic rhinitis and, when it is so, these are due to an overlapping bacterial infection, leading to rhino-sinusitis, characterized by purulent nasal discharge, persistent fever, headache, facial pain and cough.

Actually, chronic rhinitis can recognize several etiologies (vasomotor, occupational, hormonal, atrophic, iatrogenic, idiopathic), but the most consistent group is represented by allergic rhinitis, which is estimated to affect 10%-20% of pediatric population worldwide.

Allergic rhinitis is caused by an IgE-mediated sensitization to environmental allergens, such as dust, pollens, domestic animals and moulds. Depending upon the specific pattern of sensitization, allergic rhinitis can be intermittent (or seasonal) and persistent (or perennial), although the distinction is not always obvious, as some people can be sensitized to several allergens. Therefore, the diagnosis of allergic rhinitis is correctly made whenever the nasal symptoms are associated to a profile of allergic sensitization (which must be documented by skin prick tests and/or the dosage of serum of allergen specific IgE), which is consistent with the clinical picture and its temporal pattern[1,2].

Once the diagnosis of allergic rhinitis is established, the general clinical management is constituted by the avoidance of allergen exposure, whether it is practicable, and by the control and/or the prevention of nasal symptoms by nasal or systemic anti-histamine drugs, intranasal steroids, leukotriene-receptor antagonists and, in a lesser extent, cromolyn sodium. Among those drugs, intranasal steroid have been demonstrated to be able to produce the greatest relief, being able to improve significantly the symptoms related to the nasal obstruction. Unfortunately, all these drugs control the symptoms, but cannot cure the allergic disease[3].

Allergic rhinitis has been considered for long time as being just a nuisance disorder. However, nasal symptoms can interfere with daily activities importantly and can disrupt or alter the sleep pattern, leading to negative consequences on patient's social life and intellectual performance. Moreover, according to the "allergic/atopic march" hypothesis and to the "united airways disease" concept, allergic rhinitis can be associated to lung function test abnormalities and/or anticipate the onset of asthma. Thus, the appropriate therapy of allergic rhinitis could help to prevent the progression to more serious respiratory diseases, in addition to ameliorating patient's life quality. Such a goal may be reached through the inclusion of specific immunotherapy (SIT) in the early treatment of allergic rhinitis, before it evolves to asthma: Indeed, SIT - unlike symptomatic drugs - aims at modulating the immune mechanisms underlying the allergic disease and, currently, it is the only available treatment which modifies the disease process[4].

SUBLINGUAL IMMUNOTHERAPY FOR ALLERGIC RHINITIS

Basically, SIT consists in the administration of increasing doses of specific allergens up to a maintenance dose, which can be repeated according to different schedules depending on the allergic disease and its pattern of sensitization.

SIT can be mainly administered by two ways: Subcutaneously (SCIT) or sublingually (SLIT). Although in many European countries SCIT is still the most common way to administer allergy immunotherapy, actually sublingual immunotherapy (SLIT) is getting growing success, especially in the pediatric population: It is usually preferred because it is easier to be administrated and it hasn't been associated to systemic and life-threatening adverse reactions[5,6].

SLIT should result in the progressive acquisition of the immune tolerance against a specific allergen. Several cellular and humoral immune mechanisms have been proposed. The main immunological modifications related to the SLIT desensitization process can be summarized briefly, as it follows: Emergence of regulatory T cells (Treg), shifting of T helper polarization toward Th1 cells, increased production of interleukin (IL)-10 and Transforming growth factor-β, immunoglobulin class-switching from specific IgE to IgA and IgG4 isotypes (which would compete with IgE to bind cellular receptors, reducing allergen-mediated release of inflammatory molecules)[7].

In 2013, the European Academy of Allergy and Clinical Immunology (EAACI) edited an important position paper on pediatric rhinitis, providing several evidence-based insights on diagnostic and therapeutic aspects. In this document, SLIT is confirmed as an effective treatment for grass pollens and house dust mite allergic rhinitis and this concept is labeled through a force of this statement of grade A, according to the system for grading clinical recommendation in evidence-based guidelines[1,8].

Such a recommendation was reached through the evaluation of available studies, considering the results of several reviews and meta-analysis. However, most clinical trials regarded mainly the adult population and specific pediatric studies are much fewer. For instance, the important systematic review of the literature made by Radulovic *et al*[9] concluded that SLIT is an effective and safe therapy for allergic rhinitis. Although this analysis considered randomized, double-blind, placebo-controlled (RDBPC) clinical trials, actually it included

patients of any age, both children and adults, affected with allergic rhinitis (with or without allergic asthma)[9].

Similarly, the World Allergy Organization (WAO) Position Paper also stated that the indication to SLIT in the treatment of IgE-mediated allergic respiratory diseases is well established in children, provided the diagnostic work-up has been appropriate[10]. Moreover, several systematic reviews supported the specific use of SLIT in the treatment of allergic rhinitis in children. In 2006, Penagos *et al*[11] made a pivotal meta-analysis of randomized controlled trials (RCTs) of SLIT in the treatment of allergic rhinitis in pediatric patients, concluding that SLIT with standardized extract is an effective therapy in this field. More recently, Kim *et al*[5] and Larenas Linnemann *et al*[12], in their reviews, reinforced the evidence supporting the efficacy and the safety of SLIT for the treatment of allergic respiratory diseases.

However, in the medical literature, the RCTs concerning specifically the role of SLIT in pediatric allergic rhinitis are, actually, fewer than expected. We performed a specific search through PUBMED (search terms: Allergic rhinitis, children, SLIT) and it returned 201 references: Almost all (195) were published after the year 2000. Among those, we found 56 reviews and/or meta-analysis; in the remaining part, considering only english-written papers, we found 35 RCTs and 11 retrospective and/or observational studies regarding pediatric allergic rhinitis (associated to grass pollen and house dust mite sensitization). Moreover, many of these RCTs were small trials, including less than 100 patients.

In this practical review, we attempt to highlight and comment the major evidences on the use of grass pollen and dust mite SLIT against allergic rhinitis in children, deriving from available RCTs being strictly oriented to allergic rhinitis and limited to pediatric population.

SLIT FOR GRASS POLLEN ALLERGIC RHINITIS IN CHILDREN: RCTS

In our search, the first randomized, double-blind, placebo-controlled (RDBPC) study on SLIT in children (n = 22) affected with seasonal allergic rhinitis was written by Wüthrich *et al*[13] in 2003: After 2 years of treatment, authors detected a statistically significant reduction ($P < 0.05$) in the drug consumption in the SLIT group and such an effect resulted to be more relevant in the second year of therapy.

In 2004, Bufe *et al*[14] published a multicenter RDBPC study, including 161 children with seasonal rhino-conjunctivitis: The authors were able to find a significant ($P = 0.046$) benefit of SLIT after 3 years of treatment, but such a positive result was limited to the group of children with severe symptoms. Similarly, Rolinck-Werninghaus *et al*[15] enrolled 97 children (3-14 years) with allergic rhinoconjunctivitis to grass pollen: They treated the active group by a 5-grass mixture SLIT (3 times/wk), documenting a positive effect in term of reduction of both multiple symptoms-medication score ($P < 0.05$) and medication score ($P = 0.0025$) rather than isolated symptom score.

Again in 2004, the multicenter study by Novembre *et al*[16], including 113 children (5-14 years) supported the beneficial effect ($P < 0.05$) of 3 years' coseasonal SLIT based upon the medication score. Another important value of this work was the demonstration that SLIT could reduce the incidence of asthma in children with grass pollen rhino-conjunctivitis. Indeed, they calculated a 3.8 relative risk of development of asthma in the control group, which was not related to differences in sex, presence of household pets, family allergic background or exposure to passive smoking[16].

A large perspective study was performed by Röder *et al*[17] in a primary care setting: 204 patients (aged 6-18 years), coming from general practitioners' office (not from allergy referral centers), were randomized to receive SLIT (five grasses pollen extract) or placebo, based on a diagnosis of allergic rhino-conjunctivitis. However, in this clinical setting, SLIT did not result to be effective in ameliorating the allergic symptoms nor in reducing the need of medications[17].

In 2009, Wahn *et al*[18] published the largest multi-national RDBPC study (n = 278 children, aged 5-17 years), by using five-grass pollen tablet (300 IR, Index of reactivity) in a pre-co-seasonal scheme. SLIT treated patients showed a highly significant improvement compared to placebo, both in term of symptoms score ($P = 0.001$) and in term of use of medications ($P = 0.0064$). The clinical benefit was evident also considering each symptom individually, including nasal congestion and conjunctivitis. Interestingly, this study covered a period as long as 8 mo, which means that the clinical improvement became evident in a relatively short period of time, compared to previous studies encompassing 2-3 years' follow-up. Moreover, this study included also poly-sensitized children, showing a comparable improvement as well as mono-sensitized patients: that reinforced the concept that the multi-sensitization is not an absolute limit to the access to SLIT, provided that the allergy evaluation is appropriate[18].

In the same year, Bufe *et al*[19] carried out a similar research by the use of a different SLIT product, namely 75.000 Units SQ-standardized grass allergen tablets, which contain approximately 15 μg Phl p5 (Phleum pratense major allergen 5), whereas a dose of 300 IR five grasses extract corresponds to 20 μg Phl p5. A total of 253 children (aged 5-16 years) were randomized and treated according a pre-co-seasonal scheme. SLIT group showed a significant 24% reduction of symptom score ($P = 0.0195$) and 34% reduction of medication score ($P = 0.0156$) compared to placebo group, considering the entire grass pollen season[19].

In 2010, Halken *et al*[20] published another multin-ational RDBPC study, which included 267 pediatric patients (aged 5-17 years). Patients were treated according to a pre-co-seasonal schedule for one year and the SLIT group received five-grass pollen 300 IR tablet daily. As previously

reported, the benefit of SLIT was confirmed even in the first pollen season: The relative mean improvement of symptom score was around 28% compared to placebo group ($P < 0.001$) and the relative mean improvement of medication score was almost 50% ($P = 0.01$)[20].

In 2011, the first RDBPC trial performed in North America has been published. Blaiss *et al*[21] randomized 345 pediatric subjects to receive 75000 SQ tablets or placebo. Study population was made by children and adolescent affected with grass pollen induced rhino-conjunctivitis and some presented asthmatic co-morbidity too; moreover, 85% patients were multi-sensitized. Patients were treated according to pre-co-seasonal scheme before and during the 2009 grass pollen season and all efficacy parameters (symptom score, medication score, total combined score) improved significantly in the treated group compared to controls (in the extent of 25%, 81% and 26%, respectively)[21].

Recently, in 2012, a small RDBPC trial by Ahmadiafshar *et al*[22] published the only english-written study performed outside western countries. It included 24 children (5-18 years) and patients were treated for 6 mo with five-grass pollen 300 IR extract: As well as previous trials, the benefit of SLIT was confirmed and was reported as being evident after 4 mo of therapy[22]. In the same year, Wahn *et al*[23] published another multicentric RDBPC trial including 207 children affected with rhinitis/rhinoconjunctivitis with/without asthma, where the outcome was evaluated by the comparison of the area under the curve (AUC) of the symptom-medication score before and after the treatment. Patients experienced a clear improvement thank to the SLIT and the efficacy resulted to be statistically significant, even considering separately the symptoms score and the medication score[23].

SLIT FOR POLLEN-INDUCED PEDIATRIC ALLERGIC RHINITIS: GLOBAL CLINICAL EVIDENCE

A summary of pediatric RDBPC trials we reported in the previous paragraph is made in Table 1. It is evident that almost all the aforementioned studies supported the efficacy of grass pollen SLIT in order to improve the burden of symptoms and medications of allergic rhinitis in children. Among those, many are well-conducted trials and some are multicentric studies being large enough to draw consistent conclusions on the efficacy of SLIT in this setting as well as its good safety.

The only trial where a clear benefit of SLIT was not evident is the one performed by Röder *et al*[17], but it seems important to underline actually the fact that the study population was not made of patients evaluated at allergy referral centers[19]. This aspect could have affected the results for several reasons. Patients managed in the primary care setting could show greater variability in the severity of allergic rhinitis; moreover, many patients included in this study resulted to be sensitized to several environmental allergens and a good correlation between symptoms and sensitization, which can require some specific allergy expertise, has been stressed as being a main aspect for the correct indication and efficacy of SLIT. Indeed, the large multicentric trials performed in North America, which included mostly multisensitized patients (85% of study population), provided results consistent with a clear benefit of SLIT in grass-pollen induced rhino-conjuctivitis[21].

Therefore, in our opinion, these experiences together demonstrate how the multi-sensitization is not a limit for the use of SLIT in children affected with grass-pollen allergic rhinitis, provided that an accurate selection of allergic patients, that SLIT is offered to, can be made. According to the EAACI position paper, a clear relationship between the occurrence of nasal symptoms and the exposure to grass pollen, especially in multi-sensitized patients, should be ascertained before prescribing SLIT, in order to obtain a good efficacy from this expensive treatment[1].

Moreover, also the severity of allergic rhinitis can impact on the evidence of a clinical improvement after the treatment with SLIT. Indeed, in order to get a study population as more homogeneous as possible, the inclusion criteria of RCTs performed at allergy referral centers are often more restrictive than those used in the daily allergy practice; however, recent observational and multi-centric studies supported the effectiveness of SLIT in real life practice[24,25].

Finally, in the measurement of the effectiveness of therapies against grass pollen allergy, allergen exposure must be considered too, as it is different over several seasons and regions. Such an aspect is thought to have even a greater impact on the analysis of grass pollen SLIT than on the evaluation of other drugs used to treat allergy symptoms acutely. Indeed, in seasonal allergy trials with grass pollen SLIT, the treatment effect resulted to greater in presence of higher pollen exposure[26]. This aspect must be considered in the individual clinical trials and this effect can be overcome through multi-centric studies and through meta-analysis pooling data from several RCTs. Recently, several post-hoc analysis have been published by using pooled data from some randomized, placebo-controlled and double-blind North American trials on timothy grass SLIT against allergic rhinitis and/or rhinoconjunctivitis in children and adolescents. This research confirmed that grass pollen SLIT administered daily, pre-seasonally and during the grass pollen season, is clinically effective and safe in children older than 5 years[27].

Another aspect to be discussed is that physicians could have the impression that SLIT is less effective than it is actually or compared to the other classes of drugs for allergic rhinitis, despite all the evidences we reported. Although that is not specific for pediatric age, a huge meta-analysis by Devillier *et al*[28] deserves to be reported, as it provided an indirect comparison between SLIT and pharmacotherapy: The administration of pollen SLIT tablet resulted in a relative clinical impact (RCI) *vs* placebo greater than that observed with second-

Table 1 Randomized double-blinded placebo controlled trials on grass pollen sublingual Immunotherapy for the treatment of allergic rhinits in children

Ref.	Year	Age	No. of patients	Product	Efficacy parameters	Duration	Statistical significance	Other observation
Wüthrich *et al*[13]	2003	4-11	22	ALK-Abello'	Medication score	2 yr	$P = 0.05$	A difference in drug consumption has been shown only in the second year
Bufe *et al*[14]	2004	6-12	161	Sublivac BEST, HAL-allergy	Clinical Index (combining symptom and medication score)	3 yr	$P = 0.046$	A significant difference was shown in patients with severe symptoms
Rolinck-Werninghaus[15]	2004	3-14	97	Pangramin-SLIT ALK-SCHERAX	Multiple symptom – medication score	32 mo	$P = 0.498$	Symptom score did not reveal significant difference; medication score improve significantly ($P = 0.0025$)
Novembre *et al*[16]	2004	5-14	113	ALK-Abello'	Medication score	3 yr	$P < 0.05$	Significant improvement was shown after the second year; symptom score did not improve significantly
Röder *et al*[17]	2007	6-18	204	Oralgen Grass Pollen, Artu Biologicals	Medication and symptom score	2 yr	NS	Study population was enrolled from general practices
Wahn *et al*[18]	2009	5-17	278	5-grass tablets 300IR,	Rhinoconjunctivitis total symptom score	6 mo	$P = 0.001$	SLIT was started 4 mo before before the pollen season; both symptom score and medication score improved singularly too
Bufe *et al*[19]	2009	5-16	253	Stallergenes SQ-standardized grass allergen tablet (Grazax)	Medication and symptom score	4-6 mo	$P < 0.02$	SLIT was started 8 to 23 wk before the estimated pollen season in 2007
Halken *et al*[20]	2010	5-17	267	5-grass tablets 300IR,	Medication and symptom score	6 mo	$P < 0.01$	SLIT was started 4 mo before the estimated pollen season
Stelmach *et al*[29]	2011	6-18	60	Stallergenes Staloral 300IR, Stallergenes	Combined symptom and medication score	2 yr	$P < 0.01$	Both pre-coseasonal and continuous regimen were efficacious in the same extent
Blaiss *et al*[21]	2011	5-17	345	SQ-standardized grass allergen tablet (Grazax)	Medication and symptom score	6 mo	$P < 0.01$	SLIT started 8 wk before the pollen 2009 season; 89% patients were multi-sensitized
Wahn *et al*[23]	2012	4-12	207	6-grass pollen aqueous extract (AllerSlit, Allergopharma)	Area under the curve of symptom-medication score	6-8 mo	$P = 0.004$	Patients were treated with a pre-coseasonal regimen; after this first phase, unblinding was made and all patients were treated
Ahmadiafshar *et al*[22]	2012	5-18	24	Staloral 300IR, Stallergenes	Medication and symptom score	6 mo	$P < 0.05$	SLIT was started 8-10 wk before pollen season

SLIT: Sublingual Immunotherapy; NS: Not significant.

generation H1-antihystamines and montelukast, and it was comparable to nasal corticosteroids[28]. Most recent RCTs demonstrated that SLIT is beneficial even since the first year of treatment, provided that an appropriated scheme of treatment is instituted before the pollen season. Previously, in the study by Stelmach *et al*[29], where the pre-co-seasonal and the continuous schedule were compared after a 2-years perspective RDBPC trial, both protocols resulted to be associated to a significant improvement in the total symptom and medication scores and there was no significant difference between them. Actually, the pre-co-seasonal group showed a lower improvement for nasal symptoms than the continuous schedule[29]. Similarly, the results emerging from an open randomized controlled study by Pajno *et al*[30] observed that the continuous protocol performed in a better way than the pre-co-seasonal schedule in the first pollen season, whereas in the following years they were rather equivalent.

Therefore, based upon most recent studies, a good efficacy of a pre-co-seasonal treatment beginning around 4 mo before the pollen season has been showed. Differences in both the efficacy endpoint - in the research setting - and the clinical results - in the daily allergy practice - could be due not only to the variable scheme of vaccine administration, but also to different allergen formulation and product standardization, whose discussion overcomes the purpose of the present analysis.

Finally, it must be underlined the optimal profile of safety of grass pollen SLIT, which is confirmed by all RCTs and systematic revisions regarding children and adolescents affected with allergic rhinitis. No death or life-threatening events resulted to be associated to the treatment. Treatment related adverse events have been limited to mild to moderate local symptoms, such as oral pruritus, ear pruritus and throat irritation, reported in 15%-30% of subjects.

In conclusion, available pediatric RDBPC trials as well as reviews/meta-analysis clearly demonstrated the effectiveness and the safety of five-grass pollen

SLIT administered with the appropriate scheme and formulation (*e.g.*, 300 IR drops, 300 IR tablets, 75000 SQ-standardized tablets). Particularly, the pre-co-seasonal schedule is the most used and it is beneficial even in the first year of treatment, if it is started appropriately (3-4 mo before the supposed beginning of the pollen season).

Of course, despite these good evidences supporting grass pollen SLIT in the treatment of allergic rhinitis, some issues need consideration and further research, such as the use of different vaccines and the variable follow-up in the aforementioned studies and the lack of SLIT *vs* SLIT and SLIT *vs* SCIT trials. However, current evidences can be considered strong enough to support prescription of grass pollen SLIT to all pediatric patients suffering from grass pollen allergic rhinitis, after an appropriate diagnostic assessment by an allergy specialist, who will plan a correct schedule for SLIT administration and will provide an adequate follow-up.

SLIT FOR HOUSE DUST-MITE ALLERGIC RHINITIS IN CHILDREN: RCTS

Available RCTs concerning the efficacy of dust mite SLIT on pediatric allergic rhinitis are relatively poor and most have been made in the last few years. Indeed, the first multicenter RDBPC trial was produced by Tseng *et al*[31] in 2008. This study included 59 children (aged 6-18 years) from Taiwan and the treatment group received a standardized extract of Dermatophagoides pteronyssinus (D.p.) and Dermatophagoides farinae (D.f) up to 20 drops of a 300 IR/mL formulation, as a 5 mo' maintenance dose, which was reached in a period of 3-4 wk. Here, the authors were not able to demonstrate a significant benefit in either symptoms or medication score after 6 mo of SLIT. However, they described a significant serological response in patients treated with SLIT, in term of increase of specific IgG4 to D.f-D.p. ($P < 0.001$) and specific IgG4/IgE ratio ($P = 0.01$), which is reputed to be one mechanism of the potential efficacy of SLIT in allergic diseases[31].

Previously, we were able to find one retrospective analysis by Nuhoglu *et al*[32] in 2007, regarding 39 children affected with dust mite allergic rhinitis, which reported a positive impact of SLIT on nasal symptoms, in addition to a significant decrease of asthma attacks[32]. Moreover, in 2003 Marcucci *et al*[33] performed a 3 years' partially double-blind case-control clinical study including 24 children (aged 4-15 years) complaining dust mite allergic rhinitis for at least 2 years. In the first year of follow-up, patients were randomized to receive dust mite SLIT or placebo; subsequently, also children in the placebo group were switched to the SLIT treatment until the end of the study. The first double-blind placebo-controlled phase was not able to demonstrate a significant amelioration of symptoms and drug scores for rhinitis; however, intra-group comparison of the effect of SLIT in term of cumulative yearly nasal symptoms score revealed a significant reduction in the second ($P = 0.01$) and, even more, in the third year ($P < 0.001$) of SLIT treatment compared to first year[33,34].

All these studies suggested the potential role of SLIT on dust mite pediatric allergic rhinitis, but none of them satisfied the standard quality parameters needed to draft strong evidence-based conclusions.

The first small RDBPC trial supporting the safety and the effectiveness of SLIT in house dust mite allergic rhinitis in children (aged 7-15 years) was published in 2010 by Yonekura *et al*[35]. They randomized 31 subjects and used a dust mite extract (containing 5 μg/mL of Der f 1 allergen) for 40 wk. The authors were able to find a significant reduction of symptom scores between the active group and the placebo group after 32 wk of treatment ($P < 0.05$); furthermore, whereas the placebo group reported no significant benefit at the 40th week (compared to the beginning of the study), in term of symptom scores, the active group showed a significant intra-group amelioration after SLIT treatment ($P = 0.03$). Indeed, at the end of the trial, 33% patients reported a clear improvement of symptoms, whereas placebo patients showed no more than a slight amelioration; moreover, the authors reported that half children, showing an important reduction of nasal symptom scores at the end of the treatment, had a beneficial effect persisting up to one year later. However, this study was not able to document a parallel improvement on medication score and the response to SLIT was quite variable among the patients[35].

The paper written by de Bot *et al*[36] in 2012 investigated the results of SLIT for house dust mite allergic rhinitis in a population of children recruited in primary care settings rather than in referral centers for allergy. They included 251 patients, aged from 6 to 18 years, and performed a 2 years' RDBPC trial, being the greatest RCTs so far. Unfortunately, this study found no significant improvement in allergic children treated with dust mite SLIT compared to placebo. However, the authors themselves hypothesized some probable limitations of the present study, such as the relative low cumulative dose of allergen they used to treat the patients or a lower clinical severity of symptoms presented by patients followed in a primary care setting, compared to a referral center[36].

In the same year, we can find two more studies on dust mite pediatric allergic rhinitis, which showed some points of interest, in our opinion, despite their numerical and/or design limitations. Han *et al*[37] treated with SLIT 54 youngsters (aged 6-18 years) in parallel to 22 adults, showing a similar tendency to the amelioration of symptom and medication scores in both age groups after one year of treatment[37]. Barberi *et al*[38] performed a 2 years' small case-control study, treating 30 children with dust mite respiratory allergy with symptomatic drugs alone or with SLIT and drugs on demand. They observed a significant amelioration of symptoms and of drug utilization in patients treated with SLIT, in addition to the evidence of the induction of a condition of allergenic hypo-reactivity through the measurement of serum IL-10

Table 2 Randomized double-blinded placebo controlled trials on house dust mite sublingual Immunotherapy for the treatment of allergic rhinitis in children

Ref.	Year	Mean age (yr)	No. of patients	Product	Efficacy parameters	Duration	Statistical significance	Other observation
Marcucci *et al*[33,34]	2005	4-15	24	Aqueous solution (ALK-Abello')	Symptoms score	1 yr	NS	A significant difference was recorded in the last trimester of the year; the study was carried on after the first year in open way
Tseng *et al*[31]	2008	6-18	59	Staloral (Stallergenes)	Symptoms score	6 mo	NS	In treated group a slight improvement was recorded. Specific IgG4 and IgG4/IgE significantly increased in SLIT group
Yonekura *et al*[35]	2010	7-15	31	Extract of house dust mite (Torii Pharmaceutical)	Symptom score	40 wk	$P < 0.05$	The improvement in SLIT group increased progressively according to the duration of the therapy
de Bot *et al*[36]	2012	6-18	251	Oralgen House Dust Mite (Oralgen Mijten)	Symptom score	2 yr	NS	Study population was recruited in primary care setting
Aydogan *et al*[41]	2013	5-10	22	Staloral (Stallergenes)	Medication and symptom score	12 mo	NS	-

SLIT: Sublingual Immunotherapy; NS: Not significant.

and Th2-dependent cytokines[38].

In 2013, Wang *et al*[39] obtained a significant result supporting the efficacy of SLIT in dust mite allergic rhinitis in a multicenter RDBPC trial, including 120 patients (aged 4-60 years). A similar output was previously described also by another RDBPC study (by Lee *et al*[40]), which enrolled 134 patients (aged 4-53 years), half of them were poly-allergen sensitized patients. They showed that both mono-sensitized and poly-allergic patients, recruited in allergy referral centers, can get a comparable and significant improvement of nasal symptom and medication scores, after at least 1 year of treatment with house dust mite SLIT[40]. Unfortunately, both trials included a small proportion of children and an age-specific analysis was not made.

In the same year, Aydogan *et al*[41] published a small RDBPC trial with 22 children (aged 5-10 years), but they were not able to demonstrate the superiority of SLIT to placebo after 12 mo of treatment.

However, very recently, Shao *et al*[42] published the results of a large (n = 264) randomized and placebo-controlled, but open-label trial, including children (aged 3-13 years) affected with dust mite allergic rhinitis. They were able to demonstrate a significant ($P < 0.01$) reduction of nasal symptoms and medication scores, starting from 6-7 mo of treatment. Moreover, as the study included even 133 children aged 3-5 years, they reported also that, in the SLIT group, the therapeutic response was comparable in children older and younger than 5 years[42].

SLIT FOR HOUSE DUST-MITE PEDIATRIC ALLERGIC RHINITIS: GLOBAL CLINICAL EVIDENCE

Our brief analysis showed that the clinical research, addressed to evaluate specifically the effectiveness of SLIT against house dust mite allergic rhinitis in children, is quite poor (Table 2). We were not able to find randomized double-blind placebo controlled trial showing clearly and conclusively the improvement of children affected with house dust mite allergic rhinitis through SLIT. Thus, evidences supporting the effectiveness of SLIT on dust mite rhinitis in children are largely derived from studies on adults and from trials where actually patients were affected by asthma and the nose disease represented more a co-morbidity than a primary end-point of the research[6]. Actually, the only multicenter RDBPC trial assessing the specific effect of SLIT on pediatric rhinitis was not able to show a significant clinical improvement: Maybe a six month's period of study was too short in order to achieve a positive conclusion, as actually several immunological changes, proposed as inducing tolerance in the setting of allergy, have been described in patients receiving dust mite SLIT[30].

Environmental pollutants might affect the outcome of SLIT, worsening the nasal inflammation due to house dust mite allergy. However, as regards pediatric allergic rhinitis, we found very few studies addressing this topic. Interestingly, Marogna *et al*[43] conducted a prospective study showing that the exposure to passive smoke significantly reduces the clinical response to SLIT in children affected with allergic rhinitis due to house dust mite.

However, as a final remark, it deserves to be told that the usefulness of HDM-SLIT must be sought in some indirect beneficial effects, as the prevention of asthma development, though the potential modification of the natural history of the respiratory allergic disease, and the reduction of respiratory infections too. As regards the latter aspect, allergic children are known to have more frequent and more severe respiratory infection than non-allergic controls. Indeed, the persistent mucosal inflammation in the nose of house dust mite allergic

people compromise the mechanical barrier against external infectious agents and can constitute a favorable environment for microbial proliferation; moreover, the defective production of anti-viral cytokines and the over-expression of some epithelial adhesion molecules in patients with allergic rhinitis increase the susceptibility to viral infections. Recent evidences supported that HDM-SLIT can reduce the burden of recurrent respiratory infections in allergic children and some observational studies suggested that SLIT-treated children significantly developed fewer respiratory infections compared to controls and also the use of antibiotics was reduced[44,45].

CONCLUSION

As well as the EAACI position paper on pediatric rhinitis, several reviews and meta-analysis concluded for a general efficacy and safety of AIT for pediatric rhinitis and rhino-conjunctivitis. Recently, Kim *et al*[5], trough their systematic review, inferred a moderate-strength and general evidence that SLIT improves pediatric allergic rhinitis and conjunctivitis through a reduction of symptoms and/or a decrease of drug consumption. Similarly, Pleskovic *et al*[46] concluded that SLIT is a good option for the treatment of children with grass pollen and dust-mite allergic rhino-conjunctivitis.

Similarly, our brief and practical review supports the global effectiveness of SLIT intended to treat grass pollen and house dust mite allergic rhinitis in children, but some differences must be made, in our opinion, based on current clinical evidences.

As concerns grass pollen SLIT, several RDBPC trials of good standard quality are available and almost all produced clinical data showing a positive effect of SLIT in the control of allergic symptoms and/or drug request and also in the prevention of the development of asthma.

However, the evidence of the clinical efficacy of house dust mite SLIT on pediatric allergic rhinitis is milder. Indeed, RCTs and good standard quality studies exploring this aspect are less abundant and smaller; therefore, in our opinion, more trials are needed to consolidate the recommendation for dust mite SLIT in pediatric allergic rhinitis.

These conclusions are comparable to the evidences emerging from the analysis performed recently by Larenas Linnermann *et al*[12] These authors concluded that the evidence is strong for grass pollen SLIT efficacy in the treatment of pediatric allergic rhinitis, whereas the evidence for house dust mite SLIT effectiveness is still considered "of moderate-low quality".

Finally, we think that it should be stressed the concept that SLIT for pediatric allergic rhinitis seems to be more efficacious if the prescription of SLIT derives from an experienced diagnostic pathway and if an appropriated follow-up is planned.

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MINIREVIEWS

Clinical spectrum of primary ciliary dyskinesia in childhood

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Abstract

Although the triad of bronchiectasis, sinusitis and situs inversus was first described by Kartagener in 1933, the clinical spectrum of primary ciliary dyskinesia is still under investigation. Heterotaxy defects as well as upper and lower respiratory tract symptoms are the main manifestations in childhood. It is now recognized that situs inversus is encountered in only half of patients. The first lower respiratory symptoms may be present from infancy as neonatal respiratory distress. The most common lower airway manifestations are chronic wet cough, recurrent pneumonia and therapy resistant wheezing. Patients are at risk of developing bronchiectasis which may even be the presenting finding due to delayed diagnosis. Upper respiratory tract infections such as nasal congestion, nasal drainage and recurrent sinusitis as well as otologic manifestations such as otitis media or otorrhea with conductive hearing loss are also often encountered. It seems that the type of ciliary ultrastructure defects and the involved mutated genes are associated to some extent to the clinical profile. The disease, even in nowadays, is not recognized at an early age and the primary care clinician should have knowledge of its clinical spectrum in order to select appropriately the children who need further investigation for the diagnosis of this disorder.

Key words: Primary ciliary dyskinesia; Kartagener's syndrome; Immotile cilia; Heterotaxy; Respiratory tract

Core tip: The clinical spectrum of primary ciliary dyskinesia (PCD) has been recently better understood through the evolution of electron microscopy techniques, molecular genetics and imaging of the respiratory tract. Herein, we highlight the clinical profile of the disease from infancy to adolescence, focusing on clinical studies of children with a laboratory confirmed diagnosis of PCD. Additionally, the currently recognized associations of the type of ciliary ultrastructure defects and involved mutated genes with the clinical spectrum of the disease are presented. This information is of interest for the paediatrician in order to conduct a timely investigation of children with symptoms suggestive of PCD.

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INTRODUCTION AND HISTORICAL REVIEW

Primary ciliary dyskinesia (PCD) is an autosomal recessive disorder characterized by cilia dysfunction. It is a rather rare disorder with a prevalence which ranged from 1.3 to 111 diagnosed cases per million inhabitants aged 5-14 years in different European countries[1].

A case of PCD was first reported in 1904 as an association of bronchiectasis and situs inversus by Siewert[2]. Later in 1933, Kartagener described the classic triad of bronchiectasis, sinusitis and situs inversus in a group of patients[3]. Today it is well known that situs inversus is present in only half of PCD cases and therefore it is not a necessary prerequisite for the characterization of the disease. In 1976, Afzelius[4] studied mucocilia motion in subjects with PCD who produced immotile sperm while electron microscopy indicated absence of dynein arms of cilia from the relevant cells.

The aim of this review was to describe the clinical spectrum of PCD in childhood an entity which is recently better recognized thanks to the availability of modern screening techniques and the genetic identification of this disorder. Heterotaxy defects, upper and lower respiratory tract features are the main manifestations of PCD in childhood which are herein presented. Infertility which may affect males and females with PCD in adulthood is beyond the scope of the current review.

CILIA STRUCTURE AND FUNCTION

A basic knowledge of cilia structure and related function is a prerequisite for the understanding of the clinical features of PCD. Cilia are long protuberances extending from the cell body of certain eukaryotic cells. They are categorized as motile and non-motile (sensory) cilia. Herein the structure and function of motile cilia are described as only this type of cilia is involved in the pathogenesis of PCD.

The axoneme is the core of a motile cilium. The axonemal cytoskeleton consists of a "9 + 2" arrangement of microtubules. Nine peripheral microtubules surround a central inner pair[5]. Nexin links connect the nine peripheral doublets which are connected to the central pair by radial spokes. Outer and inner dynein arms are motor proteins that are attached to the outer microtubules providing energy for ciliary movement. Each cilium is anchored to the cell by the basal body. Each ciliated epithelium cell has approximately 200 cilia which beat in a coordinated fashion and contribute through this function to the respiratory epithelial defence mechanisms.

There is also a specific type of cilia with a "9 + 0" arrangement which has nine peripheral doublets and dynein arms but lacks the central pair of microtubules[6]. Cells of the ventral node have a single motile cilium of this type per cell. The rotary pattern of the beating of the nodal cilia may confer to organ laterality during embryogenesis[7].

HETEROTAXY DEFECTS

Situs inversus totalis is encountered in approximately half of patients with PCD as it is corroborated by many studies[8-10]. Heterotaxy defects are attributed to the loss of function of nodal cilia during embryogenesis[7]. There is a case report[11] of monozygotic female twins with PCD, one with situs solitus and the other with situs inversus totalis. This observation suggests that situs inversus is a random event in the foetal development of patients with PCD. However, with the advances in genetics it has been shown that subjects with central apparatus defects and RSPH1 mutated genes do not have laterality defects which is in line with the recognition that the "9 + 0" embryologic nodal cilium does not contain radial spokes and is unaffected by central apparatus defects[12]. Boon *et al*[13] also found that situs inversus was significantly less frequent in subjects with PCD and normal ultrastructure and in those with central pair abnormalities, compared to those with dynein deficiency.

Patients with normal ultrastructure, as the researchers suggested, may represent a combined group of patients with authentic normal ultrastructure and patients with unrecognizable subtle central pair abnormalities. The latter group was not expected to have situs inversus and therefore the proportion of situs inversus occurrence in the whole group of patients with presumably normal ultrastructure would have been expected to be lower.

In addition to situs inversus, other heterotaxy defects have been encountered in patients with PCD. Situs solitus and situs inversus totalis were identified in 46% and 47.7% of patients respectively in a retrospective review of 337 patients with PCD[10], whereas 6.3% of patients had other heterotaxy defects (situs ambiguous). It is of interest that approximately half of patients with heterotaxy defects also had cardiac and/or vascular malformations, a prevalence much higher than in the general population. In another series of patients with PCD[14], situs ambiguous prevalence was nearly twice (12.1%) than that reported by Kennedy *et al*[10]. However, in accordance with Kennedy's study results[10] cardiovascular malformations were also identified in nearly half of patients with PCD and situs ambiguous.

It should be mentioned that the presence of situs inversus contributes to the earlier diagnosis of PCD as median age at diagnosis of PCD in Europe was 3.5 years for subjects with situs inversus compared with 5.8 years for those with situs totalis[1].

LOWER RESPIRATORY TRACT MANIFESTATIONS

Features in neonatal period

The first lower respiratory symptoms of PCD may be present from infancy as neonatal respiratory distress.

However, even in the presence of early symptoms the diagnosis may be delayed until late childhood[15]. Transient tachypnoea of the newborn characterized by tachypnoea starting soon after birth and resolving by the 5th day of life is a well known cause of respiratory distress in term and near term neonates[16]. It is speculated that it is associated with the delayed absorption of foetal lung fluid. It seems that ciliary motility contributes to the foetal lung fluid clearance and as a consequence fluid is not cleared rapidly in neonates with PCD and respiratory symptoms present often shortly after birth. In different series of patients with PCD, neonatal respiratory distress frequency range from 43% to 74% and this percentage may be rather an underestimation due to recall bias, which is usually anticipated in retrospective studies[8,9,17-19]. In a case control study[15], the most common diagnosis in the PCD cases with neonatal respiratory distress was neonatal pneumonia, whereas the most common diagnosis in the control subjects of that study was transient tachypnoea. Furthermore the administration of oxygen treatment was more frequent in the PCD cases as well as the length of treatment in days. The combination of situs inversus, oxygen therapy for longer than 2 d and/or lobar collapse on chest X-ray (CXR) has a sensitivity of 87% for detecting PCD, whereas the combination of oxygen therapy for longer than two days and/or lobar collapse on CXR has a sensitivity of 83% for predicting PCD. Approximately half of the PCD cases (48%) had situs inversus. The median age of diagnosis in this subgroup was 0.83 years compared with a median age of 5 years at diagnosis for the subgroup without situs inversus.

Features from infancy to adulthood

The most common clinical manifestations of lower airways involvement are chronic wet cough, recurrent pneumonia and therapy-resistant wheezing. Recurrent cough and lower respiratory tract infections were among the presenting clinical history features in more than 60% of children in a series of children with PCD from Australia[9], in 83% in another series from the United Kingdom[17], whereas all children with PCD had a clinical history of a productive cough in another study from the United States[18]. Patients with PCD are at risk of developing bronchiectasis which may even be the presenting finding due to delayed diagnosis. In the series of patients from Australia[9] bronchiectasis was the presenting history in 32% of children. A diagnosis of PCD was established as the underlying cause of bronchiectasis in 1%-17% of children with imaging evidence of non-cystic fibrosis (CF) bronchiectasis who attended paediatric chest clinics[20-23]. Although development of bronchiectasis increases with age[18], it has even been described in toddlers with PCD[24].

As is now well recognized, high resolution computed tomography (HRCT) is a highly sensitive imaging modality for diagnosing bronchiectasis[22,25]. Using this non invasive technique in children with PCD and indications of severe lung involvement, based on clinical and/or radiological parameters, bronchiectasis was found in 73% of them in a series of 26 children with PCD who also had available a HRCT[8]. Bronchiectasis were detected in all of the adults and in 56% of children with PCD in another series of patients with PCD reported by Kennedy *et al*[26]. Other findings of HRCT imaging were mucus plugging, peribronchial thickening, consolidation, ground glass opacification, air trapping, atelectasis[8,26]. The most frequently affected lobes were the right middle lobe and lingula followed by the lower lobes[8,26-28] in contrast to what is observed in CF patients[28]. Using a modified Brody composite HRCT scan scoring system, Santamaria *et al*[28] showed that the total HRCT score was significantly higher in CF patients compared to PCD patients. In that study the total HRCT scan score as well as the bronchiectasis subscore was significantly negatively related to FEV1 and FVC indices. Nevertheless spirometry was less accurate than HRCT for the evaluation of the progression of lung disease in PCD patients, as it was shown by Maglione *et al*[27]. It was of note that in that retrospective study[27], patients underwent lung function tests and HRCT at least twice and no relationship was found between the change of a total HRCT scan score and FEV1. In contrast it was observed that lung function remained stable or even improved despite the deterioration of total HRCT scan score at the second evaluation. It is also of interest that, although at both evaluations the total HRCT scan score as well as bronchiectasis subscore were significantly negatively related to FEV1 and FVC, there were patients with normal spirometry and substantial lung imaging abnormalities at the baseline HRCT. The abovementioned data suggest that spirometric indices are not accurate enough to detect patients with structural lung changes. Most recently it was shown by Boon *et al*[29] that lung clearance index (LCI) was a more sensitive functional marker of lung structural abnormalities compared with FEV1 in patients with PCD.

The microbiology of lower airways infections in PCD patients was investigated in a cohort of children and adults with PCD[18] revealing that the most common culprit was *Haemophilus influenzae* followed by *Staphylococcus aureus, non-mucoid* and *mucoid Pseudomonas aeruginosa,* and nontuberculous mycobacteria. However, in this cohort *mucoid Pseudomonas aeruginosa* was isolated mainly in subjects older than 30 years of age. In another cohort[30] of children and adolescents with PCD, *Streptococcus pneumonia* and *Moraxella catarrhalis* were also isolated, whereas *mucoid Pseudomonas aeruginosa* was recovered in 5% of children.

UPPER RESPIRATORY TRACT MANIFESTATIONS

Nasal congestion and nasal drainage typically present from the neonatal period are among the characteristic symptoms that occur in 76%-100% of children in different cohorts of patients with PCD[17,18]. Acute and/or

chronic rhinosinusitis are also common in older children and it was seen among the symptoms that were present at the time of diagnosis in 11% of children in the series described by Coren *et al*[17] and in 71% of children in the series presented by Hosie *et al*[9]. Sommer *et al*[31] found that 59% of children who attended a PCD clinic documented recurrent problems of rhinosinusitis with 32% of them having needed antibiotics more than 30 times. Frontal and/or sphenoidal aplasia or hypoplasia also seem to be common in children with PCD as Pifferi *et al*[32] disclosed these findings in 73% of children with PCD (aged 8-17 years) who underwent a computed tomography (CT) scan of paranasal sinuses. Nasal polyps were identified in about one-third of patients in the cohort of Boon *et al*[13] during the follow up when the median age of the total group was 17.7 years. In contrast Rollin *et al*[33] did not find any polyps in a group of 30 children with PCD. However, the patient age of the latter group ranged from 1-14 years, with a mean age for the Kartagener's syndrome patients being 6 years and the mean age of the PCD patients being 9 years. The differences therefore between the findings from these two studies may simply imply that nasal polyposis tends to occur in patients with PCD at an older age.

Otologic manifestations, such as chronic otitis media with effusion, recurrent acute otitis media and chronic or recurrent otorrhea with conductive hearing loss[2] are also encountered very often among children with PCD. Serous otitis media was present at the time of diagnosis in 28/55 patients in the series presented by Coren *et al*[17] while hearing loss was found in 14/55 patients in this study. Similarly recurrent otitis media was among the presenting symptoms in 49% of children with PCD in another cohort[9]. It is of note that 38% of patients with PCD were diagnosed by their ENT doctor as found by Sommer *et al*[31] but at an older age compared to patients diagnosed by other specialists.

The prevalence of otologic manifestations is even higher than the abovementioned proportions during the course of the disease. In the survey by Sommer *et al*[31] it was shown that 81% of children with PCD had a history of recurrent otitis media and as much as 38% of the patients needed more than 30 antibiotic treatments in their life. However, it seems that recurrent acute otitis media decreases with age and is not present in patients older than 18 years of age[34] while otitis media with effusion is still frequent even in subjects over 18. In the same study[34], it was shown that the occurrence of chronic otitis media increased until the age of 18 and the majority of these patients experienced otorrhea. Retraction pocket, cholesteatoma and tympanic perforation were among the otologic complications observed in this group of patients.

It should also be mentioned that the majority of patients with recurring otitis media received ventilation tubes and about one-third of them needed more than three tympanostomies according to the findings of Sommer *et al*[31] The role of tube placement in children with PCD and recurrent ear problems is controversial but it is beyond the aim of this review to present and evaluate the management options for recurrent ear problems in this population. Although data from different studies differ regarding the frequency of auditory impairment[31,34,35], it seems that its prevalence progressively decrease with age.

UPPER AND LOWER RESPIRATORY TRACT MORBIDITY AND ULTRASTRUCTURE

Recent advances in PCD genetics have allowed the investigation of the relationship between specific ciliary ultrastructure defects and disease associated mutated genes with the clinical profile and progression of PCD. It was found that children with outer dynein defects (ODA) and ODA plus inner dynein defects (IDA) do not differ significantly to children with IDA and central apparatus defect with microtubular disorganization (IDA/CA/MTD) with respect to clinical respiratory features and respiratory pathogens[30]. In another genetic study, Knowles *et al*[12] showed that subjects with PCD and biallelic mutations in RSPH1 differed from those with classic PCD and dynein arm defects, showing a lower prevalence of neonatal respiratory distress and later onset of recurrent wet cough. In accordance to this observation, FEV1 was higher in RSPH1 cases compared to those with classic PCD.

Boon *et al*[13] evaluated PCD patients with normal and abnormal ultrastructure and they did not find any difference regarding lung function parameters, imaging findings and lower respiratory tract features. The type of ciliary ultrastructure did not seem to have any association with the prevalence of upper respiratory tract manifestations in children with PCD[13,30,36].

RARE FEATURES

Hydrocephalus has been described in association with PCD in a small number of patients[37] and is attributed to the impaired beating of cilia which is necessary for cerebrospinal fluid circulation.

Recently it was recognized that a number of clinical phenotypes exist that are associated with the dysfunction of non motile cilia[6]. These diseases are known as ciliopathies. However, it is beyond the scope of this review to present all human ciliopathies.

PSYCHOSOCIAL IMPACT OF THE DISEASE

As is evident by the abovementioned features, PCD would be expected to have a significant impact on health which could possibly affect the quality of life of affected children and their families. It was found that quality of life was worse in patients who had severe disease which required more aggressive treatment[38].

It was also recently shown[39] that children with PCD had higher scores compared to the control group

regarding internalizing problems such as withdrawn, somatic complaints and anxiety/depression. Therefore the psychosocial impact of the disease should also be taken into consideration by the physicians who take care of children with PCD. However, it is beyond the scope of this review to present the treatment options[40] for children with PCD, such as regular respiratory monitoring, physiotherapy, antibiotic treatment and maybe psychological support

CONCLUSION

The clinical features of PCD are nowadays well recognized but clinical suspicion of the disease in absence of heterotaxy remains rather low, although first manifestations may be present from infancy. The primary care clinician should have knowledge of the clinical spectrum of this condition in order to select appropriately the children who need further investigation for the diagnosis of PCD.

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Cutting-edge technologies for diagnosis and monitoring of snoring in children

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Abstract

Snoring is a very common problem in children and may be an indication of obstructive sleep apnea (OSA). Appropriate diagnosis is of importance due to detrimental effects of OSA. Polysomnography is considered the gold standard for the diagnosis of OSA. However, it is impractical for several reasons and this is why other tests have been developed as alternatives to formal polysomnography (PSG) for the assessment of children with snoring. In this mini-review basic features of PSG as well as alternative tests are presented and future perspectives are provided in addition to current guideline for the diagnosis and monitoring of childhood snoring. The aim of this review is to highlight briefly currently developed technologies that seem promising for the evaluation of snoring.

Key words: Snoring; Sleep apnea; Polysomnography; Molecular markers; Microelectronics

Core tip: There are several methods allowing for the screening of obstructive sleep apnea (OSA) patients in a large scale, either in the field of molecular diagnosis or in the field of microelectronics Miniaturization technology as well as advances in wireless devices connectivity and data processing allows for more affordable, convenient and reliable recording of parameters such as oxygen saturation, actigraphy and others. In addition, advances in molecular biology allows for the detection of genetic and non-genetic biomarkers of sleep apnea. However the aforementioned markers and their combinations remain to be validated. Until then polysomnography is considered the gold standard for the diagnosis of OSA.

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INTRODUCTION

Snoring is the most commonly presented symptom

of obstructive sleep apnea (OSA) in children. The estimated prevalence for snoring is 10% to 12%, whereas the estimated prevalence of OSA is only 1% to 3%[1-3]. However, due to the detrimental effects of OSA, children who snore need medical advice and possibly polysomnography (PSG), the sleep test that is considered the gold standard for the diagnosis of OSA[4].

The American Academy of Pediatrics (AAP) clinical practice guideline on diagnosis and management of childhood obstructive sleep apnea syndrome recommends overnight PSG for the confirmation of OSA[5]. In addition to identifying the presence of OSA, PSG also helps define its severity, which can aid in perioperative planning. However, despite the AAP recommendations and documented utility of PSG, only about 10% of pediatric otolaryngologists in United States[6] and probably much less in the rest of the world, obtain a preoperative PSG before tonsillectomy for sleep disordered breathing.

There are several reasons that can explain the variability in obtaining PSG prior to tonsillectomy or for the evaluation of snoring in general. Lack of access, cost, time expended, and concern over the child's emotional distress are the main reasons that explain why other tests have been developed as alternatives to formal PSG for the assessment of children with snoring. However, their role is still controversial.

In this mini-review basic features of PSG as well as alternative tests are presented and future perspectives are provided in addition to current guideline for the diagnosis and monitoring of childhood snoring. The aim of this review is to highlight briefly currently developed technologies that seem promising for the evaluation of snoring even though they have not been proven and qualified in real field.

Polysomnography

Formal PSG requires hospitalization or one night stay in a sleep laboratory. Several parameters are recorded simultaneously (Table 1) that allow for the estimation of specific indexes, with apnea-plus-hypopnea index (AHI) being the most utilized for diagnosis and staging of obstructive sleep apnea. Nevertheless, even the use of AHI is problematic in children since the clinically valid cut-off for normal AHI is unclear in this age group and no consensus has been achieved as to whether children with AHI values between the normal cut-off [< 1/h of total sleep time (TST)] and 5/h TST should undergo adenotonsillectomy[7,8].

Portable monitoring devices

Portable monitoring devices, also referred to as out-of-center sleep testing (OCST), have evolved as an alternative to overnight, attended, in-laboratory PSG in selected patients. Advantages of portable monitoring devices (PM) include its convenience (it can be performed in the patient's home) and its lower costs. However, the major disadvantage is that for most of these devices, fewer physiologic variables are measured than with PSG, which can lead to misinterpretation of the results.

The United States Centers for Medicare and Medicaid Services have released guidelines that state that results from OCST can be used to support a prescription for positive airway pressure therapy in adults[9]. The American Academy of Sleep Medicine has also released clinical practice guidelines to guide clinicians in the use of OCST[10,11]. There are three types of PM: Type Ⅱ device, which has a minimum of 7 channels (*e.g.,* EEG, EOG, EMG, ECG-heart rate, airflow, respiratory effort, oxygen saturation). This type of device monitors sleep staging so the AHI can be calculated; Type Ⅲ device which has a minimum of 4 channels and Type Ⅳ device which usually measure only 1-2 parameters (*e.g.,* oxygen saturation); Type Ⅰ refers to polysomnography which is not actually a portable monitoring device.

At minimum, PM must record airflow, respiratory effort, and blood oxygenation[10,12], thus type IV devices are not supported officially. For example, oximetry has a high positive predictive value (97%) for diagnosis of obstructive sleep apnea, but because not all apneas result in a drop in saturations the negative predictive value is low (53%)[13]. This is because simple oximetry cannot detect: (1) events that result in arousal without desaturation; (2) how long the patient slept; (3) carbon dioxide elevation; (4) prolonged flow limitation without discrete desaturation; or (5) whether they achieved rapid eye movement sleep (the period when respiratory events are most common)[4,14].

In general, false negative rates may be as high as 17% in unattended PM studies and the role of PM, as an alternative to formal PSG, in assessing children with sleep disordered breathing is controversial[10]. Unattended PM for the diagnosis of OSA should be performed only in conjunction with a comprehensive sleep evaluation. Moreover, in-laboratory polysomnography should be performed in case the PM test is technically inadequate or does not provide the expected result[10].

Miniaturization technology as well as advances in wireless devices connectivity and data processing allows for more affordable, convenient and reliable recording of parameters such as oxygen saturation, actigraphy and others. Thus the future of portable monitoring, especially in conjugation with other tests, seems promising.

Additional tests

An extended review of PSG and related monitoring is beyond the scope of this article. Furthermore, measures derived from PSG are poor predictors of OSA-associated morbidities[15]. The aforementioned tests can be combined with a validated questionnaire (*e.g.,* health status or quality of life questionnaire). Such questionnaires have been shown recently to be of benefit for childhood obstructive sleep apnea course prognosis[16] and can be utilized in the decision making process, *e.g.,* prior to a tonsillectomy.

Other modalities that are being investigated for the diagnosis and management of sleep apnea are genetic

Table 1 Parameters most commonly recorded in a polysomnography study

Pulse oximetry
Airflow from nasal canula thermistor and/or X-flow (AASM recommends RIP technology)
Snoring
End-tidal CO_2
Esophageal pressure and other methods for monitoring respiratory effort
ECG/heart rate or heart rate variability
Arterial tonometry
Electroencephalography
EOG
Actigraphy
Body position
Chin EMG
Limb EMG
Additional channels, *e.g.*, for CPAP/BiPap levels, pH, *etc.*

AASM: American academy of sleep medicine; RIP: Routing information protocol; ECG: Electrocardiograph; EOG: Electro-oculogram; EMG: Electromyography; CPAP: Continuous positive airway pressure.

Table 2 Potential biomarkers of obstructive sleep apnea and/or its comorbidities in children

Non-genetic	Genetic
8-isoprostane	CRP 1444C/T
Adiponectin	CRP 1919A/T
APOEe4	IL-6-174C/IL-6 597A
Catecholamines	NOS1 and NOS3 16SNPs
Catestatin	EDN2 and EDN3 5 SNPs
CRP	MIF gene SNP rs10433310
IL-6	NADPH oxidase (NOX) rs6520785 and rs4673
HOMA	ApoE rs405509
MRP8/14	
TNF-α	
Urinary neurotransmitters	

CRP: C-reactive protein; NADPH: Nicotinamide adenine dinucleotide phosphate; IL: Interleukin; TNF: Tumor necrosis factor.

and non-genetic biomarkers (Table 2). As mentioned earlier, PSG results are poor predictors of OSA-related morbidities and there is the need of tests that can identify the most "vulnerable" patients, who would more likely benefit for specific therapeutic interventions[8]. Of the potentially promising morbidity biomarkers, plasma IL-6 and high sensitivity C-reactive protein appear to exhibit a favorable profile, and may discriminate OSA patients with and without morbidities in both adults and children. MRP 8/14 have been utilized as a cardiovascular morbidity-associated biomarker in children. In addition, urinary neurotransmitters may also provide a good tool for screening OSA cognitive morbidity in children[8].

The above mentioned biomarkers are non-genetic, their concentrations can be measured with various methods, *e.g.*, ELISA, chromatography and others, and depend on the course of the disease, thus they have the potential to provide information related to prognosis and response to treatment. On the contrary, gene polymorphisms (single nucleotide polymorphisms, insertion/deletion and copy number variants) show the genetic predisposition for OSA and are independent of the course of the disease. Because of the lack of genome-wide studies on the field, especially in children, there are only very few SNPs (Single Nucleotide Polymorphisms) that have been associated with obstructive sleep apnea and its comorbidities[17-19] (Table 2). Since simple SNPs or sequences cannot be patented, what is expected in the near future is that panels (or combination) of them that can be IP protected, to arise and to be validated.

Later developments in the field of chromatography and molecular biology techniques, such as multiplex PCR and sequencing, allow for the detection of various markers not only in serum but also in other samples such as saliva, urine and exhaled breath condensate. This is of special important for children, because nconvenient and painful blood tests can be avoided. Moreover, the cost of these methods has already been reduced and is almost certain that we will witness further costs reductions in the near future. Thus, methods allowing for the screening of OSA patients in a large scale already exist, either in the field of molecular diagnosis or in the field of microelectronics. These methods have the potential to provide us with affluent data. The field of sleep disorders will be revolutionized in case accurate verification of this data, probably in the form of validated and patented algorithms, is accomplished.

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Short and long term prognosis in perinatal asphyxia: An update

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Abstract

Interruption of blood flow and gas exchange to the fetus in the perinatal period, known as perinatal asphyxia, can, if significant, trigger a cascade of neuronal injury, leading on to neonatal encephalopathy (NE) and resultant long-term damage. While the majority of infants who are exposed to perinatal hypoxia-ischaemia will recover quickly and go on to have a completely normal survival, a proportion will suffer from an evolving clinical encephalopathy termed hypoxic-ischaemic encephalopathy (HIE) or NE if the diagnosis is unclear. Resultant complications of HIE/NE are wide-ranging and may affect the motor, sensory, cognitive and behavioural outcome of the child. The advent of therapeutic hypothermia as a neuroprotective treatment for those with moderate and severe encephalopathy has improved prognosis. Outcome prediction in these infants has changed, but is more important than ever, as hypothermia is a time sensitive intervention, with a very narrow therapeutic window. To identify those who will benefit from current and emerging neuroprotective therapies we must be able to establish the severity of their injury soon after birth. Currently available indicators such as blood biochemistry, clinical examination and electrophysiology are limited. Emerging biological and physiological markers have the potential to improve our ability to select those infants who will benefit most from intervention. Biomarkers identified from work in proteomics, metabolomics and transcriptomics as well as physiological markers such as heart rate variability, EEG analysis and radiological imaging when combined with neuroprotective measures have the potential to improve outcome in HIE/NE. The aim of this review is to give an overview of the literature in regards to short and long-term outcome following perinatal asphyxia, and to discuss the prediction of this outcome in the early hours after birth when intervention is most crucial; looking at both currently available tools and introducing novel markers.

Key words: Perinatal asphyxia; Neurological outcome; Hypoxic ischaemic encephalopathy; Cerebral palsy; Cognitive

outcome

Core tip: Perinatal asphyxia is a significant cause of acquired brain injury occurring in the neonatal period. A reliable early marker for predicting injury severity and sequelae remains elusive. The advent of therapeutic hypothermia as an effective neuroprotective intervention has changed the prognosis for affected infants. In this review we summarise what is known about the short and long term outcome for infants with perinatal asphyxia in the pre- and post-cooling era. We also describe currently available early indicators of outcome and introduce the exciting field of emerging novel biomarkers, both chemical and physiological.

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BACKGROUND

Perinatal asphyxia describes the interruption of blood flow or gas exchange to and from the fetus in the perinatal period[1]. This may be prolonged partial asphyxia, sudden sub-total asphyxia due to a sentinel event or a combination of both[2]. Hypoxic-ischaemic injury to the brain and vital organs may result if the perinatal asphyxia is of a sufficient degree or prolonged beyond the ability of the fetus to compensate[3-5]. Approximately 20 per 1000 deliveries will require significant resuscitation, with biochemical and clinical evidence of perinatal asphyxia[6]. Of these only 1.6 per 1000 will go on to develop signs of evolving encephalopathy consistent with hypoxic-ischaemic encephalopathy (HIE)[7]. HIE must be differentiated from other causes of neonatal encephalopathy (NE), such as sepsis, meningitis or a metabolic disorder[1,8,9]. There may be a high suspicion of hypoxic-ischaemic injury following a known perinatal insult such as placental abruption or cord accident or if typical clinical signs, biochemical evidence of metabolic acidosis or depressed Apgar scores are present. However it can be very difficult to make this differentiation quickly after birth[10]. Approximately 50%-80% of NE can be attributed to hypoxia-ischaemia and given the potential benefit of early treatment, the need to identify infants with hypoxic-ischaemic induced encephalopathy is becoming increasingly important[1,11-13].

The aim of this review is to provide an overview of the literature on short and long-term outcome following perinatal asphyxia in the pre- and post-cooling era. We also aim to discuss the ability of currently available tools and novel markers to predict outcome in the early hours after birth when intervention is most crucial.

CURRENT MARKERS FOR PREDICTION OF OUTCOME

The advent of therapeutic hypothermia as a neuroprotective treatment for those with moderate and severe encephalopathy has improved prognosis[14,15]. Hypothermia is, however, a time sensitive intervention, with a very narrow therapeutic window and must be instigated within 6 h or ideally sooner following delivery to be effective[16]. So the challenge has become the prompt identification of those infants with signs of perinatal asphyxia who are most at risk of developing moderate or severe HIE. Prompt identification of those who will benefit from current and emerging neuroprotective therapies will help guide appropriate application of resources and permit prognostication. Currently available indicators such as blood biochemistry, clinical examination and electrophysiology all have limitations and their predictive power has been affected by the interceding intervention of therapeutic hypothermia; yet they still remain at the core of our predictive armamentarium in the critical first postnatal hours (Table 1).

Acid-base balance

A disturbance in acid-base balance is one of the earliest and most sensitive signs of fetal distress. The degree of acidosis is measured by scalp or cord pH, with acidosis being used to determine the need for intervention. A pH of < 7.00 gives a 50% chance of abnormal outcome, however the positive predictive value for significant encephalopathy is low[17]. This prediction might be improved by focusing on metabolic acidosis, and in particular lactate level. However several large trials have shown that lactate monitoring during labour does not improve our ability to detect or prevent adverse labour outcomes compared to pH monitoring alone and may in fact increase rates of instrumental deliveries unnecessarily[18,19].

Apgar score

Almost all infants are scored at birth through the eyes of Virginia Apgar, with midwives worldwide using her score for describing the condition of the infant at birth. However, Apgar scores suffer from poor sensitivity and specificity, as 80% of those with an Apgar score of $\leqslant$ 7 at 5 min will have a normal outcome[17]. Often felt to be useful at extremes, 1 in 5 babies with an Apgar score of 0 at 10 min will survive to school age without moderate or severe disability[20]. A further difficulty is the subjective nature of the Apgar score, which leads to high levels of inter-observer variability. Subjective real time clinical scores have been shown to overestimate Apgar scores by a median value of 2.4 compared to later video enhanced estimation[21]. Attempts have been made to improve on the conventional Apgar score with Expanded and Combined versions that take aspects of neonatal resuscitation into account[22,23]. In particular, the Combined Apgar score at 5 min after birth has shown some promise in the prediction of perinatal acidosis

Table 1 Predictors of outcome

Predictors of outcome	Pros	Cons
Standard		
Acid-base balance	Widely available test, can be measured early by scalp and cord sampling	Cannot differentiate degree of severity of injury, invasive testing
pH	Responds early to HI	Low PPV for abnormal outcome
Lactate	Better reflects metabolic mechanism	No advantage over pH
Apgar score	Quick assessment of neonatal condition at birth, non-invasive	High inter-observer variability, poor predictor of long-term outcome
Clinical examination	Non-invasive, good to track changes in clinical state as injury evolves, predictive at discharge	Requires clinical experience, affected by intubation and medications and hypothermia, poor predictor of long-term outcome
EEG/aEEG	"Gold standard", early predictive value if normal, value of subclinical seizure detection, non-invasive	Requires resources, equipment to apply, clinical expertise to interpret
Novel		
HRV	Differentiates severity of HIE, non-invasive	Requires specialist equipment
MRI/MRS	Specific patterns of injury aid prognosis, early changes apparent	Requires specialist equipment, requires transfer of sick infant to MRI machine/department, requires infant to remain still for prolonged periods
Biomarkers	Very promising in pilot studies	None validated for clinical use
Serum	Reflects systemic biochemical state	Mixed markers from cerebral and other organ dysfunction, only small volumes available, invasive testing
Cord blood	Large volumes possible, available early	Mixture of fetal and placental blood
CSF	Reflects cerebral markers	Very difficult to sample
Urine	Relatively easy to sample	Affected if significant renal disease
Proteomics	Relatively stable and easy to test	Requires specialist equipment, response to injury may be delayed
Metabolomics	Rapidly responsive to changes in biochemical state	Requires specialist equipment, highly sensitive to environmental factors
Transcriptomics	Involved in critical processes of cell cycle and cell death, very stable	Requires specialist equipment, most markers are completely novel and difficult to identify, they may also regulate multiple pathways

The current standard tools and the novel emerging techniques to predict outcome in perinatal asphyxia are outlined with their respective advantages and disadvantages. HI: Hypoxia-ischaemia; EEG: Electroencephalograph; aEEG: Amplitude-integrated electroencephalograph; HRV: Heart rate variability; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; HIE: Hypoxic-ischaemic encephalopathy; CSF: Cerebrospinal fluid.

(sensitivity 97% and specificity 99%) and HIE (P = 0.01 if score is < 10), though it cannot distinguish severity of HIE, and long term outcome data is unavailable[24].

Clinical examination

The neurological examination of a neonate is a clinical skill learnt through experience and exposure. Standardised scores have been developed, and widely used in an attempt to improve interobserver reliability[25-27]. However, the examination of a sick neonate is hampered by the need for sedative medications, anti-convulsants and intubation. We have shown that in full term infants, the best prediction of outcome is achieved by the examination at discharge. Examination on the first day after birth, even using a standardised method is not good for the prediction of outcome at two years[28]. More recent studies have shown that therapeutic hypothermia reduces our ability to accurately estimate the neurological state of the infant[29].

Electrophysiological monitoring

Electroencephalography (EEG) and amplitude integrated EEG (aEEG) have both been shown to offer excellent predictive ability as early as 3-6 h following delivery[30]. Outcome is strongly linked with the severity of EEG abnormalities seen. EEG and aEEG abnormalities evolve over the first 72 h, and so the timing of the recording is crucial to interpretation[31]. Early return of sleep wake cycling and normalization of background EEG abnormalities are good prognostic indicators[32,33]. The link between prognostic ability and timing of this evolution is altered by therapeutic hypothermia, so that delayed recovery may still be associated with a normal outcome[34]. A normal EEG recorded soon after birth is highly associated with a normal outcome at 2 years[35]. However, an abnormal EEG soon after birth may recover over subsequent days but if it remains abnormal at 48 h a poor prognosis is highly likely[35]. The PPV of a severely abnormal aEEG for death or disability at 6 h is 0.63 when assessed by the voltage grading scheme[34] and 0.59 when the aEEG is assessed by the pattern grading scheme[30,36,37]. These values drop slightly but not significantly in cooled infants[34]. In experienced hands EEG or aEEG provide an accurate assessment of the grade of encephalopathy and are excellent adjuncts to clinical decision making.

Multichannel EEG monitoring is essential for the detection of neonatal seizures, which occur frequently in infants with moderate and severe HIE. These seizures are difficult to predict or detect clinically and are associated with poor prognosis[38-41]. aEEG alone will miss focal or low amplitude seizures and requires expert interpretation[42,43]. We hope that in the future cot-side automated seizure

detection tools will be available to improve detection, and thereby the treatment of seizures in HIE[44].

NOVEL MARKERS FOR THE PREDICTION OF OUTCOME

There is increasing interest in the possibility of developing more accurate, early and reliable markers for predicting long term outcome in HIE. These bio- and physiomarkers may take the form of physiological monitoring [EEG and heart rate variability (HRV)], neuroradiological, or biochemical. In fact the ideal marker may be a combination of many of these (Table 1).

Reduced HRV has shown potential for the assessment of HIE severity and the prediction of long term outcomes[45,46].

Radiologically improvements in magnetic resonance imaging has improved our ability to delineate patterns of injury and thereby, aid in prognosis[47]. Piglet models of phosphorous-MRS profiles within the first 2 h post-injury can predict the evolution of injury severity[48].

Blood biomarkers have also shown promise in predicting injury severity and outcome. Although no definitive blood biomarker has entered into routine clinical use, there are a number which have shown promise based on pilot work in small cohorts. Protein markers, such as UCH-L1, IL-6 and IL-16 and Activin A are altered significantly in cord bloods taken at birth from infants with HIE[49-51]. In addition GFAP and S100B have shown elevations slightly later, reaching a peak at 24 h[49,52]. Animal and, more recently, human studies have shown significant alterations in the metabolomic profile of infants with HIE[53-55]. Transcriptomics has also shown promise in differentiating infants with perinatal asphyxia and HIE[56] Some evidence is also available showing that circulating microRNAs in maternal blood may be useful for the detection of hypoxia in the intrapartum period[57]. Other bodily fluids such as urine and CSF have also been the subject of biomarker discovery work[58]. A previous meta-analysis by Ramaswamy *et al*[59] in this area reported cerebrospinal fluid neuron-specific enolase and IL-1β to be a potential markers of abnormal outcome in survivors.

This list of novel biomarkers is by no means exhaustive but gives an indication of the proactive research ongoing in this rapidly emerging field. In the future one or a combination of these markers may help to offer early, rapid and reliable identification of infants suitable for neuroprotective intervention and may also provide further insight into the complex biochemical responses of the body to hypoxic-ischaemic injury.

TREATMENT OF HYPOXIC-ICHAEMIC ENCEPHALOPATHY

Based on substantial evidence from multiple randomized controlled trials, therapeutic hypothermia is now standard of care for infants with moderate and severe HIE in the majority of neonatal units where the necessary resources are available[14,15,60-62]. Indications for treatment vary somewhat between centres but usually involve some combination of biochemical and clinical evidence of perinatal asphyxia with overt clinical manifestations of encephalopathy often based on the recruitment criteria of the larger trials of therapeutic hypothermia[60,61].

Unfortunately, using these current standard clinical markers, it is estimated that approximately 15%-20% of infants are mis-classified as having either a mild or no encephalopathy and are therefore not offered therapeutic hypothermia, worsening their long term prognosis[63].

OUTCOME IN PERINATAL ASPHYXIA

The majority of infants who require significant resuscitation at birth recover quickly and have no signs of encephalopathy. These children, in general have a normal outcome and function in line with their peers academically[64]. For this reason, at present, neuroprotective intervention has been reserved for infants with moderate or severe HIE as outlined above. However, several large population based studies now suggest that outcome in children with perinatal asphyxia without clinical encephalopathy is not completely normal. Odd *et al*[65] demonstrated an increased risk of low IQ at 8 years in this group compared to a control group. This is concerning due to the potential risk of a huge burden of more subtle disability (Table 2).

SHORT TERM OUTCOME IN HIE

For those infants who develop HIE, the most commonly used grading system remains the Sarnat score, with infants graded as mild, moderate or severe depending on their clinical signs[66]. The approximate breakdown tends to be mild (39%), moderate (39%) and severe (22%)[7]. The management and outcome varies significantly with grade of HIE.

Of those with moderate HIE, approximately one third will develop clinical and electrographic seizures in the neonatal period[39]. These seizures will usually commence between 18 and 20 h following delivery and will last for minutes to hours[67]. Following the cessation of seizures the encephalopathy may gradually improve to the point where oral feeding can recommence and care normalised. Both seizure burden and the time to achieve full oral feeding are useful in predicting the long term outcome of the infant[39,41]. The overall death rate in NE of all grades is 9.9% in developed countries but this rises acutely to 30% among those who qualify for cooling and precipitously to 76.8% when we consider severe encephalopathy alone[7,14].

LONG TERM OUTCOME IN HIE

Prior to the cooling era approximately 26.4% of infants with NE survived with moderate to severe neurodevelopmental impairment and a further 14% survived with mild impairment. Reported rates of cerebral palsy following NE vary but are generally around 10%-13% among survivors

Table 2 Outcomes in perinatal asphyxia

Short-term		
	Death	
	HIE	
	Seizures	
Long-term		
	Motor	Cerebral palsy
	Sensory	Hearing loss
		Visual impairment
	Cognitive	Episodic and working memory
		Attention
	Educational	Increased support requirements
		Lower test scores
	Behavioural	Attention
		Explosiveness
		Irritability
	Neuropsychiatric	Psychotic symptoms
	Neurodevelopmental	Autistic spectrum

A summary table of reported outcomes in perinatal asphyxia and hypoxic-ischaemic encephalopathy; HIE: Hypoxic-ischaemic encephalopathy.

of moderate to severe encephalopathy[68,69]. The risk is increased threefold where there is a history of neonatal seizures[68]. Dyskinetic CP and spastic quadriplegia are the most common subtypes with 80% of dyskinetic CP attributable to perinatal hypoxia-ischaemia at term[69]. Sensory disruption is also increased following hypoxic-ischaemic injuries. Rates of hearing loss are reported to be as high as 17.1% in those with other persistent neurological deficits[70]. Up to 41% of infants with a diagnosis of NE have an abnormality in some element of visual function in the first year of life, and where associated with moderate to severe basal ganglia changes and severe white matter changes on MRI this rises to 100%[71].

Therapeutic hypothermia has improved the outlook for infants with moderate to severe HIE, with increased likelihood of survival with normal IQ (RR = 1.31) and improved survival without neurological abnormalities (RR = 1.6) following therapeutic hypothermia at follow-up at 6-7 years of life[14].

It is important to note that learning deficits may be present with or without motor or sensory dysfunction. Impairments in episodic memory associated with reduced hippocampal volume has been found in children following perinatal hypoxic-ischaemic injury but without associated neurological deficits[72]. Robertson and Finer showed a reduction in school readiness scores as well as attention scores and increases in symptoms of explosiveness and irritability at 5.5 years in survivors of moderate encephalopathy without other disability[73]. Marlow *et al*[74] also demonstrated memory and attention/executive function impairments in the severe encephalopathy group and increased special educational needs and lower achievement on national curriculum attainment scores in both moderate and severe groups at 7 years[74]. Odd *et al*[64] have shown that infants with encephalopathy had lower working memory, reading accuracy and comprehension scores and increased requirement for educational support (OR = 6.24) between 8 and 11 years. A Swedish population based study examining the long term outcome following moderate encephalopathy has shown that in late adolescence the rates of disability are even higher, with 30% having CP, and 70% of those without CP having cognitive disability which interfered with their daily life[75].

NE has also been associated with increased behavioural difficulties. Those children with a history of moderate and severe encephalopathy have a significant increase in parent and teacher reported hyperactivity[74]. There is also a reported increase in autistic spectrum disorders in these children by 5 years (RR = 5.9)[76]. Adverse perinatal events are also associated with an increased risk of psychotic symptoms including schizophrenia[77,78].

The longer we follow these children the more evident it becomes that perinatal asphyxia and HIE have significant long term non-motor effects.

CONCLUSION

It is important to end with the note that the statistics quoted thus far have predominantly focused on high income countries, where research is most active. However, the greatest burden of disease is in low and middle income countries. Worldwide 10 million infants a year will suffer perinatal respiratory depression, of which 1.15 million will develop clinical encephalopathy. In countries with low neonatal mortality rates (NMR < 5) the incidence of NE is 1.6 per 1000 births rising to 12.1 per 1000 deliveries in countries with high NMR (> 15)[7]. It is estimated that 23% of neonatal deaths worldwide can be attributed to asphyxia which equates to nearly 1 million neonatal deaths per year; and in a countries with high neonatal mortality rates the death rate is 8 times that of countries with low NMRs[79]. Lack of modern obstetric care, inadequate neonatal resuscitation and lack of therapeutic hypothermia will cause this gap to widen. We need to strive for effective, reliable and inexpensive measures to enable early identification of infants at risk of long term injury, where low cost interventions, such as cooling, are potentially feasible and can produce significant and lifelong improvements on quality of life for these children, their parents and their communities[80].

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MINIREVIEWS

Oral medications regarding their safety and efficacy in the management of patent ductus arteriosus

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Abstract

Patent ductus arteriosus (PDA) is a common clinical condition in preterm infants which is inversely related to birth weight and gestational age. Cyclooxygenase inhibitors such as indomethacin and ibuprofen which block the prostaglandin conversion from arachidonic acid are the most commonly used drugs for ductal closure. This review focuses on the safety and efficacy oral medications in the management of PDA in preterm infants. Ibuprofen seems to be the first choice due to its higher safety profile, as it is associated with fewer gastrointestinal and renal side effects when compared to indomethacin. PDA closure rates are better with oral than with intravenous ibuprofen probably due to the pharmacokinetic of the drug. However, these medications were reported to be associated with several adverse including transient renal failure, gastrointestinal bleeding and perforation, hyperbilirubinemia and platelet dysfunction. Paracetamol seems be an alternative to PDA therapy with lower adverse events and side effects.

Key words: Efficacy; Ibuprofen; Oral; Paracetamol; Patent ductus arteriosus; Preterm infant; Safety

Core tip: Regarding to the management of patent ductus arteriosus (PDA) in preterm infants, neonatologists and cardiologists have not reached a consensus on which PDAs to treat, when to treat, and how to treat. Currently, ibuprofen seems to be the first choice due to its higher safety profile, as it is associated with fewer gastrointestinal and renal side effects when compared to indomethacin. PDA closure rates are better with oral than with intravenous ibuprofen. Recent studies suggest that paracetamol can be a medical alternative in the management of PDA with similar efficacy but lower side events than nonsteroidal anti-inflammatory drugs.

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INTRODUCTION

Patent ductus arteriosus (PDA), of which incidence is inversely related to gestational age (GA), is the most common cardiac condition among preterm infants. It is estimated to be 55% in preterm infants born before 28 wk' GA and weighing < 1000 g[1,2]. Several comorbidities are associated with a PDA, but whether PDA is responsible for their development or not is still unclear[3,4].

The treatment options for PDA closure are pharmacological and surgical. Prostaglandin-H_2 synthetase (PGHS) enzyme system, which has two active sites as cyclo-oxygenase (COX) and peroxidase (POX), produces circulating prostaglandins that regulate ductal patency[5,6]. Nonsteroidal anti-inflammatory drugs (NSAIDs), especially indomethacin and ibuprofen, are widely used for management of hemodynamically significant (hs)-PDA[7,8]. Ductal closure rate of PDA's pharmacological treatment is among 70%-85%[9-11]. COX-1 is constitutively expressed in different tissues, all NSAIDs can determine many side effects, mainly in cerebral, gastrointestinal and renal districts. In addition, there are some known contraindications such as renal failure, thrombocytopenia, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and severe hyperbilirubinemia for ibuprofen or indomethacin administration. Therefore, there is a burden for alternative therapies which may result in at least equal closure rates but with fewer side effects[12-14].

Paracetamol (acetaminophen), unlike ibuprofen, directly inhibits the activity of prostaglandin synthase by acting at the POX region of the enzyme. Paracetamol inhibition is facilitated by a decreased local concentration of hydroperoxides[15,16]. The role of paracetamol as an alternative therapy for hs-PDA closure has gained attention in recent years because of the potential adverse effects of COX inhibitors[17-19]. In our previously reported case series, we showed that intravenous (IV) paracetamol could be an alternative treatment in patients in whom feeding was contraindicated or who had feeding intolerance[19]. Our recent studies show that paracetamol in oral form can be used successfully as the primary choice in PDA closure[20,21].

The main point of this review is the safety and efficacy oral medications in management of PDA in preterm infants. One commonly used therapeutic (oral ibuprofen) and a new alternative medication as oral paracetamol are discussed.

ORAL IBUPROFEN

Ibuprofen currently appears to be the drug of choice depending on its similar efficacy but lower side effect profile in comparison to indomethacin in closing PDA. It is effective in closing PDA without reducing renal, cerebral or intestinal blood flow[22-24]. The rate of PDA closure in preterm infants varies both due to the dose regimens and the repeated courses of ibuprofen. The recommended dose regimen is 10 mg/kg loading dose followed by 5 mg/kg per day every 24 h for next two days[25,26]. A higher dose regimen as 20-10-10 mg/kg can result in a higher closure rate especially in lack of response to ordinary regimen, but must be balanced with side effect profile of the drug[26]. Individualizing the treatment by dosing COX inhibitors based on plasma concentrations has been discussed in the literature. The serum concentration after the first dose of ibuprofen was reported as the most important factor for a successful ductal closure[27].

Ibuprofen prophylaxis is also reported in various studies. Recently, Cochrane update[28] evaluated seven studies comparing prophylactic ibuprofen with placebo/no intervention. According to their results ibuprofen decreases the incidence of PDA on day three, the need for PDA treatment with NSAIDs and surgical ligation. In aspect of side effects, ibuprofen prophylaxis negatively affects renal function, increases risk of gastrointestinal bleeding but has no significant differences in mortality, IVH and bronchopulmonary dysplasia (BPD). In conclusion, this meta-analysis included two prophylaxis studies with oral ibuprofen and concludes that until long-term follow up results of these studies are published, no further trials of prophylactic ibuprofen are recommended. Similarly, we had terminated our recent study with oral ibuprofen prophylaxis according to observed serious side effects such as gastrointestinal bleeding, isolated intestinal perforation and renal failure in first days of life[29].

Aly *et al*[30] compared intravenous indomethacin and oral ibuprofen and the results of the study showed that oral ibuprofen is as effective as intravenous indomethacin. Because of preference of ibuprofen in contrast to indomethacin, new researches have focused on oral ibuprofen. A prospective- randomized study by Cherif *et al*[31] showed that ductal closure rate with oral ibuprofen was at least as effective as the intravenous route (84.3% *vs* 62.5%, $P = 0.04$) and oral ibuprofen was associated with fewer side effects. Our randomized controlled trial (RCT) demonstrated that oral ibuprofen was more successful than IV ibuprofen (84.6% *vs* 62%) in the management of PDA in very low birth weight (VLBW) infants. A higher increase in cystatin-C level, a marker of impaired renal function, with oral ibuprofen than intravenous form indicated that infants with borderline renal function should be carefully monitored[10]. In a similar designed study now in extremely low birth weight preterm infants, we demonstrated a similar initial closure rate but a higher reopening rate in infants who received ibuprofen when compared to our previous study in VLBW preterm infants[10,11]. A meta-analysis including three trials comparing oral with IV ibuprofen ($n = 236$) showed a significantly lower failure rate of PDA closure in favor of oral ibuprofen (RR = 0.42; 95%CI: 0.26-0.67); (RR =

-0.22; 95%CI: -0.35 to -0.11); NNT 5 (95%CI: 3-9) with similar rates of side effects[32]. Recent Cochrane review in 2015 concluded that oral ibuprofen was associated with a decreased risk of failure to close a PDA in comparison to IV ibuprofen[33].

Oral ibuprofen is associated with GI bleeding, NEC and spontaneous intestinal perforation (SIP)[34-36]. However, SIP was reported in both arms of intravenous and oral administration of the drug in RCTs comparing oral and intravenous ibuprofen or intravenous ibuprofen and indomethacin for PDA treatment. Additionally, the meta-analysis by Ohlsson failed to detect a statistically significant difference between oral ibuprofen and intravenous ibuprofen for all the gastrointestinal complications associated with administration of NSAIDs (GI bleeding, NEC and SIP)[37]. We suggest to use oral ibuprofen after oro-gastric feeding and flush it with 1-2 mL of distilled water to decrease its osmolarity related side effects on GIS.

Ibuprofen can compete with bilirubin for albumin binding sides and may induce bilirubin encephalopathy[38,39]. There is no definitive opinion on the effect of ibuprofen on bilirubin. *In vitro* studies suggest that ibuprofen may displace bilirubin from albumin binding sites, since it is 99% protein bound, increasing the risk of kernicterus[38]. Zecca *et al*[40] discussed the role of competition between ibuprofen and bilirubin and showed that ibuprofen use was associated with increase in total serum bilirubin levels and longer phototherapy duration.

Persistent pulmonary hypertension of the newborn (PPHN) was also observed, soon after the administration of IV ibuprofen, in the context of a randomized prophylactic trial, which was prematurely discontinued before full enrolment due to the development of this adverse effect[41]. After administration of oral ibuprofen, PPHN has not been observed in any study. Gournay *et al*[41] alerted physicians about the possibility of PPHN after the loading dose of ibuprofen, and hypothesized that PPHN could be related either to the early drug administration or to a drug-induced pulmonary microembolism.

In conclusion, ibuprofen is contraindicated in treatment of PDA in preterm infants with PDA-dependent congenital heart disease, renal failure, severe hyperbilirubinaemia, sepsis, NEC, gastrointestinal perforation, active bleeding from any site, severe thrombocytopenia and hypersensitivity to ibuprofen[42].

Oral paracetamol: A new approach to PDA treatment

Paracetamol is emerging as a possible alternative to indomethacin and ibuprofen following a chance observation made by Hammerman *et al*[17] in a baby with PDA who was given paracetamol for pain relief. The effect of paracetamol is at the peroxidase segment of prostaglandin synthase[43].

There has been increasing interest on the use of paracetamol for the treatment of PDA in the last few years. In the first case series by Hammerman *et al*[17] oral paracetamol (15 mg/kg per dose/6 h for 3 d) was effective in five patients who did not respond to ibuprofen. In our previous case series with a median GA of 28.5 wk and a median birthweight of 995 g, paracetamol was administered after a median of 9.5 d (5-27) from birth in 8 preterm infants who did not respond to 2 sequential courses of ibuprofen and/or for whom treatment with ibuprofen was contraindicated[18]. The hs-PDA closed in 7 of the infants[18]. In our other case series, we used intravenous paracetamol in 10 preterm infants with hs-PDA in whom feeding was either not tolerated or contraindicated, and the PDA closure was successful in all patients[19]. In a case series by Yurttutan *et al*[20] that was conducted to investigate the efficacy of paracetamol as the first choice for the treatment of PDA in 6 preterm infants, 5 infants were successfully treated.

Our recent prospective RCT demonstrated that the PDA closure rate was similar for ibuprofen (77.5%) and paracetamol (72.5%) after the first course of the treatment[21]. In addition, both oral medications were well-tolerated and deemed safe in terms of renal and liver variables, as well as a lack of statistically significant difference in major complications (renal tolerance, hypertransaminasemia, hyperbilirubinemia, gastrointestinal bleeding, NEC, IVH, BPD, and ROP). Similarly, Dang *et al*[44] randomized 160 babies born before 34 wk to oral ibuprofen *vs* oral paracetamol in a non-blinded trial. Overall closure rates were similar at 79% *vs* 81% respectively with less gastrointestinal bleeding and less jaundice in the paracetamol group. There was not any significant differences in other side effects.

In particular, a reduced efficacy of paracetamol was observed in uncontrolled studies for extremely preterm neonates (GA < 28 wk)[45]. This phenomenon is not surprising because in more immature neonates, the expression of prostaglandin receptors is greater in the wall of the ductus, and extremely preterm neonates have a thin-walled ductus arteriosus that fails to develop extensive neointimal mounds. Due to these structural limitations in these subjects, functional closure induced by PGHS inhibitors is less frequently followed by the structural closure of the ductus[5,46].

IV paracetamol may transiently increase liver enzymes concentration in patients[47]. Alan *et al*[48] reported 3 patients with transient increased transaminases, which they observed with IV paracetamol use. Moreover, serious acute liver toxicity events have been reported in neonates when using intravenous formulation of paracetamol[49-52]. The slow oxidative metabolism of neonates, production of toxic metabolites in their livers, and increased rate of glutathione synthesis are mechanisms that may confer protection in the context of an overdose[52-54]. N-acetylcysteine, which detoxifies the toxic metabolite N-acetyl-p-benzoquinone imine, appears to be safe in the neonate but there is no data on its use in patients treated for PDA[52,55].

Measurement of serum paracetamol concentration was performed in only two studies with PDA management.

Table 1 Summary of the studies comparing oral ibuprofen and others (IV ibuprofen/indomethacin, oral paracetamol)

Ref.	Comparison (*n*)	Gestational age (wk)	Method	Ductal closure rates		Comparison of adverse effects	Conclusion
Aly *et al*[30] (LOE 1A)	IV INDO (9) Oral IBU (12)	IV INDO: 32.9 ± 1.6 Oral IBU: 31.2 ± 2.5	Prospective, randomized, single mask	Oral IBU 83%	IV INDO 78%	Oral IBU = IV INDO	Oral IBU could be an easy to administer and efficacious alternative treatment.
Cherif *et al*[31] (LOE 1A)	IV IBU (32) Oral IBU (32)	IV IBU: 28.3 ± 1.1 Oral IBU: 29.3 ± 1.2	Prospective, randomized, single mask	Oral IBU 70.30%	IV IBU 70%	Oral IBU < IV IBU	Early ductal closure with oral IBU is as good as IV route
Gokmen *et al*[10] (LOE 1A)	IV IBU (50) Oral IBU (52)	IV IBU: 28.7 ± 2.1 Oral IBU: 28.5 ± 1.9	Prospective, randomized	Oral IBU 84.6%[1]	IV IBU 62%	IV IBU = Oral IBU	Oral IBU is more effective than IV IBU for ductal closure in VLBW infants
Erdeve *et al*[11] (LOE 1A)	IV IBU (34) Oral IBU (36)	IV IBU: 26.3 ± 1.3 Oral IBU: 26.4 ± 1.1	Prospective, randomized	Oral IBU 83.3%[1]	IV IBU 61.70%	BPD is lower with oral IBU	Oral IBU is as effective as IV IBU for PDA closure even in < 1000 g preterm infants.
Keady *et al*[42] (LOE 1B)	Oral PARA (80) Oral IBU (80)	Oral PARA: 31.2 ± 1.8 Oral IBU: 30.9 ± 2.2	Prospective, randomized	Oral PARA 81.20%	Oral IBU 78.80%	Oral PARA < Oral IBU	Oral PARA was comparable to IBU in terms of the rate of ductal closure and even showed a decreased risk of hyperbilirubinemia or gastrointestinal bleeding.
Oncel *et al*[21] (LOE 1B)	Oral PARA (40) Oral IBU (40)	Oral PARA: 27.3 ± 1.7 Oral IBU: 27.3 ± 2.1	Prospective, randomized	Oral PARA 72.50%	Oral IBU 77.50%	Oral PARA = Oral IBU	Oral PARA is as effective as oral IBU for PDA closure.

[1]Differences were statistically significant ($P < 0.05$). LOE: Levels of evidence; IBU: Ibuprofen; INDO: Indomethacin; IV: Intravenous; PARA: Paracetamol; PDA: Patent ductus arteriosus; BPD: Bronchopulmonary dysplasia; VLBW: Very low birth weight.

Table 2 Comparison of adverse effects of oral ibuprofen and paracetamol[3]

	Oral ibuprofen	Oral paracetamol
Renal side effects	+/-	-
NEC	+	-
Spontaneous intestinal perforation	+	-
Gastrointestinal system bleeding	++	-
IVH	+	-
BPD	+/-	-
Alteration of platelet function	+	-
Decrease in cerebral blood flow	-	-
Hyperbilirubinemia	+/-	-
Hypertransaminasemia	-	+

NEC: Necrotizing enterocolitis; IVH: Intraventricular hemorrhage; BPD: Bronchopulmonary dysplasia.

In particular, Oncel *et al*[19] measured serum levels of paracetamol on days 1 (7.3 mcg/mL), 2 (15.5 mcg/mL) and 3 (14.7 mcg/mL) of treatment; while in the study by Yurttutan *et al*[20] evaluated serum paracetamol only after 24 h from the first dose and values ranged from 5 to 18 mcg/mL. All these values were within the therapeutic range for children (10-30 mcg/mL)[56].

Terrin *et al*[45] evaluated 2 RCTs and 14 uncontrolled studies on paracetamol use for the management of PDA. This meta-analysis of RCTs does not demonstrate any difference in the risk of ductal closure. Proportion meta-analysis of uncontrolled studies demonstrates a pooled ductal closure rate of 49% (95%CI: 29%-69%) and 76% (95%CI: 61%-88%) after 3 and 6 d of treatment with paracetamol, respectively. Safety profiles of paracetamol and ibuprofen are similar. Meta-analysis demonstrated an efficacy of paracetamol comparable with that reported for ibuprofen. Efficacy of paracetamol seems to depend on GA and postnatal age of neonate and on modalities of drug administration[45].

The Cochrane review[57] which compared the effectiveness and safety of paracetamol *vs* ibuprofen combined two studies with 250 preterm infants in total. The success rate for paracetamol in ductal closure was similar to that of ibuprofen in addition to similar adverse events. However, infants who were treated with paracetamol had a lower risk of hyperbilirubinaemia than those treated with ibuprofen. Data on adverse effects on the developing brain from paracetamol in an experimental study and an association between prenatal paracetamol and the development of autism or autism spectrum disorder in childhood limits its wide use. Since no long term follow-up data are available for paracetamol use, it can not be recommended as the first line treatment choice.

CONCLUSION

Regarding to the management of PDA in preterm neonates, neonatologists and cardiologists have not reached a consensus on which PDAs to treat, when to treat, and how to treat. Currently, more neonates are managed conservatively, and the number of infants receiving surgical ligation is declining; however, there is a need for RCTs concerning the effect of this approach on long-term cardiovascular, pulmonary, and neurodevelopmental health.

Ibuprofen seems to be the first choice due to its

higher safety profile, as it is associated with fewer gastrointestinal and renal side effects when compared to indomethacin. PDA closure rates are better with oral than with intravenous ibuprofen. Indomethacin and ibuprofen remain the mainstays of medical management, whereas acetaminophen use is emerging as a less toxic option. Recent studies suggest that paracetamol can be an alternative in the management of PDA with similar efficacy but lower side events than NSAIDs.

The summaries of the some of the studies about oral ibuprofen and paracetamol are shown in Table 1. Considering the potential adverse effects of drugs, a careful monitoring including feeding intolerance, abdominal distension, oliguria and hypertension, and laboratory evaluation for renal and hepatic side effects in case of any need during and following day after the treatment is highly recommended. However, safety evaluation should also always consider long-term consequences of clinical and subclinical side effects. Comparison of adverse effects of oral ibuprofen and paracetamol are summarized in Table 2. Safety should be investigated especially in extreme preterm infants before routine use of paracetamol for PDA closure. We suggest that further prospective, randomized controlled trials are needed to evaluate the efficacy of oral *vs* intravenous paracetamol or intravenous paracetamol *vs* intravenous ibuprofen/indomethacin for the closure of PDA.

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MINIREVIEWS

Current views of the relationship between *Helicobacter pylori* and Henoch-Schonlein purpura in children

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Abstract

Helicobacter pylori (*H. pylori*) is one of the factors involved in the pathogenesis of various gastrointestinal diseases and may play a potential role in certain extra-intestinal diseases. *H. pylori* infection are mainly acquired during childhood, and it has been reported that in endemic areas of China the infection rates are extraordinarily higher in HSP children, particular those with abdominal manifestations. Furthermore, eradication therapy may ameliorate Henoch-Schonlein purpura (HSP) manifestations and decrease the recurrence of HSP. Therefore, results suggested that detection of *H. pylori* infection by appropriate method ought to be applied in HSP children. Current evidences indicate that local injury of gastric mucosa and immunological events induced by *H. pylori* infection are involved in the development of HSP. Increased serum IgA, cryoglobulins, C3 levels, autoimmunity, proinflammatory substances and molecular mimicry inducing immune complex and cross-reactive antibodies caused by *H. pylori* infection might play their roles in the course of HSP. However, there are no investigations confirming the causality between *H. pylori* infection and HSP, and the pathogenesis mechanism is still unclear. More bench and clinical studies need to be executed to elaborate the complex association between *H. pylori* and HSP.

Key words: *Helicobacter pylori*; Henoch-Schonlein purpura; Children

Core tip: This is the first comprehensive review to report current clinical and bench studies focusing on the potential role of Helicobacter pylori infection in Henoch-Schonlein purpura children. We also presented the possible mechanism underlying their association and the questions need to be addressed in the future studies.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative spiral, flagellated and microaerophilic bacterium colonizing human gastric mucosa as a significant factor involved in the pathogenesis of various gastrointestinal diseases. Evidences indicate that this bacteria may participate in certain extra-intestinal disease progression *via* various comprehensive mechanisms[1-3]. Recently, *H. pylori* infection or *H. pylori* induced gastritis was observed to be related to iron-deficiency anemia (IDA)[4-8], and the eradication therapy was reported to be effective in improving ferritin level or even curing IDA[4-12]. Similar relationship between idiopathic thrombocytopenic purpura (ITP), a common hematologic disease in children, and *H. pylori* infection was also revealed by amount of physician-conducted clinical studies[13-18]. In the Asia-Pacific Consensus Guidelines and European Helicobacter and Microbiota Study Group Consensus 2012, it was recommended that eradication of *H. pylori* infection was necessary in certain patients with chronic ITP[19,20]. Furthermore, IDA and ITP were considered to be the extra-intestinal diseases related to *H. pylori* infection confirmed by many clinical trials[4,6-8,21-24]. Several relatively weaker evidences indicated that *H. pylori* infection or its related immune response possibly had interferences with some other extra-intestinal diseases, like cardiovascular, neurological and endocrine disorders[25-30].

H. PYLORI INFECTION AND HENOCH-SCHONLEIN PURPURA

Henoch-Schonlein purpura (HSP) is a common disease in children. It is characterized by IgA-deposits in vessel walls and renal mesangium and defined as acute leukocytoclastic vasculitis of small vessels. Although it is known that the cause of HSP is various, infectious agents are considered as the most important etiological factors[31,32]. Besides the purpura, gastrointestinal manifestations, usually noted as abdominal colic and intra-gastrointestinal hemorrhage, are concomitant during the course of disease and associated with therapeutic strategy and prognosis.

On the other hand, the prevalence of *H. pylori* ranges from 20% to 80%, which makes its infection popular worldwide[33]. Patients get infected predominantly in childhood and persists germ-carrying status mostly through their lifetime[34]. Few infected-individuals will develop upper gastrointestinal disorder, majority of them keep asymptomatic lifelong. Thus many of these children get diagnosed only after other diseases causing intestinal manifestations.

The possible relation between *H. pylori* infection and HSP was firstly enlightened by several cases reports in adults suffering HSP and gastritis simultaneously[35-37]. The *H. pylori* infection could be detected by both ^{13}C-urea breath test. The golden standard of diagnostic relied on gastric mucosal biopsy. Reinauer *et al*[35] reported that in a HSP and chronic gastritis case with diagnosed *H. pylori* infection, the purpura, intestinal symptoms and albuminuria disappeared after eradication treatment. However, the patient was detected to be infected again while the purpura recurred 10 mo later, while the symptoms improved after elimination of *H. pylori*. Mozrzymas *et al*[38] and Mytinger *et al*[39] respectively presented the cases of children with this issue. It was also reported that in children with HSP and duodenal ulcer, purpura manifestations were ameliorated after *H. pylori* eradication was utilized.

Quantity of articles in China reported their investigations on the potential association between *H. pylori* infection and HSP[40-50]. Different from the literatures of cases from Western country, quite a lot of Chinese studies had enough sample sizes to perform cohort study, thus the results might be more reliable. Yuan *et al*[46] reported a retrospective study with the largest sample size, which included 186 HSP patients and 150 control cases. Anti-Hp IgG test was utilized as diagnostic method to detect *H. pylori* infection. Forty point nine percent (76/186) of patients in HSP group and 15.3% (23/150) of controls were confirmed to be infected. Based on the outcomes, the authors concluded that the infection was related to HSP occurrence[46]. In another research with the largest follow-up sample size, Li *et al*[43] claimed that OCA (O: Omeprazole; C: Clarithromycin; A: Amoxicillin) eradication treatment was effective in preventing HSP recurrence in those cases infected by *H. pylori* simultaneously, which were confirmed by rapid urease test (RUT).

A meta-analysis had been made to get the pooled *H. pylori* infection rate and identify the relativity between the two diseases[51]. One thousand three hundred and nine cases, including 749 HSP children and 560 healthy controls were enrolled in the pool analysis. The infection rates among the HSP children showed a wide range, which was from 22% to 75%, while those were only 3% to 44% in the healthy controls. Utilizing the data from 10 studies, the meta-analysis got a conclusion that this bacterial infection was statistically significantly associated to the increased occurrence of HSP with nearly 4 folds of risks in Chinese children (OR = 3.80, 95%CI: 2.54-5.68, $P < 0.001$). This study also claimed that the eradication therapy might play a protective role in the HSP recurrence, based on the data of 4 available studies (RR = 0.38, 95%CI: 0.25-0.58, $P < 0.001$) (Table 1).

It was interesting to see that the infection rate in HSP children reported in China varied in regions, which might be the outcome of combination of the different *H. pylori* infection prevalence and HSP incidence rate. In addition, researcher agreed that there was a geographic

Table 1 Brief view of current clinical control studies that focusing on the relationship between Henoch-Schonlein purpura and *Helicobacter pylori* infection in Chinese children

Ref.	Year	Total	Healthy control	HSP	Gastrointestinal HSP	HP in HSP children (%)	HP in control (%)	Eradication therapy
Wang *et al*[40]	2004	65	30	35	30	22.86	3.33	Yes
Zhang *et al*[41]	2004	120	60	60	-	38.33	23.33	No
Lv *et al*[42]	2005	62	28	34	11	23.53	3.57	No
Li *et al*[43]	2006	270	120	150	90	60.00	44.17	Yes
Chen *et al*[44]	2006	62	28	34	11	23.53	3.57	No
Wang *et al*[45]	2007	98	30	68	36	44.12	6.67	Yes
Yuan *et al*[46]	2007	336	150	186	118	40.86	15.34	Yes
Li *et al*[47]	2008	69	30	39	-	74.36	43.33	Yes
Li *et al*[48]	2008	102	42	60	40	58.33	28.57	Yes
Xia *et al*[49]	2008	67	30	37	37	54.05	23.33	No
Gao *et al*[50]	2009	120	40	80	51	62.50	12.50	No

HSP: Henoch-Schonlein purpura.

variation of *H. pylori* strains varies around the world[52]. Cytotoxin-associated gene A (Cag-A) positive strains was dominant among the isolated East-Asia *H. pylori*, whereas cag-A negative could be identified in up to 20% to 40% strains from Europe or Africa. Cag-A positive *H. pylori* strains from above continent showed differences in the repeating sequences numbers from each other, which resulted in variant abilities to infect the host and cause manifestations[53,54]. Similar status was observed when taking *vacA*, another important virulence of *H. pylori*, into consideration[55,56]. This might be the background of why HSP cases with concurrent *H. pylori* infection were rare in western countries (especially those developed one) but commonly encountered in East-Asia area. Thus, the current foundation of assuming the potential relation between *H. pylori* infection and HSP in Western population might not be that solid as in Eastern population.

The diagnosing method was another part that might influence the practice of exploring such possible relations. All the case reports confirmed bacterial infection with biopsy, which was the gold standard of *H. pylori* infection[35,38,39]. However, only 3 of these cohort studies above applied RUT, which was based on the tissues biopsied using endoscopy[43,45,47]. Five studies diagnosed the infection with urease breath test, the others only adopted serum anti-Hp immunoglobin (IgG mainly) test to identify the diagnosis[40,42,46,48,50]. It was known to all that IgG could be detected in the humoral immune system long after *H. pylori* infection or eradication, thus there might be several false positive cases confounded in the samples.

Another concern was the gastro-duodenoscopic manifestations of HSP. In these patients with obvious abdominal symptoms, endoscopy was considered to be a useful tool to confirm the diagnosis and exclude other surgical emergencies. It was reported that duodenum was the most common site of lesions, other sites like gastric antrum, body and angle, but never cardia or esophagus[57]. Endoscopic findings include Erythema, edema, petechiae, ulcers and other intraluminal lesions consisted of common endoscopic findings of HSP[58]. These manifestations overlapped with those of *H. pylori* infections more or less, thus bacteria detection was crucial in the treatment of certain patients.

It was unable to distinguish the *H. pylori* infection timing during the progression of HSP by using current study evidences. Intestinal manifestations may occur at any period of HSP courses, which would be the clue to detecting the *H. pylori* infection. No evidences were able to clarify whether the patients got infected before or after HSP symptoms appeared. It was reported that anti-*H. pylori* IgG level was relatively higher in HSP patients serum, comparing to that in healthy controls, while it was far from revealing the influence of bacterial infection on this autoimmune disorder[59]. Even clinic studies suggested there was strong relationship between *H. pylori* infection and HSP; researchers could not confirm that bacterial infection triggering the development of HSP. In addition, although HSP could be triggered by other infectious conditions, particular some respiratory infections, the limitation of their retrospective background made it impossible to exclude all the infectious or allergic diseases.

Moreover, there were no uniform criteria or parameters to evaluate the effectiveness of *H. pylori* eradication therapy in treating those HSP children suffering the infection. Because of their retrospective basics, the studies which indicated the effectiveness of eradication therapy in control HSP recurrence were not high quality evidences. Prospective well-designed clinical trials might eliminate the skepticism. Therefore, it was urgent to find out the appropriate diagnosing methods and indicators for detecting *H. pylori* infection. It was also necessary to establish the standard to assess the effectiveness of eradication therapy in HSP children.

BIOLOGIC MECHANISM BENEATH HSP AND *H. PYLORI* INFECTION

It is known to all that pathogenesis of HSP remained unclear. The clinical characteristics of HSP were the consequences of systemic leukocytoclastic vasculitis

with polymeric immunoglobulin A (pIgA), activated complements (C3 or C5) and certain fibrinogen/fibrin deposited in vessel walls, without IgG or IgM deposition. The immune complex between these elements in skin, gut, kidney and other organs resulted in the purpura, intestinal manifestation, nephritis and other relatively rare symptoms. Most investigators agreed that IgA1 was crucial in the progression of HSP[60-62]. Thus it could be speculated that any pathogens that were capable of initiation type Ⅲ allergic reaction with elevating serum IgA1 antibody levels and conducted systematic vasculitis might be indispensable in HSP progression.

H. pylori infection could also be diagnosed in IgA nephropathy patients, which shared several similarities with HSP. High level of serum anti-Hp IgA and disposition of pIgA in glomerular were two significant ones among the characteristics[63]. *H. pylori* infection can cause the incline of the serum levels of IgA, C3 and cryoglobulins, which is deduced to promote the immune complexes formation and increase the risk of HSP occurrence[64]. A study in adult patients revealed that, when compared to healthy controls, anti-Hp IgG levels in the acute phase of HSP and anti-Hp IgA/IgG ratios in the remitting phase were significantly higher[65]. However, there was no solid evidence of bench studies clarifying that whether the immune responses or abnormalities induced by *H. pylori* infection was associated with HSP or responsible for triggering the pathological process of the disease.

H. pylori infection resulted in bacterial invasion into gastric mucosa, which led to the direct damage to the physical barrier. Strong systemic humoral and cellular immune responses might be induced. It was assumed that such immune response might be able to coordinate the cross-talk between the infection of *H. pylori* and certain extra-gastrointestinal diseases, embracing autoimmunity, pro-inflammatory substances and molecular mimicry inducing immune complex and cross-reactive antibodies[66-69]. During the course, Ig A was secreted by the mucosa. Although this antibody was capable of inhibiting the adoption of bacterial antigen, preventing the adhesion and movement of *H. pylori*, and neutralization of toxin[63], the secretion was commonly over-activated.

H. pylori infection prognosis relied on the interaction among variant factors, such as virulence of dominant bacteria strain, host characteristics, and environmental influences. The product of vacuolating toxin gene A (*vacA*) and *cagA* were the main virulence factors of *H. pylori*. The *vacA* and *cagA* alleles, encoding the most important *H. pylori* virulence proteins *VacA* and *CagA*, contribute to the isolation of China and Western countries bacterial strains for the functional polymorphism. Based on the high toxigenicity of Chinese *H. pylori* strains and relatively low toxigenicity of strains in western countries, we hypothesize that *vacA* or *cagA* might participate in the progression of HSP through a complicate and unknown mechanism. Experimental research focusing relationship of *H. pylori* and atherosclerosis indicated that *cagA* antigen mimicry the peptides of vascular wall, which also suggested that *cagA* antibody would damage the endothelium[70]. Another study suggested that *cagA* increased the secretion of IgA1 a dose-/time-dependent manner. Furthermore, it also indicated that *cagA* could promote the underglycosylation of IgA1 in B cells[71].

H. pylori infection also conducted the massive secretion of inflammatory mediators, like interleukin (IL)-6, IL-12, IFN-γ, TNF-α, *etc*. By their complicated interaction network, these cytokines participated in the inflammatory response directly or indirectly. Cellular immune response triggered by the infection was another mechanism that might influence the course of HSP. It was reported that $CD4^+$/Treg cells proliferation was incited by *H. pylori* infected dendritic cells with the mediation of IL-1β, the secretion of which was stimulated by *vacA* and γ-glutamyl transpeptidase[72-74]. However, no significant difference in Treg cell level was identified between HSP patients and healthy controls[75,76]. In contrast, Th17 cells activation was also reported to be a functional part of *H. pylori* induced inflammation, and its concentration was demonstrated to be higher in HSP cases[77]. These results suggested that more details of cellular immune reaction beneath the fact of *H. pylori* infection needed further studies to explore.

Molecular mimicry was another approach of *H. pylori* in inducing autoimmune diseases. For example, human Lewis determinants [Le(x) and/or Le(y)] and H determinants expression could be detected in a majority of isolated *H. pylori* strains. While in some other strains, the detected components changed to Le(a), Le(b) and sialyl-Le(x)[78,79]. All the determinants were located in the O-chain of the surface lipopolysaccharide. In the preliminary researches, it was indicated *H. pylori* could evade host responses and evoke autoantibody responses to Le antigens with the help of certain molecular mimicry. Moreover, one study hypothesize that anti-Le autoreactive antibodies induced by *H. pylori* infection were involved in the progression of autoimmune disorders[80]. However, there is lack of clinical evidences could support this issue till now. The role of molecular mimicry in immune disorders, like HSP, requires further comprehensive analysis of T cells and autoantibodies functions. More functional research and clinical studies may focusing on Le antigens and other components in surface lipopolysaccharide of *H. pylori*.

CONCLUSION

Extra-gastric disorders were important aspects of *H. pylori* infection and diseases-correlated to the progression, which was proved by more and more clinical researches in children. Current studies suggested the latent relationship between the infection and HSP in children. Therefore, detecting *H. pylori* carrying status in HSP children, particular those with abdominal manifestations is indispensable in endemic areas. Diagnostic methods which are able to confirm the current infection situation are recommended to detect existence of *H. pylori* in HSP patients. However, it remained unclear how the

bacterial infection got involved in the progression of HSP. Considering the evaluation of the eradication therapy effectiveness in HSP children with *H. pylori* infection is not available, more robust evidences, such as randomized, placebo-controlled, double-blind large sized studies with appropriate diagnostic methods, would be conducted to reveal the potential association between *H. pylori* and HSP and to judge whether eradication therapy should be applied in those children.

Yet, despite some investigation suggested correlations of *H. pylori* infection with HSP in children, there remained many unanswered questions need to be addressed, which may lead to a further comprehension of *H. pylori*'s role in HSP, and to improve therapeutic and preventative strategies: (1) Latest clinic reports had significant drawbacks of sample size and study method. Large sample sized prospective clinic studies or nation-wide epidemiological studies need to be conducted to confirm the correlation or causality between *H. pylori* infection and HSP; (2) Most of current clinical studies were from Asia, particularly from China. Researchers might need to consider whether *H. pylori* strains with high toxicity differed from those with low toxicity in inducing or exacerbating HSP; (3) Further researches are also required to explore whether *H. pylori* infection is the cause of HSP or just only concurrent infection; (4) It is also necessary to know whether the existence of *H. pylori* induces those abdominal manifestations in HSP progression; (5) Long-term intensive follow-up of HSP recurrence post radical therapy is needed to identify the possible relationship between HSP infection and *H. pylori*, and to see the effect of such treatment on controlling recurrence; (6) Future studies answer that whether endoscopy can be a supplementary diagnostic tool when suspected HSP patient with significant digestive symptoms but no typical purpura; and (7) Basic mechanism of crosslink between the two diseases requests more bench studies to illuminate.

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ORIGINAL ARTICLE

Retrospective Study

Validation of a pediatric bedside tool to predict time to death after withdrawal of life support

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Abstract

AIM: To evaluate the accuracy of a tool developed to predict timing of death following withdrawal of life support in children.

METHODS: Pertinent variables for all pediatric deaths (age ⩽ 21 years) from 1/2009 to 6/2014 in our pediatric intensive care unit (PICU) were extracted through a detailed review of the medical records. As originally described, a recently developed tool that predicts timing of death in children following withdrawal of life support (dallas predictor tool [DPT]) was used to calculate individual scores for each patient. Individual scores were calculated for prediction of death within 30 min (DPT30) and within 60 min (DPT60). For various resulting DPT30 and DPT60 scores, sensitivity, specificity and area under the receiver operating characteristic curve were calculated.

RESULTS: There were 8829 PICU admissions resulting in 132 (1.5%) deaths. Death followed withdrawal of life support in 70 patients (53%). After excluding subjects with insufficient data to calculate DPT scores, 62 subjects were analyzed. Average age of patients was 5.3 years (SD: 6.9), median time to death after withdrawal of

life support was 25 min (range; 7 min to 16 h 54 min). Respiratory failure, shock and sepsis were the most common diagnoses. Thirty-seven patients (59.6%) died within 30 min of withdrawal of life support and 52 (83.8%) died within 60 min. DPT30 scores ranged from -17 to 16. A DPT30 score ⩾ -3 was most predictive of death within that time period, with sensitivity = 0.76, specificity = 0.52, AUC = 0.69 and an overall classification accuracy = 66.1%. DPT60 scores ranged from -21 to 28. A DPT60 score ⩾ -9 was most predictive of death within that time period, with sensitivity = 0.75, specificity = 0.80, AUC = 0.85 and an overall classification accuracy = 75.8%.

CONCLUSION: In this external cohort, the DPT is clinically relevant in predicting time from withdrawal of life support to death. In our patients, the DPT is more useful in predicting death within 60 min of withdrawal of life support than within 30 min. Furthermore, our analysis suggests optimal cut-off scores. Additional calibration and modifications of this important tool could help guide the intensive care team and families considering DCD.

Key words: Death; Organ donation; Children; Donation after circulatory death

Core tip: Donation after circulatory death (DCD) has gained acceptance as a way of increasing the number of organs available for transplantation. In order for DCD to occur, organs must be harvested within 30 or 60 min of withdrawal of support. A tool that predicts time of death after withdrawal of support in children has been created but not validated by an external source. In this study, we apply the newly created Dallas Predictor Tool to an external pediatric sample and show it to be an accurate predictor of death within 60 min of withdrawal of support. The tool would require additional calibration to be a good predictor of death within 30 min.

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INTRODUCTION

In the United States, the number of patients awaiting organ transplantation far exceeds the number of organs available from living or brain dead donors[1,2]. In August 2015, there were 133661 patients waiting for organ transplantation in the United States, yet there were only 29532 transplants performed during the previous year with organs from 14413 donors, highlighting the marked disparity between need and supply[3]. That disparity also exists in the pediatric age range, considering that there are currently 2036 patients younger than 18 years of age awaiting transplants, despite 1795 transplants performed in 2014[3].

In donation after circulatory death (DCD), organs are recovered from a donor that dies during controlled withdrawal of life support[4-6]. Typically, in the United States, a potential DCD donor is a terminally ill patient with a clear advance directive or a surrogate decision maker who, in conjunction with the medical team, believes that the best course of action is withdrawal of life support. Should there be agreement on the opportunity for DCD and proper consent, life support is withdrawn under controlled conditions and organs (usually kidneys and liver) can be harvested upon declaration of death by cardiopulmonary criteria following a pre-determined time interval. Although DCD has become more frequent in the past decade, still the majority of transplanted organs are recovered after donation following neurological death (DND)[3]. Various studies have shown that outcomes following DCD transplants are similar to those following DND transplants[6-8]. Therefore, increasing utilization of DCD is one mechanism to increase the availability of organs for patients on the transplant wait list and decrease waiting time[9].

Organ viability from DCD donors is predicated on a minimal interval between withdrawal of support and organ removal. If excessive time elapses between withdrawal of support and circulatory death, the donor will become ineligible. Although no evidence-based consensus on what constitutes "excessive time" exists, an organ typically is no longer considered transplantable if time from withdrawal to death is greater than 30 min for a liver and 60 min for kidneys[10]. The uncertainty of suitability of organs relative to the time of death in addition to usual end-of-life considerations may lead to undue stress on the donor's family, potential transplant recipients and medical teams. Therefore, improved ability to predict the amount of time from withdrawal of support to circulatory death could enhance the DCD process and facilitate increased donation rates.

A tool that predicts the likelihood of death within the organ recovery window has been developed and used in adult patients for several years[11]. The Wisconsin DCD Evaluation Tool predicted suitability for DCD in adults 83.7% of the time within 60 min after withdrawal of support[11]. More recently, a pediatric tool was developed through analysis of 518 deaths at Children's Medical center dallas, referred here henceforth as the dallas predictor tool (DPT)[1]. The DPT was created using data from a single institution and external validation has not been reported. Validation of this tool could help physicians determine *a priori* whether a pediatric patient might be eligible for organ donation following withdrawal of life support and help inform families considering this type of organ donation.

The objective of this study is to characterize the process of death following withdrawal of support in the pediatric intensive care unit (PICU) of an academic

Table 1 Dallas predictor tool score calculation[1]

	30 min predictor (DPT30)	60 min predictor (DPT60)
Model parameter	Point score	Point score
Age 1 mo or younger	-9	-9
Norepi, epi or phenyl > 0.2 mcg/kg per minute	11	10
ECMO	11	17
PEEP > 10 cmH_2O	5	11
Spontaneous ventilation	-8	-12
Lowest possible score	-17	-21
Highest possible score	27	38

DPT: Dallas predictor tool; Norepi: Norepinehrine; Epi: Epinephrine; Phenyl: Phenylephrine; ECMO: Extracorporeal membrane oxygenation; PEEP: Positive end-expiratory pressure.

children's hospital and evaluate the performance of the DPT in predicting time to death after withdrawal of support in this remote pediatric sample.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, we performed a detailed retrospective chart analysis of all deaths that occurred after withdrawal of support in the PICU at UH Rainbow Babies and Children's Hospital from January 1st 2009 to June 30th 2014. The inclusion criteria for this study were all patients 21 years of age or younger admitted to PICU who died after withdrawal of life support. Patients were excluded if they were older than 21 years of age, died during active resuscitation or were declared brain dead.

Patients were identified using our own PICU database. Medical records for these patients were reviewed to evaluate whether they met the inclusion criteria. Data from patients meeting the inclusion criteria were abstracted into a protected spreadsheet for subsequent analysis. Extracted data included demographic information, time of admission, time of withdrawal of support, time of death, diagnoses, co-morbidities, vital signs, support modalities (*e.g.,* mechanical ventilation, renal replacement therapies, extracorporeal life support), vasoactive and inotropic support, results from laboratory testing related to renal and hepatic function, infectious status and mechanism of death. The dataset was then used to externally validate the accuracy of the existing pediatric DCD tool (DPT)[1] for this remote sample.

We utilized the DPT to calculate scores for likelihood of death within 30 min (DPT30) and 60 min (DPT60) for each patient with clinical data obtained just prior to withdrawal of life support using the criteria specified in Table 1. The score was then used to predict the likelihood of a patient dying within 30 min or 60 min from withdrawal of life support. The predictive accuracy of the DPT tool was calculated by correlating the scores and the actual time interval between withdrawal of life support and death.

Data were treated with descriptive statistics using dedicated software (SigmaPlot, Systat Software Inc, San Jose, CA). Receiver operating characteristic (ROC) curves were created using a dedicated web-based ROC analysis calculator[11]. ROC data were used to determine the optimal cut point in the range of DPT scores for best sensitivity and specificity. This optimal cut point was then used to determine the overall classification accuracy, which we defined as the added percentage of patients correctly predicted to be dead or alive at 30 min and 60 min by using the optimal score cut point.

RESULTS

During the 66-mo study period, there were 8829 admissions to the PICU resulting in 132 deaths and a mortality rate of 1.5% (Figure 1). Death followed withdrawal of life support in 70 patients (53%). Of those, 8 patients were excluded from the data analysis for not having sufficient data for retrospective calculation of the DPT scores. Therefore, 62 patients who died following withdrawal of life support were included in the data analysis. Among the remaining 62 patients for whom support was not withdrawn, 37 deaths (28%) occurred during attempts to resuscitate (failed CPR), 16 (12%) patients met brain death criteria, and 9 (7%) deaths occurred in patients with a "do not attempt resuscitation" (DNAR) order but without active withdrawal of life support.

The mean age of patients analyzed in our sample was 5.3 years (SD: 6.9 years). The median time to death after withdrawal of life support was 25 min (range: 7 min to 16 h 54 min). Thirty-seven patients (59.6%) died within 30 min of withdrawal of life support and 52 (83.8%) died within 60 min. Common diagnoses included respiratory failure (32.2%), hypoxic-ischemic encephalopathy (19.3%), cardiorespiratory arrest (16.1%), congenital heart disease (16.1%) and shock (14.5%).

Death within 30 min after withdrawal of life support (DPT30) scores ranged from -17 to 16 (Table 2). A DPT30 score $\geqslant$ -3 was most predictive of death, with sensitivity of 0.76, specificity of 0.52, area under curve (AUC) of 0.69 and an overall classification accuracy of 66.1% (Table 2 and Figure 2). Death within 60 min after withdrawal of life support (DPT60) scores ranged from -21 to 28 (Table 3). A DPT60 score $\geqslant$ -9 was most predictive of death, with sensitivity of 0.75, specificity of 0.8, AUC of 0.847 and an overall classification accuracy of 75.8% (Table 3 and Figure 3). Organs were actually donated after circulatory arrest following withdrawal of life support (DCD) from 2 patients in our sample. The interval time to death after withdrawal of life support in those patients was 35 min and 38 min, with liver and kidneys harvested in those procedures. There was also 1 case of attempted but unsuccessful DCD, where parents consented to donation but the child died after the 60-min time limit following withdrawal of life support.

DISCUSSION

Data from the Organ Procurement and Transplant

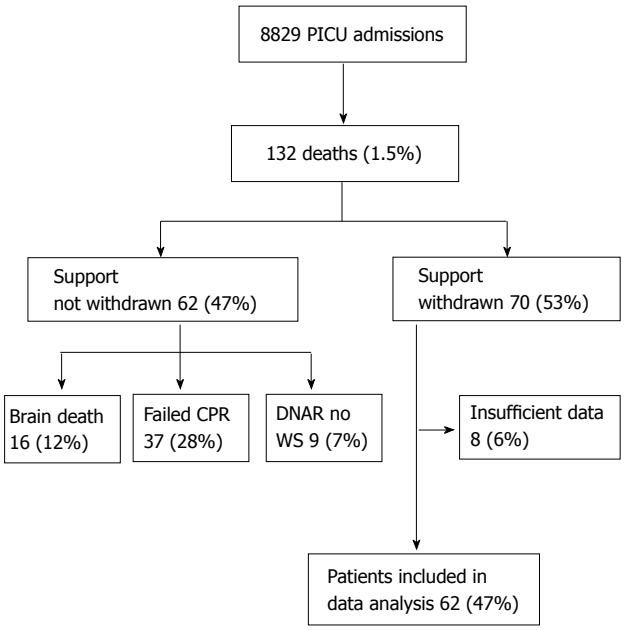

Figure 1 Pediatric intensive care unit admissions and deaths. PICU: Pediatric intensive care unit; CPR: Cardiopulmonary resuscitation; DNAR: Do not attempt resuscitation; WS: Withdrawal of support.

Network show that the number of patients awaiting an organ transplants continues to grow every year[2]. A national survey of donor hospitals identified 1330 eligible pediatric organ donors with consent rates of nearly 69%[12]. However, within that group there were only 37 pediatric DCD donors yielding 103 transplanted organs[12]. Another study evaluating the potential for DCD at a children's hospital showed that 5.5% of all patients who died in a PICU would have been potential candidates for organ donation through DCD[13]. However, that figure is higher (58%) when considering only those patients not receiving CPR or without a contraindication for donation, such as target organ dysfunction[13]. A more recent study involving children in the neonatal, cardiovascular and pediatric intensive care units found that the number of pediatric potential candidates for DCD was significantly larger than the number of potential candidates for donation after neurologic determination of death, but that the actual donation rate was significantly lower[9]. With external validation of the DPT and its increased use, it might be possible for pediatric intensivists to identify with a greater degree of certainty which patients might be eligible for DCD following withdrawal of life support and counsel the family accordingly. This tool may also help minimize the stress, frustration, and inefficient use of resources associated with donation failure by enrolling patients found to be highly likely to die within 60 min following withdrawal of life support.

The criteria used to calculate the DPT score are simple and intuitive. It is reasonable to expect that critically-ill patients who are incapable of producing spontaneous respirations, those who require significant mechanical ventilator support, high doses of vasoactive or inotropic drugs, or extracorporeal life support would have a shorter

Table 2 Scores for dallas predictor tool 30 min

Cutpoint	Dead (1)	Alive (0)	Total	Sensitivity	Specificity
-17	1	1	2	1.0000	0.00
-9	1	0	1	0.9730	0.04
-8	7	12	19	0.9459	0.04
-3	1	0	1	0.7568	0.52
0	10	7	17	0.7297	0.52
2	2	1	3	0.4595	0.8
3	1	0	1	0.4054	0.84
5	0	2	2	0.3784	0.84
7	1	0	1	0.3784	0.92
8	0	1	1	0.3514	0.92
11	7	1	8	0.3514	0.96
16	6	0	6	0.1622	1.00
Total	37	25	62		

Table 3 Scores for dallas predictor tool 60 min

Cutpoint	Dead (1)	Alive (0)	Total	Sensitivity	Specificity
-21	1	1	2	1.0000	0.0
-12	12	7	19	0.9808	0.1
-9	1	0	1	0.7500	0.8
-1	1	0	1	0.7308	0.8
0	15	2	17	0.7115	0.8
1	1	0	1	0.4231	1.0
5	1	0	1	0.4038	1.0
8	2	0	2	0.3046	1.0
10	7	0	7	0.3462	1.0
11	2	0	2	0.2115	1.0
16	1	0	1	0.1731	1.0
17	1	0	1	0.1538	1.0
19	1	0	1	0.1346	1.0
21	3	0	3	0.1154	1.0
28	3	0	3	0.0577	1.0
Total	52	10	62		

interval between withdrawal of life support and circulatory death. The original development and application of the DPT has an overall classification accuracy of 74.5% and 87.3% for death within 30 and 60 min after withdrawal of life support[1]. However, those figures were obtained by applying the DPT to the very sample used to develop it. While the DPT score has shown promise in that initial publication, it had not been validated through a remote sample until the current study.

Our data suggest that the DPT is clinically relevant in predicting time from withdrawal of life support to death. We note that the DPT60 score has higher classification accuracy than the DPT30 score and a more robust AUC. In general, the classification accuracy in our data was lower than that noted in the original Dallas study[1]. The overall classification accuracy for DPT30 at our institution was 66.1% while the accuracy in the Dallas study was 74.5%[1]. Similarly, the accuracy for DPT60 at our institution was 75.8% compared to the accuracy of 87.3% noted in the Dallas study[1]. Despite these differences, we believe that the DPT60 score can be used as an accurate predictor of death within 60 min following withdrawal of life support. Our analysis also suggests that optimal

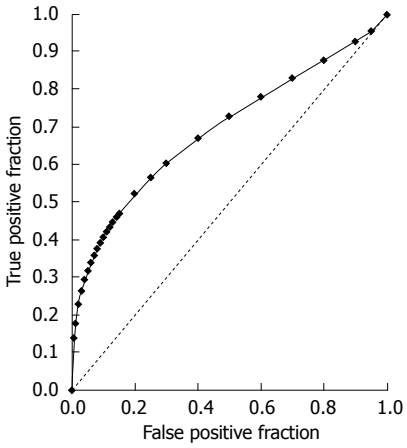

Figure 2 Receiver operating characteristic for prediction of death within 30 min of withdrawal of life support (DPT30). Area under the curve = 0.69.

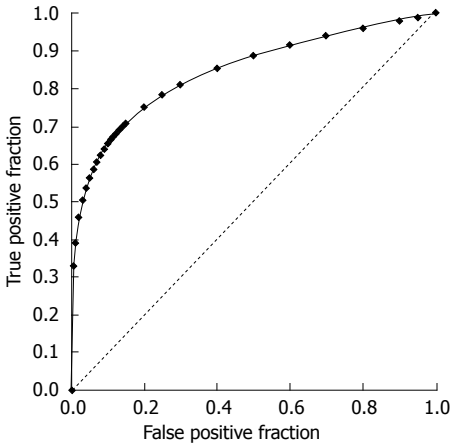

Figure 3 Receiver operating characteristic for prediction of death within 60 min of withdrawal of life support (DPT60). Area under the curve = 0.87.

cutoff scores for best accuracy vary between samples. The optimal cutoff scores of -3 and -9 for DPT30 and DPT60 for our study, respectively, differed considerably from the original Dallas study[1], underscoring the need for additional calibration and modifications of the tool so as to arrive at more widely applicable cutoff points.

In our study, there were only 3 attempts at DCD and only 2 successful donations, highlighting the fact that this form of organ donation is still the exception among pediatric patients. However, should each one of the 62 eligible patients have consented for DCD prior to withdrawal of support, 37 patients would have been eligible to donate a liver (death within 30 min) and 52 patients would have been eligible to donate kidneys (death within 60 min).

Our study is limited by factors inherent to its retrospective nature, specifically the accuracy of documentation of end-of-life events for these patients. However, clinical data and times of withdrawal of life support and death are extensively and redundantly documented at our institution, so the likelihood of this type of error is minimal. Nevertheless, a prospective study would be required to completely validate these data and test the real time prospective applicability of this tool. The sample size in our study was considerably smaller than in the original Dallas study (62 patients *vs* 518 patients, respectively). This relatively small sample could lead to sampling error and potentially impact the accuracy of the DPT score in an external cohort. However, if the DPT score is accurate it should be predictive in any cohort irrespective of the diagnostic profile and associated comorbidities of the external cohort.

In conclusion, A simple, convenient and accurate tool that predicts time to death after withdrawal of life support in children, such as the DPT would be an important adjunct to the decision-making process regarding DCD. In this external cohort, the DPT is clinically relevant in predicting time from withdrawal of life support to death. Our data show that the DPT is more useful in predicting death within 60 min than within 30 min of withdrawal of life support. The predictive accuracy of the DPT30 score is not as high and may require recalibration or incorporation of additional variables to become more clinically useful.

COMMENTS

Background

The number of patients awaiting organ transplantation far exceeds the number of organs available from living or brain dead donors in the United States. Donation after circulatory death (DCD), a form of donation where organs are recovered from a donor that dies following controlled withdrawal of life support, has been seen as an alternative to increase availability of organs and decrease waiting time. The ability to accurately predict the time interval between withdrawal of support and death is important in the DCD process because it can help inform the medical decision-makers (patient and family) and the medical team on the likelihood of death within the acceptable donation time window. This can help decrease the emotional stress associated with unsuccessful DCD on the donor family, potential organ recipient and medical teams. A pediatric tool that predicts the likelihood of death within the DCD time window has recently been develop but not yet validated externally. In this study, the authors apply this newly developed tool to a remote pediatric sample to evaluate its sensitivity, specificity and overall classification performance.

Research frontiers

Accurately predicting the time elapsed between withdrawal of support and death could have major implications in the process of DCD. This study is the first attempt to externally validate the dallas predictor tool (DPT); its results will help guide the application of this tool to remote samples.

Innovations and breakthroughs

In this study, the DPT accurately predicted death within 30 min of withdrawal of support in 66.1% of subjects, and death within 60 min of withdrawal of support in 75.8% of subjects. The authors have shown that the DPT accuracy is lower when applied to an external sample. The DPT may require recalibration or incorporation of additional variables to become more clinically useful, particularly for the 30 min time window.

Applications

This study suggests that the DPT can predict death within 60 min in over 75% of patients and can be used to inform the suitability of a potential pediatric donor being considered for DCD.

Terminology

DCD: Organ donation after circulatory death is a process by which organs are

recovered from a donor that dies during controlled withdrawal of life support. DPT: The dallas predictor tool is method that predicts the likelihood of death within 30 or 60 min of withdrawal of life support in children.

Peer-review

The manuscript is well written and covers a gap in knowledge on this topic. In this manuscript, DPT is clinically relevant in predicting time from withdrawal of life support to death. Precisely, DPT is more useful in predicting death within 60 min of withdrawal of life support than within 30 min. Additional calibration and modifications of this important tool could help guide the intensive care team and families considering DCD.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of the therapeutic evolution in the management of airway infantile hemangioma

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Abstract

AIM: To analyze the evolution in the management of airway infantile hemangioma (AIH) and to report the results from 3 pediatric tertiary care institutions.

METHODS: A retrospective study of patients with diagnosis of AIH and treated in 3 pediatric tertiary care institutions from 1996 to 2014 was performed.

RESULTS: Twenty-three patients with diagnosis of AIH were identified. Mean age at diagnosis was 6 mo (range, 1-27). Single therapy was indicated in 16 patients and 7 patients received combined therapy. Two therapeutic groups were identified: Group A included 14 patients who were treated with steroids, interferon, laser therapy and/or surgery; group B included 9 patients treated with oral propranolol. In group A, oral corticosteroids were used in 9 patients with a good response in 3 cases (no requiring other therapeutic option), the other patients required additional treatment options. Cushing syndrome was observed in 3 patients. One patient died of a fulminant sepsis. Open surgical excision and endoscopic therapy were performed in 11 patients (in 5 of them as a single treatment) with a response rate

of 54.5%. Stridor persisted in 2 cases, and one patient died during the clinical course of bronchial aspiration. In group B, oral propranolol was used in 9 patients (in 8 of them as a single treatment) with a response rate of 100%, with an mean treatment duration of 7 mo (range, 5-10); complications were not observed.

CONCLUSION: Our experience and the medical literature support the use of propranolol as a first line of treatment in AIH.

Key words: Infantile hemangioma; Propranolol; Surgery; Airway; Fibrobronchoscopy

Core tip: Through this study we want to highlight the importance of early use of propranolol in the treatment of airway infantile hemangioma. We also want to show our experience with other treatment options including corticosteroids, interferon and surgical and endoscopic treatments used before the propranolol era.

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INTRODUCTION

Even though infantile hemangiomas (IH) are the most common head and neck tumors during childhood, the airway is uncommon location, accounting for only 1.5% of all pediatric laryngeal lesions[1]. Symptoms at presentation of infantile hemangioma (AIH) are related to the grade of airway obstruction, which becomes more evident during periods of agitation, crying, or respiratory infections. Stridor, usually biphasic but more prominent during inspiration, is the most common presentation symptom. Diagnosis is performed by bronchoscopy image which typically reveals a unilateral, soft, submucous and reddish mass[2]. IHs are usually not present at birth; they proliferate during the first year of life, and then they involute. For AIH, the treatment goal is to provide an airway adapted for the development of these children. Multiple modalities, both medical and surgical, have been used for its treatment including external irradiation[3], tracheostomy[4], surgical resection[5], systemic or intralesional corticosteroids[6,7], laser vaporization[8] and interferon[9], but many have significant risks and complications. Until recently, the most common medical therapy for AIH was high-dose systemic corticosteroids, but this often results in significant well-known adverse effects including hypertension, irritability, and cushingoid appearance[10]. The introduction of propranolol by Leaute-Labreze in 2008 for the treatment of IH has revolutionized its management. Potential modes of actions for propranolol include vasoconstriction, a down-regulation of angiogenetic factors like vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and an up-regulation of apoptosis of capillary endothelial cells[11]. Our aim was to analyze the evolution in the management of AIH and to report the results from 3 pediatric tertiary care centers.

MATERIALS AND METHODS

A retrospective study of all patients with diagnosis of AIH treated in 3 pediatric tertiary care institutions during a period of 18 years (1996-2014) was performed. Variables analyzed included gender, age at diagnosis, symptoms at presentation, lesion location, grade of airway obstruction (according to Cotton classification), treatment, complications and survival. In all the patients, diagnosis was obtained by endoscopic direct visualization of the lesion using a flexible fibrobronchoscope. Assessment of airway compromise was performed according to Cotton classification which divides airway obstruction into four categories[2] (grade Ⅰ: Lesions have less than 50% obstruction, grade Ⅱ: Lesions have 51% to 70% obstruction, grade Ⅲ: Lesions have 71% to 99% obstruction and grade Ⅳ: Lesions have no detectable lumen or complete stenosis). Treatment option depended on symptoms at presentation, grade of respiratory impairment and time at diagnosis. Retrospective analysis divided patients into 2 groups according to the treatment received. Group A: Patients treated with oral corticosteroids (methylprednisolone at 2 mg/kg per day or dexamethasone at 0.5 mg/kg per day), interferon (1-3 $\times$ 10^6 U/m^2, 3 times a week), endoscopic laser therapy (Diode laser) and/or surgery (open surgical excision through an anterior midline cricothyroidotomy, resection of the hemangioma and laryngotracheoplasty with costal cartilage graft if required). Group B: patients treated with oral propranolol, at a maximum dose was 2 mg/kg per day, divided in 2 doses. Prior to propranolol treatment initiation, an electrocardiogram, blood pressure and heart rate monitoring and serum glucose level were performed in all the patients. The response to each treatment was evaluated in all patients according to the clinical course and fibrobronchoscopic exam.

RESULTS

From 1996 to 2014, twenty-three patients with diagnosis of AIH were treated in 3 pediatric tertiary care hospitals (Table 1). There were 16 females and 7 males with a mean age at diagnosis of 6 mo (range, 1-27). All the patients were referred to our hospitals due to stridor and respiratory distress. Of the 23 patients, 14 were between the age range of 1-3 mo with impossibility for extubation. The remaining older patients, had sequelae from AIH as stridor and dyspnea by airway obstruction.

Table 1 Patient characteristics

	Age (mo)	Gender	Symptoms at diagnosis	Lesion location	Degree of SGE (Cotton scale)	Treatment	Outcomes
1	2	F	Stridor	Subglottic	Ⅱ	Corticosteroids	Asymptomatic
2	3	F	Stridor	Glottis and subglottic		Interferon, corticosteroids	Asymptomatic
3	1	M	Stridor	Subglottic	Ⅱ	Corticosteroids	Asymptomatic
4	1	F	Stridor	Subglottis and trachea	Ⅰ	Resection and cricothyroidotomy	Asymptomatic
5	1	M	Stridor, dyspnea	Supraglottis and subglottis	Ⅲ	Laryngotracheoplasty	Dysphonia
6	14	M	Stridor, dyspnea	Subglottic	Ⅲ	Corticosteroids, laser, resection and cricothyroidotomy	Asymptomatic
7	27	F	Stridor	Subglottic	Ⅱ	Laser, laryngotracheoplasty	Exitus
8	2	F	Stridor, dyspnea	Subglottic	Ⅲ	Laryngotracheoplasty	Dysphonia
9	4	F	stridor, dyspnea	Subglottic	Ⅲ	Corticosteroids, laryngotracheoplasty	Dysphonia
10	3	F	Stridor, dyspnea	Subglottic	Ⅲ	Laryngotracheoplasty	Transitory stridor
11	5	F	Stridor, dyspnea	Subglottic	Ⅲ	Laryngotracheoplasty	Asymptomatic
12	16	M	Stridor, dyspnea	Glottis and subglottic	Ⅰ	Corticosteroids	Asymptomatic
13	5	F	Stridor, dyspnea	Subglottic	Ⅲ	Corticosteroids, resection and cricothyroidotomy	Transitory stridor
14	3	F	Stridor	Subglottis and trachea	Ⅰ	Corticosteroids, laryngotracheoplasty	Asymptomatic
14	19	M	Stridor	Subglottic	Ⅰ	Propranolol	Exitus
16	5	F	Stridor	Supraglottis	-	Propranolol	Asymptomatic
17	26	M	Stridor	Subglottic	Ⅰ	Propranolol	Asymptomatic
18	5	F	Stridor, dyspnea	Subglottic	Ⅲ	Corticosteroids, propranolol	Asymptomatic
19	3	F	Stridor	Subglottic	Ⅱ	Propranolol	Asymptomatic
20	3	M	Stridor	Subglottic	Ⅰ	Propranolol	Asymptomatic
21	2	F	Stridor	Subglottic	Ⅰ	Propranolol	Asymptomatic
22	2	F	Stridor	Subglottic	Ⅰ	Propranolol	Asymptomatic
23	3	F	Stridor	Subglottic	Ⅰ	Propranolol	Asymptomatic

F: Female; M: Male; SGE: Subglottic stenosis.

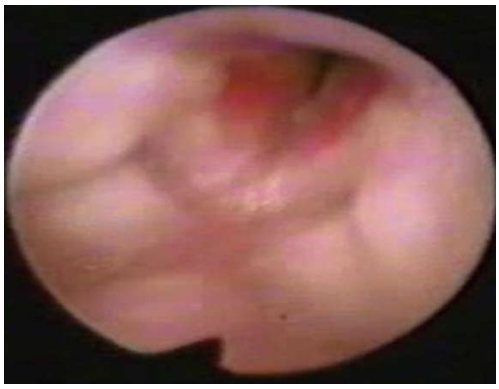

Figure 1 Fibrobronchoscopic view of a supraglottic infantile hemangioma.

Flexible fibrobronchoscope showed airway diameters ranging from 2.8 to 3.6 mm. Lesions showed a unique location in 18 patients (17 in subglottis and 1 in supraglottis). Five patients presented at joint location (1 in supraglottis and subglottis, 2 in glottis and subglottis and 2 in subglottis and trachea). Reduction of the cross-sectional area of the airway at the subglottic region prior to treatment initiation was observed in 22 patients: Grade Ⅰ of Cotton classification in 10 patients, grade Ⅱ in 4 patients and grade Ⅲ in 8 patients. The patient with the supraglottis lesion did not have reduction of the cross-sectional area of the airway (Figure 1). Six patients had an associated facial hemangioma and 2 of them were diagnosed with PHACES syndrome (Figure 2).

Single therapy was indicated in 16 patients, whereas 7 non-responder patients received combined therapy. In group A (n = 14), 4 patients had subglottic stenosis grade Ⅰ, 3 grade Ⅱ and 7 grade Ⅲ. In 8 patients single therapy was indicated, 3 of them received exclusive oral corticosteroids (methylprednisolone at 2 mg/kg per day or dexamethasone at 0.5 mg/kg per day) for a mean time of 8 wk (range, 4-24) with complete response and without complications. Five patients underwent surgery exclusively. Four patients were treated with laryngotracheoplasty with graft and one with resection and cricothyroidotomy. Mean time of intubation after surgery was 7 d (range, 4-11 d) with need for reintubation in 1 case secondary to an increase of respiratory distress.

Complete response was observed in 40% of the patients. Stridor persisted in 1 patient and dysphonia was observed in 2 cases. Complications included one pneumothorax after reintubation and 1 infection of surgical wound. The other 6 patients in this group A, received combined therapy with corticosteroids, interferon (in one patient at a dose of 1×10^6 U/m^2, gradually increased to 3×10^6 U/m^2, 3 times a week) and open surgery/laser due to a poor response to single therapy (three patients were treated with laryngotracheoplasty and graft, three patients with resection and cricothyroidotomy and 2 patients initially were treated with endoscopic therapy by Diodo laser, that were subsequently treated with surgical resection). Complications in this group included Cushing

Table 2 Patient evolutions after treatment *n* (%)

Evolution after treatment	Group A *n* = 14					Group B Oral propranolol *n* = 9	
	Oral corticosteroids		INF	Open surgical resection and endoscopic therapy			
	Single treatment *n* = 3	Combined treatment *n* = 6	Combined treatment *n* = 1[1]	Single treatment *n* = 5	Combined treatment *n* = 6	Single treatment *n* = 8	Combined treatment *n* = 1
Asymptomatic	3 (100)	0 (0)	0 (0)	2 (40)	4 (66.6)	8 (100)	1 (100)
Symptomatic	0 (0)	6 (100)	1(100)	3 (60)	2 (33.3)	0 (0)	0 (0)
Dysphonia	0 (0)	0 (0)	0 (0)	2 (40)	1 (16.6)	0 (0)	0 (0)
Stridor	0 (0)	5 (83.3)	1 (100)	1 (20)	1 (16.6)	0 (0)	0 (0)
Complications	0 (0)	3 (50)	0 (0)	1 (20)	1 (16.6)	0 (0)	0 (0)
Exitus	0 (0)	1 (16.6)	0 (0)	0 (0)	1 (16.6)	1 (12.5)[2]	0 (0)

[1]Only one patient was treated with interferon, but the same patient was also treated with corticosteroids and surgery, which is included in the 6 patients with combined treatment; [2]Not related to propranolol therapy. INF: Interferon.

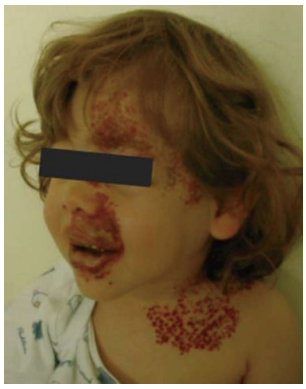

Figure 2 PHACES syndrome in a patient with airway infantile hemangioma.

syndrome in 3 cases that required other therapeutic alternatives for poor response to steroids. Dysphonia was observed in 2 cases after surgical treatment, and in 2 cases reintubation was necessary secondary to increased respiratory distress.

Response rate after surgery in patients with combined therapy was 66.6%. One patient died of a fulminant sepsis and other patient died during the clinical course of bronchial aspiration (Table 2).

In group B (*n* = 9) patients were treated with propranolol at a maximum dose of 2 mg/kg per day, divided in 2 doses. Six patients presented with subglottic stenosis grade Ⅰ, 1 grade Ⅱ and 1 grade Ⅲ; the lesion was localized in the supraglottis in 1 patient. In 8 patients, propranolol was used as monotherapy. One patient had previously received corticosteroids and endoscopic therapy with Diodo laser, without response. Response rate after propranolol therapy was 100%. Mean duration of treatment was 7 mo (range, 5-10), and complications were not observed. One patient died secondary to a congenital hypertrophic cardiomyopathy, not related to treatment with propranolol (Table 2).

DISCUSSION

AIH is a challenging entity that usually presents with inspiratory and expiratory stridor at 3 or 4 wk after birth which becomes more evident during periods of agitation, crying, or respiratory infections. This delayed presentation after birth is secondary to the natural course of IH with a progressive growth during the early proliferative phase[12-14]. Most authors agree that IH shows a rapid growth until 6-12 mo of age followed by involution after 18 or more months[15]. Up to 50% of these patients have cutaneous IH[16], with a typical beard-area distribution and whose presence may guide to the clinical diagnosis of AIH in patients with respiratory symptoms (Figure 3). Some authors have described association of AIH with PHACES syndrome[17]. In our series, 6 (26%) of the patients had an associated facial hemangioma and 2 of them had a PHACES syndrome.

Management and treatment guidelines for the treatment of AIH are not well established and different treatment options have been reported[12,15,17]. There seems to be a consensus regarding tracheostomy as a therapeutic approach that currently seems to be abandoned by virtually all authors[18]. Systemic corticosteroids can be effective in halting further growth of AIH during the proliferative phase, with success rates ranging from 60% to 90%[19,20]. However, efficacy rates may be lower in large, function-threatening AIH, and adverse effects may be intolerable (Cushing syndrome, growth retardation, hypertension, and immunodeficiency), reported in 12.9% of the cases and verified in our experience[21-23]. Interferon was widely heralded for treatment in refractory AIH, but it has a significant risk of neurotoxic effects (spastic diplegia), especially in very young infants under 6 mo of age[24]. In our series, interferon was only used in a patient, without complications, but with poor response.

Open surgical resection, first described by Sharp in 1945[25], showed a success rate of 98%. Bitar *et al*[23] operated on 50 patients with AIH who required a mean intubation or stenting period of 9 d, and carried a 10% complication rate, including subglottic stenosis, bleeding, and wound infections. Although in our experience we observed a global response rate in surgical patients of 54.5% (patients treated with single and combined therapy), we believe this therapeutic option is too invasive in the propranolol era. However, a role for

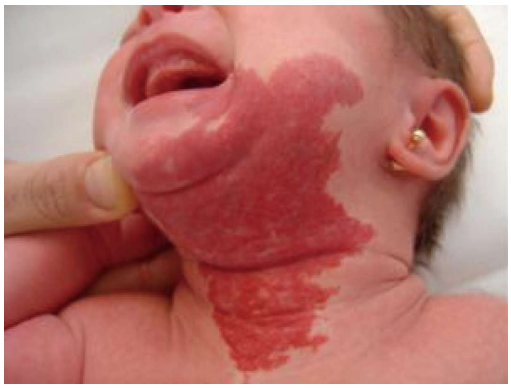

Figure 3 Infantile hemangioma in a beard-area distribution in a patient with airway infantile hemangioma.

surgical resection in combination with propranolol may exist for early emergency cases in which waiting for medical treatment response is not an option. Complications associated with AIH surgery include dysphonia (observed in 3 of our patients who underwent laryngotracheoplasty with graft). Open surgical resection should be considered only for selected cases, after failure of other treatments.

The CO_2 laser was considered as the initial treatment of choice although it is not very specific for the treatment of these lesions and it has a limited effectiveness in coagulation of the hemangioma. Published series observed up to 20% of residual subglottic stenosis in patients treated with this technique. The neodymium laser (Laser Nd:YAG) is considered an useful laser coagulator although large lesions may cause damage to the surrounding tissues and probably increase the risk of subglottic stenosis[17,24]. Other authors prefer the potassium-titanyl-phosphate laser (KTP), arguing that it is absorbed mainly by hemoglobin, making it ideal for treating vascular lesions[26]. Saetti *et al*[20] carried out a retrospective medical records review of all patients treated for congenital subglottic hemangiomas, and they observed a success rate of 95% in patients treated with diode laser as primary treatment, with a complication rate of 9%. In our experience, the 2 patients treated with laser therapy required additional surgery for persistent symptoms.

Peridis *et al*[27] performed a meta-analysis, on the effectiveness of propranolol for the treatment of AIH in 36 patients. In a retrospective manner, they analyzed the effectiveness of propranolol *vs* steroids, CO_2 laser or vincristine in predominantly case reports with relatively small sample sizes in each treatment group. It could be demonstrated that propranolol is the most effective treatment as compared to former treatments. In our series, we observed a response rate of 100% for patients treated with oral propranolol. No adverse reactions were documented. Lou *et al*[28], carried out a meta-analysis including 35 studies to identify studies which estimated the efficacy of propranolol therapy in infants with hemangiomas of all sites of the body. They evaluated the efficacy of propranolol *vs* other treatments. Sixteen studies with 45 IH cases and 45 controls compared the efficacy of propranolol with other treatment modalities in treating AIH. Heterogeneity was absent (Q = 5.00, I^2 = 0.0%, P = 0.986). They observed that propranolol therapy is more effective in treating AIH (OR = 20.91, 95%CI: 7.81-55.96, P < 0.001). Potential risks associated with propranolol include bradycardia, hypotension, and hypoglycemia[29,30]. To reduce the rate of adverse reactions, Bajaj *et al*[17], gave some recommendations for the use of propranolol in infantile isolated subglottic hemangioma prior to treatment that included a detailed history and clinical examination, inspection of the whole body for hemangiomas, as well as cardiovascular and respiratory assessment. Pre-treatment tests should include electrocardiogram, heart rate and blood pressure monitoring.

Not only the effectiveness of propranolol in the management of AIH is important, but also its efficiency in terms of cost when it is compared to other therapeutic options which involve more use of hospital resources in these complex cases. Further cost-effectiveness studies are required to better define the exact cost of treating patients with AIH. The optimal duration of propranolol treatment is unknown, but it is currently accepted that the patients should remain on propranolol until the hemangioma enters the phase of involution, which usually occurs after the first year of life. Vlastarakos *et al*[31] performed a meta-analysis that included 17 studies with 61 patients treated with propranolol, observing a rate of relapse of 11.5% after withdrawal of propranolol. This was not observed in our patients cohort.

Though our retrospective study has several limitations that should be considered in the interpretation of our findings, including the small number of patients in the study cohort and the referral bias inherent in our status as referral centers for pediatric airway disorders, we consider propranolol is currently the first line treatment for symptomatic AIH, considering its efficacy and relatively mild side effects. The two cohorts, pre-propranolol group and propranolol group, were not randomized and other reasons beside propranolol might have contributed to the better outcome of the propranolol group. Pre-propranolol group contained more patients with advanced disease compared to propranolol group (Cotton grade Ⅱ and Ⅲ, 71% *vs* 22%). This could be explained by the fact that patients with more advanced disease may have a delayed referral to institutions with pediatric airway expertise. Early initiation of oral propranolol might avoid this advanced stage.

In conclusion, the management of AIH has evolved from surgical resection and systemic steroids to oral propranolol in the last 7 years. Bronchoscopy plays an important role in the diagnosis and evaluation of treatment response. Our experience as referral centers for pediatric airway disorders and the medical literature support the early use of propranolol as a first line of treatment in AIH due to its benefits in terms of effectiveness and efficiency. Surgical and/or endoscopic approach represent a second line therapeutic option for

non-responder patients to propranolol. Management of children with AIH should be performed in pediatric institutions with expertise in both, vascular anomalies and airway disorders.

COMMENTS

Background

The management of airway infantile hemangioma has evolved from surgical resection and systemic steroids to oral propranolol in the last 7 years. The authors present an experience as referral centers for pediatric airway disorders, which is in accordance with the most recent published medical literature regarding the use of propranolol as a first line of treatment in airway infantile hemangioma.

Research frontiers

Further research studies should be performed in order to investigate the role of other betablocker agents in the treatment of airway infantile hemangioma.

Innovations and breakthroughs

The authors' status as referral centers for pediatric airway disorders and vascular anomalies has permitted us to obtain a greater experience in the management of these challenging patients.

Applications

Since the introduction of propranolol in 2008 for the treatment of infantile hemangioma, this agent has become first line treatment for lesions located in the airway. Historically, this has been a challenging site for the occurrence of infantile hemangioma, but propranolol treatment has dramatically changed the prognosis of these young patients. The study analyzes the evolution in the management of airway infantile hemangioma.

Terminology

Infantile hemangioma is the most common vascular tumor in children that has a rapid growth phase (1-3 mo of age), followed by a slow growth phase (3-12 mo of age) and involution (1-10 years of age).

Peer-review

In the paper, the authors present a nice and conclusive overview on the clinical presentation and the treatment of airway infant hemangiomas, highlighting the revolutionary advance achieved by the introduction of propranolol in hemangioma treatment. The paper is well written, with good language, its content is conclusive and it is very important to distribute the beneficial experiences with propranolol.

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ORIGINAL ARTICLE

Retrospective Study

Expression of pain and distress in children during dental extractions through drawings as a projective measure: A clinical study

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Abstract

AIM: To evaluate the efficacy of drawings as a projective measure of pain and distress in children undergoing dental extractions.

METHODS: Children in the age range of 4-13 years with existence of untreatable caries or over-retained primary teeth, indicated for extractions were included. Pain was assessed using one behavioral, faces, legs, activity, cry and consolability (FLACC) scale; and a self report measure; faces pain scale-revised (FPS-R), at two points of time, after completion of local anesthetic administration and after extraction. The general behavior of children was assessed with Wright's modification of Frankl rating scale. At the end of the session, children were instructed to represent, themselves along with the dentist and their experiences of the dental treatment through drawing. The drawings were scored utilizing Child drawing: Hospital scale (CD: H) manual and correlated with FLACC, FPS-R and Frankl using Pearson correlation test.

RESULTS: A positive correlation, though statistically not significant, was observed between CD: H scores and all other considered parameters (Frankl, FPS-R and FLACC) in the present study.

CONCLUSION: Drawings could not act as surrogate measure of child's pain; however, they acted as a narrative of his/her experiences and reflection of inner

emotions. Hence, drawings can be used as an additional dental armamentarium.

Key words: Anxiety; Child; Distress; Drawings; Pain

Core tip: Assessing the effect of an invasive dental treatment, like extractions, on children is very important. To achieve this, drawings can be addressed as a method for working with children. They act as narrative of children's painful experience and emotions.

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INTRODUCTION

Pain is an unpleasant combination of sensations and emotions, which is difficult to describe. As the threshold for the pain varies from person to person, only the person experiencing the pain can explain its intensity and nature. Child's pain is complex and varies with his/her cognitive, emotional and social experience[1,2], necessitating an accurate assessment. Dentistry involves numerous procedures, which may be perceived as painful by a child; local anesthetic administrations and extractions being the most painful of all, which can cause psychological distress[3,4]. Hence, a multilevel approach of assessing the procedural pain in dentistry is essential, as neglecting their experience can lead to development of anxiety in the child, which becomes a major barrier in accepting dental treatment during their future visits[5]. Thus, correct appraisal of pain helps in understanding their interest in seeking treatment in the future, assessing their behavior in succeeding visits as well as customizing the guidance for the child.

Procedural pain can be assessed using behavioral [faces, legs, activity, cry, consolability scale (FLACC)/sound, eye, motor scale][6,7], self report measures [facial pain scale-revised (FPS-R)/pain thermometer/visual analogue scale/colour analogue scale/finger span test][8-12] and/or a combination of these approaches. However, depending on the child's age and development, the ability of these measures to quantify and qualify the pain experience of a child varies[13]. Thus, communication with the child, in verbal/non-verbal/compounded means, plays a vital role in evaluating their pain. However, children may or may not have the ability and/or vocabulary to express their feelings, fears and concerns verbally[14]. Most of the children disguise the inner fears of their painful experience[15], which becomes another drawback of verbal communication. Thus, there is a need to use some non-verbal technique that explores their inner emotional status and enhances the verbal communication. One such technique is the use of drawings, a pleasant exercise, which tends to project the things felt as important by a child[16,17]. Children's drawing is thought to reflect his/her inner world; depicting various feelings and relating information concerning intelligence, psychological status and interpersonal style[18-24]. Thus, drawings ameliorate the communication capacity of the child and help in verbalizing their distress. Free drawings (child is free to draw anything without directions or instructions), bridge drawings (child is asked to draw about future expectations and relative threat), volcano drawings (child is asked to draw his/her means to manage anxiety), person picking an apple from a tree (to know the child's coping ability and resourcefulness), kinetic family drawings (child asked about family dynamics), human figure drawings (asked to draw a picture of a person) are the various means employed in studies on children drawings, of which, human figure drawings are popular clinically[25].

Scoring systems for drawings were also developed, of which Good enough-Harris test, Koppitz developmental scoring system, Draw-a-person quantitative scoring system are renowned[26,27]. To assess the emotional status of hospitalized school age children, Child drawing: Hospital (CD: H) manual was specially developed[28,29]. This manual was applied in pediatric dental settings to assess the effect of pulp therapy and/or restorative treatments for carious primary molars[30]. The present study was performed to determine the efficacy of drawings using CD: H manual in depicting the experiences of children undergoing local anesthetic (LA) administrations and extractions of primary teeth.

MATERIALS AND METHODS

The study was performed in Narayana Dental College and Hospital, Nellore, India during the period July 2012 to June 2014.

Sample

After obtaining institutional ethical clearance (as per Code of Ethics of the World Medical Association and Declaration of Helsinki, 1964, as revised in 2004), children who met all inclusion criteria were selected: (1) age range of 4 to 13 years (irrespective of gender and ethnic characteristics); (2) existence of untreatable carious or over-retained primary teeth, indicated for extraction; (3) complete physical and mental health without any confounding medical history; (4) interested in drawings; and (5) whose parents gave their consent to participate in the study.

Children indicated for extraction of teeth as a part of emergency/immediate phase treatment, those with very negative behavior[31] during initial examination and who were reluctant to draw picture were excluded.

About CD: H scale

CD: H scale was employed in the present study, as it

is a proven instrument with good internal validity[28] developed as a means of measuring the emotional status of hospitalized school aged children based on the theoretical foundation of drawings as a projective measure of children's state of anxiety. This manual consists of three parts, A, B and C. Part A focuses on the facets such as position, action, length, width, size of the child, his/her eyes and facial expression, colour predominance, number of colors used, use and placement on paper, stroke quality, inclusion and size of dental equipment and developmental level of the child as projected from their drawings. Part B focuses on omission, exaggeration, de-emphasis and distortion of body parts along with transparency and shading, whereas, part C represents general gestalt of the picture. The levels of anxiety, based on the scores obtained from CD: H scores are, $\leqslant$ 43: Very low stress, 44-83: Low stress, 84-129: Average stress, 130-167: Above average; and 168 and over: Very high stress; the detailed description of which can be read from CD: H manual[28].

CD: H scores obtained in the present study were correlated with FLACC, FPS-R scores and behavior of the children as assessed with Frankl's behavior rating scale. FLACC scale was considered due to its simplicity of application in clinical settings, that consists of five behavioral categories, facial expression, leg movement, bodily activity, cry or verbalization, and consolability[32]; each rated on a scale of 0 to 2 to provide a maximum overall pain score of 10, an acceptable ordinal convention point. Its validity was also proved in children, adults with cognitive impairment, and critically ill adults[33-35]. To achieve, self report of pain possible on the widely accepted 0 to 10 metric, FPS-R, adapted from the Faces pain scale was employed[8,36]. This was considered in the study due to the ease of administration and absence of smiles and tears in the faces, which is an added advantage[36].

Interventions

LA was administered for all the recruited children and extraction of the intended tooth performed following a standard protocol with routine behavior guidance techniques consistently by all the operators (two male and two female pediatric dentists) which was videotaped. The behavior of the child during oral examination, intraoral radiography, topical anaesthetic application, LA administration, extraction and departure from dental chair was rated using Wright's modification of Frankl rating scale. The overall score was obtained by summing the ratings on all the above mentioned occasions; if the child was positive on at least half of the situations, he/she was designated as positive (+) and if otherwise as negative (-). If there was no negative score in any of the occasion, the child was designated as definitely positive (++)[31]. As a behavioral measure of pain and distress, FLACC scale[37] was used to score the LA administration and extraction procedures separately. FPS-R[8], a self-report measure, was also recorded at two points of time, after completion of LA administration and after extraction. All the above scorings were recorded by two investigators who were not involved in the treatment procedure (RK and SP).

At the end of the therapeutic session, one of the investigators (SP) seated each child in a position where they can observe the complete clinical area. The A4 sheet paper and crayons box (exposing all the colours) were placed on the table in front of children. They were instructed to represent, by drawing, themselves along with the dentist and their experience of the dental treatment; while drawing neither parent/s nor dentist guided the children. If the children were not eager to draw at that point of time, they were excluded from the study. No time limit was given and children were informed that they can stop drawing whenever they want to. If the children were very distracted, the above directions were repeated. After completion of drawing, the details of the children (including outpatient number, date of birth and gender) were noted on the back of the drawing paper, whereas, explanations for the drawing were noted on separate paper. The drawings were analyzed by one Pediatric dentist (SN) and a clinical psychologist (who was blinded to the behavior of children in clinic) separately based on the manual. Any disagreements between the two were discussed and crosschecked with explanations given by the children; and after getting common consensus, final scores for drawings were given.

Sample size determination

Based on the findings of a previous study conducted with sample size of 54, which compared drawing scores, applying CD: H manual, with behavioral measure of pain; and considering the findings of our pilot study on 10 children with behavioral measure as the primary outcome, and self report measure and behavioral ratings as secondary outcomes, with the level of significance set at 0.05, power of 80%, a minimal sample size of 100 was determined.

Statistical analysis

Cohen's kappa was employed to measure the reliability of the obtained data (both inter-rater and intra-rater). Inter-rater reliability between two investigators (SP and RK) for FLACC and Frankl scores were 0.91 and 0.89 respectively. Intra-rater reliability for FLACC and Frankl (scored after two weeks on the basis of videotaped treatment procedure) were 0.96 and 0.90. The drawings of these children were scored once by both the Pediatric dentist (SN) and a clinical psychologist and reproducibility of CD: H scores were found to be $r = 0.85$, $r = 0.88$.

The data was assessed for the difference in distribution of participants based on age, gender and influence of accompanying person using χ^2 test; the differences between/among the variables in various groups was evaluated using one way ANOVA followed by post hoc comparisons. The correlation between the variables (bivariate correlation) was assessed with Pearson

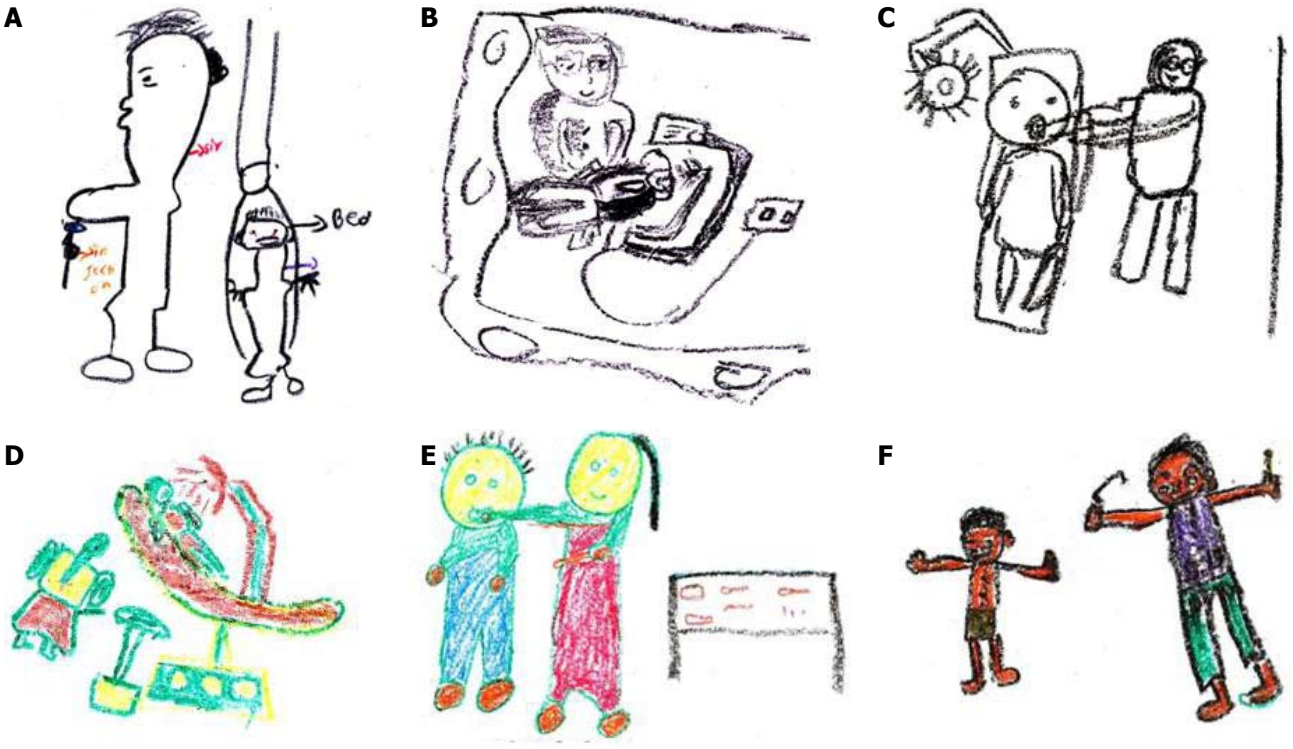

Figure 1 Samples of children's drawings. A: Ages 11 years; gender: boy; Franki: 4. FLACC score (LA): 2 (mild discornfort), FLACC score (Ext): 2 (mild discornfort); FPS-R score (LA): 6, FPS-R score (Ext): 2. Child drawing: Hospital score: 94 (average stress). The predominant colour in the drawing was black. The child included dental equipment in the drawing (syninge and dental chair) represented himself crying in the dental chair. B: Ages 12 years; gender: boy; Franki: 4. FLACC score (LA): 4 (moderate pain), FLACC score (Ext): 6 (moderate pain); FPS-R score (LA): 8, FPS-R score (Ext): 8. Child drawing: Hospital score: 67 (low stress). The child used only black colour and included dental equipment in the drawing including cabin partitions. C: Ages 13 years; gender: boy; Franki: 4. FLACC score (LA): 2 (mild discornfort), FLACC score (Ext): 1 (mild discornfort); FPS-R score (LA): 8, FPS-R score (Ext): 0. Child drawing: Hospital score: 92 (low stress). The child used only black colour and included dental equipment. It was an action picture showing extraction of his tooth by the doctor. Child omitted noses, ears and hair for himself. D: Ages 11 years; gender: boy; Franki: 3. FLACC score (LA): 3 (mild discornfort), FLACC score (Ext): 0 (mild discornfort); FPS-R score (LA): 2, FPS-R score (Ext): 0. Child drawing: Hospital score: 68 (low stress). The child used only small part of paper for his drawing and included dental equipment (syninge and dental chair). However, the predominant colour used green. E: Ages 12 years; gender: boy; Franki: 4. FLACC score (LA): 2 (mild discornfort), FLACC score (Ext): 0 (mild discornfort); FPS-R score (LA): 2, FPS-R score (Ext): 6. Child drawing: Hospital score: 49 (low stress). Child drew an action picture if he is undergoing extraction and also included dental equipment (Try with instruments arranged on it). Note that the noses and ears are missing in his human figures. F: Ages 10 years; gender: boy; Franki: 4. FLACC score (LA): 5 (mild discornfort), FLACC score (Ext): 0 (mild discornfort); FPS-R score (LA): 2, FPS-R score (Ext): 0. Child drawing: Hospital score: 64 (low stress). Child drew himself in a very happy mood, although he included dental equipment (extraction instrument and LA spray). FLACC: Faces, legs, activity, cry, consolability scale; FPS-R: Facial pain scale-revised; LA: Local anaesthetic administration; Ext: Extractions.

correlation test.

RESULTS

A total of 107 children (58 boys and 49 girls) completed the study, out of the 110 participants. Three children willingly participated at the beginning of the study, but, after extraction dissented to draw. The mean age of the children who completed the study was 10.1 years (range: 4-13). The mode for the Frankl score of participants was 4 (range: 2-4). The mean FLACC score during LA administration was 2.8 ± 1.7 (range: 0-10) and during extractions it was 2.24±2.04 (range: 0-10). The mode for FPS-R after LA administration was 2 (range: 0-10) and after extraction it was 0 (range 0-10). The mean CD: H score of participants was 74.1 ± 16.2 (range of 36-112). Some samples of children's drawings are presented in Figure 1.

Differences in distribution of participants

The sample was grouped based on the age, gender and accompanying person. Thus, 7 participants (6.5%) were 4-6 years old, 33 (30.8%) were > 6-13 years and 67 (62.6%) were > 9-13 years old; 58 participants (54.2%) were boys and 49 (45.8%) were girls; 55 (51.4%) children were accompanied by mother, 31 (29%) and 21 (19.6%) by father and guardian respectively. The distribution of participants in various scoring categories of Frankl, FLACC, FPS-R and CD: H scores based on age, gender and accompanying person are presented in Tables 1 and 2. Significant differences were not observed with the distribution of participants in various categories of CD: H, FPS-R and Frankl. However, there was a statistically significant difference in the distribution of participants based on FLACC scores among various age groups ($P < 0.01$ during LA administration and extractions) (Table 2).

Differences based on age, gender and influence of accompanying person

The differences between/among scores recorded in groups divided based on age, gender and accompanying

Table 1 Distribution of Child drawing: Hospital scale and facial pain scale-revised scores based on age, gender and accompanying person

Variables		Mean ± SD	CD: H Classification					FPS-R (local anaesthetic administration)					FPS-R (extractions)				
			⩽ 43	44-83	84-129	130-167	> 168	Mode	0	2-4	6-8	10	Mode	0	2-4	6-8	10
Age	4-6	76.43 ± 16.08	0	4	3	-	-	8	1	2	2	2	0	2	0	3	2
				3.73%	2.80%				0.93%	1.86%	1.86%	1.86%		1.86%		2.8%	1.86%
	> 6-9	76.06 ± 15.36	0	21	12	-	-	10	5	11	7	10	0	8	8	10	7
				19.6%	11.20%				4.67%	10.28%	6.54%	9.34%		7.47%	7.47%	9.34%	6.54%
	> 9-13	72.87 ± 16.75	3	43	21	-	-	2	6	38	17	6	0	17	24	18	8
			2.80%	40.18%	19.60%				5.60%	35.51%	15.88%	5.60%		15.88%	22.42%	16.82%	7.47%
	Significance		0.70[NS]					0.10[NS]					0.44[NS]				
Gender	Boys	78.03 ± 15.29	0	35	23	-	-	2	7	22	17	12	0	14	17	17	10
				32.71%	21.49%				6.54%	20.56%	15.88%	11.2%		13.08%	15.88%	15.88%	9.34%
	Girls	69.41 ± 16.18	3	33	13	-	-	2	5	29	9	6	0	13	15	14	7
			2.80%	30.8%	12.14%				4.67%	27.10%	8.41%	5.60%		12.14%	14.01%	13.08%	6.54%
	Significance		0.08[NS]					0.17[NS]					0.97[NS]				
Accom-panying person	Mother	72.55 ± 15.61	1	39	15	-	-	2	5	27	14	9	0	13	14	15	13
			0.93%	36.4%	14.01%				4.67%	25.23%	13.08%	8.41%		12.14%	13.08%	14.01%	12.14%
	Father	77.61 ± 17.15	1	16	14	-	-	2	5	14	8	4	2	10	15	6	3
			0.93%	14.95%	13.08%				4.67%	13.08%	7.47%	3.73%		9.34%	14.01%	5.60%	2.80%
	Guardian	72.90 ± 16.36	1	13	7	-	-	2	2	10	4	5	8	4	13	10	1
			0.93%	12.14%	6.54%				1.86%	9.34%	3.73%	4.67%		3.73%	12.14%	9.34%	0.93%
	Significance		0.47[NS]					0.90[NS]					0.12[NS]				

CD: H: Children drawing: Hospital scale; FPS-R: Facial pain scale-revised; NS: Not significant, SD: Standard deviation.

Table 2 Distribution of faces, leg, activity, cry, consolability scale and frankl scores based on age, gender and accompanying person

Variables		FLACC (local anaesthetic administration)					FLACC (extractions)					Frankl (total score)			
		Mode	0	1-3	4-6	7-10	Mode	0	1-3	4-6	7-10	Mode	2	3	4
Age	4-6	4	0	2	5	0	3	1	3	1	2	3	0	4	3
				1.86%	4.67%			0.93%	2.80%	0.93%	1.86%			3.73%	2.80%
	> 6-9	4	0	16	14	3	4	4	14	12	3	4	4	5	24
				14.95%	13.08%	2.80%		3.73%	13.08%	11.20%	2.80%		3.73%	4.67%	22.42%
	> 9-13	2	4	52	11	0	2	19	41	7	0	4	7	9	51
			3.73%	48.59%	10.28%			17.75%	38.31%	6.54%			6.54%	8.41%	47.66%
	Significance		< 0.01[1]				< 0.01[1]					0.06[NS]			
Gender	Boys	2	2	37	17	2	2	14	29	12	3	4	3	11	44
			1.86%	34.57%	15.88%	1.86%		13.08%	27.10%	11.20%	2.80%		2.80%	10.28%	41.12%
	Girls	2	2	33	13	1	2	10	29	8	2	4	8	7	34
			1.86%	30.80%	12.14%	0.93%		9.34%	27.10%	7.47%	1.86%		7.47%	6.54%	31.77%
	Significance		0.95[NS]				0.82[NS]					0.16[NS]			
Accompanying person	Mother	2	1	34	19	1	2	9	32	11	3	4	7	9	39
			0.93%	31.77%	17.75%	0.93%		8.41%	29.99%	10.28%	2.80%		6.54%	8.41%	36.44%
	Father	2	3	21	6	1	0	13	14	4	0	4	2	2	27
			2.80%	19.6%	5.60%	0.93%		12.14%	13.08%	3.73%			1.86%	1.86%	25.23%
	Guardian	2	0	15	5	1	2	2	12	5	2	4	2	7	12
				14.01%	4.67%	0.93%		1.86%	11.20%	4.67%	1.86%		1.86%	6.54%	11.20%
	Significance		0.34[NS]				0.07[NS]					0.10[NS]			

[1]Significant at 0.01 level. FLACC: Faces, leg, activity, cry, consolability scale; NS: Not significant.

person, were analyzed, and significant differences were not observed based on age and accompanying person in CD: H, FPS-R or Frankl scores. However, there was a statistically significant difference in CD: H scores between boys and girls (Table 3) and in the FLACC scores recorded among the age groups, during LA administration (post hoc showing difference between > 6-9 and > 9-13 age groups) as well as extractions (post hoc showing difference between > 6-9 and > 9-13 and 4-6 and > 9-13 age groups). Significant difference was also observed in FLACC values recorded during extractions among the groups divided based on the accompanying person (post hoc showing difference between the group of children, accompanied by mother and those by father as well as between the groups accompanied by father and guardian) (Table 4).

Correlations

There was a positive correlation between CD: H scores and all the other considered parameters (Frankl, FPS-R

Table 3 Differences between/among scores (Child drawing: Hospital scale and facial pain scale-revised) in groups divided based on age, gender and accompanying person

Variables	Groups	Mean ± SD	One way ANOVA *P* valve	Post hoc comparisons	Post hoc *P* valve
CD: H	Age groups (4-6, > 6-9, > 9-13)	4-6: 76.4 ± 16.1 > 6-9: 76.1 ± 15.4 > 9-13: 72.9 ± 16.7	0.61[NS]	4-6 *vs* > 6-9 > 6-9 *vs* > 9-13 4-6 *vs* > 9-13	1.00[NS] 0.66[NS] 0.86[NS]
	Gender (boys and girls)	Boys: 78.0 ± 15.3 Girls: 69.4 ± 16.2	0.01[1]	--	--
	Accompanying person (mother, father, guardian)	Mother: 72.6 ± 15.6 Father: 77.6 ± 17 Guardian: 72.9 ± 16.4	0.36[NS]	Mother *vs* father Mother *vs* guardian Father *vs* guardian	0.38[NS] 1.00[NS] 0.59[NS]
FPS-R (LA)	Age groups (4-6, > 6-9, > 9-13)	4-6: 6.0 ± 4.0 > 6-9: 5.5 ± 3.8 > 9-13: 4.1 ± 2.9	0.07[NS]	4-6 *vs* > 6-9 > 6-9 *vs* > 9-13 4-6 *vs* > 9-13	0.92[NS] 0.14[NS] 0.33[NS]
	Gender (boys and girls)	Boys: 5.0 ± 3.5 Girls: 4.2 ± 3.1	0.24[NS]	--	--
	Accompanying person (mother, father, guardian)	Mother: 4.8 ± 3.9 Father: 4.1 ± 3.3 Guardian: 4.8 ± 3.6	0.63[NS]	Mother *vs* father Mother *vs* guardian Father *vs* guardian	0.64[NS] 1.00[NS] 0.80[NS]
FPS-R (Ext)	Age groups (4-6, > 6-9, > 9-13)	4-6: 6.0 ± 4.3 > 6-9: 4.9 ± 3.9 > 9-13: 4.0 ± 3.5	0.28[NS]	4-6 *vs* > 6-9 > 6-9 *vs* > 9-13 4-6 *vs* > 9-13	0.78[NS] 0.54[NS] 0.41[NS]
	Gender (boys and girls)	Boys: 4.7 ± 3.8 Girls: 4.2 ± 3.6	0.50[NS]	--	--
	Accompanying person (mother, father, guardian)	Mother: 5.0 ± 3.9 Father: 3.1 ± 3.3 Guardian: 5.0 ± 3.4	0.06[NS]	Mother *vs* father Mother *vs* guardian Father *vs* guardian	0.08[NS] 1.00[NS] 0.70[NS]

[1]Significant at 0.01 level. CD: H: Children drawing: Hospital scale; FPS-R: Facial pain scale-revised; L.A: Local anaesthetic administration; Ext: Extractions; NS: Not significant.

and FLACC) which was not statistically significant. However, there were some statistically significant positive correlations, as well as some non-significant negative correlations between CD: H and other parameters based on age, gender and accompanying person which are represented in Table 5. In children belonging to 4-6 year age group, FPS-R and FLACC during LA administration were significant and correlating positively with CD: H scores, whereas others were not. In > 6-9 and > 9-13 year age groups, there were non-significant associations between CD: H scores and all other considered parameters. In the data segregated based on the gender, there were no statistically significant correlations between the CD:H scores and other parameters. The data segregated based on accompanying person also showed non-significant associations, except FLACC scores, during extraction in children accompanied by mother and FPS-R during LA administration in children accompanied by guardian, showing significant positive correlations.

DISCUSSION

Drawing ability in children shows predictable, observable and measurable stages that coincide with cognitive and motor development; better representational and detailed with age. By the age of 4 years, children drawings emerge to have identifiable human figures and by the end of 13 years they reach a stage where drawings tend to become more natural, with true representation of things. As CD: H is a manual based on human figure drawings (HFDS), in the present study, children in the age range of 4 to 13 years were included. The data was also segregated for analysis into 4-6, > 6-9 and > 9-13 based on the development of the quality and content of HFDS[16]. Scoring systems also exist in human drawing tests, such as Good enough-Harris, Koppitz developmental system and Draw-a-person quantitative system, however, CD: H was employed in the present study, as it is exclusively developed for assessing the emotional status of hospitalized children.

Before discussing the correlations, the distribution of participants as observed in the present study needs attention, as it revealed fluctuations on the observational scale. Significant differences were observed in FLACC scores among the three age groups considered. In > 9-13 year age group, all the children during LA administrations and majority of the children during extractions, scored 0 in FLACC. The mean scores were also less in > 9-13 year age group, for the differences among the scores recorded. These observations are in accordance with the reported drawback of FLACC, *i.e.,* older children tend to mask the expression of pain[38-42]. Another observation in the present study was; the mean FLACC scores were statistically less significant in children accompanied by father, compared to those accompanied by mother/guardian, which can be due to the authoritative nature of father in the culture of the study population that might have influenced the externalization of pain by the children accompanied by their father.

Correlations of CD: H scores with FPS-R, FLACC and

Table 4 Differences between/among scores (faces, leg, activity, cry, consolability dcale and frankl) in groups divided based on age, gender and accompanying person

Variables	Groups	Mean ± SD	One way ANOVA *P* valve	Post hoc comparisons	Post hoc *P* valve
FLACC (LA)	Age groups (4-6, > 6-9, > 9-13)	4-6: 3.9 ± 1.9	< 0.01[2]	4-6 *vs* > 6-9	0.97[NS]
		> 6-9: 3.7 ± 2.2		> 6-9 *vs* > 9-13	< 0.01[2]
		> 9-13: 2.3 ± 1.2		4-6 *vs* > 9-13	0.06[NS]
	Gender (boys and girls)	Boys: 2.9 ± 1.8	0.61[NS]	--	--
		Girls: 2.8 ± 1.6			
	Accompanying person (mother, father, guardian)	Mother: 3.0 ± 1.6	0.60[NS]	Mother *vs* father	0.62[NS]
		Father: 2.6 ± 1.8		Mother *vs* guardian	1.00[NS]
		Guardian: 3.0 ± 1.9		Father *vs* guardian	0.75[NS]
FLACC (Ext)	Age groups (4-6, > 6-9, > 9-13)	4-6: 3.9 ± 2.8	< 0.01[2]	4-6 *vs* > 6-9	0.67[NS]
		> 6-9: 3.2 ± 2.4		> 6-9 *vs* > 9-13	< 0.01[2]
		> 9-13: 1.6 ± 1.5		4-6 *vs* > 9-13	0.01[2]
	Gender (boys and girls)	Boys: 2.3 ± 2.2	0.93[NS]	--	--
		Girls: 2.2 ± 1.9			
	Accompanying person (mother, father, guardian)	Mother: 2.5 ± 1.9	< 0.01[2]	Mother *vs* father	0.02[1]
		Father: 1.3 ± 1.5		Mother *vs* guardian	0.62[NS]
		Guardian: 3.0 ± 2.4		Father *vs* guardian	0.01[2]
Frankl (total)	Age groups (4-6, > 6-9, > 9-13)	4-6: 3.4 ± 0.5	0.68[NS]	4-6 *vs* > 6-9	0.86[NS]
		> 6-9: 3.6 ± 0.7		> 6-9 *vs* > 9-13	0.69[NS]
		> 9-13: 3.7 ± 0.7		4-6 *vs* > 9-13	0.94[NS]
	Gender (boys and girls)	Boys: 3.7 ± 0.6	0.17[NS]	--	--
		Girls: 3.5± 0.8			
	Accompanying person (mother, father, guardian)	Mother: 3.6 ± 0.7	0.17[NS]	Mother *vs* father	0.32[NS]
		Father: 3.8 ± 0.5		Mother *vs* guardian	0.82[NS]
		Guardian: 3.5 ± 0.7		Father *vs* guardian	0.22[NS]

[1]Significant at 0.05 level; [2]Significant at 0.01 level. FLACC: Faces, leg, activity, cry, consolability scale; LA: Local anaesthetic administration; Ext: Extractions; NS: Not significant.

Table 5 Correlation of Children drawing: Hospital Scale with facial pain scale-revised, faces, leg, activity, cry, consolability scale and frankl

Variables	Groups		CD:H	FPS-R (LA)	FPS-R (Ext)	FLACC (LA)	FLACC (Ext)	Frankl (Total)
Age	4-6	Correlation	1	0.87	-0.17	0.84	0.71	-0.14
		Significance	-	0.01[2]	0.72[NS]	0.02[1]	0.07[NS]	0.76[NS]
	> 6-9	Correlation	1	-0.09	-0.24	0.20	-0.12	0.27
		Significance	-	0.63[NS]	0.19[NS]	0.26[NS]	0.50[NS]	0.63[NS]
	> 9-13	Correlation	1	0.21	0.17	-0.08	0.05	0.07
		Significance	-	0.09[NS]	0.17[NS]	0.53[NS]	0.67[NS]	0.56[NS]
Gender	Boys	Correlation	1	0.11	-0.12	0.12	0.09	0.01
		Significance	-	0.40[NS]	0.37[NS]	0.38[NS]	0.52[NS]	0.94[NS]
	Girls	Correlation	1	0.18	0.18	0.11	0.07	0.15
		Significance	-	0.22[NS]	0.21[NS]	0.46[NS]	0.65[NS]	0.32[NS]
Accompanying person	Mother	Correlation	1	0.18	0.10	0.19	0.28	0.01
		Significance	-	0.20[NS]	0.47[NS]	0.17[NS]	0.04[1]	0.98[NS]
	Father	Correlation	1	-0.06	-0.01	0.02	0.08	0.1
		Significance	-	0.74[NS]	0.97[NS]	0.91[NS]	0.68[NS]	0.60[NS]
	Guardian	Correlation	1	0.55	0.11	0.20	-0.12	0.33
		Significance	-	0.01[2]	0.65[NS]	0.38[NS]	0.61[NS]	0.14[NS]
Total		Correlation	1	0.17	0.04	0.12	0.08	0.12
		Significance	-	0.09[NS]	0.72[NS]	0.21[NS]	0.44[NS]	0.24[NS]

[1]Significant at 0.05 level; [2]Significant at 0.01 level. NS: Not significant; CD: H: Children drawing: Hospital Scale; FPS-R: Facial pain scale-revised; FLACC: Faces, leg, activity, cry, consolability scale; L.A: Local anaesthetic administration; Ext: Extractions.

Frankl revealed interesting findings. Considering the total sample, CD: H was positively correlating with all the other parameters though not significant statistically. These findings are in accordance with a previous study, which proved drawings as a projective measure for children's distress in pediatric dentistry[30]. However, these correlations showed variations when the sample was segregated in the present study. In the age specific groups, we found significant positive correlation of CD: H with FPS-R and FLACC for LA administration was observed in 4-6 year group, and non-significant relations in older age groups. This can be due to curtailment of emotions on the dental chair by these older children, as well as drawing activity, considered as unrelated to

dentistry by them, might have lead to disparity in CD: H and FLACC/FPS-R scores. In the accompanying person category, a significant positive correlation of drawing scores with FPS-R for LA administration were observed in the guardian group; liberty to choose their expression of pain in the self-report scale by those children, who were not accompanied by parents can be a possible explanation for this. Significant positive correlation was also observed between CD: H and FLACC during extractions, in the children accompanied by mother. This can be due to free expression of pain physically, when companioned by mother.

Gender difference in anxiety of children was reported frequently in the existing literature; some reporting high anxiety scores in girls[40,43,44], where as others depicting no difference[42]; In the present study we attempted to assess the gender difference in expression of pain, using self report, observational measures and in the drawings. Significant differences were observed in CD: H scores, with boys reporting high mean scores, compared to girls. All the remaining parameters, like FLACC and FPS-R, the mean scores were higher in boys, compared to girls, which can be due to the tolerance capacity of girls being more, compared to boys[45].

Scoring of drawings using CD: H was practically easy, but, this manual was originally developed to determine the effect of hospitalization on children[29]. When the same instrument was employed for assessment of dental treatments, some of the items in the scoring system were not applicable to dental settings; necessitating revision and simplification of this instrument. In part A; the first item position of the child, needs modifications, most of the proposed positions were not suitable for drawings in the dental operatory. The scoring of items; action, length and width of the person, considered in the CD: H, might have been subjected to bias because, the differences noted might be due to drawing abilities of children, rather than pain and anxiety. Other controversial aspects found in the present study were the colour predominance and stroke quality. As children were provided with only crayons, almost all the children used black crayon as replacement for pencil to draw the outline of their drawings, which became the predominant color most of the times. Difficulty in scoring the quality of strokes, which were drawn with crayons, is a point to ponder. In part B, transparency, exaggeration and de-emphasis items can be eliminated as they do not adapt well to our dental scenario. Finally, the part C is prone for subjective variations, thus, omitting that part can lead to simplification of the instrument.

An attempt was made to observe drawings of children and their FLACC as well as FPS-R scores at an individual level which disclosed the utility of the present study. Some of the children with low scores on both FLACC and FPS-R drew dental equipment in their drawings and represented themselves in either helpless condition or crying in the dental chair. On the other hand, children who scored high values in FLACC and FPS-R, scored low in CD: H and presented themselves in happy mood. This clearly projects the major difference between drawings and other parameters; as, observational and self report measures represent fleeting emotions when the child is on dental chair, whereas, drawings symbolize the lasting feelings of a dental treatment. These enduring emotions are crucial for customizing our guidance techniques in future visits and for assimilating dental interest in children. This study, thus, has been proved as a means to discern the inner emotional disturbances originated in a child due to a painful dental treatment, and the way this can be used to guide the behaviour of the child in his/her future dental treatments. Drawings in the field of pediatric dentistry can be furthered studied by testing their validity in assessing the emotional condition of the child before treatment and depicting his/her subjective fears in their first dental visit.

The LA administration and extractions in the present study were performed by more than one pediatric dentist. However, this will not bias the results of the present study, as it is a factor that has a consistent influence on all the parameters considered to measure pain of a single child. The major limitation of the present study was disregarding the effect of schooling and intelligence, which are proposed to influence the drawings of children[19,26,27,46]. However, we substantiate our study, with the studies that proved no effect of these factors on drawing talent of children[18,47-49].

In conclusion, The present study clearly demonstrated that, scoring of children's drawing using CD: H manual, though authentic, has limited validity to measure the pain experience of children undergoing local anesthetic administration and extraction of primary teeth. Drawings could not act as surrogate measure of pain; however, we should not conclude an end to the use of drawings in a dental setting, as they act as narrative of children's painful experience and emotions. They are an easy, interesting exercise for children that can be employed as an additional measure of understanding the exact source of anxiety and/or to know the objective fears created due to a painful experience. Drawings address a method for working with children, and we should never underestimate the effect of our behavior and responsiveness on children. The most affirmative point in the present study was, the children after experiencing a stressful activity, got distracted due to the drawing and were leaving the dental operatory with a happy mood.

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COMMENTS

Background

During day to day pediatric dental practice, communication with children is significant, to assess the procedural pain and its impact on them. Non-verbal communication can explore the inner emotional condition, compared to verbal, as children may or may not have the ability and/or vocabulary to express their feelings, fears and concerns verbally. Drawings, being a pleasant exercise for children, have been considered as a measure to determine the pain and

distress in children undergoing dental extractions.

Innovations and breakthroughs

In pediatric settings, this is the second study in literature that determined the procedural pain experienced by children during dental treatments, first being the study done by Aminabadi *et al* in 2011. Aminabadi *et al* have tested the procedural pain during pulp therapy and/or restorative treatments for carious primary molars. However, in dentistry, out of the numerous procedures perceived as painful by a child, local anesthetic (LA) administrations and extractions are the most painful of all, which can cause psychological distress. Hence, the present study is a breakthrough to know the efficacy of drawings in depicting the experiences of children undergoing LA administration and extraction of primary teeth.

Applications

Drawings acted as a narrative of children's painful experience and emotions. They were an easy, interesting exercise for children and hence, can be employed as an additional measure of understanding the exact source of anxiety and/or to know the objective fears created due to a painful experience. Drawings addressed a method for working with children; after experiencing pain, they got distracted due to the drawing exercise and left the dental operatory with a happy mood.

Terminology

Pain drawings: Pain drawings are simple line drawings of the human figure on which patients can indicate their pain for both clinical information and research. Anxiety: Anxiety is a personality trait and is an apprehension, tension or uneasiness that stems from anticipation of danger, the source of which is largely unknown or unrecognized. Objective fear: It is acquired objectively or produced by direct physical stimulation of the sense organs, but not of parental origin, which are disagreeable and unpleasant in nature.

Peer-review

The work stresses on the relevance of non-pharmaceutical efforts to relieve childrens' pain in medical procedures, as well as, presents an interesting and helpful methodology that should also be made available to others.

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ORIGINAL ARTICLE

Observational Study

Dental knowledge and awareness among grandparents

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Author contributions: Oberoi J contributed to the principal investigator, data collection, classification, and compilation; Kathariya R made the contributions to drafting of article, statistical analysis, formatting, and revising it critically for important intellectual content and made the final approval of the version to be submitted; Panda A conceived, guided and design of the study; Garg I, as the secondary investigator, made the classification, and acquisition of data; Raikar S revised and read the final version.

Institutional review board statement: The study was approved by the Institutional Scientific and Ethics committee, and reviewed by the Institutional Review Board of Padmashree Dr. D.Y. Patil Dental College and Hospital, Nerul, Navi Mumbai- 400614, Maharashtra India, With the Ethics Clearance Number: 2013-2014/5/1301.

Informed consent statement: Participation in the study was voluntary. The grandparents, who volunteered to take part in the study, signed a consent form. The questionnaire was translated into a local language for ease of understanding. The questionnaire was read for the grandparents who could not read and their answers were recorded. The questionnaires were completed in the waiting area prior to the patient's appointments.

Conflict-of-interest statement: I confirm that the manuscript is original and has not been published elsewhere. Nor is it sent to any other journals for consideration. The manuscript in its submitted form has been read and approved by all authors. There is no financial relationship between any author and any commercial firm(s), which may pose a potential, perceived, or real conflict of interest.

Data sharing statement: Study participants gave informed consent for data sharing. Technical appendix, statistical code, and dataset are available with the corresponding author at rkathariya@gmail.com.

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Abstract

AIM: To investigate grandparent's knowledge and awareness about the oral health of their grandchildren.

METHODS: Grandparents accompanying patients aged 4-8 years, who were living with their grandchildren and caring for them for a major part of the day, when both their parents were at work were included in the study. A 20-item questionnaire covering socio-demographic characteristics, dietary and oral hygiene practices was distributed to them. The sample comprised of 200 grandparents (59 males, 141 females). χ^2 analysis and Gamma test of symmetrical measures were applied to assess responses across respondent gender and level of education.

RESULTS: Oral health related awareness was found to be low among grandparents. In most questions asked, grandparents with a higher level of education exhibited a better knowledge about children's oral health. Level of awareness was not related to their gender.

CONCLUSION: Oral hygiene and dietary habits are established during childhood. There is a great need for dental education of grandparents as they serve as role models for young children.

Key words: Grandparents; Awareness; Primary teeth; Children; Oral health

Core tip: An observational study evaluating the attitude and knowledge of grandparents as they serve an important role as caregivers in their grandchildren's lives. There is a great need for dental education of grandparents as they serve as role models for the young.

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INTRODUCTION

With changing family patterns, increased life expectancy, growing numbers of dual-worker households and higher rates of family breakdown, grandparents are now playing an increasing role in their grandchildren's lives[1-3]. Grandparents are an important resource for both parents and children. They routinely provide child care, financial assistance and emotional support. Occasionally they are called upon to provide much more, including temporary or full time care and responsibility for their grandchildren. Child and adolescent psychiatrists recognize the important role many grandparents play in raising their grandchildren[1].

The changing role of grandparents in society has led to a greater responsibility on them as nurturers, mentors, and teachers and they also play a crucial part in modelling a good lifestyle for the child. Moreover, in everyday life, grandparents function as role models for their grandchildren, and therefore, grandparents' knowledge, awareness and dental hygiene practises may play an important role in influencing children's behaviour and attitude towards good oral health care. Hence, in order to improve children's oral health status, grandparents should be considered as one of the key people involved in and influencing children's lives and the health care that they receive. A considerable amount of research dealing with the role that parents[4,5] (and mothers in particular)[6,7] play in influencing the oral health status of children has been done, but there is dearth of literature investigating the role grandparents play in influencing children's oral health status. A review of literature revealed only one study[8], where knowledge of caregivers, which included grandparents (107 grandparents out of 615 caregivers, *i.e.,* 17.4%) was studied. Thus, this study was carried out to investigate the knowledge, awareness, beliefs and practises of grandparents related to their grandchildren's oral health.

MATERIALS AND METHODS

Before the start of the study, the study protocol was approved by the Ethics Committee of the Dr. D.Y. Patil Dental College and Hospital, Navi Mumbai. A questionnaire was prepared to assess the knowledge and awareness of grandparents regarding the oral health of their grandchildren. Grandparents accompanying patients aged 4-8 years attending the outpatient department of Pediatric and Preventive Dentistry of the Dr. D.Y. Patil Dental College and Hospital, Navi Mumbai, who were living with their grandchildren and caring for them for a major part of the day, when both their parents were at work, were explained the purpose of the study. Participation in the study was voluntary. The grandparents who volunteered to take part in the study and signed a consent form, were distributed the questionnaires in the waiting area of the outpatient department. The questionnaire was translated into a local language for ease of understanding. The questionnaire was read for the grandparents who could not read and their answers were recorded. The questionnaires were completed in the waiting area prior to the patient's appointments. The questionnaire comprised of 20 questions and the participants were asked to select one appropriate option for each question. The demographic information collected from the questionnaire included age of the grandchild, and gender and educational qualification of the grandparent. Literature was consulted regarding the knowledge of mothers/parents in regard to their children's dental health and the existing questions were adapted for this survey[4-8]. A pilot study was conducted by asking 20 grandparents and members of staff to complete the questionnaire. The feedback was positive but indicated that use of the terms "pedodontists" and "malocclusion" was causing some confusion. As a result, these were replaced with "pediatric dentists" and "crooked teeth" respectively, to improve understanding. Completed questionnaires were collected and passed blind to an independent statistician where they were analysed for response frequency and the results tabulated. The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., version 15.0 for Windows). Descriptive statistics and χ^2 analysis for non-parametric data with the appropriate degrees of freedom were performed on the data to assess responses to the questionnaire items across respondent

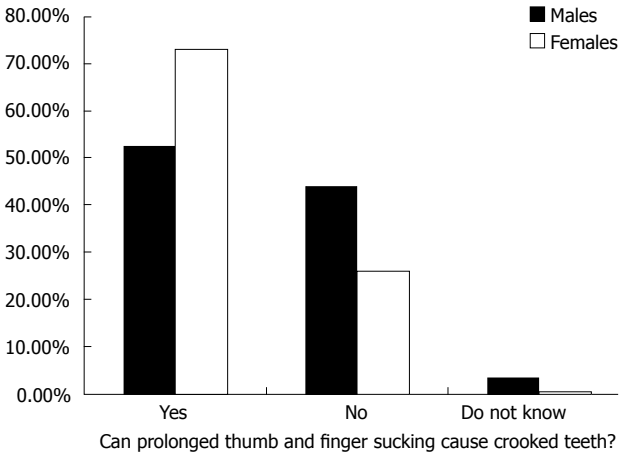

Figure 1 Gender based analysis.

gender and level of education. In addition, Gamma test of Symmetrical Measures was also applied for analysis across education levels. Statistical significance was determined at $P \leqslant 0.05$.

RESULTS

A total of 200 grandparents participated in the study. Out of these 141 (70.5%) were females and 59 (29.5%) were males. Out of 200 grandparents, 40 (20%) were illiterate and 114 (57%) had up to higher secondary education. The number of grandparents having graduate and post graduate qualifications, was 38 (19.0%) and 8 (4%) respectively. The results were analysed on the basis of gender and level of education.

Statistically significant difference ($P \leqslant 0.05$) between genders was seen only in one question, that is, female grandparents (73%) were more aware than their male counterparts (52.5%) that prolonged sucking habits could result in malocclusion (Figure 1). In all other questions, the difference seen between the responses of both the genders was statistically insignificant.

When response of the grandparents was compared to the level of education, a higher level of awareness was positively correlated with a higher level of education but not in all questions and not consistent with the increase in the level of education. Statistically significant difference ($P \leqslant 0.05$) between different levels of education was seen in five questions (Figure 2). When asked whether they were aware of paediatric dentists, 30%, 39.5%, 57.9% and 62.5% of illiterates (henceforth referred to as category Ⅰ), higher secondary educated (henceforth referred to as category Ⅱ), graduates (henceforth referred to as category Ⅲ) and post graduates (henceforth referred to as category Ⅳ) respectively (total 42%), replied in the affirmative (statistically significant) (Figure 2). A total of 51% grandparents (47.5%, 48.2%, 60.5% and 62.5% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively), thought frequent visits to the dentist were important. When asked whether they had ever tried to treat the child for any dental related problem at home, 35%, 30.7%, 23.7% and 50% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively, replied in the affirmative (total 31%). Majority (67%) of the grandparents (65%, 64.9% 68.4% and 100% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively) said that prolonged thumb and finger sucking can cause crooked teeth. A vast majority (88.5%) of the grandparents (92.5%, 84.2%, 94.7% and 100% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively) knew that brushing teeth could prevent dental problems. Regarding the availability of specialized toothbrushes and pastes only for children, 37.5%, 57%, 65.8% and 75% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively, were aware of the same (statistically significant) (Figure 2), whereas 17.5%, 13.1%, 5.3% and 12.5% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively, were aware only of specialized brushes for children and not of pastes. A majority (78.5%) of grandparents (65%, 81.6%, 78.9% and 100% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively) said that they gave as much importance to the care of their teeth as to other parts of their body. When asked whether maternal dental health could affect child's future dental health and general health, only 30%, 40.4%, 50% and 75% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively, replied in the affirmative (statistically significant) (Figure 2). Many of the grandparents were also unaware of the age at which the first dental check up of the child should be done. Only 17.5%, 11.4%, 7.9% and 37.5% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively, said that the first dental checkup should be at or before 1 year of age (total 13%), whereas the rest of the grandparents gave varied answers like 2 years (20.5%), 3 years (13%), after 4 years (20.5%) and when required (33%). The high level of unawareness was also evident by the responses to the question about when one should start brushing the child's teeth. A total of 27.5% grandparents (22.5%, 23.7%, 42.1%, and 37.5% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively) said that brushing should be started at or before 1 year of age, whereas others gave varied answers like 2 years (31%), 3 years (25.5%), after 4 years (14.5%) and do not know (1.5%). Most of the grandparents were well aware of the total number of permanent teeth with 87.5%, 79.8%, 84.2% and 100% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively giving the answer as 32, but most were not aware of the number of milk teeth with only 7.5%, 15.8%, 13.1% and 50% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively (total 15%), giving the answer as 20. A total of 60.5% grandparents (42.5%, 59.6%, 76.3% and 87.5% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively) said that milk teeth were important (statistically significant) (Figure 2), whereas a total of 47.5% grandparents (45%, 38.6%, 68.4% and 87.5% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively) said that problems of milk teeth could affect permanent teeth. Only 36% of grandparents (37.5%, 28.9%, 50% and 62.5% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively) knew that dental decay could be transmitted by sharing of spoons and cups. When asked whether prolonged bottle or breast feeding could affect dental health, 49.5% grandparents (47.5%,

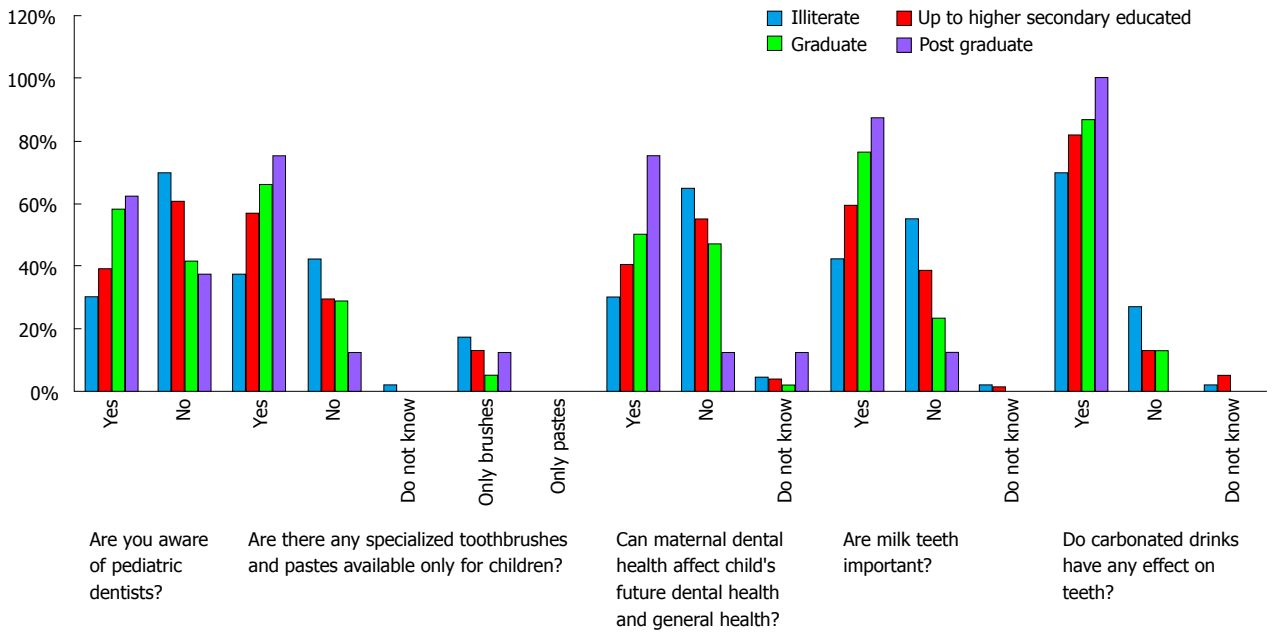

Figure 2 Analysis based on level of education of the grandparents.

45.6%, 60.5% and 62.5% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively) replied in the affirmative. A total of 32.5% grandparents (40%, 33.3%, 28.9% and 0% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively) said that it was alright to put children to bed with a bottle. A total of 36.5% of grandparents (37.5%, 28.9%, 50% and 75% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively) said that use of fluorides could strengthen teeth. A vast majority (81%) of grandparents (70%, 81.6%, 86.8% and 100% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳrespectively) knew that carbonated drinks had ill effects on teeth (statistically significant) (Figure 2). A vast majority (95%) of grandparents (100%, 93.8%, 92.1% and 100% of categories Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively) also knew that frequent snacking of sweet and sticky foods had ill effects on the teeth.

DISCUSSION

In the present study, the sample selected was dominated by female grandparents (70.5%) and a majority of the grandparents fell in the up to higher secondary educated group (57%). To the best of our knowledge no other study has been done to evaluate the level of dental awareness among grandparents, so a direct comparison of the above findings was not possible. In this study it was seen that the level of awareness about oral health was low among grandparents. A majority of them were not aware about paediatric dentists or specialized dentists for children. Awareness about the same was higher in the more educated groups but even among the post graduates, many were not aware of the same. There was no significant difference found between the genders. The grandparents were also not aware about the importance of frequent visits to the dentist so that any decay or condition can be recognized and rectified at an early stage. This indicates that there is an immediate and great need for education of caregivers like grandparents. The importance of such facts needs to be emphasized by paediatricians who see children at regular intervals or for vaccinations. Alternatively nurses can also be trained to impart this information in paediatric and vaccination wards of hospitals so that it can have an impact on maximum people.

When asked whether they had tried to treat their grandchildren at home with home remedies, the results obtained were surprising. It was found that people who were illiterates were in the habit of taking the children to a dentist whereas 50% of the postgraduates had tried their hand at treating the child themselves. People need to be educated that they should not try to treat children themselves, especially when the child cannot be relied upon to explain the symptoms correctly due to young age and lack of previous experience of dental pain. Children's understanding of pain and their ability to describe it changes in a predictable developmental sequence[9]. As the experience of pain is inherently personal and subjective, it is not directly accessible to others and requires considerable judgment and skill on the part of observers in the use of cues that are available, if inferences are to be accurate[10]. It should be stressed to the caregivers that they should always consult a specialist and not try to treat the children themselves as this may lead to wastage of precious time and the child may have to bear consequences that are permanent and irrevocable.

The grandparents showed good knowledge about the harmful effects of prolonged sucking habits. The female grandparents were much more aware about the same than their male counterparts, the difference being statistically significant ($P < 0.05$) (Figure 1). The reason for this can be that as females are more aesthetically

oriented[11] and spend more time looking after and caring for their grandchildren, they may notice little changes in the facial structure that occur during the growing up stages of the child.

When the responses of the same question were compared with the level of education, the surprising result was that the level of awareness was the same in the illiterates, up to higher secondary educated and the graduates (65%) but jumped to 100% in the postgraduates. The reason for this could be that the postgraduates, because of higher level of knowledge and understanding, probably come in contact with information from different sources such as media and newspapers, books and internet and hence, are more aware. The awareness about the deleterious effects of prolonged sucking habits need to be imparted to everybody so that such habits can be stopped before they have any effect on the oral structures.

The knowledge about the advantages of regular brushing was very good across genders and at all levels of education, probably because of the role of media in promoting tooth brushes. The awareness about specialized toothbrushes and pastes for children need to be improved, especially in caregivers of young children as children below 2 years of age should not be given fluoridated toothpastes, unless considered at moderate or high caries risk[12] and such small children won't be able to manoeuvre an adult brush in their small mouths. This can be achieved through the use of broadcast media, such as televisions. Another important source of information can be pharmacists who can help promote these by giving information to customers, especially as old people are likely to visit them more.

A majority of grandparents did not know about the transmission of cariogenic bacteria from mothers to their children[13,14], and the fact that it could increase the risk and severity of caries in very young children[15,16]. This knowledge was higher in the groups with a higher level of education but even among the well educated grandparents, a considerable proportion was not aware of the same (Figure 2). To improve this, workshops/lectures can be started in community centres or in places like meditation centres, laughter clubs, societies and book clubs etc. which are routinely frequented by the aged. Regarding the awareness about the appropriate age for the first dental visit and the age to start brushing the child's teeth, mixed results were obtained and no particular trend was followed. This shows that even people who have the highest level of education are not aware about basic and important health recommendations while caring for a child. Again the paediatrician or the nurses at hospitals and vaccination centres can help in spreading awareness about the same. Caretakers should be educated that regular tooth cleaning needs to be started early in life, as soon as the first primary tooth erupts[12].

Most grandparents knew about the number of permanent teeth in the mouth but not about the primary teeth. This could be due to the age old myth that as milk teeth are ultimately going to fall off, they are not important. A large number of the grandparents even acknowledged that they did not consider primary teeth to be of any importance and that they did not think that problems of primary teeth could affect permanent teeth. This misconception leads to neglect of the child's oral health by caregivers and because of bad habits instilled early in life, such children grow up to be adults who do not take good care of their teeth. The importance of primary teeth needs to be emphasized by paediatricians and general dentists so that this mindset can be changed. It has been reported in previous studies[17,18] that the low value attributed to primary teeth is an obstacle to developing effective prevention programs.

The practice of sharing foods and utensils by adults has been associated with early infection with *Streptococcus mutans* in infants[19,20]. Grandparents are often in the habit of checking the temperature of the food before giving it to the child by tasting it. This can be harmful as it can introduce caries causing microorganisms into the child's mouth if the same spoon or cup is used. Grandparents need to be educated about the harmful effects of such practices which they consider normal and routine.

Majority of the grandparents did not know about the harmful effects of prolonged bottle or breast feeding or the advantages of fluorides. Awareness of the same was more in the higher educated but not consistently or significantly. Knowledge about the deleterious effects of putting a child to bed with a bottle and use of carbonated drinks by older children was more in the higher educated grandparents (Figure 2).

There is a great need for education of grandparents regarding their grandchildren's oral health. This can be done by holding demonstrations and lectures/workshops in community centres. Also small demonstrations can be prepared and delivered in waiting areas of hospitals, nursing homes and dental clinics by volunteers or small documentaries can be made for televisions which are repeatedly played in the waiting area. Also nurses and other health personnel can be trained to impart information in vaccination centres. Paediatricians can also help in imparting information and guidance when the child is brought for any treatment. Posters regarding oral health related facts about children can be put up in paediatric wards and dental clinics/vaccination centres. All these measures can improve the preventive dental care children receive at home and their use of professional dental services, ultimately, bringing us closer to our international oral health goals for children.

COMMENTS

Background

In today's changing society where both parents are working, grandparents assume an important role as caregivers in their grandchildren's lives. There is a great need for dental education of grandparents as they serve as role models for the young. The attitude and knowledge of grandparents was evaluated in this study so as to implement changes to improve the oral hygiene standard of children.

Research frontiers

To the best of our knowledge, no such study has been done where only grandparents were evaluated for the role that they play in influencing children's oral health status. A review of literature revealed only one study where knowledge of caregivers, which included grandparents (107 grandparents out of 615 caregivers, *i.e.,* 17.4%) was studied. It has been seen that improving the knowledge of mothers has a positive influence on the children's oral health status.

Innovations and breakthroughs

The major conclusion from the article is that there is a great need for education of grandparents regarding their grandchildren's oral health. Since a lot of grandparents are playing a major role in caring for the children while both their parents are working, steps must be taken to ensure that they know how to take care of the oral hygiene of the children. Till now, major stress was given in imparting this knowledge to only parents, especially mothers.

Applications

To eliminate any disease, the first step is to gain knowledge of how that disease is contracted. Since dental caries cannot be reversed, to control it, we need to prevent its onset. This can only be done by maintaining proper oral hygiene. If children are educated about the value of maintaining proper oral hygiene, good habits can be instilled in them from a young age. Since grandparents play a big role in taking care of the children and serve as role models for them, they need to be educated about how to take care of their grandchild's oral health.

Terminology

Streptococcus mutans is facultative anaerobic, Gram-positive coccus-shaped bacterium commonly found in the human oral cavity and is a significant contributor to tooth decay.

Peer-review

An interesting article that provides a different perspective to the prevention of dental caries. It shows how caretakers need to be educated if we want the next generation to be free of oral diseases.

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ORIGINAL ARTICLE

Randomized Clinical Trial

Effects of carob-bean gum thickened formulas on infants' reflux and tolerance indices

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Clinical trial registration statement: The study is registered at http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4334. The registration identification number is NTR4334.

Informed consent statement: Written informed consent was obtained from the parents of all infants that were found to be eligible to be included in the study, prior to study enrollment.

Conflict-of-interest statement: Anne Schaafsma works for Friesland Campina. None of the other authors has any conflicts of interest to declare.

Data sharing statement: No further data is available.

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Abstract

AIM: To examine the effect of carob-bean gum (CBG) thickened-formulas on reflux and tolerance indices in infants with gastro-esophageal reflux (GER).

METHODS: Fifty-six eligible infants (1-6 mo old) were randomly allocated to receive for two weeks a formula with either 0.33 g/100 mL (Formula A) or 0.45 g/100 mL (Formula B) of cold soluble CBG galactomannans respectively, or a formula with 0.45 g/100 mL of hot soluble CBG galactomannans (Formula C). No control group receiving standard formula was included in the study. Data on the following indices were obtained both at baseline and follow-up from all study participants: 24 h esophageal pH monitoring indices, anthropometrical indices (*i.e.*, body weight and length) and tolerance indices (*i.e.*, frequency of colics; type and frequency of

defecations). From the eligible infants, forty seven were included in an intention-to-treat analysis to examine the effects of the two-week trial on esophageal 24 h pH monitoring, growth and tolerance indices. Repeated Measures ANOVA was used to examine the research hypothesis.

RESULTS: Regarding changes in 24 h pH monitoring indices, significant decreases from baseline to follow-up were observed in the "Boix Ochoa Score" (*i.e.*, an index of esophageal acid exposure), in the total number of visible refluxes and in all symptoms related indices due to acid reflux only for infants provided with Formula A, while no significant changes were observed for infants provided with Formulas B and C. In addition, the significant decreases observed in two symptoms related pH monitoring indices (*i.e.*, "Symptom index for reflux" and "Percentage of all reflux") for infants provided with Formula A were also found to differentiate significantly compared to the changes observed in the other two groups (P = 0.048 and P = 0.014 respectively). Concerning changes in anthropometric indices, body weight significantly increased among infants provided with Formulas A and C, but not for infants provided with Formula B. As far as tolerance indices were concerned, the numbers of total and diarrheic defecations increased significantly only in infants provided with Formula B and these changes were significantly higher compared to the decreases observed in infants fed with Formulas A and C (P = 0.003 and P = 0.015 respectively. Lastly the number of colics significantly decreased in all infants, irrespective of the tested formula.

CONCLUSION: Formula A (*i.e.*, 0.33 g/100 mL of cold galactomannans) was effective in reducing certain pH-monitoring indices of uncomplicated GER, increased body weight and was well-tolerated by infants.

Key words: Reflux; Carob bean gum; Galactomannans; Infants; Formula

Core tip: The present study showed that Formula A was more effective in decreasing esophageal acid exposure, the total daily number of visible and measurable refluxes, as well as acid reflux related symptoms, while such changes were not observed for the infants fed with Formulas B and C. Furthermore, a significant increase of body weight was observed for infants fed with Formulas A and C while that was not observed for infants fed with Formula B, probably due to the increased number of diarrheic and total defecations recorded in this group. These findings indicate that Formula A, containing 0.33 g/100 mL of cold soluble galactomannans, seems to be more effective in reducing certain pH-monitoring indices of uncomplicated gastro-esophageal reflux, increasing body weight and being well-tolerated by infants.

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INTRODUCTION

Gastro-esophageal reflux (GER) is defined as the involuntary passage of gastric contents (*e.g.*, saliva, ingested foods and drinks, gastric secretions, pancreatic or biliary secretions) into the esophagus and does not refer to any specific etiology with or without regurgitation and vomiting[1]. The term regurgitation is specifically used if the reflux dribbles effortlessly out of the mouth[2]. GER is a common and global problem affecting about 50% of all babies up to the age of two months and has a peak incidence at the age of three months. Only some infants will develop pathologic gastro-esophageal reflux disease (GERD), in which clinical problems are related to excessive passage of acid gastric contents. GERD should be suspected if the regurgitating infant shows one or more other symptoms such as crying, fussing or arching of the back, refusal to feed, failure to thrive, hematemesis, occult blood in the stool, anemia or refusal to eat[2,3]. Uncomplicated GER should be suspected in infants with uncomplicated recurrent regurgitation[1]. In some cases GER may affect thrive because of caloric insufficiency and potentially lower dietary nutrients' intake. There is often abnormal sucking and swallowing and weight gain may be poor.

Since infant regurgitation is a transient problem, treatment goals are to provide effective reassurance and symptom relief. Infants with GER may feel unhappy and parents often seek medical attention. The use of anti-reflux formulas and formulas with added thickening agents [*e.g.*, processed rice, corn or potato starch, guar gum or carob-bean gum (CBG)] results in a decrease of visible regurgitation[4]. CBG or locust bean gum is refined from the endosperm of seeds of the carob tree (Ceratonia siliqua). Eighty-five percent of the product is in the form of galacto-mannose oligo/polysaccharide having the monosaccharides mannose and galactose in a ratio of 4:1, about 5% is protein, and the final 10% is water. This galactomannan is indigestible but fermentable by colonic bacteria[5]. Because of this fermentable characteristic, some infants may react with abdominal pain, colic and diarrhea. In fact these adverse effects are normal for fiber ingestion and not specifically associated with CBG. Nevertheless, it seems that CBG is safe for its therapeutic use in term infants to treat GER from birth onwards[6]. Commercially available anti-reflux formulas currently contain CBG galactomannans at a concentration of 0.45 g/100 mL. However, Miyazawa *et al*[7,8] published studies in 2006 and 2007 reporting that lower dosages of CBG (0.35 g/100 mL) are effective too, at least with regard to visible refluxes. Although for these reasons the amount of CBG could be reduced to 0.35-0.40 g/100 mL, the

effect of these lower concentrations on measurable refluxes is not known.

The primary objective of the current study was to examine the efficacy of formulas containing cold *vs* hot soluble CBG galactomannans (at a concentration of 0.45 g per 100 mL) and the effect of feeding infants with a lower concentration of galactomannans (*i.e.*, 0.33 g per 100 mL) on visible and measurable refluxes assessed by 24 h pH impedance monitoring. Furthermore, a secondary objective was to determine whether the decrease in the concentration of galactomannans and the change from hot to cold soluble galactomannans affects weight gain and tolerance indices (*i.e.*, stool frequency and consistency, colic) in infants.

MATERIALS AND METHODS

Study design

The current study was a randomized, partly double blind clinical trial initiated on July 2013 and completed on July 2014 at the Second Pediatric Clinic in the University Hospital "St. Marine" Varna, Bulgaria. Informed consent was obtained from the parents of all infants that were found to be eligible to be included in the study. Prior to study's initiation and during the first screening phase, eligibility of infants to participate in the study was assessed according to the following inclusion criteria: Availability of parents/infants to participate in the study throughout the intervention period; less than ¼ of daily milk consumption coming from breast milk; no use of any anti-reflux formulae or medications that can affect gastrointestinal tract motility; no history, diagnosis or illness from cow's milk protein allergy (*i.e.*, positive IgE and/or positive skin prick test to cow's milk), wheezing, aspiration caused pneumonia, apnea, anemia, bleeding, laryngitis, urinary tract infection, diarrhea, neurologic deficits and any known organic or metabolic cause of reflux. Further to the initial screening phase, a total number of 56 one to six month-old infants that were born full-term, fulfilling all above inclusion criteria and diagnosed with GER (based on a score > 7 in the GER Orenstein questionnaire[9] as filled in by parents at inclusion) were considered eligible and entered the study. Eligible infants were randomized into three study groups based on the type of formula provided to them: Formula A containing 0.33 g/100 mL cold soluble galactomannans; Formula B containing 0.45 g/100 mL cold galactomannans; and Formula C containing 0.45 g/100 mL of hot soluble galactomannans. The cold soluble form of galactomannans is heated during production to be pre-gelatinised and gets gelatinised when dissolved in lukewarm water (*i.e.*, of approximately 45 ℃). The hot soluble form of CBG galactomannans is only minimally heated during production and needs to be dissolved in hot water (*i.e.*, of approximately 90 ℃) to be gelatinised. The difference in water temperature explains why this study could not be double blind for all study groups. More specifically, parents whose infants were allocated to Formulas A and B were instructed to use lukewarm water, whereas those parents whose infants were allocated to Formula C were instructed to use hot water for the preparation of the relevant milk formulae. Further to the above although the intervention was double blind for the study groups receiving Formula A and Formula B, this was not feasible for the Formula C treatment arm.

Following the first screening and before allocation of eligible infants to the study groups all infants were fed with a standard infant formula (Frisolac Gold 1, Friesland Campina, the Netherlands) for seven consecutive days, which served as a "run-in" period before the initiation of the intervention. On day seven, baseline anthropometric and 24 h pH impedance monitoring measurements were conducted. From day eight to day 21 the infants received the intervention Formula A, B or C. Allocation of infants to each one of three treatment arms was based on a standard table developed by a statistician (StatistiCal B.V., Wassenaar, The Netherlands), randomly assigning a different numerical code to each study participant receiving one of the three test formulae. On day 22 the final anthropometric and 24 h pH impedance monitoring measurements were conducted. Formula C was the reference formula and was provided to parents in the standard Friso Comfort packaging. The other two test formulae were provided in blank sachets labeled with either "A" or "B". The product developer kept the decoding information in a sealed envelope, which was opened after completion of the intervention and evaluation of the study results.

Measurements

The measurements conducted and the data collected in the present study are summarized below.

Gastro-esophageal reflux questionnaire: The gastro-esophageal reflux questionnaire (GERQ) is an instrument developed and validated for diagnosis of GER in infants and toddlers from 1 to 14 mo old[9,10]. Based on the scoring (*i.e.*, GERQ score) derived from the answers provided by mothers, infants with a GERQ score > 7 (*i.e.*, score indicative of possible GER) were considered eligible to participate in the study. The appropriateness of using the Orenstein questionnaire to identify infants with GER in the current study was also confirmed by the pH monitoring indices values obtained at baseline. Specifically, all eligible children identified by Orenstein questionnaire were also found to have pH indices above the references values suggested by Kitz *et al*[11] at baseline.

Three-day diaries: A 3-d diary was provided to mothers both at the start and at the end of the intervention period (*i.e.*, the diaries were filled in by mothers from day four until day six and from day 18 to day 20), in order to record "tolerance" indices (*i.e.*, type and frequency of colic and defecations) and information regarding the amount of formula consumed by their infants during the day. Regarding colic, that was defined based on the classic

definition of infantile colic and specifically an approach based on the rule of threes: *i.e.*, fussy crying that lasts for 3 h per day and for 3 d per week[12]. Regarding defecations, the total number of infants' defecations was recorded by mothers in the diaries, while a visual chart, *i.e.*, the *Bristol Stool chart* (BSC), that classifies defecations based on 7-point stool hardness scale (1, hard; 7, watery) was used to define constipation; diarrhea and ideal-stool defecations. BSC is currently the most popular scale/tool used in many clinical trials also conducted on infants and children to assess stool consistency[13]. Regarding the amount of formula consumed by their infants during the day, mothers were asked to keep a record reporting the exact volume of milk formula prepared and the exact volume of milk formula left over after each feeding. This information was recorded during the total intervention period in relevant record sheets that were provided to mothers. Mothers received both written and verbal instructions for the correct completion of the diaries and the record sheets.

Anthropometrical measurements: Body weight of infants was measured, as an average of two separate measurements, on a calibrated scale (Digital baby weight scale Seca 374) to the nearest 10 g, without cloths and diapers. Recumbent length of infants was measured as an average of two separate measurements, using a length board (Seca 416 infantometer for measuring babies and toddlers) to the nearest 1 cm according to standard instructions.

Gastro-esophageal reflux monitoring: Gastro-esophageal reflux was quantitatively assessed *via* combined measurements of the intra-esophageal pH and multiple electrical impedance[14,15], using the Digitrapper pH-Z ambulatory 24 h pH and impedance recorder (Digitrapper, Sierra Scientific Instruments, Los Angeles, CA) and the relevant software (AccuView pH-Z). According to its principle of operation, this method measures the electrical impedance changes between two neighboring electrodes during the passage of a bolus inside a luminal organ (*i.e.*, retrograde bolus movement in the esophagus in the current study). An age-appropriate catheter was used in the current study depending on the infant's length and was placed trans-nasally above the upper boarder of the lower esophageal sphincter. The correct positioning of the catheter during the 24 h esophageal pH monitoring was assessed *via* X-ray at both baseline and follow-up examination. The purpose of X-ray was to ensure that the catheter was positioned above the stomach and specifically three vertebrae above the diaphragm following the guidelines from the European Society for Pediatric Gastroenterology, Hepatology and Nutrition[1].

Esophageal pH impedance monitoring was performed continuously for 19-24 h at the two time points of measurements, *i.e.,* before the initiation and at the end of the intervention. At the end of each recording, data were analyzed using the AccuView pH-Z™ software version 5.2 (Given Imaging Ltd, Israel) and results were expressed in 10 pH impedance monitoring indices. Among the 24 h pH monitoring indices, the recording of the "symptom-related" indices required caregiver's interference by pressing an "event button" any time the baby was crying or was showing signs of anxiety or discomfort (according to parent's/caregiver's perception). This was not required for all other pH indices *(i.e.*, "non-symptom related" ones).

Statistical analysis

The sample size estimation in the present study was based on the experience gained from a previous intervention study[16] conducted also with Bulgarian infants, examining the same outcomes (*i.e.*, the same pH monitoring indices) as the current study. Based on the observed changes in pH monitoring indices observed in this previous intervention study, a minimum sample size of 30 subjects (or 10 subjects per treatment arm) was considered adequate to provide in the present study a statistical power of 90%.

The effect of the intervention scheme on pH monitoring, growth and tolerance indices was examined using intention-to-treat (ITT) analysis. Multiple imputations were performed to estimate missing follow-up data due to drop-outs and the pooled imputed data were used in all subsequent analyses. All data were reported as mean (SD) and as mean change (95%CI) over baseline. Normality tests were used to determine normality of distribution of the examined variables. Repeated measures analysis of variance (Repeated Measures ANOVA) was used to assess the significance of the differences between groups at baseline and follow-up examination (Treatment effect), the significance of the changes observed within each group (Time effect) and the significance of the differences among groups in the changes from baseline to follow-up examination (Treatment X Time Interaction effect). The between-group factor was the study groups (*i.e.*, Formula A *vs* Formula B *vs* Formula C); the within-group factor was the time-point of measurement (*i.e.*, baseline, follow-up). In all analyses, adjustments were made for the average volume of milk consumed by infants per day during the intervention period. All *P*-values reported were two-tailed. Statistical analysis was conducted with the use of the SPSS statistical analysis software for Windows (version 21.0). The level of statistical significance was set at $P \leqslant 0.05$. The statistical methods of this study were reviewed by Dr. Kourlaba Georgia from The Stavros Niarchos Foundation-Collaborative Center for Clinical Epidemiology and Outcomes Research.

Ethics statement

The study was approved by the Medical Ethical Committee of the "St. Marina" University Hospital of Varna (Ethical approval No. 13/03.28.2013) and was implemented in accordance to the signed protocol and the rules for good clinical practice. The study was registered in the Netherlands Trial Register: NTR4334.

RESULTS

Figure 1 presents a flow diagram of infants that were

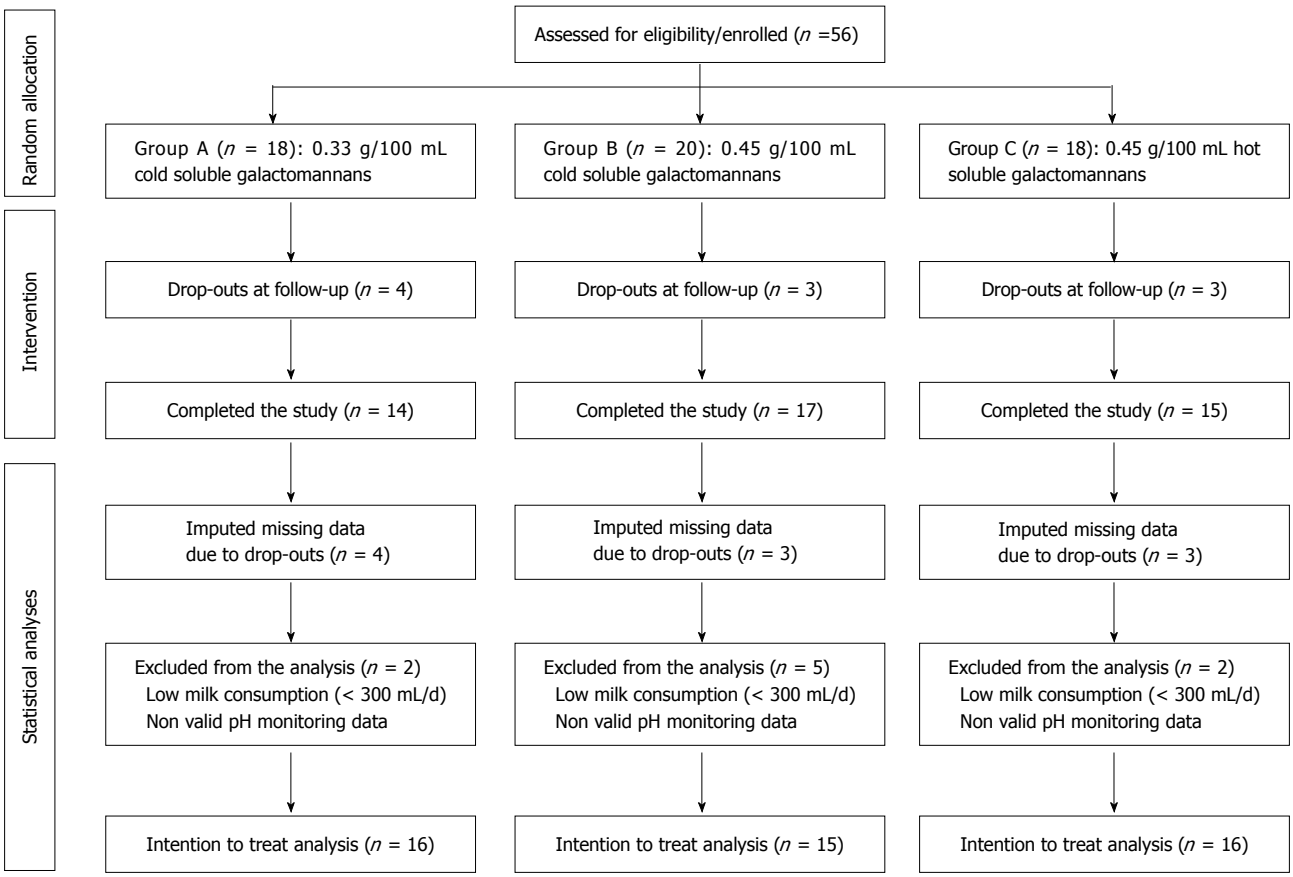

Figure 1 Flow of study participants through the trial.

included in the statistical analysis. More specifically, 56 eligible infants were identified at the initial screening phase. From these 56 infants, 10 infants either dropped out at follow-up or did not perform the 2nd 24 h esophageal pH monitoring due to parental refusal to provide consent for the follow-up pH measurement. Nevertheless, as these 10 infants were actually subjected to treatment almost throughout the intervention period, multiple imputations were conducted to estimate their missing data at follow-up examination and these infants were reinstated in the study sample for which the ITT analysis was performed. Before performing the ITT analysis, a thorough examination of the collected data revealed that for five infants at least one of the two 24 h pH impedance monitoring measurements was non-valid (*i.e.*, mainly due to the incorrect positioning of the catheter), while in four infants the average daily milk consumption was quite low (*i.e.*, below 300 mL per day) throughout the intervention period. These nine infants were excluded from the ITT analysis, which was finally performed for a total sample 47 infants. The results from these analyses are presented in Tables 1-3 and in Figure 2.

Tables 1 and 2 present the changes in the "non-symptom related" and "symptom related" 24 h pH monitoring indices, respectively. According to the data presented in Table 1, significant decreases from baseline to follow-up examination were observed for the "Boix Ochoa Score" and the "Number of refluxes per day" (by 72.0 and 231.8 respectively), only for the Formula A group (percent changes from baseline in the three study groups are also presented in Figure 2). Still, these changes did not differentiate significantly with the changes observed in the other two study groups. No other significant findings were observed for the rest of the "non-symptom related" 24 h pH monitoring indices examined in the present study. Based on the data displayed in Table 2, significant decreases were observed from baseline to follow-up examination for all "symptom related" 24 h pH monitoring indices only for infants fed with Formula A. Furthermore, in two out of the four "symptom-related" indices examined, the decreases observed for infants fed with Formula A from baseline to follow-up examination (*i.e.*, by -18.2 in SI and by -16.9% in the percentage of all refluxes) were significantly higher compared to the relevant changes in other two groups (*i.e.*, $P < 0.05$).

Table 3 summarizes the changes observed in growth and tolerance indices. As far as growth indices were concerned, body weight significantly increased for infants fed with Formula A (by 0.57 kg or 40.7 g per day) and C (by 0.79 kg or 56.4 g per day). Nevertheless these changes from baseline to follow-up examination were not found to differentiate significantly among the three study groups. Furthermore, no significant differences were observed among groups with regards to recumbent length, which increased significantly in all three study

Table 1 Changes in "non-symptom related" 24 h pH monitoring indices from baseline to follow-up examination by study group

	Baseline		Follow up		2-wk change		*P*-value (treatment x time)
	Mean	(SD)	Mean	(SD)	Mean change	(95%CI)	
Reflux Index (%)							0.484
Formula A (n = 16)	11.4	-10.3	8.97	-8.23	-2.52	(-9.48 to 4.45)	
Formula B (n = 15)	6.47	-5.67	10.1	-13.1	3.44	(-3.85 to 10.7)	
Formula C (n = 16)	10.3	-12.6	9.42	-10.2	-0.67	(-7.77 to 6.44)	
P value (Treatment effect)	0.247		0.901				
Longest reflux (min)							0.445
Formula A (n = 16)	19.3	-15.4	13.9	-8.69	-5.16	(-13.8 to 3.48)	
Formula B (n = 15)	15.7	-18.4	11.8	-7.27	-3.31	(-12.3 to 5.73)	
Formula C (n = 16)	14.4	-9.47	17.6	-16.6	2.48	(-6.32 to 11.3)	
P value (Treatment effect)	0.664	0.219					
Total time below pH 4 (min)							0.722
Formula A (n = 16)	12.2	-12.1	7.85	-7.64	-4.5	(-13.6 to 4.58)	
Formula B (n = 15)	11.5	-20.3	10.3	-13.1	-1.7	(-11.2 to 7.80)	
Formula C (n = 16)	9.66	-12.9	9.84	-10.3	0.72	(-8.54 to 9.98)	
P value (Treatment effect)	0.944		0.655				
Reflux below pH 4 for more than 5 min (n/d)							0.712
Formula A (n = 16)	6.42	-7.19	4.6	-5.21	-1.76	(-5.89 to 2.38)	
Formula B (n = 15)	4.08	-4.28	4.33	-4.83	0.48	(-3.85 to 4.80)	
Formula C (n = 16)	5.53	-8.34	5.96	-5.86	0.15	(-4.06 to 4.37)	
P value (Treatment effect)	0.446		0.452				
Boix Ochoa Score[1]							0.198
Formula A (n = 16)	107.6	-163	36.6	-29.4	-72.0[3]	(-131.6 to -12.5)[3]	
Formula B (n = 15)	53	-78.1	45	-41.8	-12.3	(-74.6 to 50.0)	
Formula C (n = 16)	57.2	-80.7	52.1	-49.8	-0.08	(-60.8 to 60.7)	
P value (Treatment effect)	0.346		0.381				
Total refluxes per day (n/d)[2]							0.385
Formula A (n = 16)	377.3	-524.5	142.9	-118	-231.8[3]	(-437.9 to -25.8)[3]	
Formula B (n = 15)	169.3	-217	128	-97	-30.9	(-246.6 to 184.8)	
Formula C (n = 16)	307.3	-475.4	220.4	-266.8	-99.2	(-309.5 to 111.1)	
P value (Treatment effect)	0.343		0.234				

[1]Global measure of esophageal acid exposure; [2]Indicative of the total number of visible and measurable refluxes during the 24 h monitoring; [3]Indicate statistical significant findings. The "non-symptom related" 24 h pH monitoring indices include those indices recorded during the 24 h pH monitoring procedure, not requiring caregiver's interference by pressing the "event button. Adjustment was made for the average volume of milk consumed by infants per day during the intervention period.

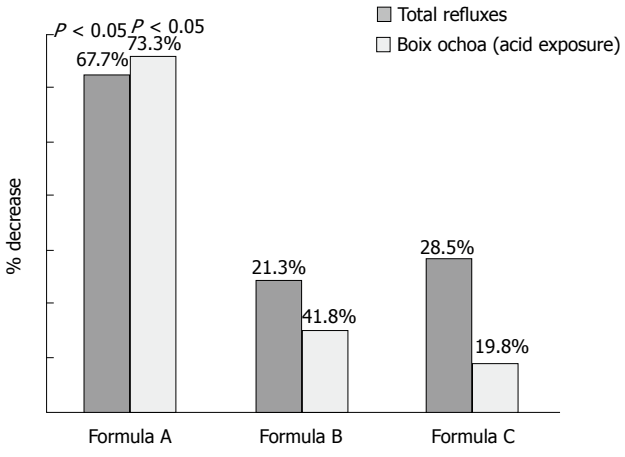

Figure 2 Percent decreases from baseline to follow-up in the "Boix Ochoa Score" index and "number of refluxes per day" in the Formula A (0.33 g/100 mL cold carob-bean gum), B (0.45 g/100 mL cold carob-bean gum) and C (0.45 g/100 mL hot carob-bean gum) groups.

groups. Regarding tolerance indices, the number of diarrheic and total defecations, increased significantly from baseline to follow-up examination by 5.47 and 6.02, respectively, only for infants fed with Formula B. On the contrary, a significant decrease by 5.72 in the number of total defecations was observed for infants fed with Formula C. Furthermore the increases observed in the number of diarrheic and total defecations for infants fed with Formula B were significantly higher compared to the changes observed in the other two groups (P = 0.015 and 0.003, respectively). Lastly, the total number of colics decreased significantly form baseline to follow-up examination in all three study groups, but no significant differences in these changes were observed among groups.

DISCUSSION

In the current study, among the several pH monitoring indices examined, only "Boix Ochoa score" and the "Total number of refluxes per day" showed significant decreases for infants fed with Formula A, while no significant changes were observed for infants fed with Formulas B and C. Furthermore, Formula A was found to be more effective in decreasing acid reflux-related symptom indices compared to the two other formulas (Table 2). Similarly, to the present study the majority of previous clinical trials assessing the

Table 2 Changes in "symptom related" 24 h pH monitoring indices from baseline to follow-up examination by study group

	Baseline		Follow up		2-wk change		*P*-value (treatment x time)
	Mean	(SD)	Mean	(SD)	Mean change	(95%CI)	
Symptom index for reflux (SI)							0.048[3]
Formula A (n = 16)	39.7	-26.2	21.6	-14.5	-18.2[3]	(-31.8 to -4.57)[3]	
Formula B (n = 15)	24.5	-27.2	19.7	-20.8	-5.21	(-19.5 to 9.03)	
Formula C (n = 16)	27.7	-20.6	33.7	-24.8	6.49	(-7.39 to 20.4)	
P value (Treatment effect)	0.213		0.119				
Symptom association probability[1]							0.096
Formula A (n = 16)	87.4	-25.2	49.5	-42.5	-37.9[3]	(-64.6 to -11.3)[3]	
Formula B (n = 15)	54.6	-47.3	58.7	-40.2	3.82	(-24.1 to 31.7)	
Formula C (n = 16)	82.9	-33.8	57.8	-38.3	-24.8	(-52.0 to 2.37)	
P value (Treatment effect)	0.031		0.762				
Percentage of acid refluxes[2] (%)							0.067
Formula A (n = 16)	39.8	-26.1	22.6	-15.0	-17.2[3]	(-30.8 to -3.66)[3]	
Formula B (n = 15)	24.6	-27.3	19.4	-20.8	-5.53	(-19.7 to 8.65)	
Formula C (n = 16)	27.7	-20.4	33.3	-25.3	5.93	(-7.89 to 19.8)	
P value (Treatment effect)	0.21		0.152				
Percentage of all reflux (%)							0.014[3]
Formula A (n = 16)	47.9	-22.3	31.0	-18.1	-16.9[3]	(-31.3 to -2.28)[3]	
Formula B (n = 15)	35.1	-23.6	36.8	-28.7	1.78	(-13.3 to 16.9)	
Formula C (n = 16)	33.7	-22.3	48.2	-28.8	14.4	(-0.28 to 29.2)	
P value (Treatment effect)	0.167		0.201				

[1]Probability that symptom and reflux are not associated solely by chance; [2]Percentage of acid refluxes out of the total number of refluxes occurring during the 24 h monitoring; [3]Indicate statistical significant findings. The "symptom related" 24 h pH monitoring indices include those indices recorded during the 24 h pH monitoring procedure requiring caregiver's interference by pressing the "event button". Adjustment was made for the average volume of milk consumed by infants per day during the intervention period.

effectiveness of formulas containing different types and concentrations of various thickening agents found no significant differences on the most commonly pH indices examined, *i.e.*, the Reflux Index, the number of reflux episodes lasting more than 5 min and the duration of the longest reflux episodes[4]. The only exception were two clinical trials, out of 14, that reported significant decreases in these three pH indices after providing formulas thickened with re-gelatinised corn-starch *vs* a control group receiving a standard formula, for four weeks[17,18]. However, considering the above, direct comparisons of the current study with these two studies are probably not feasible, mainly because of the shorter intervention period, the different thickening agent and the lack of a control group in the current study.

Similar favourable changes in the aforementioned three pH monitoring were also reported by Marinova and Stoimenova[16] on infants fed for two weeks with a formula containing 0.5 g/100 mL of hot-soluble CBG galactomannans. In this study infants were provided with the thickened formula after having been fed with a standard formula for two weeks. These favourable changes observed over the total intervention period of four weeks could be also partially attributed to the gastro-esophageal maturation. Although the same thickening agent was used as in the current study, these findings are not directly comparable to the current ones due to the slightly higher concentration of CBG galactomannans in the tested formula and the different equipment and analysis software used for the 24 h pH monitoring.

Reduced intake of calories and nutrients due to GER and consequently poor growth is of concern. In line with other studies[4], the present study showed increases of body weight during the 2-wk intervention period. These increases were significant for infants fed with Formulas A and C and were 40.7 and 56.4 g per day, respectively (Table 3). The findings of the present study regarding the concentration of CBG in Formula A (*i.e.*, 0.33 g/100 mL) and the weight gain observed seem to be comparable with previous studies providing CBG in similar concentrations. More specifically, in the study of Miyazawa *et al*[19], when 0.35 g/100 mL CBG-galactomannans were provided a weight gain of 29.3 g per day was observed after one week of intervention. In the study of Vandenplas *et al*[20] when 0.33 and 0.36 g/100 mL CBG-galactomannans (*i.e.*, calculated with 13 g of infant milk powder per 100 mL and 85% galactomannans in CBG) were provided, the weight gains observed were 37 and 24 g per day, respectively, after two weeks of intervention and 27.5 and 25 g per day, respectively, after four weeks of intervention. Taken together, it seems that the increase in body weight as seen in group A is comparable to the increases reported in other studies also using CBG thickened formulas in similar concentrations as in Formula A. However, regarding the increase in body weight observed in Formula C, this was higher compared to those reported in other studies providing similar or higher concentrations. For instance in the study of Vivatvakin and Buachum[21], when a comparable product with an even higher CBG concentration (*i.e.*, 0.5 g/100 mL) than Formula C was provided, a weight gain of 24.5 g per day was observed after two weeks of intervention. The higher mean volume of milk formula consumed by infants fed with Formula C

Table 3 Changes in growth and tolerance indices from baseline to follow-up examination by study group

	Baseline		Follow up		2-wk change		*P*-value (treatment x time)
	Mean	(SD)	Mean	(SD)	Mean change	(95%CI)	
Growth indices							
Weight (kg)							0.648
Formula A (n = 16)	5.8	-1.34	6.37	-1.11	0.57[3]	(0.14 to 0.99)[3]	
Formula B (n = 15)	5.36	-1.44	5.91	-1.37	0.51	(-0.06 to 0.96)	
Formula C (n = 16)	5.33	-1.73	6.06	-0.97	0.79[3]	(0.35 to 1.22)[3]	
P value (Treatment effect)	0.355		0.40				
Length (cm)							0.917
Formula A (n = 16)	61.2	-5.57	63.2	-5.07	1.93[3]	(0.59 to 3.27)[3]	
Formula B (n = 15)	59.4	-6.23	61.5	-6.02	2.07[3]	(0.67 to 3.48)[3]	
Formula C (n = 16)	60.2	-3.76	62.5	-3.53	2.33[3]	(0.96 to 3.70)[3]	
P value (Treatment effect)	0.543		0.631				
Tolerance indices							
Total number (3 d) of hard stools[1]							0.723
Formula A (n = 16)	0.5	-2.00	0.48	-1.07	-0.01	(-0.81 to 0.79)	
Formula B (n = 15)	0.2	-0.56	0.55	-1.45	0.4	(-0.44 to 1.24)	
Formula C (n = 16)	0.13	-0.50	0.17	-0.47	-0.02	(-0.83 to 0.80)	
P value (Treatment effect)	0.62		0.291				
Total number (3 d) of diarrheic defecations[2]							0.015[3]
Formula A (n = 16)	8.38	-11.6	5.31	-5.63	-2.88	(-7.91 to 2.16)	
Formula B (n = 15)	5.6	-4.81	10.3	-10.1	5.47[3]	(0.0 to 10.7)[3]	
Formula C (n = 16)	11.1	-10.7	6.77	-6.68	-5.3	(-10.4 to -0.16)	
P value (Treatment effect)	0.163		0.176				
Total number of defecations (3 d)							0.003[3]
Formula A (n = 16)	10.7	-10.4	7.59	-4.23	-2.89	(-7.42 to 1.64)	
Formula B (n = 15)	7.33	-3.81	12.5	-9.05	6.02[3]	(1.28 to 10.8)[3]	
Formula C (n = 16)	12.8	-9.39	8.07	-5.70	-5.72[3]	(-10.3 to -1.10)[3]	
P value (Treatment effect)	0.153		0.040[3]				
Number of colics per day							0.569
Formula A (n = 16)	3.31	-2.72	1.34	-1.33	-1.99[3]	(-3.02 to -0.95)[3]	
Formula B (n = 15)	4.42	-2.44	1.59	-1.61	-1.87[3]	(-2.96 to -0.79)[3]	
Formula C (n = 16)	2.79	-1.55	1.5	-1.18	-1.24[3]	(-2.30 to -0.19)[3]	
P value (Treatment effect)	0.868		0.735				

[1]Hard stools are indicative of constipation and were corresponding to the Bristol stool chart types 1 and 2; [2]Diarrheic defecations were corresponding to the Bristol stool chart types 5, 6 and 7; [3]Indicate statistical significant findings. Adjustment was made for the average volume of milk consumed by infants per day during the intervention period.

(*i.e.*, 841.3 mL) compared to infants fed with Formulas A (*i.e.*, 756.7 mL) and B (*i.e.*, 711.9 mL) in the present study as well as to infants in the study of Vivatvakin and Buachum (*i.e.*, 589.5 mL)[21] might provide an explanation for these differences. However, as the exact volume of breast milk consumed by infants in the present study could not be recorded or estimated, the reasoning provided above might not fully explain the observed weight gain in group C.

In studies examining the effect of other thickening agents instead of CBG on weight gain some mixed results were observed. Xinias *et al*[17] reported no significant differences in weight gain between the experimental and control groups after four weeks of intervention with cornstarch-thickened formulas. Furthermore, Chao and Vandenplas[22] reported no significant differences in body weight gain between the control and intervention groups during the first two weeks, but significantly higher increases at four and eight weeks of intervention compared to the control group. Similarly, in another study by Chao and Vandenplas[23], when rice-thickened formula was provided, significantly higher weight gains were observed at four and eight weeks of intervention for the intervention compared to the control group.

Regarding changes observed in tolerance indices, the present study showed a significant increase in the number of diarrheic and total defecations from baseline to follow-up for the infant fed with Formula B. In contrast, no such unfavorable adverse effects were observed for infants fed with Formulas A and C, potentially indicating that this might be an adverse effect only of Formula B providing 0.45 g/100 mL of cold soluble CBG-galactomannans. This observation could further provide an explanation for the non-significant increase of body weight recorded for infants fed with Formula B, while body weight significantly increased among infants in the other two study groups. Of course the subjective assessment and recording of these indices by parents/caregivers might have also produced bias that needs to be considered when interpreting these findings.

The results of the present study should be interpreted under the light of its strengths and limitations. Regarding strengths, the inclusion of a "run-in" period in the study protocol and the measurement of reflux by pH-monitoring increase methodological integrity and decrease possible bias in data collection and results.

However, the use of fairly new pH-monitoring equipment can be considered as a limitation of the current study, since direct comparisons with previous studies and results/outcomes may not be feasible or appropriate. Furthermore, the absence of a control group can be considered as another limitation of the current study, since this might have limited the ability to have a more clear view on the effectiveness and tolerance of the three anti-reflux formulas under study. Lastly, although the number of infants examined in the present study was relatively small, the imputation of missing data as part of the ITT analysis resulted to a sufficient sample size and as such to adequate statistical power for the analyses. Nevertheless, future intervention studies with larger samples sizes should be implemented in order to shed more light on this field.

In conclusion, the present study showed that Formula A was more effective in decreasing esophageal acid exposure (as indicated by the Boix Ochoa Score), the total daily number of visible and measurable refluxes, as well as acid reflux related symptoms, while such changes were not observed for the infants fed with Formulas B and C. Furthermore, a significant increase of body weight was observed for infants fed with Formulas A and C while that was not observed for infants fed with Formula B, probably due to the increased number of diarrheic and total defecations recorded in this group. These findings indicate that Formula A seems to be more effective in reducing certain pH-monitoring indices of uncomplicated GER, increasing body weight and being well-tolerated by infants.

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COMMENTS

Background

Gastro-esophageal reflux (GER) is a common and global problem affecting about 50% of all babies up to the age of two months and has a peak incidence at the age of three months. Only some infants will develop pathologic gastro-esophageal reflux disease, in which clinical problems are related to excessive passage of acid gastric contents. Uncomplicated GER should be suspected in infants with uncomplicated recurrent regurgitation. In some cases GER may affect thrive because of caloric insufficiency and potentially lower dietary nutrients' intake which may lead to poor weight gain. The use of anti-reflux formulas with added thickening agents, such as carob-bean gum (CBG), can decrease the frequency and intensity of GER.

Research frontiers

Commercially available anti-reflux formulas currently contain 0.45 g/100 mL hot-soluble CBG galactomannans. With the exception of one study, there are no other randomized clinical trials available in the literature examining the effectiveness of anti-reflux formulas containing less than 0.45 g/100 mL hot-soluble CBG galactomannans on reflux and tolerance indices. In addition there are no reports examining the effectiveness of cold *vs* hot-soluble CBG galactomannans on reflux and tolerance indices.

Innovations and breakthroughs

The current study is the first to examine the effectiveness of formulas containing cold or hot soluble CBG galactomannans in different concentrations (*i.e.*, 0.45 g or 0.33 g/100 mL) on reflux indices assessed by 24 h pH impedance monitoring as well as on tolerance indices (*i.e.*, defecations and colic).

Applications

The formula containing 0.33 g/100 mL of cold-soluble CBG galactomannans was effective in reducing certain pH-monitoring indices of uncomplicated GER, increased body weight and was well-tolerated by infants.

Terminology

GER is defined as the involuntary passage of gastric contents into the esophagus and does not refer to any specific etiology with or without regurgitation and vomiting. The term regurgitation is specifically used if the reflux dribbles effortlessly out of the mouth.

Peer-review

In their work, the authors present a very clear and well conducted, controlled randomized study analyzing the effects of three different anti-reflux formulas for infants with GER (excluding complicated cases). The study include not too many, but a sufficient number of patients, it was performed for a relatively short period of time, but probably just sufficient. It is well described, and the results are conclusive and helpful.

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CASE REPORT

Tourette syndrome associated with attention deficit hyperactivity disorder: The impact of tics and psychopharmacological treatment options

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Abstract

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by multiple chronic motor and vocal tics beginning in childhood. Several studies describe the association between TS and attention deficit hyperactivity disorder (ADHD). Fifty percent of children diagnosed with ADHD have comorbid tic disorder. ADHD related symptoms have been reported in 35% to 90% of children with TS. Since ADHD is the most prevalent comorbid condition with TS and those with concomitant TS and ADHD present with considerable psychosocial and behavioral impairments, it is essential for clinicians to be familiar with these diagnoses and their management. This paper highlights the association between treating ADHD with stimulants and the development of tic disorders. The two cases discussed underscore the fact that children with TS may present with ADHD symptomatology prior to the appearance of any TS related symptoms. Appropriate management of TS in a patient diagnosed with ADHD can lead to quality of life improvements and a reduction in psychosocial impairments.

Key words: Tourette syndrome; Psychopharmacology; Attention deficit hyperactivity disorder; Tics

Core tip: Tics can be a symptom of Tourette syndrome

(TS). Attention deficit hyperactivity disorder (ADHD) has the highest comorbidity with TS. Psychopharmacological treatment of ADHD with stimulants may cause, or exacerbate pre-existing, tics. Because of this, providers may be reluctant to use stimulants in patients with comorbid tic disorders. However, the role of stimulants in the treatment of TS associated with ADHD, when the benefits outweigh the risks, cannot be over emphasized as a comprehensive approach, considering all treatment options for managing TS and ADHD will yield better outcomes.

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INTRODUCTION

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by multiple chronic motor and vocal tics developing before adulthood[1]. Tics are sudden, rapid, recurrent, non-rhythmic, stereotyped and involuntary motor movements or vocalizations. They are classified as either simple or complex, with the former affecting several muscle groups. Motor tics can affect any part of the body with varying location, frequency and complexity of movements which may change over time. Vocal tics, also known as phonic tics, are involuntary sounds produced by air motion through the nose, mouth, or throat[1,2]. See Table 1 for types and description of tics[1,3].

Although the American Psychiatric Association Diagnostic and Statistical Manual, Fifth Edition (DSM-5) diagnostic criteria for TS necessitate the presence of both multiple motor and one or more vocal tics, they need not occur concurrently. The tics may wax and wane in frequency and must have lasted for more than one year since first onset. Substance induced etiologies, for example cocaine use, and general medical conditions such as Huntington's disease or post viral encephalitis, are exclusionary criteria[1].

The Tourette Syndrome Classification Study Group defined TS as the presence of motor and vocal tics with frequent tics almost daily for at least one year, with an onset before age 21. In addition, the symptoms should be observed by an examiner[3]. See Table 2 for definitions and classification of tic disorders.

The prevalence of tic disorders in the classroom is between 5% and 20% of children, with impairments occurring in 1-10 per 1000[4-6]. Tic disorders have comorbidity with other disorders including obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), learning difficulties and sleep abnormalities[2,5,6]. Leckman[7] (2002), reported the average age of onset of TS symptoms as seven years with a range from three to eight years. However, the DSM-5 gives the average tic onset age as between four and six years with peak severity being between 10 and 12 years[1]. See Figure 1 for clinical course of TS.

ADHD is the most common childhood psychiatric disorder with an estimated prevalence of 2% to 15%[8]. The onset of ADHD symptoms is usually between four and five years of age, thus generally appearing before the onset of tics[9]. ADHD related symptoms have been reported in 35% to 90% of children with TS[2,4,5,10]. TS with concomitant ADHD can cause significant psychosocial and behavioral impairments[11]. We present two cases of adolescent TS associated with ADHD and hypothesize that stimulant medications did not exacerbate the former disorder in these patients.

CASE REPORT

Case 1

An 8-year-old boy was referred to the child psychiatric clinic by his school due to his use of inappropriate language. He was diagnosed with ADHD at 4 years of age. At age six he was treated with stimulants, including methylphenidate and mixed amphetamine salts. Significant improvement of his ADHD symptoms occurred with immediate release mixed amphetamine salts, but the medication was discontinued due to excessive blinking and bilateral hand tics. Of note, the child's maternal uncle had a history of TS. The stimulant was discontinued and, 4 wk later, the tics subsided. However the blinking continued intermittently. As a result, child neurology was consulted and clonidine 0.1 mg at night was prescribed to manage the ADHD and insomnia. On this regimen the boy's parents noted a lessening of his hyperactivity and impulsivity, but a continued poor attention span. The child started using profanity at school, which led to his being bullied as well as his eventual suspension from school. Both the neurologist and the child psychiatrist agreed to re-evaluate the child for possible TS. The neurological examination was essentially normal. His EKG and routine blood tests, including a CBC, CMP and a lead level, were non-significant. Based on his history and clinical examination, a diagnosis of TS was made. He was started on immediate-release dexmethylphenidate 5 mg twice daily, gradually increased after 4 wk to 10 mg twice daily for the ADHD related symptoms. His regimen was later simplified by changing to a morning dose of 25 mg of the extended-release form. The core TS symptoms were treated with risperidone 0.125 mg twice daily, increased after 6 wk to a maintenance dose of 0.5 mg twice daily. The severity of his tics was monitored using the Yale Global Tic Severity Scale (YGTSS). After 6 mo of treatment, the boy's vocal tics completely subsided. He continued to have intermittent blinking, but with a significant reduction in frequency from once every few minutes to less than 10 times per day.

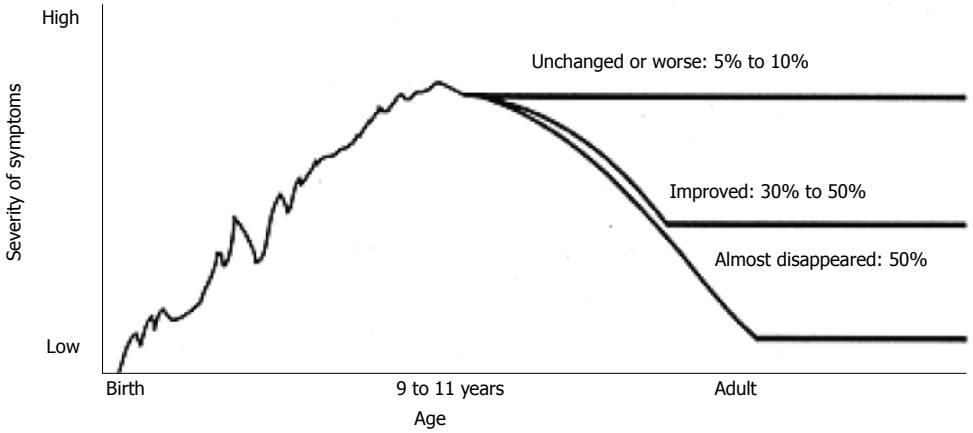

Figure 1 Onset of Tourette syndrome is before 7 years of age. It is usually recognized 2-3 years after onset. TS peak severity is at 9-11 years of age. Approximately 5%-10% have intensifying course. Approximately 85% experience a reduction of symptoms during and after adolescence[9]. TS: Tourette syndrome.

Table 1 Types and description of tics

	Simple	Complex
Vocal or Phonic	Simple phonic/vocal tics: These are sudden meaningless noises or sounds Examples: Throat clearing, coughing, spitting, barking, hissing, sucking, clacking, gurgling, sniffing, grunting	Complex phonic/vocal tics: These are sudden and more meaningful words, syllables or phrases Examples: Echolalia (repeating words or phrases spoken by others), palilalia (rapid repetition of one's own words or phrases), and coprolalia (compulsive utterance of obscene words or phrases) Coprolalia is not pathognomonic of tourette syndrome. In fact less than 10% of tourette syndrome patients exhibit coprolalia. Hence, coprolalia is not required in diagnosing tourette syndrome
Motor	Simple motor tics: Rapid, meaningless contractions of one or a few muscles Examples: Eye blinking, shoulder shrugging, head jerking, hand clapping, neck stretching, mouth movements, head, arm or leg jerks, and facial grimacing	Complex motor tics: Less common, typically more purposeful movements with a slower and longer nature. The movements appear more coordinated and may involve a cluster of movements Examples: Facial gestures, dystonic postures, throwing, arm thrusting, touching objects or people, stereotyped imitation of the movements (echopraxia) and obscene gestures (copropraxia)

Table 2 Definitions and classification of tic disorders

Classification of tic syndromes/tourette's disorder. Tourette Syndrome Classification Study Group. Tourette Syndrome Criteria: (TSCSG 1993)
A Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently
B The tics occur many times a day, nearly every day, or intermittently throughout a period of more than a year
C The anatomic location, number, frequency, complexity, type, severity of tics changes over time
D Onset before age 21
E Involuntary movements and noises cannot be explained by other medical conditions
F Motor and/or vocal tics must be witnessed by a reliable examiner directly at some point in the illness or be recorded by videotape or cinematography

Case 2

A 10-year-old boy with a 4 year history of ADHD combined type, as well as a learning disorder, experienced an initial good response to extended release methylphenidate. However, after 8 mo of management with this formulation at 36 mg each morning, his parents discontinued the medication due to worsening bilateral eye blinking. The methylphenidate was replaced with 10 mg of atomoxetine daily, with a gradual increase over a 2 mo period to 100 mg daily. After 2 mo on this regimen, the boy's ADHD symptoms worsened, the frequency of blinking increased and he experienced vocal tics. During re-evaluation, the child reported a history of "cursing" people for more than 2 years. He could avoid directing profanity at others by retreating to the restroom to curse. After developing a good alliance with his psychiatrist, he reported having a secret "dictionary," which was coprographic in nature, listed profane words beginning with A through Z, and included obscene drawings. The boy regularly read the dictionary to decrease the urge to directly curse at others. After a comprehensive evaluation, he was diagnosed with TS and comorbid ADHD. The ADHD symptoms were well controlled on 15 mg of immediate-release dexmethylphenidate in the morning and 10 mg in the afternoon. Clonidine

Table 3 Common differential diagnoses of tics

Stroke
Dystonia
PANDAS
Encephalitis
Head trauma
Epileptic seizures
Sydenham's chorea
Carbon monoxide poisoning
Functional movement disorders in children
Chromosomal disorders such as Down syndrome and Fragile x syndrome
Genetic conditions (such as Huntington's disease, Wilson's disease and Tuberous sclerosis)
Stereotypy (in developmental disorders such as Autism spectrum disorders and Stereotypic movement disorder)
Medication-induced tics (*i.e.*, Neuroleptics, Stimulants, Antiepileptics, Lithium)

PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections.

0.05 mg at night was added to treat his TS symptoms. He experienced drowsiness which subsided after 3 wk and within 2 mo clonidine was increased to 0.1 mg twice daily. The boy's ADHD and TS symptoms significantly subsided on the combination of dexmethylphenidate and clonidine.

DISCUSSION

TS affects people of all racial and ethnic groups. The Centers for Disease Control and Prevention (CDC) reports that the disease is more likely among non-Hispanic white people than among Hispanic or African American individuals[12]. There is also a predilection in males three times that of females. In the United States, an estimated 3 in 1000 children between 6 and 17 years of age have TS, with an incidence twice as high among 12-17 years old *vs* 6-11 years old[12]. The prevalence of the disorder varies between 0.4% and 3.8% internationally, with a lower rate in sub-Saharan Black Africans[6,13-15]. In the United Kingdom the prevalence is between 0.46% and 1.85% for those between the ages of 5 and 18, with an average prevalence of 1%[5,13].

Multifactorial pathogeneses have been attributed to TS. There is a prevalence of 5% to 15% in first-degree relatives of those with TS. A higher ratio of concordance in monozygotic twins as compared to dizygotic twin pairs exists[5,6]. The mode of inheritance is believed to operate mainly through a dominant gene. Boys with the gene(s) are three or more times likely than girls to manifest TS symptoms[12]. Longitudinal studies show some evidence that gender and stress-related hormonal factors are entwined in the disorder's pathogenesis[16]. There is also speculation about the role of gonadal androgens during the very early stages of central nervous system development *in utero*. Some clinical trials support the view that a change in the hormonal contexture during adolescence and adulthood affects tic severity[17]. In addition, monoamine neurotransmission has been implicated in the neurobiology of TS. Positron emission tomography and single-photon emission computer tomography studies suggest an abnormal regulation of dopamine production and metabolism in TS leading to higher dopamine levels[5], and lower levels of serotonin and glutamate have been found in such individuals[5]. Brain findings are usually normal in these patients. However, in a subpopulation, brain magnetic resonance imaging (MRI) scan studies have demonstrated an increased number of subcortical hyperintensities and reduced neuronal activity in the basal ganglia. Increased brain activity in the prefrontal, parietal, temporal, and cingulate regions has also been reported[2,5,6]. Volumetric imaging studies have demonstrated smaller caudate volumes[2,5,6,9,14,15]. Furthermore, children with TS tend to have smaller corpus callosum, while adults with TS have larger corpus callosums as compared to the normal population[2,5,6,9,14,15]. The TS subgroups with ADHD comorbidity appear to have increased left amygdala volume as compared to those without comorbidity[18,19]. Other implicated etiological factors of TS include intrauterine exposure to alcohol and cigarette smoke, a complicated birth, and low birth weight[2,14,15]. Possible autoimmune causes have also been considered based on studies linking TS and exposure to group A β-hemolytic streptococcal infections (GABHS) complicated by Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS)[7,12].

A TS diagnosis is based on clinical history and examination. When clinically indicated, routine laboratory and radiological investigations should be considered to rule out other causes of tic disorders. See Table 3 for common differential diagnoses of TS[1,3,6,9,12,13,20]. In order to document the quality and quantity of tics, some experts recommend video-recording by parents and teachers[2]. A standardized rating scale such as the YGTSS may be useful for diagnosing and monitoring treatment response[5,21]. Although brain MRI scans will likely be normal in TS, brain imaging is indicated in those suspected of having neuroinflammatory/degenerative conditions, for example Sydenham's chorea. In addition, DNA testing should be considered in individuals with family history of Huntington's chorea (especially DNA microarray technology)[2,5,6]. Heavy metal toxicities should be considered, including lead, as well as serum copper and ceruloplasmin if Wilson's disease is suspected[5,6,14,15]. Electroencephalography (EEG) may be useful when myoclonic epilepsy is suspected[2,14,15]. A throat swab should be considered in patients who have history of pharyngitis to rule out GABHS and PANDAS[2,5,6,9,12,14,15].

The CDC has conducted a number of studies examining comorbidities in TS. Children and adolescents with TS have higher risk of comorbid learning, behavioral, and social problems. Approximately, 79% of children with TS have at least one comorbid mental health, behavioral or developmental condition[12,22]. Among children with TS, 64% have ADHD, 43% have behavioral problems such as oppositional defiant disorder or conduct disorder, 40% have anxiety, 36% suffer from depression, and 28% are

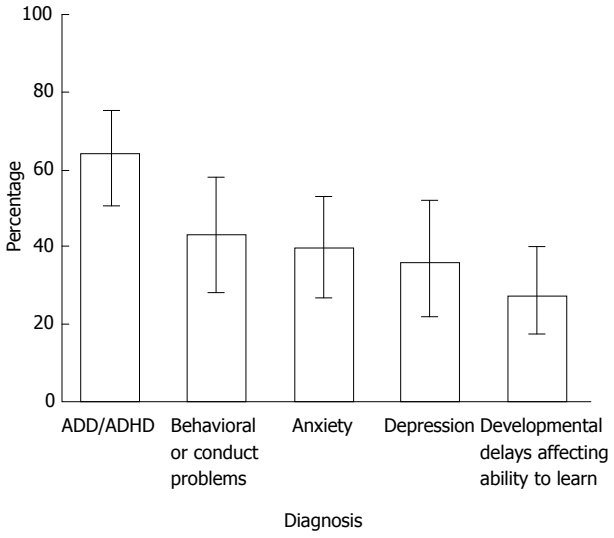

Figure 2 Adapted with permission from CDC. Prevalence of selected diagnoses among persons aged 6-17 years with tourette syndrome. ADD: Attention deficit disorder; ADHD: Attention deficit hyperactivity disorder.

developmentally delayed[22]. See Figure 2 for prevalence of comorbid diagnoses among 6 to 17 years old with TS[22]. Other clinical symptoms associated with TS include stuttering, aggressive and antisocial behavior, impulsivity, exhibitionism, sleep disturbances and self-injurious behaviors[5]. Since ADHD is the highest comorbid condition with TS, it is essential for clinicians to be familiar with the diagnosis and management of these conditions.

In recent years, there has been considerable research on the psychopharmacology of TS associated with ADHD. The psychopharmacological management of children with TS associated with ADHD should be tailored towards the clinical presentation and severity of the illness[11,23]. Leckman *et al*[20] 2002, suggested prioritization of pharmacological interventions based on the degree of distress and impairment. Since the natural course of tics is either short-term intermittent episodes or long-term waxing and waning of symptoms, medication options should be tailored to minimize side effects while maximizing treatment benefits[2,20]. Pharmacological management of TS associated with ADHD is similar to other childhood psychiatric disorders in that few of the medications commonly utilized are FDA approved[24].

Several studies have demonstrated the effectiveness of stimulants in alleviating ADHD symptoms. Contrary to previous notions that stimulants can worsen tics in TS, some studies have shown contrary results. A critical review of the literature reported that group data analysis showed no significant increase in tics when stimulants are used in patients with tics as compared with controls[10]. This conclusion was also supported by the Tourette Syndrome Study Group in a multicenter, randomized, double-blind 16 wk clinical trial in which 136 children with ADHD and a chronic tic disorder were randomly administered clonidine, methylphenidate, combined clonidine and methylphenidate, or placebo. The group concluded that the combination of methylphenidate and clonidine is effective for ADHD in children with comorbid tics and that prior recommendations to avoid methylphenidate because of concerns of worsening tics are unsupported by the trial[25].

Studies have shown that the motor and behavioral symptoms associated with TS respond well to most typical and atypical antipsychotic medications. The typical antipsychotic drugs, such as haloperidol, fluphenazine and pimozide, with a high tendency to block postsynaptic dopamine (D2 receptors) are the treatment of choice due to their greater effectiveness[2,22,26]. However, typical antipsychotics remain a second-line treatment option because of side effects including extrapyramidal side-effects (EPSE) and tardive dyskinesia (TD) for haloperidol, and cardiotoxicity for pimozide[22,26]. Other side-effects include sedation, orthostatic hypotension, dry eyes and mouth, urinary retention and confusion. Neuroleptic malignant syndrome (NMS) is a rare but serious adverse-event characterized by lead pipe rigidity, autonomic instability, increased heart rate, fever, and rhabdomyolysis.

The atypical neuroleptic medications such as risperidone, ziprasidone, olanzapine, aripiprazole, and quetiapine, which selectively block postsynaptic dopamine D2 receptors, have had some encouraging outcomes in the treatment of tics associated with TS[2,22,23,26,27]. Close monitoring when using these medications is essential especially in pediatric populations with higher risks of developing metabolic syndrome and EPSE. The mechanisms of action of atypical neuroleptic drugs are different from conventional medications in that atypicals have greater affinity for serotonin receptors (especially 5-HT2A) than D2 receptors, thus generally causing minimal EPSE, milder increases in prolactin and lesser tendencies to induce TD[28,29]. Risperidone is associated with orthostasis, and more EPSE than other atypical agents. It also causes significant hyperprolactinemia which in turn can cause adverse events including gynecomastia in boys. Prolactin monitoring has been recommended in those treated with risperidone. Olanzapine is associated with higher incidences of sedation and metabolic syndrome. Quetiapine can lead to sedation and anti-cholinergic side effects, while ziprasidone can cause dry ejaculation and a prolonged Q-T interval[2,22,23,26-29].

Clonidine and guanfacine are sympatholytic agents that lower blood pressure and heart rate. Their mechanisms of action involve alpha-2A adrenoceptor selective agonists. The use of this group of medications for TS is supported by a few controlled studies[22,26]. Clonidine in divided daily doses, ranging from 0.1 to 0.3 mg, has been associated with favorable outcomes in pediatric populations[2,22,23,26,30]. Also, guanfacine in divided daily doses of 0.5 to 3 mg has been recommended for milder TS[2,22,23,26]. Associated adverse-effects of clonidine and guanfacine include sedation, dry mouth, headache, postural hypotension and dizziness, and sudden discontinuation can induce a hypertensive crisis. It is essential to monitor blood pressure and heart rate and obtain a baseline EKG when using clonidine or guanfacine[23,31,32]. Sudden discontinuation, especially of clonidine, should be avoided due to risk of

rebound hypertension.

The data are mixed concerning the use of antiepileptic drugs such as levetiracetam and topiramate in the treatment of TS[22,33]. Other reported alternative pharmacological treatments of tics in TS include tetrabenazine, ropinirole, botulinum toxin, baclofen and clonazepam but the evidence is limited[2,22,23,26,34].

Since this paper focuses on the psychopharmacological management of TS and ADHD, psychological interventions are not addressed in detail. There are evidence-based non-pharmacological treatment options for TS associated with ADHD[35,36]. With regard to non-psychopharmacological management of tics, studies have revealed better outcomes from habit reversal therapy and, exposure and response prevention strategies[35,36]. In addition, treating OCD symptoms associated with TS may potentially reduce tics and ADHD symptoms[26,36,37]. Selective serotonin re-uptake inhibitor (SSRI) antidepressants are the preferred pharmacological treatment for OCD. Multiple studies support the role of cognitive behavioral therapy (CBT) for behavioral management of OCD in TS[26,36-38].

Recent studies have revealed promising outcomes from transcranial magnetic stimulation (TMS)[39,40] and deep brain stimulation surgery[41-43] in the treatment of medication resistant tics associated with TS.

In conclusion, ADHD has a high correlation with TS and patients with ADHD are more likely to develop tic disorders, with or without treatment with stimulants. Tics which appear during the treatment of ADHD with stimulants may be due to a naturally developing tic disorder in which the tics have the usual waxing and waning pattern of occurrence, intensity, and frequency and may have developed even without the use of stimulants. The decision to use, or to continue to use, stimulants must be made on a case-to-case basis. Overall the treatment of ADHD with appropriate psychopharmacological agents, including stimulants, is suggested if the treatment benefits outweigh the potential medication risks.

Medication management of TS associated with ADHD is quite variable. The choice of appropriate pharmacological agent(s) should depend on the severity of the impairments. Starting with a non-stimulant agent such as guanfacine or clonidine is recommended, as they are effective in alleviating both symptoms of TS and ADHD. The newer long acting preparations of guanfacine approved for ADHD may be the most reasonable agents to consider first. If the TS is not severe, but the ADHD is disabling, the option of treating the ADHD with a stimulant should be considered. The course and severity of tics should be monitored with a reliable TS rating scale, such as the YGTSS. It is also recommended that, in order to prevent any future debilitating disease process, careful history taking be done in diagnosing and managing of symptoms of TS associated with ADHD.

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COMMENTS

Case characteristics

Two boys, ages 8 and 10 years old, with Attention deficit hyperactivity disorder (ADHD) are treated with stimulants and experience the emergence of tics, later diagnosed as tourette syndrome (TS).

Clinical diagnosis

Case 1: Inappropriate language/profanity, vocal tics and inattention, impulsivity and hyperactivity. Case 2: Bilateral blinking, vocal tics, profanity, impulsivity and hyperactivity.

Differential diagnoses

With regard to the etiology of tics, Stroke, Dystonia, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections, Encephalitis, Head trauma, Epileptic seizures, Sydenham's chorea, Carbon monoxide poisoning, Functional movement disorders, Chromosomal and Genetic disorders, Stereotypy and Medication-induced tics should be considered.

Laboratory diagnosis

All laboratory studies were within normal limits.

Pathological diagnoses

Both cases were examples of TS associated with ADHD.

Treatment

In both cases stimulants were used to treat ADHD, however the TS was treated with clonidine in the first case and risperidone in the second.

Related reports

Tics can present as an adverse effect of stimulants. However, given the high comorbidity of ADHD with TS, emerging tics can be symptom of TS, which typically manifests temporally later than ADHD. In the cases presented, both boys were changed to non-stimulant medications after developing tics, which led to suboptimal treatment of their ADHD symptoms. The second child actually experienced a worsening of TS symptoms on the non-stimulant medication. Despite providers' reluctance to prescribe stimulants due to fear of causing tics or worsening pre-existing tics, evidence has shown that stimulants can be beneficial in the treatment of TS associated with ADHD. In fact, using stimulants may reduce the severity of the tics and improve the quality of life of patients with these disorders.

Term explanation

TS is a neurodevelopmental disorder characterized by multiple chronic motor and vocal tics developing before adulthood. ADHD, also a neurodevelopmental disorder, presents with a persistent or on-going pattern of inattention and/or hyperactivity and impulsivity, which interferes with typical development and quality of life. ADHD is associated with difficulties in achieving and sustaining attention, and with executive function and working memory.

Experiences and lessons

There is a misperception that stimulants are contraindicated in patients with tic disorders due to the potential to cause or exacerbate tics, however, the role of stimulants in the treatment of TS, when the benefits outweigh the risks, cannot be over emphasized.

Peer-review

The manuscript is an informative review regarding the diagnosis and management of Tourette syndrome associated with ADHD. It is deemed to be of academic value and worthy of publishing.

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CASE REPORT

Acute lobar nephritis in children: Not so easy to recognize and manage

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Abstract

Acute lobar nephritis (ALN) is a localized non-liquefactive inflammatory renal bacterial infection, which typically involves one or more lobes. ALN is considered to be a midpoint in the spectrum of upper urinary tract infection, a spectrum ranging from uncomplicated pyelonephritis to intrarenal abscess. This condition may be difficult to recognize due to the lack of specific symptoms and laboratory findings. Therefore the disease is probably underdiagnosed. Computed tomography scanning represents the diagnostic gold standard for ALN, but magnetic resonance imagine could be considered in order to limit irradiation. The diagnosis is relevant since initial intravenous antibiotic therapy and overall length of treatment should not be shorter than 3 wk. We review the literature and analyze the ALN clinical presentation starting from four cases with the aim to give to the clinicians the elements to suspect and recognize the ALN in children.

Key words: Acute lobar nephritis; Children; Computed tomography; Magnetic resonance imagine; Upper urinary tract infection

Core tip: Acute lobar nephritis (ALN) is a renal bacterial infection presenting difficult diagnosis due to the lack of specific symptoms and laboratory findings. Suspecting ALN in children with septic fever with or without clinical signs should be part of the diagnostic tool of clinicians. The diagnosis is relevant both to prefer intravenous antibiotic therapy and suggest an overall length of antibiotic treatment not shorter than 3 wk. We review the literature and analyze the ALN clinical presentation, with the aim to give to the clinician the elements to suspect, diagnose and accurately treat ALN in children.

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INTRODUCTION

Acute lobar nephritis (ALN), also known as acute focal bacterial nephritis, is a localized non-liquefactive inflammatory renal bacterial infection, which typically involves one or more lobes[1,2]. It presents as an inflammatory mass without frank abscess formation[3]. ALN is considered to be a midpoint in the spectrum of upper urinary tract infection (UTI), a spectrum ranging from uncomplicated pyelonephritis to intrarenal abscess[4]. According to some authors[5], this spectrum lacks a dynamic progressive nature and two patterns, based on computed tomography (CT) findings, are described: Simple ALN, which represents progression of acute pyelonephritis (APN), and complicated ALN, which may progress into renal abscess without or even with treatment[6]. The typical presentation of ALN shares some common clinical and laboratory features with both renal abscess and APN including septic fever, flank pain, sick appearance, nausea or vomiting, elevation of inflammatory markers, pyuria and bacteriuria[1,7]. According to a recent study patients with ALN are febrile for longer after hospitalization and have more nausea/vomiting symptoms than those with APN[8]. A timely diagnosis is relevant because under-diagnosis may result in late renal scarring, and/or evolution in renal abscess, which in turn may lead to hypertension or renal failure[9].

CASE REPORT

Case 1

A 4-year-old girl was admitted with a 2 d history of high fever and abdominal pain. Fever persisted despite an oral amoxicillin-clavulanate treatment prescribed by her family physician.

The patient's medical history was remarkable for an episode of APN 2 years before, successfully treated with oral antibiotics. At admission she was febrile and looked sick with an unremarkable physical examination. White blood cell count (WBC) was 24.600/mm^3, C-reactive protein (CRP) 24.52 mg/dL (normal range 0-5 mg/dL) and erythrocyte sedimentation rate (ESR) 97 mm/h (normal range 0-20 mm/h). Urinalysis revealed leukocyturia (200 WBC/mm^3 at standard optical microscopy) without bacteriuria. Urine cultures were repeatedly negative as was chest X-ray. Abdominal ultrasonography (US) showed a nonspecific diffuse increased echogenicity of the right kidney, which appeared smaller than the left; no focal masses were detected on both kidneys. A CT scan showed multiple lesions with irregular margins and variable size in the right kidney, which appeared hypodense after contrast medium administration (Figure 1). ALN was diagnosed and a three weeks intravenous antimicrobial therapy with ciprofloxacin and tobramycin was started with clinical improvement. Voiding cystourethrography (VCUG) and dimercaptosuccinic acid (DMSA) renal scintigraphy performed 6 mo later showed a reflux with associated renal scarring nephropathy.

Case 2

A 13-year-old boy was admitted after 3 episodes of high fever in the last 2 mo, without an obvious focus. During the first episode, the boy was confused and agitated; CT and magnetic resonance imagine (MRI) of the brain, cerebrospinal fluid (CSF) examination, electroencephalography (EEG), chest X-rays, urinalysis with standard optical microscopy, urine culture were normal; blood test showed increased CRP (10.8 mg/dL). Empirical therapy with acyclovir and ceftriaxone was started with clinical success, maintained for 5 d and switched to oral treatment for 5 more days. The boy was discharged with a diagnosis of suspected encephalitis. After 2 wk of wellness, the patient presented fever, vomiting and drowsiness. MRI of the brain was normal. Chest X-ray and echocardiogram were also normal. CRP was 13.9 mg/dL. Abdominal US was negative. Empirical treatment with ceftriaxone was started with rapid improvement. The boy was discharged after 5 d of intravenous therapy; at home he continued with 3 d oral amoxicillin-clavulanate. Four days after the end of treatment, he was admitted for the third time with fever and vomiting. On examination, he was in good clinical condition. The abdomen was soft, slightly painful in the right flank. CRP was 10.4 mg/dL. Urinalysis with optical microscopy, chest X-rays and abdominal US were negative. An abdominal CT scan was performed. The scan (Figure 2) revealed multiple poorly defined hypodense areas after contrast medium administration in the right kidney, compatible with ALN. One of these areas presented a 5 mm colliquative part in the middle, attributable to an abscess. An abdominal US was repeated (Figure 3) with power-doppler analysis showing at least two hypoperfused areas at the right kidney. The patient's medical history was unremarkable; no previous UTIs were reported. Intravenous antimicrobial therapy with tobramycin and teicoplanin was started and maintained for 3 wk, followed by oral amoxicillin-clavulanate for other 3 wk.

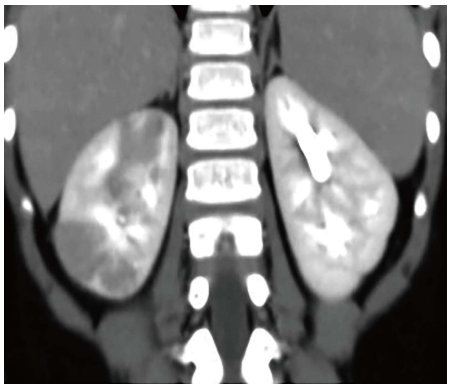

Figure 1 Case 1: Abdominal computed tomography. Computed tomography scan of the abdomen after intravenous contrast injection reveals multiple wedge-shaped hypo dense non enhanced lesions in the right kidney, more visible in the upper and lower pole.

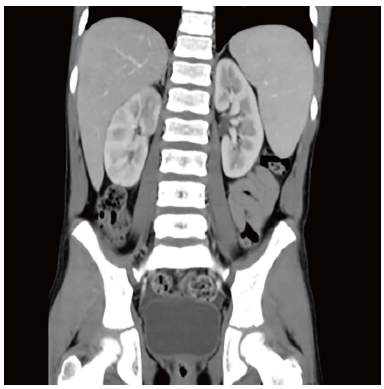

Figure 2 Case 2: Abdominal computed tomography. Abdominal computed tomography after contrast medium administration, showing a notable hypodense area in the upper pole of right kidney.

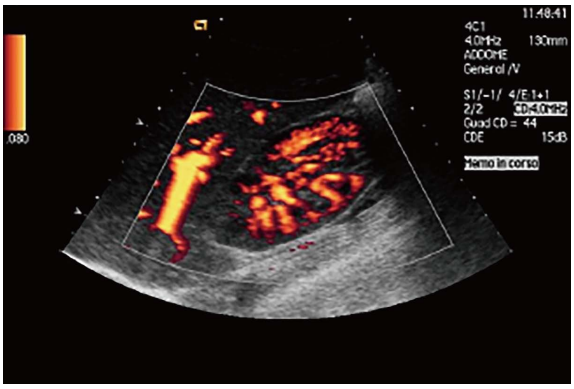

Figure 3 Case 2: Abdominal ultrasound. Abdominal ultrasonography with power-doppler analysis shows two hypoperfused areas at the upper pole of right kidney.

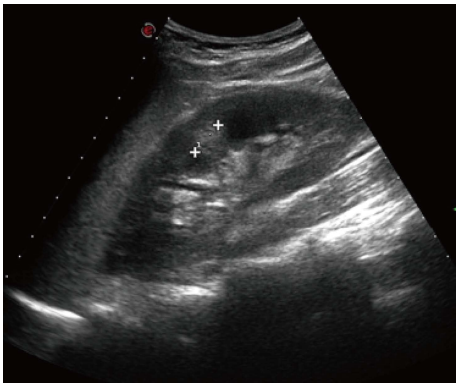

Figure 4 Case 3: Abdominal ultrasonography. Abdominal ultrasonography shows an increased volume of the left kidney with a small hyperechoic mass (1 cm diameter) in the middle zone of the kidney.

Case 3

A 17-year-old girl was admitted with a 2 d history of high fever, chills and pain on the left flank. On physical examination, she looked sick; the abdomen was soft and painful in the left flank. WBC count was normal (8340/mm^3), while there was a marked increase of both CRP (25.33 mg/dL) and ESR (62 mm/h). Urinalysis revealed leukocyturia (50 WBC/mm^3 at standard optical microscopy) but no bacteriuria. Urine and blood cultures were repeatedly negative. Abdominal US (Figure 4) showed an increased volume of the left kidney with a small hyperechoic mass (1 cm diameter), consistent with ALN. Intravenous therapy with ceftriaxone and tobramycin was started; after 48 h the patient was still febrile and sick, therefore treatment was switched to intravenous ciprofloxacin, teicoplanin and cefotaxime. There was a slow and gradual clinical improvement and after 72 h, the fever disappeared. Intravenous antimicrobial therapy was maintained for three weeks.

Case 4

A 6-year-old girl presented with a 24 h history of high fever, vomiting and abdominal pain on the left iliac fossa without diarrhea. Physical examination was unremarkable except for an abdominal evoked pain in the left iliac fossa. WBC was 21.190/mm^3, CRP 34 mg/dL. Urinalysis with standard optical microscopy was negative and therefore urine cultures were not performed. Chest X-ray was normal. Abdominal US showed an increased volume of both kidneys; CT scan was then performed revealing multiple wedge-shaped cortical hypodense lesions in both kidneys, more represented in the left one (Figure 5). Intravenous therapy with ceftriaxone was started; after 48 h, the patient was still febrile and sick, so intravenous netilmicin was added with clinical improvement. The therapy was continued for 10 d, then switched to oral ciprofloxacin, for additional 2 wk.

DISCUSSION

When should ALN be suspected?

ALN may be difficult to recognize due to the frequent absence of specific signs and symptoms and the wide differential diagnosis (Table 1). Specific symptoms as flank pain or laboratory findings (positive urinalysis and bacteriuria) may be absent. Therefore the disease is probably underdiagnosed[10]. Nevertheless, fever with septic features (sick appearance, malaise, chills, and nausea or vomiting), increased inflammatory indexes

Table 1 Clinical and laboratoristic acute lobar nephritis differential diagnosis

	Clinical and laboratoristic ALN differential diagnosis
APN	Leukocyturia and bacteriuria
Appendicitis[26]	Mc Burney, Blumberg and Rovsing's sign, right iliac fossa pain, typical age
Gastroenteritis[27]	Diarrhea, dehydration's signs
Infected urachal cyst[28]	Belly button discharge
Nephrolithiasis[29]	Colic pain, familiarity, previous episode, micro/macrohematuria, Giordano's sign
Pancreatitis[30]	Typical pain, serum amylase and lipase elevated
Pelvic inflammatory disease[31]	Sexually active female, irregular periods, vaginal discharge, dyspareunia, lower abdomen pain
Pneumonia[32]	Dyspnea, cough, typical auscultation, Sat O_2 < 96%
Sickle cell disease[33]	Anemia, decreased haptoglobin, sickle cell, ethnicity

Differential diagnosis with other conditions such as abdominal abscess, infected intestinal duplication and nephrolithiasis need radiological evaluation. ALN: Acute lobar nephritis; APN: Acute pyelonephritis.

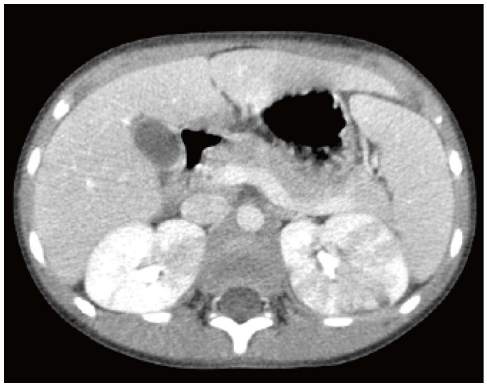

Figure 5 Case 4: Abdominal computed tomography. Computed tomography scan of the abdomen after intravenous contrast injection reveals multiple wedge-shaped cortical hypodense lesions in the both kidneys, more represented in the left one.

and/or abdominal pain, should suggest a deep bacterial infection. The diagnosis of this condition is relevant due to the need of a specific therapeutic approach.

How to confirm the ALN diagnostic suspect?

Sonographically, ALN presents as focal hypoperfused lesions with poorly defined irregular margins disrupting cortico-medullary differentiation. Masses can be respectively hyper-, iso-, or hypo-echogenic depending on the temporal sequence of the lesions and resolution of the disease[11,12]. Renal pole swelling has also been reported[11,13,14]. Although renal US is an effective diagnostic method, there may be false positive and false negative results[13,15], and often a false negative US is frequently reported. A study[16] demonstrated that isolated severe nephromegaly (defined as renal length of greater than mean +3 SD for age) has a diagnostic sensitivity of 90%; the finding of a focal renal mass increases the sensitivity to 95% (compared with the gold standard CT), with a specificity of 86.4%. The diagnostic gold standard for ALN is CT scanning[11,13,15,17]. CT images of the involved areas are usually normal in non-enhanced scans but appear as wedge-shaped, poorly defined regions of decreased nephrogenic density after contrast medium administration[11,13]. With the aim to avoid radiation exposure, MRI should be strongly considered[18]; in fact CT scan results in a small but not negligible increased lifetime risk for cancer[19,20]. Enhanced ultrasound in the near future could replace CT scan because of comparable sensitivity and specificity. Unfortunately second-generation contrast agents are off-label in children, even if there are no adverse events documented in literature[21]. Static scintigraphy with DMSA, the gold standard to identify renal involvement in UTI, has no application in the differential diagnosis of this condition showing only focal uptake defects with the means of a hypoactive area in the renal parenchyma. In the literature, positive urine culture rate has a wide variability; the bias probably depends on the ability of different centers to diagnose ALN, particularly when urinalysis and urine are negative. When positive, results are not different from other forms of UTI: The most represented urinary pathogen is *Escherichia coli* in 40%-75% of the cases, while other gram negative germs are less frequent; gram positive germs infection is unusual[8,10,22].

Treatment

Treatment is based on antibiotic therapy. Empiric approach, before antibiogram response when available, should be targeted at gram negative germs. Intravenous administration is recommended at least until 2 to 3 d after defervescence with a possible switch to oral treatment. A study suggested that a 3 wk antimicrobial therapy protocol should constitute the treatment of choice for all radiographically documented patients with ALN[22]. Surgical intervention is needed in the 25% of the cases where the lesion turns to renal abscess[23].

Integrating literature evidence and daily clinical practice: The diagnostic clues

These 4 cases presented with high fever, toxic appearance and abdominal pain. Only 1 case presented with flank pain, a specific UTI symptom not reliable before age of 6-8 years. Furthermore, as a confounding factor, urinalysis showed leukocyturia only in 2 cases, both with no bacteriuria at microscopy and negative urine cultures (one of these children started antibiotic treatment prior to admission). The other 2 patients presented negative microscopic and dip stix urinalysis. In case 4, urine cul-

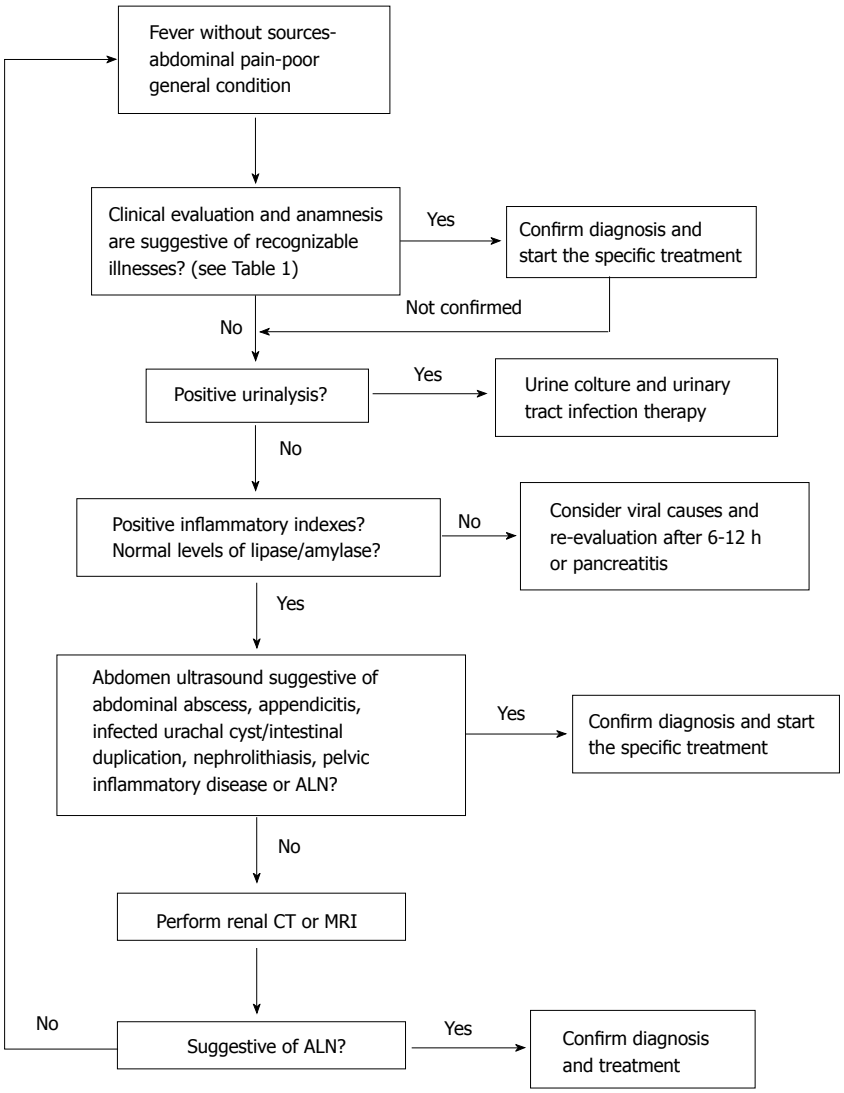

Figure 6 Diagnostic algorithm to suspect and then recognize acute lobar nephritis in children. ALN: Acute lobar nephritis; CT: Computed tomography; MRI: Magnetic resonance imagine.

ture was reported not performed because of the negative urinalysis. Our findings are in line with previous published reports. Evaluating data of 25 children diagnosed with ALN, some authors[10] showed that the main clinical presentation was represented by septic temperatures and rapid deterioration of clinical condition, characteristics that were present in all the children. Only the older children (10 out of 25), with a mean age of 8 years, suffered from specific symptoms such as flank pain, whereas younger children presented with unspecific symptoms such as vomiting, lethargy, abdominal pain or poor feeding. Laboratory findings showed always an elevation of CRP, ESR and WBC. Leukocyturia and bacteriuria were not found in all of the children but in 18/25 and 20/25 respectively. Positive urine cultures were found in 20/25 children; however 4 of 5 children with negative urine cultures had been pretreated with oral antibiotics prior to admission. In our experience, CT scan was performed in 3 cases. In case 3, US images were so typical (enlargement of the kidney and presence of a mass) that we decided not to obtain CT scans, in order to avoid irradiation of the patient. Case 2 is noteworthy because CT revealed multiple lesions, one of these with a 5 mm colliquation area, probably an ALN evolution in abscess. US power Doppler, performed the day after, identified upper UTI compatible lesions. According to some authors, ALN should be considered as complicated UTI. Further radiological examination as VCUG is thus considered mandatory for the detection of urinary tract anomalies, known as the main underlying predisposing factors of ALN in children[24,25]. This series highlights the lack of specific clinical presentation of ALN. This condition should be suspected in front of a child with high fever, poor general condition and elevation of inflammatory markers, without an apparent infective focus even in presence of negative abdominal ultrasound, urinalysis and microscopy. Alternatively ALN should be suspected in patients with APN not responsive to antibiotic treatment. We suggest avoiding CT scan when sonographic criteria of severe nephromegaly and focal mass are present and to perform MRI instead of CT in the other cases, in order to minimize radiation exposure. We present a diagnostic algorithm

that could be used to suspect and then recognize ALN in children (Figure 6).

COMMENTS

Background

Clinicians often take on challenge with septic fever without clear clinical signs; the authors report four cases presenting with acute lobar nephritis (ALN), an underestimated condition, with the aim to give to the clinicians the instruments to suspect and diagnose ALN. A timely diagnosis is relevant because under-diagnosis may result in late renal scarring, and/or evolution in renal abscess, which in turn may lead to hypertension or renal failure.

Research frontiers

Important areas of research could be evaluate the sensitivity and specificity of both magnetic resonance and intravenously enhanced ultrasound in diagnosing ALN with the aim to avoid computed tomography and then to spare radiations.

Innovations and breakthroughs

In literature there is lack of data about ALN in childhood. The authors report of four cases of pediatric ALN, rising diagnostic and therapeutic issues. Furthermore the authors describe their experience about MR or enhanced ultrasound study of kidney in diagnosing ALN. These techniques are not mentioned elsewhere in the ALN diagnosis.

Applications

All children with septic fever with or without abdominal pain should raise in the clinicians the suspect of deep bacterial infection. For a correct diagnosis it is essential both performing urinalysis before antibiotic therapy and abdominal imaging.

Terminology

Enhanced ultrasound is a free radiation imaging technique consisting in instillation of microbubble in bladder or vein emphasizing structures. Unfortunately, its use in children is still off-label.

Peer-review

This is a series of 4 cases with acute lobar nephritis in children discussing the clinical presentation, radiological features, treatment and management issues.

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Minimizing pediatric healthcare-induced anxiety and trauma

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Abstract

Frequently, episodes of care such as preventive clinic visits, acute care, medical procedures, and hospitalization can be emotionally threatening and psychologically traumatizing for pediatric patients. Children are often subject to psychological trauma, demonstrated by anxiety, aggression, anger, and similar expressions of emotion, because they lack control of their environment. This sense of helplessness, coupled with fear and pain can cause children to feel powerless in healthcare settings. These emotional responses can delay important medical treatment, take more time to complete and can reduce patient satisfaction. Healthcare professionals are uniquely positioned to prevent healthcare-induced trauma and reduce healthcare-induced anxiety. This article introduces a new way to choice, agenda, resilience and emotion (CARE) for pediatric patients in the healthcare setting by implementing the four following treatment principles called the care process: (1) Choices: Offer power in a powerless environment; (2) Agenda: Let patients and families know what to expect and what is expected of them; (3) Resilience: Highlight strengths and reframe negatives; and (4) Emotional support: Recognize and normalize common fears and responses. Engaging the CARE principles helps patients and families feel empowered and mitigates, reduces, and may even ameliorate risk of anxiety and trauma responses.

Key words: Inpatient; Ambulatory; Pediatric patient compliance; Patient experience; Pediatrics; Anxiety; Healthcare-induced trauma

Core tip: In an effort to reduce healthcare-induced distress leading to anxiety, trauma, and trauma responses in pediatric patients, this author has developed four principles in the choice, agenda, resilience and emotion (CARE) process to deliver emotionally-safe treatment to children: (1) Choices: Provide power in a powerless environment; (2) Agenda: Letting the patient and family know what to expect and what is expected of them; (3) Resilience: Start with strengths and reframe negatives; and (4) Emotions: Recognize and normalize common fears and responses. Through the process of implementing CARE, a child's healthcare-induced distress can be minimized.

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INTRODUCTION

Pediatric patients visit primary healthcare providers in ambulatory settings an average 31 times from birth to age 21 for general wellness visits[1]. Additionally, in 2012 alone, 5.9 million United States children were hospitalized[2], adding to the average number of medical interactions. Annually, millions of children further encounter ancillary medical caregivers, including medical assistants, nursing staff, laboratory and radiology technologists, occupational, speech, and physical and mental health therapists. These children can also be passive participants in sometimes-stressful conversations with administrative professionals regarding finances and insurance coverage. Most concerning, up to 20% of the population reports feeling "white coat syndrome" when coming into contact with medical doctors[3].

Children commonly report feeling afraid or anxious as they anticipate and engage in healthcare settings with medical professionals[4-6]. Due to their developmental level and limited cognitive development, children use behavior, instead of words, to communicate the emotions they feel. Common behavioral demonstrations of fear, anxiety, and helplessness include aggression, withdrawal, lack of cooperation, and regression[7]. Of note, psychological and behavioral distress has been present regardless of the incidence of invasive or painful healthcare[7]. This distress impedes provider execution of medical protocols, thus requiring more time in the treatment process.

Being that children are as emotive as they are cognitive, during episodes of care, interactions with medical providers can enhance anxiety or trauma, or at worst, cause trauma[8-12]. It is important for medical providers to learn to mitigate psychological trauma in pediatric care. Left untreated, childhood trauma caused by healthcare-induced anxiety can cause significant mental health issues in a child's life[4,5,13-15]. Trauma predisposes children to various forms of psychopathology including anxiety[15], major depression[13], and behavior problems[14], which can increase cost of care in the future.

Current strategies for reducing anxiety and stress in children include distraction[16], creating an inviting physical environment[17], child and parental preparation[16,18] and positive staff interactions[16]. Although these aspects of pediatric patient care are important, they are limited in scope to meet the emotional needs of a stressed child. In an effort to reduce healthcare-induced distress leading to anxiety, trauma, and trauma responses in children, this author developed four principles in the choice, agenda, resilience and emotion (CARE) process: (1) Choices: Provide power in a powerless environment; (2) Agenda: Letting the patient and family know what to expect and what is expected of them; (3) Resilience: Start with strengths and reframe negatives; and (4) Emotions: Recognize and normalize common fears and responses. Through the process of implementing CARE, a child's healthcare-induced distress can be minimized. This article will introduce a new way to CARE for the psychosocial needs of pediatric patients across all healthcare settings.

ANXIETY AND TRAUMA IN THE HEALTHCARE SETTING

Throughout a child's life, approximately 15% to 20% will encounter some form of relatively severe trauma[19,20]. Developmentally speaking, even common events, including medical care[4,5], can lead to heightened anxiety, and trigger trauma responses in children[20-24]. Because children are bewildered in an unknown medical environment, as caregivers are taking over control of their bodies, they feel a loss of autonomy and control. Further, unmet needs, sense of danger, and lack of competence amplify anxiety[25]. Children fear mutilation, and suffer from guilt, pain, rage, and similar manifestations specific to their developmental level[4,5,8-12]. Anxiety-provoking experiences such as hospitalizations and medical care can effect a child's physical growth, personality, or emotional development[20-24]. In some cases anxiety-based trauma may prejudice the development of behavioral, emotional, or cognitive disorders[26,27].

Findings from longitudinal studies have delineated three broad sets of factors that predict differential risk in developing psychopathologies[24]. The factors noted include: (1) children who exhibit high degrees of psychopathology before traumatic exposure; (2) level of exposure and frequency of exposure to trauma[28]; and (3) social factors emerge as the strongest predictors of risk among traumatized children[15,22,23]. Many children who have been exposed to acute trauma have shown relatively strong outcomes with socially-supportive environments[29]. Additional risk factors include children with limited intellectual ability, female, younger age, instability in family life, and intense exposure to frightening events; children with these risk factors may recover at a slower pace and may need professional intervention[15]. Children, as well as their parents and guardians, are psychologically unprepared for anxiety and the resulting emotional strain from a medical crisis.

FACES OF HEALTHCARE-INDUCED TRAUMA

Most people can relate to an experience in their lives during which a healthcare visit or medical procedure was upsetting and anxiety-provoking. Some may even describe their experience as traumatizing. Distressing scenarios might include vaccinations as a child, a medical diagnosis with a poor prognosis, or perhaps a diagnosis requiring surgery. This author recalls an early childhood experience of undergoing anesthesia for a peritonsillar abscess. Her fear of and fight against needles prohibited a pre-op IV start and a mask was placed over her nose and mouth. She gasped for air, all the while pleading to the anesthesiologist she could not breathe. Her fear was dismissed and minimized when the anesthesiologist responded by telling her "she was fine". This author remembers feeling like she was in danger because she felt as if she could not breathe. She had no pre-surgical preparation for the sudden fear and panic. Had she been told in advance what it might feel like to have a mask placed over her face, or to know it is a common feeling to gasp for air as part of the anesthesia process, her fears and therefore healthcare-induced trauma, would have been prevented. Sadly, this is not an uncommon experience for children in healthcare settings.

Another example is Amelia, an 18-mo old, female recovering from acute stress disorder due to healthcare-induced trauma resulting from repeated episodes of care in the Emergency Department (ED) at a highly regarded Children's Hospital for flu-like symptoms causing severe dehydration leading to listlessness. Each time she was taken to the ED by her high-functioning parents, they were instructed to hold her down for catheterization in order to obtain a urine sample to rule out bacterial infection. Additionally, she was held down for intravenous (*IV*) fluids tube insertion, which was difficult to insert and took several attempts to place. This process of catheterization and *IV* attempts repeated itself several times as she was evaluated by the physician in the ED, released, evaluated again in the ED, admitted into the hospital, discharged, and then re-admitted. This little girl was scared, confused, and seemingly terrorized by strangers (medical providers) and those she trusted (parents). Each of these ED admissions took hours to complete as the child lay helpless in defense to the medical professionals that needed to triage and treat her illness. The parents looked on with bewilderment, doing their best to keep calm despite their daughter's condition.

Upon hearing the parent's distress over the psychological state of their child throughout the course of hospitalization and discharge, a Child Life Specialist provided the patient's mother with this author's name and recommended that she follow-up for her daughter's post-hospitalization mental health care. At first they saw no reason to call, then after a few weeks, the author saw the child at an office visit and evaluated her. Behavioral issues, intense separation anxiety, refusal to allow diaper changes without being held down, and severe sleeping issues were noted on the intake form as new or regressive behaviors. The author went to work immediately with bi-weekly play therapy appointments, giving the toddler control and power in the playroom by inviting her to direct her own play (non-directive play therapy[30]). The goal was to invite some semblance of power in her life after the medical care experience ripped away what she knew of safety and security. After 16-sessions over 8-wk, the child's symptom's completely resolved and she was back to her usual self. To be clear, it took one month before mental health intervention for the trauma to get worse, and 2 mo of psychological treatment to resolve.

Medical providers must be aware of the impact of these potential scenarios and act quickly and proficiently to ease the fear, anxiety and trauma for pediatric patients in their care. The impact of fear and anxiety relating to medical care can persist long after the encounter and will influence coping in the moment and management of future painful or anxiety provoking medical experiences[31].

COPING AND THE PEDIATRIC PATIENT

Research indicates there is a clear correlation between healthcare, hospitalization and coping with anxiety for children[4,5,32-38]. Children's cognitive development prohibits their capacity to define the parameters of an event, specific to the duration or intensity[25,39]. They are often inaccurate in their assessment of when an event actually occurred[39]. Because of this, children can be triggered into a trauma response by feeling that they are experiencing more frequent or severe medical care than actually occurred.

Trauma causes increased levels of catecholamines (epinephrine and norepinephrine), which results in increased sympathetic nervous system activity[40]. It also decreases corticosteroids, and serotonin, which results in the inability to moderate the catecholamine-triggered fight or flight responses[40]. In children, these physiological responses commonly result in dissociative patterns such as a freeze or surrender response. Children may surrender in helplessness, hide from the frightening experience, cling to an attachment figure or object, be unable to communicate their needs clearly, or be overcome with disabling emotion[40].

Coping in children and adults universally includes three facets, none of which are one-dimensional: (1) active *vs* avoidant; (2) internal *vs* external; and (3) emotionally-focused *vs* problem-focused[36]. Researchers[41] found that avoidant coping is used more during the acute phase of healthcare or hospitalization and active coping was used more often in the recovery phase. By focusing children's attention

on a specific aspect of medical care, they feel better equipped to recover faster than children who are avoidant in their experience. This focus introduces internal locus of control.

An internal locus of control refers to the belief that events or outcomes come as a result of one's own choices and actions; an external locus of control is described as less influenced by one's own choices and actions and more predisposed by outside influences[42]. Choosing an internal locus of control correlates positively with active coping approaches, such as seeking information about the illness or procedure and alertness to stressful stimuli[43,44]. In young children aged 0-2, the internal locus of control is associated with attachment of the primary caregiver and the child will rely upon them for age-appropriate information and for physical safety. An external locus of control has been shown to be interrelated with avoidant coping strategies, such as avoiding information about the event, denying worries, and distancing one's self from stressful stimuli[43-45]. This response is commonly displayed in children with a disruptive or avoidant attachment pattern with their primary caregiver.

As coping behaviors differ from child to child, the role of a safe and empowering medical professional is all the more important. If a child does not possess a strong attachment to their primary caregiver, such as a parent, medical personnel may need to step in and offer the child additional assistance in identifying their internal locus of control. Choices foster personal power to children and can encourage a strong internal locus of control. Those that deliver healthcare should have awareness and training in how to treat children appropriately based on style of coping in hopes of decreasing levels of perceived trauma and healthcare-induced anxiety.

A NEW WAY TO CARE

When asked, most patients and their family members communicate the desire for respect, communication, appreciation, and confidence in the skill of the caregiver. In an effort to meet patient needs and increase patient satisfaction with hospital staff interaction, Quint Studer of Studer Group[46] developed 5 fundamentals of service to increase patient satisfaction: (1) Acknowledge: Acknowledge the patient by name. Make eye contact. Ask: "Is there anything I can do for you?"; (2) Introduce: Introduce yourself, your skill set, your professional certification, and experience; (3) Duration: Give an accurate time expectation for tests, physician arrival, and tray delivery; (4) Explanation: Explain step by step what will happen, answer questions, and leave a phone number where you can be reached; and (5) Thank: Thank the patient for choosing your hospital, and for their communication and cooperation. Thank the family for assistance and being there to support the patient.

Although these 5 steps may offer respect, communication, appreciation and confidence in the skill of the caregiver, it fails to address a very important need in patients - emotional containment and support. Current research and literature is limited regarding ways to reduce healthcare-induced distress. Recognizing the unique emotional and relational needs of pediatric patients, this author developed a new way for medical providers to CARE while interacting with pediatric patients: Choices, agenda, resilience and emotional support.

CARE: CHOICES

When children are brought into healthcare settings, they often feel scared, are often in pain, and are expected to adjust to new settings and submit to the bewildering array of questions, exams, tests, and treatments with little to no preparation. Their largest fear is of the unknown[47,48]. Therefore, it is crucial medical professionals take time to explain to the child the reason for the treatment in a developmentally-appropriate manner. Children need as much control and choice as possible[49,50]. If this informative step is not accomplished, anxiety increases. When anxiety increases, feelings of helplessness result. Helplessness results in lack of cooperation[48]. Furthermore, trust is broken once the child feels anxiety-stricken. Patients and their family members are empowered by choice.

The power-differential is clear and felt between patient and provider. By simply providing developmentally-appropriate choices, anxiety can be reduced and emotional containment can be provided to a patient. Power through choice-giving in a medical setting can seem laborious to medical providers at first, but rather simple to implement once there is a common understanding of the goal. The goal is to empower patients and their families in an effort to provide psychological-control of the environment. Surely there are circumstances requiring urgent or emergent care, but overall, a few extra seconds of choice-giving in the moment can go far to reduce perceived or actual psychological trauma immediately and in the long-term and improve patient cooperation[4]. Further, it sets up expectations for future episodes of care.

Examples of medical professionals taking power from patients include: Requiring the patient take off their clothes and get up on the exam table; speaking to the parent only, about the child, during the visit; choosing the pace and flow of the exam; holding children down for injections, venipuncture, intravenous fluids starts, or examination; and, prohibiting the patient to explore the room, instruments being used, or to ask questions. Patients without power are immediately vulnerable to increased anxiety and can even be triggered into a trauma response. Healthcare providers must be cognizant of their power to

potentially cause the medical care process to become a traumatic event for patients, regardless of their age or developmental stage.

The goal of healthcare providers should be to empower patients in their medical care experiences. Providing an empowering environment significantly decreases a patient's risk for healthcare-induced trauma and other undesirable psychological effects of treatment. Examples of medical professionals offering power to a pediatric patient are as follows: Asking the patient where they would like the medical provider to start the exam (*e.g.*, "Would you like me to listen to your heart first or look in your ears first?"); Asking the patient which ear they would like to be examined first (*e.g.*, "Would you like me to look into your left ear or right ear first?"); Letting the patient decide which arm is used to measure blood pressure (*e.g.*, "You get to decide. Should I squeeze your left arm or your right arm to measure how fast your blood is pumping through your body?"); Proving small choices about seemingly insignificant matters, such as having socks on or off (*e.g.*, "You can leave your socks on or off for today's exam. Which do you choose?"); and finally, instilling power by normalizing that a patient may have questions they wish to be answered (*e.g.*, "What questions do you have today?") Each of these word-choice examples provides context of how a small shift in language can foster empowerment to a patient in a medical provider's care.

Genital exams can be a potentially trauma-provoking experience for a child -especially in children with a prior sexual trauma. One in five girls and one in twenty boys is a victim of child sexual abuse[51]. Communicating openly and offering choices to the patient will go far to create an environment of safety and empowerment. Speaking directly to the patient, providing the reason for the genital exam, what is being assessed, and how it may help will let the patient know exactly what to expect. If there are several family members present, ask patients whom they would like in the room. Wait for permission to begin the examination. If necessary, ask for permission to touch the child's genitals, explaining that it's safe because a parent is present. For example during a well-child exam say, "Today I need to check your private area to make sure it is growing the way it should. I will just take a quick look and I might need to feel different places on it to make sure everything is okay. Who would you like to be in the room during the exam? It's okay to ask your brother or dad to leave. You get to decide… With your mom right here, can I begin?".

The result is empowerment and emotional safety for a child, in a potentially traumatizing situation. The physician can set up an environment of trust and safety that will serve as a foundation to medical care for the rest of the patient's life. If a physician is forceful, uses parents to hold a child down, dismisses the child's fear or fight response-verbally or physically-without validating the emotions, assumes permission to examine the patient's genitals, or fails to give the child power of who was present in the room for the examination, there may be a different outcome. Choices communicate power and care.

CARE: AGENDA

Fear and anxiety can increase when patients are unsure or unprepared for what is going to happen in an episode of care. Trauma is a normal response to fear, especially in pediatric patients. In an effort to mitigate trauma responses, providers can provide their agenda to patients and their families. The agenda includes what to expect during the healthcare visit and what is expected of them. Introducing detail makes the unpredictable, predictable - and fear dissipates. The benefits are clear. When patients know what to expect and what is expected of them, they feel more in control of the situation and are therefore less fearful, anxious, and less likely to have trauma responses.

In outpatient settings, a physician may choose to set the agenda in the following manner for a well-child exam: "In our time together today we have 20 min…; I'm going to talk to you (child) and then talk to your dad…; Then I'm going to listen to your heart, and take a look inside your ears, nose and mouth…; After I take a look at everything, we will discuss other choices that need to be made today, such as vaccines…; And then, you will get to choose a sticker on the way out!"

Hospital providers have additional stressors, such as urgent and emergent medical conditions to treat and manage. With these considerations in mind, the following recommendations should help communication with children and their families in inpatient settings: "'I'm going to track how you are breathing and how fast your blood is pumping through your body-the process is called getting vital signs'; 'Then I'm going to ask you and your mom a lot of questions to get to know you'; 'Things move quickly around here. Then suddenly they stop. It could feel frustrating to wait'; 'You may have to wait a while for the doctor to come in'; 'I will ask you to change your clothes'; 'I will hook you up to a machine that tracks your breathing-it makes beeping sounds, that's normal'; 'If the doctor wants to see what's going on inside of your body, I might take a sample of your blood and it pinches a bit'. 'We might go to a special room that doesn't have many lights and take pictures of your body. It's called an X-ray and it's important to stay really still for the pictures'".

Setting the agenda and making expectations clear to the patient and their families is a vital part of preventing healthcare-induced anxiety and trauma responses. Each of the above statements of explanation and expectation can act as a preventive measure to create emotional and psychological safety for pediatric patients and their families. By adding a

few moments of explanation, healthcare providers can aid in establishing rapport and trust that will last throughout a child's lifetime of engaging with medical professionals. Further, a few moments of explanation on the front end will save time in the long run.

CARE: RESILIENCE

Identifying a patient's resilience, or strengths, is a powerful marker of establishing a trust-filled relationship. Beginning a healthcare visit with a patient's strengths and identifying how a patient and their family have managed other struggles in their life immediately fosters rapport and trust. For example: "What was helpful when you sought out help for this previously?" or "What else should I know about you in order to best understand your situation and help you today?" "That seems really important to you - tell me more about it".

During an evaluation process, by starting with a patient's strengths, a medical professional also communicates to the patient that even if there are concerns, the provider wants to hear about what is good. This may be the only time in the day a child hears about their positive qualities. Further, by asking a parent to identify their child's strengths with the child present, it aids to strengthen the parent-child relationship. A note of caution, if a child is present in an office visit, which they almost always are, providers should limit negative talk about the child. For example, night enuresis is a shame-filled topic for many school-aged children and can be exacerbated by critical evaluation with a medical provider. Further, behavioral issues, including attention deficit hyperactivity disorder symptoms, can equally be shame-inducing topics for children.

A practical way of addressing the issue of concerns and problems is instead of asking, "What are your concerns and what problems do you have?" ask, "What would you like to be different?" There is a therapeutic and psychological difference in the way this question sounds to and is internalized by a child. Examples to empower patients by identifying strengths are as follows: ""Tell me what's going really well in your life right now...' 'What are you the most proud of in your child?' 'What is the best thing in your life?' 'What are you really, really good at?' 'What is the best thing about being (child's) parent?'"

Each of these examples are a quick re-frame of common and necessary questions around problems and concerns that healthcare providers ask children and their caregivers. By starting with strengths and re-framing negative talk around the child a healthcare provider continues to make actionable principles to decrease anxiety and trauma responses in the healthcare setting, regardless of what brings the child in for medical treatment. Focusing on resilience and strengths communicates great respect to a patient and family members.

CARE: EMOTIONS

It is common and expected for pediatric patients and their families to experience myriad emotions with each healthcare encounter. Medical professionals serve their pediatric patients well by making a concerted effort to normalize common emotions, including fears. By creating freedom for patients to experience and convey emotions, the healthcare provider communicates the patient's emotions are valuable, worth listening to, and creates opportunity for deeper connection in the patient-provider relationship. When patients feel understood and validated, they feel safe - mental health professionals call this relational process attunement. Patients want to know everyone feels afraid sometimes. Reflect emotions when they are observed clearly. Express wonder about emotions that are unclear.

Practically speaking, the following, said in a soft and comforting tone of voice, depicts reflecting and normalizing emotions in the healthcare setting: ""Sometimes I feel nervous when I meet new people too'; 'It's okay to feel scared or nervous'; 'It looks like you feel worried'; 'I wonder if you are feeling afraid or unsure'; 'There's a lot of sounds here - that can feel overwhelming'; 'You look suspicious - it's okay to ask me any questions you may have'".

The effort to emotionally attune with patients bolsters their trust in their medical provider, creates safety in the unknown environment, and decreases acute anxiety and healthcare-induced trauma. This is not always a natural skill and it takes practice to reflect emotion accurately and curiously; however, the benefits are well worth the effort as it aids in the patient-provider relationship for the long-term, including increase in patient-experience, which is important to all medical providers and health systems.

CULTURAL CONSIDERATIONS OF CARE

As medical providers serve a variety of people from numerous cultures and ethnicities, it is important to address clinical considerations impacting the CARE protocol as it pertains to diversity awareness. Begin by identifying the cultural background of the patient. From there, what is known about the culture, ethnicity, and preferences of the patient? With all multicultural issues, medical providers must begin medical relationships with a respectful curiosity and an intentional invitation to understand differences and similarities. Of note, some cultures desire a lot of interaction with their providers, others do not. Among other things, some patients with differing race or cultural experiences from the provider may prefer that the provider assume a power position in regard to decision-making and avoid collaboration about process and course of treatment. Ask patients what needs to be known about their values surrounding healthcare.

Healthcare-induced anxiety and trauma can present differently in varying cultures. Some cultures celebrate emotional awareness and attunement; and equally, some cultures shun emotional awareness and attunement. It is important to recognize these values in one's patient population and to be cautious in implementing protocols and interventions that could cause more emotional distress to a patient. When in doubt, ask the patient. Patients and their family members are often more than happy to provide context and information surrounding their values and definition of excellent medical care.

CONCLUSION

Pediatric patients require an extra level of care in their healthcare process. They require added patience, flexibility, and containment for their ever-changing emotions. Their primary need is to know they are safe and to be given age-appropriate and developmentally-appropriate information in order to combat heightened anxiety levels and trauma responses, which can hinder the delivery of quality healthcare and create harmful long-term psychological effects. Healthcare providers have a valuable opportunity to control the negative outcome of pediatric stress in the medical setting, no matter their function in a child's episode of care. By utilizing the four principles in the CARE protocol: (1) Choices: Provide power in a powerless environment; (2) Agenda: Letting the patient and family know what to expect and what is expected of them; (3) Resilience: Start with strengths and reframe negatives; and (4) Emotions: Recognize and normalize common fears and responses providing emotional support, children will feel emotionally safe and protected in their medical treatment.

Understanding the risk of anxiety and trauma in pediatric patients with regard to receiving medical care is imperative to effective outcomes. Although universal application can be made to patients throughout the lifespan, the mission of CARE is to provide a voice to the world's most vulnerable, powerless, and disregarded population in medical care-children. The CARE protocol was developed to foster trust in medical care providers and to mitigate the risk of anxiety and trauma in pediatric patients while receiving necessary and pertinent medical care. Most patients remember how they feel about an episode of care, not what was said or done. CARE enough to allow pediatric patients to feel empowered and safe in their healthcare experience.

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REVIEW

Resuscitation of extremely preterm infants - controversies and current evidence

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Abstract

Despite significant advances in perinatal medicine, the management of extremely preterm infants in the delivery room remains a challenge. There is an increasing evidence for improved outcomes regarding the resuscitation and stabilisation of extremely preterm infants but there is a lack of evidence in the periviable (gestational age 23-25 wk) preterm subgroup. Presence of an experienced team during the delivery of extremely preterm infant to improve outcome is reviewed. Adaptation from foetal to neonatal cardiorespiratory haemodynamics is dependent on establishing an optimal functional residual capacity in the extremely preterm infants, thus enabling adequate gas exchange. There is sufficient evidence for a gentle approach to stabilisation of these fragile infants in the delivery room. Evidence for antenatal steroids especially in the periviable infants, delayed cord clamping, strategies to establish optimal functional residual capacity, importance of temperature control and oxygenation in delivery room in extremely premature infants is reviewed in this article.

Key words: Extremely preterm infants; Resuscitation; Antenatal steroids; Delayed cord clamping; Ventilator support; Oxygenation in delivery room; Temperature stability

Core tip: Management of extremely preterm resuscitation is one of the most challenging aspects of perinatal medicine. There is increasing evidence towards a trend for a more gentle measure of resuscitation to avoid injury both immediate and long term. In this article, we review the evolving strategies to aid the complex process of adaption to extra uterine life for extreme preterm infants.

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INTRODUCTION

The physiological adaptation to extra uterine life for a preterm neonate involves a series of complex processes, it is more pronounced in extremely preterm gestation (gestational age less than 27 wk)[1]. Aerating the fluid filled lung and thereby attaining an adequate functional residual capacity, ability to perform gas exchange and switching to an oxygen enriched metabolism, establishing adult type circulation with stable haemodynamics along with maintaining body temperature are some of the key processes that occur within the first few minutes of life in any new-born[2]. Furthermore, in the extremely preterm infants there is an overriding need for intervention to enable them to adapt to the above processes. Periviable infants are fragile and have many features that increase the difficulty of stabilisation immediately after birth.

Experimental and clinical studies done in past few decades related to resuscitation of preterm infants have shown that interventions by trained personnel during this critical period can not only improve immediate survival but also reduce long term morbidity[3,4]. There is also growing evidence that some of these interventions can also trigger inflammatory and oxidative cascades injuring the organs, predisposing to long-term conditions[3]. This evidence have supported in developing a trend towards gentle management in delivery room in the first "golden hour"[5]. Data for stabilisation and resuscitation of periviable neonate is still limited. The aim of this article is to review the evolving approaches in resuscitation of extremely preterm infants. We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials and performed a manual search of references in narrative and systematic reviews. Search terms included "neonate", "newborn", "resuscitation", "delayed cord clamping", "antenatal steroids", "resuscitation of extremely preterm", "continuous positive airway pressure", and "sustained inflation".

DISCUSSION

Having an experienced neonatal resuscitation team during delivery, for appropriate stabilisation and resuscitation, improve outcome[6-9]. Multiple studies have demonstrated improved outcomes for very low birth weight babies born in tertiary care centres *vs* out born infants[6-9]. The combined risk of death and major morbidities such as neuro-disability at 36 wk, chronic lung disease and hospital stay in extremely low birth weight (500-999 g) infants born in tertiary maternity hospitals as compared to non-tertiary centres has recently been reported (OR = 3.86; 95%CI: 2.21-6.76) in a large cohort by Binder *et al*[6].

Antenatal steroids

Antenatal corticosteroids have been proven to accelerate foetal lung development and reduce neonatal morbidity and mortality when given between 28 and 34 wk of gestation[6]. However, there is only limited research to guide their use in the peri-viable period (22-26 wk gestational age). To date, there have been 6 prospective and retrospective cohort studies evaluating ante-natal corticosteroids use in the periviable period (Table 1); these studies have used the same dosing schedule of betamethasone as the antenatal steroid.

Majority of these studies exhibited OR for neonatal death of 0.6 with antenatal steroid treatment, which is the same relative benefit demonstrated for corticosteroid use in later gestation. Amongst infants born at < 26 wk of gestational age, 7-9 mothers need to receive antenatal steroids to prevent 1 neonatal death. In this group of infants use of antenatal steroids have also been shown to reduce the incidence of intraventricular haemorrhage (IVH) as an outcome. Tyson *et al*[11] have looked at the follow-up of periviable infants exposed to antenatal corticosteroids compared to those not treated with steroids. They demonstrated that when evaluated at 18-22 mo, the infants that delivered between 22 and 25 wk of gestation continued to demonstrate a reduction in mortality (OR = 0.55; 95%CI: 0.45-0.66). One must remain cautious while making decisions based on cohort studies, which have the potential for unintended bias. While further studies such as randomised clinical trials would be beneficial, the current available evidence strongly suggest that antenatal corticosteroids have value when given in the periviable period and should be offered when clinically appropriate. This benefit is clear from 23 wk onwards as seen by the above studies. It is less certain whether they should be utilized at 22 wk or less due to lack to data in this gestation. Because of the uncertainty in gestational age prediction, it is suggested that they should be used at this gestational age if preterm birth appears to be imminent.

Delivery room resuscitation

Delayed umbilical cord clamping: Delaying umbilical cord clamping in term infants is generally considered to be beneficial[16]. The evidence for benefit of delayed cord clamping in preterm infants is not clear. Maintaining blood supply to heart while pulmonary vascular system gets replenished contributes to keeping an adequate left ventricular output, thereby avoiding reduced blood flow to the brain, coronary arteries, kidneys and rest of the body[17]. A systematic review by Rabe *et al*[16] reviewed 15 studies on delayed cord clamping in preterm infants. They concluded that providing additional placental blood to the preterm infants by delaying cord clamping for 30 to 120 s, rather than early clamping, seems to be associated with less need for transfusion, better circulatory stability, less IVH (all grades) and lower risk for necrotising enterocolitis (NEC). However primary outcomes of death as well as death or neuro-disability at 2-3 years were inconclusive. The optimal

Table 1 Studies reporting the outcomes of antenatal steroid use in periviable births

Ref.	Year published	Country of origin	No. of babies	Birth weight (g)	Gestational age (GA)	Mortality OR (95%CI)	IVH OR (95%CI)
Costeloe *et al*[10]	2000	United Kingdom	811	400-1000	< 26 wk	0.6 (0.34-0.89)	0.39 (0.2-1.0)
Tyson *et al*[11]	2008	United States	4446	400-900	< 26 wk	0.6 (0.23-0.78)	-
Hayes *et al*[12]	2008	United States	450	400-550	< 23 wk	0.3 (0.2-0.65)	-
Mori *et al*[13]	2011	Japan	11607	400-1000	< 26 wk	0.7 (0.44-1.24)	0.65 (0.21-1.68)
Bader *et al*[14]	2010	Israel	3450	400-1000	< 26 wk	0.6 (0.4-0.68)	-
Carlo *et al*[15]	2011	United States	10541	400-1000	22-25 wk	0.58 (0.52-0.65)	0.55 (0.50-0.62)

OR: Odds ratio; IVH: Intra-ventricular haemorrhage.

time to clamp the umbilical cord remains controversial. In all the studies, early clamping was defined as less than 15 s, the definition of late clamping was varied from more than 30 s to 3 min. There are several small randomized control trials that have compared early (< 15 s) with late clamping (> 30 s) following preterm birth and there are several prospective observational studies[18-22]. However, there is limited data in periviable or non-vigorous preterm infants demonstrating improved mortality and morbidity following delayed umbilical cord clamping. A recent experimental study in lamb model demonstrated the effects of early *vs* delayed cord clamping on transitional haemodynamics[23]. They reported that delayed cord clamping after initiation of positive pressure ventilation and establishment of functional residual capacity markedly improved cardiovascular function by increasing the pulmonary blood flow and stabilising the cerebral haemodynamics transition.

Although experimental studies support delayed cord clamping having a positive effect on the preterm, the setup needed to practically perform resuscitation manoeuvres with an intact cord still remains an impediment. There is lack of evidence for delayed cord clamping in a preterm who is moderately depressed. An alternative to this of cord milking has been suggested as a more rapid method to influence placental transfusion[16,23,24]. This technique requires clamping the cord near the placenta and stripping around 20 centimetres, 2-4 times, from placental to foetal side. This can be performed within a few seconds. There have been five randomised control trials have been performed in preterm infants, but only with small number of preterm infants[24-28]. Rabe *et al*[24], Hosono *et al*[25] and March *et al*[26] have looked at need for the blood transfusions and the number in preterm babies, while Takami *et al*[27] and Katheria *et al*[28] have looked at haemodynamics following milking of cords. Further larger studies are needed for this procedure. There are some concerns that milking might not replicate the haemodynamic benefits of delayed cord clamping[29]. Retrospective studies have shown Haemoglobin levels at birth of > 12 g/dL results in reduced mortality and improved morbidity in preterm infants < 32 wk of gestational age[30,31].

Several trials are currently on-going for both delayed cord clamping in preterm infants as well as for milking of cord as an alternative[32,33]. A recent multicentre feasibility study of delayed cord clamping in preterm infants less than 32 wk gestation in United Kingdom (United Kingdom CORD trial) has compared early < 20 s to delayed cord clamping for at least 2 min. The study has been concluded and the results are awaited[32]. A large randomised trial is currently been undertaken in Australia which is nearing completion of recruitment[33]. The CORD trial will contribute to an international collaborative individual patient meta-analysis of similar trials of enhanced placental transfusion, including the Australian Placental Transfusion trial. Altogether, these trials will enrol 2000-5000 very preterm infants, which are expected to improve our current understanding and evidence of delayed cord clamping in these infants and its impact on survival and neurodevelopment in childhood.

Stabilising temperature of preterm infants: Preterm infants lack adequate brown adipose tissue and therefore cannot activate thermogenesis. They quickly lose heat in the delivery room by evaporation of amniotic fluid, by conduction of heat from the body touching cool surfaces, by convection and radiation to cooler surroundings. They are highly susceptible to hypothermia unless preventive efforts are made. A study has shown that for every 1 ℃ below 36 ℃ on admission temperature, mortality increases by 28%[34]. Increasing the ambient temperature of delivery room to at least 26 ℃ before the delivery is an important intervention[35]. Both hypothermia and hyperthermia during stabilisation can be detrimental[36]. All extremely preterm infants should be brought in the resuscitaire under radiant heat and wrapped in polyethylene or polyurethane bags or wrap, up to their shoulders without drying[37-39]. This reduces heat loss and maintains adequate humidity. All subsequent stabilisation and assessment should be done through the plastic bag. Multiple studies have shown that plastic bags improve temperature upon admission[39,40] but there are no studies powered for clinical outcomes like death and long term neurodevelopmental outcome[40]. Preterm infants can be placed on a chemically activated thermal mattress in combination[41]. The head should be

Table 2 Overview of the results of the studies comparing continuous positive airway pressure and invasive ventilation

Ref.	Total number	Gestational age (GA) in wk	Death or BPD CPAP	Death or BPD non CPAP	Death or BPD relative risk (95%CI)	Days needing mechanical ventilation CPAP	Days needing mechanical ventilation non CPAP	Days needing mechanical ventilation *P* value
Morley *et al*[51]	610	25-28	108/307	118/303	0.9 (0.73-1.11)	0-11	11-14	< 0.001
SUPPORT[52]	1316	24-27	323/663	353/653	0.9 (0.81-1.00)	2-32	2-36	0.01
Sandri *et al*[54]	208	25-28	53/103	32/105	1.01 (0.7-1.57)	1-14	1-18	< 0.01
Dunn *et al*[53]	648	26-29	68/223	138/425	0.94 (0.74-1.19)	1-8	1-10	0.01

Infants randomised to prophylactic surfactant group and intubate, surfactant, or extubate group were combined in the intubation group. CPAP: Continuous positive airway pressure; BPD: Bronchopulmonary dysplasia.

covered by a hat. Care should also be taken to ensure that hyperthermia is avoided. Monitoring infants' temperature is of paramount importance. Perinatal hyperthermia is associated with respiratory depression as well as risk of adverse neurological outcome[36]. Every hospital delivering high risk infants should have protocols for controlling delivery room temperature, systematic use of plastic bags and hats, monitoring temperature during stabilisation and transport to avoid hypothermia or hyperthermia. Admission temperature is an integral part of the Clinical risk Index for Babies Ⅱ (CRIB Ⅱ) score. The CRIB score was developed to predict mortality for infants born at less than 32 wk gestation at birth and was derived using data from infants admitted to four UK tertiary neonatal units from 1988 to 1990[42]. This score has been widely used to quantify the risk of mortality among very preterm infants[42]; it is assessed in the first 12 h of birth. The CRIB score was modified in 2003 as CRIB Ⅱ score[43], where gestational age and birth weight together with admission temperature and base excess were added to predict mortality. The new score was intended to improve predictions for smaller, very premature infants and to exclude variables that could be influenced by care given to the infant. Score for acute neonatal physiology (SNAP) is another mortality prediction score developed in United States[44] a simpler version called SNAP Ⅱ was developed later using data from 30 American units[45]. Admission temperature was one of the important components of these mortality prediction scores.

Respiratory support in stabilisation

Ventilatory support: Despite considerable advances in perinatal-neonatal care, there is a trend for increased incidence of bronchopulmonary dysplasia among survivors of prematurity[46,47]. Appropriate respiratory support in the delivery room can ensure reduction in the damage caused to the lungs. Preterm infants are unique due to their poor respiratory drive, structurally immature lungs, surfactant deficiency and highly non-compliant chest wall. Respiratory support should improve lung compliance thereby achieving adequate minute ventilation, decrease work of breathing and provide assisted ventilation as required. In order to ensure good gas exchange, consistent functional capacity has to be established, while avoiding areas of atelectasis and over distension.

Use of positive end expiratory pressure (PEEP) during intermittent positive pressure ventilation (IPPV) or use of continuous positive airway pressure (CPAP) alone, after birth to facilitate alveolar recruitment and to avoid barotrauma and volutrauma from mechanical ventilation is recommended[48]. CPAP can help establish and maintain a functional residual capacity in preterm lung, thereby improving pulmonary haemodynamics and respiratory distress[48]. Most neonatal resuscitation guidelines (NRP/NLS) have supported the use of CPAP as a mode of ventilator support for preterm babies soon after birth[49].

A systematic review with meta-analysis in 2013 by Schmölzer *et al*[50] evaluated the difference of outcomes between invasive and non-invasive respiratory support in preterm infants at birth. Four randomised controlled trials were evaluated and they concluded that nasal CPAP initiated in the delivery room compared with intubation reduces death or bronchopulmonary dysplasia in very preterm babies (Table 2)[51-54]. The meta-analysis suggested that one additional infant could survive to 36 wk without bronchopulmonary dysplasia for every 25 babies treated with nasal CPAP in the delivery room rather than being intubated and mechanically ventilated. Pooled analysis showed a significant benefit for the combined outcome of death or bronchopulmonary dysplasia, or both, at 36 wk corrected gestation for babies treated with nasal CPAP: RR = 0.91; 95%CI: 0.84-0.99; RD = -0.04; 95%CI: -0.07 to -0.00; NNT of 25.

However none of these trials included infants less than 23 wk and only 1 trial had infants at 24 wk gestation. There are four small studies in periviable babies comparing invasive and non-invasive ventilation. Finer *et al*[55] demonstrated that although about half of 24 wk GA infants can be stabilised on CPAP in the delivery room, very few infants of less than 24 wk GA avoided delivery room intubation.

These trials indicate that despite a strategy of CPAP use after birth in extremely low gestational age infants, rates of bronchopulmonary dysplasia (BPD) or death at 36 wk postmenstrual age (PMA) remain high, ranging from 41% to 64%[52,56,57].

CPAP should not be used in place of positive

pressure ventilation when respiratory effort is poor or absent[54,58]. In a recent study, it was shown that a stepwise PEEP strategy after birth improved gas exchange, lung mechanics and end expiratory volume without increasing lung injury in preterm lambs[59].

Sustained inflation (SI) has been suggested as an alternative to CPAP. Sustained inflation is application of higher pressure (25 cm H_2O) for a prolonged time than normal (15-25 s)[60]. A systemic review in 2014 by Schmölzer *et al*[61] compared sustained inflation *vs* positive pressure ventilation. Four RCTs were analysed showing SI improves functional residual capacity (FRC) and therefore the need for mechanical ventilation during the first 72 h, the pulmonary protective effect is lost in the subsequent development to BPD[62-65]. Further clinical trials are required to evaluate the efficacy, including risk of pneumothorax, long term outcomes and safety, of this lung aeration manoeuvre at birth.

The Sustained Aeration of Lung (SAIL) trial, a large, international multi-centred randomised trial is currently on-going evaluating sustained inflation *vs* positive pressure ventilation[66]. This prospective randomized controlled unblinded trial will recruit 600 infants of 23 to 26 wk gestational age who require respiratory support at birth. Infants in both arms will be treated with PEEP 5 to 7 cm H_2O throughout the resuscitation. The study intervention consists of performing an initial SI (20 cm H_2O for 15 s) followed by a second SI (25 cm H_2O for 15 s), and then PEEP with or without IPPV, as needed. The control group will be treated with initial IPPV with PEEP. The primary outcome is the composite outcome of bronchopulmonary dysplasia or death at 36 wk post-menstrual age.

Oxygenation in delivery room: Preterm infants are deficient in anti-oxidative protection and are highly susceptible to oxygen toxicity thereby exacerbating morbidities[67]. Avoiding hypoxemia and hyperoxaemia during resuscitation is essential. Blended oxygen and pulse oximetry play an important role in titrating the delivery of oxygen. Due to inherent technology behind the pulse oximetry measurements saturation values less than 60%-70% are inaccurate[68]. Pulse oximetry should be placed on the right hand or arm to evaluate the pre-ductal oxygen levels; it also measures heart rate accurately, which helps in the resuscitation. The optimal initial fraction of inspired oxygen (FiO_2) for resuscitating/stabilising premature infants is not known. A recent meta-analysis by Saugstad *et al*[69] in 2014 for optimal initial fraction of oxygen in less than 32 wk gestation analysed 10 published studies covering 677 infants. It shows that the outcomes of starting with a low initial FiO_2 (0.21-0.30) were as good as starting with a high FiO_2 (0.6-1.0). Oxygen should be individually titrated based on the neonate's response.

Harling *et al*[70] performed the first resuscitation trial of infants of less than 31 wk GA with either 50% or 100% oxygen for the entire time of the resuscitation and found no significant differences in cytokines, death, or survival without BPD. All subsequent trials in preterm infants comparing a high *vs* low oxygen concentration utilized a targeted oxygen saturation strategy. The room air *vs* oxygen administration in preterm Resuscitation (ROAR) study randomised 106 infants $\leqslant$ 32 wk gestation comparing three O_2 strategies: 100% throughout (High oxygen group), 100% initially (Moderate oxygen group) and 21% (Low oxygen group) initially. The last two groups had the FiO_2 titrated until a SpO_2 of 85% to 92% was reached[71]. This study demonstrated that targeting resuscitation SpO_2 values was feasible for very preterm infants. Ezaki *et al*[72] studied infants < 35 wk' gestation born by caesarean section. Twenty one infants received 100% oxygen and 23 were treated with a targeted oxygen saturation strategy. They reported lower 5 min Apgar scores, and higher total hydro peroxides in the 100% oxygen group which implies an improved outcome with targeted oxygen saturation strategy. None of the studies have evaluated long term outcomes in these infants, which is of utmost importance. That is why larger prospective randomised controlled trials with long term outcome measures are required.

There are several experimental and clinical studies to assess the initial oxygen concentration during resuscitation[73,74]. The To2pido (Targeted oxygenation in the resuscitation of premature infants and their developmental outcome) study is an international, multicentre trial currently set up in Australia, Malaysia, and Singapore and with centres starting in India[75]. It is to determine the outcome of very premature infants (< 30.6 wk gestation) who have had resuscitation at birth starting with either room air or 100% oxygen. The trial is currently recruiting and the target number of infants to be recruited is 1892. The primary outcome is said to be death at 2 years and secondary outcomes are evidence of bronchopulmonary dysplasia at 36 wk gestation or major disability at 2 years of age. The Premature Infants Resuscitated with Oxygen or Air (PRESOX) trial, which is planning to recruit 1260 infants, is a prospective randomized clinical trial of extremely premature infants that will assess the use of a low and high oxygen concentration for the initial resuscitation[76]. This proposed trial will use targeted oxygen saturation levels over the first 15 to 20 min of life to compare a low and a higher initial oxygen level for the resuscitation of such infants, and is powered to evaluate short term outcomes of survival without oxygen at 36 wk and survival without retinopathy of prematurity, and the long term outcome of survival without significant neurodevelopmental impairment at 2 years of age.

In 2010, Dawson *et al*[75] developed SpO_2 reference range for the first ten min of term, preterm and extremely preterm infants. Three databases were merged, two from Australia and one from Spain to

evolve this range. At present Dawson's nomogram is the best available reference range for titration of oxygen in preterm infants. However it should be noted that the reference range was based on the infants who were breathing in air. A study by Vento *et al*[76] in 2013 showed that preterm infants requiring CPAP but in air attained higher saturation significantly earlier than in Dawson's nomogram.

There is growing interest in monitoring CO_2 levels in delivery room and using it as a tool for assessment of functional residual capacity. A systematic review in 2014 by Hawkes *et al*[77] reviewed the current evidence for CO_2 monitoring. These mainly included observational studies with only one RCT. Observational studies have a higher degree of bias and can also mask cause and effect relationships or, alternatively, suggest correlations where there are none. The conclusion was that CO_2 detection may be of particular benefit for preterm infants in the delivery suite. However, there is a need for further research into CO_2 detection, in particular, capnography, as a means of confirming effective IPPV in neonatal resuscitation.

CONCLUSION

Resuscitation and stabilisation of a preterm neonate consists of complex decisions and tasks undertaken by the team. In recent years, there is growing evidence for providing a gentle, least invasive support in the delivery room to reduce immediate and long term morbidities. There needs to be further research in all the aspects of resuscitation especially for periviable neonate.

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REVIEW

Antiseptic use in the neonatal intensive care unit - a dilemma in clinical practice: An evidence based review

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Abstract

Infants in the neonatal intensive care unit are highly susceptible to healthcare associated infections (HAI), with a substantial impact on mortality, morbidity and healthcare costs. Effective skin disinfection with topical antiseptic agents is an important intervention in the prevention or reduction of HAI. A wide array of antiseptic preparations in varying concentrations and combinations has been used in neonatal units worldwide. In this article we have reviewed the current evidence of a preferred antiseptic of choice over other agents for topical skin disinfection in neonates. Chlorhexidine (CHG) appears to be a promising antiseptic agent; however there exists a significant concern regarding the safety of all agents used including CHG especially in preterm and very low birth weight infants. There is substantial evidence to support the use of CHG for umbilical cord cleansing and some evidence to support the use of topical emollients in reducing the mortality in infants born in developing countries. Well-designed large multicentre randomized clinical trials are urgently needed to guide us on the most appropriate and safe antiseptic to use in neonates undergoing intensive care, especially preterm infants.

Key words: Antiseptics; Disinfectants; Topical; Neonate; Preterm; Very low birth weight infant; Chlorhexidine; Povidone-iodine; Alcohol

Core tip: Topical antiseptic agents play a crucial role in the prevention of nosocomial infections in infants admitted to neonatal intensive care unit. There is a paucity of good quality studies to guide us on the most effective and safe antiseptic preparation, concentration and combination for use in neonatal skin disinfection. Further research is urgently needed to identify the most appropriate and safe antiseptic use in neonates including preterm and very low birth weight infants.

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INTRODUCTION

Sepsis is one of the leading causes of death in infants admitted to the neonatal unit[1-5]. Neonatal sepsis is also associated with significant morbidity including prolonged hospital stay and increases in health care costs[6,7]. Studies have shown that sepsis in preterm and very low birth weight infants (VLBW) infants could lead to significant neurodevelopmental morbidity secondary to associated white matter injury[8-10]. Healthcare associated infections (HAI) account for vast majority of neonatal sepsis, with Catheter Related Bloodstream Infection (CRBSI) being the most common nosocomial infection[11,12]. The neonatal units, to reduce or prevent the HAI/CRBSI have adopted several strategies and use of an effective topical antiseptic agent is one of the integral components[11,13,14]. Centers for Disease Control and Prevention (CDC)[15] has made a specific recommendation for skin preparation before cannulation and central venous catheter insertion for adults and children 2 mo or older. Similarly United Kingdom national evidence based guidelines[16] recommend the use of 2% chlorhexidine gluconate (CHG) in 70% Isopropyl alcohol for skin antisepsis prior to venous cannulation and Central Venous Catheter (CVC) insertion in the same age group. However there is no specific guidance recommendation on antiseptic of choice for infants less than 2 mo. Wide range of antiseptics has been used in neonatal units all over the world, but good evidence is lacking, and the most appropriate and safe antiseptic solution to use on the skin remains controversial. The purpose of this review is to comprehensively examine the available literature on use of topical antiseptics in neonates and to identify evidence based recommendations for clinical practice. In this review we did not include the evidence of antiseptic use for hand hygiene in neonatal units.

BACKGROUND

HAI is a major problem in neonates that incur significant health and economic burden to the society. Gray *et al*[17] reported that nosocomial infections related to coagulase negative staphylococcus prolonged the hospital stay by 14.0 ± 4.0 d ($P < 0.01$) and an associated increase in hospital charges of $25090 ± 12051 ($P < 0.05$). In another report nosocomial infections were found to increase costs by 26% in < 750 g and 80% in 1250-1500 g infants and the length of stay was increased by 4-7 d in VLBW infants[18].

Preterm neonates are prone for infection because they have functionally immature immune system with extremely low immunoglobulin levels, complement activity, and neutrophil storage pool and function[19]. In addition, preterm infants lack an effective skin barrier. Stratum Corneum, which is responsible for providing an effective epidermal barrier, is not well developed until 32-34 wk of gestation. For babies born < 34 wk, it takes about 4-5 wk for the skin to mature which makes them more vulnerable to infections during this period[20-22]. Other risk factors for hospital-acquired infections include the presence of intravascular catheters, other invasive devices, mechanical ventilation, parenteral nutrition and use of broad-spectrum antibiotics[23].

CRBSI is the most common HAI[12] and is estimated to cause up to 70% of all hospital acquired infections in preterm infants[11]. Catheter hub colonisations followed by exit site were the strongest predictors of CRBSI in NICU[24]. Multi-faceted interventional strategies in the form of care bundles have been developed in neonates worldwide to reduce the HAI. There are several reports from all over the world, that catheter care bundles can reduce the risk of nosocomial and CRBSI[11,13,25]. One of the key steps included within the care bundles is that skin is appropriately disinfected to prevent the entry of microorganisms as well as to reduce the risk of subsequent infection. It is widely accepted; from adult and paediatric studies that CHG is most effective for skin antisepsis[26] and is recommended as best practice in various guidelines[15,16].

Antiseptics used in neonatal units

An ideal antiseptic agent should be effective against a wide range of microorganisms, have an immediate onset of action, have residual and long term effect, not be inactivated by the presence of organic material *e.g.,* blood, have minimum toxic effects on the skin and the organ systems[27,28]. A variety of topical antiseptics have been used in varying concentrations and combinations. Surveys from United States, United Kingdom, Australia and New Zealand showed that CHG, alcohols and Povidone-Iodine (PI) are the most commonly used agents in neonatal units[29-32].

Table 1 summarises the mechanism of action, spectrum of activity and disadvantages of individual antiseptic agents used in neonates[33,34].

Chlorhexidine: CHG a cationic bisguanide, first discovered in the United Kingdom is the most widely used antiseptic agent[35]. It is effective against gram-positive bacteria, somewhat less active against gram negative but is effective against resistant organisms including Methicillin Resistant Staphylococcus aureus (MRSA), Vancomycin resistant enterococcus (VRE), Streptococci and Pseudomonas[33,34,36]. CHG has significant residual activity and addition of alcohol based preparations results in significantly greater residual activity than alcohol alone. It also acts in the presence of organic material like blood or biofilm[33,34,36]. Its antimicrobial activity is slower than that of alcohols.

Table 1 Characteristics of topical antiseptic agents used in neonates (World Health Organization 2009)

Antiseptic agent	Mechanism of action	Advantages	Disadvantages	Preparations/ compounds
Chlorhexidine	Disruption of cytoplasmic membranes Denaturation of proteins	Broad spectrum antimicrobial activity Kills yeasts Intermediate onset of action Activity not affected by organic material Residual activity	Non-sporicidal Not effective against mycobacteria Local dermatitis Neurotoxicity Non-sporicidal	0.25%, 0.5%, 1%, 2%, 4% - aqueous and alcohol based
Alcohols	Damages cell membrane Denaturation of proteins	Broad spectrum antimicrobial activity Faster onset of action	Not active in presence of organic material No residual activity Skin reactions Systemic absorption	Ethanol, isopropyl alcohol, methanol
Iodine	Forms complexes with proteins and lipids Impaired protein synthesis and alteration of cell membranes	Broad spectrum antimicrobial activity Sporicidal Effective against mycobacteria Has some residual activity	Skin irritation Systemic absorption with hypothyroidism	10% povidone-iodine
Hexachlorophene	Inactivates essential enzyme systems	Good activity against gram positive, weak against gram negative	Residual activity Neurotoxicity	Currently not recommended for bathing neonates

Alcohols: Alcohol can be used alone or in combination with other antiseptics, most common being CHG. Alcohols have excellent *in vitro* germicidal activity against gram positive and gram-negative bacteria including MRSA and VRE, mycobacteria and a variety of fungi. They are most effective between concentrations of 60%-80% and have a faster onset of action but no residual activity. They are not active in the presence of organic material.

Iodine: Iodine has been recognised to have antiseptic properties since 1800s and has now been replaced by iodophors. Iodophors are composed of elemental iodine and a polymer carrier of high molecular weight. The amount of iodine present determines the level of antimicrobial activity[33,37]. Combining iodine with polymers increases the solubility, promotes sustained release of iodine and reduces the skin irritation[33,37]. Most common polymers iodophors used are polyvinyl pyrrolidone (povidone) and ethoxylated non-ionic detergents (poloxamers).

Hexachlorophene: Hexachlorophene is a bisphenol compound with three chlorine molecules. It was widely used in hand washing and routine bathing of neonates in hospitals. It is bacteriostatic and is the weakest of all the antiseptic agents mentioned in the Table 1[33]. It does have some residual activity. Hexachlorophene used for washing and cord care reduced *Staphylococcus aureus (S. aureus)* colonisation and related omphalitis. However in 1970 following cases of vacuolar encephalopathy its use has been withdrawn[38]. Following this a number of investigations have revealed that incidence of *S. aureus* infections had gone up and some places restarted the use of hexachlorophene[39,40].

Octenidine: Octenidine is a bis-pyridine compound, a cationic substance that binds to the microbial envelopes, cell membranes and destroys the cell wall of microorganisms by disrupting their metabolism[41]. It has a broad spectrum antimicrobial activity against gram positive and gram negative bacteria[42,43], is effective against resistant organisms including MRSA, vancomycin resistant *Staphylococcus aureus* (VRSA)[44], extended spectrum beta-lactamase producing bacteriae (ESBL)[45] and pseudomonas[46]. It has a low virucidal activity especially against hepatitis B virus and herpes simplex viruses but has no effect on other viruses, spores or protozoa[41]. Like Chlorhexidine it has significant residual activity up to 24 h[47] and the antiseptic effect is retained even in the presence of organic material[44,48]. Octenidine is often used in combination with alcohol preparations either phenoxyethanol or propanol.

A survey from 90 NICUs in United States on CHG use, reported that 61% of the units used CHG containing preparations. Twenty-one neonatal units used alcohol based CHG preparations[30]. Heron *et al*[31] surveyed the use of antiseptics across 57 neonatal units in the United Kingdom in 2013. They reported seven different antiseptics were in use and 53% of the units used alcohol based CHG preparations in contrast to findings of an early survey from 2007 (14% *vs* 53%). Majority of the units used alcohol based CHG irrespective of GA, birth weight[31]. These surveys actually reflect the changes in clinical practice following national recommendations to use alcohol based CHG antiseptic solutions, the evidence of which is mainly

derived from studies on adults and older children.

ARE THE ANTISEPTICS USED IN NEONATES EFFECTIVE?

Antiseptics have been used in neonates for a range of different procedures and interventions, in different concentrations and combinations. We reviewed the current literature based on their purpose of use and to identify a preferable effective antiseptic type and preparation over other agents.

Antiseptics use to reduce neonatal skin colonisation

Several interventions have been tried to decrease the colonisation of newborn skin with pathogenic organisms and associated sepsis. There are studies, which looked at the use of emollients, antibiotics, vaginal CHG washes during labour, umbilical cord cleansing and whole body washing to reduce the infection rates.

Vaginal CHG washes during labour: A large randomized clinical trial (RCT) conducted in South Africa, compared 4005 mothers and their 4072 neonates treated with 0.5% CHG wipes against 4006 mothers and 4057 neonates in the control group. Results from this study showed that CHG wipes did not reduce neonatal sepsis (3% *vs* 4%; CI: 19-24; *P* = 0.65) or GBS colonisation in neonates (54% *vs* 55%; efficacy -0.05%; CI: 9.5-7.9)[49]. Saleem *et al*[50] conducted a placebo controlled RCT on 5008 women in labour and their infants, to compare the effect of CHG vaginal and infant wipes, on reduction of neonatal sepsis and perinatal mortality. CHG vaginal and infant wipes did not show a significant reduction in neonatal sepsis and mortality (3.1% *vs* 3.4%; RR = 0.91; CI: 0.67-1.24) or composite outcome of neonatal sepsis and perinatal mortality (3.8% *vs* 3.9%; RR = 0.96; CI: 0.73-1.25)[50].

Ohlsson *et al*[51] conducted a systematic review to determine whether vaginal CHG during labour reduced early onset GBS infections. Authors found that Vaginal CHG washes/gel reduced the GBS colonisation of neonates, however this was not associated with significant reduction in GBS sepsis. Moreover, women who received CHG washes developed mild side effects. The quality of the included studies varied and was low. Therefore authors concluded that use of Vaginal CHG is not currently recommended especially in the era of intrapartum antibiotic prophylaxis.

Topical ointments: Preterm infants are prone for infections as they do not have an effective epidermal skin barrier and topical emollients could theoretically provide an effective barrier to prevent infections. Darmstadt *et al*[52] from Bangladesh, in their prospective RCT involving a total of 497 preterm infants, compared the effect of aquaphor ointment and sunflower oil against controls in reducing the neonatal mortality. Results of the study showed that sunflower oil reduced the mortality by 26% (hazard AR = 0.74; CI: 0.55- 0.99, *P* = 0.04) and aquaphor reduced the mortality by 32% (hazard AR = 0.67; CI: 0.57-0.92; *P* = 0.01). This study did not compare neonatal sepsis rates. In another large RCT, Edwards *et al*[53] compared the mortality and nosocomial bacterial sepsis rates (NBS) following the use of aquaphor ointment in preterm infants with birth weight < 1000 g. This group did not a show a significant reduction in combined death or NBS (33.6% *vs* 30.3%, ARR = 1.07; CI: 0.89-1.27; *P* = 0.22). However, the emollient group was noted to have a higher incidence of NBS and Coagulase negative Staphylococcus infections (18.6% *vs* 13.3%; ARR = 1.4; CI: 1.08-1.83)[53]. In their systematic review, Conner *et al*[54] reported that prophylactic application of topical ointment in preterm infants has been associated with significant increase of coagulase negative staphylococcal (RR = 1.31; 95%CI: 1.02-1.70) and other nosocomial infections. They concluded that topical ointment should not be used routinely in preterm infants.

A recent systematic review[55] including the studies from developing countries, has reported that topical emollient therapy significantly reduced neonatal mortality by 27% (RR = 0.73; 95%CI: 0.56-0.94) and hospital acquired infection by 50% (RR = 0.50; 95%CI: 0.36-0.71). Topical emollient therapy may be a promising intervention to reduce neonatal mortality in developing countries but evidence is against this in developed countries.

Umbilical cord care: Umbilical cord has been recognised as a site of colonisation with bacteria especially *S. aureus* and as a source of infection in neonates. Several studies have reported the prophylactic use of CHG reduced the colonisation rates[55-58]. Verber *et al*[56] in their prospective study on a total of 202 infants, reported that CHG reduced the umbilical cord colonisation rates by more than half, compared to the control group (16% *vs* 41%; RR = 0.39; CI: 0.24-0.64). In another double blind comparative study, Oishi *et al*[58] compared the effect of 80% ethanol in CHG against 80% ethanol alone on a total of 100 infants, in reducing umbilical cord colonisation by *S. aureus*. They identified that ethanol in CHG was more effective than ethanol alone in reducing colonisation with *S. aureus* (25% *vs* 58%; *P* < 0.05). However, concerns have been raised that CHG delays the separation of cord[57,58]. Three large block randomised control trials in developing countries[59-61] have shown that use of 4% CHG for umbilical cord care has significantly reduced the mortality (RR = 0.81; 95%CI: 0.71-0.92) and omphalitis (RR = 0.48; 95%CI: 0.40-0.57) in community settings. A recent Cochrane meta-analysis[62] involving 12 trials all over the world confirmed these benefits in developing countries. However there was no strong evidence to suggest that this might be beneficial in

developed countries due to the lack of high quality studies involved[62,63] and therefore dry cord care is recommended at present.

Regular bathing with CHG on HAI: In adults and older children in intensive care, daily bathing with CHG washcloths have shown a significant reduction in nosocomial infections (4.78 cases *vs* 6.6 cases per 1000 patient-days, $P = 0.007$)[64] and [4.1 cases *vs* 10.4 cases of primary blood stream infections (BSIs) per 1000 patient-days with CI: 1.2-11.0; $P = 0.01$][65]. Climo *et al*[64] in addition reported that regular CHG bathing reduces the colonisation from multidrug resistant organisms (5.1 cases *vs* 6.6 cases per 1000 patient-days, $P = 0.03$). Spencer *et al*[66] reported a similar finding with use of Octenidine in adults from a surgical intensive care unit, with 75% reduction in MRSA colonisation.

Large randomised controlled trials from Pakistan and South Africa did not show any significant reduction in mortality or sepsis in neonates who had prophylactic whole body cleansing with CHG wipes[49,50]. Quach *et al*[67] who studied the effect of 2% CHG body wash on 195 infants with birth weight of 1000 g or more and a systematic review on whole body cleansing in neonates did not show any beneficial effect on mortality RR = 0.91, CI: 0.8-1.04, however there was a substantial heterogeneity amongst the included studies (I^2 = 80.2%) and therefore evidence is lacking to support CHG washes in neonates at present[68].

Recommendations: (1) There is sufficient evidence to conclude that application of CHG to umbilical cord can prevent omphalitis and neonatal mortality in developing countries (Level 1A). More research is needed regarding the concentration of CHG preparation, duration, frequency and timing of application. In the absence of good evidence to support this in developed countries, dry cord care is recommended (Level 2D); and (2) Vaginal CHG during labour is not recommended based on the available evidence (Level 2B). Topical emollients are not routinely recommended for use in preterm infants in developed countries (Level 2C), however may have an impact in reducing neonatal sepsis and mortality in developing countries with high neonatal mortality rates (Level 2B). We do not recommend regular CHG bathing on the basis of current literature evidence (Level 2C).

Antiseptic use for venepuncture/cannulation/blood culture

Venepuncture and intravenous cannulation breach the skin integrity increasing the risk of hospital acquired infections from invasion of microorganisms colonising the skin and intravenous catheter. Blood culture contamination is a challenging problem in clinical practice with reported contamination rates of 0.6%-6%; that can lead to unnecessary investigation and treatment in otherwise well babies[69,70]. Therefore it is important that we use antiseptics that could prevent HAI and reduce blood culture contamination rates.

Only a few studies were published in literature on use of antiseptics in neonatal population for prevention of infections related to venepuncture, blood culture sampling or cannulation. Malathi *et al*[71] compared the skin clearance using 0.5% CHG in 70% IPA and 10% PI for intravenous cannulation. In the first part skin swabs were taken following routine cannulation and in the second part swabs were taken after skin cleansing with various durations of exposure to either alcoholic CHG or PI. Skin cleansing with antiseptics achieved a reduction of bacterial colony counts in 90%-99% and authors reported no difference between the two groups[71]. Lilley *et al*[72] conducted a prospective randomised controlled trial to compare 0.5% CHG and 0.05% CHG for skin antisepsis prior to intravenous cannulation. A total of 85 neonates were randomly allocated for exposure to different concentrations of CHG and skin surface swabs were taken before and after cannulation. Authors found that 0.5% CHG produced better bacterial clearance than 0.05% CHG (92% *vs* 38%, $P = 0.002$)[72]. Another RCT in neonates with birth weight of $\geqslant$ 1500 g compared the effect of 1% aqueous CHG with 10% PI on blood culture contamination rates[73]. Use of 1% CHG was associated with fewer positive blood culture results in neonates > 1500 g. However this study was non-blinded, did not control drying times and antiseptics were washed off after 30 s. None of the above studies reported clinically relevant outcomes such as sepsis rates, other morbidity or deaths.

A Canadian group[74] is currently conducting a large RCT comparing the efficacy of 2% CHG in 70% IPA against 2% aqueous CHG prior to venepuncture that has recently completed recruitment. Around 460 babies with birth weight of < 1500 g were recruited onto the study and bacterial swabs before and up to 24 h after cleansing were taken for microbiological analysis. While we are still awaiting final study results, interim results showed identical bacterial clearance rates in both groups suggesting that alcoholic component is probably not required in very low birth weight babies. There is not much evidence available in neonates for guidance on appropriate topical antiseptic agent prior to venepuncture, blood culture sampling or intravenous cannulation.

Antiseptic use for PICC/CVC/umbilical catheter insertion

Skin commensals are the most common bacteria to colonise the central venous catheters[75]. Ponnusamy *et al*[76] showed that colonisation rates of proximal catheter segments were higher than catheter tips from asymptomatic infants (78% *vs* 43%, P = 0.004). Same group in their retrospective study on 187 peripherally inserted central venous catheter

(PICC) removals reported that a positive exit site skin swab is associated with an 8 fold increase of catheter colonisation (OR = 2.13; CI: 1.18-3.08; $P \leqslant 0.001$), and a 14 fold increase of CRBSI (OR = 2.00; CI: 0.44-4.14, $P = 0.01$)[77].

A multicentre prospective non-randomised clinical trial was conducted in two epochs by Garland *et al*[78] to compare the effects of CHG and PI on catheter colonisation rates. In a total of 826 catheters in 254 infants 0.5% CHG significantly reduced the catheter colonisation rates (4.7% *vs* 9.8%, RR = 0.5, CI: 0.3-0.9; $P = 0.01$). There were only 2 cases of CRBSI and therefore it was not possible to draw any conclusions on their effect on clinical outcomes[78]. Same group conducted a large multicentre RCT to compare the effect of CHG impregnated dressing and PI on outcomes of CRBSI, CLABSI and Catheter colonisation. Three hundred and thirty-five neonates were randomised to CHG impregnated dressing after 70% alcohol cleansing and 370 to skin disinfection with PI. Neonates randomised to the CHG impregnated dressing had reduced colonisation rates (15% *vs* 24%, RR = 0.6; CI: 0.5-0.9; $P = 0.004$). There were no differences observed in CRSBI or CLABSI. However, significantly more babies < 1000 g (15% *vs* 0%) developed contact dermatitis in the CHG + 70% IPA group. These results suggest that CHG + 70% IPA is more effective but safety issues need to be addressed[79].

Andersen *et al*[37] reported a significant reduction in BSIs (21% *vs* 9%; CI: 0.19-1.0; $P = 0.05$) with 2% CHG compared to PI in two cohorts of VLBW infants ($n = 174$) over 12 mo period before and after implementing multifactorial prevention strategies. However there were 4/36 cases of contact dermatitis in infants with birth weight less than 1000 g and therefore studies on weaker solution was recommended. During this period they also implemented several other interventions including changes in hand washing practice, standardisation of intravascular device insertion with specialised packs and mandatory removal or replacement of peripheral IV after 48 h, to reduce nosocomial infections that could have contributed to the reduction in BSI. Another retrospective study comparing 10% PI and 0.5% CHG in 70% IPA for PICC insertions in two different time periods reported no differences in sepsis or CRBSI rates[80]. Jeffries *et al*[81] in their retrospective study compared the short-term outcomes following use of CHG or PI prior to PICC insertion. There was no observed difference between the two groups in mortality or other short-term outcomes in VLBW infants. Kieran *et al*[82] recently completed a large RCT comparing the efficacy of 2% CHG in 70% IPA with 10% PI to reduce CRBSI in preterm infants. Three hundred and ten preterm infants < 31 wk gestation were randomised to CHG or PI group for PICC/Umbilical catheter insertion. CRBSI rates were similar in both groups. However significant differences were observed in PI group for hypothyroidism (8% *vs* 0%; $P = 0.002$) and all of them required treatment with Thyroxine. No adverse skin reactions were reported[82].

Duration of antiseptic application for effective skin disinfection

In a retrospective study in preterm neonates comparing duration of antiseptic usage with bacterial colony counts in skin swabs, Malathi *et al*[71] have reported that 30 s cleansing with 0.5% CHG in 70% IPA or 10% PI was more effective than 5 or 10 s cleansing in reducing the bacterial colony counts from skin swabs.

CHG vs povidone iodine

There is enough evidence in adults to suggest that CHG containing solutions are more effective than PI for skin preparation for surgery and PICC/CVC insertions[26,83]. But in neonates this has not been studied in great detail. *In vitro* studies to compare the efficacy of CHG against PI on 33 MRSA isolates showed that PI achieved a significantly higher logarithmic reduction factor of >5 (tube dilution method 4.879 *vs* 3.004, $P < 0.001$; microtitre plate dilution method 4.5 *vs* 2.73, $P < 0.001$), suggesting that PI is better than CHG in microbiological studies against MRSA strains[84]. In another microbiological study from Birmingham, United Kingdom, Adams *et al*[85] compared the efficacy of 2% CHG in 70% IPA with 5 different antiseptics (70% IPA, 0.5% CHG, 2% CHG, 0.5% CHG in 70% IPA, and 10% PI) against *S. epidermidis*. They found that 2% CHG in 70% IPA and PI achieved a significant $\log_{10}$ reduction factor of > 5 (4.7 *vs* 2.3-3.6, $P = 0.0001$) against *S. epidermidis* biofilm compared to other antiseptics but there was no statistical difference between CHG and PI (4.7 *vs* 4.4; $P = 0.28$). Clinical studies in neonates involving 0.5% CHG in 70% IPA did not find any significant differences between the two antiseptics in terms of bacterial clearance rates[71,80]. These studies were small and did not include clinical outcomes. A large prospective controlled trial compared the two antiseptics and found that 0.5% CHG in 70% IPA is more effective in reducing the catheter colonisation compared to PI in neonates. There were not enough infection rates to compare between the two groups[78]. A non-blinded RCT showed that 1% CHG achieved better blood culture contamination rates compared to 10% PI[73]. Jeffries *et al*[81] reported no differences between CHG and PI in mortality or other short-term morbidity outcomes in VLBW infants.

In a large RCT on a total of 705 neonates, Garland *et al*[79] compared CHG impregnated dressing followed by IPA cleansing against PI in neonates demonstrated that CHG significantly reduced catheter colonisation (15% *vs* 24%; RR = 0.6; CI: 0.5-0.9; $P = 0.004$)

but there was no difference in CRBSI. A large RCT involving 310 preterm infants comparing 2% CHG in 70% IPA and PI has completed recruitment recently[82], the results are awaited; this might give us further insight about a better choice of antiseptics in preterm infants.

Concentration of CHG 0.5% vs 1% vs 2%

There are a handful of studies in neonates that compared the efficacy of different concentration of CHG. Adams *et al*[85] showed that 2% CHG is more effective than 0.5% CHG in reducing colony forming units. In a prospective RCT 0.5% CHG was found to be superior to 0.05% CHG in bacterial clearance as identified from skin swabs[72].

Alcoholic vs aqueous CHG preparations

Studies have shown in adults and children that Alcohol containing CHG solutions are more effective than aqueous solution[86]. However, up to date there are no studies to support this in neonates. On the other hand, serious concerns have been raised from several case reports that alcoholic component is associated with severe chemical burns in neonates particularly in extreme preterm and VLBW infants (Table 2). *In vitro* studies have shown that alcohol based CHG achieved better bactericidal activity than aqueous CHG of the same concentration[85]. Shah *et al*[74] completed a RCT comparing the efficacy and safety of aqueous CHG against alcoholic CHG in preterm neonates. Preliminary results showed similar bacterial clearance, which may suggest that aqueous CHG is as effective as alcoholic CHG.

Octenidine

Octenidine, as a topical antiseptic agent has been used in some European countries for more than 2 decades for prevention of skin, wound and oral cavity infections. Efficacy studies involving Octenidine have largely been restricted to *in vitro* microbiological studies or involving adult patients; studies on octenidine use in term or preterm neonates are scarce.

In vitro study by Junka *et al*[46] compared the efficacy of Octenidine, Ethacridine and Povidone Iodine against the biofilms of pseudomonas and *S. aureus*. Authors reported that Octenidine was effective in eradicating the bacteria from biofilms made by pseudomonas in 30 min and was more efficient than ethacridine and PI (100% OH *vs* 66% PI *vs* 0% ethacridine). Similarly Octenidine was as effective as PI (100% in 1 min) and more efficient than ethacridine (100% *vs* 60%) in clearing the biofilms by *S. aureus*.

In another *in vitro* study by Amalaradjou *et al*[44] Octenidine hydrochloride was effective not only in preventing the biofilm formation but also in rapidly inactivating the pre-formed biofilms by *S. aureus*, MRSA, VRSA. Goroncy-Bermes *et al*[45] have showed similar results with Octenidine against ESBL producing bacteria in comparison with CHG and polyhexamethylen biguanide.

Clinical studies have been noticeably small in numbers evaluating Octenidine as an antiseptic agent in comparison with other agents such as CHG. Octenidine has been shown to be effective in preventing MRSA colonisation as well as in eradicating MRSA when used as whole body wash[87]. Spencer *et al*[66] in their 2 year retrospective uncontrolled study on daily bathing with Octenidine for adults in intensive care unit reported a significant reduction in MRSA acquisition from 25 to 6 (Mean reduction 76%, CI: 42%-90%, $P < 0.01$) and an associated reduction in MRSA bacteremia from 3 to 0. A recent study from Lithuania evaluating Octenidine's effect on MRSA decolonisation showed that Octenidine was completely effective in decontaminating 67% of adult patients and was very well tolerated[88]. In a recent cluster cross over study on 10936 patients who received either soap and water or Octenidine body wash for 6 mo period found that there was no significant difference between the two groups in MRSA colonisation (3% *vs* 3.3%; OR = 0.89; CI: 0.72-1.11; $P = 0.31$)[89]. There were no studies that compared Octenidine with other antiseptic agent in RCTs.

A pilot study by Dettenkofer *et al*[90] in 2002 showed that Octenidine was more effective than ethanol in reducing the CVC insertion site colonisation rates. Tietz *et al*[91] also reported similar observations in an uncontrolled observational study in immunocompromised patients. Dettenkofer *et al*[92] in their RCT compared the efficacy of Octenidine against 74% ethanol when used as a skin antiseptic agent for CVC/PICC insertion in 400 adult patients. Authors reported that Octenidine combination with 30% propanol and 45% propanol was superior to 74% ethanol with 10% propanol combination in reducing the skin colonisation rates around CVC (OR = 0.21; CI: 0.11-0.39; $P < 0.0001$), catheter tip colonisation rates (7.9% *vs* 17.8%; OR = 0.39; CI: 0.2-0.8; $P = 0.009$) and catheter related bloodstream infections (OR = 0.44; CI: 0.18-1.18; $P = 0.08$)[90]. Bilir *et al*[93] in their non-blinded randomised trial on 57 patients reported that CHG was more effective than Octenidine or Povidone Iodine in reducing CVC insertion site colonisation rates, catheter hub colonisation and CRBSI rates.

These studies have been conducted in adult population and there has been a noticeable lack of studies involving Octenidine use in term and preterm neonates.

RECOMMENDATIONS

Based on current evidence

It is possible to conclude CHG may be a better option compared to PI given that PI is associated with

Table 2 Studies reporting adverse effects of chlorhexidine use in neonates

Ref.	Design/type	Patient characteristics (*n*)	Type of antiseptic used	Purpose of antisepsis	Adverse reaction	Systemic effects	Comments
Garland *et al*[78]	Prospective study	Neonates (*n* = 111)	0.5% CHG in 70% IPA	PICC insertion	None reported	Not reported	GA not reported
Garland *et al*[79]	RCT	Neonates (*n* = 335, including 98 babies < 1000 g)	0.5% CHG and 70% IPA, CHG impregnated dressing after cleansing	PICC insertion	19 cases of contact dermatitis of which 15 are < 1000 g	Not reported	Occlusive dressing could be the cause of contact dermatitis
Bührer *et al*[102]	Prospective study	Preterm < 27 wk GA (*n* = 24)	2% phenoxyethanol and 0.1% octenidine	Skin care	Transient erythema in a 23 wk gestation baby	Absorbed systemically but no adverse effects reported	
Pezzati *et al*[57]	RCT	Preterm < 34 wk (*n* = 101)	4% CHG aqueous solution	Umbilical cord care	None	Not reported	Mostly above 28 wk
Andersen *et al*[37]	Prospective study	VLBW < 1500 g (*n* = 36)	2% aqueous CHG	PICC, cannula insertion	Skin erythema and burn	Not reported	Recommended alternative safer agent
Visscher *et al*[22]	Pilot study	Neonates (*n* = 40; 14 of which < 30 wk)	2% CHG in 70% IPA	PICC insertion	Erythema and dryness	Not reported	Could be from dressing
Schick *et al*[98]	Case report	Preterm < 28 wk GA (*n* = 2)	IPA	Umbilical catheterisation	Skin burn (2^{nd}/3^{rd} degree burn)	Not reported	
Harpin *et al*[95]	Case report	Preterm 27 wk GA (*n* = 1)	Methylated spirit (95% ethanol and 5% wood naptha)	Umbilical catheterisation	Haemorrhagic skin necrosis	Very high ethanol and methanol levels in blood	Use of alcohol antiseptics in preterm neonates potentially dangerous
Watkins *et al*[99]	Case report	Extreme LBW babies (*n* = 2)	Iso propyle alcohol	Umbilical catheterisation	Skin burns	Not reported	Care must be taken in selection of such solutions
Brayer *et al*[100]	Case report	Preterm at 35 wk (*n* = 1)	Isopropyl alcohol	Umbilical catheterisation	Severe skin burn	Not reported	
Reynolds *et al*[96]	Case report	Preterm infants 24 wk (*n* = 2)	0.5% CHG + 70% methanol	Umbilical catheterisation	Extensive abdominal skin burns	Not reported	Avoid pooling of the antiseptic solution and use Saline for cleaning to wash antiseptic
Mannan *et al*[101]	Case report	Preterm 26 wk GA (*n* = 1)	0.5% CHG + 70% alcohol	Umbilical catheterisation	Extensive abdominal skin burns	Not reported	Alcohol containing preparations should be avoided in NICUs
Bringué Espuny *et al*[97]	Case report	Preterm 26 wk (*n* = 2)	0.5% CHG + methanol	Umbilical catheterisation	Skin burns	Not reported	Use of alcoholic preparations should be avoided in preterm
Lashkari *et al*[103]	Case report	Preterm 25 wk GA (*n* = 1)	2% aqueous CHG	Umbilical catheterisation	Skin burn	Not reported	Cleansing with Normal saline could potentially reduce the exposure and burns

CHG: Chlorhexidine; GA: General availability; NICU: Neonatal intensive care unit; IPA: Iso propyle alcohol; PICC: Peripherally inserted central venous catheter; VLBW: Very low birth weight infants; RCT: Randomized controlled trial.

significant systemic absorption and hypothyroidism. However safety issues of CHG preparations still remain a concern. Results from a recently completed RCT[82] may give us a definitive answer.

Aqueous or alcohol based CHG is as effective - results of the on-going trial would hopefully give us some answers.

It is not possible to recommend a one particular concentration of CHG is better than the others in preterm infants because of its mutually conflicting efficacy and safety profile.

Are the antiseptics used in clinical practice safe in neonates?

Topical antiseptic agents used in adults and older children have been considered safe with no significant adverse effects noted. Studies have reported that Chlorhexidine has been well tolerated and is safe in term neonates following exposure for vaginal washing, umbilical cord care and whole body cleansing[57,94]. However, safety profile of antiseptics has not been extensively studied in preterm neonates. Skin of a preterm infant is immature, lacks an effective barrier

and is vulnerable to local damage and systemic absorption of toxic chemicals.

Local adverse reactions: Local adverse reactions have been reported with almost all the topical disinfectants used in neonatal population. Skin irritation in form of erythema and contact dermatitis is the most commonly reported adverse event after a topical antiseptic use. A national survey in the United States reported that 51% (28 of 55) of NICUs using CHG noted adverse reactions involving the skin and none of them reported systemic side effects[30]. Chemical burns were reported by 61% (17 of 28) of NICUs using CHG and 13 of the 17 centres (76%) reported that burns occurred in neonates with birth weight < 1500 g. In another survey from the United Kingdom[31] 30 of 57 (53%) neonatal units used alcohol based antiseptic agents and 7 of 57 (12%) NICUs reported skin burns.

In Table 2 we have summarised the studies that evaluated side effects of aqueous and alcoholic antiseptic preparations in neonates. An RCT, few prospective studies and several case reports have reported chemical skin burns in extreme premature babies secondary to use of methylated spirit[95], methanol[96,97], IPA[98-101] and 2-phenoxyethanol with 0.1% Octenidine[102]. In all of these case reports skin damage was attributed to the alcohol component of the antiseptic. However, a prospective study on VLBW infants reported local reactions to aqueous based 2% CHG preparation[37]. Similarly another case report of an extensive chemical burn related to the use of 2% aqueous CHG in an extreme preterm infant was reported and attributed this to excessive application and prolonged skin exposure to CHG[103].

Systemic absorption: Studies have reported that CHG can be absorbed in term neonates comparable to those in adults and not have any significant side effects[104]. Few studies have reported systemic absorption of CHG in preterm infants. Milstone *et al*[105] demonstrated that Chlorhexidine inhibits L1 cell adhesion molecule mediated neurite growth of cerebellar granule neurons. This along with hexachlorophene's vacuolar encephalopathy raised concerns regarding neurotoxicity. In the reported studies, although CHG is detected in their bloods, none of them have reported any side effects including neurotoxicity or skin toxicity[106-108]. However the sample population in these studies did not include extreme preterm infants and only very few babies had their levels checked during the first 2 wk when skin is most immature. Safety of systemic absorption in preterm infants has not been studied in great detail and significance of raised CHG concentrations is yet to be determined in clinical studies.

Further research should focus on differences in CHG absorption between aqueous and alcohol based CHG preparations, to identify the strength of solution that is safe and effective to be used on preterm infants, on potential toxicity of absorbed CHG to identify a threshold at which this could occur.

Alcohol based preparations: Studies on systemic absorption of alcohol in neonates following topical antisepsis are very limited. Harpin *et al*[95] in 1982 reported very high levels of methanol and ethanol in a 27 wk gestation baby following use of methylated spirit on skin for antisepsis.

Iodine containing preparations: Preterm infants are vulnerable to iodine exposure than term infants because of increased skin permeability, immaturity of thyroid gland and Wolff-Chaikof effect, and reduced renal clearance. Smerdely *et al*[109] reported 50 times higher urinary iodine levels, raised thyrotropin levels above 36micromoles/L and significantly lower thyroxine levels in 25% of infants iodine exposed (n = 36) preterm infants compared to CHG exposed (n = 27) infants. In a cohort study comparing 73 preterm infants exposed to iodine containing antiseptics against 55 exposed to CHG antiseptics, mean thyrotropin levels were significantly higher in iodine group (15.4 mIU/L *vs* 7.8 mIU/L, $P < 0.01$)[80]. Khashu *et al*[110] reported hypothyroidism in an extreme preterm infant following repeated and prolonged use of topical povidone iodine for wound cleaning. This required treatment with thyroxine and took 8 wk to resolve. There are a few other studies and several case reports of hypothyroidism following use of Iodine containing topical antiseptics in neonates especially preterm infants. Aitken *et al*[111] in their systematic review reported that there is evidence of thyroid dysfunction in preterm infants exposed to iodinated antiseptics with an incidence ranging from 12-33 per 100 infants. However, none of the studies reported long term neurodevelopmental outcomes. Authors concluded that it was not possible to establish relationship between exposure of iodine and occurrence of hypothyroidism due to the quality of studies included. They concluded that use of iodine containing solutions should be restricted in preterms with CHG being an alternative.

Octenidine containing preparations: Octenidine when used in adults for body wash was well tolerated and did not cause any adverse effects[87]. Bührer *et al*[102] in their prospective study reported the use of Octenidine in extreme preterm infants born before 27 wk gestation for routine skin antisepsis during the first week. They found that Octenidine was well tolerated with only one infant developing a transient erythematous rash. However, phenoxyethanol was absorbed into the systemic circulation but readily excreted in urine. Although there were no systemic side effects noted authors suggested using Octenidine without phenoxyethanol combination in neonates.

Wagner *et al*[112] in their *in vitro* study on impact of antiseptic agents on radical metabolism, antioxidant stress and genotoxic stress in human blood cells

compared Octenidine with PI. They reported that PI reduced superoxide dismutase (SOD) activity by 40%, Glutathione peroxidase activity (62%) and alpha tocopherol more than Octenidine. There were no differences observed in Total antioxidative capacity or malondialdehyde in ghosts. Authors concluded that exposure of healthy blood cells to Octenidine concentrations up to 0.05% for 30 min were safe compared to PI.

Recommendations

CHG and Alcohol preparations have been associated with severe local reactions, whereas Iodophors are associated with increased risk of systemic absorption and potential toxicity. Large studies are urgently needed to establish the safety of topical antiseptics used in neonates especially in preterm infants with focus on following: (1) differentiate Aqueous or alcoholic component of CHG as the reason for skin irritation in preterm neonates; (2) ideal CHG concentration that can be safely used in preterm neonates; (3) CHG concentrations in blood and their effect on long-term neurodevelopment outcomes; (4) isopropyl alcohol absorption studies and effect on short term and long term outcomes; and (5) systemic absorption of topical iodine containing solutions and their effects on thyroid function and long-term neurodevelopmental outcomes.

In the meantime we recommend the following on the basis of current evidence: (1) Extreme caution is recommended for use of topical antiseptics particularly alcohol based preparations in extreme preterm infants (Level 2D); (2) Care must be taken to avoid pooling of the solution under infant and washing with normal saline after cleansing with topical antiseptic may prevent severe chemical burn in extreme premature babies (Level 2D); and (3) Povidone Iodine for skin antisepsis should be avoided in extreme preterm infants (Level 2C).

CONCLUSION

Skin disinfection with an effective topical antiseptic agent could be useful in prevention of HAI. Although many antiseptics have been used in neonates for several decades, there is no clear guidance regarding the best antiseptic for use in neonatal intensive care unit. Current evidence based on their efficacy and safety studies, does not support the use of one antiseptic agent over another. Two large RCTs have completed recruitment, but few more large multicentre trials are warranted to determine the most effective antiseptic preparation, concentration and combination for use in neonatal skin disinfection. Large trials are also needed to study the adverse effects of different antiseptics, effects of systemic absorption on developing organ systems in preterm infants with a particular focus on long term neurodevelopmental outcomes.

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REVIEW

Fetal programming and early identification of newborns at high risk of free radical-mediated diseases

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Abstract

Nowadays metabolic syndrome represents a real outbreak affecting society. Paradoxically, pediatricians must feel involved in fighting this condition because of the latest evidences of developmental origins of adult diseases. Fetal programming occurs when the normal fetal development is disrupted by an abnormal insult applied to a critical point in intrauterine life. Placenta assumes a pivotal role in programming the fetal experience *in utero* due to the adaptive changes in structure and function. Pregnancy complications such as diabetes, intrauterine growth restriction, pre-eclampsia, and hypoxia are associated with placental dysfunction and programming. Many experimental studies have been conducted to explain the phenotypic consequences of fetal-placental perturbations that predispose to the genesis of metabolic syndrome, obesity, diabetes, hyperinsulinemia, hypertension, and cardiovascular disease in adulthood. In recent years, elucidating the mechanisms involved in such kind of process has become the challenge of scientific research. Oxidative stress may be the general underlying mechanism that links altered placental function to fetal programming. Maternal diabetes, prenatal hypoxic/ischaemic events, inflammatory/infective insults are specific triggers for an acute increase in free radicals generation. Early identification of fetuses and newborns at high risk of oxidative damage may be crucial to decrease infant and adult morbidity.

Key words: Fetal programming; Oxidative stress; High-risk newborn; Biomarkers; Perinatal medicine; Metabolic syndrome

Core tip: The adverse outcomes on the offspring born from altered gestation are already known. The consequences of these perturbations have been demonstrated even after many decades from birth. In this review we summarize gestational conditions associated to fetal programming and elucidate the mechanisms involved in such kind of occurrence. We also describe to what extent oxidative stress (OS) is involved in a very wide spectrum of genetic, metabolic, and cellular responses, through the gene expression

regulation, and cell growth modulation. By virtue of these properties, OS has been nominated as the lowest common denominator of adult disease programming.

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INTRODUCTION

The last century witnessed the rise in chronic cardio-metabolic diseases in which metabolic-syndrome (MetS) represents a major health problem regarding morbidity and mortality[1]. MetS is characterized by a number of related disorders, such as visceral obesity, glucose intolerance, disturbed plasma lipids concentration, high blood pressure, and increased risk of developing cardiovascular diseases and type 2 diabetes[2]. Smoking, high-fat diets, abdominal obesity[3-5], insulin resistance[6,7], physical inactivity[4,8], aging[9], and hormonal imbalance[10] have been identified as the main risk factors for several years.

Pediatricians have serious concerns with MetS because adult lifestyle is not the only determinant. In the last decades, a worldwide series of epidemiological studies have provided evidence for the association between perturbation of fetal environment and major risk factors for cardiovascular disease, diabetes, and MetS in adult life[11-15]. This has been called "fetal/early origins of adult disease" by David Barker. The hypothesis predicts that environmental factors, particularly nutrition, act in early life to program the risks for adverse health outcomes later in life[16]. Refinements of this idea of "fetal programming" focus on the processes of developmental plasticity, which in normal situations provide the settings for homeostatic mechanisms to ensure an adequate amount of nutrients to the most vital organs at the expenses of other less vital organs (the thrifty phenotype hypothesis)[17]. These changes in phenotype can become permanent and can generate a mismatch with adult environment that would lead to the development of metabolic diseases in adulthood[18]. The latter phenomenon gave rise to the new concepts of "metabolic memory"[19], "fetal primed"[20], and "developmental plasticity"[21].

The aim of this paper is to review all the gestational conditions associated to fetal programming and elucidate mechanisms involved in such kind of process. Identifying a lowest common denominator could be essential to contrive prevention strategies, treatment, and appropriate follow-up to high-risk newborns.

FETAL PROGRAMMING

Fetal programming occurs when the normal pattern of fetal development is disrupted by an abnormal stimulus or insult applied to a critical point in intrauterine life. Pregnancies complicated by diabetes, small for gestational age (SGA) or large for gestational age (LGA) offspring, pre-eclampsia and conditions such as hypoxia, oxidative and nitrosative stress are associated with programming. Placenta plays a key role in developmental plasticity. Vasculature and trophoblast are both involved in overall placental transport[22,23]. Changing developmental signals or the amount of substrate of the fetus produces an alteration of fetal development which ultimately leads to cardiovascular or metabolic diseases later in adult life[24]. Alterations in placental vasculogenesis[25], trophoblast expression of transporters[26], trophoblast enzyme activity, and hormone production[27] occur in pregnancies complicated by IUGR, pre-eclampsia or diabetes.

Mothers with insulin-dependent diabetes are prone to hyperglycemia in the first trimester of gestation that generates an up-regulation of Glut1 and System A (a sodium-dependent transporter of neutral amino acid) in the trophoblast leading to accelerated fetal growth in late gestation[28]. The activity of System A is reduced in placentas with intrauterine growth restriction (IUGR)[29,30]; moreover, inhibition of System A in rats causes growth restriction[31]. Glut transporters function and expression are also influenced by glucocorticoids, which are produced by trophoblast and regulated by the activity of 11-β-hydroxysteroid dehydrogenase (11βHSD). Exposure of the rat fetus to excess maternal or exogenous glucocorticoids causes growth restriction, hypertension and hyperglycaemia[32,33]. The trophoblast expresses 11βHSD-2 that converts cortisol to inactive cortisone and this may protect the fetus against high levels of maternal cortisol[34]. In humans, mutations in the 11βHSD-2 gene have been reported in association with low birth weight. Reduced 11βHSD-2 activity and increased fetal cortisol levels have been reported in association with IUGR[35].

Hypoxic conditions in pregnancy are strongly involved in fetal programming. Oxygen regulates development of the villous vascular tree and villous trophoblast proliferation due to hypoxic regulation of angiogenic mediators as vascular endothelial growth factor (VEGF) and placental growth factor (PLGF). Hypoxia acts *via* the transcription of hypoxia-inducible factor-1α (HIF-1α) that activates gene transcription in response to varying oxygen concentration. For example, at 10-12 wk of gestation, the trophoblast is exposed to a hyperoxic challenge during the transition from histiotrophic nutrition to intervillous blood flow vascularization[36]. Low oxygen tension inhibits trophoblast differentiation to the invasive extravillous trophoblast pathway, hence the switch in oxygenation activates trophoblast invasion and subjects the cell to oxidative and nitrosative stress. A pathological increase of oxidative stress (OS) is found in pregnancy complicated by pre-eclampsia or diabetes[37].

On the basis of the latter consideration, in order to

confirm the hypothesis of *in utero* programming process and analyze the mechanisms involved, many authors have conducted experimental studies throughout various animal models of fetal programming based on fetal insult induced by placental insufficiency, hypoxia, maternal undernutrition, and maternal exposure to stress and increased plasma glucocorticoids levels[38-44].

PROGRAMMING OF INSULIN RESISTANCE, OBESITY, AND TYPE Ⅱ DIABETES

Insulin resistance may come from fetal adaptation to an adverse intrauterine environment during a critical period, thus leading to programming of fetal gene expression[45,46]. Insulin plays a central role in fetal growth. During the first two years of life SGA newborns are usually able to catch-up growth by increasing their growth velocity and recovering the weight of AGA counterparts[47]. The dynamic changes that occur during this period suggest a critical role of adipose tissue in the development of metabolic complications. Ibáñez *et al*[48] stated that this early growth, in SGA newborns, was associated with development of central adiposity and insulin resistance between 2 to 4 years of age. The same correlation was found in early adulthood by Leunissen *et al*[49]. Following these epidemiological data, MetS was renamed as "the small baby syndrome"[50]. This fitted well with Hertfordshire's findings according to which the highest risk of cardio-metabolic diseases was in men and women who had evidence of early-life deprivation (considering weight at birth or in early childhood) and who had become overweight as adults ("small becoming big")[51]. However, we currently known that not only those subjects born with low birth weight, but also poor maternal nutrition increase maternal weight gain[52,53] and that large-for-gestational age newborns have increased metabolic risks[54].

Not only are diabetic mothers hyperglycaemic but they also have elevated circulating lipids and amino-acid. The fetal pancreas and liver are stimulated to secrete increased insulin and insulin-like growth factors that are growth-promoting hormones in the fetus. This results in the well-described diabetic mother's macrosomic infant. Low-grade inflammation has been reported to be a link between insulin resistance, obesity, and type 2 diabetes[55]. Adipokines and cytokines affect insulin sensitivity through their ability to interfere with insulin signaling[56]; these molecules also modulate inflammation[57]. Adiponectin, which is produced by the enhanced adipose tissue, acts as insulin-sensitizing, antiatherogenic, and anti-inflammatory hormone[58]. Some scholar have shown that women with gestational diabetes mellitus (GDM) express a decreased concentration of adiponectin and an increased level of TNF-α and IL-6[57,59]. Lihn *et al*[60] suggest that this happens due to TNF-α and IL-6 downregulation of adiponectin expression. Leptin, which is a hormone produced by placenta and by adipocytes principally[61], is involved in weight gain regulation by interacting with neuropeptide-Y in the hypothalamus[62]. Beyond its properties as appetite-suppressant agent, Leptin is also capable of regulating lipid metabolism. Atègbo *et al*[57] have shown high leptin level in mothers with GDM and, in contrast, a reduced level of leptin in their macrosomic children. Leptin, as pro-inflammatory factor, may contribute to the inflammatory state during gestational diabetes. Conversely, low leptin level in macrosomic babies may contribute to weight gain since leptin-deficient rodents[62] and human[63] have been shown to develop obesity. According to the hypothesis of "Metabolic Memory", these alterations may permanently increase the risk of trend in high food taking, overweight, obesity, and diabetogenic status in offspring during adult life[19]. An example of metabolic memory is revealed by Franke *et al*[64] who have shown that diabetic pregnancy in rats alters the differentiation of the newborns' hypothalamic neurons. The impairment of these neurons may be avoided by normalizing glycemia among diabetic pregnant rats[64]. This metabolic imprinting could generate an intergenerational effect in which children risk becoming overweight or obese post-natally. Furthermore, if the child is female, she risks becoming diabetic during pregnancy, thus exposing the fetus to another route of later metabolic risk[19].

PROGRAMMING OF HYPERTENSION AND CARDIO VASCULAR DISEASE

Experimental models of fetal programming induced by gestational protein restriction[65,66], maternal stress[67], hypoxia[68] or placental insufficiency[69] demonstrate that vascular dysfunction and hypertension are related to a marked increase in glucocorticoid (GC) expression and/or marked decrease in the expression of 11β-HSD2. In these studies, the exposure to exogenous GCs generates a reduction in nephron number[70], vascular dysfunction[71], alterations in the renin-angiotensin system (RAS)[72], disruption in hypothalamic-pituitary-adrenal (HPA) axis[73-76], and hypertension[77,78] in the litter. Reduction in nephron number may affect the renal excretory function, thus contributing to the fetal programming of hypertension. However, some models demonstrate that a decrease in nephron number is sensitive to the timing of the insult[77,79] and the early-mid nephrogenesis phase is the most critical window to promote the modification in fetal kidney[80]. This change in phenotype may alter the mechanisms of adaptation to renal damage in adult life[81,82]. Otherwise other systems, which are critical to the long-term control of blood pressure, may contribute to program hypertension. As is clearly known, vascular dysfunction is implicated in the pathophysiology of hypertension[83] and plays

a critical role in the development of cardio-vascular (CV) disease[84]. Many clinical studies have observed an impaired vascular function in healthy children with low birth weight[85,86], thus suggesting that vascular consequences of fetal programming may precede the development of adult CV disease. Vascular endothelial cell play a pivotal role in CV system by producing a collection of vasoactive agents whose functions include vasodilatation, vasoconstriction, and vascular growth[86]. This axiom is confirmed by animal models in which fetal insult, which is induced by nutritional restriction, placental insufficiency or hypoxia, leads to vascular dysfunction due to the impairment of endothelium-dependent nitric oxide (NO) availability[87-89]. During hypoxia, an imbalance in potent vasoactive factors is generated and an increase in total peripheral resistance is programmed, thus contributing to the development of hypertension. The RAS is another system strongly involved in blood pressure regulation and CV disease programming[90]. In the rat, RAS blockage during the nephrogenic period leads to a marked reduction in nephron number[91,92]. Although suppression of the RAS is observed at birth, hypertension is established by inappropriate activation of the RAS later in life[93-95]. According to the thrifty phenotype hypothesis, blood flow redistribution to critical organs such as the brain and heart occurs at the expense of other organs such as the liver, kidney, muscles and skin, thus resulting in exposure to hypoxia, with modifications in the hypoxia inducible factor (HIF) pathway[21]. HIF regulates several pathways, including the sympathetic nervous system, *via* stimulation of tyrosine hydroxylase[96]. Numerous models of fetal programming confirmed an increased amount of circulating catecholamines during placental insufficiency and gestational protein restriction[97-99]. The data are supported by the evidence that renal denervation delays the development of hypertension in prepubertal offspring[100] and abolishes hypertension in adult male IUGR offspring[101]. All these alterations in phenotype appear to contribute to hypertension in response to certain fetal insults, thus highlighting the complexity of the pathways involved in the fetal programming of hypertension and CV disease.

OS FETAL PROGRAMMING HYPOTHESIS

OS occurs when the production of free radicals (FRs) exceeds the capacity of antioxidant defenses[102]. It represents an imbalance between the production of reactive species and the capacity of biological system to readily detoxify the reactive intermediates or repair the resulting damage.

FRs can be produced through many processes. FR are generated primarily within the mitochondrial respiratory chain, which is fundamental for ATP production in mammalian cells. During the respiratory process, oxygen (O_2) is utilized as an electron acceptor and completely reduced to water through the acquisition of four electrons. Once this process is completed through subsequent steps, radical formation becomes possible. NO can be also a FR source because it contains an unpaired electron in the outer orbital.

Nitric oxide synthase (NOS) catalyzes the formation of NO. It reacts relatively slowly with O_2 thus producing the orange-brown gas nitrogen dioxide ($^{\cdot}NO_2$), a highly reactive FR[103]. Hypoxia-ischemia sets in motion several pathways involving intracellular calcium release and activation of nitric oxide synthetase leading to increased FR generation[104].

Other potential endogenous sources of FRs include inflammatory cell activation (through Nicotinamide Adenine Dinucleotide Phosphate Reduced oxidase of phagocytes and some endothelial cells), monoxygenase system, nitric oxide synthase, and several other enzymes involved in the inflammatory process[105]. The burden of FR can be further amplified by the presence of "free" metals such as iron, copper, and manganese that are released from metalloprotein complexes[106]. Iron, can damage tissues by catalyzing the conversion of superoxide and hydrogen peroxide to FR species through the Haber-Weiss and Fenton reactions when it is unbound to plasma proteins[107].

Additional endogenous sources of cellular FR are activated neutrophils, eosinophils, and macrophages[108]. Notwithstanding the source of FRs, they are really dangerous because of their toxic effects that are able to damage all cell components, including proteins, lipids and DNA. OS may operate directly through the modulation of gene expression or indirectly through the adverse effects of oxidized molecules at critical developmental windows.

Therefore, OS causes a very wide spectrum of genetic, metabolic, and cellular responses and many oxidative conditions are able to modulate gene expression, stimulate cell growth or cause a protective temporary growth-arrest[109]. Necrosis is the most extreme outcome and involves direct cell destruction.

Recently, Leal *et al*[110] have shown that there is a change in the prooxidant and antioxidant defences strictly related to pregnancy process. During pregnancy, OS plays a major role in maternal-fetal interface insofar as it is essential for embryo and tissue development. Maternal diabetes, prenatal hypoxic/ischaemic events, inflammatory/infective insults are specific triggers for an acute increase in FRs, thus generating an adverse intrauterine environment with impaired fetal development[111,112]. Pro-OS is also a common feature for adverse (poor or excessive) fetal growth, preterm birth, smoking, malnutrition, overnutrition, infection and inflammation[113-116]. Consequently, OS may be the key link underlying the programming associations between adverse fetal growth/preterm birth and elevated risks of chronic diseases.

The role of OS in the pathogenesis of insulin dependent diabetes mellitus has been implicated in several

studies[117,118] and there is evidence that both free-radical production and antioxidant defences are disturbed in Diabetes[119]. Hyperglycemia leads to an increased production of FRs through different metabolic pathways. In short, hyperglycemia increases formation of advanced glycation end product (AGE) and activates the hexosamine biosynthetic pathway, thus leading to the formation of glucosamine-6-phosphate that competes with glucose-6-phosphase dehydrogenase and limits the synthesis of nicotinamide adenine dinucleotide (NAD). As is clearly known, NAD is necessary for reduced glutathione (GSH) rebuilding. Moreover, activation of the polyol and protein kinase C pathways, together with oxidases activation, may also be responsible for increased FRs production[120]. Hence, end products of abnormal glucose metabolism lead to an increased formation of FRs. When FRs production overcomes fetal and placental antioxidant capacity, transcription factors (TFs) such as nuclear factor-κB, activator protein-1, and HIF-1 are activated and lead to insulin resistance due to the phosphorylation (inactivation) of insulin receptor substrate-1 (IRS-1). Inhibition of IRS-1 leads to reduced membrane translocation of glucose transport protein as glucose transporter-4 (GLUT-4), thus generating a reduction of glucose insulin-dependent uptake. Moreover, FRs are able to down-regulates GLUT-4 transcription directly[120]. Consequently, extracellular hyperglycemia occurs. However, glucose can enter all cells virtually through insulin-independent GLUTs such as GLUT-1 and GLUT-3. This raises intracellular glucose concentration and enhances FRs generation, which, again, impairs insulin and signals the establishment of a vicious circle. TFs may also directly induce the expression of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor-α or monocyte chemoattractant protein-1 that will cause insulin resistance. Recent studies in animal models have observed that manipulating anti/pro- oxidant balance in pregnancy could alter blood pressure and vascular reactivity in rat offspring[121,122]. Such emerging evidence confirms that both the insulin functional axis and blood pressure could be sensitive targets to OS programming.

OS has been demonstrated in pregnancies with fetal growth restriction[123]. Fetal growth restriction is often complicated by intrauterine hypoxia and impaired blood flow to the fetus. Intrauterine hypoxia may induce FRs generation and fetal OS. It has been demonstrated that increased isoprostanes concentrations, which are reliable markers of lipid peroxidation in amniotic fluid, indicate fetal growth restriction and also induce damage to amniotic epithelium and chorioamniotic collagen. This aspect is clarified by recent data demonstrating that F2-isoprostanes concentrations are significantly higher in pregnancies with premature rupture of membranes than in normal ones[123]. FRs may disrupt amino acid binding in proteins and polyunsaturated fatty acids of the membrane lipid bilayers, thus causing cell dysfunction, modification of chorioamniotic biology and predisposition to premature rupture of membranes.

By favouring intracellular release of NPBI into plasma, asphyxia and acidosis supply redox-cycling iron, thus predisposing to OS[124-127]. NPBI leads to the catalysis of superoxide anion ($O_2^{-\cdot}$), hydrogen peroxide (H_2O_2), and the generation of the damaging hydroxyl radical ($^{\cdot}OH$). In presence of free iron, huge increases in FRs generation are possible and likely to cause tissue damage. Plasma NPBI may leak into the brain through a damaged barrier and is particularly damaging insofar as it is taken up by cells directly. When NPBI gains access to the extracellular space, its uptake by cells is enhanced by intracellular calcium and paradoxically also by increased levels of intracellular iron. Differentiating oligodendrocytes are particularly vulnerable to FRs damage because they are rich in iron, which is required for differentiation[128].

A recent *in vivo* and *ex vivo* rat model of IUGR underlines that delays in oligodendrocyte differentiation and myelination are probably due to bone morphogenetic protein 4 (BMP4) up-regulation induced by OS. When BMP4 expression in oligodendrocyte increases, impaired differentiation occurs. A normal myelination has been observed abrogating BMP signaling[129].

Down syndrome comes from an exceeding chromosome 21 in cellular karyotype. Superoxide dismutase (SOD) gene is localized on chromosome 21. This enzyme has the capacity to detoxify cells from superoxide anion *in vivo* with the participation of catalase and glutathione peroxidase. Consequently increased SOD production leads to high H_2O_2 generation, which can itself be toxic and also interfere with SOD activity[130]. An increased level of 8-iso-PGF2a isoprostane, was found in amniotic fluid of pregnancies with a Down syndrome foetus[131]. The immature oligodendroglial cells are glutathion peroxidase and catalase deficient so overexpression of SOD can be dangerous, instead of being protective. The early occurrence of OS in pregnancies with trisomy 21 and their subsequent oxidative damage as major contributing factor in brain aging and cognitive function decline are probably due to the overexpression of SOD, which comes from the supernumerary chromosome. SOD is also overexpressed in the immature brain, especially under stressful conditions (such as hypoxia)[132].

CONCLUSION

During early life, many gestational conditions may represent an important determinant of future health. Whereas the dominant focus of experimental studies to date has been on defining the phenotypic consequences of fetal-placental perturbations, the emphasis has now shifted to determining those initiating mechanisms underlying the programming process. The size and scope of this field has grown to include OS as the lowest common denominator.

During normal pregnancies, oxidants have many physiological functions, which promote and control cellular fate and which play a crucial role in normal development through cellular signalling. In absence of a parallel increase in antioxidative activity, OS will result. Overproduction of reactive oxygen species can lead to massive cellular damage by acting on proteins, lipids, and DNA. This unbalance may change the course of pregnancy and generate a cascade effect that leads to the genesis of *in utero* programming of adult diseases. It is clear that placenta is not simply a passive participant in pregnancy supplying maternal substrates to the fetus. It adapts to the maternal environment and changes both its structure and function. Placenta thus assumes an active role in programming the fetal experience *in utero* that leads to disease in adult life. Since placenta serves as barrier against oxidative insult to maintain the homeostasis of fetal intrauterine environment, it is plausibly that placenta adaptation occurred in response to such altered maternal environment may be the general underlying mechanism that links altered placental function to fetal programming. It can also been hypothesized that programming process is extended in early postnatal life for premature infants. Premature neonates experience a hyperoxic challenge as they have to grow up in an oxygen-rich environment post-natally. Moreover, these biological systems are prone to oxidative insults because of their resilience and maturity stage at the time of insult. There could be a different timing of insult, plausibly prenatal and early postnatal periods are the most critical "windows" to OS programming insults.

The challenge for the future is to develop new effective antioxidant therapies and to demonstrate their benefits in treatments. However, whether antioxidant supplementation, or a diet rich in antioxidants, can avoid consequences of OS programming in the off-spring or not is yet to be elucidated. Longitudinal studies evaluating the panel of OS biomarkers and elucidating the molecular mechanisms that engender OS in perinatal period are needed before antioxidant therapies are accepted in clinical practice.

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MINIREVIEWS

Facility-based constraints to exchange transfusions for neonatal hyperbilirubinemia in resource-limited settings

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Abstract

Several clinical guidelines for the management of infants with severe neonatal hyperbilirubinemia recommend immediate exchange transfusion (ET) when the risk or presence of acute bilirubin encephalopathy is established in order to prevent chronic bilirubin encephalopathy or kernicterus. However, the literature is sparse concerning the interval between the time the decision for ET is made and the actual initiation of ET, especially in low- and middle-income countries (LMICs) with significant resource constraints but high rates of ET. This paper explores the various stages and potential delays during this interval in complying with the requirement for immediate ET for the affected infants, based on the available evidence from LMICs. The vital role of intensive phototherapy, efficient laboratory and logistical support, and clinical expertise for ET are highlighted. The challenges in securing informed parental consent, especially on religious grounds, and meeting the financial burden of this emergency procedure to facilitate timely ET are examined. Secondary delays arising from post-treatment bilirubin rebound with intensive phototherapy or ET are also discussed. These potential delays can compromise the effectiveness of ET and should provide additional impetus to curtail avoidable ET in LMICs.

Key words: Bilirubin encephalopathy; Kernicterus; Intensive phototherapy; Laboratory services; Neonatal care; Developing countries

Core tip: Exchange transfusion (ET) is effective in preventing bilirubin-induced neurologic dysfunction in infants with severe hyperbilirubinemia. However, the timely initiation of this emergency procedure is frequently constrained by delays at various critical stages from the time the decision to commence ET is made and when ET is actually conducted. These delays must be carefully identified and appropriately addressed in each clinical setting to minimize their adverse impact in the provision of effective ET in low- and middle-income countries. Intensive phototherapy

should also be considered a priority during this interval to minimize avoidable ETs.

Mabogunje CA, Olaifa SM, Olusanya BO. Facility-based constraints to exchange transfusions for neonatal hyperbilirubinemia in resource-limited settings. *World J Clin Pediatr* 2016; 5(2): 182-190 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i2/182.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i2.182

INTRODUCTION

Exchange transfusion (ET) is a definitive and effective therapy for preventing kernicterus, usually where intensive phototherapy is either lacking or proves to be ineffective in arresting rapidly rising bilirubin levels in infants with severe neonatal hyperbilirubinemia or symptoms of acute bilirubin encephalopathy (ABE)[1,2]. The procedure is not risk-free however, as it may be associated with such complications as sepsis, electrolyte imbalance, air embolism, portal vein thrombosis, cardiac overload, thrombophlebitis, thrombocytopenia, necrotizing enterocolitis, and the transmission of blood-borne diseases, even in settings with advanced clinical care[3-6]. Several guidelines for the management of neonatal hyperbilirubinemia in developed and developing countries recommend immediate ET for infants with, or at risk of, acute or chronic bilirubin encephalopathy[2,7,8]. This is primarily because the timing of ET vis-à-vis the complex interaction between the level and duration of exposure of the neuronal cells to unbound bilirubin crucially affects intervention outcomes[9]. However, this timely goal is rarely achieved in many low- and middle-income countries (LMICs), where excessive rates of ET persist as a result of weaknesses in the health-care delivery system in these locations[10-13]. For example, it is not uncommon for a severely jaundiced infant to first present in a hospital not adequately equipped to provide emergency care, including ET, and are thus subsequently referred to a better equipped hospital[11,14]. This experience often results in considerable delay in providing ET[15]. Several reports also suggest that delays of up to 24 h from the time the decision to carry out ET is made and when treatment is received by the affected infant in the same hospital are not uncommon[6,14,15], compared to the estimated 4-6 h in developed countries[16]. Such delays are likely to account for the high incidence of bilirubin-induced neurological dysfunctions (ABE and kernicterus) and the associated devastating consequences in many LMICs[15,17,18]. This paper, therefore, sets out to identify commonly reported facility-based challenges in providing timely and effective ET in hospitals designated for such an emergency procedure in LMICs.

DATA SOURCES

We conducted an electronic search of PubMed, Scopus, Ovid EMBASE, and the Cumulative Index to Nursing and Allied Health Literature to retrieve articles published between January 1990 and June 2015 on exchange transfusion for hyperbilirubinemia in resource-limited countries. The search terms used were "neonatal hyperbilirubinemia", "neonatal jaundice", "exchange transfusion", "bilirubin encephalopathy", and/or "kernicterus". The terms "resource-limited", "resource-constrained", and "resource-poor" countries are used interchangeably to refer to the 91 LMICs with a per capita gross national income (GNI) of $\leqslant$ $6000 using the Human Development Report 2013 published by the United Nations Development Program as previously reported (Table 1)[8,15]. These countries have an average life expectancy of 63.3 years and a median national frequency of 8.2% (inter-quartile range: 3.3%-14.6%) for glucose 6-phospho-dehydrogenase (G-6-PD) deficiency. Only articles or reports published from these 91 countries were reviewed. As this paper was designed as a narrative review, no systematic evaluation of the retrieved articles and reports was planned.

BILIRUBIN METABOLISM AND NEUROTOXICITY

The metabolism of bilirubin has been well described in the literature[19-21]. Essentially, bilirubin production is a normal process of human physiology and begins from the degradation of heme from senescent red blood cells (Figure 1). Once produced, bilirubin is conjugated in the liver with glucuronic acid to form bilirubin glucuronide. Conjugated bilirubin is then conveyed across the canalicular membrane through the biliary tree to the intestinal lumen for excretion. Newborns, especially premature infants, have an immature bilirubin conjugation and excretion system. As a result, they have limited ability to conjugate bilirubin and excrete unconjugated bilirubin readily. These limitations account for an imbalance between bilirubin production and elimination. In effect, neonatal jaundice occurs when the rate at which bilirubin is produced exceeds the rate of elimination, reflecting the total bilirubin load in the body after birth, to become visible in the skin as yellow pigment. In full-term infants, serum bilirubin concentrations, known as physiologic jaundice, peak at 5 to 10 mg/dL in the first three days of life and decline thereafter to values commonly found in adults of approximately 1 mg/dL. However, in a few infants, serum bilirubin concentrations may become pathologic and exceed 17 mg/dL, which is indicative of a disorder that requires treatment. Total bilirubin levels beyond 17 mg/dL, especially in infants with predisposing hemolytic conditions, may lead to the

Table 1 Low and middle-income countries with ≤ $6000 gross national income per capita

SN	Country	Region	Life expectancy (yr)	GNI per capita ($)	Annual live births ('000)	Hospital delivery (%)	G6PD deficiency freq
1	Afghanistan	SOA	49.1	1000	1408	33	7.4
2	Angola	SSA	51.5	4812	803	46	15.3
3	Armenia	ECA	74.4	5540	47	99	-
4	Bangladesh	SOA	69.2	1785	3016	29	3.8
5	Belize	LAC	76.3	5327	8	89	2.2
6	Benin	SSA	56.5	1439	356	87	23.0
7	Bhutan	SOA	67.6	5246	15	63	5.9
8	Bolivia, Plurinational State of	LAC	66.9	4444	264	68	0.2
9	Burkina Faso	SSA	55.9	1202	730	66	9.4
10	Burundi	SSA	50.9	544	288	60	7.2
11	Cambodia	EAP	63.6	2095	317	54	14.3
12	Cameroon	SSA	52.1	2114	716	61	12.5
13	Cape Verde	SSA	74.3	3609	10	76	0.1
14	Central African Republic	SSA	49.1	722	156	53	9.2
15	Chad	SSA	49.9	1258	511	16	13.4
16	Comoros	SSA	61.5	986	28		14.0
17	Congo	SSA	57.8	2934	145	92	22.5
18	Congo, Democratic Republic of the	SSA	48.7	319	2912	75	19.2
19	Côte d'Ivoire	SSA	56.0	1593	679	57	15.0
20	Cuba	LAC	79.3	5539	110	100	-
21	Djibouti	MEN	58.3	2350	26	87	0.8
22	Egypt	MEN	73.5	5401	1886	72	-
23	El Salvador	LAC	72.4	5915	126	85	3.3
24	Eritrea	SSA	62.0	531	193	26	4.0
25	Ethiopia	SSA	59.7	1017	2613	10	1.0
26	Fiji	EAP	69.4	4087	18		-
27	Gambia	SSA	58.8	1731	67	56	11.5
28	Georgia	ECA	73.9	5005	51	98	1.1
29	Ghana	SSA	64.6	1684	776	67	19.6
30	Guatemala	LAC	71.4	4235	473	51	2.7
31	Guinea	SSA	54.5	941	394	39	11.7
32	Guinea-Bissau	SSA	48.6	1042	59	42	8.4
33	Guyana	LAC	70.2	3387	13	89	3.0
34	Haiti	LAC	62.4	1070	266	25	5.2
35	Honduras	LAC	73.4	3426	205	67	2.9
36	India	SOA	65.8	3285	27098	47	8.0
37	Indonesia	EAP	69.8	4154	4331	55	7.1
38	Iraq	MEN	69.6	3557	1144	65	10.6
39	Jordan	MEN	73.5	5272	154	99	10.0
40	Kenya	SSA	57.7	1541	1560	43	11.3
41	Kiribati	EAP	68.4	3079	22	66	-
42	Kyrgyzstan	ECA	68.0	2009	131	97	0.3
43	Lao People's Democratic Republic	EAP	67.8	2435	140	17	15.6
44	Lesotho	SSA	48.7	1879	60	59	-
45	Liberia	SSA	57.3	480	157	37	9.5
46	Madagascar	SSA	66.9	828	747	35	19.4
47	Malawi	SSA	54.8	774	686	73	20.8
48	Mali	SSA	51.9	853	728	45	12.2
49	Marshall Islands	EAP	72.3	4040	27	85	-
50	Mauritania	SSA	58.9	2174	118	48	9.6
51	Micronesia, Federated States of	EAP	69.2	3352	3		-
52	Moldova, Republic of	ECA	69.6	3319	44	99	-
53	Mongolia	EAP	68.8	4245	65	99	-
54	Morocco	MEN	72.4	4384	620	73	-
55	Mozambique	SSA	50.7	906	889	58	12.1
56	Myanmar	EAP	65.7	1817	824	36	6.1
57	Namibia	SSA	62.6	5973	60	81	2.8
58	Nepal	SOA	69.1	1137	722	35	5.3
59	Nicaragua	LAC	74.3	2551	138	74	1.5
60	Niger	SSA	55.1	701	777	17	5.3
61	Nigeria	SSA	52.3	2102	6458	35	16.9
62	Pakistan	SOA	65.7	2566	4764	41	15.0
63	Palestine, State of	MEN	73.0	3359	33		-
64	Papua New Guinea	EAP	63.1	2386	208	52	7.4
65	Paraguay	LAC	72.7	4497	158	82	3.2
66	Philippines	EAP	69.0	3752	2358	44	2.5

67	Rwanda	SSA	55.7	1147	449	69	5.8
68	Samoa	EAP	72.7	3928	4	81	-
69	Sao Tome and Principe	SSA	64.9	1864	5	79	7.4
70	Senegal	SSA	59.6	1653	471	73	15.1
71	Sierra Leone	SSA	48.1	881	227	50	7.9
72	Solomon Islands	EAP	68.2	2172	17	85	22.3
73	Somalia	SSA	51.5	150	416	9	3.1
74	South Sudan	SSA					-
75	Sri Lanka	SOA	75.1	5170	373	98	2.9
76	Sudan	SSA	61.8	1848	1447	21	15.3
77	Swaziland	SSA	48.9	5104	35	80	8.7
78	Syrian Arab Republic	MEN	76.0	4674	466	78	-
79	Tajikistan	ECA	67.8	2119	194	88	0.8
80	Tanzania, United Republic of	SSA	58.9	1383	1913	50	16.4
81	Timor-Leste	EAP	62.9	5446	44	22	5.0
82	Togo	SSA	57.5	928	195	67	21.2
83	Tonga	EAP	72.5	4153	3	98	-
84	Tuvalu	EAP	67.5	5650		93	-
85	Uganda	SSA	54.5	1168	1545	57	14.5
86	Uzbekistan	ECA	68.6	3201	589	97	1.0
87	Vanuatu	EAP	71.3	3960	7	80	8.0
88	Vietnam	EAP	75.4	2970	1458	92	8.9
89	Yemen	MEN	65.9	1820	940	24	4.6
90	Zambia	SSA	49.4	1358	622	48	21.0
91	Zimbabwe	SSA	52.7	424	377	65	14.8

By world region, 42 (46%) of these countries are from Sub-Saharan Africa, 18 (20%) are from East Asia and the Pacific, 10 (11%) are from Latin America and the Caribbean, 8 (9%) are from the Middle East and North Africa, 7 (8%) are from South Asia, and 6 (6%) are from Europe and Central Asia. These 91 countries have an average life expectancy of 63.3 years, account for 64.2% of the roughly 135 million total annual global live births, and have a median institutionalized delivery of 65% (IQR: 43.8%-82.8%). These countries also have a median G6PD deficiency national frequency of 8.2% (IQR: 3.3%-14.6%). GNI: Gross national income; EAP: East Asia and the Pacific; ECA: Europe and Central Asia; LAC: Latin America and the Caribbean; MEN: Middle East and North Africa; SOA: South Asia; SSA: Sub-Saharan Africa.

movement of unconjugated bilirubin into brain cells to cause acute bilirubin encephalopathy. Continued exposure to free bilirubin may lead to irreversible damage or chronic bilirubin encephalopathy. Timely intensive phototherapy and ET can arrest this progression and prevent or minimize bilirubin-induced mortality and long-term neurologic morbidity.

PATHWAY TO ET AND POTENTIAL CHALLENGES IN LMICs

The facilities and techniques for undertaking ET in LMICs have been well described in the literature[4,8]. The clinical criteria for initiating ET have also been discussed in greater detail elsewhere[8,22]. Typically, regardless of the total plasma/serum bilirubin (TSB) level, a "crash-cart approach" (initiation of immediate intensive phototherapy and fluid supplementation, followed by ET) is recommended for infants with early signs and symptoms of intermediate/advanced ABE (lethargy, hypotonia, poor feeding, seizures, opisthotonos, and impaired level of consciousness) with or without evidence of neurotoxicity risk factors (prematurity, isoimmune hemolytic disease, G6PD deficiency, asphyxia, sepsis, acidosis, and hypoalbuminemia). It is also worth noting that the clinical diagnosis of hemolytic jaundice remains a challenge owing to the lack of advanced tests like end-tidal carbon monoxide (ETCO), eosin-5-maleimide flow cytometry to identify red blood cell membrane defects, and next-generation sequencing of relevant genes for mutations and polymorphisms[23].

Studies describing the process from when the decision to conduct ET has been made and the actual execution of ET systematically were surprisingly rare from our literature review[4,9,24,25]. We therefore also relied on our practice experience spanning over three decades in providing newborn care in a LMIC. For example, from 2012 to 2014, approximately 120 ETs were conducted annually in our hospital, Massey Street Children's Hospital in Lagos, which is the oldest children's hospital in Nigeria[26]. Typically, in most clinical settings, once the need for ET has been established by the resident physician and the consultant, the typical steps to ET can be summarized as shown in Figure 2. The delays that may be encountered at any of these stages are described as follows:

Providing intensive phototherapy preparatory to ET

Effective phototherapy has been shown to reduce the need for ET in several studies[27-31]. An effective phototherapy device should produce specific blue-light wavelengths (peak emission: 450 ± 20 nm), preferably in a narrow bandwidth to about 80% of an infant's body surface area[32]. The light source may be fluorescent tubes, halogen lamps, or light emitting diodes. Whatever the light-source, conventional phototherapy should have an irradiance of at least 8-10 $\mu W/cm^2$ per nanometer, and intensive phototherapy should have an irradiance

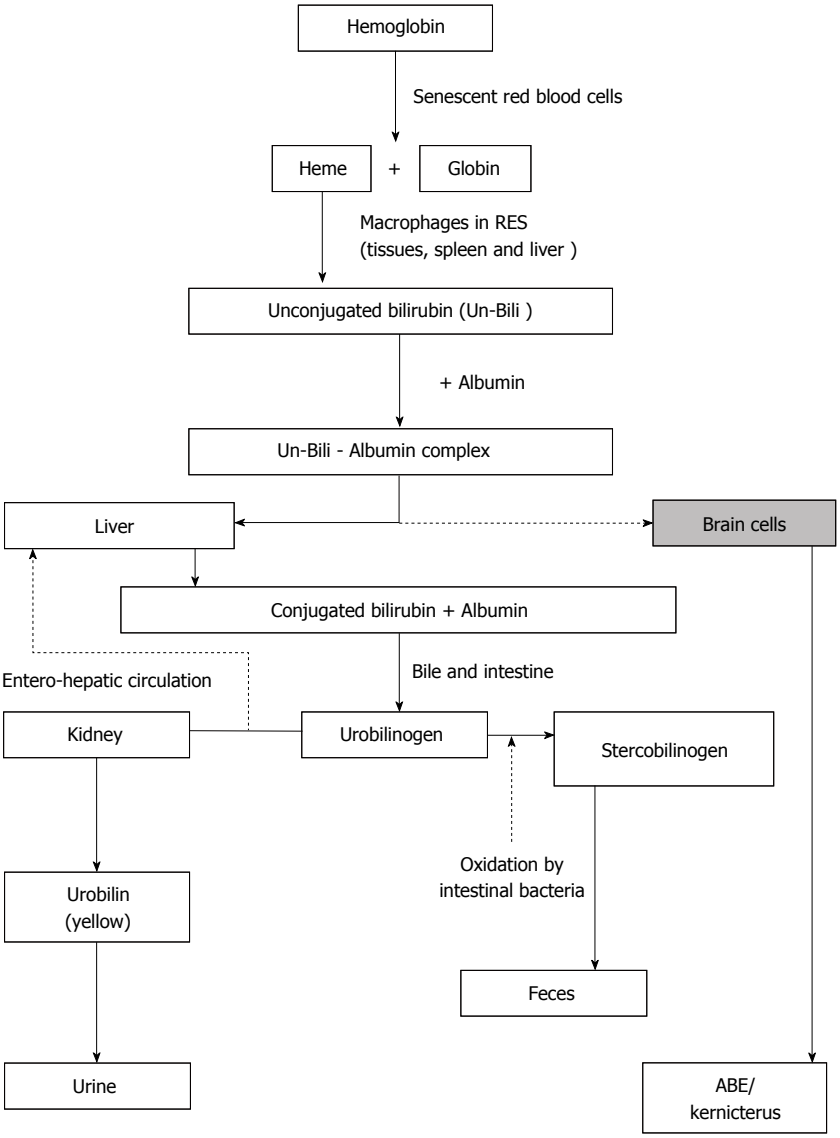

Figure 1 Metabolic pathway of bilirubin neurotoxicity. ABE: Acute bilirubin encephalopathy.

of $\geqslant$ 30 μW/cm^2 per nanometer (from either a single or multiple phototherapy units). The lack of effective phototherapy in many hospitals has been reported in several studies[33-36]. In one survey from Nigeria, for example, the vast majority (94%) of 63 phototherapy devices tested in twelve referral-level hospitals delivered irradiance of $\leqslant$ 10 μW/cm^2 per nanometer and none were $\geqslant$ 30 μW/cm^2 per nanometer[35].

Ineffective phototherapy is frequently attributed to erratic power supply, inadequate skin exposure (due to overcrowding from multiple infants being placed under a single device), sub-optimal irradiance levels, and poor device maintenance. A lack of intensive phototherapy during the waiting period for ET often results in a high incidence of kernicterus prior to ET and ultimately compromises the effectiveness of ET[11]. It is therefore not surprising to find adverse neurodevelopmental outcomes post-ET[17,18,37,38]. To ensure effective phototherapy, it is essential that the devices are properly monitored, regularly maintained, and that the staff are well trained to provide the best possible care for the affected infants preparatory to ET. The potential use of filtered sunlight phototherapy is currently being piloted and holds promise in tropical LMICs where effective conventional electric blue-light phototherapy devices cannot be routinely assured[39,40].

The administration of intravenous fluid supplementation should be considered for infants with evidence of dehydration, especially as a result of late presentation. This intervention has been found to decrease the need for ET by up to 70% without any long-term adverse effects[4,41]. Similarly, the use of intravenous immunoglobulin may be helpful in reducing the need for ET in infants with isoimmune hemolytic jaundice[4,42].

Obtaining informed consent and blood samples

Information on grouping and cross-matching, as well as baseline investigations such as full blood count, sodium, potassium, calcium, TSB, magne-

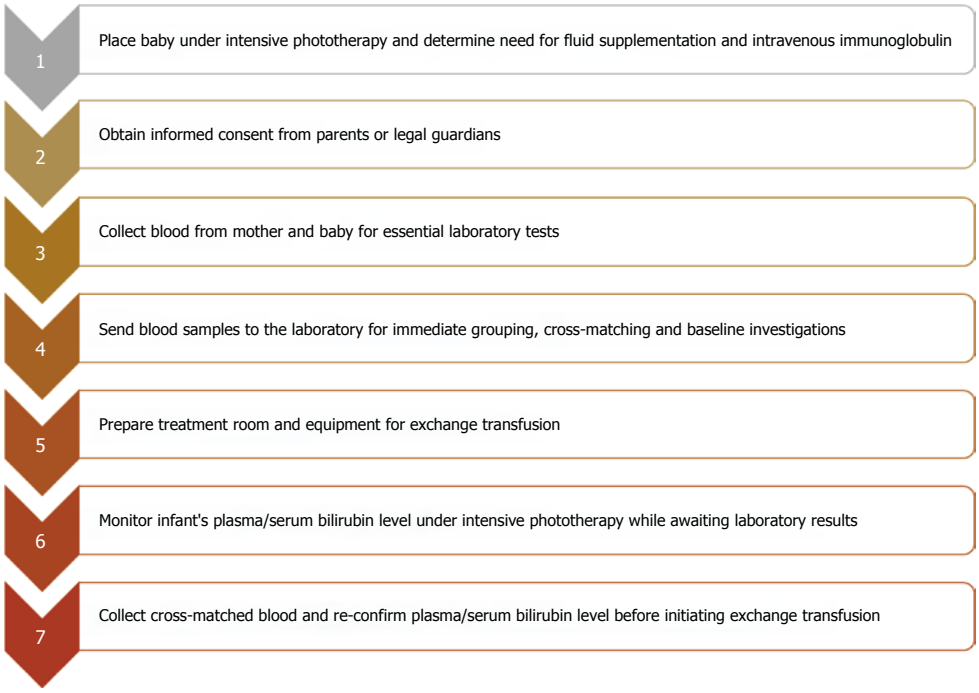

Figure 2 Sequence of events and sources of potential delays following the decision to initiate exchange transfusion.

sium and glucose, are required before initiating ET. Ethical considerations forbid blood or blood product transfusion without informed consent. However, delay in getting informed consent because the mother is not available, (due to death, critical illness, or being in another hospital) or the person with parental right is unavailable is not uncommon[6]. Delay may also be encountered in trying to convince parents who are reluctant to give consent on religious grounds[11]. Additionally, the mother's blood may not be available in time, owing to critical illness or the mother being admitted to another hospital. Difficulties may also be encountered where the mother is unavailable due to premature death. These potential sources of delay should be anticipated and addressed appropriately. It is important that prenatal maternal education be considered, especially in settings where religious beliefs are likely to delay consent for ET.

Transportation of blood samples to and collection of cross-matched blood from the laboratory

The volume of requested blood will depend on the decision for a single (estimated blood volume × baby's weight in kilograms) or double volume (estimated blood volume × 2 × baby's weight in kilograms) ET. Given the wide prevalence of G6PD deficiency in many LMICs, it is not uncommon for centers to have a standing rule for double-volume ET that removes 85% of the infant's red blood cells with up to 50% TSB decline and a potential rebound to two-thirds pre-exchange level, effectively removing one-third pre-exchange TSB level[4]. However, failure to request the right amount of blood is not unusual and often results in a delay or wastage. In fact, it is more common to find clinicians over-ordering just to be assured of the availability of sufficient blood. This often results in wastage of blood and remains a potential source of friction between clinicians and the laboratory personnel[43].

Getting blood samples to the laboratory may be challenging where the functional laboratory and blood bank are outside the immediate vicinity of the hospital, as frequently encountered in many LMICs. Laboratories are often centralized to serve diverse requirements from multiple clinical units. Information from the lab may therefore be difficult to track. Where the laboratory is accessible, hospital personnel may not be immediately available, due to shortage of staff, to collect the blood as soon as the laboratory sends information to the ward that it is ready. To facilitate efficient communication with laboratory personnel, it is important to designate somebody for this task well in advance, if possible.

Preparing room and equipment for ET

The ET room must be warm and ready with essential items for the procedure, such as IV infusion pump, arterial line pack, blood warmer, and protective goggles, as well as automated monitors for cardiac, blood pressure, oxygen saturation, and respiratory function. Emergency trolley and suction equipment with appropriate catheters should be checked, stocked, and nearby. Many of these items may not be readily available and a significant number of critical items may also have to be purchased by the infant's family. Where there is no designated room for ET, a suitable area has to be identified and screened off for the procedure. The need for infection control and keeping the baby warm must be considered.

Timely availability of laboratory results

In most hospitals, all laboratory services are centralized, implying that requests from ET personnel, even when urgent, have to be queued on arrival with other urgent requests. Laboratories in LMICs encounter several challenges that compromise their efficiency in achieving optimal turn-around time on the various requests for special investigations. These include inadequate and not up-to-date facilities, inadequate personnel, inadequate stock of blood, and, occasionally, inadequate blood samples for the required investigations.

Screening donor blood for hepatitis and human immunodeficiency virus is standard in many LMICs, but tests for G6PD status, cytomegalovirus (CMV), and malaria are often excluded, especially in regions where malaria is endemic. This may lead to using G6PD-deficient, CMV, or malaria-packed blood for ET. The use of G6PD-deficient blood has been associated with recurrent hemolysis and rebound TSB that often leads to repeat ET[44]. In the absence of blood warmer, the added time interval required to warm blood to body temperature may also prolong waiting time. Most laboratories lack diagnostic facilities for hemolytic disorders of newborns, and this frequently delays effective treatment for the affected infants.

A shortage in the number of laboratory personnel available to perform all the necessary laboratory analysis is also an important source of delay. A laboratory scientist who is in charge of carrying out the grouping and cross matching of blood for ET may be simultaneously engaged on other benches. This situation often leads to delays in issuing out blood for ET. Additionally, if the request for cross-matching gets to the laboratory very late in the day, call personnel in charge of several benches may have to be called in for grouping and cross-matching.

Blood samples from the baby may also be insufficient. Laboratory staff often complain about very small blood samples from the baby because of the method of grouping and cross-matching. A follow-up request for more blood from the laboratory causes further delay. The choice of blood, especially when the mother's blood is not available, may also compound the problem. In situations where the mother is dead or critically ill, the best blood for ET is fresh O Rhesus "D" negative blood, but this is very scarce. Fresh whole blood less than 48 h old and not more than five days old is preferred for ET. However, since this is unattainable in most cases, the consequence is another delay in ET[13]. All blood donors should be voluntary according to internationally laid down guidelines, but blood banks in many LMICs find it difficult to convince individuals to donate blood. The end-result is delayed ET for newborns at risk of ABE/kernicterus while the perennial problem, of insufficient blood in the blood bank, persists. If the blood group that is compatible with the newborn and the mother is not available in the blood bank, other blood banks will have to be contacted, and this may extend to days before the compatible blood unit becomes available. The packed cell volume (PCV) of the donor blood is not expected to be less than 40% for male donors and 38% for female donors. However, the lack of adequate blood supply to blood banks often accounts for the reluctance of blood banks in rejecting donors with low packed red blood cell volume. Performing ET with low PCV donor blood is sub-optimum, leading invariably to additional transfusion with packed red cells.

TSB monitoring and re-confirming need for ET

Availability of real-time TSB measurement is imperative, but seldom achieved due to of the lack of a functional side laboratory with bilirubinometers in many neonatal intensive-care units. As a result, TSB monitoring still has to rely on sending blood samples to the main designated hospital laboratory for analysis. Even when intensive phototherapy is provided, the need for ET may be contingent on several factors, including accurate knowledge of the risk status of the infant and the presence of hemolytic disease. Where ET is successfully avoided as a result of the provision of effective phototherapy, the result is often unutilized blood from the blood bank. While this pattern is desirable and unavoidable, it has the impact of depleting the blood bank and causing unnecessary delay in meeting future requirements for ET. It is important to be alert to the likelihood of TSB rebound after otherwise successful intensive phototherapy, especially in infants with hemolytic jaundice. Lack of close monitoring of the affected infants may result in initially withholding ET, only for it to be later required. Failure to recognize the possibility of declining TSB level following intensive phototherapy coincident with the clinical onset of kernicterus could also be a source of potential delay[45]. It is important to view such a decline as a prognostic sign for neurologic dysfunction, rather than a sign of clinical improvement, before or after phototherapy.

The ET procedure itself seeks to remove or reduce circulating antibody-coated red blood cells and/or products of hemolysis in various immune or non-immune hemolytic anemias and other red cell enzyme deficiencies. This is accomplished by repeatedly exchanging small samples (5-10 mL/kg) of blood *via* an arterial catheter and replacing simultaneously with fresh donor blood providing fresh albumin with binding sites for bilirubin by continuous infusion into a peripheral or central vein. The procedure can typically last between 2 to 4 h depending on the choice between single or double volume ET.

Limited skill by clinicians can result in further delays. For example, inability to cannulate the umbilical vein and leakage of blood between the catheter and umbilical vein may unduly prolong the procedure. Difficulties may also be encountered in withdrawing blood in spite of

the apparently successfully introduction of an umbilical catheter[46].

OTHER CONSIDERATIONS AND WAY FORWARD

Post-ET monitoring is necessary because of the likelihood of repeat ET after a rebound of high TSB level due to unrecognized hemolytic disease, with potential secondary delays[28,30,44]. Not all attending clinicians in emergency situations are skillful in providing ET, even where facilities are available, and this may result in delays in getting a suitable individual when all preparations have been made. In settings where ET is infrequent, lack of expertise may be a source of delay, especially when referral to another hospital becomes imperative[14]. Lack of a clearly-defined protocol or failure to adhere to an existing protocol is likely to cause delay as a result of communication gaps among team members. Where ET protocol requires the express approval of a consultant before execution by attending junior physicians, this may result in more potential delays. When more than one infant requires urgent ET and resources are limited, identifying and prioritizing the infant(s) most at-risk of kernicterus may also inevitably result in delay for some infants. Additionally, inadequate support staff may be a source of delay in providing seamless communication with the laboratory and/or a skilled assistant for the procedure. In some settings, patients may be required to bear the costs of the laboratory investigations requested by the attending physicians, especially in private hospitals[47,48]. Inability to meet such expenses is also a potential source of delay in providing timely ET[49].

The nature and scope of these delays are likely to vary within and across LMICs. Perhaps the overarching implication of these challenges is the impetus to avoid ET as much as possible by facilitating early presentation and timely provision of effective/intensive phototherapy, as well as investment in functional, readily accessible, and appropriately staffed laboratories in all hospitals that offer emergency care for newborns. Side laboratory with facilities for real-time bilirubin measurements should be made available in all neonatal units. Education of mothers and caregivers on the value of timely presentation and intervention in preventing bilirubin-induced mortality and long-term neurodevelopmental disorders should be routinely offered during antenatal visits. There is also a need for better communication and understanding between clinicians and laboratory personnel, especially with regards to the challenge of minimizing wastage of blood due to over-ordering[43].

While the focus of this review is primarily to serve the needs of clinicians in LMICs, the emerging and rising profile of global child health makes the topic also relevant to clinicians in the developed world.

CONCLUSION

ET is widely embraced as an effective treatment for infants with, or at risk of, bilirubin-induced neurologic dysfunctions (ABE and kernicterus) in LMICs. However, several potential delays are associated with the various critical steps prior to the initiation of ET after the need for this emergency procedure has been established. Efforts to minimize these delays, including efficient laboratory and logistical support, are imperative in ensuring timely and efficacious ET. Timely, effective, and intensive phototherapy should also be routinely provided to curtail the prevailing high rates of avoidable ET in LMICs.

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ORIGINAL ARTICLE

Retrospective Study

Nurse practitioner coverage is associated with a decrease in length of stay in a pediatric chronic ventilator dependent unit

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Author contributions: Rowan CM and Cristea AI collected the data; Taylor NM conducted the statistical analysis; Rowan CM drafted the first draft of the paper; the entire author group discussed the study design, reviewed the data analysis and critically reviewed and approved the manuscript.

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Abstract

AIM: To hypothesize a dedicated critical care nurse practitioner (NP) is associated with a decreased length of stay (LOS) from a pediatric chronic ventilator dependent unit (PCVDU).

METHODS: We retrospectively reviewed patients requiring care in the PCVDU from May 2001 through May 2011 comparing the 5 years prior to the 5 years post implementation of the critical care NP in 2005. LOS and room charges were obtained.

RESULTS: The average LOS decreased from a median of 55 d [interquartile range (IQR): 9.8-108.3] to a median of 12 (IQR: 4.0-41.0) with the implementation of a dedicated critical care NP ($P < 1.0001$). Post implementation of a dedicated NP, a savings of 25738049 in room charges was noted over 5 years.

CONCLUSION: Our data demonstrates a critical care

NP coverage model in a PCVDU is associated with a significantly reduced LOS demonstrating that the NP is an efficient and likely cost-effective addition to a medically comprehensive service.

Key words: Nurse practitioners; Length of stay; Cost effective health care; Ventilation; Pediatrics

Core tip: This is a retrospective study to review the care of patients requiring care in the pediatric chronic ventilator dependent unit from May 2001 to May 2011 comparing the 5 years prior to the 5 years post implementation of the critical care nurse practitioner (NP) in 2005. The average length of stay decreased from a median of 55 d [interquartile range (IQR): 9.8-108.3] to a median of 12 (IQR: 4.0-41.0) with the implementation of a dedicated critical care NP ($P < 0.0001$). Post implementation of a dedicated NP, a savings of 25738049 in room charges was noted over 5 years.

Rowan CM, Cristea AI, Hamilton JC, Taylor NM, Nitu ME, Ackerman VL. Nurse practitioner coverage is associated with a decrease in length of stay in a pediatric chronic ventilator dependent unit. *World J Clin Pediatr* 2016; 5(2): 191-197 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i2/191.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i2.191

INTRODUCTION

Transitioning children with chronic ventilator dependence delivered through a tracheostomy to their home environment reduces costs, enhances their quality of life, and helps with integration back into their families and communities[1]. Especially for children, the hospital is not an ideal location to aid their physical and psychological development[2,3]. However, children with chronic ventilator dependence present unique challenges to discharge planning. In 1998, the American College of Chest Physicians estimated that 10000 to 20000 people were receiving assisted ventilation at home[1]. This number will most likely continue to grow. One study found that pediatric long term ventilation discharges had increased 55% between 2000 and 2006[4]. As the number of patients with home mechanical ventilation increases, their hospital length of stay (LOS) has a multifactorial impact on healthcare usage. These patients have multiple medical problems making medical discharge progress slow. In fact, this group has been shown to have a significantly longer LOS[4]. Families require considerable education and training, specifically in tracheostomy care and ventilator management. The training process and transition to the home environment can be very overwhelming for families[5,6]. Social, insurance and financial issues can delay discharge. Previous studies have shown the addition of a nurse practitioner (NP) to various types of medical care teams significantly reduced the hospital LOS[7-10]. We hypothesize that a dedicated critical care NP would decrease the LOS in a pediatric chronic ventilator dependent unit (PCVDU), thus significantly impacting hospital costs.

MATERIALS AND METHODS

Study design

Charts were retrospectively reviewed for all patients who required care in the PCVDU from May 2001 through May 2011 to determine the effect of the critical care NP on LOS. This study was done at a large quaternary care pediatric hospital. In May of 2005, a dedicated pediatric nurse practitioner with critical care services was added to the care team for these patients and in October of 2008, an additional pediatric nurse practitioner was hired enabling daily NP coverage of the PCVDU. The NPs received additional training on managing chronic ventilation from the physician director of the Home Ventilator Program *via* both lectures and bedside instruction. Prior to the introduction of the NPs, the patients were covered only by the attending physician, who was also responsible for the medical care of an additional pediatric intensive care unit. The NPs were involved in the care of all patients requiring mechanical ventilation. They rounded on the patients, helped to formulate care plans for the day, discussed care plan with consultants, participated in care and discharge conferences, and updated families. Their main responsibility was coverage of the PCVDU. They were first line responders for questions from bedside nurses and respiratory therapists (RTs) throughout the day. They modified the plan and initiated orders as needed. Outside of the PCVDU, the NPs served as members of the rapid response and cardiopulmonary resuscitation teams, as well as provided assistance in the pediatric intensive care unit (PICU) as able. The same two NPs were present throughout the study period offering a better continuity of care and, therefore, facilitating ventilator weaning. The pediatric home ventilator program discharge criteria and training closely follows the American Thoracic Society guidelines. Bedside nurses and RT dedicated to this unit trained the family in the child's daily care and home ventilation.

Patients in the PCVDU were also co-managed by the developmental pediatrics team. This team was responsible for addressing developmental concerns, rehabilitation therapies, nutrition, and arranging outpatient follow up. The developmental team included a pediatric nurse practitioner during the week and resident coverage overnight and on the weekends. The staffing model for the developmental team was unchanged during the study period.

Table 1 Comparison of admissions: 5 years before and after nurse practitioner coverage

	Pre NP coverage	Post NP coverage
Total number of admission	158	311
Average annual patient days	10493	8812
Median length of stay	55 d (IQR: 9.8-108.3)	12 d (IQR: 4.0-41.0)

NP: Nurse practitioner; IQR: Interquartile range.

We compared the five years prior to the implementation of the critical care NPs to the five years post implementation. Also, the time with partial NP coverage was then compared to daily NP coverage. Partial coverage was defined as 5 d (approximately 40 h) per week, with the remaining days covered by the attending physician alone. Full NP coverage had a critical care team NP involved in the patient care every day. The NP coverage was only available during the day throughout the study period. The critical care attending physician managed the children overnight. PCVDU LOS, diagnosis, and disposition at discharge were collected. Diagnoses were grouped into seven categories based on the most common diagnoses admitted to our PCVDU: Bronchopulmonary dysplasia (BPD), neurologic disorders, multiple congenital anomalies, congenital heart disease, congenital diaphragmatic hernia, traumatic injury, and miscellaneous.

The financial data for bed/room charges alone was obtained from hospital accounting and did not include physician fees, therapy charges, medications, radiologic studies, or equipment. Room charges were all adjusted for inflation based on 2011 room charge values. Cost-effectiveness was determined by comparing room charges pre and post implementation of an NP.

Our PCVDU is a six bed unit dedicated to the care of children requiring long term mechanical ventilation. The majority of patients developed chronic respiratory failure within the same hospital admission and subsequently required home mechanical ventilator support through a tracheostomy. It comprises a variety a patients with the majority being neonates with BPD, but older children with neurologic, congenital anomalies, cardiac conditions and traumatic injuries are also admitted to this unit. The majority of the admissions are transfers from the neonatal intensive care unit. As such, the families require a comprehensive home mechanical ventilation and tracheostomy education program. Patients admitted to this unit are patients that have been decided to need chronic ventilation *via* a tracheostomy and have been determined to be safe outside of the PICU. Active ventilator weaning, adjustments and transitions to a home ventilator occur in this unit. Any form of ventilation, *i.e.*, full mechanical support to CPAP is all *via* tracheostomy. Seldom, when there is a significant shortage of critical care beds, children that have already undergone the initial training are admitted to this unit for other medical or social concerns. The vast majority of patients that have home ventilation and return to the hospital for any reason are admitted to the general PICU service and not the chronic ventilation unit.

Descriptive statistics are given by medians and interquartile ranges (IQRs) for continuous variables. To determine differences between groups, Mann-Whitney *U* test and the Kruskal-Wallis test were used for continuous variables. Chi squared analysis was used to determine *P* values for categorical variables. All analytic assumptions were checked to ensure proper outcome reporting. Associations were considered significant at a *P*-value of < 0.05. We used Statistical Package of the Social Science (SPSS) Statistical software for Windows, Version 20.0 (SPSS Inc., Chicago, IL, United States) and Microsoft Office Excel (Microsoft Corporation, Redmond, WA).

RESULTS

There were 469 admissions identified over the 10 year study period. The admissions' characteristics before and after beginning of NP coverage are described in Table 1. Demographics for these patients are as follows: The pre-NP coverage group was 38.6% female compared with 46.3% in the post-NP coverage group (*P* = NS). The pre-NP coverage group had a median age of 6 mo (IQR: 4-12) while the post-NP coverage group had a median age of 12 mo (IQR: 5-30) ($P < 0.001$). The decrease in the average LOS pre- and post-NP was significant with a *P* value < 0.0001 (Figure 1).

Daily NP coverage was provided for 200 of the 311 admissions with dedicated critical care NP involvement. The remaining 111 patients had NP coverage 5 d a week. When comparing partial NP coverage to daily NP coverage, there was once again a statistically significant decrease ($P < 0.0001$) from median 27.5 d (IQR: 7.75-75.25) to median 8 d (IQR: 3.0-28.0) (Figure 2).

There were seven diagnosis groups: BPD, neurologic disorders, multiple congenital anomalies, congenital heart disease, congenital diaphragmatic hernia, traumatic injury, and miscellaneous. BPD was the most common. Table 2 displays the total number of patients admitted with each diagnoses over the 10 year study period.

When comparing the LOS pre- and post-implementation of the critical care NP by diagnosis, we found a statistically significant decrease in several categories including BPD, congenital anomalies, congenital heart disease, and the miscellaneous group (Table 2).

We also investigated the disposition at discharge and compared the LOS pre- and post-NP. The dispositions at discharge were either to home, general pediatric ward (if the patient no longer required chronic ventilator support), an extended care facility,

Table 2 Number of admissions and median length of stay with interquartile range for each diagnosis over the 10 year study period, comparing pre and post nurse practitioner

Diagnosis	Total admissions	Admissions pre-NP	Admissions post-NP	Length of stay (d) pre-NP	Length of stay (d) post-NP	*P* value for length of stay
Bronchopulmonary dysplasia	140	61	79	68.0 (11.0-111.0)	18.0 (3.0-67.0)	$P < 0.001$
Neurologic disorder	119	35	84	19.0 (4.0-50.0)	12.0 (4.0-28.5)	$P = 0.246$
Multiple congenital anomalies	94	28	66	62.5 (16.0-126.5)	10.5 (5-32.8)	$P = 0.005$
Congenital heart disease	50	18	32	72.0 (47.5-138.8)	9.0 (2.3-18)	$P < 0.001$
Congenital diaphragmatic hernia	15	5	10	3.0 (1.0-107.0)	22.5 (8.5-37.8)	$P = 0.902$
Trauma	10	1	9	2.0 (2.0-2.0)	23.0 (4.0-40.0)	Could not be assessed
Miscellaneous	41	10	31	45.5 (13.8-98.3)	11.0 (5.0-39.0)	$P = 0.017$

Values are displayed as medians and interquartile ranges. *P* values obtained from Kruskal-Wallis test. NP: Nurse practitioner.

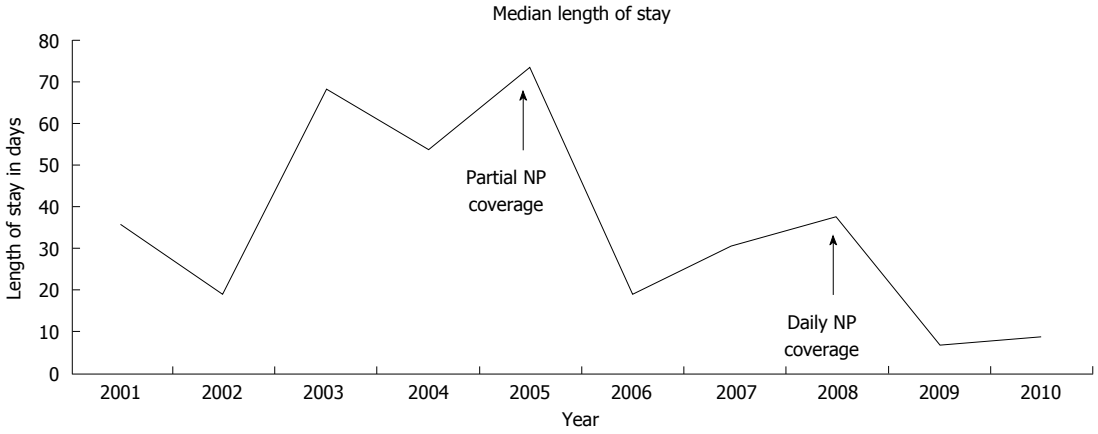

Figure 1 Median length of stay. In the figure above, the length of stay in days is plotted out over the course of the study from 2001 to 2010. The addition of partial NP coverage began in 2005 when the length of stay was highest. Daily NP coverage began in 2008. NP: Nurse practitioner.

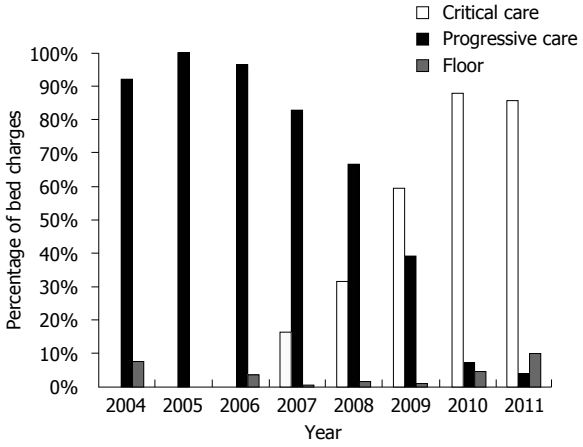

Figure 2 Percentage of bed charges during the length of the study. Over the course of our study, the average room charge per patient stay decreased as the dedicated NP was introduced into the PCVDU. The addition of the NP did not add specific charges as their services were bundled into the hospital and physician charges. NP: Nurse practitioner; PCVDU: Pediatric chronic ventilator dependent unit.

a rehabilitation facility, an outside hospital (a local community hospital closer to the family's home), the pediatric intensive care unit, or death. Table 3 illustrates the number of admissions and their disposition at discharge.

The majority of patients were discharged to home. Readmission to this unit is exceedingly low. When chronic ventilation patients return to the hospital, they are admitted to the PICU for acute issues to be resolved. Comparing LOS for these patients discharged home pre- and post-NPs, we found a significant decrease. Table 3 compares LOS pre- and post-NPs for each disposition at discharge.

The average room charge per patient stay prior to the NPs was approximately 188437. This charge decreased to approximately 105678 post implementation of the dedicated critical care NP. This is a savings of 82759 for room charges alone per patient per stay. Taking this average savings per patient, 25738049 were saved in room charges over the 5 year period since the start of a dedicated NP to the PCVDU (Figure 2). The NP did not add specific charges to the care of these patients as their services are bundled within the hospital and physician charges.

DISCUSSION

This study demonstrates a decrease in LOS in a PCVDU with the addition of dedicated critical care NP coverage. The mean LOS was reduced by over 75% (median 55 d compared to 12 d). Our results are similar to other studies showing that that the addition of a NP reduces LOS in trauma patients[8-10]. Our most

Table 3 Disposition at discharge from the pediatric chronic ventilator dependent unit

Disposition	Total number of admissions	No. of admissions pre-NP	No. of admissions post-NP	Length of stay (d) pre-NP	Length of stay (d) post-NP	*P* value
Home	339	105	234	68 (14.0-112.5)	14 (4.0-48.0)	$P < 0.0001$
General ward	32	14	18	13.5 (2.5-124.3)	4 (1.8-7.3)	$P = 0.05$
Extended care facility	19	4	15	37.5 (2.0-148.0)	5 (3.0-24.0)	$P = 0.84$
General rehabilitation facility	3	1	2	27 (27.0-27.0)	29 (25.0-29.0)	Could not be assessed
Outside hospital	6	4	2	74 (15.0-105.3)	19 (16.0-19.0)	$P = 0.36$
PICU	60	25	35	19 (9.5-49.5)	12 (5.0-43.0)	$P = 0.35$
Death	10	5	5	35 (22.0-62.0)	13 (2.0-23.0)	$P = 0.05$

A comparison of admissions and length of stay pre and post implementation of the start NP coverage. Values displayed are Medians with interquartile ranges. *P* values obtained from Kruskal Wallis test. NP: Nurse practitioner; PICU: Pediatric intensive care unit.

recent LOS with daily NP coverage (mean 19.82 d) is now below the reported mean LOS of 26.1 d obtained from a multicenter database[4]. The addition of NPs to the medical team has also been linked to shorter emergency department LOS and improved patient flow[11,12]. Adult literature shows a one day reduction in LOS with the addition of a NP to the team[13]. Our study provides one of the first accounts of the association of a NP on LOS in a PCVDU.

A limitation of this study is that it is difficult to retrospectively determine other factors affecting LOS. The pre-NP median patient age and post-NP median patient age are significantly different. This could have affected LOS in the post-NP group. One may consider that discharging an older ventilator dependent child may be easier. An older patient may reach acceptable ventilator settings for home more expediently and/or be generally more stable. These factors may have contributed to shorter LOS.

Some factors that may have affected LOS were minimized. There were no changes in physician groups or physician staffing that provided care for these patients except for the addition of the dedicated NP. We are reporting one institution's experience and practices may be different at other institutions. The same medical director and clinical nurse specialist of the home ventilator program were involved with the program for the entire study period.

It also would have been beneficial to have family surveys to describe their experience in the PCVDU before and after the implementation of the NPs to describe improved family satisfaction. While we speculate the acuity of illness was increasing throughout the study period and feel this is supported with the increasing amount of critical care charges noted in our PCVDU, we do not have acuity scores to further confirm this speculation.

Another limitation relates to the lack of description of total hospital LOS. Changing admission criteria or longer neonatal or pediatric intensive care unit stays prior to PCVDU may affect LOS. The total hospital LOS in our institution would likely be skewed by the prolonged variable neonatal course many of these patients have prior to being admitted to the PCVDU. A trend toward higher acuity in this unit, supported by the increasing number of critical care charges, may imply that we are admitting patients sooner to the unit. One would expect this to increase LOS, but we actually found a reduction.

The decrease in LOS by the addition of the NPs is likely multifactorial. The addition of a dedicated practitioner allowed for closer monitoring and prompt implementation of necessary ventilator and medication adjustments. This facilitated faster adjustments, allow the patient to more rapidly reach a medically stable state suitable for home. This is evident when examining the LOS pre- and post-NPs for patients discharged to an extended care facility where family education is not imperative. The dedicated NPs also improved coordination of care within our unit, especially with plans surrounding discharge. The NPs could ensure that the proper inter-professional staff, such as social work, nursing, and home care, had all been contacted in a timely fashion when the patient was nearing discharge. This dedicated coordination of care is essential in the successful discharge of ventilator dependent patients[14]. The NP had dedicated time to address concerns regarding family education and training and could be a sounding board for families in stressful situations. They also provided a consistency of care that likely contributed to the reduction in LOS. This is illustrated in our dramatic reduction in LOS for patients who are discharged to home.

This impact on LOS was consistent across diagnoses with the most impressive reduction noted in children with BPD. This is important in our particular population where BPD was the most common underlying diagnosis. While there have been advances in the care of BPD, the most significant advance was the use of surfactant. Our study period takes place after surfactant became a standard of care. Nevertheless, it is likely that advances in modern medicine have contributed to the reduction in LOS that we found in this study. However, the significant drop in LOS despite underlying diagnosis makes it unlikely that this is due to advances in medical care alone. Undoubtedly, we have made some medical progress for many of the underlying diseases seen

in our population. Also, with the advancements in technology and increased insurance/hospital costs, the general trend has led to parents caring for sicker children at home[15]. These factors alone are unlikely to be a cause of the significant reduction in LOS. Examining Figure 1, it is noticeable that there has been a trend toward decreasing LOS through the study time period; however, there is a sharp decline around the time of the introduction of partial NP coverage, and another sharp decline around the time of full NP coverage. However, from 2001 to 2003, there seems to be a trend toward increasing LOS. We venture this is secondary to increasing patient acuity. This is supported by a shift in bed charges from floor charges to progressive care charges to critical care charges. This trend toward higher acuity continued even throughout the implementation of the NPs.

We also noted a decrease in LOS across dispositions at discharge, with the most notable being disposition to home. Since the majority of our patients are discharged to home, this has the greatest overall effect on our LOS. We did not find a change in the LOS in those patients that went to the PICU or those that died. This is not surprising. We would not expect a change in the LOS of either of these dispositions. If the child is going to need a higher level of care, this will happen regardless of the presence of an additional member to the team. The latter half of the study period noted an increase in the disposition to a general rehab unit. This correlates with the accreditation of our hospital as a level 1 trauma center causing our patient population to slightly change. The small number of deaths in the unit is generally parental decisions to withdraw support and are probably unaffected by the presence of a dedicated NP.

Our cost savings data is striking. By the addition of full NP coverage for this chronic ventilation unit, we found an estimated reduction in hospital charges over a 5 year period of almost $26 million dollars. This has been accomplished despite an increase in acuity of illness that has led to a shift from progressive care charge to critical care charge, as is illustrated in Figure 2. The above mentioned reduction reflects room charges alone. This financial analysis does not include physician fees, therapy charges, medications, or equipment, which may significantly increase cost savings. There may also be other cost savings advantages by reducing LOS. We speculate that a shorter LOS correlates with decrease in the risk of hospital acquired infections. In addition to patient morbidity and mortality, catheter associated blood stream infections, catheter associated urinary tract infections, and hospital acquired pneumonia all have a significant cost burden on the healthcare system. It is also likely that a shorter LOS improves patient satisfaction. These findings would be important to validate at other pediatric chronic ventilation units.

COMMENTS

Background

As the hospital is not the ideal location to aid in the physical and psychological development of children, it is greatly important to transition the child with chronic ventilator dependence delivered *via* a tracheostomy to their home environment. While the transition reduces costs, enhances the quality of life and places the child with their loving support network, the discharge of this population from the hospital requires advanced planning due to the unique challenges they present. In this study, the authors hypothesized that a dedicated critical care nurse practitioner (NP) would decrease the length of stay (LOS) in a pediatric chronic ventilator dependent unit.

Research frontiers

Prior to the introduction of the dedicated NP in the pediatric chronic ventilator dependent unit (PCVDU), each patient was covered only by the attending physician who was also responsible for the medical care of an additional pediatric critical care unit, limiting the time the physician could dedicate to the successful transition of these patients from the hospital to home. The results of this study suggest the success of the dedicated NP in decreasing the LOS for the authors' chronic ventilator dependent patients.

Innovations and breakthroughs

The dedicated NPs served as the front line staff for the authors' chronic ventilator dependent patients. The NP for each patient rounded with the medical team, helped to formulate the care plan for the day, discussed the patient's care with consultants, participated in care conferences, and updated the families. They responded to questions from the respiratory therapists and bedside nurses and had the ability to modify the plan and initiate orders as needed. The dedicated NP served as a key member of the patient's developmental team during the hospital stay with a focus on discharging the patient to home. The study shows that the addition of the dedicated NP reduced the LOS for the authors' chronic ventilator patients.

Applications

The success of the dedicated NP in the PCVDU at reducing LOS could translate to other units of the hospital, reducing LOS as well as hospital costs.

Terminology

NP: A nurse practitioner with advanced nursing education; PCVDU: The pediatric chronic ventilator dependent unit; LOS: Length of stay; RT: Respiratory therapist; PICU: Pediatric intensive care unit.

Peer-review

The manuscript is an inspiring work depicting success in implementing nurse practitioners in a discharge process from PCVDU.

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ORIGINAL ARTICLE

Observational Study

Parental acceptability of the watchful waiting approach in pediatric acute otitis media

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Informed consent statement: All involved parents gave their informed consent (verbal, as accepted by the hospital Helsinki committee) prior to study inclusion. All details that could disclose the identity of the subjects under study were omitted/anonymized.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at eugenel@bgu.ac.il. Participants gave verbal informed consent for data sharing and the presented data were anonymized and risk of identification is low.

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Abstract

AIM: To determine parental knowledge about acute otitis media (AOM) and its antibiotic therapy, antibiotic resistance and the willingness to comply with the watchful waiting (WW) approach in primary care settings in southern Israel.

METHODS: The study was conducted in 3 primary care clinics and the pediatric emergency room of Soroka University Medical Center. Questionnaires (20 questions on education background, previous AOM experience, knowledge on antimicrobial resistance and attitude *vs* the WW approach) were filled by 600 parents (150 at each centers) of children < 6 years of age.

RESULTS: Mothers represented 69% of parents; 2% had an education of < 10 school years, 46% had high-school education and 17% had an academic degree. 69% parents reported previous experience with AOM and 56% thought that antibiotics represent the only treatment for AOM. Knowledge on bacterial resistance to antibiotics was reported by 57% of the parents; 86% parents were willing to accept/probably accept the WW approach for their children. Logistic regression analysis revealed a significant association between parental education and knowledge about bacterial resistance to antibiotics and that previous experience with AOM was significantly associated with reluctance to accept the WW approach. More parents with knowledge on bacterial resistance were willing to accept the WW approach compared with parents without such knowledge. No correlation was found between the education level and willingness to accept the WW approach.

CONCLUSION: A significant correlation was found between previous parental education and experience with AOM and the knowledge about antibiotic use, bacterial resistance and acceptance of the WW approach.

Key words: Acute otitis media; Children; Antibiotics; Parents; Watchful waiting; Bacteria; Resistance

Core tip: The 2004 and 2013 guidelines of the American Academy of Pediatrics suggest the use of a watchful waiting (WW) approach to antibiotic therapy in a selected group of children with acute otitis media (AOM). We determined the parental knowledge about AOM and its antibiotic therapy, antibiotic resistance and the willingness to comply with the WW approach in primary care settings and found a significant correlation between parental education level, previous experience with AOM, knowledge about antibiotic use and about bacterial resistance and the acceptance of the WW approach.

Broides A, Bereza O, Lavi-Givon N, Fruchtman Y, Gazala E, Leibovitz E. Parental acceptability of the watchful waiting approach in pediatric acute otitis media. *World J Clin Pediatr* 2016; 5(2): 198-205 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i2/198.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i2.198

INTRODUCTION

Acute otitis media (AOM) is the most common cause of pediatric physician visits and for antibiotic therapy and is common in children between the ages of 6-24 mo[1]. Although, spontaneous recovery from AOM has been documented in 70% of AOM cases, it is acceptable to treat AOM with antibiotics at the time of diagnosis, mainly since it is very difficult distinguish between the AOM cases that will resolve spontaneously and those that will not[2].

In the past few years, antibiotic therapy for AOM has been complicated by emergence of bacterial resistance to antibiotics[2]. In 2004, the American Academy of Pediatrics published its guidelines on antibiotic therapy for AOM[3]; these guidelines were later accepted by the Israeli Pediatric Association[4]. The guidelines suggest the use of a watchful waiting (WW) approach to antibiotic therapy in a selected group of children with AOM, an approach reinforced by the 2011 guidelines[5]. The WW approach distinguishes between a positive diagnosis of AOM, and AOM severity: mild, moderate and severe. This approach is still controversial; it was first developed by the Dutch College of General practitioners during the 1980's, and in principle allows for withholding immediate antibiotic therapy from children with a mild to moderate severity-AOM and > 2 years of age, and in children who have a mild to moderate severity-AOM with an uncertain diagnosis and aged between 6-24 mo[6-10]. The WW approach can be implemented only if medical supervision is available, with a re-evaluation 24-48 h after the initial diagnosis and prompt initiation of antibiotic therapy in patients who did not improve.

The consequences of this WW approach include a substantial decrease in expenses related to AOM therapy as a result of less antibiotic prescription, and a possible decrease in development of bacterial resistance in pathogens associated with AOM[3,5,11-14].

The aim of this study is to delineate parental knowledge about antibiotic therapy of AOM and the WW approach in the primary care setting and the Pediatric Emergency Room. We also studied the effect of parental education, prior experience with AOM and prior information on the WW approach, on these parameters.

MATERIALS AND METHODS

The overall population of the southern Israel was > 700000 inhabitants in 2012, of them > 250000 children < 18 years of age. The city of Beer-Sheva has a population of > 200000 inhabitants with a pediatric population > 50000 children < 18 years of age. The community pediatric medical services are provided by 1 central child health center and numerous regular community clinics. The Soroka University Medical Center is the only medical center providing medical services to the whole population of Southern Israel. The PER of the Soroka University Medical Center accepts around 36000 visits/year.

Questionnaires were filled by parents of children <6 years of age, in the waiting rooms of 4 primary care clinics in Southern Israel: (1) the child health center (Center A); (2) one community clinic (Center B), both

Table 1 Characteristics of the groups of parents enrolled *n* (%)

Characteristic	Total *n* = 600	Center A *n* = 150	Center B *n* = 150	Center C *n* = 150	Center D *n* = 150
Enrolled parent					
Mother	414 (69)	105 (70)	96 (64)	116 (77)	97 (65)
Father	186 (31)	45 (30)	54 (36)	34 (23)	53 (35)
Mother age					
20-30 yr	150 (36)	44 (42)	42 (44)	36 (31)	28 (29)
31-40 yr	214 (52)	53 (51)	48 (50)	65 (48)	57 (59)
> 40 yr	50 (12)	8 (7)	6 (6)	24 (21)	12 (12)
Father age					
20-30 yr	31 (17)	5 (11)	14 (26)	5 (15)	7 (13)
31-40 yr	116 (62)	35 (78)	30 (56)	16 (47)	35 (66)
> 40 yr	39 (21)	5 (11)	10 (18)	13 (38)	11 (21)
Working mothers	316 (76)	82 (78)	75 (78)	86 (74)	73 (75)
Housewives	98	23 (22)	21 (22)	30 (26)	24 (25)
Working fathers	171	41 (91)	51 (94)	30 (88)	49 (92)
Unemployed fathers	15 (8)	4 (9)	3 (6)	4 (12)	4 (8)
Parental education					
< high school	13	2 (1)	0	6 (4)	5 (3)
High school	278	68 (45)	54 (36)	88 (59)	68 (45)
College	209	55 (37)	62 (41)	42 (28)	50 (34)
> college	100	25 (17)	34 (23)	14 (9)	27 (18)
Parental past experience with otitis					
Yes	411	112 (75)	101 (68)	100 (67)	98 (65)
Not	181	37 (25)	47 (31)	48 (32)	49 (33)
"I don't know"	8	1 (1)	2 (1)	2 (1)	3 (2)

in Beer-Sheva; (3) the Ofakim community clinic (Center C) in the development town of Ofakim; and in (4) the Pediatric Emergency Room (PER, Center D) of Soroka University Medical Center, Beer-Sheva. The study was conducted between September 2006 and May 2007. The parents were asked about the number of children in the family, previous experience with a child with AOM, level of education, knowledge on AOM, antibiotic resistance, the acceptance of the WW approach to antibiotic therapy in AOM and the source of acquisition of this knowledge.

The study was approved by the institutional review board of the Soroka University Medical Center, Beer-Sheva, Israel (protocol WW 001 from 02/07/2006).

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences 16.0 (SPSS 16.0) software. The data were analyzed using the chi square test and the Fisher's exact test as appropriate, a *P* value below 0.05 was considered significant. Multivariate analysis for willingness to accept the WW approach was performed. Variables that were found to be with a *P* value < 0.05 were included, with exclusion of confounding variables. The statistical review of the study was performed by a biomedical statistician.

RESULTS

A total of 600 parents were enrolled (150 in every one of the 4 locations of the study). None of the parents approached in the 4 centers refused to complete the questionnaire. The characteristics of the 4 groups of parents enrolled are presented in Table 1. All parents were from 20 to 45 years old; 414 (69%) were mothers. The age of the mothers was similar except for more mothers > 40 years old in Center C (*P* < 0.02 compared with Centers A and B). Most of the mothers, 316/414 (76%), were employed. Out of the 600 parents, 12 (2%) had an education of < 10 school years, 278 (46%) had high school education and 100 (17%) had an academic degree. Experience with a previous child who had AOM was reported by 441/600 (69%) of parents without a significant difference between the locations of the study.

The data on parental knowledge on AOM therapy are presented on Table 2. A total of 441 (69%) reported some previous experience with AOM, with no statistical difference between the 4 centers. Only 55/600 (9%) parents reported no knowledge on the topic of AOM. Most of the parents, 332/600 (56%), thought that antibiotics were the only therapeutic modality for AOM. Only 14/600 (2%) of the parents believed that there was no need for any type of therapy for AOM. The possibility of spontaneous resolution of AOM without any therapy was known by 269/600 (45%) of the parents without statistically significant differences between parents from the 4 locations of the study. However, 162/600 (27%) of the parents believed that resolution of AOM was not possible without therapy and that AOM must be treated with antibiotics. Knowledge about bacterial resistance to antibiotics was reported by 344/600 (57%) of the parents (Table 2). Pain (reported by 30% of the parents who expressed concerns on unsuccessful outcomes without antibiotic therapy) and

Table 2 Parental knowledge on acute otitis media treatment *n* (%)

CCCCC treatment/statement	Total *n* = 600	Center A *n* = 150	Center B *n* = 150	Center C *n* = 150	Center D *n* = 150
Antibiotics[1]	332 (56)	82 (55)	100 (60)[a]	74 (50)[a]	76 (51)
Ear drops[1]	147 (25)	55 (37)	26 (17)	31 (21)	35 (23)
Tympanocentesis[1]	26 (4)	4 (2)	2 (1)	9 (6)	11 (8)
Paracetamol[1]	6 (1)	0	3 (2)	2 (1)	1 (1)
Homeopathic drops[1]	20 (3)	0	7 (4)	6 (4)	7 (4)
No need to treat	14 (2)	0	4 (2)	5 (3)	5 (3)
"I don't know"	55 (9)	9 (6)[c]	8 (5)[c]	23 (15)[c]	15 (10)[c]
Recovery w/o antibiotics is possible					
Yes	269 (45)	61 (41)	70 (47)	64 (43)	74 (50)
No	162 (27)	32 (21)	32 (21)	54 (36)	44 (29)
"I don't know"	169 (28)	57 (38)	48 (32)	32 (21)	32 (21)
Knowledge on antibiotic resistance					
Yes	344 (57)	117 (78)[b]	89 (59)	58 (39)[b]	80 (53)
No	144 (24)	14 (9)	29 (19)	64 (43)	37 (25)
"I don't know"	112 (19)	19 (13)	32 (22)	28 (18)	33 (22)
Parental concern on unsuccessful outcome w/o antibiotics					
Yes	442 (74)	111 (74)	110 (73)	101 (67)	120 (80)
Not	158 (26)	39 (26)	40 (27)	49 (33)	30 (20)
Parental concern on unsuccessful outcome w/o antibiotics	*n* = 442	*n* = 111	*n* = 110	*n* = 101	*n* = 120
Pain and suffering	131 (30)	37 (33)	28 (25)	35 (35)	31 (26)
High fever	110 (25)	21 (19)	26 (24)	32 (32)	37 (31)
Other complications	201 (45)	53 (48)	56 (51)	34 (33)	52 (43)

[1]"Only"; [a]$P < 0.05$ (χ^2); [c]$P < 0.05$ (χ^2); [b]$P < 0.001$ (χ^2).

Table 3 Parental knowledge about the watchful waiting approach for acute otitis media therapy *n* (%)

Statement	Total *n* = 600	Center A *n* = 150	Center B *n* = 150	Center C *n* = 150	Center D *n* = 150
Physician recommendation in the past					
Yes[1]	194 (40)	69 (61)[b]	41 (37)[b]	40 (32)[b]	44 (32)[b]
Not[1]	291 (60)	44 (39)	69 (63)	85 (68)	93 (68)
Not relevant	115 (19)	37 (25)	40 (27)	25 (17)	13 (9)
Acceptance of WW recommendation					
Yes	337 (55)	79 (52)	70 (47)[a]	92 (61)	95 (63)[a]
Probably yes	178 (30)	45 (30)	51 (34)	46 (31)	36 (24)
No	5 (9)	22 (15)	17 (11)	5 (3)	7 (5)
"I don't know"	33 (6)	4 (3)	12 (8)	7 (5)	12 (8)
Want to be included in physician decisions					
Yes	552 (92)	135 (90)	129 (86)	143 (95)	145 (97)
Probably yes	36 (6)	11 (7)	17 (11)	6 (4)	2 (1)
No	5 (1)	3 (2)	0	0	2 (1)
"I don't know"	7 (1)	1 (1)	4 (3)	1 (1)	1 (1)

[1]From all parents with past experience with otitis media; [a]$P < 0.05$ (χ^2); [b]$P < 0.001$ (χ^2). WW: Watchful waiting.

prolonged fever (25%) were the two major concerns amongst the parents in respect to AOM outcome without antibiotic therapy.

The data on parental knowledge about the WW approach for AOM treatment are presented in Table 3. The WW approach was reported to have been previously offered to 194/485 (40%) of parents. WW was offered significantly more in Center A (69/113, 61%) *vs* 41/110 (37%), 40/125 (32%), and 44/137 (32%) of the parents in Centers B, C and D, respectively, $P < 0.001$. The willingness to use the WW approach in AOM was reported in 337/600 (55%) parents, while another 178/600 (30%) reported that they would probably agree to this approach, leading to a total of 507/600 (85%) parents that would be willing or probably willing to accept this approach. Nearly all parents, 576/600 (98%), expressed the willingness to take part in the decision making process concerning treatment in AOM, without significant differences between the 4 centers.

Only 214/600 (35%) of the parents knew about the association between antibiotic resistance and antibiotic therapy. The main side effects of antibiotic therapy that were known to the parents were: Diarrhea (revealed in 27% of all questioned parents), "weakening of the immune system" (23%), rash (22%), abdominal pain

Table 4 Logistic regression analysis: Parameters influencing the parental willingness to accept the watchful waiting approach

Parameters	*P* value	OR	(95%CI)	
			Lower	Upper
Previous AOM history	0.012	0.341	0.148	0.778
Knowledge on antibiotic resistance	0.026	2.001	1.087	3.685
Parental education	0.028	1.461	0.789	2.706
Parental age	0.607	0.986	0.936	1.040

AOM: Acute otitis media.

(21%), and vomiting (17%); 12% of the parents did not know about any possible adverse effects of antibiotics.

The primary care physicians were the most common source of parental knowledge about AOM (357/600, 59%). In addition, friends and relatives, television and the internet were common sources of information (304/600, 50%; 291/600, 48% and 289/600, 48% respectively). Written journals, pamphlets and well-baby care centers were less common sources of information (161/600, 27%; 90/600, 15% and 55/60, 9% respectively).

Statistical analysis

Pearson correlation revealed a significant association between parental education and knowledge about bacterial resistance to antibiotics (71.1% of the parents with an academic degree had such knowledge compared with only 41% in parents with high school education or < 10 years of education, $P < 0.01$, $r = 0.283$). A significant inverse correlation was found between previous experience with AOM and willingness to accept the WW approach: 86.3% of the parents that did not have experience with a child with AOM were willing to accept the WW approach *vs* only 70.6% of parents who had previous experience with AOM, $P = 0.017$, $r = -0.101$. A significant correlation was found between parental knowledge about bacterial resistance to antibiotics and willingness to accept the WW approach: 93.4% of the parents with this knowledge were willing to accept the WW approach *vs* only 87.4% of the parents who did not know about bacterial resistance to antibiotics, $P = 0.015$, $r = 0.102$. There was a nonsignificant trend towards correlation between the level of parental education and willingness to accept the WW approach; 93.1% of the patients with academic degrees were willing to accept the WW approach *vs* 88.7% of parents without academic education, $P = 0.068$, $r = 0.077$.

Logistic regression analysis (including the following parameters: previous experience with AOM, parental knowledge on antibiotic resistance, parental education and parental education) revealed that the willingness to accept the WW approach was significantly inversely correlated with previous experience with AOM ($P = 0.012$) and directly correlated with parental knowledge on antibiotic resistance ($P = 0.026$) (Table 4).

DISCUSSION

AOM is the most common bacterial disease in children and AOM treatment accounts for more than 50% of antibiotic prescriptions for children, and approximately 5 billion dollars in annual costs in the United States[15-19]. Many studies have shown relatively low efficacy for antibiotic therapy in AOM[7,20-25]. Since there is a spontaneous recovery rate of 70%-90% in AOM, only one patient out of 7-14 children with AOM will have a substantial benefit from antibiotic therapy[22,26,27]. Furthermore, the advantages of antibiotic therapy in children with AOM may be offset by side effects of antibiotic therapy, costs, increased bacterial resistance and the loss of the opportunity to include the parents in the medical decisions regarding antibiotics for their children[28]. In accordance to these drawbacks related to the indiscriminate use of antibiotics, recent data from United States showed major declines in antibiotic prescribing in children, as a result of educational campaigns aimed at both parents and clinicians[29-31].

The increase in bacterial antibiotic resistance is causing considerable concern[32,33]. This concern, together with the possible other side effects of antibiotic therapy, makes the WW approach for the treatment of AOM interesting and attractive[3-6,8-10,14,34,35]. However, most of the parents in USA believe that antibiotics are necessary for the treatment of AOM[36] and many physicians think that the parents want antibiotics for treatment of AOM in their children, and this is reflected in antibiotic prescriptions[37,38].

Since AOM has been traditionally treated with antibiotics, the willingness of primary care physicians and parents to accept the WW approach requires careful evaluation. In a study that included 16 medical centers in Massachusetts, 2054 parents and 160 physicians were asked about their willingness to accept the WW approach for treatment of AOM[39]. Only 32% of the parents were willing to fully or partially accept the WW approach, with an increase in acceptance in parents with a higher education and in those who received prior explanations about this approach. Amongst physicians, 38% reported that they never or almost never used the WW approach in children with AOM older than 2 years, 39% used this approach rarely, 17% often and 6% used this approach most of the time[39]. Therefore, it is obvious that there is a need for significant changes in knowledge and attitude toward the WW approach in parents and physicians as well.

Pshetizky *et al*[40] studied in southern Israel the willingness of the parents of 81 children aged 3 mo-4 years diagnosed with AOM to take part in the therapeutic decision making process together with their physicians[37]. The authors reported that after short explanations about the likelihood of spontaneous recovery and the possible problems that may be associated with antibiotic therapy, the shared decisions

could result in a 50% decrease in antibiotics use[40].

In this study we examined knowledge and attitude in parents of young children towards therapy in AOM. We focused on antibiotic therapy, it's efficacy in AOM, possible complications, and antibiotic resistance to antibiotics. Furthermore, we also studied parental willingness and knowledge about the WW approach in AOM, their previous experience with AOM, level of education, and correlated these variables with the approach towards WW. We recruited parents from 3 primary care clinics in southern Israel, and from the pediatric ER of the only medical center in the area. The pediatric population of Southern Israel is extremely heterogeneous in terms of its ethnic composition and socioeconomic status and therefore the findings presented in this study cannot be extrapolated to other geographic areas of the country and of course not to the whole Israel population.

We found that parental knowledge about AOM therapy (in general) and antibiotic therapy (specifically) is unsatisfactory. Our study revealed that around half of the parents believed that antibiotics are the only therapeutic option in AOM or perceived the disease as a self limited disease. Furthermore, only 36% of the parents knew that bacterial antibiotic resistance was associated with widespread antibiotic therapy. A vast majority of the parents, 85%, were willing to accept or probably accept the WW approach in a shared decision with their primary care physician. Nearly all of the parents, 98%, wanted to take an active part in the decision about antibiotic therapy in AOM. Logistic regression analysis revealed a significant correlation between parental education and knowledge about bacterial resistance to antibiotics. Previous experience with AOM was found to be significantly associated with unwillingness to accept the WW approach in AOM.

Previous experience with AOM was found to be significantly associated with unwillingness to accept the WW approach in AOM. The willingness to accept the WW approach in AOM in relation to previous parental experience with AOM has not been studied previously; we were somewhat surprised to discover that parents with previous experience with AOM were less willing to accept the WW approach. Although, the finding that a higher level of education is associated with knowledge about bacterial resistance to antibiotics has been previously reported[39,41-43], parents in this study showed a much higher acceptance of the WW approach in AOM (85% in this study *vs* 34% in another study[39]). This finding raises many questions and requires further studies to clarify the possibility of effective implementation of the WW approach in AOM, at least in southern Israel. On the other hand, we are certain that educational programs about the proper use of antibiotics and concerns about increasing bacterial resistance to antibiotics can change the opinions and knowledge that we have examined in this study regarding antibiotic therapy for AOM.

In summary, our study determined the parental knowledge about AOM and its therapy, antibiotic resistance and the willingness to comply with the WW approach in primary care settings and found a significant correlation between parental education and experience with AOM and the knowledge about antibiotic use, bacterial resistance and acceptance of the WW approach.

COMMENTS

Background

The observation option ("watchful waiting", WW) in the treatment of acute otitis media (AOM) was reconsidered during the last years as an appropriate management option for certain children. The diseases management is based on diagnostic certainty, age, severity of illness and assurance of follow-up. The American Academy of Pediatrics and other medical associations around the world recommend this option in children > 6 mo of age who do not present with severe illness, or in whom the diagnosis is uncertain. In contrast, immediate antibiotic therapy is recommended for children < 6 mo of age and for all those with a severe form of the disease. Nevertheless, for children in the desired age ranges, previous reports have consistently shown that most children do well, without serious adverse sequelae, even without antibiotic therapy. Furthermore, the implementation of the WW method strategy could reduce substantially the use of antibiotics in children and play a major role in decreasing the antibiotic resistance.

Research frontiers

Since AOM has been traditionally treated with antibiotics, the willingness of primary care physicians and parents to accept the WW approach requires careful evaluation. A majority of physicians reported using at least occasionally the WW method, but few use it frequently. Many parents have concerns regarding the WW method, but acceptability was found increased among those more educated and those feeling included in the therapeutic decision process. Information on knowledge and attitude of parents of young children towards therapy in AOM in southern Israel is limited. The objectives of the present study were to determine parental knowledge about AOM and its antibiotic therapy, antibiotic resistance and the willingness to comply with the WW approach in primary care settings in southern Israel

Innovations and breakthroughs

The present study enrolled parents from 3 primary care clinics in southern Israel, and from the pediatric ER of the only medical center in the area. The study revealed that around half of the parents believed that antibiotics are the only therapeutic option in AOM or perceived the disease as a self-limited disease. Only one third of the parents knew that bacterial antibiotic resistance was associated with widespread antibiotic therapy. A vast majority of the parents were willing to accept or probably accept the WW approach in a shared decision with their primary care physician. Nearly all of the parents wanted to take an active part in the decision about antibiotic therapy in AOM. Logistic regression analysis revealed a significant correlation between parental education and knowledge about bacterial resistance to antibiotics. Previous experience with AOM was found to be significantly associated with unwillingness to accept the WW approach in AOM.

Applications

The data presented in this study suggest that the WW option is a valuable and accepted treatment for AOM not only from the point of view of the medical practitioners, but also from the parents of the children sick with this extremely common pediatric condition. Since the pediatric population of southern Israel is extremely heterogeneous in terms of its ethnic composition and socioeconomic status, the findings presented in this study cannot be extrapolated to other geographic areas of the country and of course not to the whole Israel population. Further studies on knowledge and attitude of parents of young children and also of medical practitioners towards therapy in AOM and the WW option in Israel may provide additional information leading to a broad

implementation of the WW policy in the country.

Terminology

The WW approach to antibiotic therapy of AOM in children refers to withholding immediate antibiotic therapy from children with a mild to moderate severity-AOM and > 2 years of age, and also in children aged 6-24 mo who have a mild to moderate severity-AOM; The WW approach can be implemented only if medical supervision is available, with a re-evaluation in 24-48 h after the initial diagnosis and prompt initiation of antibiotic therapy in patients who did not improve.

Peer-review

The central research question is to describe parental knowledge and opinions about the watchful waiting approach in AOM. The settings are 3 primary care centers and one pediatric emergency room in southern Israel.

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Systematic review of character development and childhood chronic illness

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Abstract

AIM: To review empirical evidence on character development among youth with chronic illnesses.

METHODS: A systematic literature review was conducted using PubMed and PSYCHINFO from inception until November 2013 to find quantitative studies that measured character strengths among youth with chronic illnesses. Inclusion criteria were limited to English language studies examining constructs of character development among adolescents or young adults aged 13-24 years with a childhood-onset chronic medical condition. A librarian at Duke University Medical Center Library assisted with the development of the mesh search term. Two researchers independently reviewed relevant titles (n = 549), then abstracts (n = 45), and finally manuscripts (n = 3).

RESULTS: There is a lack of empirical research on character development and childhood-onset chronic medical conditions. Three studies were identified that used different measures of character based on moral themes. One study examined moral reasoning among deaf adolescents using Kohlberg's Moral Judgement Instrument; another, investigated moral values of adolescent cancer survivors with the Values In Action Classification of Strengths. A third study evaluated moral behavior among young adult survivors of burn injury utilizing the Tennessee Self-Concept, 2nd edition. The studies observed that youth with chronic conditions reasoned at less advanced stages and had a lower moral self-concept compared to referent populations, but that they did differ on character virtues and strengths when matched with healthy peers for age, sex, and race/ethnicity. Yet, generalizations could not be drawn regarding character development of youth with chronic medical conditions because the studies were too divergent from each other and biased from study design limitations.

CONCLUSION: Future empirical studies should learn from the strengths and weaknesses of the existing literature on character development among youth with chronic medical conditions.

Key words: Positive youth development; Character development; Adolescents; Chronic illness; Childhood

Core tip: This study reviewed empirical evidence on character development among youth with chronic medical conditions. Only three quantitative studies were found that met the review inclusion criteria. Different measures of character were evaluated including moral reasoning, moral concept, and character virtues. Collectively, the findings were not generalizable and were too divergent to support or contradict each other. The strengths and weaknesses of the emerging literature offer insights into how best to design future studies on character development among youth with chronic illnesses.

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INTRODUCTION

As more and more adolescents with chronic illness survive into adulthood it is vital that we understand how best to support their development into thriving adults. The study of chronic illness in adolescence has been approached from many aspects of development including social development, emotional development, and cognitive development[1,2]. Yet, little is known about the Positive Youth Development (PYD) of these youth which focuses on the development of strengths in adolescence that is associated with positive outcomes[3].

PYD, as described by Richard M Lerner, PhD, is a model that has been validated using a global measure and sub-constructs consisting of Five C's: Character, caring, connectedness, competence, and confidence (Table 1)[4,5]. All six factors are stable measures across developmental stages from childhood to adulthood and are modifiable based on experiences and environmental resources[6-8]. Youth with higher scores for PYD and the Five C's have higher contribution to society and lower rates of problem behaviors and depression[6]. Accordingly, many youth programs that have been designed to improve outcomes target character development defined by personal standards, moral behavior, or personal strengths (*e.g.,* diligence)[9,10].

For youth with chronic illnesses, a strong character is commonly acknowledged as an essential trait given the persistent health challenges they face[7,8]. Anecdotally there are many stories which attest to the strength of children living with chronic medical conditions. To quote one such newspaper article describing a 15 years old with cancer: "(She) has been a symbol of courage and strength for those who know her[11]." Similar sentiments and accounts of character growth due to the illness experience were noted in qualitative interviews that we conducted of adolescents with chronic conditions and their parents (unpublished data).

However, rigorous empirical research on character development among adolescents with chronic illnesses is in a nascent state. Key questions remain as to whether or not character development is different for youth with chronic medical conditions and what specific attributes of character should be targeted for interventions. To answer these inquiries, there are a variety of theoretical frameworks, research study designs, methods (*i.e.,* measures and approaches), and statistical techniques that can be used. Also, the influence of the disease state-type, onset, severity, and prognosis - must be taken into consideration. In addition, thought has to be given to the developmental stage of interest to select the most appropriate evaluation. Given the complexity, emerging quantitative research on this topic has the potential to be varied and divergent.

Accordingly, the aim of this study was to conduct a systematic review of studies investigating character development among adolescents and young adults with chronic medical conditions. Our objectives were to synthesize the existing empirical research and provide recommendations for future directions. We sought to find quantitative research that measured character, moral development, or moral behavior to be consistent with Lerner's PYD definition[4]. To identify character traits across different diseases, we utilized a non-categorical approach for childhood chronic illnesses.

MATERIALS AND METHODS

Search terms

The mesh search term was created by a librarian at Duke University Medical Center Library, combining words related to character development, chronic conditions, and childhood.

Character development: Positive youth development, character development, personality development, altruism, character, empathy, integrity, conscientiousness, courage, social values, virtues, emotional maturity, loyalty, moral, open-mindedness, sincerity

Chronic conditions: Diabetes, cancer, epilepsy, seizures, neoplasms, inflammatory bowel disease, crohns disease, ulcerative colitis, asthma, burns, headaches, cerebral palsy, deafness, blindness, hemophilia, celiac disease, migraine disorders, HIV, neurofibromatosis, sickle cell disease, anemia, obesity, congenital heart

Table 1 Definitions of the five C's of positive youth development[4]

PYD five C's	Definitions
Competence	Positive view of one's actions in domain specific areas including social, academic, cognitive, and vocational. Social competence pertains to interpersonal skills (*e.g.*, conflict resolution). Cognitive competence pertains to cognitive abilities (*e.g.*, decision making). School grades, attendance, and test scores are part of academic competence. Vocational competence involves work habits and career choice explorations
Confidence	An internal sense of overall positive self-worth and self-efficacy; one's global self-regard, as opposed to domain specific beliefs.
connection	Positive bonds with people and institutions that are reflected in bidirectional exchanges between the individual and peers, family, school, and community in which both parties contribute to the relationship
Character	Respect for societal and cultural rules, possession of standards for correct behaviors, a sense of right and wrong (morality), and integrity
Caring and compassion	A sense of sympathy and empathy for others

Table 2 Summary of studies measuring character development of youth with chronic conditions

Ref.	*n*	Subjects	Measures	Results
Sam *et al*[15]	15	Deaf Ages 12-15 yr	Kohlberg Moral Judgment Instrument	Moral reasoning for deaf participants was at a lower/basic stage of development compared to norms
Guse *et al*[13]	42	21 cancer survivors 21 healthy peers Matched on age, race, and gender Ages 12-19 yr (mean = 16 yr)	Values in Action Inventory for Youth	No difference in mean scores
Russell *et al*[14]	85	Burn survivors Ages 18-30 yr (mean = 21 yr)	Tennessee Self-Concept scale - Moral subscale	Scores on moral subscale lower than norms (P = 0.036). Subscale includes moral identity, satisfaction, and behavior

disease, cystic fibrosis, spina bifida, hemophilia, muscular dystrophy, chronic illness, chronic disease.

Childhood: Pediatric, adolescent, adolescence, teen, teenager, child, youth.

Data sources

The contents of the PubMed and PSYCHINFO databases were searched from inception through November 2013. References of relevant publications were also reviewed to identify additional titles. The searches were limited to English language publications with participants 13-24 years of age. The full search strategy is available from the corresponding author.

Study selection

Two reviewers independently reviewed all titles produced by the initial searches (n = 549) and excluded those that were definitively irrelevant to the search intent. Any titles which were insufficiently clear to make such a determination were retained for review at the abstract level. All of the remaining abstracts (n = 45) were then independently screened for the following inclusion criteria: (1) population of children or adolescents up to 21 years of age with a chronic condition; and (2) examined some aspect of character development. Those meeting the criteria were included in the study. Figure 1 provides a PRISMA flowchart depicting the number of publications included and excluded at each stage of review[12]. Biostatistics were not used for sampling purposes, summarization of the data, analysis, interpretation, or inference. The statistical methods of this study were reviewed by Sherika N Hill, PhD from Duke University and deemed appropriate for a systematic literature review.

RESULTS

Three studies were identified that met inclusion criteria and examined character development among participants with childhood-onset chronic conditions[13-15]. Two studies found lower scores indicative of character deficiencies for individuals with chronic conditions compared to normative samples while one study found adolescents with a chronic condition to be similar in character to healthy peers matched by age and sex[13-15]. All of the studies were prospective, observational, cross-sectional, survey-based, and informed by self-report. However, they differed in their designs (type of comparison group), methods (samples, recruitment, measures, survey administration), and analyses (statistical approaches).

The study findings are summarized in Table 2. The first study by Sam and Wright[15] (1988) examined moral reasoning among 15 deaf adolescents as compared to population norms using modified versions of dilemmas from Kohlberg's Moral Judgment Instrument. Deaf adolescents' moral reasoning was more basic (Stage 1 and 2 of the Pre-conventional Level) compared to advanced stages of reasoning (Stages 2, 3 or 4 of Conventional Level) of the referent group[15]. In the second study, Guse and Eracleous[13] (2011) compared responses to the Values in Action Inventory Classification of Character Strengths for Youth of 21 adolescent

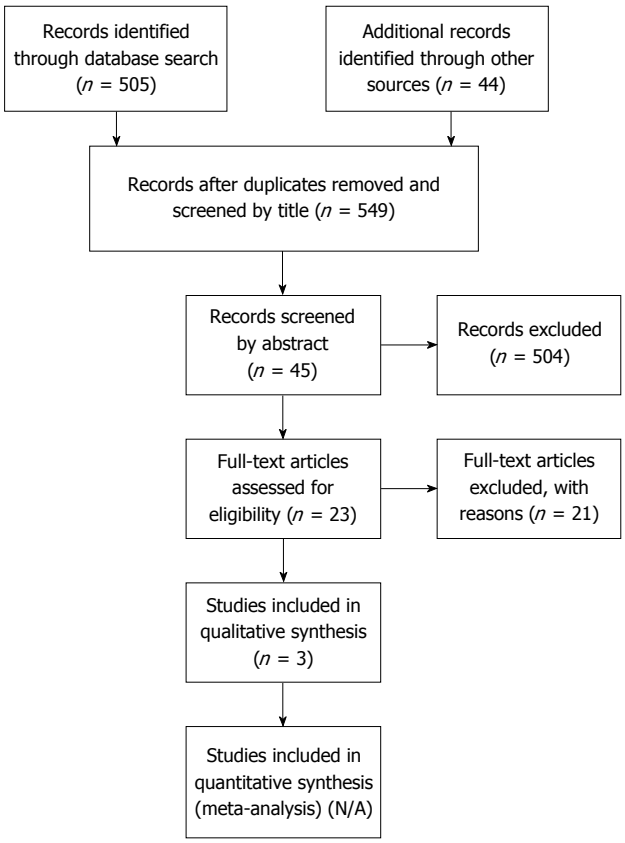

Figure 1 PRISMA flow diagram[12]. For search of PubMed and PSYCHINFO databases using mesh search terms for character development, chronic conditions, and childhood. N/A: Not applicable.

cancer survivors to healthy peers matched on age, sex and race/ethnicity[13]. There was no difference in scores between groups on the 5 character virtues and 15 character strengths tested. Russell *et al*[14] (2013) conducted a third study that examined moral self-concept among 82 young adults who were burn survivors from childhood using the Tennessee Self-Concept Scale 2nd edition. The burn survivors had a significantly lower score (P = 0.036) on the Moral Subscale compared to a reference population[14].

DISCUSSION

The emerging research on character development among youth with chronic medical conditions is too disparate to draw conclusions. There were only three studies that met our search criteria dating back to the inception of PubMed and PSYCHINFO. Each study used a different measure of character which did not overlap in how they operationalized moral themes. Further, the social context of the study participants varied greatly from young deaf adolescents, to Australian cancer survivors, to adult burn survivors. Lastly, study design limitations such as small convenience samples further limited generalizability. Consequently, the results from the studies neither supported nor contradicted one another in advancing our understanding of character development among youth with chronic conditions.

Nonetheless, future studies can learn from the strengths and weaknesses of the emerging evidence. To operationalize character, different measures of moral development were examined. The Kohlberg Moral Judgement Instrument ranked beliefs regarding social norms while the Values In Action Classification of Strength for Youth (VIA-Youth) tallied virtues pertaining to universal constructs of goodness and the Tennessee Self-Concept (TSC) Scale scored perceived self-control[13-15].

The Kohlberg Instrument proposes that there are stages of progressive moral reasoning that ascend from an egocentric to altruistic sense of fairness[16]. A key strength of this character assessment is that moral development is presented as a continuum that can evolve as an individual ages, matures, or have critical experiences. Accordingly, the tool would be useful to track changes in moral reasoning over time. Researchers should be cautious, however, in interpreting results. For one, it is not clear if a lower, basic stage of moral reasoning represents a character deficit, developmental delay, or a lack of life experience. Secondly, critics question whether youth can fully appreciate the relationship dynamics presented in scenarios that are: (1) purely fictional in nature; and (2) have mature themes such as spousal or parental love[17]. Thirdly, scholars argue that Kohlberg's instrument is gender-biased because the moral reasoning stages are derived from an all-male sample, resulting in lower scores for females[18]. Consequently, given that more than half of Sam and Wright subjects were female, sex differences instead of disease influences may offer a better explanation as to why deaf children had a lower stage of moral reasoning compared to instrument norms[15].

The VIA-Youth also has noteworthy merits and shortcomings to guide future research. The tool was designed to be comprehensive, gender-neutral, and cross-culturally relevant in testing universal themes of good character virtues and strengths[19]. These features make the evaluation ideal for diverse samples and questions regarding personality traits. As a trade-off, however, the self-administered survey requires keen self-awareness to accurately score 198 items and takes more than 30 min to complete. Researchers should be aware that these features could be challenging for adolescents. Case in point, one could argue that cancer survivors and healthy peers scored similarly on the VIA-Youth in the Guse and Eracleou study, selecting all mid-point responses for most items, because adolescents in general lack introspection skills as a result of their developmental stage or that respondents suffered from testing fatigue given the long, intensive survey[13,19,20].

The TSC Scale is less demanding on respondents and provides specific targets for intervention as key strengths[14]. Moral Self-Concept in the TSC is very

narrowly defined as personal satisfaction with one's self-control[14]. Accordingly, lower scores such as those reported by Russell *et al*[14] suggest that interventions could target either burn survivors' personal expectations or their internal self-regulation skills. A drawback to the TSC is that the instrument is not specific to adolescents. The reference population is 13-90 years old[14].

Collectively, the three studies highlight study design issues that should be addressed in future empirical studies. For instance, the study by Sam and Wright suggests that deaf children may experience a more pervasive form of isolation because of the specialized school environment[15]. To account for disease-specific influences, future studies should seek to have a healthy comparison group as well as comparison groups of different medical conditions. Moreover, future studies should choose sampling and analytical strategies a priori that either limit or control for systematic biases introduced by weakness in the study design and methods. Although Guse and Eracleous utilized a comparison group that was matched on age, sex, and race/ethnicity, they did not address the selection bias (*i.e.,* study subjects who selected/chose to participate in study were different from the general population) that resulted from using a convenience sampling approach[13]. Finally, future research should assess character changes within and between individuals from childhood to adulthood to identify aberrant developmental effects. In doing so, the study by Russell *et al*[14] would have been more informative in delineating whether the low satisfaction scores were attributable to the chronic medical condition or the challenging experience of transitioning to adulthood.

In conclusion, this literature review sets the stage for future studies of character development among adolescents with chronic illnesses. More empirical evidence is needed to inform interventions and provide a better understanding of how adversity affects character development during adolescence in general. Building character strengths broadly, and moral development specifically, is important to ensure that adolescents thrive as they transition into adulthood.

COMMENTS

Background

As more adolescents with chronic illness survive into adulthood, it is vital to understand how best to support their development into thriving adults; however, little is known about the Positive Youth Development (PYD) of these youth which focuses on the development of strengths in adolescence.

Research frontiers

The study of chronic illness in adolescence has been approached from many aspects of development including social development, emotional development, and cognitive development. Given the persistent health challenges among youth with chronic illnesses, a strong character is commonly acknowledged as an essential trait among this population. However, rigorous empirical research on character development among adolescents with chronic illnesses is in a nascent state.

Applications

Collectively, the three studies included in this review highlight study design issues that should be addressed in future empirical studies. To account for disease-specific influences, future studies should seek to have a healthy comparison group as well as comparison groups of different medical conditions. Moreover, future studies should choose sampling and analytical strategies a priori that either limit or control for systematic biases introduced by weakness in the study design and methods.

Terminology

Positive Youth Development - a strengths-based perspective regarding the development and positive growth of adolescents and young adults.

Peer-review

The author conducted a systematic review to find character strengths among youth with chronic illness, found that there was no empirical research regarding this area of study, and proposed how to design future studies on this research.

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Should dopamine be the first line inotrope in the treatment of neonatal hypotension? Review of the evidence

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Abstract

AIM: To determine if dopamine is effective in treating neonatal hypotension and safe to use comparing to other inotropes.

METHODS: This is a review of evidence on inotropic treatment of neonatal hypotension. Databases searched were MEDLINE and the Cochrane Library, a total of 134 studies were identified. Only studies with high quality evidence (level 1a and b and 2a) were included. After review, only eight studies were included in the final analysis. Pooled risk ratios derived for each outcome [Mantel-Haenzel (M-H) fixed effect] with CI, as reported in the Cochrane reviews were plotted in forest plot form.

RESULTS: Eight articles met inclusion criteria, which all included treatment in preterm infants. Dopamine increased mean arterial blood pressure (BP) (n = 163; r = 0.88, 95%CI: 0.76 to 0.94) and systolic BP (n = 142; r = 0.81, 95%CI: 0.42 to 0.94) comparing to placebo. Dopamine has been shown overall to be statistically more effective in increasing BP than dobutamine (n = 251, r = 0.26, 95%CI: 0.20-0.32). However there were no differences in short term outcomes (periventricular leucomalacia, periventricular haemorrhage) and mortality between both drugs. There is no statistical evidence of dopamine being more effective than adrenaline or corticosteroids. There was no difference in morbidity and mortality outcomes when dopamine was compared to hydrocortisone (RR 1.81, 95%CI: 0.18 to 18.39) or adrenaline.

CONCLUSION: In preterms, dopamine is the most studied drug, and we suggest it could be used as first line treatment in hypotension.

Key words: Hypotension; Preterm; Inotrope; Dopamine; Dobutamine; Adrenaline/epinephrine; Corticosteroids

Core tip: Hypotension is a common feature in the preterm infant. The aim of this systematic review was

to determine, after review of evidence, if dopamine would make a good first line drug therapy for hypotension in the neonatal population. Dopamine was shown across trials to increase blood pressure more effectively than dobutamine. There was no difference in morbidity and mortality outcomes when dopamine was compared to hydrocortisone or adrenaline. In preterm infants, dopamine is the most studied drug, and in general safer than others to use, we therefore cautiously suggest it could be used as first line treatment in hypotension.

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INTRODUCTION

Hypotension is a problem frequently encountered on the neonatal intensive care unit. It is more common in preterm infants. The prevalence is said to be up to 45% in infants with a birth weight < 1500 g[1]. Indeed, in preterm infants, organ development is still in process, and imposes challenges with fluid homeostasis[2]. Low blood pressure (BP) is also frequent in the sick term infant.

The main purpose of treating hypotension is to prevent end organ damage. Statistically, low BP is associated with short and long term adverse effects. In the extreme preterm, hypotension is associated with increased mortality, cerebral lesions[3], intraventricular haemorrhage[4], periventricular leucomalacia and neurodevelopmental morbidity[5].

BP equals flow multiplied by resistance, hence depends on the cardiac output and the vascular resistance[6,7]. In very low birth weight infants (VLBW), the aetiology of hypotension is unclear: Variable left ventricular output (LVO), a large patent ductus arteriosus (PDA), and myocardial dysfunction may contribute to low BP in this population. Volume depletion is not a common cause in preterm hypotension[8].

The normal physiological BP of a newborn infant remains unknown[9]. It is believed to vary with postnatal age and gestation[10]. Thus, the definition of hypotension is variable, but it seems like the most common one used by clinicians is the following: The mean arterial BP should be maintained at, or greater than the gestational age in weeks; this definition is based on statistics rather than physiology[9], and has been recommended by the British Association of Perinatal Medicine. This definition has also been used in numerous randomised control trials[11]. A borderline low BP below the number arrived at by using the gestational age does not necessarily require treatment, and it is up to the clinician's discretion to also evaluate end organ perfusion and decide on treatment. Furthermore, low mean arterial BP in sick preterm infants could compromise cerebral autoregulation. Cerebral autoregulation is essential because it ensures appropriate cerebral blood flow, which is one of the major determinants of oxygen delivery to the brain. The minimal BP required to maintain cerebral perfusion is unknown[8].

The choice of first line inotropic support has been dependent on clinicians. A homogeneous evidence-based treatment will benefit clinicians. This would allow health professionals to assess the problem further and consider next steps, whilst effectively treating hypotension in a safe way. By definition, a first line therapy should be effective, safe, and available. Dopamine is a precursor of noradrenaline, it is a hormone and neurotransmitter of the catecholamine and phenethylamine families. To increase BP, dopamine has a vasoconstrictive effect and may cause decreased blood supply and oxygen to certain organs. Dopamine effect is dose dependent[6] and acts on dopamine, alpha, and beta receptors; it also has a serotoninergic action[12].

The aim of this review is to determine, after appraisal of available evidence, if dopamine is effective in treating hypotension and safe to use compared to other inotropes, and therefore if dopamine would make a suitable first line drug therapy for hypotension in the neonatal population. Objective of this systematic review was to summarise all available high-level evidence comparing dopamine with other inotropes regarding effectiveness on hypotension, mortality, neurological outcome and adverse effects in the neonatal population.

MATERIALS AND METHODS

Definitions

For the purpose of this article, the definition of hypotension stated by the authors of reported studies included in this review has been used.

Data sources

Medline *via* Healthcare Database Advanced Search and the Cochrane Library were searched. Reference lists of articles identified were checked resulting in further articles retrieved. Articles from the personal libraries of the investigators were also included. Only published studies were included.

Search terms and strategies

The search was done in February 2015. The following MeSH terms were used: "Hypotension" (major), "Dopamine" (explode), "Dobutamine" (explode), "Hydrocortisone" (explode), "epinephrine" (explode), "norepinephrine" (explode). Results were limited to "Human" and "Age Group Newborn Infant birth to 1 mo".

The following results were obtained with Medline search:

Hypotension (Major) AND Dopamine (explode) - 56

Table 1 Levels of evidence, according to the oxford centre for evidence based medicine

Level of evidence	Type of study
1a	Systematic review (with homogeneity) of RCTs
1b	Individual RCT (with narrow confidence interval)
1c	All or none (when patients died before the treatment became available, and now some survive)
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT)
2c	"Outcomes" research, ecological studies
3a	SR (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

RCT: Randomized clinical trial.

results

Hypotension (Major) AND Dobutamine (explode) - 23 results

Hypotension (Major) AND Epinephrine (explode) - 16 results

Hypotension (Major) AND Norepinephrine (explode) - 3 results

Hypotension (Major) AND Hydrocortisone (explode) - 36 results

The search gave us a total of 134 articles. After the duplicates were removed, there were a total of 86 articles.

Study selection

All titles and abstracts were read by 2 independent reviewers. Inclusion criteria applied were: Levels of evidence 1a, 1b and 2a (Table 1). All abstracts were read and screened, and only the ones with a high level of evidence were kept. After this screening process, 22 studies were noted to be irrelevant to our question, and 56 did not qualify as level 1 or 2 evidence (16 observational studies, 10 review articles, 10 letters, 3 retrospective studies, 12 already included in Cochrane reviews, 4 case reports, 1 on-going randomised control trial) (For PRISMA flow chart of study selection, Figure 1).

Figures

Figures 2 and 3 were made using Excel version 14.0 (Microsoft Office 2011 for Mac). Pooled risk ratios derived for each outcome [Mantel-Haenzel (M-H) fixed effect] with CI, as reported in the Cochrane reviews were plotted in forest plot form. Straight mark scatter charts were used to make these figures. The aim was to give a good visual representation of key outcomes of the Cochrane reviews regarding hypotension.

RESULTS

Dopamine effect on BP

A recent meta-analysis by Sassano-Higgins *et al*[13] showed that dopamine increases BP significantly in the hypotensive preterm infant and that it has a greater efficacy than other forms of therapy. In this review, after looking at 26 studies, whether random or fixed effect meta-analysis, it was found that there was a significant association between administrating dopamine and treatment success. Dopamine increased mean arterial BP (12 studies; n = 163; r = 0.88, 95%CI: 0.76 to 0.94) and systolic BP (8 studies; n = 142; r = 0.81, 95%CI: 0.42 to 0.94). All the 12 studies were prospective case series without any controls examining the treatment success of dopamine.

Dopamine vs dobutamine

Dobutamine is a synthetic catecholamine which acts essentially on beta receptors, creating an adrenergic effect[14]. Dobutamine is the second most commonly used inotrope to treat hypotension in the preterm infant[15]; it is thought to have the same benefits as dopamine but without the peripheral vasoconstrictive effect[16].

Three articles containing trial data on a comparison of dopamine and dobutamine were identified.

The Cochrane review by Subhedar *et al*[16] compared dopamine and dobutamine. The main aims of this review were: Comparing the effectiveness of the treatment in reducing mortality and long-term outcomes (neurodevelopmental outcome at 2 years), in reducing the incidence of adverse neuroradiological sequelae (severe periventricular haemorrhage and/or periventricular leucomalacia), increasing systemic arterial BP and/or cardiac output, and to compare the frequency of adverse effects between both drugs. A total of 5 randomised control trials were included, with a total of 209 infants. Comparing dopamine *vs* dobutamine, there was neither a difference in mortality (RR 1.17, 95%CI: 0.47 to 2.92; RD 0.02, 95%CI: -0.12 to 0.16), nor in the incidence of periventricular leucomalacia (RR 0.43, 95%CI: 0.12 to 1.52; RD -0.08, 95%CI: -0.19 to 0.04), or in the incidence of grade 3 or 4 periventricular haemorrhages (RR 0.73, 95%CI: 0.15 to 3.50; RD - 0.02, 95%CI: -0.13 to 0.09), or in the incidence of tachycardia (RD -0.06, 95%CI: -0.25 to 0.14) (Figure 2). No studies looked at the long-term neurodevelopmental outcome. In treating hypotension, dopamine was more successful than dobutamine as evident from a significantly reduced risk of treatment failure (RR 0.41, 95%CI: 0.25 to 0.65). LVO was analysed in one paper[17] in the Cochrane review. Initially the raw numbers showed a drop in LVO with dopamine, compared to a rise in LVO with dobutamine. However the Cochrane review excluded this outcome from the analysis as the calculation of absolute changes was not possible. The authors concluded that dopamine was more effective than dobutamine in the short-term treatment of hypotension. As there were no statistical differences in long term outcomes and safety, no firm recommendations could be made.

The meta-analysis by Sassano-Higgins *et al*[13]

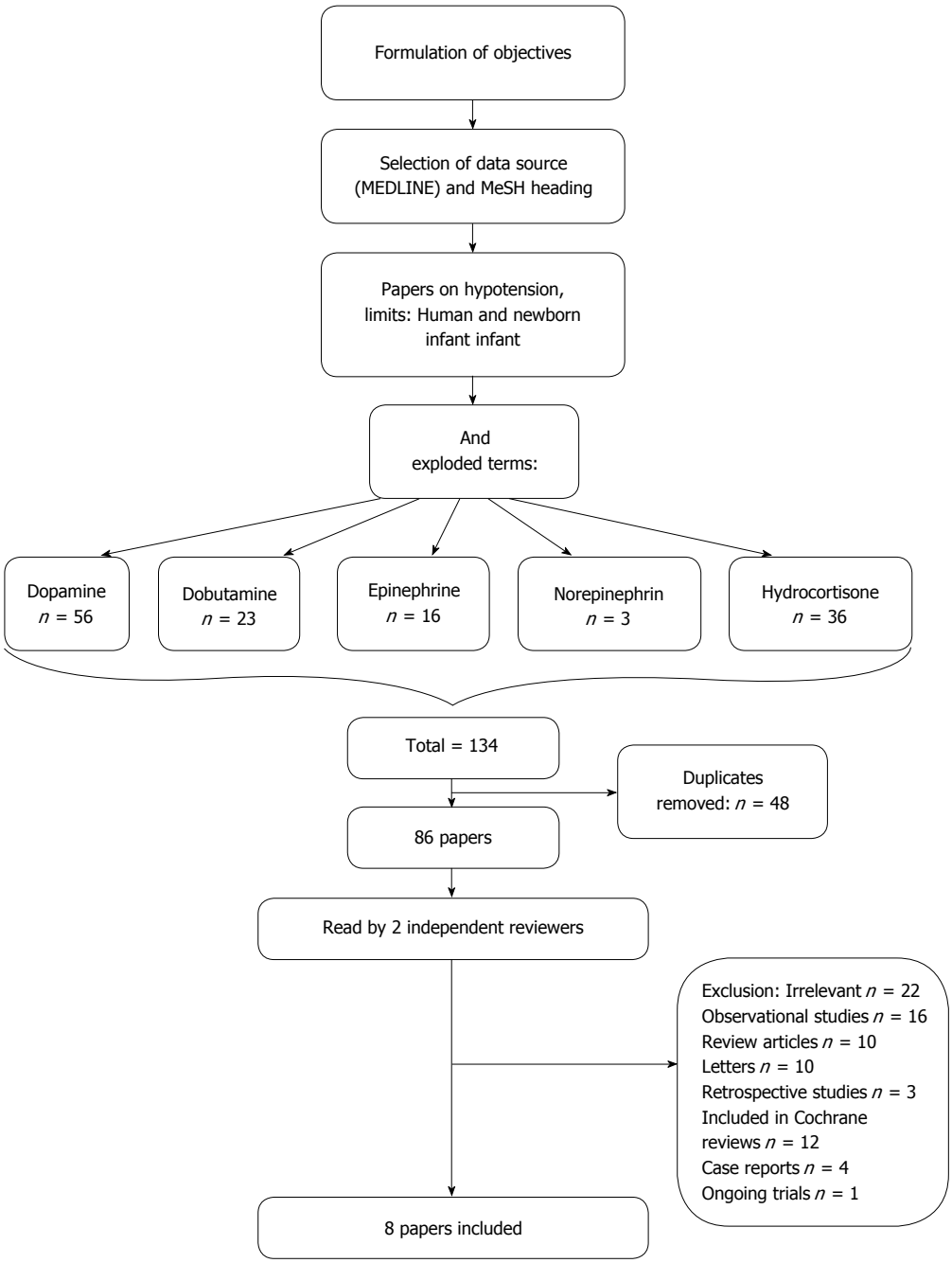

Figure 1 PRISMA flow chart of study selection comparing dopamine *vs* other inotropes in neonates.

mentioned in the above paragraph on dopamine and its effects on BP, contained a subgroup analysis where dopamine was compared with dobutamine. Dopamine administration was associated with a significantly greater overall efficacy for increase in BP than dobutamine (7 studies; *n* = 251; *r* = 0.26; 95%CI: 0.20 to 0.32). There were no statistically significant differences in adverse neurological outcomes between dopamine and dobutamine. This meta-analysis contained two additional studies in addition to the five studies included in the Cochrane review by Subhedar *et al*[16] (2003). The latter excluded the study by Miall-Allen *et al*[18] (1989) because it was a non-randomised study reporting the effect of addition of dobutamine in hypotensive preterm infants who did not respond to dopamine. Furthermore, it was a prospective case control study. Filippi *et al*[19]'s primary objective was endocrine effects of dopamine and dobutamine. This study did not meet the inclusion criteria for a Cochrane review. Short-term improvement in BP was analysed in the Cochrane review, looking at 4 articles with successful treatment of hypotension. Each article looked at individually, concluded in an increase of BP. A pooled estimate was not done regarding short-term effect on BP with both drugs in view of the variation in measuring and reporting BP in the included studies. However, in the meta-analysis[13], pooled analysis of the 7 studies (*n* = 251, *r* = 0.26, 95%CI: 0.20-0.32)

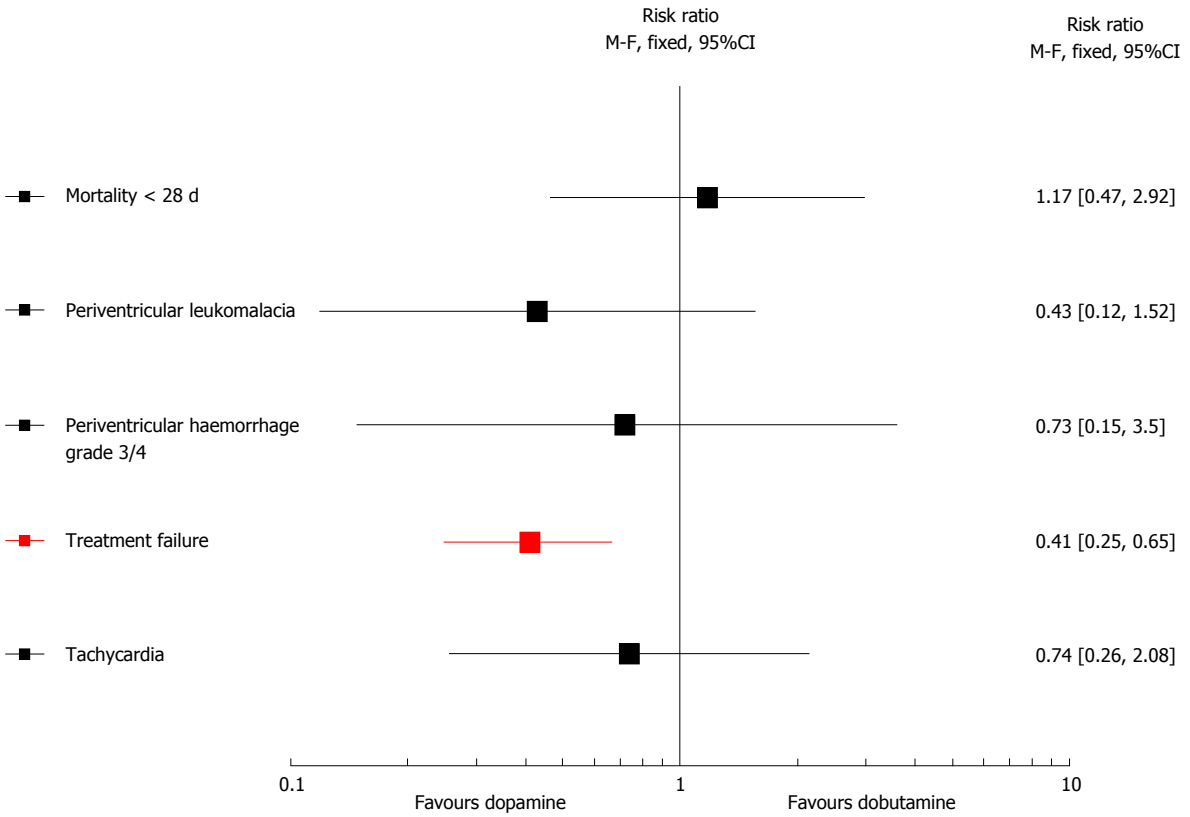

Figure 2 Outcomes of the Cochrane review comparing dopamine *vs* dobutamine in preterm infants.

showed that dopamine had a greater efficacy in increasing the BP compared to dobutamine.

However, dopamine is also thought to have endocrine adverse effects. Indeed exogenous dopamine infusion suppresses PRL, thyroid stimulating hormone (TSH) and T4 secretion by acting on specific dopamine D2 receptors[20]. It is believed that in preterm infants, unlike in adults, dopamine crosses the blood brain barrier and exerts its effects directly at the hypothalamic level as well as on the dopamine receptor trophic cells[21]. Filippi *et al*[19]'s study, which was not included in the Cochrane review, compared the endocrine effects between dopamine and dobutamine in VLBW, in a randomised prospective trial published in 2007. Thirty-five hypotensive infants were randomised into 2 groups, whether they received dopamine or dobutamine for hypotension after 2 boluses of crystalloid. In the group of infants treated with dopamine, levels of TSH, total thyroxine (T_4), prolactine (PRL), and growth hormone (GH) were significantly reduced after 12 h, comparing to the dobutamine group ($P < 0.01$). However after stopping dopamine, from the first day onwards, levels of TSH, T4 and PRL increased briskly. There was also a mild but non-significant increase in GH. Dobutamine did not affect hormone levels. The authors conclude that dopamine induces suppression of pituitary function, but it is a transient effect.

Dopamine vs adrenaline

Adrenaline [= Epinephrine (EP)] is a potent inotrope, and chronotrope, which acts on alpha and beta-receptors. It acts as a systemic and pulmonary vasodilator in low doses, and when doses are increased, it increases systemic pressure more than pulmonary pressure[22].

Three articles were identified comparing adrenaline and dopamine: Two randomised controlled trials and one Cochrane review.

In 2005, the randomised control trial by Valverde *et al*[23] compared 2 groups of preterm infants < 32 wk < 1501 g with low BP receiving either dopamine (DP) or adrenaline at increasing doses. Fifty-nine infants were included. The study was ongoing at the time of the Cochrane review; therefore it hasn't been completely included. Treatment success by obtaining an optimal BP was present in 96.3% of patients with dopamine and 93.7% with adrenaline; there was no statistical significance between these 2 groups. Amongst the primary outcomes, the only one that varied between the 2 groups was the heart rate. Indeed, the heart rate was increased in both dopamine and adrenaline groups [at time of obtaining optimal BP: 157 beats per minute (bpm) *vs* 169 bpm respectively], but was significantly higher in the adrenaline group ($P = 0.03$). There was no other statistically significant difference in the primary outcomes (systemic and cerebral haemodynamic variables) or secondary outcomes (acid-base status, blood lactate concentration, glycaemia, haematocrit) between both treatment groups. Cerebral blood volume (CBV), measured by

near infrared spectroscopy (NIRS), was analysed in both groups, and it was noted that drug-induced changes varied with gestational age. In very preterm infants < 28 wk, the EP- induced increase in CBV was greater than with dopamine. However, DP-induced increase in CBV was greater in less preterm infants (> 28 wk).

A randomised control trial in 2006 by Valverde *et al*[23] compared 2 groups of preterm infants < 1501 g and < 32 wk gestation, receiving either dopamine or adrenaline, and short and medium term outcomes were measured. This trial was not included in the Cochrane review from Paradisis *et al*[24]. The study was mentioned in the Cochrane review, but had only been published as an abstract for a meeting as the above study by Pellicer *et al*[25]. Looking into details of the study by Pellicer *et al*[25] and Valverde *et al*[23], the list of authors are identical but the order of the authors differs; the included cohort of infants is the same (period of inclusion, inclusion and exclusion criteria), however the primary outcomes are different as Pellicer looks more at cerebral haemodynamics, whereas Valverde analysed systemic effects and clinical outcomes. In Valverde's article, both groups were comparable, although randomisation technique was not explained. There was no difference in treatment failure in both groups (dopamine: 36%; epinephrine: 37%). Withdrawal occurred later in the dopamine group. Infants in the adrenaline group had higher lactates, higher blood sugars and lower base excesses ($P < 0.05$). There was no difference in medium term comorbidities (enteral nutrition tolerance, gastrointestinal complications, severity of lung disease, PDA, cerebral ultrasound diagnoses, retinopathy of prematurity) and mortality. Authors conclusion was that compared to dopamine, adrenaline had the same effect on BP, but also had transitory effects on lactate metabolism. As there is no further evidence to explain or confirm these side effects it is difficult to recommend adrenaline over dopamine as a first line therapy in treatment of hypotension for the preterm infant.

A Cochrane review in 2004[24], updated in 2009 but with no changes made to the conclusion, looked at the effectiveness and safety of adrenaline in comparison with no treatment and other inotropes (dopamine, dobutamine, noradrenaline, or isoprenaline). Only one study published in an abstract form comparing dopamine and adrenaline was included. It was a very selective group with infants only above 1750 grams. There was a significant increase in the BP in the adrenaline and the dopamine group, however the significance of the difference was not reported. Outcomes like mortality, neurodevelopment, and peri or intra ventricular haemorrhage were not reported. This Cochrane review concluded that there was not enough evidence to show an effect of adrenaline in preterm infants with cardiovascular compromise.

Dopamine vs steroids

Glucocorticoids increase vascular tone and myocardial contractility by increasing responsiveness to circulating catecholamines. In preterm infants, immaturity may also lead to limited adrenal reserves, being one the causes of low BP[26], therefore the use of steroids as treatment for hypotension is logical. In daily clinical practice, steroids are usually used for refractory hypotension. One Cochrane review analysed the effect of steroids in neonatal hypotension.

The population targeted is the preterm infant. Hydrocortisone is the most common steroid used in the treatment of neonatal hypotension.

The Cochrane review by Ibrahim *et al*[27] included, in addition to the comparison of corticosteroids *vs* placebo, also a comparison of steroids with dopamine. The primary objective was to investigate the effect of corticosteroids as a primary treatment of hypotension, and the secondary outcome was to look at benefits or adverse effects of steroid therapy (mortality, IVH grade 3 or 4, periventricular leukomalacia, chronic lung disease in surviving infants, necrotizing enterocolitis, bacterial sepsis). The population studied was all preterm infants < 37 wk and less than 28 d old with hypotension. A total of 4 studies were included. In this article, as the main focus is dopamine, therefore only the comparison of steroids and dopamine has been reviewed, which is based on one randomised controlled trial by Bourchier *et al*[28]. There was no statistically significant difference in effect of hydrocortisone on mortality comparing to dopamine (RR 1.81, 95%CI: 0.18 to 18.39; RD 0.04, 95%CI: -0.12 to 0.20), or on morbidities like infection comparing to dopamine (RR 0.60, 95%CI: 0.20 to 1.82; RD -0.13, 95%CI: -0.39 to 0.14), and hyperglycaemia comparing to dopamine (RR 1.27, 95%CI: 0.48 to 3.33; RD 0.07, 95%CI: -0.21 to 0.35) (Figure 3). Long-term neurodevelopmental outcome was not reported. Authors concluded that there was insufficient evidence to support routine use of corticosteroids as first line treatment of hypotension in preterm infants.

All inotropes

There was one high-level evidence paper comparing different inotropes: A systematic review by Dempsey *et al*[29] in 2007. One of the aims of the article was to compare the effectiveness of different inotropes. Pubmed search was performed looking for studies comparing 2 interventions, and seeking important clinical outcomes (survival, brain or lung injury, long-term neurodevelopmental outcome). Only randomised control trials in hypotensive preterm infants were included. This systematic review compared dopamine with other inotropes. In the comparison with dobutamine, only articles already included in Subhedar's Cochrane review were found, and concluded the same as above: Dopamine is more likely to increase BP than dobutamine. Four further studies were identified

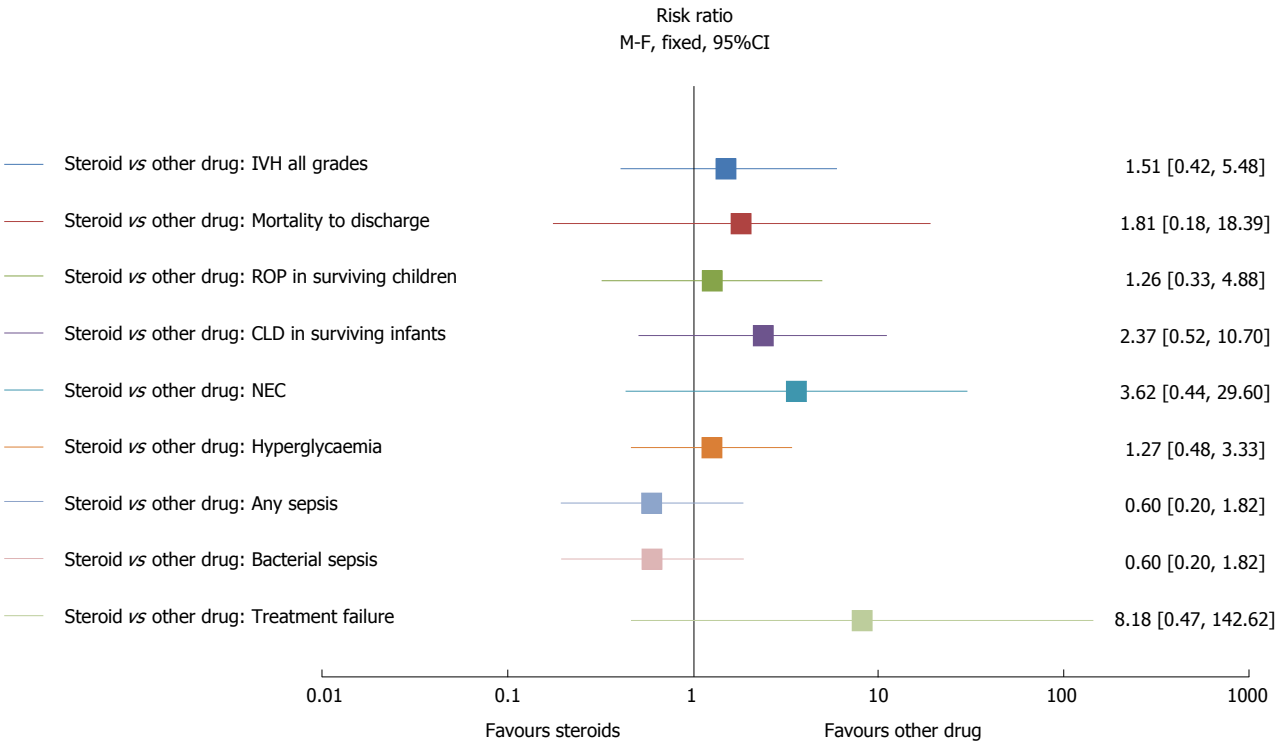

Figure 3 Outcomes of the Cochrane review comparing outcomes of steroids *vs* other drugs (only article included in the analysis compared dopamine to steroids).

comparing dopamine to other inotropes regarding blood flow, which was irrelevant to our question, but showed that dopamine decreased LVO. Some studies were identified reporting a comparison of dopamine and adrenaline, but there was little evidence to support the use of this drug according to this review (2 studies). The authors concluded that there are many small studies addressing short-term effects of various catecholamines on physiological variables, but that there is no evidence regarding clinically important outcomes.

DISCUSSION

Even though various inotropes are used, Dopamine still seems to be the one which is most commonly prescribed in hypotension in all infants, including VLBW infants[15]. We looked at the evidence supporting the usage of dopamine and summarized this in Table 2. In this review, we wanted to determine whether dopamine could be used as a first line therapy. By definition, a first line therapy should be effective, safe to use with minimal side effects and easily available. Having a standardised approach to hypotension would make practice more homogeneous; this has its advantages and inconveniences. A universal initial approach allows one to start treatment and then consider other options according to the underlying pathology. In treatment of hypotension, there is no evidence to support the use of volume expansion, whether saline, or albumin[30,31]. Dopamine has been shown overall to be statistically more effective in increasing BP and with less treatment failure than dobutamine[16], There is no statistical evidence of dopamine being more effective than adrenaline or corticosteroids. There were no papers of high evidence looking at treatment of hypotension with noradrenaline. Nevertheless, adrenaline has been shown to have more side effects than dopamine by increasing lactate, blood sugars, and lowering base excess[23]. There is not enough evidence regarding mid and long term outcomes to support the usage of hydrocortisone as a first line drug[27]. The meta-analysis by Higgins *et al*[32] showed that hydrocortisone successfully increases BP. This article was not included in our review, as it did not compare steroids to other inotropes. Antenatal steroids are believed to have a positive effect on low BP in the preterm infant[33].

Dopamine is more effective than dobutamine in increasing BP, but there was no statistical significance in the differences of other outcomes (mortality, periventricular flare, intraventricular haemorrhage grade 3-4, tachycardia)[16]. In the articles analysed, doses of dopamine used were not specified, but this drug was administered at a treatment dose for hypotension. This is important as low doses of dopamine (0.5-2 micrograms/kg per minute) act on dopaminergic receptors which usually increases renal perfusion. Medium doses (2-6 micrograms/kg per minute) act on beta-receptors causing vasodilatation and a positive inotropic and chronotropic effect (increasing output and heart rate). At high doses (> 6-10 micrograms/kg per minute), dopamine acts on alpha-receptors leading mainly to peripheral vasoconstriction[8]. In preterm infants there are

Table 2 Review of evidence

Ref.	Title of study	Study group	Study type (evidence)	Outcome	Key result	Comment
All inotropes						
Dempsey *et al*[29]	Treating hypotension in the preterm infant: When and with what: a critical and systematic review	Preterm infant	Critical systematic review	Which preterm may benefit from treatment and with what intervention	17 studies reviewed. No threshold BP that was predictive of a poor outcome. None of the interventions (volume expansion, catecholamines or steroids) for hypotensive infants improved the outcome	Not able to comment which inotropes were beneficial
Dopamine						
Sassano-Higgins *et al*[13]	A meta-analysis of dopamine use in hypotensive preterm infants: Blood pressure and cerebral hemodynamics	Preterm infants	Meta analysis	Dopamine effect on Hypotension CNS injury	Dopamine increases mean arterial blood pressure (12 studies; n = 163; r = 0.88, 95%CI: 0.76 to 0.94) and systolic blood pressure (8 studies; n = 142; r = 0.81, 95%CI: 0.42 to 0.94). Dopamine administration was associated with a significantly greater overall efficacy for increase in BP than dobutamine (7 studies; n = 251; r = 0.26; 95%CI: 0.20 to 0.32), colloid (2 studies; n = 67; r = 0.60; 95%CI: 0.41 to 0.74) and hydrocortisone (1 study; n = 28; r = 0.40; 95%CI: 0.034 to 0.67); There were no statistically significant differences in adverse neurological outcomes between dopamine and dobutamine	Dopamine is more effective than dobutamine, colloid or hydrocortisone alone. No increased incidence of adverse effects compared to other therapies
Dopamine and dobutamine						
Subhedar *et al*[16]	Dopamine *vs* dobutamine for hypotensive preterm infants	Preterm infant	Cochrane review	Effectiveness and safety of dopamine and dobutamine in the treatment of systemic hypotension	5 trials = 209 infants. Fewer infants having treatment failure of hypotension with dopamine than dobutamine (RD -0.23, 95%CI: -0.34 to -0.13; NNT = 4.4, 95%CI: 2.9 to 7.7). No evidence of a significant difference in neonatal mortality between dopamine and dobutamine (RD 0.02, 95%CI: -0.12 to 0.16), incidence of periventricular leukomalacia (RD -0.08, 95%CI: -0.19 to 0.04), or severe periventricular haemorrhage (RD -0.02, 95%CI: -0.13 to 0.09), or incidence of tachycardia (RD -0.06, 95%CI: -0.25 to 0.14)	Dopamine is more effective than dobutamine in the short term treatment, none of the studies reported the incidence of adverse long term neurodevelopmental outcomes
Filippi *et al*[19]	Dopamine *vs* dobutamine in very low birthweight infants: Endocrine effects	VLBW	Prospective RCT (non-blinded)	Endocrine effects of dopamine and dobutamine in hypotensive VLBW	Suppression of TSH, T(4) and PRL was observed in dopamine-treated newborns from 12 h of treatment onwards, whereas levels of growth hormone reduced significantly only at 12 h and 36 h of treatment (P < 0.01). TSH, T(4) and PRL rebound was observed from the first day onwards after stopping dopamine. Dobutamine administration did not alter the profile of any of the hormones and no rebound was observed after stopping treatment	Dopamine induced a transient pituitary suppression, comparing to dobutamine. But this is totally reversible
Dopamine and adrenaline						
Pellicer *et al*[25]	Cardiovascular support for low birth weight infants and cerebral hemodynamics: A randomized, blinded, clinical trial	LBW	RCT double blinded	Quantitative changes in cerebral concentrations of oxyhemoglobin and deoxyhemoglobin, cerebral intravascular oxygenation (HbD), and cerebral blood volume	Among hypotensive LBW infants, cardiovascular support with low/moderate-DP or low-dose EP increased cerebral perfusion. Low-dose EP was as effective as low/moderate-dose DP in increasing MBP among LBW infants. Heart rate was higher in the EP group than in the DP group (respectively 167 *vs* 159 when optimal BP was obtained)	Low-dose EP was as effective as low/moderate-dose DP in increasing MBP among LBW infants. EP led to a higher heart rate than DP

Valverde *et al*[23]	Dopamine *vs* epinephrine for cardiovascular support in low birth weight infants: Analysis of systemic effects and neonatal clinical outcomes	LBW	RCT	Short-term changes in heart rate, mean BP, acid-base status, lactate, glycemia, urine output, and fluid-carbohydrate Debit. Medium-term morbidity, enteral nutrition tolerance, gastrointestinal complications, severity of lung disease, patent ductus arteriosus, cerebral ultrasound diagnoses, retinopathy of prematurity, and mortality	Mean blood pressure showed a significant increase from baseline throughout the first 96 h with no differences between groups (dopamine: 36%; epinephrine: 37%). However, epinephrine produced a greater increase in heart rate than dopamine. After treatment began, epinephrine patients showed higher plasma lactate (first 36 h) and lower bicarbonate and base excess (first 6 h) and received more bicarbonate, and had higher blood glucose levels ($P < 0.05$). For medium-term morbidity, there were no differences in neonatal clinical outcomes in responders	Transitory adverse effects of epinephrine on carbohydrate and lactate metabolism could undermine the use of epinephrine as a first-line inotrope in preterm infants who are prone to such metabolic disturbances
Paradisis *et al*[24] (2004, reviewed in 2009)	Adrenaline for prevention of morbidity and mortality in preterm infants with cardiovascular compromise	Preterm infant	Cochrane review	Effectiveness and safety of adrenaline compared to no treatment or other inotropes in reducing mortality and morbidity in preterm infants with cardiovascular compromise	One trial comparing adrenaline with dopamine infusion was included. It enrolled hypotensive, predominantly preterm infants in the first 24 h. Only infants > 1750 g are included in this review. Both adrenaline and dopamine significantly increased heart rate and mean BP, with no statistically significant effect on left or right ventricular outputs. No significant difference was reported between the 2 inotropes	The study was reported as being randomised and double blinded, but methods were not reported. Published abstract, side effects and safety were not reported
Dopamine and steroids						
Ibrahim *et al*[27]	Corticosteroids for treating hypotension in preterm infants	Preterm infant	Cochrane review	Effectiveness and safety of corticosteroids used either as primary treatment of hypotension or for the treatment of refractory hypotension	4 studies were included in this review enrolling a total of 123 babies. In one study, persistent hypotension was more common in hydrocortisone treated infants as compared to those who received dopamine as primary treatment for hypotension (RR 8.2, 95%CI: 0.47 to 142.6; RD 0.19, 95%CI: 0.01 to 0.37). There were no statistically significant effects on any other short or long-term outcome	Long term benefit or safety data is lacking with steroids

DP: Dose dopamine; EP: Epinephrine; RCT: Randomized clinical trial; LBW: Low birth weight; VLBW: Very low birth weight; TSH: Thyroid stimulating hormone.

differences in receptor maturation depending on the gestation. Hence there is a vasoconstrictive effect in preterms even if dopamine is used at medium doses[34].

On a short term scale, dopamine induces transient and reversible pituitary suppression, however despite this endocrine effect, there is no clinical implication on the infant: Comparing to dobutamine there were no changes with regards to the heart rate, oxygen requirement, fluid intake and mean urine output[19]. However, even though there was significantly decreased, but reversible levels of TSH, T4, and PRL, the long term outcome of this transient suppression remain unknown[19]. In the Cochrane review by Subhedar *et al*[16], the effects of dopamine and dobutamine on the left ventricular outflow could not be compared in view of unpublished raw data, yet in a non statistical approach, it seems that dobutamine had more effect on increasing left ventricular outflow.

It is also important to remember the physiological effect of these drugs: Dopamine has a vasoconstrictive effect when acting on the alpha-receptors[6]. Peripheral vasoconstriction by definition will increase systemic BP, but it will also reduce the flow and oxygenation, potentially leading to hypoperfusion in organs such as the brain, the kidneys and the skin[35]. The underlying cause and pathophysiology of decreased BP is essential to take into consideration when treating. Thus it is important to consider different agents in specific situations such as volume deficiency, cardiac failure, sepsis or adrenal insufficiency.

This review was initially aimed at all infants admitted to the neonatal unit, however all evidence points towards the use of inotropes in the preterm infants, therefore the recommendations from this article are aimed at preterm infants with initial hypotension. Therefore, individual treatment for specific conditions was not addressed in this review. Another limitation is that only papers published with high levels of scientific evidence, in the top of the evidence pyramid, have been analysed. Additionally, the literature collected did not focus on direct long-term side effects of the drugs (such as direct effects on brain perfusion and development), independently from their effects on BP.

Other than the above-mentioned inotropes, there are some new drugs such as Milrinone, which is an inotrope/vasodilator and phosphodiesterase inhibitor, and mainly used post cardiac surgery to improve cardiac output. It inhibits an enzyme, which results in an accumulation in cyclic adenosine monophosphate increasing cardiac muscle

contractility, and relaxation of the smooth vascular muscle allowing treatment of pulmonary hypertension. Side effects include arrhythmias[36]. Other drugs like levosimendran and terlipressin, have inotropic effects, but there is not enough evidence in the preterm to promote their usage.

The current practice of treating hypotension concentrates on improving the number of the BP, but one may argue it is important to consider the blood flow as well. This idea emerged in 1928 from Jarisch "It is a source of regret that measurement of flow is much more difficult than measurement of pressure. This has led to an undue interest in BP measurements. Most organs however, require flow rather than pressure[37]". There are current studies looking at the flow, and the effect in the management of low BP by inotropes: Neocirculation is looking at the effect of dobutamine on the superior vena cava flow[38], and the TOHOP study looking at NIRS for objective end organ perfusion as an adjunct to management of hypotension[39]. Controversially, other trials are looking at whether hypotension needs to be treated in the initial period of life of a preterm infant; the concept of permissive hypotension is becoming more common. Even though it is known that low BP in a preterm infant is associated with adverse outcomes, it remains unknown whether treatment of hypotension improves the outcome. The on-going HIP trial is aiming to determine whether there is a difference in short and long-term outcome in preterm infants in managing hypotension with volume and dopamine *vs* a permissive placebo approach[11].

In this review, we are only able to comment on preterm infants. Term infants usually have multiple aetiologies for hypotension like hypovolaemia, cardiogenic shock, septic shock, endocrine causes like congenital adrenal hyperplasia, sedation drugs[40], and there have been no studies with high levels of evidence which have compared various inotropes in a term infant.

In preterm infants, dopamine is the most studied drug, is more effective in increasing BP than dobutamine. There was no difference in morbidity and mortality outcomes when dopamine was compared to hydrocortisone or adrenaline. In preterm infants, dopamine is effective, and in general safer than others to use. All evidence points towards the fact that dopamine can be considered as a first line inotrope in preterm neonatal hypotension.

COMMENTS

Background

Different inotropes are used in the treatment of neonatal hypotension. Clinicians have their own preferences in using particular inotropes as a first line, depending on the unit policy and their previous personal experience.

Research frontiers

Controversies exist on the best initial approach of what inotrope to use in the management of neonatal hypotension. There are new studies investigating the necessity of inotropic support and increasing blood pressure.

Innovations and breakthroughs

This study reviewed current evidence on different inotropes commonly used, and concluded that dopamine is a safe and effective option for the treatment of neonatal hypotension.

Applications

Hypotension in the neonatal population, specially in preterm infants, is a common problem faced daily by clinicians. Having an evidence-based approach is in the best clinical interest of the patients.

Terminology

Cerebral autoregulation: Process which aims to maintain adequate and stable cerebral blood flow; Periventricular leucomalacia: White brain matter injury characterized by necrosis of white matter near the lateral ventricles; Preterm: Birth of a baby at less than 37 wk of gestation.

Peer-review

This is a nice systematic review providing good insight into commonly used inotropic agents in neonatal care, focusing on preterm infants.

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Adenomyomatosis of the gallbladder in childhood: A systematic review of the literature and an additional case report

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Abstract

AIM: To investigate the diagnostic and therapeutic assessment in children with adenomyomatosis of the gallbladder (AMG).

METHODS: AMG is a degenerative disease characterized by a proliferation of the mucosal epithelium which deeply invaginates and extends into the thickened muscular layer of the gallbladder, causing intramural diverticula. Although AMG is found in up to 5% of cholecystectomy specimens in adult populations, this condition in childhood is extremely uncommon. Authors provide a detailed systematic review of the pediatric literature according to PRISMA guidelines, focusing on diagnostic and therapeutic assessment. An additional case of AMG is also presented.

RESULTS: Five studies were finally enclosed, encompassing 5 children with AMG. Analysis was extended to our additional 11-year-old patient, who presented diffuse AMG and pancreatic acinar metaplasia

of the gallbladder mucosa and was successfully managed with laparoscopic cholecystectomy. Mean age at presentation was 7.2 years. Unspecific abdominal pain was the commonest symptom. Abdominal ultrasound was performed on all patients, with a diagnostic accuracy of 100%. Five patients underwent cholecystectomy, and at follow-up were asymptomatic. In the remaining patient, completely asymptomatic at diagnosis, a conservative approach with monthly monitoring *via* ultrasonography was undertaken.

CONCLUSION: Considering the remote but possible degeneration leading to cancer and the feasibility of laparoscopic cholecystectomy even in small children, evidence suggests that elective laparoscopic cholecystectomy represent the treatment of choice. Preoperative evaluation of the extrahepatic biliary tree anatomy with cholangio-MRI is strongly recommended.

Key words: Adenomyomatosis; Children; Gallbladder; Laparoscopy; Ultrasound

Core tip: Adenomyomatosis of the gallbladder (AMG) in childhood is an extremely rare condition, with only few cases reported so far. We provided a detailed systematic review on diagnostic and therapeutic assessment of children with AMG.

Parolini F, Indolfi G, Magne MG, Salemme M, Cheli M, Boroni G, Alberti D. Adenomyomatosis of the gallbladder in childhood: A systematic review of the literature and an additional case report. *World J Clin Pediatr* 2016; 5(2): 223-227 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i2/223.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i2.223

INTRODUCTION

Adenomyomatosis of the gallbladder (AMG) is a degenerative and acquired disease characterized by a localized or diffuse proliferation of the mucosal epithelium which deeply invaginates and extends into the thickened muscular layer of the gallbladder[1-3]. Although AMG is found in up to 5% of cholecystectomy specimens in adult populations, this condition in childhood is extremely rare, with only few cases reported so far. Clinical presentation of AMG in childhood is non-specific, with most patients complaining of abdominal pain. The diagnosis is generally based on imaging and the suspicion of AMG is usually raised by ultrasounds (US). Focusing on diagnostic and therapeutic assessment, a detailed systematic review of AMG in child populations is also provided. We present an additional case of diffuse AMG and pancreatic acinar metaplasia (PAM) of the gallbladder mucosa in an 11-year-old boy, successfully managed with laparoscopic cholecystectomy.

Case presentation

An 11-year-old boy was referred to our Emergnecy department with a one-year history of sporadic post-prandial abdominal pain, non-bilious vomiting and nausea. HCV-related hepatitis and pancreatic adenocarcinoma occurred respectively in the child's father and grandfather. Physical examination upon admission was unremarkable. Blood tests only showed augmentation (2 × *n*) of seric gamma-glutamyl transferase (GGT). Abdominal US revealed diffuse thickening of the gallbladder, with multiple anechogenic nodular areas mainly localized in the fundus and in the body, highly suspected for adenomyomatosis. Magnetic resonance imaging (MRI) confirmed the thickening of the gallbladder and the presence of multiple endoluminal irregular filling-defects (the largest over 13 mm) with enhancement using a contrast dye. A tortuous cystic duct with an increased calibre (5 mm) was also evident (Figure 1). Standard laparoscopic cholecystectomy was programmed. Whilst waiting for surgery, ursodeoxycholic acid was administered orally at a dosage of 15 mg/kg per day. Full informant consent was obtained from the child's parents before all stages of the procedures. The laparoscopic cholecystectomy procedure went smoothly. The excised gallbladder measured 7 cm × 2 cm. Pathological examination confirmed the diagnosis of chronic hyperplastic cholecystitis with diffuse adenomyomatosis and foci of PAM (Figure 2). The postoperative recovery was uneventful. At a 28-mo follow-up the child is doing well and is completely asymptomatic.

MATERIALS AND METHODS

Data sources and extraction

This systematic review was performed according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[4]. The PubMed database was searched for original studies on AMG published since 1990, involving patients younger than 18 years of age. Eligible study designs were case report, case series and review. We omitted reports in which abstracts indicated that they were on adult population (> 18 years) and they not reported the methods of diagnosis and treatment. We then evaluated the full text of the selecte articles. The date of the last search was January 2016. For each study, data were extracted for sex and age at presentation, clinical presentation, diagnostic assessment, treatment, pathological examination and outcome.

RESULTS

The PubMed search yielded 5 potentially relevant studies[1-3,5,6], involving a total of 5 children with AMG (Table 1). All selected studies were case reports (class

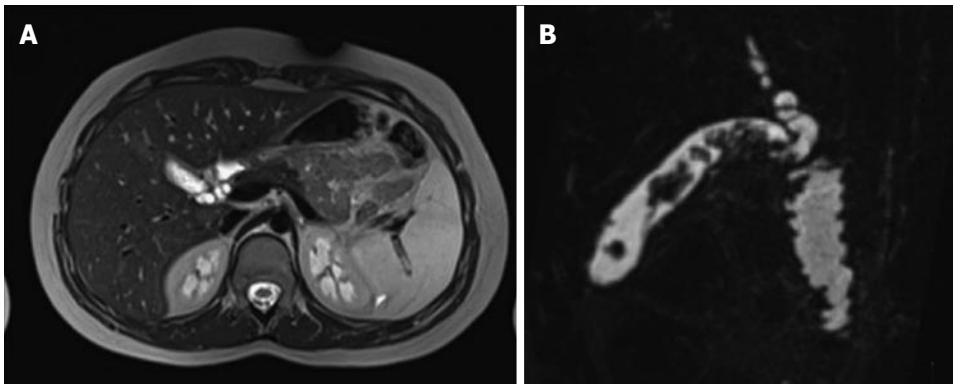

Figure 1 T2-weighted magnetic resonance imaging images confirming the irregular and diffuse thickening of gallbladder walls, more prominent in the body and in the fundus, suggestive of diffuse adenomyomatosis of the gallbladder (A and B). Nodular images with intraluminal protrusion were localized in the fundus and in the body of the gallbladder.

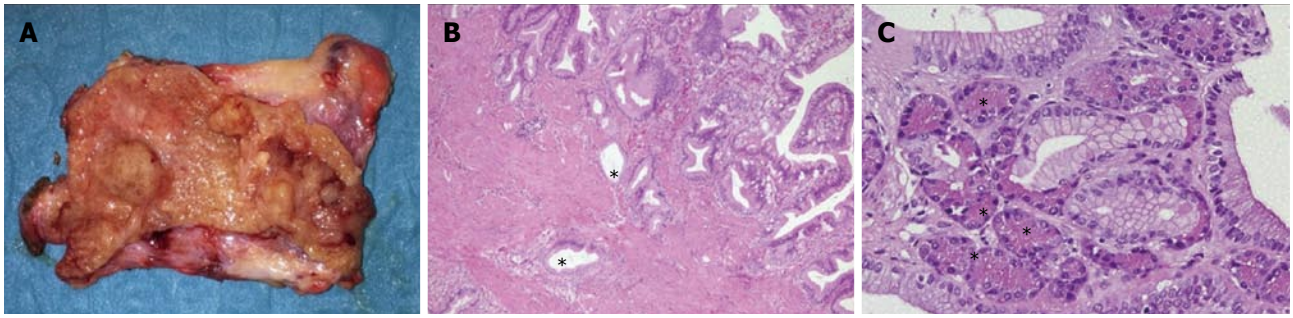

Figure 2 Intraoperative picture. A: Gallbladder specimen of 7 cm × 2 cm; B: Pathological examination showing the invagination of the gland (asterisks) into the muscular layer of the gallbladder, with the presence of glandular elements in the outer layers of the organ (hematoxilin-eosin, original magnification 4 ×); C: Heterotopic pancreatic glands (asterisks) in the context of the mucosal layer of the gallbladder (hematoxilin-eosin, original magnification 20 ×).

of evidence Ⅲ and rating scale of evidence E)[4].

Analysis was extended to our additional patient. The condition was more common in boys (67%), with a mean and median age at presentation of 7.2 years (SD + 3.1) and 6.0 years (range 4 mo-11 years), respectively (Table 1). Unspecific abdominal pain was the commonest symptom, occurring in 3 patients, while acute abdominal pain was reported in 2 patients. The remaining patient was an asymptomatic 4-mo-old girl with Beckwith-Wiedemann syndrome in whom AMG was accidentally discovered during abdominal US[5]. Besides abdominal pain, vomiting was present in 2 out of the 6 patients. Abdominal US was performed on all patients, with a diagnostic accuracy of 100%. None of the patients of the series presented gallstones or biliary sludge. Additional diagnostic examinations were performed on 4 patients, including MRI (3 patients), percutaneous transhepatic cholecystocholangiograhy (PTC) (1 patient), and Technetium 99m HIDA scan in (1 patient). Five out of the six patients underwent cholecystectomy (open procedure in 3 and laparoscopic in 2). AMG was diffuse in three patients, localized in 2 and segmental (annular) in the remaining child. At follow-up, all patients who underwent surgery were asymptomatic. In the remaining patient, completely asymptomatic at diagnosis, a conservative approach with monthly monitoring *via* ultrasonography was undertaken.

DISCUSSION

Epidemiology

Hyperplastic cholecystosis includes two types of mucosal abnormalities of the gallbladder which are usually clinical accidental findings at the time of a cholecystectomy: Cholesterolosis and adenomyomatosis[1-3]. Cholesterolosis is defined by mucosal villous hyperplasia, accumulation of cholesterol within epithelial layer; AMG is a hyperplastic lesion characterized by thickening of the muscle wall, overgrowth of the mucosa, and multiple intramural mucosal diverticula[7]. Although AMG is found in up to 5% of cholecystectomy specimens in adult populations[8], its occurrence in pediatric setting is extremely uncommon, and only five cases have been previously reported. The widespread and early use of US in pediatrics, either for recurrent or chronic abdominal pain or for other reasons, most probably will lead to emergent diagnosis, reinforcing the theory that implies that most patients with AMG might not be diagnosed until adulthood due to the absence or presence of only unspecific symptoms prior to the development of gallstones and/or cholecystitis[1-3].

Table 1 Systematic review of adenomyomatosis of the gallbladder in childhood

Ref.	Age	Sex	Clinical presentation	US findings	Additional imaging	Type	Treatment
Alberti *et al*[1]	5 yr	Male	Unspecific abdominal pain	Echogenic nodule next to the neck of gallbladder	Technetium 99m HIDA, PTC	Localized	Laparoscopic cholecystectomy
Cetinkursun *et al*[2]	6 yr	Male	Acute abdominal pain, fever and bilious vomiting	Small and multiseptated gallbladder with thickened wall	MRI	Diffuse	Open cholecystectomy
Zani *et al*[6]	5 yr	Male	Unspecific abdominal pain	Multiseptated gallbladder within the lumen	NA	Segmental (annular type)	Open cholecystectomy
Akçam *et al*[3]	9 yr	Female	Unspecific abdominal pain	Thickening of the wall of the gallbladder with echogenic areas parallel to the wall of gallbladder	MRI	Diffuse (honeycomb)	Open cholecystectomy
Zarate *et al*[5]	4 mo	Female	Incidental finding in Beckwith-Wiedemanns	Echoic foci within gallbladder wall	None	Localized	Observation
Our case	11 yr	Male	Acute abdominal pain, nausea, non-bilious vomiting	Thickening of the wall, multiple polypoid formations	MRI	Diffuse	Laparoscopic cholecystectomy

Hyperlink: http://dx.doi.org/10.3348/kjr.2003.4.2.85. MRI: Magnetic resonance imaging; US: Ultrasound scan; PTC: Percutaneous trans-hepatic cholecystocholangiography; NA: Not available data.

Etiopathogenesis and classification

The etiology of AMG still remains unclear: Co-morbidities that increase the formation of gallstones, such as congenital abnormalities of the biliary tract, hemolytic disease, total parenteral nutrition, chronic inflammatory bowel disease and obesity have been reported in adult AMG patients[1-3,8]. However, these conditions were not observed in this pediatric series. Nowadays AMG is considered a degenerative disease rather than a congenital malformation[1-3,8]. The first noticeable stage of the disease is most probably related to increased gallbladder intraluminal pressure caused by abnormalities of muscle contraction or to excessive mural absorption of bile, leading to hyperproliferation of the epithelial cells of the gallbladder mucosa and to hyperplasia of the smooth muscle[9]. As a consequence of this excessive proliferation, the epithelia invaginates into the hypertrophic muscular layer of the gallbladder forming intramural diverticula known as Rokitanski-Ashoff sinuses, that may fill with bile, biliary sludge and/or gallstone[9]. This condition is morphologically classified into three types: Generalized (or diffuse), localized (usually a single nodule in the fundus that projects into the lumen showing a polyp image at US, called "adenomyoma") and segmental (annular type with an "hourglass" configuration of the gallbladder, due to the transverse congenital septum in the body of gallbladder)[1-4,8].

In the past, attention has been drawn to the potential malignant degeneration of AMG, as different adult series have described an incidence of up to 6.4% of gallbladder cancer developing in patients with segmental AMG[2,10,11]. Nevertheless, the question whether AMG should be considered a pre-malignant lesion is still unanswered, and the risk of gallbladder cancer in patients with adenomyomatosis has not been clearly understood[3,8,11]. Also, the presence of PAM in the gallbladder, as observed in our patient, should be considered as an accidental finding unrelated to clinical or histological abnormalities, as PAM is commonly reported in other sites (gastroesophageal junction, stomach) with no clinical significance[12].

Clinical presentation and diagnostic assessment

Clinical signs and symptoms, when present, are similar to those of chronic gallbladder disease, which in childhood usually appear with a variety of atypical symptoms differing from the typical right upper quadrant pain[1-3,5,6,8,13]. Interestingly, if AMG in adults is associated with gallstones in up to 91.7% of the cases, gallstones or biliary sludge were not reported in this series[11]. Radiological diagnosis of AMG is easy and US is considered the most sensitive and specific imaging method for diagnosis[1]. AMG US findings include: Rokitansky-Aschoff sinuses, which can be found either as anechogenic (bile filled) or as echogenic foci (biliary sludge or gallstone filled), gallbladder wall thickening, US findings of ring down artifacts (Comet Tail) as a result of reverberation between the sinuses themselves, intrasinus papillary projections and polypoidal projections of at least 10 mm length[1,6]. Due to variation in morphology, adenomyomatosis can appear as diffuse gallbladder wall thickening or as focal lesions, simulating gallbladder carcinoma[2]. Additional diagnostic assessment with cholangio-RMN should be performed before surgery in order to obtain a detailed map of the extrahepatic biliary tract, as major variations and anomalies of the biliary tree have been found in up to 18% of cases and these anomalies must be identified to prevent severe lesions to the common bile duct[14]. In particular, MRI T2-weighted sequences are reported to be superior to other sequences in order to visualize the Rokitansky-Aschoff sinuses[8,9]. Diffuse-type AMG typically shows an early mucosal enhancement with subsequent serosal enhancement. On the contrary, localized AMG exhibits homogeneous enhancement, showing continuity with the surrounding gallbladder epithelium[8,9]. Furthermore, cholangio-MRI can detect stones into the choledocus[1,2,6].

Therapeutic options

The evidence regarding current management of AMG in children is poor. Whilst, in case of symptomatic patients, the need for surgery is obvious, management of asymptomatic children is still debated[5]. Considering the remote but possible degeneration leading to cancer and the feasibility of laparoscopic cholecystectomy even in small children[1,11], conservative treatment and ultrasonographic monitoring should be reserved only to patient subsets with clear contraindications to surgery. In contrast, evidence suggest that elective laparoscopic cholecystectomy represents the treatment of choice for children as well as adults. Pre-operative evaluation of the extrahepatic biliary tree anatomy with cholangio-MRI is strongly recommended.

COMMENTS

Background

Adenomyomatosis of the gallbladder (AMG) is a degenerative disease characterized by a proliferation of the mucosal epithelium which deeply invaginates and extends into the thickened muscular layer of the gallbladder, causing intramural diverticula. Although AMG is found in up to 5% of cholecystectomy specimens in adult populations, this condition in childhood is extremely rare, with only few cases reported so far.

Research frontiers

Although AMG is found in up to 5% of cholecystectomy specimens in adult populations, this condition in childhood is extremely rare, with only few cases reported so far.

Innovations and breakthroughs

Authors provide a detailed systematic review of the pediatric literature on AMG. An additional case of AMG is also presented.

Applications

This systematical review focus on diagnostic and therapeutic assessment of AMG in childhood.

Terminology

Hyperplastic cholecystosis includes two types of mucosal abnormalities of the gallbladder which are usually clinical accidental findings at the time of a cholecystectomy: Cholesterolosis and adenomyomatosis. Cholesterolosis is characterized by mucosal villous hyperplasia with accumulation of cholesterol esters within epithelial macrophages, while AMG is a hyperplastic lesion characterized by overgrowth of the mucosa, thickening of the muscle wall and intramural mucosal diverticula formation.

Peer-review

AMG in children is a very rare disease. This paper introduced a case report and a systemic review, which had a clinical guading influence.

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CASE REPORT

Diagnosis of osteopetrosis in bilateral congenital aural atresia: Turning point in treatment strategy

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Author contributions: Verma R, Jana M and Bhalla AS contributed to image analysis and diagnosis making; Kumar A and Kumar R helped in clinical evaluation and reatment planning; all contributing authors participated in complete case analysis and writing of the manuscript.

Institutional review board statement: For case reports clearance from institutional review board is not required at our institution (all india institute of medical sciences).

Informed consent statement: Written informed consent was taken at the time of carrying all investigations and for use of the case details in academic activities reassuring that anonymity and confidentiality of the patient will be maintained.

Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

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Abstract

Aural atresia is a rare congenital malformation of the external and middle ear. There are several syndromic associations of this anomaly with those involving the first and second branchial arches. Occurrence of aural atresia with sclerosing skeletal dysplasia is unknown and has never been reported. The co-existence of a sclerosing dysplasia can make the surgical treatment in aural atresia difficult and risky; and the auditory improvement may not be as expected. Moreover, internal auditory canal narrowing and hence sensorineural hearing loss in sclerosing dysplasia might add to the already existing conductive hearing loss in such patients. In this case report we have described an unknown association of bilateral microtia with sclerosing skeletal dysplasia (autosomal dominant osteopetrosis) and clinical implications of these two conditions occurring together leading to a change in the management plan.

Key words: Aural atresia; Osteopetrosis; Congenital hearing loss; Microtia

Core tip: Congenital aural atresia and microtia are one of the most challenging surgeries for an ear, nose, and throat surgeon. It is imperative to know when not to operate a patient. Improper patient selection may not benefit the patient in terms of hearing improvement rather it may further add to complications like chronic cavity infection and potential risk of facial nerve injury.

Imaging plays an important role in preoperative evaluation and selection of appropriate surgical candidates. This case shows incidental detection of previously unsuspected osteopetrosis in a child having profound congenital hearing loss due to congenital bilateral aural atresia that posed difficulty in treatment and required change in management from surgery to bone anchored hearing aid.

Verma R, Jana M, Bhalla AS, Kumar A, Kumar R. Diagnosis of osteopetrosis in bilateral congenital aural atresia: Turning point in treatment strategy. *World J Clin Pediatr* 2016; 5(2): 228-233 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i2/228.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i2.228

INTRODUCTION

Aural atresia is a rare congenital malformation affecting the external, middle and rarely the inner ear structures with an incidence of 1:10000 to 1:20000 live births[1]. It is more often unilateral, and male to female ratio is 2:1. Though the entity is usually sporadic, upto 30%-40% cases may have syndromic association with Goldenhar's syndrome, Treacher Collin syndrome, De Grouchy, Crouzon syndrome, Branchio-oto-renal syndrome and hemifacial macrosomia[2]. However, none of the described associated syndromes are known to have generalised increased bone density, and alternatively none of the sclerosing skeletal dysplasia is known to be associated with microtia.

We present an unusual case of incidental radiological detection of autosomal dominant osteopetrosis (ADOP) during pre-operative evaluation of a child with congenital bilateral microtia and its clinical implications in terms of patient management and treatment measures.

CASE REPORT

A 12-year-old adolescent female was referred to our department for High resolution computed tomography (HRCT) of temporal bone as a part of routine microtia work-up. Her both pinnae were severely malformed (Figure 1) and she had profound hearing loss since birth. She was not using any hearing aids. There was no history of similar condition in immediate or extended family members. There was no history of consanguineous marriage and drug exposure during pregnancy.

Audiometry revealed bilateral mixed (conductive as well as sensorineural) hearing loss. HRCT revealed that both cartilaginous external auditory canal (EAC) were narrowed while bony EAC and middle ear cavity were normal in size (Figure 1). Stapes was not visualised and oval window was shallow on both sides with bilateral poor pneumatisation of mastoids. There was Eustachian tube block with resultant soft tissue opacification of both the middle ears. Soft tissue opacification, ossicular erosion and erosion of tegmen tympani was also noted on right side suggesting congenital cholesteatoma (Figure 2). Besides the external and middle ear anomalies related to aural atresia the additional striking finding on CT was generalised bone thickening and sclerosis with loss of definition of the inner and outer table involving skull base and calvarial bones. There was bilateral internal auditory canal (IAC) narrowing consequent to calvarial thickening but vestibule, cochlea and the semicircular canals were normal (Figure 3).

In view of sclerosis of skull bones skeletal survey was done for further evaluation. On skeletal survey, both axial and appendicular skeleton were affected, and there was mild generalised increase in bone density with sclerosis noted along superior as well as inferior vertebral endplates. The cortico-medullary differentiation of long bones was lost (Figure 4). There was no premature sutural closure, wormian bones and the shape of skull was normal. No endobones were seen and there was no abnormal soft tissue calcification or ossification of interosseous membranes. Based on these skeletal findings metabolic cause or a sclerosing skeletal dysplasia was suspected.

Biochemical workup revealed normal renal functions (Urea = 22 mg/dL, creatinine = 0.7) and blood counts (Hb = 13.4 g%). Serum calcium (9.6 mg%), phosphorus (4 mg/dL), alkaline phosphatase (90 IU/L), parathormone (PTH = 50 pg/mL) and fluoride levels (1.5 μmol/L) were within normal limits. This ruled out the diagnosis of metabolic bone disease and a final impression of sclerosing skeletal dysplasia likely ADOP was made (Figure 4).

DISCUSSION

Microtia refers to a malformed external ear or pinna, anotia denotes a more severe degree of deformity. EAC atresia refers to a narrowed or hypoplastic external auditory canal. Aural atresia is a birth defect that is characterised by hypoplasia of the EAC; often with pinna deformity and malformations of the middle ear, and rarely the inner ear structures.

Development of external and middle ear starts at six weeks of pregnancy from first and second branchial arches and is completed by twenty weeks[3]. EAC develops from the ectodermal components of the first branchial pouch. Meatal plug (mesodermal derivative) recanalizes and forms the EAC at the end of 28th week. Failure of recanalization leads to congenital aural atresia. Owing to common developmental origin, microtia and aural atresia can be associated with other craniofacial malformations resulting from abnormal development of first and second branchial arch structures. In addition to the syndromic associations described above, various non-syndromic associations known are facial asymmetry, facial nerve weakness, cleft lip and cleft palate, urogenital defects, and

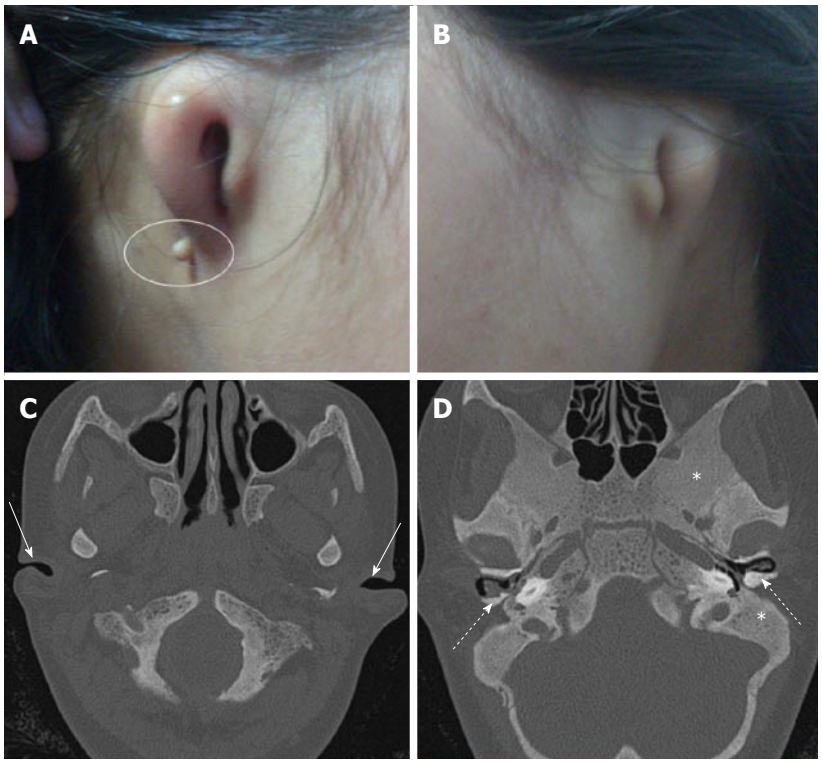

Figure 1 Bilateral dysplastic pinnae. Note preauricular skin tag on right side (circle). Axial HRCT (C and D) showing bilateral mild narrowing of cartilaginous EAC (arrows) and normal bony EAC (dotted arrow) with ear wax. Also seen are the thickened sclerotic calvarial bones with loss of normal medullary cavity (asterisk). EAC: External auditory canal.

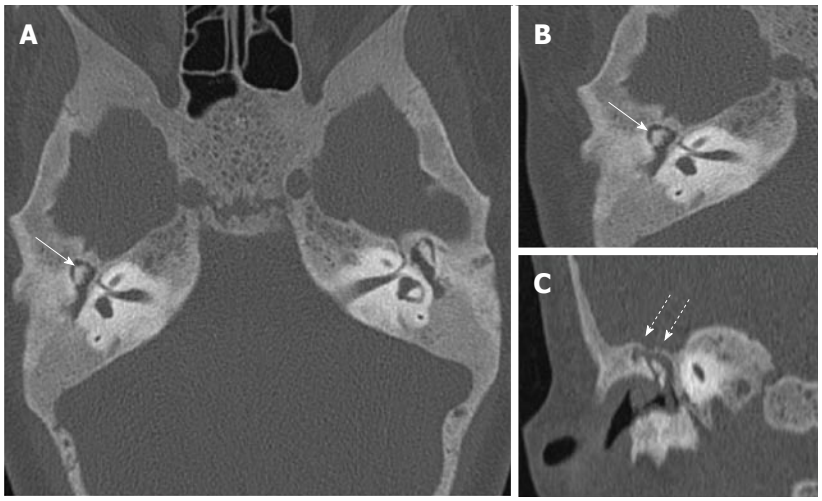

Figure 2 Axial high resolution computed tomography images. (A and B) showing soft tissue opacification in bilateral middle ears (A) with erosion of head of head of malleus (arrows). Coronal reformatted CT image (C) showing thinning and erosion of tegmen tympani (dotted arrows) secondary to cholesteatoma.

craniovertebral malformations[2,4].

Although sclerosing skeletal dysplasia like osteopetrosis can cause hearing loss by EAC and IAC narrowing due to bony involvement the deformity of pinna can not be explained. To the best of our knowledge, associations of microtia with sclerosing skeletal dysplasia has never been described in English medical literature.

Diffuse skeletal sclerosis can be caused by sclerosing skeletal dysplasias; and secondary to various other conditions such as renal osteodystrophy, hypoparathyroidism, fluorosis; Beryllium, lead and bismuth poisoning; myelofibrosis; Paget's disease (sclerosing form); and malignancies (lymphoma, osteoblastic cancer metastases)[5].

Osteopetrosis is the prototype of sclerosing skeletal dysplasia caused by deficient osteoclastic resorption of the primary spongiosa. It can be inherited both as autosomal dominant and autosomal recessive forms. Autosomal recessive osteopetrosis (AROP) has a more

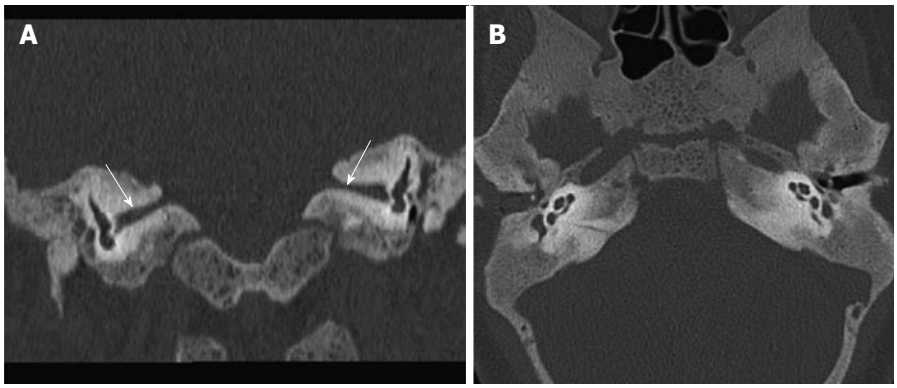

Figure 3 Coronal reformatted high resolution computed tomography. (A) image showing thickened sclerotic bones causing narrowing of bilateral internal auditory canal (arrows); normal cochlea and vestibule seen in both ears on axial high resolution computed tomography image (B).

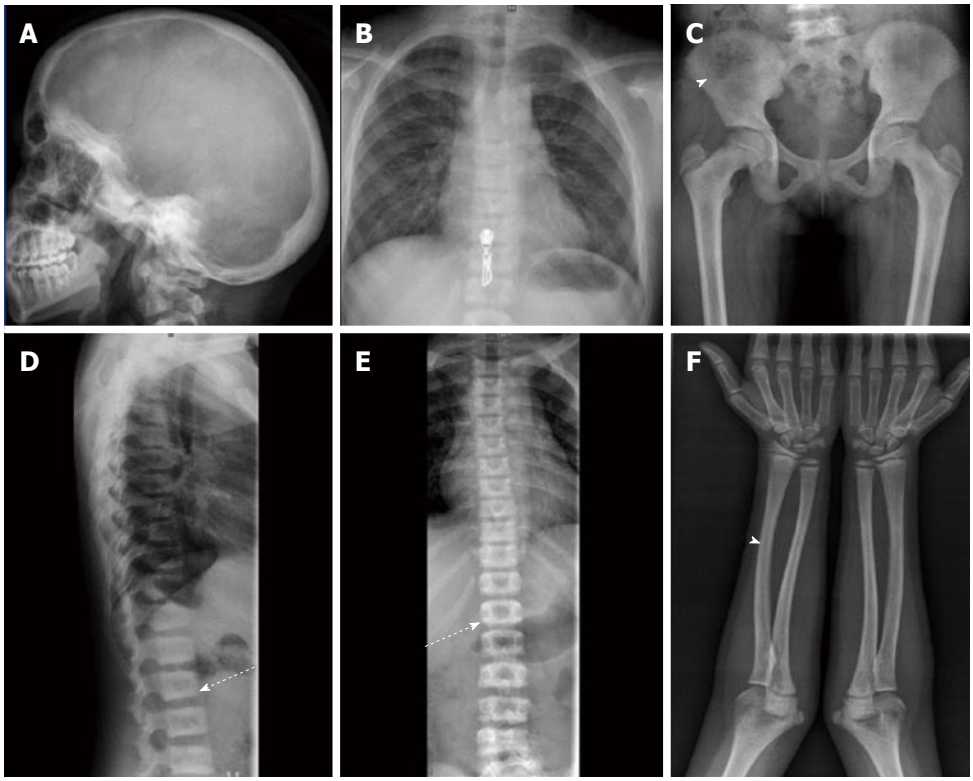

Figure 4 Skeletal survey. Note generalised increased bone density in all the radiographs (A to F). Calvarial bones as well as skull base are thickened (A), lung fields are normal with sclerotic ribs (B). No paraspinal masses to suggest extra medullary hematopoiesis. Sclerosis of pelvic bones with subtle blurring of cortico-medullary is differentiation in long bones (arrow heads). Sclerosis along vertebral endplates (dotted arrow) leading to "rugger jersy spine" (D and E).

severe disease course and early onset of disease. ADOP is ten times more common than AROP; is usually asymptomatic, and is usually discovered incidentally on plain radiographs[6,7]. It classically displays the radiographic sign of "sandwich vertebrae". The main complications are confined to the skeleton, including fractures, scoliosis, hip osteoarthritis and osteomyelitis, particularly affecting the mandible in association with dental abscess or caries. The mainstay of diagnosis is clinical and largely depends on the radiographic appearance of the skeleton. In the absence of typical radiographic findings, raised concentrations of the creatine kinase BB isoenzyme and tartrate resistant acid phosphatase (TRAP) can be helpful in making the diagnosis of ADOP[8].

The goals of management in aural atresia are: (1) cosmetic reconstruction of the pinna; (2) canal reconstruction; and (3) hearing restoration.

Successful restoration of hearing in aural atresia after surgery depends on an intact sensorineural hearing. Contraindications to surgery are significant sensory neural hearing loss (SNHL) or inner ear malformation, limited middle ear-mastoid pneumatisation or a significantly hypoplastic middle-ear cleft. Pre-surgical work-up includes evaluation of sensorineural hearing by auditory brainstem response;

and structural evaluation by HRCT of temporal bone. HRCT temporal bone is the most important imaging for pre-surgical evaluation; it differentiates surgical from non-surgical candidates and detects conditions that might increase the surgical risk (for example, anomalous facial nerve course, aberrant vascular structures, low lying tegmen tympani[9-11]). The status of atretic plate, pneumatisation of middle ear and mastoid, anatomy of ear ossicles, course of facial nerve and inner ear morphology are other important part of assessment[6]. Radiologically the most frequently followed scoring system is the Jahrsdoerfer scoring system, lesser the score poorer is the surgical outcome[10].

Causes of hearing loss in patients with osteopetrosis may vary[12]. Hearing is less commonly affected than vision, with approximately one third of patients having some degree of hearing loss. The deafness is probably secondary to a combination of bony compression of the nerve due to narrowing of IAC, sclerosis of the middle ear ossicles, chronic middle ear effusion due to Eustachian tube block, EAC and middle ear cavity narrowing. Our patient had associated pinna deformity, which can not be explained by osteopetrosis itself, and it implies that the EAC atresia in our patient is unrelated to ADOP.

Our case had microtia with bilateral cartilaginous EAC atresia and diffuse osteosclerosis. The secondary causes of osteosclerosis were excluded as she had a normal blood work-up, no history of exposure to heavy metals, normal facies, dentition, lip and palate. There was no pallor and hepatosplenomegaly. The combined clinical, radiological and biochemical picture led to diagnosis of sclerosing skeletal dysplasia which was further categorised as ADOP.

The management of our patient was difficult for multiple reasons. The expected auditory outcome was not good; firstly as she presented quite late (post-lingual deafness) and had not used hearing aids till then; secondly as there was mixed hearing loss with a sensorineural component resulting from the IAC narrowing because of ADOP. Additionally, the sclerosis of petrous and mastoid temporal bone because of ADOP made the surgery demanding; posing a high risk of facial nerve and cochlear injury resulting from excessive drilling. Since cosmetic reconstruction was still a feasible option, the patient was counselled for cosmetic reconstruction of the pinnae and Bone anchored hearing aid (BAHA) for hearing improvement. Considering poor prognosis and treatment cost patient refused the treatment and was lost to follow up.

Careful review of literature did not reveal any association of microtia and generalised increased bone density. To the best of our knowledge this is the first case describing bilateral microtia in a child with sclerosing skeletal dysplasia that was unsuspected prior to CT evaluation for microtia. The occurrence of two conditions together may be incidental or there may be some unknown unidentified association. But the importance of this diagnosis lies not on the etiological cause, rather on the treatment plan. Such co-existence can mandate a modification of treatment and careful reconsideration of the potential surgical risks. The auditory result should also be explained well to the candidate and the family.

COMMENTS

Case characteristics

Twelve-year-old female with neglected congenital profound hearing loss and malformed both pinnae.

Clinical diagnosis

Microtia and aural atresia.

Laboratory diagnosis

Normal limits.

Imaging diagnosis

Incidental generalised increased bone density. Skeletal survey consistent with autosomal dominant osteopetrosis (ADOP).

Treatment

Bone anchored hearing aid offered and cosmetic reconstruction of pinnae but refused.

Term explanation

Turning point in treatment strategy as undiagnosed ADOP precluded normal surgical management due to associated changes and potential risks.

Experience and lessons

Imaging diagnosed previously unsuspected skeletal dysplasia and teaches the lesson of proper patient selection.

Peer-review

The paper is well written.

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EDITORIAL

Reducing childhood obesity through coordinated care: Development of a park prescription program

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Abstract

Major hindrances to controlling the current childhood obesity epidemic include access to prevention and/or treatment programs that are affordable, provide minimal barriers for participation, and are available to the general public. Moreover, successful childhood obesity prevention efforts will require coordinated partnerships in multiple sectors such as government, health care, school/afterschool, and the community but very few documented sustainable programs currently exist. Effective, community-based health and wellness programs with a focus on maintaining healthy weight *via* physical activity and healthy eating have the potential to be a powerful referral resource for pediatricians and other healthcare professionals who have young patients who are overweight/obese. The Miami Dade County Department of Parks, Recreation and Open Spaces in partnership with the University of Miami UHealth Systems have created a "Park Prescription Program (Parks Rx 4Health™)" that formally coordinates pediatricians, families, parents, caregivers, and child/adolescents to provide daily obesity-prevention activities. This Parks Rx 4Health™ program that we describe here allows UHealth pediatricians to seamlessly refer their overweight and obese patients to Fit2Play™, an evidence-based, park-based afterschool health and wellness program. Measurable outcomes that include body mass index, blood pressure, fitness, and nutrition knowledge are being collected at baseline and at 3-and 6-mo after referral to document patient progress. Results are then shared with the referring physician so they can follow up with the patient if necessary. Identifying successful

models that integrate primary care, public health, and community-based efforts is important to accelerating progress in preventing childhood obesity. Effective, community-based health and wellness programs with a focus on physical activity and nutrition education could be a powerful referral resource for pediatricians who have obese patients.

Key words: Obesity; Overweight; Prevention; Community-based; Children; Adolescents; Primary care

Core tip: Childhood obesity continues to be a vexing clinical and public health challenge and is an epidemic that will not be solved in silos. Instead, coordinated, collective partnerships in multiple sectors such as government, health care, school/afterschool, the family, and the community give the most promise for sustainability of healthy weight in children and adolescents. The described Parks Rx 4Health™ program will enhance care coordination among pediatricians, families and community-based providers to encourage and monitor overweight/obese youth. It will be increasingly important to capitalize on existing resources such as local park systems to conduct prevention efforts to lower current obesity and related comorbidity trends.

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INTRODUCTION

The United States (US) Department of Health and Human Services' Healthy People 2020 Nutrition and Weight Status health indicator's goal is to "promote health and reduce chronic disease risk through the consumption of healthful diets and achievement and maintenance of healthy body weights"[1]. This initiative identifies the reduction of overweight/obesity during childhood as 1 of 10 leading public-health priorities, yet the prevalence of childhood overweight/obesity in the US continues to be a vexing public health and clinical issue, especially among ethnic minorities and low income underserved subgroups who are at increased risk for adult onset type 2 diabetes and cardiovascular disease[2,3]. For obesity prevention efforts to be successful will require coordinated, collective partnerships in multiple sectors such as government, health care, school/afterschool, workplace, and the community, yet very few sustainable programs currently exist[4].

While coordination of care for childhood obesity prevention efforts are desperately needed, they are severely lacking. Primary care providers (PCPs, such as physicians, physician's assistants, nurse practitioners, and/or registered nurses working in a primary care setting) and professionals working in out-of-school/afterschool-based settings have important roles in meeting national and international obesity prevention goals. PCPs traditionally measure patients' growth and development and treat obesity and health-related conditions, but there is a recognized need to expand these roles to include advocacy, counseling, and referring patients and their families to community-based resources, and communicating with these community-based referrals about patient participation and progress[5,6].

The institute of medicine (IOM) in its 2012 report "Accelerating progress in obesity prevention"[7] includes the goal to "expand the role of health care providers in obesity prevention". Health care providers/PCPs have a role in the following strategies recommended by the IOM to achieve this goal: (1) strategy 4-1: Provide standardized care and advocate for healthy community environments; (2) strategy 4-2: Ensure coverage of, access to, and incentives for routine obesity prevention, screening, diagnosis, and treatment; and (3) strategy 4-3: Encourage active living and healthy eating[7]. Similarly, the US preventive services task force recommendation statement says "PCPs should offer or refer children aged 6 years and older to intensive counseling and behavioral interventions to promote improvements in weight status"[8].

While the physician's role in the identification and recruitment of children and families into obesity prevention or treatment interventions is often cited as important, the literature is limited in terms of existing models that are effective and sustainable. Published studies include primarily family-based counseling and treatment programs, lasting from eight weeks to a few months and include group education sessions for parents and children, home visits, follow-up telephone calls, automated messages, and/or other family-oriented activities[4,9]. Very few incorporate any technology enhancements (*e.g.*, computer/tablet Parks Rx 4Health™ registration, tablet/phone data entry capabilities, healthy text messaging programs) that encourage bi-directional communication between PCPs, families and community-based providers to track progress and attendance, and are designed for low income, ethnic minority groups in particular[10,11]. Yet studies report that parents perceived the community-based program as an extension of their pediatrician's care due to the physician-referral of the program, and follow-up monitoring and care with patients[4].

Park-based afterschool programs have the potential to be an ideal setting for childhood obesity-prevention PCP referrals. How the existence of community parks and their health and wellness programming is related to overall physical activity levels and health of its residents is just now gaining attention in the literature[12]. Another

area of interest nationally is the concept of a "park prescription" program that links the healthcare system and public lands, such as local parks, to create healthier people[13,14]. However, none of these programs to date have: (1) linked PCPs to evidence-based programming in childhood obesity prevention efforts; and (2) have incorporated technology to create bidirectional communication between PCPs and community providers to track patient progress.

To answer the need for affordable and accessible obesity prevention and treatment programs in the community, the University of Miami Miller School of Medicine's (UMMSM) Department of Pediatrics and the Miami Dade County Department of Parks, Recreation and Open Spaces (MDPROS) have collaborated over the past 8 years to successfully develop "Fit2Play™", a 10-mo (entire school year) afterschool health and wellness program that is available to over 1500 low income, urban and suburban children annually at 35 parks in Miami Dade County (approximately 48% Hispanic, approximately 48% non-Hispanic black, mean age 9.3 years). Fit2Play™ provides the ideal PCP-referral given its (1) evidence-based results[15-17]; (2) accessibility; it is offered in multiple locations (35 park locations all over the county); (3) affordability (can be free or sliding scale based on household income but not to exceed $35/wk, which is considerably less than comparable non-evidence based programs offered locally); and (4) acceptability and endorsement by our UMMMSM physicians for referrals. We describe below the formal Park Prescription (Parks Rx 4Health™) model that has been developed from this Fit2Play™ evidence-based work.

STUDY METHODS

Study design

We are currently/prospectively conducting a Parks Rx 4Health™ pilot study that will include a total of 50 families who visit UMMSM Pediatric Clinics (general pediatrics or pediatric endocrinology) and are referred to, and enrolled in the Fit-2-Play™ afterschool program. During this pilot phase, the program is free to families that participate and is financially underwritten and trademarked by MDPROS. This study has been approved by the University of Miami Institutional Review Board. We describe the methods for this program in detail below.

Participants

The UMMSM Pediatric Clinics serve a very rich racially and ethnically diverse population of overweight/obese patients (approximately 1 out of every 3 and 1 out of every 2 ethnic minority patients are overweight/obese). Pediatricians ask patients if they are interested in participating in the Park Rx program if they meet the following inclusion criteria: (1) Child is between the ages of 6 and 14; (2) child body mass index (BMI) percentile is $\geqslant 85^{th}$ %ile for age and sex[18], is physically inactive, has systolic and/or diastolic pre-hypertension or hypertension, or has a strong family history of type 2 diabetes and/or cardiovascular disease; (3) parent is willing to enroll their child in a Fit-2-Play™ program that is located close to their child's school or home and have them attend 5 d/wk (transportation provided); and (4) parent consent for child to participate. If a child has a medical condition that excludes them from the physical fitness testing component of the study then they are not referred to Fit-2-Play™.

PROCEDURES

Initial referral process

Pre-Parks Rx 4Health™ program roll out focus groups among pediatricians identified the initial referral process as a critical point of buy-in for medical team members. They stated that if they had to pick just one key strategy that would increase program success, it would be that the in-house clinical referral process must be (1) seamless; (2) simple; and (3) short (no more than 1 min). Hence, an official Park Prescription website "landing page" was developed (Available from: URL: http://www.miamidade.gov/parks/rx4health.asp) that was loaded on all desktop computers in each patient room. This site can also be accessed *via* tablet, mobile phone, or laptop computer. This page gives specific information on park location, times, and how to live a heart-healthy life. Once the parent chooses the most convenient park location, the physician and family fill out a brief online registration form together (Available from: URL: http://www.miamidade.gov/parks/rx4-contact-form-youth-um.asp) that includes basic patient information. This preliminary registration form is sent electronically to the MDPROS wellness team (a centralized team of 6 health and wellness specialists/coaches). In turn, this team (1) within 24 h verifies that patient has been registered with Fit2Play™ at the pre-identified park; (2) calls and emails/texts each parent with a welcome message; and (3) provide further assistance necessary to complete the registration process. Parents leave the pediatrician's office with additional materials describing the details of the program and MDPROS Health and Wellness staff contact information.

Tracking of patients throughout their enrollment in Fit2Play™

All Park Prescription children have a baseline, 3- and 6-mo assessment battery completed (measurements described in detail below) by the park health and fitness team. In addition, children and parents receive encouraging text messages and emails from both their pediatricians and park coaches as they meet program milestones. Daily attendance is also recorded.

Description of Fit2Play™ afterschool program physical activity and health and wellness/nutrition education components

Fit2Play™ includes (1) 50-60 min of physical activity that incorporates multiple sports (soccer, kickball, flag


Parks Rx 4Health

Health, wellness and fitness report card

Patient's ID# _____ Physician's name _____

Measures	Baseline/Date	Lates/Date
Height	____ / ____	____ / ____
Weight	____ / ____	____ / ____
Blood pressure	____ / ____	____ / ____
Pulse	____ / ____	____ / ____
Circumference measure		
Midarm	____ / ____	____ / ____
Waist	____ / ____	____ / ____
Hip	____ / ____	____ / ____
Skinfold measure		
Tricep	____ / ____	____ / ____
Bicep	____ / ____	____ / ____
Subscapular	____ / ____	____ / ____
Suprailiac	____ / ____	____ / ____
Flexibility		
Sit and reach	____ / ____	____ / ____

Testing and measures - comments

Program attendance - comments

Comments

Figure 1 Park Rx 4Health™ participant health report card.

football, dodgeball) and activities from Sports, Play and Active Recreation for Kids[19,20], an evidenced-based, outcome oriented structured active recreation program for children with a focus on developing and improving motor skills, movement knowledge, and social and personal skills; and (2) a health and wellness/nutrition education component where children participate in 30 min education lessons 1-2/times per week that incorporate EmpowerMe4Life[21], a nutrition education curriculum grounded in the American Heart Association's scientific recommendations in promoting heart-healthy lifestyles. This curriculum promotes being several health messages (physical activity, nutrition, sleep, screen time) and has been expanded over the years to include modules for younger (ages 6-9) and older (ages 10-14) participants that include more in-depth materials.

Closing the communication loop between pediatricians and community-based providers

Every three months, pediatricians receive a patient "report card" (Figure 1) on primary clinical outcome measurements including height, weight and blood pressure. MDPROS Park Health and Wellness staff also include attendance numbers for the pediatrician's review. MDPROS Parks Rx 4Health™ software is pre-programmed to assist with a 6-mo pediatrician follow-up visit and sends pediatrician, parent and park staff scheduling reminders. This entire referral and follow-up process is shown visually in Figure 2.

MEASURES

Individual-level measures

MDPROS Parks Rx 4Health™ software is programmed to collect/track the following measures on the children referred to Fit2Play™:

Demographic questionnaire: A baseline questionnaire captures (1) age, sex, and race/ethnicity for children and parents; (2) parent medical history; and (3) any other relevant medical and/or personal history (*e.g.*, previous sports injuries, allergies); all of the following measures are taken at baseline and at the follow-ups.

Height and weight: Height (by stadiometer) and weight (by digital scale) are converted to age and sex adjusted BMI scores and percentiles[18,22].

Waist and hip circumference: Waist and hip circumferences are measured to the nearest 0.1 cm using a non-stretchable plastic tape measure by a standard method[23]. Waist circumference is measured over the

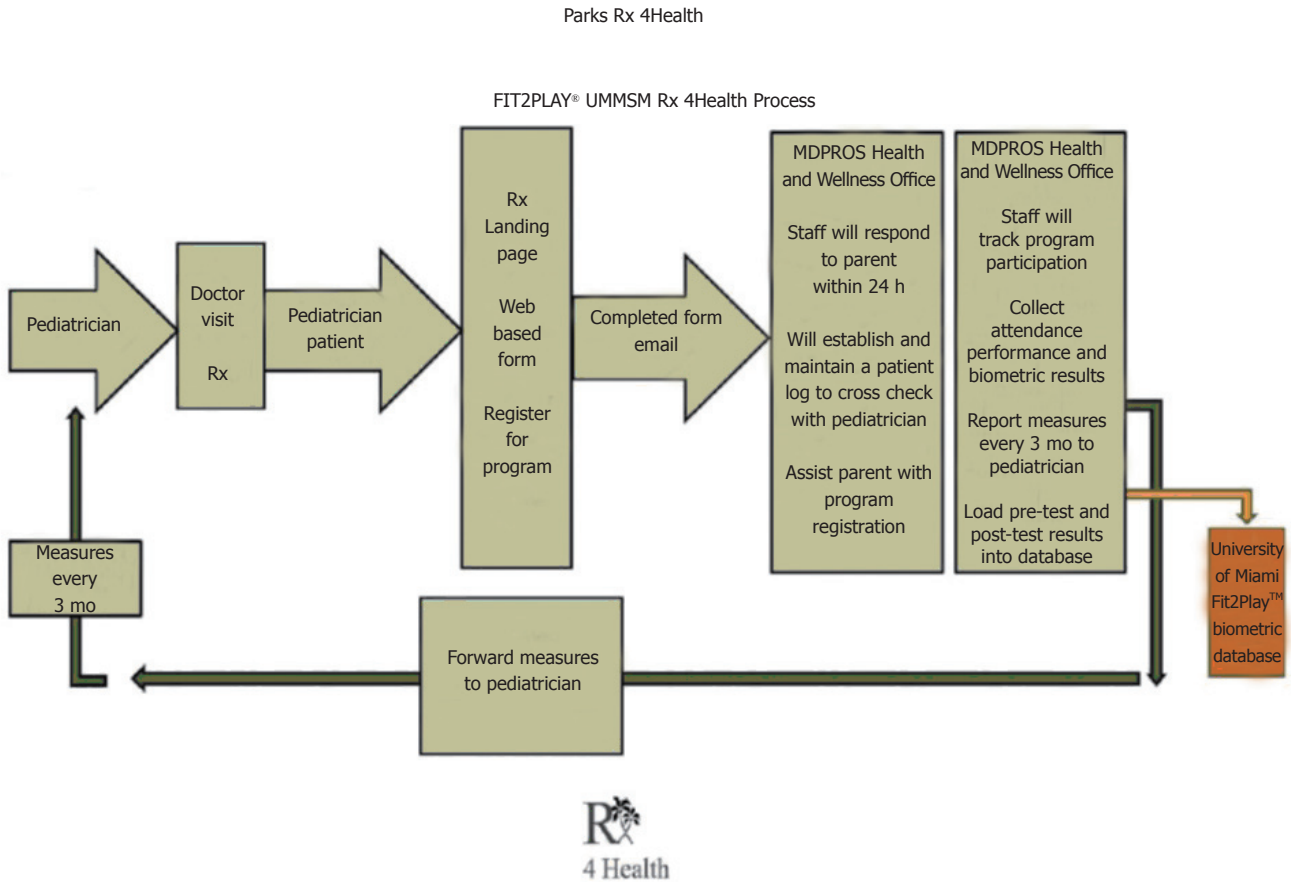

Figure 2 Park Rx 4Health™ project flow.

navel at the end of gentle exhalation and hip circumference is measured at the maximum circumference over the buttocks. A total of three waist and hip circumference measures are taken for each child and the average used for the analysis.

Skinfold measurements: Bicep, triceps, subscapular, and suprailiac skinfold thicknesses are measured to the nearest 0.1 mm following standard procedures[22]. These 4 thickness values are combined and analyzed using the Durnin formula to estimate percent body fat[24].

Blood pressure: Blood pressure is taken using the American Heart Association Guidelines[25]. Each child has a total of 3 blood pressure measurements taken where the first one is dropped and the second two are averaged for analysis[26].

Physical fitness: The following battery of physical fitness tests[27] is conducted: (1) Sit and Reach[28]. The child sits on the floor with legs extended straight in front. Feet are placed against the front of the test box and are approximately 6 inches apart. The subject extends the arms forward, placing the index fingers of both hands together with knees straight. The score is the most distant point reached by the fingertips in the best of 3 trials; (2) Progressive Aerobic Cardiovascular Endurance Run (PACER) test[29]. The PACER test is a maximal aerobic fitness test and is a timed fitness run test. The test involves continuous running between the two lines in time to recorded beeps. The time between recorded beeps decrease each minute (level) requiring an increase in pace. The subjects continue until they are unable to keep pace with the beeps. Participants are compared to established national standards; (3) Timed Sit-ups[27]. For the sit-up test the child lies with knees bent and arms across the chest. The participant will complete as many sit-ups as possible in the 60 s allotted time period; (4) Timed Push-ups[27]. For the push-up test the participant completes as many push-ups as possible in the 60 s allotted time period; and (5) 400 Meter Run[27]. Shorter distance runs are included as options for younger children. Younger children can be prepared to run the mile (6-7 year olds - ¼ mile; 8-9 years old - ½ mile).

Mental health measures: The following 3 assessments are administered at initial enrollment and at the end of the school year or at the 6-mo follow-up only; (1) Rosenberg Self Esteem Scale[30], a simple 10 item questionnaire asking participants on a 4-level Likert Scale about how they feel about themselves. Self-esteem is one measure of a children's overall mental health; (2) Social Anxiety Scale for Adolescents[31], a 22-item questionnaire that assesses participant's level of social anxiety (how much they worry about what others

Table 1 Abbreviated reach, effectiveness/efficacy, adoption, implementation, and maintenance item(s) and methods/approach/measure

Study topic area: Childhood obesity prevention *via* coordination of care, Parks Rx 4Health™	Study setting: Pediatric Primary Care Clinics, MDPROS-based afterschool Fit2Play™ program
Dimensions/item	Method/approach/measure
Reach	
Characteristics of participants compared to non-participants or to target population	Proportion of family/patient referrals who register for Fit2Play™, continue to participate for entire 6 mo Proportion of pediatricians who make referrals *via* Parks Rx 4Health™
Effectiveness	
Measure of primary outcome with or w/o comparison to a public health goal	Proportion of youth participants who improve in above listed individual measures (BMI, BP, fitness, *etc.*)
Measure of broader outcomes (*e.g.*, other outcomes, measure of life improvements, or potential negative outcome)	Mean improvement of cardiovascular health, physical activity levels, anthropometrics; satisfaction with Parks Rx 4Health™ program
Adoption-setting level	
Characteristics of settings participating (comparison and intervention) compared to either: non participants or relevant resource data	Overall satisfaction with Parks Rx 4Health™ program (pediatrician referral process, Fit2Play™ program, family/child Fit2Play™ participants/completers *vs* non-completers)
Use of qualitative methods to understand adoption at setting level	Focus group with pediatricians, park coaches and children; process evaluation with pediatricians, park coaches and parents
Implementation	
Percent of perfect delivery (adherence or consistency)	Pediatrician and Parent Satisfaction Survey, Parks Rx 4Health™ adherence measure
Adaptations made to intervention during study	Focus groups with pediatricians and park coaches at end of study
Maintenance - individual level	
Measure of primary outcome at follow-up after final intervention contact	Proportion of children participants who continue in Fit2Play™ Proportion of pediatricians who make Parks Rx 4Health™ referrals
Qualitative data to understand long -term effects	Pediatrician, Family and Park Health and Wellness Coaches Satisfaction Survey
Maintenance - setting level	
Program is ongoing at ⩾ 6 mo post-study funding	Proportion of pediatricians using Parks Rx 4Health™ 3-mo post-pilot phase
Some measure/discussion of alignment to organization mission or sustainability	Adoption of Parks Rx 4Health™ program by the National Recreation and Park Association, promotion by the American Academy of Pediatrics

MDPROS: Miami Dade County Department of Parks, Recreation and Open Spaces; BMI: Body mass index.

think of them, *etc.*). Social anxiety disorder is common among youth, often emerging during adolescence and the benefits of participating in a park-based group afterschool program have not been previously described; and the (3) pediatric Quality of Life Inventory ™[32] that assesses how the participant currently feels about their overall quality of life. The utility of pediatric quality of life measurement in population health outcome evaluation from the perspective of children in large pediatric populations has several distinct benefits beyond the clinical setting but has been largely unexplored in a park-based setting.

Process measures

Process measures are a priority as they are key in tracking the uptake of implementation (Table 1). Data are collected from pediatricians, park health and wellness specialists/coaches, and families (parents and child participants) by observations, self-report satisfaction surveys, focus groups, questionnaires and process surveys.

It is critical that obesity prevention coordination efforts are guided by a clear framework. The reach, effectiveness/efficacy, adoption, implementation, and maintenance (RE-AIM) framework, highly compatible with development of community-based public health interventions[33-37] is used to guide our integration and dissemination of the Parks Rx 4Health™ program. The dimensions of the framework, (1) reach (the absolute number, proportion, and representativeness of individuals who are willing to participate); (2) effectiveness (impact of an intervention on outcomes, including potential negative effects, quality of life, and economic outcomes); (3) adoption (absolute number, proportion, representativeness of settings and intervention agents willing to initiate a program); (4) implementation (intervention agents' fidelity to various elements of an intervention's protocol including consistency of delivery as intended, intervention time and cost); and (5) maintenance (extent to which a program/policy becomes institutionalized or part of the routine organizational practices and policies, but also has individual-level outcomes) all have applicability to the Parks Rx 4Health™ program.

RE-AIM was initially designed to help evaluate interventions and public health programs, to produce a more balanced approach to internal and external validity, and to address key issues important for dissemination and generalization[33]. RE-AIM has been applied to policies[34,35] and community-based multilevel interventions[36], and to reduce health disparities in previous studies[37]. Within this framework, it has been recommended that childhood obesity interventions use multiple disciplines and perspectives in creating and implementing programs, integrate research and practice partnerships, and assess the potential of intervention

strategies to reduce health disparities[36,37]. To date, the complexity of the community-based childhood obesity prevention intervention implementation process has not been well-studied or understood, especially in highly diverse communities. This is true particularly in low resource setting and for populations traditionally underrepresented in obesity prevention research, for which dissemination and implementation may not be a simple process, particularly when multiple entities are involved (PCPs, community-based programs, families)[37].

Data analysis

Proportions and means are the primary scales of the dependent outcomes used to evaluate program outcomes. While not the only statistical approach available, we chose to use the generalized linear model (GZLM) to model the impact of the Parks Rx 4Health™ program for all the dependent effects. We chose this specific approach because much like the general linear model that allows for variation in type and scale characteristics of the independent effects, the GZLM extends this versatility to include various types of dependent variables. Rather than applying different statistical techniques based on the scale properties of the dependent variables (*e.g.*, analysis of variance for continuous data, contingency tables for proportion, *etc.*), the GZLM model accounts for the scale type of the dependent variable *via* model specification. The relationship between the independent variables and the dependent outcomes are specified by way of a link function that defines the functional form of this relationship (*e.g.*, when the dependent variable is a proportion, a logistic link function might be used). Through different specifications of the link and probability functions, one generalized model is used to examine the statistical relationships between the design parameters (*i.e.*, independent variables) and the dependent variables, regardless of their scale properties. Additionally, statistical consideration is given to repeated measures which needs to be considered in the current Park Rx 4Health model. One of the major benefits of the program to pediatricians is that they can track how their patient is doing in the program throughout the school year and thus they request multiple data collection time points. Although an additional independent factor (*i.e.*, time) can be included in the GZLM (*i.e.*, generalized mixed model), the results may be better interpreted when analyzed as separate short and long-term models. This is an important issue in the current model, because the time lapse between the pre- and post-test measurement will vary by patient, and thus the introduction of an interim value may be important.

Measures taken at baseline will be included in the GZLM as covariates to insure pretest balance and as a control on regression to the mean. In studies involving weight loss or change, initial weight is a covariate that is often included in the statistical model since weight gain or loss is correlated with initial values. This dictates a statistical approach to the data analysis which accounts for the difference scores from baseline to post-treatment measurements as the dependent outcome using the baseline measurement as the covariate. SAS and JMP (SAS Institute, Cary, NC) are the primary statistical software packages used for all analyses.

Quality control

To ensure Park Rx program quality control, the following strategies are implemented: (1) MDPROS field staff are properly trained in standardized Parks Rx 4Health™ methods of outcome measures and data collection; (2) activities, personnel, data and the database are well-organized and maintain proper documentation; and (3) all required reports to physicians are delivered in a timely manner. Appropriate data safety checks are conducted prior to, during, and after the completion of data collection activities such as adding upper and lower bounds to the possible ranges of outcome variables to decrease the incidence of data entry error. Prior to the initiation of any data collection, pilot runs involving measurement and data collection and entry mockups are used to establish process capability. Finally, MDPROS field teams conduct weekly field audits to ensure that all Parks Rx 4Health™ data are recorded correctly and completely.

Lessons learned

There have been many important lessons learned as we continue in our roll out pilot phase of the UMMSM-MDPROS Parks Rx 4Health™ program. At both a pre- and 4-mo follow-up focus group, our pediatrician team emphasized the importance of (1) a seamless and quick referral process and (2) receiving follow-up information on their patients to keep them engaged in the program. Because it is typical for a pediatrician to see their patients only once a year, the Parks Rx 4Health™ program provides a significant incentive for their participation to learn about not only if they are consistently engaging in a healthy weight program, but they are gaining health benefits as well.

Another critical lesson learned is the importance of fluid team communication among the clinical, research and parks team members. During the first week of Parks Rx 4Health™ roll out, the pediatrician team was experiencing a technical difficulty with the web-based registration form. This was quickly resolved by the MDPROS team through one simple telephone call. Communication between MDRPOS staff and Parks Rx 4Health™ families and their children is also a critical component of program success. Parents like to hear their children are enjoying the program, and improving their health, as supported by their family pediatrician. Our Parks Rx 4Health™ children like to hear they are doing well and enjoy being encouraged daily to pursue personal health goals.

Future plans

Our UMMSM-MDPROS Parks Rx 4Health™ program will begin Phase Ⅱ with summer 2016 referrals for the

2016-2017 school year. Additional components that will be included in this phase are (1) a 2-min video loop that will play in all patient rooms for parents/families to view that will feature children participating in Fit2Play™ and describe their experiences during the program; (2) weekly nutrition and health and wellness materials that will go home on Fridays with Parks Rx 4Health™ participants. Each week will feature one key nutrition and/or physical activity message; (3) the expansion of the UMMSM-MDPROS Parks Rx 4Health™ website to include supplemental health and wellness materials and resources for families to access at any time; (4) family-based activities on weekends and after hours that both parents and children can participate in as a family. This is one of the major advantages of conducting such a program in a large urban parks system; the variety of activities available at minimum to no-cost while enjoying nature and the outdoors; and (5) the option of a consultation visit with a UMMSM faculty member to discuss family health and wellness goals and strategies to meet these goals.

Another area of scientific interest to the team is the contribution of genetics *vs* environment to the current childhood obesity epidemic, particularly because our patient population is so ethnically diverse and most have family origins from outside the United States. Genome-wide association studies in pediatric populations have produced evidence to indicate a genetic component involvement in the occurrence and development of obesity[38-41]. In particular, the fat mass and obesity-associated gene (*FTO*) has received increased attention for being associated with the development of obesity[42]. A recent meta-analysis of 12 studies (that included 5000 cases and 9853 controls) has shown that the FTO rs9939609 polymorphism is associated with the increased risk of obesity among children and adolescents[43]. However, the major proportion of study subjects were Caucasian, and FTO polymorphism have actually been shown to not affect BMI or the risk of obesity in African Americans[41], a population who has been consistently shown to be at greater risk for obesity *vs* Caucasians[2,3]. Given that the overwhelming majority of Park Rx 4Health patients are not Caucasian, and about half are non-Hispanic black, one must consider that the patient's environment is having a greater impact on their weight than their genetic predisposition. For example, studies have shown that physical activity (*vs* sedentary behavior) counters the genetic predisposition to obesity[44]. These findings have major implications to the Park Rx 4Health program because its referral program Fit2Play™ has daily non-stop physical activity as its cornerstone. So, perhaps if we do capture patients with a genetic predisposition to obesity we can influence a gene-environment interaction by keeping them consistently physically active during the pediatric years. While the literature on obesity-related gene-environment interactions is still immature, it will no doubt be an area of much scientific inquiry in the future as obesity continues to spread around the globe.

Park Rx 4Health™ impact

Our UMMSM-MDPROS Parks Rx 4Health™ program described here will move us closer to accomplishing the following Healthy People goals set by the State of FL: Goal 1: Help all children meet their full potential ("making sure children develop healthfully with regard to height, weight, *etc.*); Goal 2: Reduce mortality and morbidity in children (particularly from such chronic diseases as type 2 diabetes and cardiovascular disease); and Goal 3: Reduce disparities in child health outcomes[1]. Moreover, Section 4004(i) of the Affordable Care Act requires the Department of Health and Human Services to provide guidance to States regarding preventive and obesity-related services available to individuals enrolled in Medicaid/Children's Health Insurance Program[45]. It also requires States to design public awareness campaigns to educate Medicaid enrollees, as well as those with other insurance carriers on the availability and coverage of such services. The Park Rx 4Health™ program described here can help close the gap between patient needs and prevention service providers[46].

CONCLUSION

Identifying successful models that integrate primary care, public health and community-based efforts is important to accelerating progress in preventing childhood obesity. Effective, community-based health and wellness programs with a focus on physical activity and nutrition education could be a powerful referral resource for pediatricians who have obese patients.

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EDITORIAL

Transitioning antimicrobials from intravenous to oral in pediatric acute uncomplicated osteomyelitis

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Abstract

Osteomyelitis is a bone infection that requires prolonged antibiotic treatment and potential surgical intervention. If left untreated, acute osteomyelitis can lead to chronic osteomyelitis and overwhelming sepsis. Early treatment is necessary to prevent complications, and the standard of care is progressing to a shorter duration of intravenous (*IV*) antibiotics and transitioning to oral therapy for the rest of the treatment course. We systematically reviewed the current literature on pediatric patients with acute osteomyelitis to determine when and how to transition to oral antibiotics from a short *IV* course. Studies have shown that switching to oral after a short course (*i.e.*, 3-7 d) of *IV* therapy has similar cure rates to continuing long-term *IV* therapy. Prolonged *IV* use is also associated with increased risk of complications. Parameters that help guide clinicians on making the switch include a downward trend in fever, improvement in local tenderness, and a normalization in C-reactive protein concentration. Based on the available literature, we recommend transitioning antibiotics to oral after 3-7 d of *IV* therapy for pediatric patients (except neonates) with acute uncomplicated osteomyelitis if there are signs of clinical improvement, and such regimen should be continued for a total antibiotic duration of four to six weeks.

Key words: Antimicrobials; C-reactive protein; Intravenous; Oral; Osteomyelitis; Pediatrics

Core tip: When is an appropriate time to switch to oral antibiotics is a challenging question surrounding the treatment of acute uncomplicated osteomyelitis in pediatrics. With improvements in disease management and antibiotic therapy, the standard of care is progressing to a shorter duration of intravenous antibiotics and transitioning to oral therapy for the rest of the treatment course. This review aims to evaluate the current literature in order to help clinicians make sound decisions on when and how to transition from intravenous antibiotics to oral therapy in pediatric patients with acute uncomplicated osteomyelitis.

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INTRODUCTION

Osteomyelitis is an infection of the bone. These infections can spread to the bone numerous ways including trauma, cellulitis, septic arthritis, or bacteremia. Acute osteomyelitis in children is most commonly hematogenous in origin[1]. In high-income countries, acute osteomyelitis occurs in about 8 of 100000 children per year, but it is considerably more common in low-income countries[2]. Boys are two times more prone to acute osteomyelitis than girls[2]. While *Kingella kingae* is the most common causative organism of acute osteomyelitis below the age of 4 years[3], *Staphylococcus aureus* (*S. aureus*) is the predominant pathogen in older children, followed by *Streptococcus pyogenes*[2,4].

Osteomyelitis can be classified into three separate categories: Acute, subacute, and chronic. Osteomyelitis is considered as acute if the duration of illness is less than two weeks; subacute, if the duration is two weeks to three months; and chronic, if the duration is longer than three months[5]. Clinical manifestations of osteomyelitis can vary depending on the location of the infected bone, but since the majority of osteomyelitis in children affects the bones of the legs, a classic sign is limping or an inability to walk[6]. Other symptoms include fever, focal tenderness, visible redness, or swelling around the infected area[6]. If physical examination suggests bone involvement, then further studies are necessary. Radiograph can show signs of osteomyelitis two to three weeks after symptom onset so an early negative radiograph cannot rule out acute osteomyelitis[6]. Magnetic resonance imaging remains the most useful imaging method for diagnosing osteomyelitis, but it presents other problems such as an increase in cost and the potential requirement of sedation in pediatric patients[6].

Elevations in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) also have high sensitivities for diagnosis[6]. Both CRP and ESR are strong markers of systemic inflammation in the body, but CRP has a much shorter half-life which makes it more useful in acute osteomyelitis[6,7]. A CRP level of 2 mg/dL and above has been found to be sensitive in the diagnosis of osteomyelitis, and this level tends to descend quickly during the early treatment phase if the proper antibiotic is used[7].

The role of surgery in pediatric patients with acute osteomyelitis is not well understood because of the lack of randomized trials regarding this subject. Questions remain about the overall need for surgical intervention other than biopsy to diagnose osteomyelitis and help guide antimicrobial treatment. Conservative treatment is effective up to 90% of the time in acute osteomyelitis if it is diagnosed early in the course of illness[8,9]. Therefore, the general recommendation for acute osteomyelitis requires a prolonged course of antibiotics. In the past, four to six weeks of antibiotic therapy delivered through the intravenous (*IV*) route was the standard of care and often required the placement of a peripherally inserted central catheter (PICC) for medication administration. PICC's are effective for delivering high concentrations of antibiotics for serious infections but have several downfalls including the risk of developing other infections, thrombotic events, and mechanical complications[10]. Because of these potential problems, many clinicians have started looking into transitioning to oral antibiotics sooner. This review aims to evaluate the current literature in order to help clinicians make sound decisions on when and how to transition from *IV* antibiotics to oral therapy in pediatric patients with acute uncomplicated osteomyelitis, defined as osteomyelitis without any open wounds, fractures or adjacent joint infection and with clinical symptoms of less than 2 wk[11].

RESEARCH

MEDLINE/PubMed searches were performed by the investigators to identify all literature published over the past two decades since 1996 that addressed antibiotic management for osteomyelitis in pediatric patients. The searches were done on PubMed (http://www.ncbi.nlm.nih.gov). One set was created using the Medical subject heading (MeSH) terms "pediatric" OR "children", "osteomyelitis", "antibiotic", "intravenous", and "oral". Combining the five sets with the Boolean "AND" function yielded 61 citations. We included article types consisting of only clinical trials, journal articles, reviews, and systematic reviews. We limited our search to articles that had full text and excluded abstracts only, case reports, incomplete reports, and letters from our review.

LITERATURE EVALUATION

One of the first studies that evaluated early transition of antibiotics to oral therapy in pediatric patients with acute osteomyelitis was by Peltola *et al*[12] in 1997. This was a prospective study with the purpose of simplifying treatment of confirmed acute staphylococcal osteomyelitis in fifty children between the ages of three months and fourteen years[12]. The majority of patients were diagnosed with plain osteomyelitis without adjacent joint infection. Sixty-two percent of the patients underwent no surgery or only needle aspiration as a diagnostic tool during the treatment period[12]. Patients received either 37.5 mg/kg every 6 h of cephradine or clindamycin at 10 mg/kg every 6 h intravenously. This

cohort had an average baseline CRP level of around 7 mg/dL which continued to rise on the first couple of days and then started to decline after the antibiotic had started clearing the infection[12]. After three to four days of therapy, the antibiotic was switched to oral for a total treatment duration of three to four weeks[12]. These children had an average hospitalization of eleven days, and their CRP (*i.e.*, < 2 mg/dL) and ESR (*i.e.*, < 20 mm/h) normalized within nine days and twenty-nine days, respectively[12]. The results showed that early transition to oral antibiotics within four days did not cause any treatment failure or long-term sequelae in this cohort of pediatric patients with acute uncomplicated osteomyelitis[12]. This study was one of the first looking at a short duration of *IV* antibiotics and was able to assess several outcomes, but the results might be limited by its small sample size.

Another prospective, randomized study on the treatment of acute osteomyelitis in pediatric patients was performed in 2010[13]. One hundred and thirty-one children aged three months to fifteen years were randomized to receive either two to four days of *IV* treatment followed by oral antibiotics for either twenty or thirty days[13]. The majority of the diagnosed osteomyelitis pertained to the long bones of the lower extremity that were caused by methicillin-susceptible *S. aureus* (MSSA)[13]. Dosing of antibiotics used were clindamycin 40 mg/kg per day divided into four doses or cephradine 150 mg/kg per day divided into four doses[13]. Majority of the children went through diagnostic aspiration; only 24% of the patients did not undergo any surgery[13]. The primary outcome was the comparison of full recovery from acute osteomyelitis between the 20-d and 30-d groups[13]. CRP levels were monitored and showed an elevation on the first two days of treatment with an average baseline of 9.9 mg/dL, but this inflammatory marker began to trend down as the antibiotic course progressed with the majority of CRP levels being less than 2 mg/dL by day nine[13]. The data of this study showed excellent results for both groups, and they found that there were not any significant radiological, hematological, or clinical differences between the groups[13]. The authors concluded that a shorter 20-d course of antibiotics with only two to four days of *IV* therapy are enough for the treatment of acute osteomyelitis if the child is clinically improving and the CRP has gone down to below 2 mg/dL within seven to ten days[13]. A strength of this study is its design giving it valuable internal validity, but some children received other antibiotic in addition to the recommended agents and the treatment duration was not always the exact twenty or thirty days.

A study by Arnold *et al*[14] specifically looked at CRP levels as a marker to help clinicians decide on when to step down to oral therapy for acute bacterial osteoarticular infections. This study consisted of a primary chart review of 194 children from one month to eighteen years old with either acute bacterial arthritis (n = 32), acute bacterial osteomyelitis (n = 113), or both (n = 49)[14]. Surgical intervention was not discussed in this study. These subjects' CRP averaged at 9.1 ± 7.4 mg/dL on admission and 2.0 ± 1.8 mg/dL when the patients were transitioned to oral antibiotics[14]. The mean duration of *IV* therapy was 1.7 wk and the mean duration of total antibiotic course was 7.1 wk[14]. The most common organism causing the infection was MSSA[14]. Out of the 194 patients, all but one were successfully treated with step-down oral therapy after having clinical improvement and an elevated CRP that had decreased below 3 mg/dL[14]. The child who failed therapy was thought to have had a fragment of infected bone in the joint space that was not removed at the time of initial surgical debridement[14]. This study was able to maintain the sequence of events as a retrospective study, but capturing the information from a chart review might have led to limitations regarding data collection.

A systematic review from 2002 evaluated the appropriate duration of *IV* antibiotics for acute hematogenous osteomyelitis due primarily to *S. aureus* in children aged three months to sixteen years[10]. Two hundred and thirty children were included in this review that compared clinical cure rates at six months in patients who received seven days or less of *IV* therapy to those who received greater than one week of *IV* therapy[10]. Thirty to around ninety percent of the patients underwent surgical intervention. In most cases, it was not stated whether these procedures were for diagnostic or therapeutic purposes. The patients' CRP levels were not reported in this study. No significant difference was observed between the groups in regards to the total duration of antibiotic treatment[10]. The cure rates between the groups were statistically insignificant (P = 0.224) as the cure rate for the shorter *IV* therapy group was 95.2% (95%CI: 90.4-97.7) and the other group had a cure rate of 98.8% (95%CI: 93.6-99.8)[10]. The authors of this systematic review concluded that the efficacy is similar between a short and long course of *IV* antibiotics for the treatment of acute uncomplicated osteomyelitis in pediatric patients, and it is appropriate to switch to oral for the rest of the treatment course after seven days of *IV* antibiotics[10]. This systematic review had a good sample size, but it only looked at cohort studies and did not include results from any randomized controlled trials.

Since that time, more trials and reviews had shown similar results in that a short course of *IV* antibiotics with a transition to oral therapy did not show any differences in clinical outcomes compared to long courses of *IV* antibiotics even when the short course of *IV* therapy was given for less than one week[15-18]. For example, a prospective, bi-center study collected data on seventy consecutive children aged two weeks to fourteen years[15]. These children did not have any underlying disease or medical condition predisposing them to infection[15]. All of the cases were found to be from *S. aureus* and the median duration of hospital stay was five days[15]. Surgical intervention was not discussed in

this study. The outcomes showed that 59% of children were converted to oral therapy after three days and 86% after five days of *IV* antibiotics[15]. This study revealed that a prolonged fever (*i.e.*, > 3-5 d) and an elevated initial CRP (*i.e.*, > 10 mg/dL) resulted in patients requiring longer *IV* treatment probably because the clinicians did not want to switch to oral agents when there were persistent elevations in the inflammatory markers[15]. This study demonstrated that in otherwise healthy patients, three weeks of total antibiotic therapy should be appropriate if the patients have already finished five days or less of *IV* treatment[15]. The authors also concluded that temperature and CRP were the best quantitative measurements for monitoring and assessing patients' response to therapy[15].

Another large retrospective study was performed by Zaoutis *et al*[19] that aimed to compare the treatment failure rate between patients two months to seventeen years old (n = 1969) discharged with *IV* and oral antibiotics. One thousand and twenty-one patients had a central venous catheter placed for long-term *IV* therapy and 948 patients received oral therapy at discharge[19]. The two groups were virtually identical in terms of demographic characteristics, which included 37% of the subjects in the *IV* therapy group and 33% in the oral therapy group who had undergone a surgical procedure for diagnostic or treatment purposes[19]. The median length of stay in the hospital prior to discharge was five days for the *IV* group and four days for the oral group[19]. The primary outcome of the study was treatment failure defined as re-hospitalization within six months with an assigned diagnosis or procedure code consistent with osteomyelitis[19]. The treatment failure was 5% in the prolonged *IV* group and 4% in the oral group (OR = 0.77, 95%CI: 0.49-1.22)[19]. The authors concluded that early transition to oral therapy did not increase the risk of treatment failure[19]. A limitation of this large retrospective study is the possibility that some patients might have been admitted to other hospitals not included in this study for treatment failure or complications.

Similarly, a systematic review in 2013 assessed a primary outcome of cure rates in protracted treatment compared to a shorter duration of antibiotic therapy[18]. The results stemmed from six randomized controlled trials and twenty-eight observational studies[18]. Most of the studies included did not mention the use of surgical procedures for treatment, except for one randomized controlled trial that included 12 children who went through surgical drainage. The majority of the randomized controlled trials focused on the choice of antibiotic or total duration of treatment[18]. The bulk of the observational studies addressed the duration of *IV* treatment and were split into two groups: Short duration which consisted of all studies that had less than seven days of *IV* antibiotic therapy and long duration which included all studies that had seven days or greater of *IV* antibiotic therapy[18]. The success rate of the short-duration group ranged from 77%-100% and that of the long-duration group ranged from 80%-100%[18]. This 2013 review concluded that acute uncomplicated osteomyelitis in children greater than three months old can be treated with three to four days of *IV* antibiotics and be transitioned to oral if the child is clinically improving[18]. The authors classified the strength of their recommendations as weak because the review was derived from observational studies and a small number of randomized controlled trials with important limitations in regards to lack of blinding, small sample size, or a prolonged recruitment period.

A recent retrospective study published in 2015 evaluated the clinical outcome of 2060 children who were either discharged with *IV* or oral antibiotic[1]. The majority of patients were male, aged five to thirteen years, Caucasians, and had osteomyelitis of the leg, foot, or ankle. One thousand and five children received oral antibiotics at discharge and the remaining 1055 children received antibiotics *via* a PICC line[1]. The baseline characteristics showed that 17.1%, 39%, 13.5%, and 16.7% of participants underwent arthrocentesis, osteotomy, incision and drainage, and arthrotomy, respectively[1]. This study did not report on the participants' CRP levels. The median length of stay in the hospital was six days for both groups before being discharged with either an oral or *IV* antibiotic[1]. This study showed that treatment failure was 5% in patients discharged with oral antibiotic therapy and 6% in the group who received antibiotics through a PICC at discharge with no statistical significance (P = 0.77)[1]. A high frequency of PICC-related adverse outcomes requiring ED visits or re-hospitalization was observed in the *IV* group compared to the oral group[1]. Despite of the limited data on treating young children less than five years of age with oral therapy, this large retrospective study showed that there was not any clinically relevant difference in treatment efficacy between *IV* and oral therapy in this age group[1]. This study also looked to see if the isolation of MRSA as the cause of osteomyelitis had an impact on the effect of the treatment route, but the results did not show any difference either[1].

Dartnell *et al*[7] performed the largest systematic review on this controversy to date which included over 12000 cases of pediatric patients with acute osteomyelitis. The majority of patients presented with acute osteomyelitis of the lower extremity and initially had localized pain and fever[7]. This systematic review discussed the role of surgery, but it did not mention the overall percentage of patients in the cohort who had such intervention[7]. The initial average CRP level was elevated at 8.5 mg/dL and resulted in a peak level around day two of treatment[7]. Twelve of the included studies were described as prospective, but there was only one randomized controlled study which made statistical analysis of all these studies combined not achievable[7]. This review concluded that short-term parenteral medication is acceptable in cases of osteomyelitis when the patients do not show any signs of complications and exhibit clinical improvement and

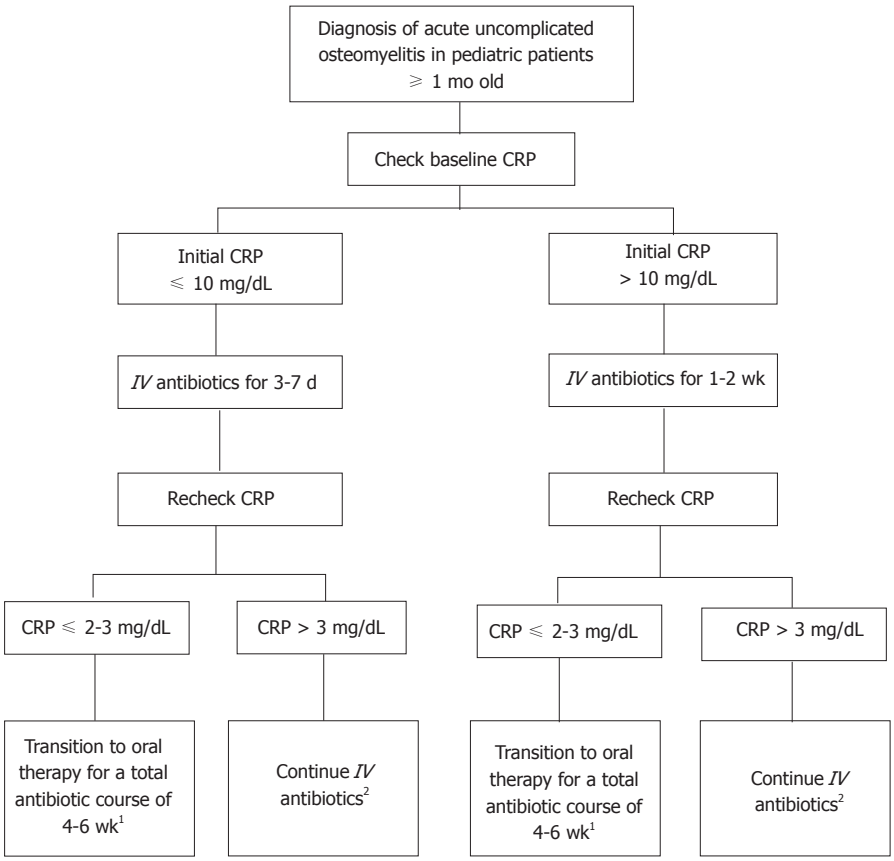

Figure 1 Proposed algorithm of the transition to oral antibiotics from intravenous therapy for pediatric patients with acute uncomplicated osteomyelitis. [1]Patient must be afebrile, have remarkably improved focal tenderness, and tolerate oral medication. If they do not meet these criteria, continue *IV* therapy until these criteria are met; [2]Consider rechecking CRP level in 3-7 d and re-evaluating the appropriateness of continuing *IV* therapy *vs* switching to an oral antibiotic for a total antibiotic course of 4-6 wk (note: The method used in this scenario has not yet been clinically studied and validated). CRP: C-reactive protein; IV: Intravenous.

normalization of hematological markers within the first few days of *IV* therapy provided that the oral antibiotic is effective, the microorganism isolated is susceptible to the administered drug, and the correct dose is used[7]. The authors also added that there is an increasing evidence that long-term *IV* therapy can do more harm than good and can lead to complications that may arise from extended *IV* treatment[7]. This systematic review did include some reports from developing countries which provided useful information, but it might lack external validity when trying to extrapolate the data to developed countries.

There is an ongoing study by Grimbly *et al*[2] that aims to evaluate the literature looking for evidence to support the optimal duration of treatment for both parenteral and oral therapy when managing acute osteomyelitis in children less than eighteen years of age[2]. The authors will conduct a comprehensive review of approximately 3400 studies; these studies will be limited to randomized and quasi-randomized controlled trials found through multiple database searches that compare an *IV* antibiotic course of less than seven days to that greater than seven days[2]. Studies included will describe the antibiotics used as well as the route and duration for at least a three-month timespan[2]. The primary outcome of this study will be the success of the treatment options by the end of therapy defined by resolution of symptoms which include pain, local tenderness, swelling, and gait abnormalities[2]. One of the secondary outcomes will be looking at surgical intervention. The results of this study will surely add to the strength of the current evidence for the early transition of antibiotics to oral in pediatric patients with acute uncomplicated osteomyelitis. Table 1 summarizes all the aforementioned studies.

CLINICAL APPLICATION

After reviewing the available literature, we recommend managing pediatric patients with acute uncomplicated osteomyelitis initially with *IV* antibiotics. Their fever curve, site tenderness, clinical status, and CRP level should be closely monitored. If there are improvements in these infection markers, the *IV* therapy can then be transitioned to oral because the latter has been shown to be just as efficacious as *IV* therapy in treating acute uncomplicated osteomyelitis. A baseline CRP level should be obtained in the patients before starting an antibiotic. After the first several days (*i.e.*, 3-7 d) of *IV* therapy, we suggest rechecking a CRP level; and if the CRP level is less than 2-3 mg/dL, the clinicians can then consider transitioning to oral antibiotics (Figure

Table 1 Published studies evaluating the transition of antibiotics from intravenous to oral for acute uncomplicated osteomyelitis in the pediatric population

Ref.	Study type	Population	Objective	Results	Conclusion
Peltola *et al*[12]	Prospective	50 children (3 mo to 14 yr)	Determined the full recovery rate and remaining health of patients transitioned to oral antibiotics at 12 mo from hospital discharge	100% had full recovery	Treatment of pediatric osteomyelitis can be simplified and costs reduced by switching to oral early on in the treatment course
Le Saux *et al*[10]	Systematic review (12 prospective studies)	230 children (3 mo to 16 yr)	Compared the cure rates at 6 mo for *IV* therapy ≤ 7 d and > 7 d	95.2% - ≤ 7 d (P = 0.224) 98.8% - > 7 d (P = 0.248)	Similar cure rates between groups Increased morbidity and cost associated with long-term *IV* therapy
Prado *et al*[17]	Retrospective	70 children (< 15 yr)	Assessed the efficacy of the transition to oral antibiotic after 7 d of *IV* therapy	No child had a complication from treatment	Seven days of an *IV* antibiotic for the initial treatment phase of acute osteomyelitis was effective in the majority of children
Zaoutis *et al*[19]	Retrospective cohort	1969 children (2 mo to 17 yr)	Compared the treatment failure rate between patients discharged with *IV* and oral antibiotics	5% - *IV* group 4% - Oral group OR = 0.77, 95%CI: 0.49-1.22	Early transition to oral therapy did not increase the risk of treatment failure
Jagodzinski *et al*[15]	Prospective cohort	70 children (≤ 16 yr)	Determined the parameters for prolonged *IV* antibiotic therapy of > 6 d	Fever > 38.4 °C for 3 to 5 d Admission CRP > 10 mg/dL	3-5 d of *IV* antibiotic therapy followed by oral therapy for 3 wk is sufficient for uncomplicated osteoarticular infections
Peltola *et al*[13]	Prospective randomized	131 children (3 mo to 15 yr)	Compared 20-d *vs* 30-d treatment with *IV* therapy for the first 2-4 d	98.5% had full recovery	Most childhood osteomyelitis can be treated for a total antibiotic course of 20 d with only 2-4 d of *IV* therapy
Dartnell *et al*[7]	Comprehensive systematic review (132 studies)	> 12000 children (< 18 yr)	Reviewed the different features of osteomyelitis to formulate a recommendation on treatment	Short course of *IV* therapy is acceptable	Clinical improvements of tenderness, normal temperature, and normalized CRP (< 2 mg/dL) are good indicators for converting *IV* antibiotics to oral[1]
Arnold *et al*[14]	Chart review	194 children (1 mo to 18 yr)	Evaluated if CRP is a good marker to use for transitioning therapy to oral	99.5% success rate	CRP (*i.e.*, < 3 mg/dL) is a useful tool along with other clinical findings to help transition to oral therapy
Liu *et al*[16]	Retrospective	95 children (≤ 17 yr)	Compared recurrence rates of osteomyelitis at discharge with *IV* or oral therapy	0% - Oral 9% - Intravenous (P = 0.59)	Early transition to oral antibiotics may offer similar recurrence rates of osteomyelitis
Howard-Jones *et al*[18]	Systematic review (28 observational and 6 randomized)	Approximately 3000 children (< 18 yr)	Compared cure rates between shorter and longer durations of *IV* therapy	77%-100% - Short duration 80%-100% - Long duration	Early transition to oral therapy after 3-4 d of intravenous therapy is as effective as longer courses[1]
Keren *et al*[1]	Retrospective cohort	2060 children (2 mo to 18 yr)	Compared therapy failure between PICC administered antibiotics and oral antibiotics	5% - Oral route 6% - PICC route OR = 1.06, 95%CI: 0.70-1.61	No advantage of antibiotics *via* PICC line Increased complications with PICC line

[1]Does not apply to neonates. CRP: C-reactive protein; IV: Intravenous; PICC: Peripherally inserted central catheter.

1). However, if the CRP is still above 2-3 mg/dL at that time, *IV* antibiotics should be continued and the CRP can be rechecked in a few more days. If the CRP level continues to increase from baseline by the fourth day of treatment, then this should alert the clinician that the patients may have developed some complications from the infection and thus may require thorough re-evaluation, a longer course of *IV* antibiotic, and/or a surgical intervention[10].

Some patients, however, may not be good candidates for switching over to oral antibiotics after a short *IV* course. If the child has fevers persisting for more than three to five days after starting treatment, then *IV* antibiotics should be continued for a longer course. Also, if the initial CRP is above 10 mg/dL, which usually correlates to a more severe and potentially complicated osteomyelitis, a longer duration of *IV* therapy may be necessary[7,15]. This clinical practice has not been studied in neonates with acute uncomplicated osteomyelitis; as a result, this population should continue receiving a longer-term of *IV* antibiotics to ensure that the infection is treated properly. Besides neonates, patients with complicated osteomyelitis such as bone fracture, bacteremia, abscess, growth arrest, or chronic infection also should not transition to oral therapy early. Patients with other comorbid conditions such as diabetes mellitus, sickle-cell disease, or children who are immuno-compromised should consider receiving a longer course

of *IV* antibiotics due to their clinical condition predisposing them to a more serious infection. Finally, patients who have a history of osteomyelitis or recent treatment failure for acute osteomyelitis should also consider a longer duration of *IV* therapy until studies are performed to evaluate the appropriateness of early transition of antibiotics to oral in this population.

Several practical advantages of a shorter course of *IV* antibiotic exist, and they include a shorter hospital stay, decreased morbidity from *IV* lines, and more cost effectiveness[12]. A common issue causing longer hospital stay is that the patients continue to have an *IV* line in place preventing discharge. Transitioning to oral therapy when clinically ready will help shorten hospitalization. Switching to oral therapy can also decrease the risk of complications related to long-term *IV* antibiotic administration. Most complications from *IV* lines are not serious, but they do result in significant increase in emergency department or clinic visits, or even hospital readmissions[14]. These complications, as a result, can increase cost burden for the healthcare system. Considering the cost of *IV* antibiotic treatment *vs* oral, there is a huge difference between the two[5]. In summary, since there are not any clinical differences observed in the early transition to oral antibiotics, clinicians can surely consider such practice in their pediatric patients with acute uncomplicated osteomyelitis.

CONCLUSION

Clinicians should consider transitioning antibiotic from *IV* to oral in pediatric patients with acute osteomyelitis when there is a downward trend in their fever curve, improved tenderness in the affected area, a reduction in CRP, and overall clinical improvement. These recommendations only pertain to patients with acute uncomplicated osteomyelitis that are responding well to early *IV* treatment. Questions relating to this clinical practice that still need to be answered include the appropriateness of such early transition in neonates and if specific organisms direct such transitions from *IV* to oral therapy.

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FRONTIER

Critical evaluation of unscientific arguments disparaging affirmative infant male circumcision policy

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Abstract

We evaluate recent claims opposing infant male circumcision, a procedure now supported by the evidence-based policy of the American Academy of Pediatrics. We find those criticisms depend on speculative claims about the foreskin and obfuscation of the strong scientific evidence supporting pediatric policy development. An argument that circumcision should be delayed to allow a boy to make up his own mind as an adult fails to appreciate the psychological, scheduling and financial burdens later circumcision entails, so reducing the likelihood that it will occur. In contrast, early infant circumcision is convenient, safer, quicker, lower risk, healing is faster, cosmetic outcome is routinely good and the lifetime benefits accrue immediately. Benefits include reduction in urinary tract infections, inflammatory skin conditions, foreskin problems, and, when older, substantial protection against sexually transmitted infections and genital cancers in the male and his female sexual partners. Some authorities regard the failure to offer parents early infant circumcision as unethical, just as it would be unethical to fail to encourage the vaccination of children. In conclusion, the criticisms of evidence-based infant male circumcision policy are seriously flawed and should be dismissed as unhelpful to evidence-based development and implementation of pediatric policy intended to improve public health and individual wellbeing.

Key words: Male circumcision; Policy; American Academy of Pediatrics; Newborn; Foreskin

Core tip: This article critically assesses an extensive compendium of detailed arguments criticizing the American Academy of Pediatrics policy in support of infant male circumcision. The article we assess is by an historian, Robert Darby, who is opposed to infant circumcision. It should be recognized that the American Academy of Pediatrics policy on infant male circumcision was developed on the basis of the latest scientific evidence. The policy reported that benefits exceed

risks and recommended unbiased education of parents and providers, as well as facilitation of access and improvement in affordability by increased third party insurance coverage. We present the scientific evidence undermining Darby's arguments. Our evaluation leads us to conclude that the criticisms by Darby should be dismissed as unreliable.

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INTRODUCTION

We evaluate very extensive criticisms[1] of the American Academy of Pediatrics (AAP) infant male circumcision (IMC) policy that found benefits of IMC substantially outweigh the risks[2]. The 34-page article asserts that, "the AAP's conclusion is untenable", because no consideration was given to broader risks than surgical complications. In essence, it argues that IMC is unethical because of: (1) supposed long-term risks resulting from loss of the foreskin; (2) that only the owner of the foreskin should decide whether he wishes to be circumcised; and (3) a claim that since the foreskin is, "erotogenic", circumcision diminishes sexual pleasure for the man.

In the interests of medical decision-making, public health policy and the rights of parents to receive accurate information to facilitate decision-making about the circumcision of a baby boy, the numerous criticisms of the AAP's policy deserve an appropriate critical response.

CENTRAL ARGUMENTS

The fundamental thesis underlying the criticisms is the statement that, "we can be confident that the average individual would be far more relaxed about losing his tonsils or appendix than an erotogenic feature of his genitals". That generalization is not supported by current medical or biological evidence.

The article cites previous criticisms of the AAP's policy[3,4], without noting detailed responses by the AAP[5] and academic experts[6] disputing those criticisms.

OTHER POLICY STATEMENTS

Outdated, non-evidence-based, IMC policy statements are cited. One, by the Royal Australasian College of Physicians[7], was found to contain fundamental flaws and failed to accurately review the literature[8].

Besides the AAP policy, evidence-based policy statements have been produced by the Centers for Disease Control and Prevention (CDC)[9] and the Circumcision Academy of Australia (CAA)[10]. Each found that benefits of IMC greatly exceed risks.

FORESKIN ANATOMY AND FUNCTION

Opponents are concerned about, "the anatomy or functions of the foreskin"[1]. Leaving speculation aside, survey evidence suggests a foreskin may make it easier for a woman to bring a man to orgasm manually, but little else[11]. A prepuce may be "healthy" and "visible", but whether it is "functional" depends on what use it is put to (discussed later). Rather than being, "of great significance to most males", strong scientific evidence indicates the foreskin poses a health risk from minor and major conditions, including genital cancers, urinary tract infections (UTI), human immunodeficiency virus (HIV) infection and other sexually transmitted infections (STIs)[2,9,12].

Foreskin removal by circumcision is referred to in the article as, "amputation"[1]. Since the medical definition of amputation is the removal of a limb, digit or the entire penis, that term is misused and inaccurate.

The article claims, "recent research", shows that the foreskin, "contains one of the densest concentrations of nerve endings in the body", citing 16-19 year-old publications[1]. In fact, current research shows that sensory nerve endings in the foreskin are actually lower in number and smaller in size than those in other glaborous (hairless) tissues[13]. The article further claims, "the foreskin is an ingenious piece of biological engineering, the functions of which are primarily erotic", that, "its specialized web of nerve endings convey fine touch sensations" and that its, "mechanical action in sliding back and forth stimulates and lubricates the glans, thus facilitating sexual activity of all kinds". Instead of citing experimental evidence from the peer-reviewed literature, it cites a book written to discredit circumcision[14].

A 300 year-old book is cited in claiming the importance of the foreskin was well understood up until the late nineteenth century. The article argues that subsequent Victorian "mistakes" about the foreskin, "have been corrected by recent research". However, two of the three publications used as support[15,16] contain serious flaws[17,18] undermining their conclusions. The third, a small telephone survey of 109 men $\geqslant$ 3 mo after circumcision[19], was too small to make accurate conclusions about sexual dysfunction, these apparently being related to diabetes or older age. Owing to phimosis, which is common in uncircumcised men, 50% of the men experienced pain during intercourse prior to circumcision, falling to 6.5% after circumcision.

SEXUAL PLEASURE INVOLVES THE GLANS

The claim that special sensory receptors in the foreskin

make it, "the principal sensory platform of the penis"[1] is no longer tenable. A recent systematic review of all histological and anatomical data on sensory receptors in the penis, including changes during puberty, concluded that, contrary to the article's claim, the foreskin has no role in sexual sensation[20]. Nerve endings involved in sexual pleasure reside in the glans, the underside being particularly sensitive. Stimulation of the exposed glans is the source of sexual sensations during sexual activity[20]. In support, a detailed systematic literature review[21], a meta-analysis of sexual dysfunction in men[22], two randomized controlled trials (RCTs)[23,24] and a large United Kingdom study[25] found male circumcision has no adverse effect on sexual function, sensitivity or sensation. Recent sensitivity testing of different penile sites dismissed the claim that the foreskin is the most sensitive part of the penis[26].

OTHER CLAIMS

The article maintains that the foreskin serves as a valve to, "let urine out" while, "blocking the entry of dirt", that it provides lubrication, that it protects the glans, the latter apparently being, "an internal organ" that is, "easily irritated" and, "eventually desensitized, if it is exposed to the abrasion of clothes, *etc.*", and that the foreskin is a, "slack tissue" somehow needed for erection[1]. Anecdotes and the author's own highly criticized[27] monograph disputing Victorian ideas[28] are used as "evidence". Scientific support for these claims is lacking.

HIGH STAKES IN THE HARM QUESTION

The statement, "if it were proved that one value of the foreskin was to enhance genital sensation and function (foreskin removal) would undoubtedly be counted as a harm"[1] has been disproved by multiple studies[20-26]. Overall, sexual function, sensation and pleasure are either the same or better after circumcision[20-26]. Instead of scientific studies, support is drawn from historical anecdotes, outmoded opinion pieces by opponents, and discredited or weak publications considered above. There may be some (not "many"), "circumcised men who resent their condition". Apart from very rare cases of damage to the penis from an inexperienced operator, any resentment is likely a result of some men with sexual dysfunctions believing claims by circumcision opponents attributing these to their IMC. Other men may read the claims and think they might be missing out on something important by lacking a foreskin.

Rather than ask why, "most men throughout the world have neither been circumcised as children nor elected the operation for themselves as adults", the article should have considered why many men are circumcised. A recent study that determined circumcision prevalence in all 237 countries and territories in the world estimated a global circumcision prevalence of 38%[29], which is high for an elective procedure. Of these, 62% were for religious reasons. Barriers to getting circumcised at a later age are substantial[30], as discussed later.

The article calls for, "advocates to prove that circumcision is both necessary and harmless". That has been accomplished. Extensive reviews of the medical literature, by the AAP[2], CDC[9], and CAA[10], have established that benefits of IMC greatly exceed risks. A CDC study of 1.4 million circumcisions in the United States found the adverse event frequency was 0.4% for IMC, but was 10-20 times higher in older children and men[31]. The vast majority of adverse events were minor and easily treatable with complete resolution.

LEGAL CHALLENGES

The article refers to, "several judgments" by "courts in Europe"[1]. There was only one such judgment. That decision, by a regional court in Cologne, was overturned by legislation enacted by the German Federal Parliament[32]. The German ethics council lent its support to circumcision of boys[33]. The article then cites a, "law reform report from Australia" that calls for, "strict regulation and partial prohibition". That report was written by a graduate student and placed on the Tasmanian Law Reform Institute website in 2012. A critical evaluation of the report by a lawyer, ethicist and medical experts found it had no basis in law, ethics or medicine[34]. The report appears to have been ignored by the Tasmanian Government.

IS CIRCUMCISION REALLY A MEDICAL ANOMALY?

Another claim is that circumcision, "requires special rules". The article did not consider the favorable risk: benefit to be sufficient reason to advocate prophylactic circumcision. It considered vaccination not to be a reasonable comparison, "because the nature, extent, risks and costs of the protection gained or claimed are quite different" and, "vaccination does not entail surgical removal of a significant body part"[1]. While vaccinations protect against many infectious diseases and cancers, IMC is a one-time intervention that provides life-long protection against a wide array of adverse medical conditions, many unrelated to infectious agents. The number of children who need to be vaccinated to prevent one infection[35] is greater than the number of boys who need to be circumcised to prevent adverse medical conditions resulting from failure to circumcise[12].

The article overstates the risks of circumcision. Apart from invoking the disproven belief that, "the foreskin has sexual functions", it suggests "many people" value the foreskin for various, "personal reasons". It cites a sexually explicit website that promotes foreskin use in sexual activities such as "docking", engaged in by some men who have sex with men. The article also cites posts

on, "Internet dating sites" and, "the distress many men feel" at having been circumcised when young. Neither represents scientific evidence.

In contradiction to a 2002 paper by circumcision opponents listing criteria that should be met before childhood circumcision would be permissible, the AAP policy states the, "best interests" of the individual and "public health justifications" are served by ensuring a baby boy is circumcised[2]. The position that circumcision is, "impermissible because it was performed on a minor without consent" does not acknowledge that the same applies to childhood vaccinations.

The claim that, "the human rights cost to the individual exceed the proven public health benefit; and the diseases from which circumcision might provide protection could be avoided through appropriate behavioral choices or otherwise managed without surgery" is not supported by evidence.

For example, circumcision is the only way to prevent balanoposthitis, which only occurs in uncircumcised males, and to reduce balanitis, which is twice as common in the uncircumcised[12].

Condoms, when used correctly and consistently, provide only partial protection against STIs, *e.g.*, 80% against HIV in a Cochrane meta-analysis[36]. However, seven RCTs (two in the United States, one in England and four in sub-Saharan African countries) found, "little clinical evidence of real-world effectiveness of interventions promoting condom use for dual protection" against HIV, but 42% effectiveness in syphilis reduction[37]. It should be noted that, unlike condoms, circumcision is a one-time intervention that provides a lifetime of protection. Condom use should nevertheless be encouraged. Together each confer greater protection than either alone.

Phimosis can be managed using steroid creams, but this requires twice-daily administration for many weeks, the creams are effective for only a portion of cases, have side-effects and, unlike circumcision, do not protect against STIs[38,39] and UTIs[40].

While circumcision does remove, "a genital feature", absence of a foreskin is preferred by most women[11,41-47]. Reasons included esthetics, better hygiene, reduced risk of infection, easier and less traumatic vaginal (or anal) penetration during intercourse, and greater overall sexual pleasure[11,44,45,48]. A large clinical trial found far more men reported an improvement in their sexual experience after having been circumcised, with few stating sex was worse[24]. A possible explanation might be that after circumcision the shaft of the penis makes closer contact with the walls of the vagina during intercourse.

The three studies cited in the article to support a premise that, "circumcision is not ordinary medical treatment"[1] were selective citations of reports by circumcision opponents. The one by Frisch *et al*[49] has been severely criticized[21,50]. The one by O'Hara *et al*[51] was a "preliminary" survey by lay anti-circumcision activists of women, "recruited through … an announcement in an anti-circumcision newsletter". Those authors acknowledged this was a "shortcoming". They stated, "this study has some obvious methodological flaws" and that, "it is important that these findings be confirmed by a prospective study of a randomly selected population of women". Since then a RCT has been conducted[45], and most of the female participants reported a better sexual experience after their male partner had been circumcised.

The claim that the foreskin is as important as the female breast is implausible. The breast is a highly visible female accouterment providing, through its milk, critical nutrition and immune protection for the newborn. In contrast, the foreskin may only be seen when a male exposes his penis. In comparing penile cancer and breast cancer prevalence, the article misleadingly cites lifetime risk for breast cancer (1 in 10), but annual incidence of penile cancer (1 in 100000) rather than lifetime risk (approximately 1 in 1000)[2,9,52].

The article argues that, "it is impossible to identify a single [boy] who died because he had not been circumcised"[1]. A large CDC study reported higher rate of serious adverse events in boys not circumcised[31]. Apart from gangrene, a potential consequence of paraphimosis, these included several types of STIs, which can lead to death[2,9,12,39,52]. UTIs, which is ten times more prevalent in uncircumcised boys[40], can result in potentially fatal complications such as meningitis and sepsis[53]. Deaths from circumcision do occur after initiation ceremonies in sub-Saharan Africa involving non-medical operators. But the claim of 117 deaths in the United States per year from circumcision is fanciful. That figure is based on the false assumption by Daniel Bollinger that the well-known sex difference in infant mortality is entirely a consequence of IMC. A similar sex-difference is seen in countries with low circumcision prevalence[54]. Deaths from medical circumcision in the United States are exceedingly rare[31].

BIOETHICS AND AUTONOMY

The ethics of IMC has been debated extensively. Scholarly assessments suggest circumcision of male minors is ethical[34,55-60]. Given the wide-ranging protection against multiple medical conditions and infections, including STIs in boys who become sexually active early, it has been argued that it would be unethical to leave boys uncircumcised[34,58]. Article 24(3) of the United National Convention on the Rights of the Child has been construed as mandating circumcision, since not circumcising boys should be deemed as prejudicial to their health[58].

In contrast to the claim about tattooing, piercing and genital cutting of girls[1], there are sound medical reasons why IMC should be regarded quite differently. While IMC has cosmetic benefits, it is not merely, "a cosmetic procedure". It provides life-long medical

benefits.

A view expressed that, "the experts are unable to agree"[1], represents obfuscation of the AAP's advice that, "parents should, weigh health benefits and risks in light of their own religious, cultural, and personal preferences, as the medical benefits alone may not outweigh these other considerations for individual families"[2]. All evidence-based policy statements support IMC on medical grounds[2,9,10,61]. As with childhood vaccination, parental consent is required. Moreover, the supposition, "if the risk/benefit equation is only slightly tilted (AAP) or equally balanced"[55] is not supported by the scientific evidence. Draft CDC recommendations state, "In a comprehensive risk-benefit analysis of [IMC] based on reviews of the literature and meta-analyses, it is estimated that over a lifetime, benefits exceed risks by a factor of 100:1"[9]. This risk-benefit analysis cited by the CDC found that the foreskin contributes to adverse medical conditions in half of uncircumcised males during their life-time[12]. Thus the data refute the assertion that a, "situation of uncertainty" exists.

The article rejects parental choice, saying that, "it does not logically follow that parents are the appropriate party to make the proverbial circumcision decision", because, "from the child's point of view" a decision made by others, "denies him autonomy and choice in a matter affecting an intimate part of his own body". An argument that a child has a right to, "bodily integrity" follows the line espoused by circumcision opponents that IMC should be banned, discouraged or at least delayed until the boy is old enough to decide for himself[62-64]. Ethics authorities have refuted this opinion[56-60,65,66]. It has been argued that being circumcised boosts autonomy more than constraining it[67]. The, "circumcision decision" is one of many decisions that a parent must make in the interests of the health of their male child. The AAP recommends that early in a pregnancy the medical practitioner should provide parents with unbiased education about risks and benefits of IMC so they have adequate opportunity to choose what is in the child's best interests should they have a boy[2].

THE BEST TIME TO CIRCUMCISE

Cogent arguments favor early parent-approved IMC over delaying circumcision until the male is old enough to decide for himself[30]. Circumcision in infancy is easier, lower-cost, more convenient, usually involves local anesthesia, healing is quick and cosmetic outcome is good as stitches are not required. In contrast, circumcision of older boys or adults is more difficult technically, poses a higher risk of adverse events[31], is more expensive, and, although can be done using local anesthesia, some operators prefer that general anesthesia be used, so further adding to cost. It means taking time off work or school, and is associated with psychological issues, including fear of pain, unfounded concern about diminished sexual pleasure, of having to undergo an operation, peer pressure not to get circumcised, sexual abstinence until healing is complete, which the man and/or his sexual partner may find unacceptable, and, when sutures are used, a cosmetic result that can be inferior to that achieved by IMC, which does not require sutures[30]. It also means years of not having been protected from adverse medical conditions that affect uncircumcised boys. Taken together, those observations provide a strong case favoring early infancy as being the best time to circumcise[30]. In light of all of this, the argument that the, "decision should still be left to the owner of the foreskin" is likely to mean circumcision will not occur, even if the older male wants to be circumcised. This probably represents the outcome desired by circumcision opponents.

While children and infants, "lack the power to make rational choices and must therefore be guided by adults"[1], it is untrue that, "circumcision is not something that has to be done before a person is capable of rational thought". Although, "children are not sexually active and thus not at risk of disease"[1], circumcision confers multiple benefits in infancy and childhood that are not related to sexual activity.

Benefits include strong protection against UTIs[40] that are common in infancy[68] and can result in permanent kidney damage[53,69-73]. Early IMC prevents phimosis, which affects 10% of uncircumcised older boys and young men[74]. Paraphimosis is less common, but can lead to penile gangrene and auto-amputation of the penis[75]. Circumcision protects against inflammatory skin conditions (balanitis and balanoposthitis) that occur in 10% of uncircumcised boys and men[30]. Uncircumcised adolescents and men have inferior penile hygiene owing to the proliferation of bacteria and accumulation of smegma under the foreskin[76-80]. The thin, fragile foreskin is easily torn and trauma due to zipper injuries can occur[81].

HUMAN PAPILLOMAVIRUS

The article disputes claims that uncircumcised men are more likely to harbor oncogenic human papillomavirus (HPV) types[1]. In doing so the references cited[82,83] are misinterpreted, as explained previously[38]. The article fails to cite extensive evidence contradicting the author's skepticism. That includes ignoring RCTs that found circumcision strongly protects men against ongogenic HPV acquisition and improves HPV clearance[84-89]. There is also RCT evidence of reduced low-risk HPV types that cause genital warts[90].

The claim that, "the development of safe, effective vaccines is rapidly making the question of circumcision irrelevant", fails to appreciate that the two current HPV vaccines do not target all of the 14 or more prevalent oncogenic HPV types, whereas circumcision offers approximately 50% protection against all oncogenic HPV types. Thus circumcision and vaccination re-

present synergistic approaches to countering the HPV epidemic[91].

The article skirts the fact that by partially protecting against oncogenic HPV types and various other STIs male circumcision provides a range of benefits to women. Virtually all cases of cervical cancer are caused by oncogenic HPVs. The risk of cervical cancer is much lower in the female sexual partners of circumcised men[92]. While over 70% of girls in early adolescence have received HPV vaccination in Australia[93], vaccine uptake in the United States has been much lower[94].

Policy recommendations of the AAP and CDC recognize cervical cancer prevention as an important benefit of IMC[2,9]. Yet, the article inaccurately states that circumcision of boys has, "zero benefit" to, "reduce the risk of cervical cancer in future female sexual partners"[1].

OTHER STI, INCLUDING HIV

Well-designed large RCTs provide the cleanest picture of the risks and benefits of circumcision compared to retrospective or observational studies. This is because confounding and bias are minimized. Three RCTs convincingly demonstrated that MC protects against heterosexual HIV infection in men[95-97]. The trials went on to demonstrate protection against other STIs such as oncogenic types of HPV[84-89], genital herpes (HSV-2)[87,98-100], *Trichomonas vaginalis* (*T. vaginalis*)[101] and *Mycoplasma genitalium* (*M. genitalium*)[102]. In addition, RCT data confirms the protective effect of MC in the female partners against oncogenic HPV types[103-105], HSV-2[106], *T. vaginalis*[107], *M. genitalium*[108], bacterial vaginosis[78,107] and genital ulceration[107]. The consistency in efficacy estimates between trials provides increased confidence in the benefits.

The claim that, "the major benefits claimed (reduced risk of STIs, HIV and various cancers) can be obtained in adulthood"[1] fails to acknowledge that the likelihood an adolescent or adult male will seek a circumcision for himself is low. Thus, parents' decision to circumcise a newborn son will ensure he has the lifelong benefits circumcision provides. Programs to encourage circumcision have been suggested by the CDC for high-risk population groups in the United States[9]. The WHO and other bodies have supported the implementation of such programs in sub-Saharan Africa since 2007. Although the article concedes that circumcision, "provides some degree of protection against HIV in certain risk situations and epidemiological environments", it then states, "there is no proof that it provides any overall protection against other STIs"[1], citing an article containing a series of meta-analyses[109]. Those meta-analyses were criticized[38]. They contained extensive flaws, data manipulation, failed to include numerous studies, including high-quality RCT data, and used uncommon statistical approaches[38].

It then states, "most [STIs] are readily curable with antibiotics", failing to realize that many common STIs (HIV, HPV and HSV-2) are viruses that cannot be cured. That exposes a lack of medical knowledge by the historian author.

WHY IS THERE OPPOSITION TO MALE CIRCUMCISION?

The article refers to a man who suffered the consequences of a botched IMC[110]. Such occurrences are exceedingly rare in the current era for circumcision performed by experienced medical professionals. The AAP policy recommends provider training to help ensure good outcomes. At the population level the frequency and severity of medical conditions arising from failure to circumcise greatly exceed that of adverse events arising after IMC[12].

The existence of, "a vigorous, community-based anti-circumcision movement in places where the practice remains common", as evidence, "circumcision is harmful and thus wrong" can be said of other fringe groups opposed to beneficial public health policies such as vaccination and water fluoridation.

FORESKIN RESTORATION AND PARTIALISM

The article cites dated opinion pieces containing anecdotes and speculation about, "serious psychological dysfunction", caused by IMC, in claiming, "some [men] resent [their IMC] sufficiently to attempt foreskin restoration"[1]. Rather than this being, "proof that they believe they have suffered sufficient harm to warrant a complex and laborious project", these men may have formed a misguided belief, as discussed earlier. Following online instructions about "restoration" of a pseudo-foreskin seems ill-advised. Not only is the process cumbersome and protracted, but has led to genital mutilation[111]. A recent meta-analysis found that sexual dysfunctions in men are common, irrespective of their circumcision status[22]. Moreover, a study prompted by reports by proponents of, "foreskin restoration", stated that there is a, "disparity between the mythology and medical reality of circumcision regarding male sexuality"[112].

A psychopathology term that fits the sexual obsession with the prepuce is termed "partialism" (see the American Psychiatric Association's Diagnostic and Statistical Manual 5th Revision (DSM-5)[113] under "Paraphilia not Otherwise Specified" (ICD-10 code CM F65.9) in the sexual and gender Identity Disorders Section). A diagnosis is made for paraphilia if, "the behavior, sexual urges, or fantasies cause clinically significant distress or impairment in social, occupational,

or other important areas of functioning". The definition of partialism is, "exclusive focus on part of the body"[114].

After "foreskin restoration", claimed benefits of, "increased sensitivity" in reality are more likely a result of the friction of the foreskin, whether intact or newly created, on the moist or sweaty glans and undersurface of the prepuce in the un-aroused state and would obviously, in the "re-uncircumcised" penis, have nothing to do with an increase in touch receptors, as in most instances nerves tend not to regenerate. Moreover, in RCTs, follow-up of young healthy men after circumcision found they experienced no decrease in sensitivity during sexual intercourse[23,24].

A detailed professional analysis of psychiatric aspects in eight patients seeking prepuce restoration noted several psychological disorders[115]. These included narcissistic and exhibitionistic body image, depression, major defects in early mothering and ego pathology. These men had a preoccupation with their absent foreskin and represented a subgroup within the community of men who have sex with men[115]. Of the 1200 members of one organization devoted to foreskin restoration, 80% were homosexual, 10% were bisexual and 10% were heterosexual. The overall membership comprised 65% who were uncircumcised, 30% who were circumcised and 5% who were partially circumcised. Although many were happy with the result, thus justifying to themselves the decision to undertake this procedure, others disliked their new genital status, even choosing to undergo re-circumcision[116].

CONCLUSION

Criticisms of the AAP policy statement supporting IMC fail to withstand scrutiny. The Hippocratic Oath states, "I will prevent disease whenever I can, for prevention is preferable to cure"[117,118]. Disease prevention is central to affirmative IMC policy recommendations. Given the immediate and lifelong protections and very low risk of adverse events, failure to recommend IMC or to suggest circumcision should be delayed seems unethical. We do not think the one-sided arguments opposing IMC are naïve. Rather, they involve deliberate obfuscation in support of an underlying agenda aimed at stopping IMC. We trust that our critical evaluation will set the record straight in the best interest of pediatrics, preventive medicine and individual wellbeing.

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REVIEW

Spectrum of intracranial incidental findings on pediatric brain magnetic resonance imaging: What clinician should know?

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Abstract

Intracranial incidental findings on magnetic resonance imaging (MRI) of the brain continue to generate interest in healthy control, research, and clinical subjects. However, in clinical practice, the discovery of incidental findings acts as a "distractor". This review is based on existing heterogeneous reports, their clinical implications, and how the results of incidental findings influence clinical management. This draws attention to the followings: (1) the prevalence of clinically significant incidental findings is low; (2) there is a lack of a systematic approach to classification; and discusses (3) how to deal with the detected incidental findings based a proposed common clinical profile. Individualized neurological care requires an active discussion regarding the need for neuroimaging. Clinical significance of incidental findings should be decided based on lesion's neuroradiologic characteristics in the given clinical context. Available evidence suggests that the outcome of an incidentally found "serious lesion in children" is excellent. Future studies of intracranial incidental findings on pediatric brain MRI should be focused on a homogeneous population. The study should address this clinical knowledge based review powered by the statistical analyses.

Key words: Intracranial incidental finding; Magnetic resonance imaging; Children; Common clinical profile; Seizure; Headache; Developmental delay

Core tip: The magnetic resonance imaging of the brain in children frequently reveals incidental findings. There is paucity in the literature, how to deal with such findings in clinical practice. This review based on existing heterogeneous reports reveals that the prevalence of clinically significant incidental findings is low and discusses options in the management of incidental findings in children.

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INTRODUCTION

Magnetic resonance imaging (MRI) of the brain is the most commonly performed investigation in the practice of pediatric neurology. During a clinical evaluation, an unexpected finding on brain MRI is a common occurrence. This heightens parental anxiety and generates explanatory discrepancies amongst physicians. Discovery of such findings on neuroimaging is not unique or limited to pediatric brain MRI. Rather, it has been reported in several other conditions such as abdominal and pelvic computerized tomography (CT) and MRI[1] or in asymptomatic ankles[2]. Additionally, these findings have been described in asymptomatic healthy volunteer adults[3], young adults in the community, and in clinic-based subjects[4].

In clinical practice, MRI of the brain is performed for a variety of indications. Infrequently, findings like pituitary adenoma, lesions of the pineal gland, or central nervous system malignancy are discovered, which have serious implications.

Authors present the evidence-based reports of the current body of knowledge regarding such findings, their clinical implications, and how these findings translate to neurologic management, and discuss a common profile to aid in the clinical management of incidental finding.

METHODOLOGY: LITERATURE SEARCH AND THE RESULTS

In November 2014, we searched Ovid MEDLINE and PubMed databases for reports on the use of brain MRI in children aged 18 years and under. We supplemented the electronic searches with surveillance of electronic tables of contents in neurological journals and by hand searching the bibliographies of pertinent articles. Two authors (Gupta SN and White AC) read the title and abstract of every study identified by the electronic searches. We critically appraised the full text of potentially eligible studies. Two authors extracted data on study design, population characteristics, and MRI parameters from each study.

Several prospective and retrospective studies have reported incidental findings in pediatric patients. The MRIs of the brain were carried out as an investigatory step in children presenting within various disciplines of pediatric medicine. The summary of identified studies is provided in the Table 1[5-22].

TERMINOLOGY

The word "incidental or unexpected" generally applies when an identified brain lesion on neuroimaging would have not been predicated by clinicians. This definition can be questioned by some in specific clinical situation. Because the discovery of such lesions in the majority of children does not alter the management, some authors have described them as "benign findings", Schwedt *et al*[8], 2006.

Multiple terminology have been used to indicate white matter lesions such as periventricular malacia, periventricular white matter changes, white-matter hyperintensity, non-specific white matter abnormalities, white matter signal abnormality, and focal white matter lesion. In the exception to periventricular malacia, the question is if the rest of these terms are the same or of different pathologies. Clinicians have been charged with the task of determining whether or not these definitions are synonymous.

CLASSIFICATION

Intracranial incidental findings are inconsistently classified. The most findings being classified based upon their clinical significance, the type of lesion, normal variant *vs* abnormal finding, and the urgency for the referral.

Jordan *et al*[21], 2010, based on the need for referral, classified incidental finding into four categories: No referral, routine referral, urgent referral, or immediate referral. Graf *et al*[7], 2010 categorized neuroimaging results as normal, remarkable without clinical action, remarkable with clinical follow-up action, and abnormal. Bryan *et al*[23], 1994 used a very different classification, but a similar method which is used to classify the Cardiovascular Health Study in adults.

Yilmaz *et al*[5], 2014 classified incidental findings in five categories as follows: (1) cerebral abnormalities relevant to headache such as a growing tumor or hydrocephalus; (2) incidental cerebral abnormalities with potential clinical significance such as Chiari type I malformations, arachnoid cysts, cysts of pineal gland, and inflammatory lesions; (3) incidental cerebral abnormalities without clinical significance such as white matter hyperintensity, periventricular leukomalacia,

Table 1 Summarizes the reports of intracranial incidental findings in children on brain magnetic resonance imaging[5-22]

Ref.	Country	Study objective /conclusion
Yilmaz *et al*[5]	Turkey	To evaluate clinical significance of MRI abnormality in children with headache/ Despite the high rate of IFs, the yield is non-contributory to diagnosis and therapy
Bayram *et al*[6]	Turkey	To describe the prevalence of WML detected on MRI in children with headaches/ Non-specific WML may be seen in children with headache. In the absence of benefit, repeated MRI studies are unwarranted. It should be tailored according to clinical course
Graf *et al*[7]	United States	Studied the frequency and consequences of IFs on non-acute pediatric headache/ The frequency and types of all IFs were generally comparable to previous studies
Schwedt *et al*[8]	United States	To study the frequency of "benign" abnormalities in children with headache, compare it with the frequency of MRI findings that dictate a change in patient management/ About 20% children with headache have benign findings that do not result in a change in management which rarely occurred in 1.2% of children in this study
Koirala[9]	Nepal	To evaluate the yield of MRI findings in patients with seizure/ The majority of abnormalities on MRI included hippocampal sclerosis and T2 hyperintensity
Kalnin *et al*[10]	United States	To characterize IFs association with seizure onset and to standardize a classification system/ The MRI and a standardized scoring system demonstrated a higher rate of IFs than previously reported. MRI parameters need to expand the definition of significant IFs
Gupta *et al*[11]	United States	To test the hypothesis that children with developmental delay are more likely to have incidental findings than are the children with normal development status/ Authors reported a higher prevalence of IFs in children with developmental delay as compared with those with normal development status
Seki *et al*[12]	Japan	To report prevalence of IFs in healthy children and to suggest an ethical and practical management protocol/ The prevalence of IFs was high but those requiring further MRI was low. Evaluating equivocal findings was the most difficult part of IFs management
Gupta *et al*[13]	United States	To elucidate the prevalence of incidental findings in a general pediatric neurology practice/ Authors reported a high prevalence of and a low rate of referrals in comparison to previous studies. This study may help guide management decisions and discussions
Potchen *et al*[14]	Malawi	To collect normative magnetic resonance imaging data for clinical and research applications/ Incidental brain magnetic resonance abnormalities are common in Malawian children
Kim *et al*[15]	United States	To elucidate the prevalence of incidental findings in a healthy pediatric population/ Frequency of important IFs was not high. But, awareness of neurologic status, the presence and variety of IFs are of vital importance for research and welfare of the child
Oh *et al*[16]	South Korea	Incidental findings in pediatric specialty clinic other than neurology To investigated the clinical characteristics of children in whom Rathke's cleft cysts were incidentally discovered and the treatment response with endocrinopathy/ Rathke's cleft cysts less than 20 mm expressing cystic intensity can be treated medically
Rachmiel *et al*[17]	Canada	To assess IFs in children with congenital hypothyroidism compared to 38 healthy controls/ Both groups had a similar incidence of structural abnormalities. There was no association between those findings and neurocognitive function
Whitehead *et al*[18]	United States	The prevalence of pineal cysts in children who have had high-resolution 3T brain MRI/ Characteristic-appearing pineal cysts are benign findings. In lack of no referable comprehensive symptoms, no follow-up is required
Mogensen *et al*[19]	Denmark	To evaluate the outcome of brain MRI in girls referred with early signs of puberty/ Girls with central precocious puberty should have a brain MRI
Perret *et al*[20]	Switzerland	The prevalence and management options of incidentally found mass lesions at pediatric clinic/ A subgroup of lesions such as tectal glioma and dysembryoplastic neuroepithelial tumor can be monitored conservatively
Jordan *et al*[21]	United States	The prevalence of incidental findings on brain MRI in children with sickle cell disease/ IFs were present in 6.6% patients and a potentially serious or urgent finding was 0.6%

All except four studies: Potchen *et al*[14], 2013, Rachmiel *et al*[17], 2013, Koirala[9], 2011, and Seki *et al*[12], 2010, were retrospective. The retrospective study by Jordan *et al*[21], 2010 was carried out as a clinical trial for sickle cell disease. Itoh *et al*[22], 1994, investigated the evolution of high-signal–intensity abnormality on T2-weighted MR images[22] which are the expected findings thus it was excluded from this review. WML: White matter lesions; IFs: Incidental findings; MRI: Magnetic resonance imaging.

subtle gliosis, silent brain infarcts or lacune, and brain microbleeds; (4) extra-cerebral abnormalities relevant to headache such as sinusitis, which was considered as the cause of headache if an otolaryngologist made the diagnosis of sinusitis; and (5) incidental extra-cerebral abnormalities such as mucosal thickening or fluid retention in sinuses or mastoid cells.

The inclusion of "normal-variants" is confusing. For example, commonly occurring pineal cysts are an asymptomatic finding. Thus, this could be considered a normal finding[24]. But in a symptomatic patient with the same pineal cyst, there may be a true clinical implication[25,26]. In some patients, a particular finding in the context of clinical presentation after all may not be incidental. Occasionally, certain findings such as arachnoid cyst may be predicted in specific clinical situations[27,28].

Some of these findings are classified arbitrarily.

Table 2 Clinical demography of intracranial incidental findings on pediatric brain magnetic resonance imaging evaluated at general neurology clinic and at research center[5-15]

Ref.	Clinical demographics					Girls *n* (%) with MRI
	Study- setting	Reason for MRI	No. of subject	No. of MRI (%)	Mean age (range) year	
Yilmaz *et al*[5]	Pediatric neurology	Head pain	449	288 (64)[1]	11.2 (NA)	189 (58)
Bayram *et al*[6]			941	527 (61)[2]	12.1 (4-16)	NA
Graf *et al*[7]			400	91 (23)[2]	10.8 (3-18)	NA
Schwedt *et al*[8]			681	218 (32)[2]	12.1 (2-18)[3]	126 (52)
Koirala[9]	Pediatric and adult neurology	Seizure	36[c]	36 (100)[3]	NA (1-16)	NA
Kalnin *et al*[10]	Radiology		349	281 (81)	9.7 (6-14)	143 (51)
Gupta *et al*[11]	Pediatric neurology	Developmental delay	2185	771 (35)	7.6 (NA)	433 (56)
Gupta *et al*[13]		General	1618	666 (41)	9.8 (0-21)	280 (42)
Seki *et al*[12]	Research Institute	Healthy children	395	89 (25)[1]	NA (5-8)	53 (44)
Kim *et al*[15]	Radiology Research		225	198 (88)[1]	11.2 (1 mo-18)	126 (56)
Potchen *et al*[14]		Community-based	102	68 (71)[1]	12.1 (9-14)	54 (55)

[1]The MRI revealing extracranial incidental findings were excluded; [2]Children with computerized tomography of the brain were excluded; [3]Only pediatric patients are presented in Table. MRI: Magnetic resonance imaging; NA: Not available.

This practice has resulted in a variety of classification systems which lack clarity. There is an obvious need for a uniform classification system.

NEUROIMAGING

MRI acquisition modalities and the parameters utilized in these studies are variable.

Conventional brain MRI

The conventional MRI was usually performed by using 1.5 Tesla magnetic field strengths scanner. MRI parameters varied but conventional short-TR and short-TE, T1-weighted, long-TR and long-TE, T2-weighted, and fast fluid-attenuated inversion recovery-weighted images were performed in majority of patients. Diffusion and perfusion diffusions images were routinely available in North American Practice of Pediatric Neurology/ Neuroradiology.

Advance MRI

Diffusion tensor imaging is an application of diffusion weighted imaging which quantifies water diffusion by measuring molecular motion of water within the brain parenchyma. Lately, this modality has been increasingly used in studying the neuroanatomy of the brain[29]. This technique is useful particularly in the investigation of white matter abnormalities.

Reporting

Official interpretations are provided by different levels of trained and Board Certified Radiologists. A very limited number of MRI studies were reviewed by Board Certified Pediatric Neuroradiologists. The reporting procedure remains subjective.

The reports should distinguish cerebellar ectopia (downward displacement of cerebellar tonsil/s less than 1 cm through foramen magnum) from Chiari type I malformation. In the face of recent genetic and phenotypic correlation, there has been a retreat from the Dandy Walker "variant", thus it may be useful to just describe the posterior fossa abnormality. Most importantly, in case of serious lesions, the radiologic characteristics particularly the integrity of the blood-brain barrier should be described in detail.

Future studies may reveal the association between a patient's clinical status and the type of finding, while advances in neuroimaging may reveal their significance. Radiologists should report all such findings within the body of the text, in addition to their subjective interpretation.

The clinical demography of intracranial incidental findings is shown in Tables 2 and 3.

PREVALENCE

The prevalence of intracranial incidental findings is shown in Figure 1.

Variability in prevalence, lowest in healthy children (8%) and the highest in a specific neurologic condition can be explained by an increasing burden of a disorder on the brain. This is probably highest in an elderly brain secondary to ischemic injury particularly to white matter. Arguably, some of the white matter changes are expected findings in neurofibromatosis type I.

Despite suggestions that prevalence rate of incidental findings have increased with frequent use of neuroimaging, during the past decade, it has remained stable in children referred for non-acute headache, Graf *et al*[30], 2008. Of note, an increasing proportion of neuroimaging studies are being ordered by primary care providers.

TYPE AND DISTRIBUTION

Three most common incidental findings

The three most commonly reported intracranial incidental findings on brain MRI in various pediatric settings

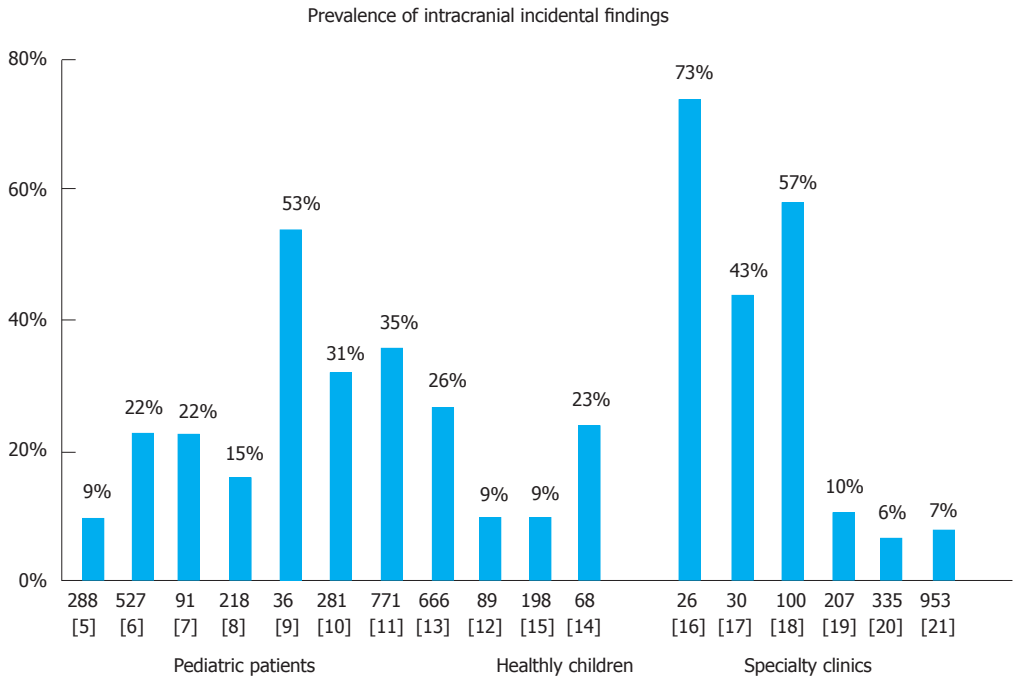

Figure 1 A comparative prevalence of incidental findings on pediatric magnetic resonance imaging of the studies. The numbers above bracket represents number of children in the study; Number in the brackets represents the reference for the study. The subjects in the studies' reference[5-13] except[12] on the left were from General Neurology Clinic. The studies'[16-21] on the right were from Specialty Clinics other than neurology. Three studies in middle; ref.[12,15] were from research in healthy children and the study[14] was community-based in healthy population.

Table 3 Clinical demography of children with intracranial incidental findings on pediatric brain magnetic resonance imaging studies at pediatric specialty clinic other than neurology[16-21]

Ref.	Study-setting	Reason for MRI	No. of subject	No. of MRI (%)	Clinical demographics	
					Mean age (range) year	Girls *n* (%) with MRI
Oh *et al*[16]	Endocrinology	Rathke's cleft cysts	34[1]	26 (76)	NA (4-18)	17 (65)
Rachmiel *et al*[17]	Endocrinology	Congenital hypothyroidism	68[2]	30 (100)	12.5 (10-15)	16 (55)
Whitehead *et al*[18]	Radiology	Pineal cyst	100	100 (100)	6.8 (1 mo-17)	52 (52)
Mogensen *et al*[19]	Endocrinology	Early puberty	229	207 (100)[3]	NA (6-9)	207 (100)
Perret *et al*[20]	Oncology	Primary brain tumor[4]	335	335 (100)	7.6 (0-18)	132 (39)
Jordan *et al*[21]	Neurology research	Sickle cell disease	953	953 (100)	9.2 (5-15)	460 (48)

[1]76% of patient with Rathke's cleft cysts were discovered during evaluations for endocrine disorders; [2]This includes 38 healthy boys 11.7 ± 1.7 years; [3]22 (11%) patients who had computerized tomography of the brain due to contraindication of MRI are not included in this table; [4]Central nervous system tumors were identified incidentally. MRI: Magnetic resonance imaging; NA: Not available.

are shown in Table 4. The types of incidental findings on MRI outside of a neurology-setting were generally comparable in these studies.

Incidental "serious brain lesion"

It should be noted that community or general pediatric neurology based studies in healthy subjects have not reported serious or progressively worsening incidentally identified lesions. Nonetheless, serious lesions have been reported by a few studies which are shown in the Table 5[31].

Morris *et al*[32] published a meta-analysis, which reviewed 16 studies of subjects within the age range of 1 to 97 years, all of whom had no neurological symptoms. All subjects had brain MRI performed for the purpose of research and for occupational or commercial screening. The authors reported 135 (0.70%) of 19559 subjects with a neoplastic incidental finding. No age specific prevalence of neoplastic lesion was available for children aged 1 to 9 years. After omitting 34 adults aged 90 to 99, only four 20 year age bands were left for analysis[32].

Serious lesions can be divided into two groups: (1) ones that are known to get worse, such as a tumor; and (2) those that have the potential for worsening over time, such as pituitary lesions, pineal cysts, or vascular malformations. Such lesions typically manifest with compressive symptoms localized to the adjacent neuroanatomical structure.

Incidental vascular malformations, although uncommon, are frequently asymptomatic, which can greatly complicate the clinical management. It should be noted

Table 4 Lists three most commonly reported intracranial incidental findings on brain magnetic resonance in various pediatric-settings[5-19]

Ref.	Three most common intracranial IFs, *n* (%)	Comment or serious finding
Yilmaz *et al*[5]	White-matter hyperintensity 14 (4.3) Old infarcts 4 (1.2), and CM I 3 (0.9)	2 (0.6%) malignant tumor and 1 hydrocephalus, 0.3% IFs were relevant to headache
Bayram *et al*[6]	Supratentorial non-specific WMC 23 (4.4)	All patients with IFs had normal development and no seizures or head trauma
Graf *et al*[7]	CM I 6 (15), arachnid cysts 6 (15), brain stem parenchymal abnormality, 4 (10)	Brain stem IFs included Dandy-Walker variant, cerebellar calcification, and tectal plate hyperintensity
Schwedt *et al*[8]	CM I 11 (4.6), nonspecific white matter abnormalities 7 (2.9), venous angiomas and arachnoid cyst each 5 (2.5)	Discovery of 4 tumors, 4 old infarcts, 3 CM I, and 2 moyamoya required a change in management
Koirala[9]	Hippocampal sclerosis, T2 hyperintense foci in various distributions, both 4 (21) each, cortical atrophy 3 (16)	Study focus was IFs in patient with seizure. The lesions were better detected by MRI than computerized tomography
Kalnin *et al*[10]	Ventricular enlargement 143 (51), leukomalacia/gliosis 64 (23), heterotopias and cortical dysplasia 33 (12)	Temporal lobe lesions were detected 15%, a higher frequency than in previous studies
Gupta *et al*[11]	Variant signal intensity 30 (18), WMC changes 23 (13), and PVL, 10 (6)	IFs were reported in children with developmental delay as to those with normal development status
Seki *et al*[12]	Cavum septi pellucid 6 (15) and Pineal cyst 2 (5), Enlarged perivascular spaces 1 (2.5)	Focus of the study was reporting of extracranial IFs in healthy children
Gupta *et al*[13]	CM I and cerebellar ectopia, 16 (3.5), Arachnoid cysts, 12 (1.8)	White matter changes were the most common IFs classified under normal-variants
Potchen *et al*[14]	PVW matter changes/gliosis 6 (6), mild diffuse atrophy 4 (4), and Empty sella 3 (3)	Incidental findings were unassociated with age, sex, antenatal problems, or febrile seizures
Kim *et al*[15]	Focal white matter lesion 3 (1.3), arachnoid cyst, frontal venous angioma, and mega cisterna magna, all three 2 (0.9) each	IFs were detected on 225 conventional research in a cohort of neurologically healthy children
IFs in pediatric specialty clinics other than neurology		
Oh *et al*[16]	Low signal intensities on T1-WI and high signal intensities on T2-WI 26 (73)	Incidence of hypointensity on T1-WI was higher in patients with Rathke's cleft cysts
Rachmiel *et al*[17]	Prominent VR perivascular spaces, cerebellar ectopia, and abnormalities in sella region all 3 (7.9) each	The comparative study found no IFs association with clinical and cognitive abnormalities
Mogensen *et al*[19]	Arachnoid cysts 5 (9.2), of which one patient had hydrocephalus	Incidental findings were unrelated to early puberty

The study by Whitehead *et al*[18], 2013, which is not listed in table, because this study was limited to prevalence of pineal cysts in children, who have undergone high-resolution 3-T MRI. CM I: Chiari malformation I; WMC: White matter changes; VR: Virchow-Robin; PVL: Periventricular malacia; PVW: Periventricular white matter changes; IFs: Incidental findings; MRI: Magnetic resonance imaging.

that none of the prospective studies reported any malignant findings as incidental. Potchen *et al*[14], 2013 prospectively reported granulomas with gliosis as a serious lesion.

Not surprisingly, a significant number of brain tumors were reported from pediatric oncologic-setting, Perret *et al*[20], 2011. The incidental serious findings in this study included low-grade glioma, craniopharyngioma, ependymoma, choroid plexus papilloma, medulloblastoma, and dysembryoplastic neuroepithelial tumor.

CLINICAL IMPLICATION

Common clinical profile

The common clinical profile of intracranial incidental findings on pediatric brain MRI is shown in the Table 6.

Multiple incidental findings

A 16-year-old girl presented with right facial nerve palsy. She had an unremarkable past medical history. A CT scan of the brain performed due to tingling feeling on the right side of her tongue revealed a partially calcified pineal cyst (Figure 2A). An MRI revealed an enhancing pituitary lesion measuring 13 mm × 10 mm × 10 mm, cerebellar ectopia (Figure 2B), and left maxillary sinusitis, which is not shown. She had no headaches, visual field defect, hearing difficulty or upper respiratory infection. The question is if her facial nerve palsy is related in any way to neuroimaging findings. The significance of more than one incidental finding is largely unknown.

More than one incidental finding is not uncommon. In the lack of any known implication some of these findings go unreported.

Four out of 18 (22%) studies listed in Table 1 reported more than one incidental finding. An average prevalence of more than one incidental finding in three studies (11, 13, and 17) was 3.8%. The forth study by Bayram *et al*[6], 2013 reported a very high prevalence (52%) of more than one white matter lesion in children with migraine. In fact the number of patients with more than one lesion exceeded the total number of the patients in this study. Authors' indicated that these were migraine associated changes in the brain[33].

Managing the MRI results

Incidentally discovered findings should always be considered in the context of the overall clinical impression. One should bear in mind the reason for performing the MRI of the brain. The answer to this

Table 5 Summarizes incidentally found "serious lesions" on pediatric brain magnetic resonance imaging

Ref.	The context in which brain MRI was ordered	Worsening course		Outcome/comment
		Known	Potential	
Yilmaz *et al*[5]	Children mean age 11.2 yr presented for headache evaluation	Malignant brain tumor and hydrocephalus	Chiari I malformation I; Relevant to headache	Tissue type of tumor in study was unspecified
Schwedt *et al*[8]	Children mean age 12.1 yr presented for headache evaluation	Tumors, moyamoya disease, and demyelinating disease	Arteriovenous malformation and intracerebral hemorrhage	Study focus was "benign" imaging abnormalities, no further information for serious lesion other than pineal tumor was available
Kalnin *et al*[10]	Children mean age 9.7 yr presented for the first onset seizure	None	Temporal lobe lesions	Various Epileptic abnormalities[1] have been associated with pediatric brain MRI
Potchen *et al*[14]	Community-based children mean age 12.1 yr	Granulomas with gliosis	Empty sella and vermian atrophy	Calcified granulomas caused by neurocysticercosis or tuberculosis occurs in the endemic part of the world
Mogensen *et al*[19]	All girls, mean age unavailable, presented for early puberty evaluation to endocrine clinic	Pontine and pineal tumor, and hypothalamic pilocytic astrocytoma	Hydrocephalus, cortical dysplasia, and chiari II malformation	A high frequency a pathological brain findings occurred in 6-8 yr old girls with precocious puberty
[2]Perret *et al*[20]	Incidentally found mass lesions management in children mean age 7.6 yr in oncology	Low-grade glioma, craniopharyngioma, ependymoma, and CPP	Medulloblastoma and fibrillary astrocytoma	Dysembryoplastic neuroepithelial tumor and tectal glioma can be monitored conservatively
Jordan, *et al*[21]	Children mean age 9.2 yr with sickle cell disease in neurology research	Chiari I malformation with large spinal cord syrinx[3]	Possible tectal glioma, Possible tumor *vs* dysplasia	Amongst 6.6% incidental findings identified, 0.6% children with sickle cell disease had potentially serious or urgent finding

[1]Various epileptic abnormalities includes leukomalacia/gliosis, encephalomalacia, any gray matter lesion, mass lesion, hemorrhage, vascular lesion, hippocampal abnormality, ventricular enlargement > 1.5 cm, or prominence of extra-axial fluid spaces > 1.0 cm[31]; [2]Of 335 newly diagnosed central nervous system tumors (CNS), 19 (5.7%) children's CNS tumors were identified incidentally; [3]Of note: Chiari I malformation with a small cervical spinal cord syrinx in asymptomatic patients is not uncommon on pediatric brain MRI. CPP: Choroid plexus papilloma; MRI: Magnetic resonance imaging.

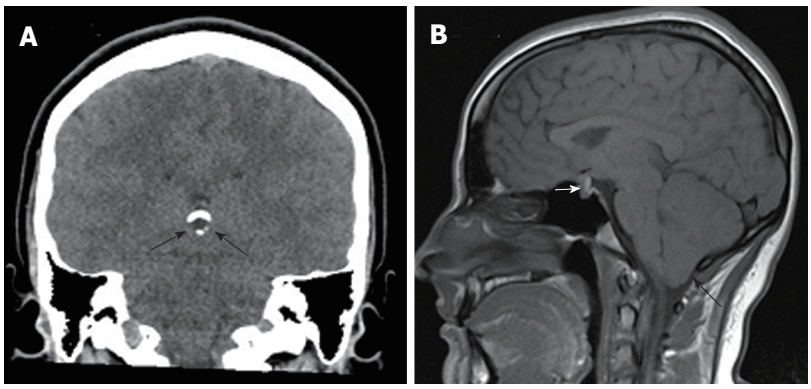

Figure 2 Three out of four incidental findings in a single 16-year-old girl who presented with right facial nerve palsy. The left maxillary sinusitis is not shown. A: Coronal non-contrasted computerized tomography of the brain shows a partially calcified cystic pineal lesion (black arrows); B: A true midline sagittal magnetic resonance image contrast enhancing pituitary mass measuring 13 mm × 10 mm × 10 mm (white arrow) and cerebellar ectopia, 7 mm (black arrow). There was no enhancement of facial nerve in vicinity of the right internal carotid canal.

question can often provide the direction for the next step of clinical management.

The MRI results are best managed at the time of planning for neuroimaging by considering the possibility of an incidental finding. Such preemptive action serves to alleviate parental concern, reduce additional medical care cost, and save physicians' time[34]. After all, incidental findings are the most common insignificant abnormal findings revealed on pediatric brain MRI.

The parental perceived importance for MRI procedure is significantly higher than those of physicians. This disassociation of perception may lead to confrontation. This could be avoided by considering the parental concern. The physician's explanation should be based upon the clinical context and what is known about the particular finding. It is only rarely that these findings perpetuate more concerns than the relief[35].

How did we manage the results of our case? The patient's right facial nerve palsy has no neuroanatomical relation with pituitary lesion, cerebellar ectopia, pineal

Table 6 A proposal for a common clinical profile of intracranial incidental findings on pediatric brain magnetic resonance imaging

	Clinical implication
Discovery of the unexpected incidental findings	Revealing during investigation enhances the patients or parents anxiety. The evidence-based knowledge will provide an additional confidence for the practicing physicians
Type of the incidental findings	Varieties of white matter changes are reported. However, these usually do not initiate a neurologic consultation. Chiari type I malformation, arachnoid cyst, and pineal cyst, all continued to be a common source of concern for some physicians
Distribution of incidental findings	Attention to the distribution of findings is a useful tool in deciding the clinical importance of such findings. A midline lesion particularly in the posterior fossa and hippocampal location is likely to have a serious clinical implication
The clinical context in which MRI was performed	This is probably the single most important step in understating the clinical implication of incidental findings (Table 6). This is particularly important when the child was referred to neurology after revealing the incidental finding on brain MRI

MRI: Magnetic resonance imaging.

cyst, and the left maxillary sinusitis. Of note; sinusitis is the most common extracranial incidental finding on brain MRI. Our patient with facial nerve palsy was treated with a 5 d course of oral steroid. She was referred to an endocrinologist for further evaluation of the pituitary lesion.

How to deal with a "serious incidental finding"?

An MRI revealing serious incidental findings requires close attention. These findings in a pediatric neurology practice remain low (0.3%-3.4%). Presently, there is no consensus regarding the optimal strategy on how to deal with these findings in practice or research[36].

In general, a midline located lesion with or without surrounding edema or contrast - enhancement needs to be further investigated. Depending upon the nature of the lesion or clinical impression, endocrinological, oncological, or neurosurgical evaluation should be considered.

Author (Gupta SN) preference is to first discuss with the interpreting radiologist and have a plan before delivery of the results to the parents. The necessity and results of such a discussion may vary depending upon the expertise of the clinician or radiologist. To characterize such a lesion systemically, the neuroradiologic differential diagnosis based on the MRI characteristics should be discussed. The presence or absence of perfusion- and diffusion-weighted MRI revealing changes in the diffusion coefficient should be documented[37]. With the use of intravenous contrast, the status of a blood-brain barrier should be evaluated. In case of non-enhancing lesions such as benign tumors, magnetic resonance spectroscopy[38] or diffuse tensor imaging may be additional use.

At times an equivocal finding may be perplexing in regards of the management strategy. In such a situation the patient should be followed clinically. Unless neurosurgical intervention is thought to be a realistic probability, the patient with incidental findings of this nature should not receive neurosurgical referral. This will prevent escalating parental anxiety.

Referral and ramification

The majority of children with intracranial incidental findings do not require clinical or neuroimaging follow-up. Scheduling further appointments merely for incidentally found findings or neuroimaging is likely to increase parental anxiety. Some parents may seek another neurologic consultation. Pituitary lesions, vascular malformations, or tumors have a true future clinical[39,40] or medico-legal implications. Fortunately, serious lesions in children remain extremely low as compared with adults or the elderly[41]. Occasionally, they require emergent medical attention and/or subsequent neurosurgical intervention.

Requiring surgical intervention

A very limited number of incidentally found serious lesions include various tumors, which neurosurgical intervention. Non-tumor serious lesions includes Chiari I malformations, syrinx of the cervical spinal cord, and Rathke's cleft cysts. Incidentally discovered lesions requiring neurosurgical interventions and their outcomes are shown in Table 7.

Perret *et al*[20], 2011, studied 335 children age < 18 years in an oncologic-setting. They reported 19 patients (5.67%) with an incidentally discovered primary brain tumor. Seven patients (2%) underwent immediate surgery; four patients had a low-grade glioma. Craniopharyngioma, ependymoma, and choroid plexus papilloma occurred one in each individual patient. The rest of the 12 (3.5%) children were treated conservatively. Of these 12 conservatively followed, 10 patients (83%) remained stable. The other 2 (17%) underwent surgery because of medulloblastoma and fibrillary astrocytoma progression. The authors of the study concluded that a subgroup of lesions such as tectal glioma and dysembryoplastic neuroepithelial tumor can be monitored conservatively.

Bredlau *et al*[42] reviewed the clinical course of 244 children over a 10 year period. The study reported 21 (8.6%) incidental brain lesions on MRI. Twelve (4.9%) patients underwent surgical resection of their lesions. Nine out of 10 patients (90%) had a posterior fossa lesion, and three out of 11 (27%) had supratentorial lesions. Authors of the study concluded that incidentally detected serious CNS lesions are small. The outcome for children with such lesions is excellent. They recommended close monitoring with serial MRIs as a safe alternative to immediate biopsy and/or resection

Table 7 Summarizes the neurosurgical intervention and their outcome in children with incidentally discovered serious lesions

Ref.	Incidentally found serious findings	No. of patients	Surgical procedure performed	Outcome
Schwedt *et al*[8]	Chiari type I malformation	3	Surgical decompression	Headache relieved in 2 patients after surgery
Jordan *et al*[21]	Chiari I malformation with spinal cord syrinx	2	Surgical decompression	Neurologic stable
Perret *et al*[20]	Pilocystic astrocytoma	2	Primary subtotal resection	Stable disease
	Craniopharyngioma	1	Primary total resection	Complete remission
	Anaplastic ependymoma	1	Primary total resection, radio-chemotherapy	Complete remission
	Choroid plexus papilloma	1	Primary total resection	Complete remission
	Medulloblastoma	1	Delayed subtotal resection, radio-chemotherapy	Neurologic stable
	Fibrillary astrocytoma	1	Delayed total resection	Complete remission
	Mature teratoma	1	Delayed subtotal resection	Neurologic stable
	Desmoplastic ganglioglioma	1	Primary total resection	Complete remission
Mogensen *et al*[19]	Pilocytic astrocytoma	1	Hypophysectomy	Patients developed pan hypopituitarism after surgery
Yilmaz *et al*[5]	Medulloblastoma	1	Urgent surgery for space occupying lesion	Headache relieved after surgery

Incidental findings; Chiari I malformation studied by Seki *et al*[12], 2010 and temporal arachnoid cyst with mass effect and cerebellar venous malformation studied by Gupta *et al*[13], 2008 all three were referred to neurosurgery, but no information regarding outcomes were available.

for select patients[42]. Of note; the data from adult patients demonstrate that most Rathke's cleft cysts the response to surgery tends to vary based on the endocrinopathology[43].

MEDICOLEGAL IMPLICATION

Dissatisfaction is an inciting event of litigation in the medical setting. Unlike research or healthy volunteer subjects, no consensus exists on how to handle incidental findings in clinical practice[44,45].

Claims of inappropriate management, ignorance, or discovery of a serious incidental finding on a later date, all have the potential to result in litigation. The discovery of incidental findings on brain MRI have led to its familiarity and a burden to clinical practice. Clinicians have an obligation of addressing the incidental finding revealed on MRI during the course of clinical evaluation. It is best prevented by pursuing before the availability of actual reports of MRI.

Based on the individual radiologist's perception, the reports of incidental findings on MRI are variable. Hence, many incidental findings might, therefore, remain unreported. Rarely, inconsistencies in reporting may be a cause for litigation.

FUTURE

Neuroimaging with diffuse tensor imaging is likely to unfold the nature of the incidental findings particularly white matter changes. In the future, they are likely to be identified with the use of a high resolution MRI sequences. Use of a standardized scoring system by radiologists will eliminate the individual variability in reporting. This will also be useful in expanding our understating of the incidental findings.

Future review should address the reason for variable prevalence and answer the question if the pattern of incidental finding relates to a specific condition such as headache, seizure, development delay, or any other neurologic condition. Most importantly, this investigation should be addressed by an adequately powered statistical analysis of retrospective or prospective studies in homogeneous populations.

CONCLUSION

The detection of intracranial incidental findings on pediatric brain MRI is of immense importance to daily radiological or clinical practice. The Radiologist should report each and every incidentally discovered finding. Individual variability in reporting of brain MRI findings can be minimized by using unified terminology, describing radiologic characteristics, and by developing a standard radiologic classification system. Because significance of these findings remains unclear, it is important to report them as they are observed, rather than a subjective description.

Intracranial incidental findings are common in both healthy children and children presenting for neurologic evaluation. Prevalence increases with disorders affecting the brain.

Whether or not a reported "incidental finding" should be assigned as clinically significant, is the clinician's prerogative. In uncertainty, the clinical context and course of the problem in question should take precedence. The spectrum of intracranial incidental findings on pediatric brain MRI presented in this review should be the basis for an evidence-based discussion. In addition, the proposed common profile will aid the clinical management of incidentally discovered findings. Most importantly, the management of an incidentally found

serious lesion demands constant surveillance in clinical practice.

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History of the infantile hepatic hemangioma: From imaging to generating a differential diagnosis

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Abstract

We aim to provide an up-to-date summary of infantile hepatic hemangioma (IHH) and its misnomers and to dialectically present the differential diagnosis of these rare entities of the liver. Eligible peer-reviewed articles on hepatic infantile hemangiomas, published between 2000 and 2015, were reviewed for this study. IHH is the most common hepatic vascular tumor in children. Once a liver mass is identified in an infant, the differential diagnosis ranges from vascular malformations to benign and malignant tumors including mesenchymal hamartoma, hepatoblastoma, metastatic neuroblastoma, so careful physical examination, imaging studies, and, if indicated, tumor markers and biopsy, are of pivotal importance to ascertain the correct diagnosis. Despite the benign nature of IHHs, some of these lesions may demand medical and/or surgical intervention, especially for multiple and diffuse IHH. Complications can include hepatomegaly, hypothyroidism and cardiac failure. Therefore, a close follow-up is required until complete

involution of the lesions. We propose an algorithm to guide the physicians towards the proper management of hepatic lesions.

Key words: Hepatic hemangiomas; Infant; Children; Vascular tumors

Core tip: Differential diagnosis of pediatric liver lesions ranges from vascular malformations to benign and malignant tumors. Infantile hepatic hemangioma (IHH) is the most common, benign, hepatic vascular tumor in infants. They are sub-classified in focal, multiple and diffuse lesions, based on degree of unaffected liver parenchyma. Despite the benign nature of IHHs, multiple and diffuse lesions can present with life-threatening complications including severe hypothyroidism and cardiac failure, requiring prompt medical intervention. Therefore, a proper diagnosis is of pivotal importance. Including severe hypothyroidism and cardiac failure, requiring prompt medical intervention, therefore, a proper diagnosis is of pivotal importance.

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INTRODUCTION

Infantile hemangiomas (IHs) are the most common benign tumor of infancy, affecting up to 10% of the pediatric population with a higher incidence in female (3:1), preterm infants, and Caucasian population. Most IHs are not present at birth but become apparent a few days to a few weeks after birth. IHs are characterized by a rapid proliferative phase in the first 6-10 mo, followed by a slow involution, which can last up to 10 years[1].

Despite their benign nature, IHs can cause severe morbidities and therefore sometimes require medical intervention[2]. IHs can range from asymptomatic to life threatening. Vital functions such as breathing, vision, and feeding can be impaired, depending on the location of the lesion.

IHs are be confirmed by positive immunostaining for glucose transporter-1 (GLUT-1), which is pathognomonic for the diagnosis of IHs, and therefore helps to distinguish IHs from other vascular anomalies[3]. While most IHs are present in the skin, IHs can occur in the viscera, with or without cutaneous manifestations. The liver is the most common site of visceral IHs, followed by the gastrointestinal system[4].

Screening for liver IHs (IHH) by ultrasonography (USG) is recommended when 5 or more cutaneous IHs are noted. However, the majority of IHHs are discovered as incidental findings during routine imaging.

IHHs are classified in three different subtypes, focal, multifocal and diffuse IHH, based on the remaining unaffected liver parenchyma.

Singular or focal lesions will often involute rapidly after birth without any complications. Multifocal lesions tend to involute in a similar pattern to cutaneous IHs, over a 6-10 year period. Diffuse lesions tend to replace almost the entire liver parenchyma, with severe complications.

These can include cardiac failure[5], high volume arteriovenous shunting[6], hypothyroidism secondary to overproduction of type III iodothyronine deiodinase[7], bleeding and abdominal compartment syndrome[8].

Therefore, once diagnosed, patients with IHHs usually require close monitoring until complete involution of the lesions.

Before the modern classification system developed by Mulliken in 1982[9], and the more recent subtyping of liver IHs by Christison-Lagay *et al*[10] in 2007, there was widespread confusion. Terminology for IHHs has been varied, a fact which can propagate the confusion and delay in the correct diagnosis and proper treatment of the affected patients. Moreover, there are several other hepatic lesions that may mimic different types of IHHs. Solitary hepatic lesions in an infant can also include, hepatoblastoma, mesenchymal hamartoma, congenital cysts (such as ciliated foregut duplication cysts) or kaposiform hemangioendotheliomas (KHEs). IHHs have also been historically called "hemangiomaendothelioma", regardless of the type of lesion.

It is therefore imperative to distinguish all 3 subtypes of true IHHs from other benign and malignant liver lesions, as this can deeply impact the management of these conditions. For this reason, we systematically review the literature in order to provide an up-to-date understanding of IHHs and their misnomers and to dialectical present the differential diagnosis of these rare entities of the liver.

RESEARCH AND LITERATURE

Eligible articles were identified thorough search of the PubMed bibliographical database extending from January 2000 to 2015. Two investigators working independently executed the search using the following keywords in all the possible combinations: Hepatic hemangioma, infantile hepatic hemangioma, liver hemangioma and visceral hemangioma. In addition, we checked all the references of relevant reviews and eligible articles that our search retrieved. Search of the literature was restricted to those articles published in English, based on the following criteria: (1) original clinical series and case reports describe infants with hepatic hemangiomas; and (2) reviews of the literature on infantile hepatic hemangiomas. The selection-process excluded at the same time: (1) studies that

Table 1 Description of the clinical, radiological, histological findings of the different subtypes of infantile hepatic hemangiomas and recommended treatment for the three different subgroups of infantile hepatic hemangiomas

IHH	Focal	Multifocal	Diffuse
Onset	Prenatal development	Postnatal (few weeks after birth)	Postnatal (few weeks after birth)
Association with cutaneous IH	Rarely	Frequently	Frequently
MRI	Solitary tumor; robust enhancement; often with Ca^{2+} and central cystic change	Hypointense to liver on T1, hyperintense on T2. Rapid enhancement. May have central flow voids on T2 spin echo sequence	Near-total replacement of the hepatic parenchyma with many lesions
CT	Rapid enhancement. Often with Ca^{2+} and central cystic changes	Homogenously; uniform or centripetal	Innumerable centripetally but rapidly enhancing lesions
Glut-1 staining	Negative	Positive	Positive
Comorbidities	Possible anemia and relatively mild thrombocytopenia; AV shunting; High-output cardiac state	High-flow shunting resulting in high-output; Cardiac failure	High-output cardiac failure; Abdominal compartment syndrome; Severe hypothyroidism
Treatment	Observation; embolization for problematic shunting	Observation; propranolol/ embolization for problematic shunting, possibly propranolol; hypothyroidism	Propranolol, thyroid hormone replacement, embolization in the cases of severe arteriovenous shunting (rare in diffuse IHHs), transplantation evaluation for the most extreme cases

IHH: Infantile hepatic hemangioma; CT: Computed tomography; MRI: Magnetic resonance imaging.

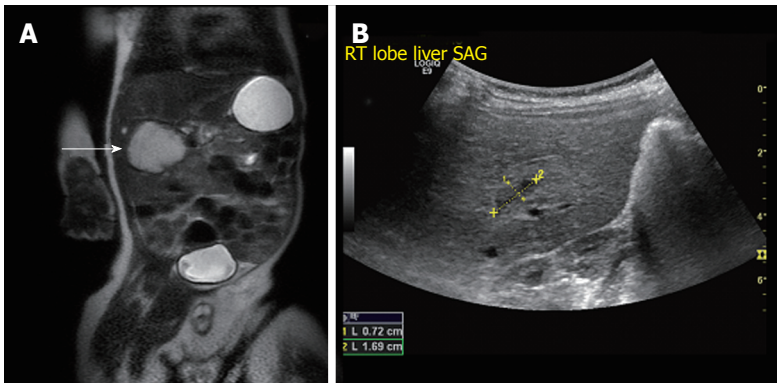

Figure 1 Focal infantile hepatic hemangiomas. A: Coronal T2 weighted MRI image through the abdomen of an 8-wk-old boy revealing a large hyperintense mass arising from the liver (arrow); B: Abdominal USG of the same patient at 17-mo-old shows a minimal residual scar (demarcated by calipers). USG: Ultrasonography; MRI: Magnetic resonance imaging.

describe malignant lesions alone; (2) lesions that are mistakenly categorized under the definition of infantile hepatic hemangiomas; (3) studies that do not contain the main outcomes of interest as described below.

In addition, historical evaluations of the failings of certain clinical treatments from beyond that timeline have been considered and included in order to present the story of IHHs as it has evolved.

CLINICAL PRESENTATION

A complete description of the clinical, radiological, histological findings of the different subtypes of IHH, and recommended treatment, can be found in Table 1. IHH lesions typically present and evolve in three different categorized patterns: Focal lesions, multifocal lesions, and diffuse lesions[11].

Focal lesions

Focal lesions are completely formed at birth and are mainly detected prenatally during routine USG. They fully involute soon after birth, sharing a similar evolution of their cutaneous counterpart, rapidly involuting congenital hemangiomas (RICHs)[10]. Similar to RICHs, focal hepatic hemangiomas stain negative for GLUT-1. Magnetic resonance imaging (MRI) shows these lesions as single hypointense areas relative to the surrounding liver parenchyma on T1-weighted sequences, and hyperintense on T2-weighted sequences (Figure 1)[12]. They often demonstrate central cystic areas that may be interpreted as central necrosis. In over 15% of cases, focal liver lesions are associated with cutaneous IHs[13]. Despite being usually asymptomatic, focal lesions can be accompanied by mild thrombocytopenia and arteriovenous shunting, which may require medical intervention if present after involution of the IHH. The presence of mild thrombocytopenia has to be distinguished from Kasabach Merritt Phenomenon (KMP) in which the symptoms of severe thrombocytopenia and coagulopathy are seen in combination with a rapidly growing vascular lesion. KMP is associated with KHE and Tufted Angiomas, rare and locally aggressive vascular infantile tumors which are part of the same neoplastic spectrum[14]. Mild coagulopathy can also occur in venous malformations and can be defined as Localized Intravascular Coagulopathy.

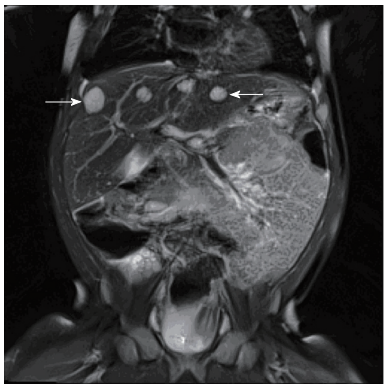

Figure 2 Multiple infantile hepatic hemangiomas. Coronal T2 weighted MRI image through the upper abdomen in a 5-mo-old girl depicts multiple well-defined, T2 hyperintense masses in the liver (arrows). This was consistent with multifocal infantile hepatic hemangiomas. MRI: Magnetic resonance imaging.

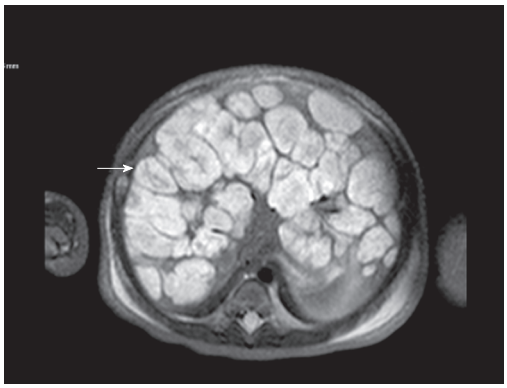

Figure 3 Diffuse infantile hepatic hemangiomas. T2 weighted axial MRI image of a 7-d-old with diffuse hemangiomas. Note the innumerable T2 hyperintense masses throughout the liver with central hypo-intense central regions (arrow). MRI: Magnetic resonance imaging.

Multifocal lesions

Multifocal lesions share a similar clinical course with cutaneous IHs. As for the cutaneous counterpart, multiple IHHs develop postnatally and exhibit a proliferating phase of around 9-12 mo in length, followed by a slow involution phase. They are more prevalent in females and Caucasians, and stain positive for GLUT-1. Multifocal IHHs can be detected on MRI as intensely enhancing spherical masses that are hypointense relative to the liver on T1-weighted sequences and hyperintense on T2-weighted sequences. They often present with a stellate (star shaped) central flow void on T2 spin echo sequences (Figure 2). Unlike focal lesions, multifocal IHHs can lead, in some cases, to moderate cardiomegaly and high-output heart failure due to arteriovenous and portovenous shunting. In over 60% of the cases, multifocal lesions are accompanied by cutaneous counterparts[5].

Diffuse lesions

Diffuse lesions are characterized by massive replacement of the hepatic parenchyma with various proliferating lesions with hyper enhancement on MRI (Figure 3). They have similar demographics with multifocal lesions, and also stain positive for GLUT-1. Association of cutaneous IH, may be present. Aortovenos, aortoportal, and venoportal shunting lead to high output cardiac failure[15]. Severe hepatomegaly may lead to compression of the systemic veins and thoracic cavity, leading to respiratory distress, abdominal compartment syndrome and multi-organ system failure. Diffuse lesions may also lead to severe hypothyroidism due to massive overproduction of type Ⅲ iodothyronine deiodinase[7] (an enzyme involved in converting thyroxine into an inactive form) and leads to acquired hypothyroidism. Therefore, it is mandatory that when diffuse lesions are suspected, thyroid hormone levels be closely monitored, as undetected hypothyroidism can cause permanent neurologic damage, impaired hemostasis, and low-flow cardiac depression[16].

DIFFERENTIAL DIAGNOSIS

Since IHHs are benign lesions, more aggressive liver malignancies need to be excluded at the time of diagnosis that at times may be challenging. Radiological imaging should be the first-line diagnostic analysis for physicians. A schematic algorithm to guide physicians through correct diagnosis and management of hepatic lesion can be seen in Figure 4.

Single lesions

Focal hepatic hemangiomas have been shown to be biologically identical to RICH. They may present with central calcifications, a finding amenable to detection by ultrasound or CT scan. Posterior acoustic shadowing and high density are the hallmarks of calcification on ultrasound and CT scan, respectively. The primary differential diagnoses include metastatic neuroblastoma, hepatoblastoma (Figure 5) and mesenchymal hamartoma (Figure 6). Primary sites of neuroblastoma (adrenal glands, organ of Zuckerkandel and paraspinal chain) should be evaluated and the urine samples should be screened for the presence of catecholamines. If the above results are unremarkable, the lesion demonstrates hyper enhancement (either on multiphase CT with iodinated contrast or MRI with gadolinium based contrast material) and there is no invasion of other structures, then a presumptive focal IHHs may be diagnosed but should still be monitored to ensure there is no further growth.

Unlike IHHs, hepatoblastomas typically demonstrate a more heterogenic signal on T2 weighted MRI. The enhancement pattern is variable after the administration of contrast. Hepatoblastomas often enhance less than the surrounding hepatic parenchyma, as opposed to the typical hyper enhancement of IHHs. When hepatoblastoma is considered in the differential diagnosis of IHH, α-fetoprotein (AFP) levels should be monitored over time. AFP is a major plasma protein produced by the yolk sac and later on from the liver during fetal

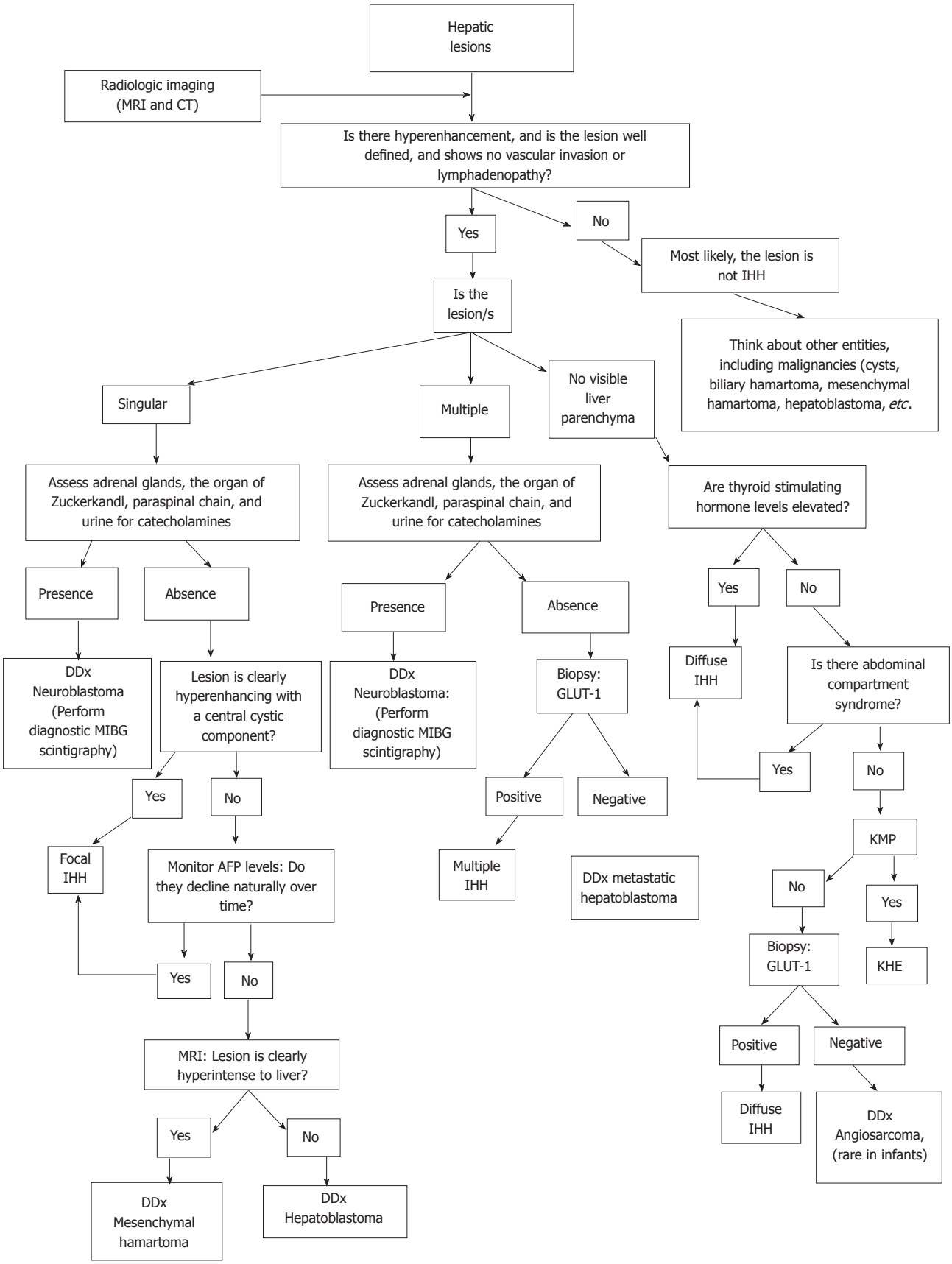

Figure 4 A schematic algorithm to guide physicians through correct diagnosis and management of hepatic lesions. IHH: Infantile hepatic hemangioma; CT: Computed tomography; MRI: Magnetic resonance imaging; DDx: Differential diagnosis; GLUT-1: Glucose transporter-1; AFP: α-fetoprotein; KHE: Kaposiform Hemangioendothelioma.

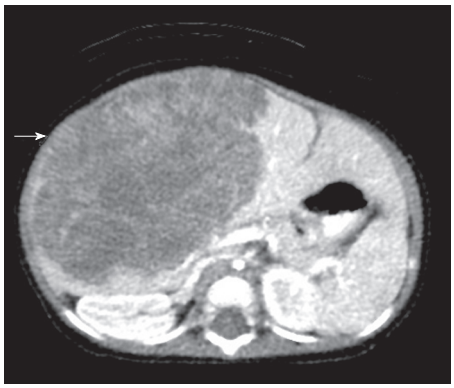

Figure 5 Hepatoblastoma. Axial computed tomography scan after the injection of IV contrast material in a 7-mo-old girl demonstrates a poorly enhancing large mass within the liver (arrow).

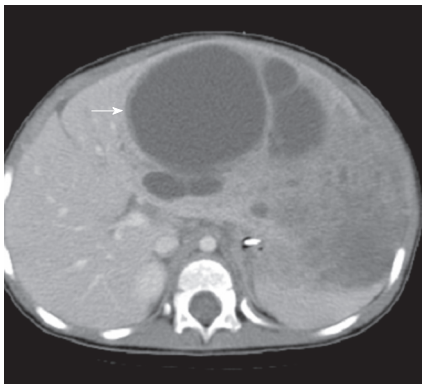

Figure 6 Mesenchymal hamartoma. 15-mo-old with abdominal distention: Axial computed tomography scan after the administration of IV contrast material demonstrates a large multi-cystic mass arising from the liver (arrow). Additional mixed solid and cystic elements are present laterally in the expanded left hepatic lobe.

development. At birth, normal infants have high AFP levels that decreases to a normal range over the first year of life. A baseline measurement in an infant with a focal hepatic lesion can be useful to be certain AFP is appropriately trending down towards the normal range, especially in a patient for whom the diagnosis of focal IHHs is later questioned. In case of hepatoblastomas, AFP levels do not decline over time.

Persistent mild elevation of AFP can also be observed in mesenchymal hamartoma. Mesenchymal hamartoma lesions typically appear distinct from IHHs, as they have predominant cystic components. However, the more mass-like variants can have some imaging overlap with IHHs. Both IHHs and mesenchymal hamartomas are benign lesions. In the literature evidence of association between these two entities has been reported[17].

Multiple and diffuse lesions

When multiple well-demarked hepatic lesions are present - particularly if they demonstrate avid enhancement at MRI, and all appear similar on each sequence - a multifocal IH is the most likely diagnosis, although an atypical presentation of neuroblastoma is still possible. When the hepatic parenchyma appears entirely or nearly entirely replaced with similar appearing lesions as previously described without other abdominal masses, diffuse IHH is likely. The diagnosis can be more confidently made in the context of supporting evidence such as profoundly suppressed thyroid function (or can say elevated TSH), bleeding or compartment syndrome. For a presumptive diagnosis of IHHs, regardless of the subtype, the enhancement pattern must be hyperacute (*i.e.,* arterial), the lesion(s) must be well defined and there must not be any vascular invasion or lymphadenopathy. If any of these criteria are not met, an alternative diagnosis should be considered. The lesion may warrant tissue sampling or resection.

Other rare tumors that can potentially mimic IHHs include the KHE. This tumor is more infiltrative appearing (less well-defined) and Kasabach-Merrit phenomenon often accompanies it. Undifferentiated embryonal sarcoma is a primary hepatic tumor, which can be included in the differential diagnosis (DDx), however it typically presents later in childhood. Though it is typically rare in infants, angiosarcoma can mimic IHH on CT and MRI. In this case of suspected malignancy, a biopsy staining for GLUT-1 positivity can rule out or confirm the diagnosis of IHHs.

Radiological imaging can prove extremely helpful to further characterize the lesion(s) and define the anatomic extent of liver involvement. For instance, radiologically IHHs can be differentiated from hepatoblastomas. Hepatoblastomas tend to appear heterogeneous on a T2 weighted MRI sequence and enhance heterogeneosly as opposed to the homogeneous and rapid enhancement of IHHs. If there are atypical features, percutaneous biopsy and staining for GLUT-1 positivity is indicated, despite the high risk of bleeding[4]. DDx includes also other benign lesions such as cysts, biliary hamartomas and arteriovenous malformations. These entities, however, present imaging characteristics in the neonates that do not overlap with IHH.

MANAGEMENT OF COMPLICATIONS

Despite the benign nature of IHs, a careful follow-up should be planned in case of hepatic lesions. Unlike focal IHHs, multifocal and diffuse IHHs may lead to severe complications and possibly death[18].

Multifocal and diffuse lesions are often associated with arteriovenus shunting. In this case, frequent echocardiograms and close cardiologic follow-ups should be recommended until complete regression of the lesion, due to increased risk of congestive heart failure secondary to high-cardiac output. Congestive heart failure represents the main cause of mortality in these patients.

In case of severe high-flow arteriovenous shunting, embolization should be considered. Shunt embolization should be attempted however only in refractory lesions and those with a worsening clinical course. Poten-

tial complications of this procedure include hepatic infarction, necrosis, cirrhosis, and sepsis. Therefore, embolization has to be performed only when expert interventional radiologists, skilled in performing intrahepatic infant embolization, are available.

As previously mentioned, another possible complication of multifocal and diffuse IHHs is severe consumptive hypothyroidism. For this reason, TSH, T3, and T4 levels should be closely monitored by specialized pediatric endocrinologists. Thyroid hormone replacement should be considered if thyroid hormone levels are low. These patients, however, require much higher doses of thyroxin to achieve a stabilizing euthyroid status than required in patients with congenital hypothyroidism due to continuous catabolism of the exogenous thyroid hormone by the deiodinase 3. As IHHs undergo involution, the hypothyroidism resolves[19]. Therefore, thyroid hormone levels represent excellent biomarkers of tumor response to IHHs treatment.

When the lesions occupy a significant portion of the liver parenchyma, hepatic transaminases, bilirubin and coagulation factors should also be included in the laboratory follow-up to monitor liver and coagulation function.

TREATMENT

Following the validated treatment algorithm developed by the Fishman's group at Boston Children's Hospital[10], focal hemangioma mostly do not require medical intervention, since they mostly involute before or soon after birth. In the rare cases associated with arteriovenous shunting, embolization should be considered. Multifocal and diffuse IHHs may require medical intervention and/or therapy. A recent study confirmed that the mortality rate is greater in patients with diffuse IHHs than in those with multifocal lesions[10]. In 2008 there was a serendipitous discovery of the effectiveness of treatment of cutaneous IH with propranolol, a non-selective ß-blocker, revolutionizing the treatment of hemangiomas by accelerating IH involution compared to other therapies[20].

IHHs have been shown to successfully respond to the propranolol, as well as the cutaneous counterpart[21-23]. Despite this, many studies published after 2008 still indicated interferon-α (INF-α) and corticosteroids for the treatment of IHHs. It is estimated that 2.5% of children who received INF-α for the treatment of vascular anomalies developed spastic diplegia (SD), while an additional 4.1% were diagnosed with a motor developmental disturbance other than SD[24].

Before propranolol was established as the mainstay therapy, corticosteroids were considered the gold-standard treatment for problematic multifocal or diffuse IHHs[25]. However failure rate was as high as 20%-30% and in 40% of cases there was only a stabilization of the lesion growth more than acceleration in the involution[26]. Moreover corticosteroids lead to significant side effects. These include growth retardation, hyperglycemia, Cushinoid syndrome, hypertension and immunosuppression[27]. It has to be mentioned, however, that even propranolol is not free from side effects and include hypotension, hypoglycemia and bradycardia and exacerbation of bronchospasm, that are much less severe than the above medications[22].

Before pharmacotherapy proved successful for the treatment of IHH lesions, and when the benign nature of IHHs had not been clearly established, surgical resection and embolization was considered the mainstay treatment[28]. Surgery for hepatic hemangiomas is rarely performed, mainly only in cases that are refractory to medical management cases. Surgery complications include internal bleeding and hepatic necrosis[29]. In rare case, patients may presents with acute IHH complications such as compartment syndrome. This represents a negative prognostic factor and if medical treatment is not effective decompressed laparotomy up to hepatic transplant should be considered.

CONCLUSION

The literature of infantile hepatic hemangiomas has been greatly confusing in the past. Recent acceptance of IHH classification and subsequent treatment algorithms have proven an advancement in the diagnosis and management of these vascular lesions. Treatment of IHHs has evolved rapidly in the past decade, especially in the studies on the efficacy of propranolol as opposed to the efficacy and problems with long-term corticosteroid treatment. The understanding of IHHs is likely nearing the tipping point into a new revolution of clinical knowledge and treatment. Based on the new classification of IHHs, we propose an algorithm to guide the physicians towards the proper management of hepatic lesions.

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MINIREVIEWS

Drug delivery interfaces: A way to optimize inhalation therapy in spontaneously breathing children

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Abstract

There are several different types of drug delivery interfaces available on the market. Using the right interface for aerosol drug delivery to children is essential for effective inhalation therapy. However, clinicians usually focus on selecting the right drug-device combination and often overlook the importance of interface selection that lead to suboptimal drug delivery and therapeutic response in neonates and pediatrics. Therefore, it is necessary to critically assess each interface and understand its advantage and disadvantages in aerosol drug delivery to this patient population. The purpose of this paper is to provide a critical assessment of drug delivery interfaces used for the treatment of children with pulmonary diseases by emphasizing advantages and problems associated with their use during inhalation therapy.

Key words: Aerosols; Inhalation therapy; Children; Masks; Mouthpiece; High flow nasal cannula; Blow-by; Hood; Spacer/valved holding chamber

Core tip: Many interfaces exist for aerosol drug delivery to spontaneously breathing children and inhalation therapy with different interfaces has become an important topic of interest among clinicians. However, clinicians usually focus on selecting the right drug-device combination and often overlook the importance of interface selection that lead to suboptimal drug delivery and therapeutic response in neonates and pediatrics. This paper provides a critical assessment of drug delivery interfaces used for the treatment of children with pulmonary diseases by emphasizing advantages and problems associated with their use during inhalation therapy.

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INTRODUCTION

There are several different types of drug delivery interfaces available on the market. Using the right interface for aerosol drug delivery to children is essential for effective inhalation therapy. However, clinicians usually focused on selecting the right drug-device combination and often overlooked the importance of interface selection that lead to suboptimal drug delivery and therapeutic response in neonates and pediatrics[1-6]. Therefore, it is necessary to critically assess each interface and understand its advantage and disadvantages in aerosol drug delivery to neonates and pediatrics. The purpose of this paper is to provide a critical assessment of drug delivery interfaces used for the treatment of children with pulmonary diseases by emphasizing advantages and problems associated with their use during inhalation therapy.

BLOW-BY

Blow-by is a technique that is used with a jet nebulizer placed within a distance from the child and directs aerosol plume towards the patient's face. Historically, aerosolized medications were delivered to neonates and pediatrics using blow-by because it was considered to be an effective technique especially for crying, fussing and uncooperative children. Also, many parents preferred to use blow-by, a mask-free aerosol delivery technique, to avoid struggling with their children during inhalation therapy.

However, there are several disadvantages of this technique. For instance, it cannot be used with pressurized metered-dose inhalers (pMDIs) with valved holding chambers (VHCs) and breath-actuated nebulizers due to poor mask seal that will inhibit valve opening[7]. Also, blow-by cannot be used with mesh nebulizers due to lack of supplemental gas flow[7]. Previous research reported that blow-by is not efficient in aerosol drug delivery to children because it results in 50%-85% lower dose than the facemask[8-11]. Therefore, using blow-by for aerosol therapy is not recommended[7,11-13].

Problems associated with blow-by highlight not only the importance of interface selection in inhalation therapy, but also finding a better alternative for delivering aerosolized medications to neonates and pediatrics. Mouthpiece, facemask, nasal mask, pasifier mask, hood, high flow nasal cannula and VHCs may be viable choices of interface in children and the following sections will describe each interface more in detail.

MOUTHPIECE

Previous *in vitro* studies showed that aerosol delivery *via* a mouthpiece may provide twice as much drug compared with a facemask and is the most effective interface in spontaneously breathing older pediatrics[14,15]. Since children less than 3 years of age cannot keep the mouthpiece in their mouth with an adequate seal during inhalation therapy, the mouthpiece is not the right interface for them[16-19]. Therefore, when a mouthpiece cannot be used by a child, choosing another interface such as facemask, high flow nasal cannula or hood is important to improve the efficiency and efficacy of aerosol drug delivery to neonates and pediatrics.

FACEMASK

Facemasks are commonly used for aerosol drug delivery to children until they develop sufficient understanding to inhale through the mouthpiece during inhalation therapy. In children who cannot use a mouthpiece until 3 years of age, clinicians should consider using a well-fitting facemask. Therefore, it is essential to select a lightweight and flexible facemask with anatomic contours and small dead space in order to increase tolerability of facemask by children during inhalation therapy[20,21]. Using smaller masks with less dead space in neonates will lead to a greater inhaled dose especially with use of aerosol devices such as mesh nebulizers or pMDIs that do not add gas to the system during treatment.

Facemasks designs can be divided into two categories: (1) front-loaded facemasks and (2) bottom-loaded facemasks. Front-loaded facemasks have small entrainment ports on the side of the mask and direct aerosol toward the oronasal area of the patient as opposed to bottom-loaded masks that direct aerosol toward the upper part of the mask. Previous research reported that aerosol deposition with the front-loaded facemask (Bubbles Fish Ⅱ Mask, PARI, Midlothian, Virginia) was greater than bottom-loaded facemask[8,22-24]. They also have lower deposition in the eye and face compared with bottom-loaded facemask designs[22,23,25].

When a facemask is used for aerosol drug delivery to neonates or pediatrics, clinicians should have a good face-mask seal to maximize the efficiency of treatment and prevent the drug from getting to the eyes and the face of children. However, keeping a good face-mask seal during inhalation therapy is frequently associated with crying and rejection of the facemask. Previous research showed that aerosol drug delivery to children will decrease significantly without an optimum face-mask seal because of leaks, crying or children intolerance of the facemask[2-4,22,25-29]. Janssens *et al*[30] suggested that administration of inhaled medications while children are asleep may be a viable option for inhalation therapy because children have more regular breathing patterns during sleep that may lead to greater lung deposition and better patient outcomes. However, Esposito-Festen *et al*[31] reported that 69% of the young children woke up and 75% of them distressed during inhalation therapy with the pMDI and VHC combination.

In the past, clinicians believed that crying improves aerosol drug delivery to children because of the large breath at the end of the cry. However, crying results in a

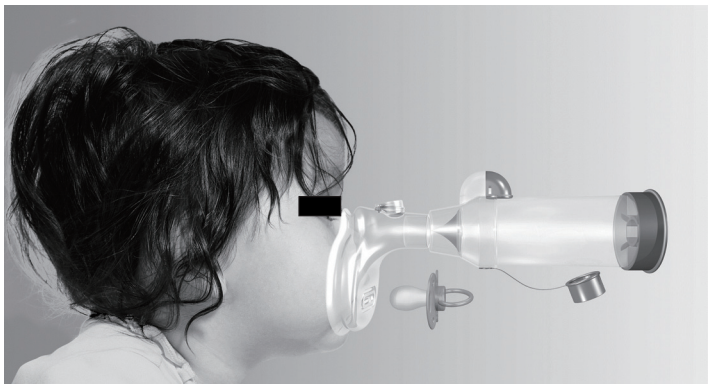

Figure 1 Soother mask (Reproduced with permission from the InspiRx, Somerset, New Jersey).

very long exhalation followed by fast and short inhalation that leads to deposition of aerosolized medications in the upper respiratory track than in the lower respiratory therapy track. Also, it is difficult to have a good seal with the facemask when a baby cries. Using a facemask with the pMDI - VHC, Tal *et al*[32] found that lung deposition of babies crying was 0.35% as opposed to 2% when they have quite breating. Similarly, Murakami *et al*[33] showed that aerosol deposition in a crying infant using a facemask with a nebulizer was negligible and Iles *et al*[34] reported a 4-fold decrease in lung deposition when infants were crying. According to the findings of the study conducted by Wildhaber *et al*[35] the gastrointestinal deposition in crying children was 50% higher than their non-crying peers.

PACIFIER MASK

As a new and innovative development of chidren-oriented drug delivery interface, the pacifier mask (Soother Mask, InspiRx, Somerset, New Jersey) was designed to achieve therapeutic lung deposition in children by eliminating their discomfort, fear and cry with the conventional facemask and keeping them calm through a pacifier. It includes the infant's own pacifier that is attached to the anterior wall of the mask (Figure 1). The infant keeps the Soother mask sealed to his face by sucking the pacifier during treatment while nasally inhaling aerosolized medications generated by pMDIs/VHCs or nebulizers during inhalation therapy[36,37]. Amirav *et al*[38] compared the Soother mask with a conventional bottom-loaded face mask on bronchodilator delivery in 12 infants less than 1 year of age. Using scintigraphic measurements of aerosol deposition in infants, they reported that lung deposition with the Soother Mask was similar to that with the conventional face mask without a pacifier[38]. Since sucking calms children, the Shooter Mask can be used for prolonged periods of time without rejection by infants and improves compliance to aerosol treatments in infants[18,36-38].

HIGH FLOW NASAL CANNULA

Infants and young children are nose breathers. Since previous research showed that nasal delivery of aerosolized medications to the lungs of infants and pediatrics is superior or more effective than oral delivery[39,40], aerosol delivery through high flow nasal cannula (HFNC) has become a popular procedure in the treatment of children with pulmonary diseases. Several *in vitro* studies evaluated aerosol drug delivery through HFNC in infants and pediatrics[41-44]. Using dose quantification with the laser diffraction technique, Bhashyam *et al*[43] determined the efficiency of inhalation therapy through adult and pediatric HFNC with a mesh nebulizer placed downstream of a heated humidifier. They reported that aerosolized medications could be efficiently delivered to pediatrics through HFNC. Ari *et al*[44] compared aerosol drug delivery with helium-oxygen mixture (heliox) and oxygen at 3 L/min and 6 L/min, using a pediatric HFNC with a mesh nebulizer placed on the inspiratory inlet of a heated humidification system. They reported that bronchodilator delivery with heliox at 3 L/min was similar to that with oxygen whereas heliox delivered 2 fold greater aerosol than oxygen at 6 L/min. Sunbul *et al*[42] evaluated bronchodilator delivery using HFNC, bubble continuous positive airway pressure (CPAP) and sigh intermittent mandatory ventilation (SiPAP) with a mesh nebulizer placed proximal to the patient interface and prior to the humidifier. Using spontaneously breathing lung model attached to a low-birth-weight anatomic nasal airway cast, they showed that aerosol delivery with SiPAP was lower than HFNC and the Bubble CPAP. Aerosol deposition through HFNC was less than 2% but higher than drug delivery with the Bubble CPAP. Also, nebulizer placement at the humidifier resulted in greater aerosol deposition in HFNC, SiPAP and Bubble CPAP[42]. According to Perry *et al*[41] HFNC should not be used for bronchodilator delivery to children because the amount of aerosol deposition obtained with different cannula sizes of flows used with HFNC was lower than the amount needed for a clinical response. Also, skin irritation and condensate accumulating in the cannula are potential issues with HFNC. Therefore, clinical studies evaluating the safety and efficacy of aerosol drug delivery with HFNC are warranted.

NASAL MASK

Nasal masks were developed in recent years to improve

Table 1 Descriptions, advantages and disadvantages of each interface used for aerosol drug delivery to spontaneously breathing neonates and pediatrics

Interface	Description	Advantages	Disadvantages	Suggestions for the best practice
Blow-by	A technique that directs aerosol plume towards the patient's face by placing a jet nebulizer within a distance from the child that ranges from 1 to 30 cm	Easy to use Comfortable and easy to tolerate by the patient A mask-free aerosol delivery technique Used with fussing, crying and uncooperative children	Inefficient aerosol drug delivery to children Drug delivery with blow-by is 50%-85% less than the facemask Cannot be used with pMDIs, breath- actuated nebulizers and mesh nebulizers	Inhalation therapy with blow-by is not efficient; therefore, it should not be used for aerosol drug delivery to neonates and pediatrics
Mouthpiece	A cylindrical tube that extends between the lips so that aerosol can pass through the oropharynx to reach lower respiratory tract	Efficient inhalation therapy in children Aerosol drug delivery with a mouthpiece is two-fold more than that with a face mask	Children less than 3 yr of age cannot use a mouthpiece An adequate consistent seal is needed during inhalation therapy	The mouthpiece should not be used for children who are less than 3 yr old When using a mouthpiece child should be encouraged to keep it in their mouth during therapy If a child cannot keep the mouthpiece in his mouth with an adequate seal during aerosol drug delivery, another interface should be used for inhalation therapy
Facemask	An interface that covers the nose and mouth. It is kept in place through an elastic band that extends beyond the back of the head or neck	Can be used in children all years of age Can be used with nebulizers and pMDIs to deliver aerosolized medications to neonates and pediatrics	A good facemask seal is needed for optimum aerosol drug delivery Is frequently associated with crying, intolerance and rejection of the mask Crying and leaks between face and mask decrease aerosol drug delivery to children	Select a lightweight and flexible facemask with anatomic contours to increase tolerability of face mask by children during therapy Choose a facemask with small dead space and have a good face-mask seal to increase delivery efficiency of inhalation therapy Use another interface if the patient starts to fuss, and cry during aerosol drug delivery with a facemask
Pacifier mask	A face mask with the attachment of the infant's own pacifier	A new and innovative facemask design that eliminates fear, discomfort and cry with the standard facemask A children-oriented drug delivery interface designed to achieve therapeutic lung deposition in children Improves compliance to inhalation therapy in infants		May be a good option for children who fuss, cry and does not tolerate other interfaces used for aerosol drug delivery in neonates and pediatrics
Nasal mask	An interface that covers the nose to allow aerosol to pass through the nasopharynx to reach the lower respiratory tract	Easy to use Better tolerance than the facemask	Aerosol delivery with the nasal mask is less than that with the standard facemask	
High flow nasal cannula	A tubing with two small prongs that are inserted into the nares to allow aerosol pass through the nasopharynx and reach the lower respiratory tract	Efficient delivery of aerosolized medications to neonates and pediatrics Children may tolerate HFNC better than the facemask	More information about the safety and efficacy of aerosol drug delivery though HFNC is needed Cannot be used with pMDIs	When using mesh nebulizers for aerosol drug delivery to neonates and pediatrics, place the nebulizer prior to the heated humidifier
Hood	An enclosure that covers the head and neck of a neonate or small children to deliver aerosol to the lungs while isolating it from ambient air	A good option for aerosol delivery to children who cannot use a mouthpiece and tolerate the facemask Likelihood of agitating infants and making them cry is low Aerosol delivery with the hood is the same as the facemask Parents prefer the hood over the mask	User may need additional training and practice to provide proper inhalation therapy with the hood More time and parts may be needed for the set-up	Use the hood for aerosol drug delivery to children who cannot use a mouthpiece and tolerate the facemask Put the infant in the face-side position when using the hood for inhalation therapy because it has less facial-ocular deposition than face-up position

Valved holding chamber	A chamber shaped interface with a one-way valve that allows aerosols to be contained in the chamber during aerosol therapy	Reduces oropharyngeal deposition Minimize hand-breath coordination during inhalation therapy Improves efficiency of aerosol therapy	Electrostatic charge and large volume VHCs result in a decrease in aerosol drug delivery to children	Wash the VHC with detergent and air dry before inhalation therapy in order to eliminate static charge and improve aerosol delivery to neonates and pediatrics Choose small volume VHCs for aerosol therapy Actuate one-dose at a time into VHC instead of multiple doses

VHC: Valved holding chambers; pMDIs: Pressurized metered-dose inhalers.

aerosol drug delivery to neonates and pediatrics. The nasal mask is a special type of mask that is placed over the nasal airway during inhalation therapy. A recent *in vitro* study showed that aerosol delivery with the nasal mask was less than that with the facemask in simulated spontaneously breathing infants and young children using a jet nebulizer[24].

HOOD

Hood is a good option for aerosol drug delivery to children who cannot use a mouthpiece and tolerate the facemask[18,45-48]. Since there is no attachment to the patient's face, the likelihood of agitating infants and making them cry with the use of hood for inhalation therapy may be less than facemasks. Aerosol drug delivery *via* hood is easy to operate and often provided when infants are asleep. Amirav *et al*[49] showed that bronchodilator delivery with the hood and facemask was similar (2.6% and 2.4%, respectively) in 14 wheezing children. Kugelman *et al*[47] reported that both treatment time and discomfort were lower in infants using the hood. In another study, Amirav *et al*[48] found that respiratory scores of infants with bronchiolitis received aerosol therapy with the hood and facemask were similar, but parents preferred the hood over the masks[48]. It is also important to ensure the optimal position of the child within the hood. Kim *et al*[50] found similar lung deposition in face-up and face down positions during hood nebulization; however, the face-side position has less facial-ocular deposition than face-up position.

VALVED-HOLDING CHAMBERS

VHCs are commonly used with pMDIs in order to decrease oropharyngeal deposition and minimize hand-breath coordination in children[12,51]. According to previous research, spacers and VHCs should be washed with detergent and air-dry to eliminate static charge and improve aerosol delivery to infants and pediatrics[52-55]. Thus, deposition of drug particles on the inner surface of the spacer or VHC will be eliminated. Another alternative would be to use anti-static spacers/VHCs during inhalation therapy in children[56].

Also, infants and toddlers may not empty aerosolized medication from a large volume spacer of 200-700 mL. Therefore, it is important to use small volume spacers or VHCs so that the concentration of aerosol in the VHC is kept higher and children can inhale all the medication in less time with fewer breaths. Parents need to be educated to actuate one dose at a time into VHC instead of multiple doses and let their children inhale from VHC right after the pMDI has been actuated[12,57].

EDUCATING PARENTS ABOUT INTERFACES USED IN INHALATION THERAPY

Typically, inhaled medications are prescribed without demonstrating parents how inhalation therapy should be undertaken with each device and interface. Therefore, parents don't know how to use each interface and how to solve problems that may arise during aerosol drug delivery to children. For instance, when their baby fights with the facemask, some parents may decide to use blow-by without knowing that it will reduce the efficiency of therapy and others force the baby to accept the facemask by holding it tightly on the baby' s face and believing that crying improves aerosol drug delivery to their children. As a result, parents report poor response to inhalation therapy to their physicians who usually decide to increase the dose or change the inhaled agent as they assume parents' technique in aerosol drug delivery is adequate[18]. Therefore, parental awareness and training on proper technique with each interface during inhalation therapy is essential. Table 1 includes descriptions, advantages and disadvantages of each interface used for aerosol drug delivery to spontaneously breathing neonates and pediatrics. After careful instructions on how to use and handle an aerosol device, clinicians should reinforce instructions on a regular basis and the choice of drug delivery interface should be re-assessed[58].

In conclusion, delivering aerosolized drugs through different interfaces to children poses a number of challenges. Clearly, there is a need to develop more acceptable and child-friendly interfaces in order to improve aerosol drug delivery to this patient population. New interfaces should take into account the special needs and respiratory characteristics of children. Meanwhile, educating parents and healthcare professionals about drug delivery interfaces used in inhalation therapy is

essential for the well-being of neonates and pediatrics.

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ORIGINAL ARTICLE

Case Control Study

Skin disease and thyroid autoimmunity in atopic South Italian children

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Author contributions: Pedullà M drafted the manuscript; Pedullà M, Fierro V and Marzuillo P participated in the conception and the design of the study; Pedullà M and Capuano F examined the patients, collected anthropometric data; Miraglia del Giudice E and Ruocco E supervised the design and execution of the study.

Institutional review board statement: An informed consent was obtained from the parents and the children all enrolled after the nature of the investigation was explained and in accordance with the approved protocol from the Institutional Review Board at the Second University of Naples.

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Abstract

AIM: To verify the prevalence of thyroid autoimmunity (TA) and the possible association between atopy and TA in children affected by skin disease.

METHODS: Three hundred and twenty-four children consecutively referred due to skin disease symptoms to our Pediatric Department were enrolled. One hundred and eighty-seven were diagnosed with atopic dermatitis (AD), 95 with acute urticaria, 40 with chronic urticaria (CU), and 2 with alopecia areata (AA). According to the work-up for atopy, the children were divided into two groups: Atopics and non-atopics. TA was diagnosed by serum thyroid peroxidase autoantibodies and/or thyroglobulin autoantibodies levels more than twice normal values over a period of two months by immunoassay.

RESULTS: In all children with skin disease, a significant prevalence of TA in atopics compared with non-atopics (13.67% *vs* 2.67%, $P = 0.0016$) and a significant association between TA and atopy (OR = 5.76, 95%CI: 1.71-19.35) were observed. These findings were confirmed as significant in children with AD: TA in atopics was 11.5%, while TA in non-atopics was

2.7% (P = 0.03, OR = 4.68, 95%CI: 1.02-21.38). In addition, atopics with CU showed a significantly higher prevalence of TA (26.9%), but none of the non-atopics showed CU (P = 0.0326). On the other hand, atopics with AA showed a 100% (2 out of 2) prevalence of TA, compared with none of the non-atopics.

CONCLUSION: In children with skin disease, atopy seems to be associated with an increased risk of TA.

Key words: Skin disease; Thyroid autoimmunity; Atopic dermatitis; Children

Core tip: We observed a significant association between atopy and thyroid autoimmunity (TA) in atopic children with skin disease. This association was confirmed in atopic children affected by atopic dermatitis. The key message from our study for pediatricians is that clinicians should always evaluate thyroid peroxidase and thyroglobulin autoantibodies in atopic children with skin disease, as these children could also have TA.

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INTRODUCTION

Recent observations have challenged the validity of the Th1/Th2 paradigm[1] and considerable effort has been focused on understanding the relationship between atopic inflammation and developing autoimmunity both in experimental models and in human populations[2].

Thyroid autoimmunity (TA) has been regularly associated with chronic urticaria (CU) both in adults[3] and in children[4] and less frequently with several dermatological diseases such as vitiligo[5], alopecia areata (AA)[6], post-adolescent acne[7] and atopic dermatitis (AD)[8]. On the other hand, even if less frequent, atopy is considered a cause of both AD and acute urticaria (AU) or CU presenting with intermittent symptoms[9] and has been associated with increased risk and severity of AA[10].

The aim of the present study is to verify the prevalence of TA and the possible association between atopy and TA in South Italian children affected by skin disease.

MATERIALS AND METHODS

From January 2013 to July 2015, 324 children consecutively referred to the Pediatric Department of the Second University of Naples for evaluation of dermatological symptoms such as erythema, pruritus, eczematous rash, xerosis, hair loss, wheals and/or angioedema were enrolled. None of the children suffered from endocrine or systemic diseases and did not show signs of genetic syndromes.

The work-up for dermatological disease included complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum levels of complement C3, C4 and C1 inhibitor, serum immunoglobulins, antinuclear antibody and anti-DNA antibody (if needed), immunoglobulin A (IgA) and IgG anti-transglutaminase, FT3, FT4, TSH, thyroid peroxidase antibodies (TPO Ab) and thyroglobulin antibodies (TG Ab), urine analysis and culture, nasal and throat swabs, and microscopic investigation of stool for *Helicobacter pylori* antigens and parasite ova. No urticarial vasculitis, physical or other types of eliciting urticaria were diagnosed. In addition, cold provocation and threshold test (ice cube and cold water) were also performed in patients to exclude physical urticaria.

None of the patients had IgA deficiency, but two patients with urticaria were diagnosed with celiac disease and excluded. Therefore, 324 children were enrolled.

The same dermatologist from the Dermatology Department of the Second University of Naples defined the dermatological diseases. On the basis of the dermatologist's diagnosis, the cohort was then divided into 4 subgroups: 187 children were affected by AD, 95 by AU, 40 by CU, and 2 by AA.

TA was diagnosed by TPO Ab and /or TG Ab (immunoassay: High-specific solid-phase technique-chemiluminescence immune-assays PerkinElmer, Turku, Finland) serum levels more than twice normal values (TPO Ab n.v. < 30 UI/mL; TG Ab n.v. < 100 UI/mL) over a period of two months.

Atopy, defined as serum-specific IgE positivity against inhalant allergens was suspected on the basis of clinical history and diagnosed by skin prick tests (SPTs) and by a specific IgE assay (> 0.36 kUA/L - ImmunoCap 0-100 Phadia AB, Uppsala, Sweden). SPTs were performed using a standard battery of aeroallergens and food allergens: House dust mite (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), *Parietaria officinalis*, grasses (*Dactylis glomerata*, *Lolium perenne*, *Phaleum pratense*), mold (Alternaria, Aspergillus, Cladosporium), dog fur, cat fur, egg, cow milk, casein, wheat, soyabean, codfish, peanut and tree-nuts (Epernox, Cedex, France). Allergens were applied to a stencil stamped on the forearm with ink and pricked with a lancet (Bayer DHS Diagnostic). Histamine chloride (10 mg/mL) was used as a positive control and the allergen diluent served as the negative control. The results were read after 15 and 30 min and the test was considered positive if the wheal was at least 3 mm in diameter compared with the negative control. Thus, on the basis of the work-up for atopy, the children affected by skin disease were divided into atopics (n = 212) and non-atopics (n = 112). None of the children received steroids or immuno-suppressive therapy for at least 3

Table 1 Differences between clinical characteristics in children with skin disease divided into atopics and non-atopics

	Atopics (n = 212)	Non-atopics (n = 112)	Statistical analysis
Age in years (mean ± SD)	6.3 ± 4.18	5.55 ± 3.67	P = 0.1
Sex (male %)	111/212 (52.8%)	48/112 (42.8%)	P = 0.26
Family history of atopy (%)	188/212 (88.67%)	93/112 (83.03%)	P = 0.91
Family history of thyroid diseases (%)	93/212 (43.86%)	43/112 (38.39%)	P = 0.6

Table 2 Thyroid autoimmunity in children with skin disease divided into atopics and non-atopics

	Thyroid autoimmunity (%)	Atopics (%)	Non-atopics (%)	Statistical analysis
All skin diseases	9.6	29/212 (13.67)	3/112 (2.67)	P = 0.0016 OR = 5.76 (1.71-19.35)
Atopic dermatitis	8.02	13/113 (11.5)	2/74 (2.7)	P = 0.03 OR = 4.68 (1.02-21.38)
Alopecia areata	100	2/2	0	NA
Chronic urticaria	17.5	7/26 (26.9)	0/14	P = 0.0326
Acute urticaria	8.42	7/71 (9.85)	1/24 (4.1)	P = 0.38

mo before the investigation. Antihistamine therapy was stopped at least 2 wk before the investigation.

An informed consent was obtained from the parents and the children all enrolled after the nature of the investigation was explained and in accordance with the approved protocol from the Institutional Review Board at the Second University of Naples.

Statistical analysis

In this observational study the t test was used to compare the difference between the mean values and a χ^2 test was used to analyze the differences between the frequencies among categorical variables assessed by Kurtosis. A P value < 0.05 was considered significant.

An odds ratio (OR) was calculated to evaluate the association between atopy and TA. This was considered significant when showing a 95%CI and excluding unity.

Statistical analyses were performed using StatGraph 3.0 for Windows.

RESULTS

Table 1 shows the differences between the characteristics of the 324 children with skin diseases divided into atopics and non-atopics.

Significant differences regarding age in years, sex, and family history of atopic and thyroidal disease were not observed between the two groups (Table 1).

It is worth noting that in all children with skin disease a significant prevalence of TA in atopics compared with non-atopics (13.67% *vs* 2.67%, P = 0.0016) and a significant association between TA and atopy (OR = 5.76, 95%CI: 1.71-19.35) were observed (Table 2). These findings were confirmed as significant in AD affected children: TA prevalence in atopics was 11.5%, while TA prevalence in non-atopics was 2.7% (P = 0.03, OR = 4.68, 95%CI: 1.02-21.38) (Table 2). In addition, atopics affected by CU showed a significantly higher prevalence of TA (26.9%) compared with non-atopics (P = 0.0326), but none of the non-atopics had CU (Table 2). On the other hand, AA atopics showed a 100% (2 out of 2) prevalence of TA compared with none of the non-atopics (Table 2).

AU atopics did not show a significant difference compared with non-atopics in terms of a significant risk for TA.

DISCUSSION

There is currently great interest in defining the link between atopy and autoimmunity.

T regulatory (T reg) cells seem to play a pivotal role in this relationship, as they are essential for the maintenance of immune homeostasis and prevention of autoimmunity[11]. There is also evidence that the number or function of T reg cells may be deficient in patients with atopy[12].

Furthermore, decoy receptor 3 (DcR3), a member of the tumor necrosis factor receptor superfamily, can promote M2 macrophage differentiation *via* epigenetic regulation, with a pleiotropic immunomodulatory effect[13]. Indeed, elevated levels of DcR3 have been found in the serum of atopic patients[14]. DcR3 can also promote tumorigenesis *via* the induction of tumor-associated macrophages[15]. It has also been proposed that atopy may have effects on the risk of cancer, but studies of thyroid cancer[16] and non-melanoma skin cancer[17] have shown no association or conflicting results related to atopy.

To date, few papers in the literature address the relationship between atopy and TA. In our study, TA prevalence in children with skin disease was 8.9% and atopics had a significant higher prevalence of TA compared with non-atopics. Moreover, they showed a significant risk for TA. We would underline a possible selection bias in our patient sample, which was selected

from children referred to a University Pediatric Center for the diagnosis and treatment of allergic disease. The prevalence of TA reported for age-matched healthy children in different geographic areas ranges from 0.3%[18] to 1.6%[19]. In a recent study conducted in a Mediterranean area similar to South Italy with regard to iodine status (Almeria, Spain), the prevalence of TA was higher and reached 3.7% in healthy children and adolescents[20].

In the four subgroups selected on the basis of different dermatological diagnoses, a significant association between TA and atopy was found only in children with AD, similar to the findings in our previously published paper[8].

We also identified 2 cases of AA, both atopics. In the literature, AA is regularly associated both with TA and atopy. This was not confirmed in our cohort as only two patients were diagnosed with AA. Barahmani *et al*[21] suggested that AA has features of both atopic and autoimmune-mediated skin disease.

Leznoff *et al*[22], for the first time, demonstrated a TA prevalence of 16% in a large population of adults with CU. Rumbyrt *et al*[23] described a TA prevalence ranging from 10% to 35% in adults with CU.

TA prevalence in our CU children was 17.5%, slightly higher than the reported prevalence in healthy children, which ranged from 4.3%[4] to 14.8%[24]. On the other hand, in our CU atopics we found a TA prevalence of 26.9%, significantly higher compared to our non-atopics (0%, $P = 0.0326$) and higher than that reported in healthy children in the literature. In addition, TA prevalence in our AU patients was 8.42% and no significant association between TA and atopy was found. It is possible that an acute atopic inflammation could contribute to the occurrence of TA in patients with AU. To date, only Gangemi *et al*[25] have identified TA positivity in 3 out of 6 adult patients affected by idiopathic acute urticaria.

To our knowledge, this is the first report to show a significant prevalence of TA in a population of atopic children affected by skin disease and a significant risk of TA in these atopics.

The key message from our study for pediatricians is that clinicians should always evaluate TPO and TG autoantibodies in atopic children affected by skin disease, as these children could have concomitant TA.

COMMENTS

Background

Thyroid autoimmunity (TA) is regularly associated with chronic urticaria both in adults and in children and less frequently with several dermatological diseases such as vitiligo, alopecia areata, post-adolescent acne and atopic dermatitis. The aim of the present study was to verify the prevalence of TA and the possible association between atopy and TA in children affected by skin disease.

Research frontiers

Important areas of research related to this study are represented by the field of pediatric dermatology and allergology. This study aimed to verify the association between TA and skin diseases in a population of atopic children.

Innovations and breakthroughs

To our knowledge, this is the first report to show a significant prevalence of TA in a population of atopic children affected by skin disease and a significant risk of TA in these atopics.

Applications

Future research is necessary to confirm the authors' findings and to understand the pathophysiological basis underlying the association between TA and skin diseases in atopic children.

Terminology

Atopy is defined as serum-specific IgE positivity against inhalant allergens suspected on the basis of clinical history and diagnosed by skin prick tests and by a specific IgE assay (> 0.36 kUA/L - ImmunoCap 0-100).

Peer-review

This is a very interesting manuscript with the aim to verify the prevalence of thyroid autoimmunity and the possible association with atopy in a restricted population showing skin disease.

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ORIGINAL ARTICLE

Case Control Study

Effects of resistance training on cardiovascular health in non-obese active adolescents

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Author contributions: Yu CCW designed and coordinated this study, interpreted the data, and draft the manuscript; McManus AM supervised statistical analyses, data interpretation and the preparation of the manuscript; So HK and Li AM assisted in the pubertal assessment for male participants and took part in the trial coordination; Chook P conducted all endothelial function measurements; Au CT contributed to data collection and statistical analyses; Kam JTC and So RCH designed and supervised the training program of this study; Lam CWK and Chan IHS are responsible for all laboratory assessments; Sung RYT supervised the whole program.

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Abstract

AIM: To determine the benefits of a 10-wk resistance

training programme on cardiovascular health in non-obese and active adolescents.

METHODS: This is a pragmatic randomised controlled intervention. The study was carried out in a Hong Kong Government secondary school. Thirty-eight lean and active boys and girls were randomised to either the resistance training group or the control group. Students in the resistance training group received in-school 10-wk supervised resistance training twice per week, with each session lasting 70 min. Main outcome measures taken before and after training included brachial endothelial dependent flow-mediated dilation, body composition, fasting serum lipids, fasting glucose and insulin, high sensitive C-reactive protein, 24-h ambulatory blood pressure and aerobic fitness.

RESULTS: The only training related change was in endothelial dependent flow-mediated dilation which increased from 8.5% to 9.8%. A main effect of time and an interaction ($P < 0.005$) indicated that this improvement was a result of the 10-wk resistance training. Main effects for time ($P < 0.05$) in a number of anthropometric, metabolic and vascular variables were noted; however, there were no significant interactions indicating the change was more likely an outcome of normal growth and development as opposed to a training effect.

CONCLUSION: Ten weeks of resistance training in school appears to have some vascular benefit in active, lean children.

Key words: Strength training; Children; Cardiometabolic risk factors; Endothelial function; School-based training program; High sensitive C-reactive protein; 24-h ambulatory blood pressure; Aerobic fitness

Core tip: We have shown that a school-based resistance training programme is adhered to and provides vascular benefit in lean children, lending support to the role school-based physical activity can play in the primary prevention of heart disease.

Yu CCW, McManus AM, So HK, Chook P, Au CT, Li AM, Kam JTC, So RCH, Lam CWK, Chan IHS, Sung RYT. Effects of resistance training on cardiovascular health in non-obese active adolescents. *World J Clin Pediatr* 2016; 5(3): 293-300 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i3/293.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i3.293

INTRODUCTION

The endothelium plays an integral role in maintaining vascular tone and reactivity and in preserving vascular health, but impaired endothelial function predisposes individuals to early atherosclerosis[1]. The cardio-protective property of physical activity is well established and resistance training, either on its own, or in combination with aerobic exercise, has proven to be particularly effective for both cardiovascular and endothelial function in adults with hypertension, chronic heart failure, or type Ⅱ diabetes[2-5]. In children and adolescents, there is growing evidence that resistance training not only increases muscle strength, but also contributes to an increase in bone strength, a desirable change in body composition, and an improvement in motor skills and sports performance[6]. We have shown considerable improvements in endothelial function following combined aerobic-resistance training and dietary modification programmes in overweight and obese children and adolescents[7]. Resistance training is potentially appealing and easy to administer within a school settings, but there is little evidence of the benefit of such training on cardiovascular and endothelial function in healthy active adolescents.

This study was therefore designed to evaluate the effectiveness of a resistance training intervention on aspects of vascular and metabolic health in normal weight 11 to 13 years old.

MATERIALS AND METHODS

Study design and subjects

Flyers were delivered to students and their parents attending a Government Secondary school in Hong Kong. Those who showed interest in the study were invited to attend an information seminar and 38 students (25 boys and 13 girls) aged 11 to 13 years old volunteered to participate. The school was chosen because it introduced a novel compulsory physical education (PE) programme comprising of one 70 min skill-based PE session per week (5 school days), plus 3 h per week of sport (students can join one of the following sports: Table-tennis, volleyball, soccer, badminton, basketball, squash, fencing, track and field, cross-country, swimming, cycling, or wushu). Although we did not assess physical activity, we believe that all the students can be classified as active on the basis of their participation in the extra sport programme. The study began at the start of the school term and all participants had been involved in the new PE programme for three weeks prior to joining the study.

All participants were classified as normal weight on the basis of having a body mass $\geqslant 40^{th}$ and $\leqslant 60^{th}$ percentile expressed in relation to height using sex, age and race specific normative charts[8]. None had congenital or chronic diseases that restricted them from physical activity. The study received ethical approval from the Institutional Review Board for Human Ethics of The University of Hong Kong and Hong Kong Hospital Authority West Cluster. Written informed consent was obtained from all participants and their legal guardians.

Procedures

Prior to the start of the training programme, our research team went to the school in the early morning to take fasting blood samples and assess body composition, pubertal stage, resting blood pressure and heart rate for all participants. Within one week participants attended the hospital laboratory twice for cardiorespiratory fitness testing and endothelial function of the brachial artery. During this baseline assessment period, the children were also fitted with an ambulatory 24-h blood pressure monitor at school early in a morning before their lessons started. The monitor was returned 24 h later to the school. This sequence of testing was repeated within 1-wk of completion of the 10-wk intervention, with the exception of pubertal rating. All baseline and post-training outcomes were assessed by individuals blinded to the grouping of the students.

After the baseline assessments, the 38 students were randomised to either the control group or resistance training group using gender specific sealed opaque envelopes. Students in the resistance training group (7 girls and 12 boys) received supervised resistance training twice per week for 10 wk, while students in the control group (6 girls and 13 boys) did not receive any resistance training. Both groups of students were asked to maintain their PE classes and their normal out-of-school lifestyle.

Intervention

The resistance training group joined twice weekly sessions in small groups (9 to 10 students per group), supervised by a professional trainer with two assistants. Each training session started with 10 min of warm-up and stretching exercises, followed by 40 min of resistance training (exercise order: Elbow extension, elbow flexion, trunk extension, trunk flexion, shoulder press, knee extension, knee flexion, push ups, squats, incline dip, hip abduction, and hip adduction), and ended with 5 min of stretching exercises to cool down. The training was carried out in circuit style and the participants were asked to complete three sets of 12 repetitions for each exercise in total. One set of a single exercise lasted for about 30 s and there was no rest between repetitions. The rest period between each set of single exercise items was about 16 s (therefore one set of all 13 exercises took about 9.7 min to finish). After that, the class moved on to the second and the third set of 13 exercises. Exercise order within each set of all exercises followed the principle of alternating upper-body exercises with lower-body exercises, or alternating pushing exercises with pulling exercises. This arrangement minimized the length of the rest periods required between exercises and maximizes the rest between body areas[9].

Training intensity was set at 12-RM (repetitions maximum), which implies the maximum amount of weight one can lift in 12 repetitions for most of the exercises (not including push-ups, incline dip, trunk extension, trunk flexion, and sit-ups). Twelve-RM was assessed at the first training session. This moderate intensity training programme is in keeping with published recommendations for safe resistance training in youth[10,11]. Equipment for the resistance training included dumbbells, sandbags, and exercise rubber tubing of varying resistances and fitness balls. After 4 wk the training load was increased by increasing the sets to four, whilst resistance remained constant.

Measurements

Anthropometric measures: Body mass was measured using electronic scales (Seca Delta Model 707, Hamburg, Germany) with subjects barefoot and dressed in light t-shirts and shorts. Body height was measured barefoot using a Harpenden stadiometer. Body fat was determined using foot-to-foot bio-electrical impedance (TBF-401, Tanita Co, Tokyo, Japan). The bio-electrical impedance measurement was arranged to be taken at the same day of fasting blood sampling at school to make sure that the measurement was taken in a fasting state and early in the morning. Participants emptied their bladder before the measurement.

Pubertal staging: Pubertal staging was assessed at baseline by a physician or nurse of our research team in school according to Tanner's indices for pubic hair, genitalia and breast development[12]. The highest rating for pubic hair, genitalia or breast development was recorded as the pubertal stage. Of the 38 participants, 2 were prepubertal (1 girl and 1 boy), 11 were stage 2 (1 girl, 10 boys), 19 were stage 3 (5 girls, 14 boys) and 6 were stage 4 (6 girls, no boys).

Endothelial function: Participants were studied fasting and at rest, between 900 and 1100 h. Brachial artery diameter was measured by high-resolution B-mode ultrasound (ATL 5000 system, L10-5 transducer, Bothell, Washington, United States) at rest, during reactive hyperaemia, again after 15 min rest, and after sublingual nitroglycerin spray (400 μg), as previously described[13,14]. Hyperaemia was induced by release of an occluding cuff, inflated to supra-arterial pressure for 5 min on the forearm distal to the site of measurement. Brachial artery diameter was measured continuously from 30 s before to > 2 min after cuff release. Flow-mediated vasodilatation (FMD) and nitroglycerin-mediated dilation (NMD) were recorded as the peak responses relative to the preceding rest measurements occurring within 90 s after cuff release and at 3 to 4 min after nitroglycerin administration. All scans were recorded on optic disc for subsequent off-line analysis, blinded as to which treatment group the subjects had been assigned. The scanning time took approximately 30 min for each student. We utilised a protocol established in our laboratory, which has been found to have good accuracy, reproducibility, and low interobserver error[15,16].

Cardiorespiratory fitness: Was assessed from a

peak oxygen uptake (peak VO_2) treadmill running test. The speed and gradient of the treadmill was increased gradually until volitional exhaustion. Gas samples were analyzed using the Medgraphics CPX/D™ metabolic cart (Medical Graphics Corporation, St. Paul, MN, United States). Heart rate was monitored continuously during the exercise test from heart rate telemetry (Polar Eletro Oy, Finland). Peak VO_2 was determined when two of the following three conditions were reached: (1) a respiratory exchange ratio > 1.0; (2) heart rate > 85% of age predicted maximum or levelled off; and (3) the student showed visible signs of exhaustion and refused to carry on despite strong verbal encouragement.

Laboratory investigations: A phlebotomist went to the school in the early morning and fasting (12 h) venous blood samples (4 mL) were drawn from all participants. Total cholesterol (TC) and triglyceride were assayed enzymatically using DP Modular Analytics, Roche Diagnostics Corp, Indianapolis, IN, United States. HDL cholesterol (HDL-C) was measured by cholesterol esterase/cholesterol oxidase coupling Trinder's reaction with pre-treatment steps using PEG modified enzyme and dextran sulphate. LDL cholesterol (LDL-C) was calculated using the Friedewald equation. Plasma glucose was measured by hexokinase method (DP Modular Analytics). Serum insulin and high sensitivity C-reactive protein (hsCRP) were determined by chemiluminescence immunoassay using the IMMULITE 1000 Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL, United States).

Blood pressure: Resting blood pressure was assessed in the laboratory from the right arm after at least 5 min of supine rest, using a standard mercury sphygmomanometer with cuffs of appropriate sizes. Korotkoff sound V was taken as the diastolic blood pressure. Heart rate was recorded by electrocardiogram. Ambulatory blood pressure (ABP) was monitored using an oscillometric monitor (SpaceLabs 90217, SpaceLabs Medical, Redmond, Washington, United States), which has been validated for use in children[17]. Systolic, diastolic and mean arterial BP were measured hourly during sleep and every 30 min when awake. The exact cut-off time dividing wake and sleep BP was defined individually according to a self-reported sleep habit diary. An appropriate sized cuff was placed on the non-dominant arm. Recordings were included in the analyses if they possessed a minimum of 14 successful readings during active wakefulness and at least 7 successful readings during sleep[17]. Individual mean systolic, diastolic and mean arterial BP were calculated for wake and sleep periods.

Statistical analysis

Histograms were produced for all variables to exclude any skew, in the presence of which the data were transformed before comparing group differences. Among all variables, fasting insulin was log transformed. Analysis of variance was used to compare baseline characteristics between the two groups. Group differences in the distribution of pubertal stage were examined using χ^2. Group (resistance training group, control group) by time (baseline, post-training) analyses of variance (ANOVA) with repeated measures were used to examine differences in the outcome measures. Analysis of covariance (ANCOVA), taking baseline scores as the covariate, was used to further deconstruct differences on fasting TC and HDL-C. A P value of 0.05 was set a priori.

RESULTS

Descriptive characteristics and markers of cardiovascular health at baseline and after the 10 wk intervention period are presented in Table 1. The distribution of pubertal ratings between the two groups was similar (resistance training group: Tanner 1 = 0, Tanner 2 = 5, Tanner 3 = 10, Tanner 4 = 4; Control group: Tanner 1 = 2, Tanner 2 = 6, Tanner 3 = 9, Tanner 4 = 2, χ^2 = 2.46; P = 0.483). There were no baseline differences between the two groups for any of the anthropometric variables. The mean attendance rate of the resistance training sessions was 83% and the students only missed sessions because of minor illness. All subjects in the resistance training group completed at least 80% of the 20 exercise sessions and were therefore all included in the final analyses. They were also able to finish all prescribed sets of exercises in each training session and there were no resistance training-related injuries.

Body height, body mass, body mass index and fat-free mass all increased significantly over the 10-wk period in both groups. No significant interactions confirmed none of the anthropometric changes over time were a result of the training programme.

Baseline differences between the resistance training group and control group were apparent for both TC and HDL-C, and ANCOVA was therefore utilised to compare values after 10 wk with pre-training levels as the covariate. No time or between group differences were found after removing the effect of baseline values for either TC or HDL-C (P > 0.05). LDL-C and insulin level decreased significantly in both groups over time.

Peak VO_2 expressed absolutely showed an increase in both groups over the 10-wk period, but when adjusted for body size, this increase was no longer apparent.

Thirty-two of the 38 participants agreed to be scanned for endothelial function before and after the intervention. Mean values for flow-mediated dilation and NMD at baseline and post 10 wk of training are provided by group in Table 2. Individual values for FMD at baseline and post 10 wk of training are presented graphically in Figure 1. A main effect of time [F(1,30) = 13.47; P < 0.001; η^2 = 0.310] and a significant interaction [F(1,30) = 9.37; P < 0.005; η^2 = 0.238] were apparent for FMD. Follow-up analyses indicated a greater increase in FMD in the resistance training group compared to the control group. Although there was a

Table 1 Descriptive characteristics at baseline and following the intervention by group

	Resistance training group (n = 19)		Control group (n = 19)		Time effect (P value)	Group effect (P value)	Interaction (P value)
	Baseline	After	Baseline	After			
Age, yr	12.3 ± 0.42	12.5 ± 0.42	12.1 ± 0.30	12.3 ± 0.30	< 0.001	0.100	1.000
Height, cm	151.4 ± 5.8	153.4 ± 5.5	151.0 ± 8.6	152.7 ± 8.8	< 0.001	0.800	0.300
Mass, kg	42.8 ± 6.7	44.3 ± 7.3	40.5 ± 7.1	41.9 ± 7.3	< 0.001	0.300	0.800
Body mass index, kg/m^2	18.6 ± 2.4	18.8 ± 2.5	17.7 ± 2.3	17.9 ± 2.1	0.048	0.200	0.700
Body fat, %	19.0 ± 6.1	19.0 ± 6.1	16.3 ± 3.7	16.3 ± 3.7	1.000	0.100	0.900
Fat free mass, %	34.9 ± 4.5	36.1 ± 4.9	33.9 ± 5.9	35.0 ± 6.1	< 0.001	0.900	0.600
SBP, mmHg	110 ± 9	107 ± 11	108 ± 11	107 ± 9	0.131	0.780	0.461
DBP, mmHg	68 ± 6	67 ± 8	67 ± 8	67 ± 7	0.652	0.751	0.557
TC, mmol/L	3.9 ± 0.6	3.7 ± 0.6	4.4 ± 0.5	4.2 ± 0.7	0.025	0.025	0.814
HDL-C, mmol/L	1.5 ± 0.2	1.5 ± 0.3	1.7 ± 0.4	1.8 ± 0.5	0.220	0.047	0.278
LDL-C, mmol/L	2.0 ± 0.6	1.8 ± 0.5	2.3 ± 0.5	2.0 ± 0.5	< 0.001	0.199	0.850
TG, mmol/L	1.0 ± 0.4	1.0 ± 0.4	0.9 ± 0.4	1.0 ± 0.4	0.554	0.756	0.848
Glucose, mmol/L	5.1 ± 0.3	5.0 ± 0.3	4.9 ± 0.3	4.9 ± 0.3	0.269	0.094	0.315
log insulin, pmol/L	4.4 ± 0.5	4.1 ± 0.3	4.0 ± 0.5	3.9 ± 0.5	0.027	0.099	0.169
hsCRP, mg/L	0.31 ± 0.45	0.25 ± 0.35	0.19 ± 0.18	0.65 ± 2.3	0.486	0.638	0.344
Peak VO_2, mL/min	1741 ± 322	1870 ± 446	1776 ± 466	1963 ± 540	0.003	0.700	0.500
Peak VO_2, mL/kg per minute	40.5 ± 7.1	41.8 ± 8.0	43.1 ± 8.8	45.6 ± 7.9	0.081	0.300	0.600

Data are presented as mean ± SD. P values were obtained from repeated measures ANOVA. SBP: Systolic blood pressure; DBP: Diastole blood pressure; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; hsCRP: High sensitive C-reactive protein; VO_2: Oxygen consumption.

Table 2 Endothelial function of the brachial artery at baseline and following the intervention by group

	Resistance training group (n = 17)		Control group (n = 15)		Time effect (P value)	Group effect (P value)	Interaction (P value)
	Baseline	After	Baseline	After			
FMD, %	8.5 ± 1.0	9.8 ± 1.3	8.8 ± 1.2	8.9 ± 0.9	0.001	0.451	0.005
NMD, %	21.7 ± 2.8	20.7 ± 1.8	22.5 ± 2.9	21.5 ± 2.7	0.011	0.336	0.985

Data are presented as mean ± SD. P values were obtained from repeated measures ANOVA. FMD: Flow-mediated dilation; NMD: Nitroglycerin-mediated dilation.

main effect of time for NMD, there was no interaction, with both groups showing a change in NMD over time (Table 2).

Mean ABP values awake and asleep are presented in Table 3. No main effects were found for either waking or sleeping diastolic ABP, nor interactions. There was no significant difference between the two groups for mean ambulatory systolic blood pressure during sleep or awake (Table 3). Sleeping systolic ABP did show a decline in both groups over the 10-wk period.

DISCUSSION

The key finding from this study was that 10 wk of resistance training resulted in enhanced endothelial function in lean, active youngsters. Improvements from baseline to 10 wk were noted in both groups for a number of anthropometric, metabolic and non-endothelial dependent vascular measures, but these were most likely simply a reflection of normal growth and development.

Accumulating evidence from the adult literature indicates that acute exercise promotes the number and activity of endothelial progenitor cells, increases blood flow and shear stress on the endothelium, which in turn causes an increase in the activity of endothelial nitric oxide synthase and vascular production of nitro-oxide[18]. Resistance exercise elevates blood flow for short periods of time under much higher pressure than sustained periods of moderate exercise and this may produce a more intensive stress stimulus for endothelial cells. In well-trained adult athletes, repetitive intensive exercise exposure has been shown to result in arterial remodelling, with and without change in dilatory capacity[19,20]. Other mechanisms such as hormonal and inflammatory effects, as well as peripheral resistance have been related to exercise-induced improvements in endothelial integrity[21]. The increase in FMD noted in the present study was apparent in the absence of any training-related change in blood pressure or markers of inflammation, and supports the proposition that resistance training most likely increases laminar shear stress, thus has a direct influence on endothelial function.

To the best of our knowledge, this is the first study to show that endothelial function can be enhanced in lean, active children following resistance training. Previous exercise interventions have focused upon normalising vascular dysfunction in groups of overweight and obese children. The relative increase in FMD from baseline

Table 3 Twenty-four hours ambulatory blood pressure at baseline and following the intervention by group

	Resistance training group (n = 19)		Control group (n = 19)		Time effect (P value)	Group effect (P value)	Interaction (P value)
	Baseline	After	Baseline	After			
Awake							
SBP, mmHg	113 ± 8	111 ± 7	110 ± 9	109 ± 8	0.100	0.200	0.700
DBP, mmHg	71 ± 5	70 ± 5	68 ± 4	67 ± 5	0.400	0.093	0.900
Mean BP, mmHg	85 ± 5	84 ± 5	82 ± 4	82 ± 5	0.400	0.100	0.800
Mean HR, beat/min	87 ± 9	86 ± 7	87 ± 9	83 ± 8	0.100	0.600	0.200
Asleep							
SBP, mmHg	103 ± 11	98 ± 8	101 ± 11	98 ± 9	0.041	0.800	0.600
DBP, mmHg	55 ± 7	54 ± 7	54 ± 6	54 ± 6	0.600	1.000	0.500
Mean BP, mmHg	73 ± 8	71 ± 7	73 ± 6	72 ± 6	0.200	1.000	0.600
Mean HR, beat/min	68 ± 6	70 ± 6	66 ± 8	68 ± 8	0.087	0.500	0.900

Data are presented as mean ± SD. P values were obtained from repeated measures ANOVA. SBP: Systolic blood pressure; DBP: Diastole blood pressure; HR: Heart rate.

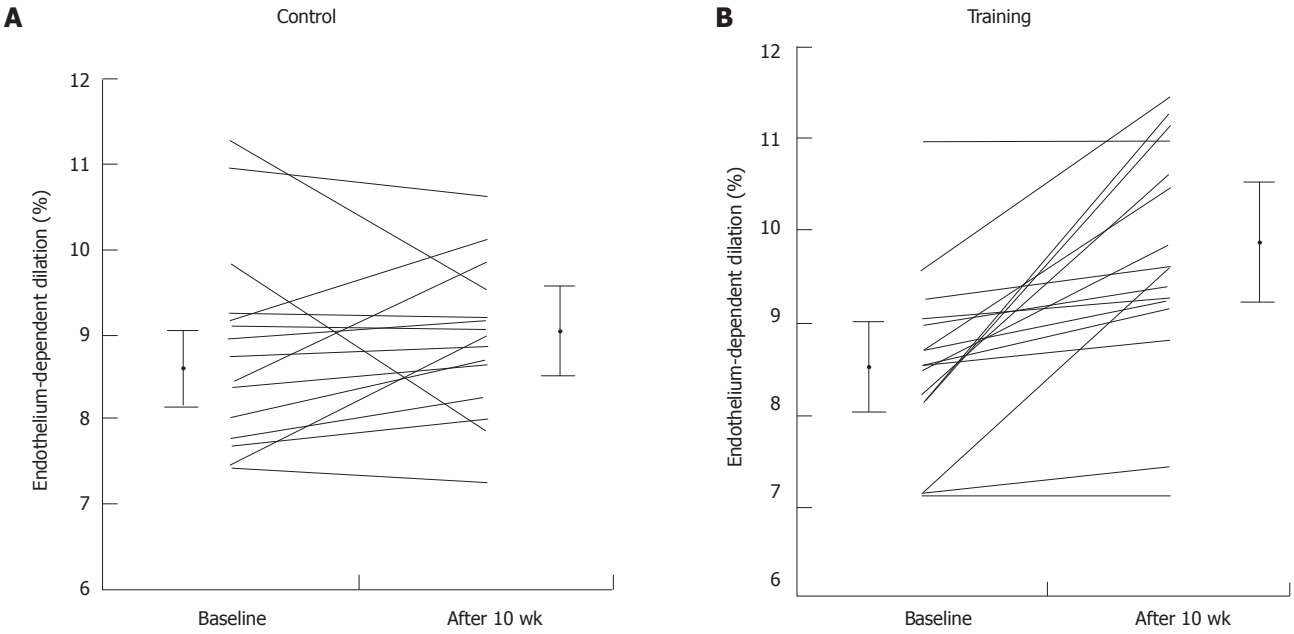

Figure 1 Individual values for flow-mediated dilation at baseline and after 10 wk of intervention in the control (A) and training group (B).

of 15% noted in our group of normal weight Chinese youngsters is marginally less than the improvement in FMD reported for overweight Chinese youngsters, where a relative increase in FMD from baseline of 18% was reported after a 6-wk diet and resistance training intervention[7].

The changes in anthropometric, metabolic and vascular variables in both groups over the 10-wk period could be in part due to active participation in the additional three hours of sport activities per week; however, these were not accompanied by an increase in aerobic fitness and are more likely a reflection of normal growth and development.

Currently there are no data on whether an increased FMD during childhood (either obese or non-obese) will translate into decreased risk of future cardiovascular risk, and only longitudinal studies will provide an answer to this question. However, various reports from the American Heart Association have reaffirmed the importance of primary cardiovascular disease prevention[22-24]. All children, not just those at risk, are thought to benefit from cardiovascular health promotion. Children and adolescents spend 7 to 8 h a day on average in school and it is therefore an ideal site for establishing appropriate behavioural patterns, particularly physical activity habits[25]. In Hong Kong the community places a strong emphasis on a student's academic performance and pays less attention to a student's physical activity. Physical activity levels in Hong Kong youngsters have been found to be low in comparison with other countries[26] with most of a child's active behaviour occurring in school, and nominal amounts of physical activity apparent in the home[27]. We have shown that a school-based resistance training programme is adhered to and provides vascular benefit in lean children, lending support to the role school-based physical activity can play in the primary prevention of heart disease.

This study is not without limitations. We have not

included strength measures in the current study. Muscular strength is likely to be improved after receiving resistance training in children and adolescents population[11,28], however, a primary consideration was compliance of participants to attend all investigations before and after the program (especially participants in the control group), and we felt assessment of strength measures would be too burdensome for participants. Participants in the resistance training group progressed to 4 sets of exercises at 12RM in most of the exercises by the end of the program and we accepted this as a reflection of their improvement in muscular strength. We did not directly assess physical activity, rather used school PE as a surrogate marker. PE in the majority of Hong Kong Government schools consists of 70 min every 10 d, of largely skill-based activity. The participants in this study received 250 min of PE every 7 d. We can probably assume that this population was engaged in more physical activity per week than many youngsters in Hong Kong; however, it would be beneficial to have a direct measure of physical activity habits in future studies.

With respect to the practical application of this study, the training programme in this study is designed in a circuit-style that is practical for schools. Schools and policy makers may consider the inclusion of resistance training as a part of a varied physical activity programme for promoting cardiovascular health in youth.

In conclusion, this study has shown that 10 wk of a school-based resistance training programme is effective in improving endothelial function in active, lean children. These findings stress even more the importance of schools offering plentiful and varied physical activity opportunities for the cardiovascular health of young people, in particular resistance exercise.

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COMMENTS

Background

The endothelium plays an integral role in maintaining vascular tone and reactivity and in preserving vascular health, but impaired endothelial function predisposes individuals to early atherosclerosis. The authors have previously reported that impairment of endothelium function in overweight and obese children can be improved following combined aerobic-resistance training and dietary modification programmes. Resistance training is easy to administer within a school settings, but there is little evidence of the benefit of resistance training on cardiovascular and endothelial function in healthy active adolescents.

Research frontiers

Primary prevention of cardiovascular disease through modification of lifestyle behaviors, such as exercise during childhood and adolescence is paramount because of the growing evidence that the origins of cardiovascular disease begin in childhood. Much of the research attention focusing on the role exercise plays in endothelial health has been on the obese child. Cross-sectional evidence has shown that the lean child is also at risk of vascular dysfunction because of insufficient physical activity and excessive sedentary behavior. This confirms the importance of strategies to encourage active lifestyles in children and adolescents, but requires better understanding of the role exercise plays in vascular health in lean children and adolescents.

Innovations and breakthroughs

Exercise and vascular function is a recent issue in healthy weight children and adolescents. This study addresses exercise induced alterations in endothelial function in healthy lean adolescents and provides novel insight into the benefits of resistance exercise training in this younger population.

Applications

The exercise training programme used in this study is designed in a circuit-style that is practical for schools. Schools and policy makers may consider the inclusion of resistance training as a part of a varied physical activity programme for promoting cardiovascular health in youth.

Terminology

Endothelium dependent flow-mediated dilation: A technique used to increase blood flow and therefore shear stress, stimulating the endothelium to release nitric oxide and induce vasodilation. Endothelial independent flow-mediated dilation: The use of an exogenous nitric oxide donor, such as nitroglycerin to induce vasodilation independent of the endothelium, reflecting vascular smooth muscle function.

Peer-review

The manuscript is well written. The study is well designed with detailed methodology to assess the change in body composition and cardiovascular function.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Prevalence of recent immunisation in children with febrile convulsions

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Author contributions: Motala L and Eslick GD acquired, analysed, and interpreted the data; Motala L and Eslick GD drafted the manuscript; Eslick GD did statistical analysis; Eslick GD is the guarantor of the study; He had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; Eslick GD organised the study concept and design.

Institutional review board statement: The study was reviewed and approved by our Ethics Committee.

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Abstract

AIM: To determine the prevalence of recent immunisation amongst children under 7 years of age presenting for febrile convulsions.

METHODS: This is a retrospective study of all children under the age of seven presenting with febrile convulsions to a tertiary referral hospital in Sydney. A total of 78 cases occurred in the period January 2011 to July 2012 and were included in the study. Data was extracted from medical records to provide a retrospective review of the convulsions.

RESULTS: Of the 78 total cases, there were five medical records which contained information on whether or not immunisation had been administered in the preceding 48 h to presentation to the emergency department. Of these five patients only one patient (1.28% of the study population) was confirmed to have received a vaccination with Infanrix, Prevnar and Rotavirus. The majority of cases reported a current infection as a likely precipitant to the febrile convulsion.

CONCLUSION: This study found a very low prevalence of recent immunisation amongst children with febrile convulsions presenting to an emergency department at a tertiary referral hospital in Sydney. This finding, however, may have been distorted by underreporting of vaccination history.

Key words: Prevalence; Immunisation; Febrile con-

vulsion; Adverse event; Vaccination

Core tip: This study found a very low prevalence of recent immunisation amongst children with febrile convulsions. This finding, however, may have been distorted by underreporting of vaccination history. The use of large linked datasets may determine a more accurate estimate of the rate of febrile convulsions due to immunisation.

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INTRODUCTION

There has been much controversy in recent years about the risks *vs* the benefits of childhood vaccination[1,2]. Vaccines may have adverse effects which range from simple fever[3] to more severe febrile convulsions[3-10]. Febrile convulsions can be defined as any seizure that is associated with fever, and not due to intracranial infection or other known cause such as epilepsy or head trauma[4,11].

Of particular interest, has been the association between the influenza, diphtheria-tetanus toxoids-pertussis (DTP) and measles-mumps-rubella (MMR) vaccines and febrile convulsions. Western Australia observed a spike in emergency department presentations for high fever and febrile convulsions in young children after vaccination with the 2010 trivalent influenza vaccine (TIV)[5]. This resulted in a country-wide suspension of the use of TIV in children aged 5 years and under[5]. Further investigation into the matter then indicated that an association between TIV and febrile convulsions in children was prevalent across the majority of Australia[5]. Following these findings, a similar study performed in the United States revealed disproportionately higher rates of febrile convulsion associated with 2010-2011 TIV administration compared with other vaccines[12]. The majority (84%) of these convulsions occurred in children under 2 years of age, and most (86%) had an onset of convulsion on the same day or the day after the vaccination[12]. The suspension of the use of TIV in children under 5 in Australia was later lifted when it was found that the risk of febrile convulsions following TIV was specific to vaccination with Fluvax® and did not apply to the use of other seasonal influenza vaccines such as Vaxigrip® or Panvax®[3,6].

Although febrile convulsions generally have an excellent prognosis, they are the commonest cause of status epilepticus in childhood[4]. Their occurrence can be extremely distressing for family members of patients, and may have serious long-term consequences that are as yet unknown. A high rate of these seizures following vaccination would have important clinical implications as it may lead to poor vaccine uptake and the risk should be diminished where possible - perhaps, by the administration of alternate safer vaccines[3,6] or by the use of antipyretics and physical methods to reduce fever[3].

The aim of this study was to determine the prevalence of recent immunisation amongst children under the age of seven presenting with febrile convulsions to a teaching hospital in Western Sydney.

MATERIALS AND METHODS

Data collection

The study was approved by the Ethics Committee of the Sydney West Area Health Service. The study population included all patients presenting to Nepean Hospital Emergency Department with febrile convulsion based on the International Classification of Diseases (ICD-10-AM) codes (R56.0).

Data extraction

Two linked databases were set up in order to de-identify the data. The first database comprised of a unique patient identification number, name and medical records number. The following variables were collected from each medical record: Age (months); gender; weight; method of transport to hospital; primary diagnosis; additional diagnosis; number of febrile convulsions during current presentation; history of fever; antipyretic given prior to febrile convulsion; maximum temperature; length of convulsion; previous history of febrile convulsion; previous history of non-febrile convulsion; precipitant to previous febrile convulsion; history of current infection; history of vaccination/immunisation; number of vaccinations; time between vaccination and febrile convulsion; type of vaccination; history of concurrent illness; family history of febrile convulsions; family history of epilepsy; and length of stay.

Statistical analysis

Patient demographic and clinical characteristics have been reported as median and range for numeric-scaled features and percentages for discrete characteristics. Factors associated with febrile convulsion were identified using unconditional logistic regression. All *P* values calculated were two-tailed; the alpha level of significance was set at 0.05. All data was analysed using STATA version 12.0 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

RESULTS

Demographics

A total of 78 patients with a mean age of 23 mo (1-63

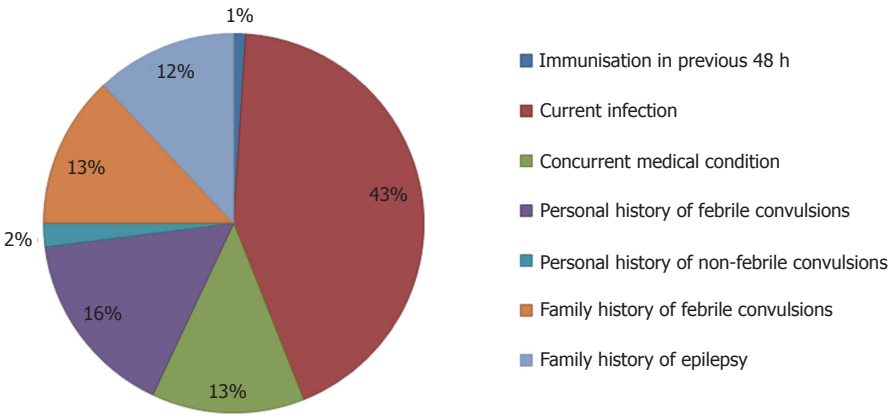

Figure 1 Risk factors for febrile convulsions.

mo; 60% male) presented to Nepean Hospital for febrile convulsions over the 19 mo period (January 2011 - July 30 2012).

Febrile convulsions

The primary diagnosis of febrile convulsion was made in 56.4% of cases, with the majority of the remaining patients being diagnosed with acute upper respiratory tract infections and a smaller number with acute intestinal infections. The mean maximum temperature reported was 39.5 ℃ (37.3 ℃-43 ℃). For each presentation, the mean number of febrile convulsive episodes was 1.7 (1-8 episodes), and the average length of convulsion was 3 min (30 s-20 min). Just over half the medical records (56%) had evidence of antipyretics administration prior to the convulsions. A large proportion of cases (89%) were given antipyretics before their convulsions, with the average time between drug administration and convulsion being 5 h and 45 min.

Risk factors

Five medical records contained information on whether or not immunisation had been administered in the 48 h preceding the febrile convulsion, with only one having clear information on immunisation (confirmed receipt of vaccination with Infanrix, Prevnar and Rotavirus) (Figure 1). Almost all patients (96%) reported a current infection as a possible precipitant to the febrile convulsion, and 25% had a concurrent medical condition such as developmental delay. For those aged > 2 years, a previous history of febrile convulsions was a significant risk factor (OR = 5.47; 95%CI: 1.92-15.60) for presentation. They were also more likely to have shorter convulsions (3 min or less) (OR = 1.67; 95%CI: 0.53-5.27). A positive family history of febrile convulsions but not epilepsy was also a potential risk factor in this age group (OR = 1.30; 95%CI: 0.44-3.84). These individuals were also more likely to have received an antipyretic at an appropriate time - that is from 20 min to 4 h prior to the convulsive episode (OR = 2.28; 95%CI: 0.52-9.99). Males were more likely to be given a primary diagnosis of febrile convulsions than females (OR = 1.72; 95%CI: 0.70-4.35).

Medical care

The mean length of stay was 2 d (1-4 d), with the most common follow-up diagnostic tests including electroencephalograms (15%) and brain magnetic resonance imaging (4%).

DISCUSSION

This study determined that there was a very low prevalence of recent immunisation amongst children with febrile convulsions presenting to a tertiary referral hospital in Western Sydney. This finding, however, may have been due to underreporting of vaccination history as the vast majority of medical records contained no information on whether or not immunisation was administered in the recent past. Only 6% of medical records contained information on immunisation.

Previous studies have shown that some vaccines such as MMR[10] and DTaP-IPV-Hib[8] were associated with an increased risk of febrile convulsions, but that this risk was small. Conversely, another study reported a significantly elevated risk of febrile seizures following receipt of DTP or MMR vaccine[7]. This study determined that a history of a current infection was the predominant precipitant for fever and thus convulsion, previous studies suggest that viral illness is the most common reason for hospitalisation with febrile convulsion[4].

Individuals older than 2 years of age were more likely to have a previous history of febrile convulsions. In terms of the average age at which febrile convulsions tend to occur, this study concurred with the findings of previous research[13] and established that this was at an age of about 2 years.

Males were more likely to be given a primary diagnosis of febrile convulsion than females. This may have been attributable to the fact that approximately 60% of febrile convulsions are known to occur in male

children[13,14], and may well indicate some degree of bias involved in diagnosis. Furthermore, male participants were found to be admitted to hospital more frequently - recent literature suggests that this excess of male admissions[15] is consistent with an increased vulnerability to illness amongst the gender[14].

The higher rate of appropriate antipyretic use that was observed amongst children with a personal history of febrile convulsions was possibly due to those parents being familiar with the occurrence of seizures and thus more cautious when fever arose. This study, much like previous reports, indicated higher rates of febrile convulsions in children with a personal or family history of these seizures[10,16].

One of the strengths of the study was that the aim, hypothesis and objectives were arrived at a priori examination of medical records. Furthermore, all medical records were thoroughly examined manually. The use of medical records as a source of data could also be considered a limitation of the study since some records were incomplete, however, this was not substantial. The sample size did not provide statistical significance for some of our results.

This study found a low prevalence of recent immunisation precipitating febrile convulsions in young children, but this finding may have been distorted by the low rates of accurate reporting of immunisation. A recommendation for future practice would, therefore, be that physicians directly request and record information on immunisation, particularly when dealing with cases of childhood febrile convulsions.

COMMENTS

Background

Febrile convulsions are an important reason for children presenting to hospital emergency departments. The causes of these febrile convulsions are varied but immunization/vaccination may be a factor.

Research frontiers

The authors' suggest that immunization associated febrile convulsions are an under-reported presentation to the emergency department. Specific studies to address this issue are required. Moreover, preventive strategies may be implemented to reduce the risk of febrile convulsions after immunization.

Innovations and breakthroughs

Vaccine safety is vitally important to the continued global approach to preventable infectious diseases both in childhood and adulthood. A greater understanding of minor and major adverse events following immunization are required. Recent high level evidence providing no link between vaccines and autism is a good example.

Applications

A greater knowledge of the potential adverse effects of immunization is important and education of patients with regards to preventive and recognition of adverse effects early is critical.

Terminology

The Measles, Mumps, Rubella vaccine protects against measles, mumps, and rubella (German measles). It is a mixture of live attenuated viruses of the three diseases, administered *via* injection. The (DTaP-IPV-Hib) includes diphtheria (D), tetanus (T) and acellular pertussis (aP) (whooping cough). Inactivated polio vaccine stands for "inactivated polio vaccine". Hib stands for *Haemophilus influenzae* type b.

Peer-review

Good study provided record based immunization history is of quality.

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ORIGINAL ARTICLE

Retrospective Study

Subclinical hypothyroidism in atopic South Italian children

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Author contributions: Pedullà M drafted the manuscript; Pedullà M, Fierro V and Marzuillo P participated in the conception and the design of the study; Del Tufo E and Grandone A examined the patients, collected anthropometric data; Perrone L and Miraglia del Giudice E supervised the design and execution of the study.

Institutional review board statement: The approved protocol from the Institutional Review Board at the Second University of Naples.

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Abstract

AIM: To verify if subclinical hypothyroidism (SCH) could be associated to atopy in children.

METHODS: Seven hundred and thirty-two Caucasian children from South Italy presenting symptoms of allergic disease were enrolled and submitted to atopy, obesity, chronic low grade inflammation, and SCH work up.

RESULTS: Four hundred and forty-five out of 705 (63.12%) children affected by allergic disease were diagnosed as atopic and 260 (36.88%) as not atopic. The SCH prevalence was 6.3%. Significant higher prevalence of SCH among atopic children with average (group 2) and high (group 3) low grade chronic inflammation compared to atopic children with mild (group 1) low grade chronic inflammation was present. Moreover, group 1 and group 2 presented an OR to show SCH of 2.57 (95%CI: 1.55-6.26) and 2.96 (95%CI: 1.01-8.65), respectively. Both in atopic and not atopic children we found C3 serum levels significantly higher in group 3 respect to group 2 and group 1. Noteworthy, among atopic patients, also total immunoglobulin E (IgE) serum levels, were significantly higher in group 3 compared to group 2 and group 1 children. In atopic children, C3 and total IgE serum values increased in parallel with the increase of C-reactive protein values, while in not atopic children this phenomenon was not evident.

CONCLUSION: The possibility exists that an increasing atopic inflammation contributes to SCH occurrence. So far this is the first report in literature showing an

association between SCH and atopy but further studies are needed to confirm our data.

Key words: Thyroid derangement; Atopy; Children; Low grade chronic inflammation; Subclinical hypothyroidism

Core tip: A high subclinical hypothyroidism (SCH) prevalence has been associated in childhood to obesity and the chronic low grade inflammation found obese children has been involved in this relationship. In our population, obesity does not influence SCH prevalence. Interestingly, we found a SCH prevalence twice higher compared to all other patients and a significant higher risk to show SCH in atopic children affected by the highest C-reactive protein values characterizing low-grade inflammation.

Pedullà M, Fierro V, Marzuillo P, Del Tufo E, Grandone A, Perrone L, Miraglia del Giudice E. Subclinical hypothyroidism in atopic South Italian children. *World J Clin Pediatr* 2016; 5(3): 306-310 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i3/306.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i3.306

INTRODUCTION

Subclinical hypothyroidism (SCH) is defined as a thyroid stimulating hormone (TSH) serum level above the statistically defined upper limit of the reference range despite normal serum free T4 (fT4) and free T3 (fT3) concentration. In addition to genetic cause, SCH has been associated to childhood obesity[1], with some slight myocardial dysfunction[2].

It has been recently demonstrated that atopy can be related to childhood obesity and that chronic low grade inflammation related to it was involved in this relationship[3-5].

The aim of our study is to verify if, as well as to obesity, SCH could be also associated to atopy in children.

MATERIALS AND METHODS

Seven hundred thirty-two Caucasian children from South Italy (age in years 6.03 ± 3.63) presenting symptoms of allergic disease (erythema, pruritus, eczematous rash, wheals, ocular and nasal pruritus and wheezing) attending consecutively from January 2013 to July 2015 the Department of Pediatrics of the Second University of Naples were enrolled. None showed any clinical symptoms of thyroid disease. All the enrolled children were submitted to atopy, obesity, chronic low grade inflammation, and SCH work up. Body mass index (BMI) was calculated by dividing weight in kilograms by height squared in meters (kg/m^2). Obesity was defined by a BMI $\geqslant$ 95th percentile[6].

In all patients, after an overnight fasting, a blood sample was obtained to evaluate C-reactive protein (CRP) and Complement C3 serum levels, measured using an Olympus AU 560 apparatus by an enzymatic colorimetric method, total and specific IgE by a fluorenzymeimmunoassay (ImmunoCap and ImmunoCap 0-100), thyroid hormones (TSH, fT3, and fT4) and anti-thyroid peroxidase antibodies (TPO-Ab) and anti-thyroglobulin antibodies (Tg-Ab), determined by high-specific solid-phase technique-chemiluminescence immunoassays (Perkinelmer, Turku, Finland).

The diagnosis of atopy suspected for clinical history and symptoms, was confirmed by levels of serum total IgE (normal value from 25 to 60 mo of age < 81 kU/L, from 61 to 156 mo of age < 101 kU/L) and specific immunoglobulin E (IgE) assay (> 0.36 kUA/L) as well as by Skin Prick Tests (SPTs). None had taken steroids or received immuno-suppressive therapy for at least 3 mo before investigation. Antihistamine therapy had been stopped at least 2 wk before SPTs were performed and serum samples were collected.

According to atopy diagnosis the children enrolled in the study were divided in two groups: Atopic and not atopic children.

Chronic low grade inflammation is diagnosed by slightly raised concentrations of inflammatory markers in the systemic circulation[7]. Therefore, to better assess the chronic low grade inflammation status we applied both in atopic and not atopic children the cut-off point described by Pearson *et al*[8] for assessing cardio vascular disease (CVD) risk. Thus we divided children in three different CRP serum values gradation groups: group 1 low grade (CRP < 0.1 mg/dL), group 2 average grade (CRP 0.1-0.3 mg/dL) and group 3 high grade (CRP > 0.3-< 1 mg/dL) of chronic low grade inflammation.

Twenty-seven children with CRP serum values greater than 1 mg/dL were excluded from the study given the possibility of an ongoing infection.

SCH was diagnosed when TSH value was higher than 5 mUI/mL, as indicated by the "European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy and in Children"[9,10], with fT3, fT4, and antithyroid antibodies values in the normal range for age and no clinical signs or symptoms of hypothyroidism[10].

Informed consent was obtained from all enrolled children and their parents and in accordance with the approved protocol from the Institutional Review Board at the University of Naples.

Skewness and Kurtosis tests were used to evaluate if the distribution of continuous variables was normal. According to distribution, the values were expressed as mean ± SD or median and minimum-maximum values. To analyze categorical variables was used *t* test for unpaired data. A χ^2 test was also used to analyze the differences between the frequencies. Mann-Whitney *U* test was used for comparison of continuous variables which did not exhibit normal distribution. A *P* value < 0.05 was considered significant.

Table 1 Clinical and laboratory differences between atopic and not atopic children affected by allergic disease

	Atopic children	Not atopic children	*P*
Patients, *n*	459/732 (62.7%)	273/732 (37.3%)	
Age expressed in years (mean age ± SD)	6.24 ± 3.55	5.82 ± 3.71	0.128
Gender (male)	245/459 (53.37%)	137/274 (50%)	0.37
Family history of atopy	365/420 (86.9%)	195/235 (80%)	0.17
Family history of thyroid disease	191/421 (45.36%)	94/235 (40%)	0.18
BMI (kg/m^2)	16.6 (10.9-36.8)	16.4 (10.7-30.17)	0.069
SCH affected (%)	33/445 (7.41%)	13/260 (5%)	0.21
SCH obeses (%)	1/33 (3%)	1/13 (7.69%)	0.48
CRP (mg/dL)	0.06 (0-10.3)	0.08 (0-7.9)	0.123
TSH (UI/mL)	2.33 (0.35-12.2)	2.24 (0.52-6.98)	0.269

P value < 0.05 was considered significant. BMI: Body mass index; SCH: Subclinical hypothyroidism; CRP: C-reactive protein; TSH: Thyroid stimulating hormone.

Table 2 Atopic and not atopic children divided into three groups on the basis of the C-reactive protein serum levels

	Atopic children			*P*	Not atopic children			*P*
	Group 1	Group 2	Group 3		Group 1	Group 2	Group 3	
CRP (mg/dL)	< 0.1	0.1-0.3	> 0.3-< 1		< 0.1	0.1-0.3	> 0.3-< 1	
SCH	18/272 (6.62%)	7/121 (5.78%)	8/52 (15.38%)	[1]0.033 OR: 2.57 (1.55-6.26) [3]0.04 OR 2.96 (1.01-8.65)	8/151 (5.29%)	3/81 (3.70%)	2/28 (7.14%)	
C3 (mg/dL)	115 (20-174)	122 (50-172)	138 (103-192)	[1]1.86e^{-8} [2]0.027 [3]0.00021	116.5 (10-170)	126 (73-177)	139 (109-170)	[1]0.000053 [2]0.0085 [3]0.024
Total IgE (kUI/L)	120 (100-2270)	123.5 (100-4328)	162.1 (124-5000)	[1]0.000017 [3]0.00045	17.4 (1.9-98)	22.45 (1.9-93)	22.43 (1.9-88.9)	

[1]Group 1 *vs* group 3; [2]Group 1 *vs* group 2; [3]Group 2 *vs* group 3. SCH: Subclinical hypothyroidism; CRP: C-reactive protein.

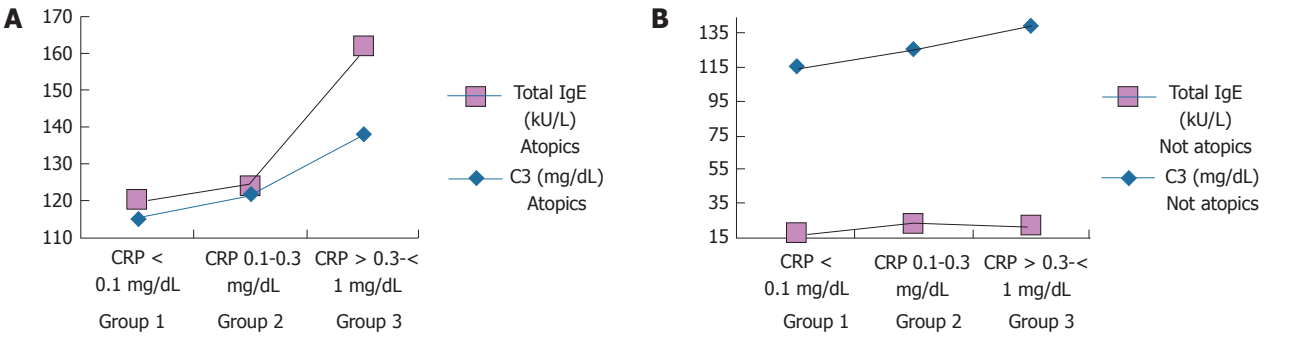

Figure 1 Complement C3 and total IgE serum levels values according to low grade inflammation in both atopic (A) and not atopic (B) children affected by allergic disease. CRP values < 0.1 mg/dL identify children with low grade of chronic low grade inflammation (group 1). CRP values between 0.1 and 0.3 mg/dL identify children with average grade of chronic low grade inflammation (group 2). CRP values > 0.3 and < 1 mg/dL identify high grade of chronic low grade inflammation (group 3). In atopic children, C3 and total IgE serum values increased in parallel with the increase of CRP values, while in not atopic children this phenomenon is not evident. A: For C3, group 1 *vs* group 3, $P = 1.86e^{-8}$; group 1 *vs* group 2, $P = 0.027$; group 2 *vs* group 3, $P = 0.00021$. For total IgE, group 1 *vs* group 3, $P = 0.000017$; group 1 *vs* group 2, $P > 0.05$; group 2 *vs* group 3, $P = 0.00045$; B: For C3, group 1 *vs* group 3, $P = 0.000053$; group 1 *vs* group 2, $P = 0.0085$; group 2 *vs* group 3, $P = 0.024$. For total IgE, group 1 *vs* group 3, $P > 0.05$; group 1 *vs* group 2, $P > 0.05$; group 2 *vs* group 3, $P \geqslant 0.05$.

Odds ratio (OR) was calculated to evaluate the association of Atopy and SCH prevalence. OR was considered significant when a 95%CI excluded unity. Statistical analysis were performed using Stat-Graphics Centurion 3.0 for Windows.

RESULTS

On the basis of atopy work-up 459 out of 705 (62.7%) children affected by allergic disease were diagnosed as atopic and 273 (37.3%) as not atopic. The overall prevalence of SCH was 6.3%.

In Table 1 we described clinical and laboratory differences between these two groups of children. No significant differences were found.

Table 2 shows clinical and laboratory data of both atopic and not atopic children divided into 3 different groups on the basis of increasing CRP serum values:

group 1 (CRP < 0.1 mg/dL), group 2 (CRP 0.1-0.3 mg/dL) and group 3 (CRP > 0.3-< 1 mg/dL). First we compared the prevalence of SCH among all the groups and no significant differences were found.

On the contrary, among atopic children, significant higher prevalence of SCH in group 3 and group 2 compared to group 1 was found (P = 0.033 and P = 0.04, Table 2). Moreover, group 3 and group 2 atopic children presented an OR to show SCH of 2.57 (95%CI: 1.55-6.26) and 2.96 (95%CI: 1.01-8.65) respectively.

Both in atopic and not atopic children we found C3 serum levels significantly higher in group 3 respect to group 2 and group 1 (Table 2). Noteworthy, among atopic patients, also total IgE serum levels, were significantly higher in group 3 compared to group 2 and group 1 children.

Figure 1 shows in both atopic (A) and not atopic (B) children complement C3 and total IgE serum levels values according to the different grading of CRP values.

In atopic children, C3 and total IgE serum values increased in parallel with the increase of CRP values, but no significant correlation was found. C3 and total IgE serum values in not atopic children showed a completely independent trend.

DISCUSSION

In our study atopic children showed a 7.41% prevalence of SCH while not atopic children allergic found in alike disease affected a 5% SCH prevalence. These frequencies are in line with the estimated prevalence of this thyroid disorder in the pediatric population[11,12].

A high SCH prevalence has been associated in childhood to obesity and the chronic low grade inflammation found obese children has been involved in this relationship[13]. In our population, obesity does not influence SCH prevalence.

Interestingly, we found a SCH prevalence twice higher (15.38%) compared to all other patients and a significant higher risk to show SCH [2.57 (95%CI: 1.55-6.26)] in atopic children affected by the highest CRP values characterizing low grade inflammation (group 3 atopics).

Atopy and the associated allergic disease are now regarded as systemic inflammatory disease that could affect the risk of atherosclerosis[14], impaired glucose tolerance[15], and coronary artery disease[16]. The chronic low grade inflammation involved in the pathogenesis of localized allergic disease causes a systemic inflammatory response that potentially could promote also SCH.

Moreover, in our atopic children the highest low grade chronic inflammation (CRP > 0.3-< 1 mg/dL) seems to correspond to the highest atopic inflammation as measured by total serum IgE values (Figure 1). The possibility exists that an increasing atopic inflammation contributes to SCH occurrence. A limitation of our study could be a recruitment bias because the patients enrolled were affected severe allergic disease needing of a specialist evaluation.

So far this is the first report in literature showing an association between SCH and atopy but further studies are needed to confirm our data.

COMMENTS

Background

Recent studies demonstrate that atopy can be associated to childhood obesity and that chronic low grade inflammation could be involved in this relationship. The aim of the study was to verify if subclinical hypothyroidism (SCH) could be also associated to atopy in children.

Research frontiers

Important areas of research related to the study are represented by the field of pediatric endocrinology and allergology. More in particular, the study aimed to hypothesize, throughout the verification of an association, the mechanisms by which atopy could lead to SCH.

Innovations and breakthroughs

This is the first report in literature showing an association between SCH and atopy with a possible causal link represented by chronic low grade inflammation.

Applications

The study can result in future researches confirming the authors' findings and, moreover, understanding the pathophysiological basis underlining the association between atopy and SCH.

Terminology

SCH is defined as a thyroid stimulating hormone serum level above the statistically defined upper limit of the reference range despite normal serum free T4 and free T3 concentration.

Peer-review

The association among obesity, chronic inflammation and SCH is a very interesting topic.

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ORIGINAL ARTICLE

Retrospective Study

Potential carrier priming effect in Australian infants after 7-valent pneumococcal conjugate vaccine introduction

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Abstract

AIM: To investigate evidence of clinical protection

in infants after one dose of 7-valent pneumococcal conjugate vaccine (7vPCV) owing to carrier priming.

METHODS: Using Australian National Notifiable Diseases Surveillance System data, we conducted a descriptive analysis of cases of vaccine type invasive pneumococcal disease (VT-IPD) during "catch-up" years, when 7vPCV was carrier primed by prior administration of DTPa vaccine. We compared the number of VT-IPD cases occurring 2-9 wk after a single dose of 7vPCV (carrier primed), with those < 2 wk post vaccination, when no protection from 7vPCV was expected yet. Further comparison was conducted to compare the occurrence of VT-IPD cases *vs* non-VT-IPD cases after a single carrier-primed dose of 7vPCV.

RESULTS: We found four VT-IPD cases occurring < 2 wk after one carrier primed dose of 7vPCV while only one case occurred 2-9 wk later. Upon further comparison with the non-VT-IPD cases that occurred after one carrier primed dose of 7vPCV, two cases were detected within 2 wk, whereas seven occurred within 2-9 wk later; suggesting a substantial level of protection from VT-IPD occurring from 2 wk after carrier-primed dose of 7vPCV.

CONCLUSION: This data suggest that infants may benefit from just one dose of 7vPCV, likely through enhanced immunity from carrier priming effect. If this is proven, an adjusted 2-dose schedule (where the first dose of PCV is not given until after DTPa) may be sufficient and more cost-effective.

Key words: Carrier priming; Conjugate vaccine; Infant; Invasive pneumococcal disease

Core tip: With the inclusion of newer conjugate vaccines with higher number of serotypes in the immunisation schedule, literature suggests that prior immunisation with tetanus/diphtheria-containing vaccines could enhance the immunogenicity of subsequently administered glycoconjugate vaccine, a phenomenon known as "carrier priming". This analysis provides evidence of substantial clinical protection ensued after one dose of 7-valent pneumococcal conjugate vaccine as result of carrier priming. This phenomenon could be implemented to enhance the immunogenicity of conjugate vaccines among vulnerable populations such as infants in resource-poor settings, travellers, immigrants and refugees.

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INTRODUCTION

Streptococcus pneumoniae (SPn) is responsible for 33% of childhood mortalities due to pneumonia worldwide[1]. Invasive pneumococcal disease (IPD) is caused by SPn and is defined as an infection confirmed by the isolation of pneumococci from a normally sterile body site, such as the blood stream and cerebrospinal fluid whereas non-invasive disease includes otitis media, sinusitis and bronchitis[2]. The incidence of IPD is often used as a measure of pneumococcal disease burden[3]. The 7-valent pneumococcal conjugate vaccine (7vPCV) was introduced to the Australian National Immunisation Program (NIP) for vaccination against SPn for medically at-risk and Indigenous children in 2001 and for all children from January 2005[4]. The dosage schedule used was three doses at 2, 4 and 6 mo of age along with other vaccines such as diphtheria, tetanus and acellular pertussis (DTPa). A concurrent catch up vaccination program was implemented for two years targeting children up to two years of age, many of whom would have received DTPa vaccine prior to their first catch up dose of 7vPCV. The use of the 3 + 0 schedule is strongly supported by a systematic review of several randomized controlled clinical trials (RCTs) of pneumonia and IPD in developing country settings[5]. A 3-dose 2-4-6 mo schedule result in the optimum antibody levels after the primary series for many serotypes. However, interestingly, the 2-dose 3-5 mo schedule demonstrated higher antibody levels for five serotypes than the 3-dose schedule (at 2-3-4 mo) and equivalent antibody responses for serotypes 6B and 23F suggesting that the optimal timing of doses is perhaps more important than the number of doses[6].

The PCV is currently available in less than 60% of countries across the world[7] as the cost of the vaccine is an important barrier. Affordability of the vaccine could be improved through adoption of schedules with reduced doses by taking the advantage of a phenomenon called "carrier priming" when PCV is administered after DTPa vaccination[8]. Carrier priming is defined as an enhanced antibody response to a glycoconjugate vaccine when an individual has been previously primed with the carrier protein[9].

PCVs utilise carrier proteins such as tetanus toxoid, diphtheria toxoid or cross-reacting material 197 of diphtheria toxin. It is apparent that there is a high resemblance between these carrier proteins and the contents of DTPa vaccine. The carrier priming effect is attributed to the development of carrier-specific T-cells in response to a preceding immunisation with a vaccine (such as DTPa) that contains antigens similar to the carrier proteins in conjugate vaccines; this has been demonstrated in various studies[8].

The catch-up vaccination program implemented in 2005 accompanying the introduction of universal 7vPCV vaccination program in Australia provides a unique opportunity to examine the potential protective effect of carrier priming on IPD. We hypothesise that

due to the effect of carrier priming, the number of vaccine type-IPD (VT-IPD) cases 2-9 wk following the administration of the first dose of 7vPCV (through catch up program in those children primed with previous dose of DTPa), would be less frequent than that of the VT-IPD cases within the first two weeks post-vaccination (where no protection is expected yet). In this analysis, we compared the number of IPD occurring after the 2nd week post-vaccination until the 9th week (the time of the next dose) to that occurring two weeks post-vaccination.

MATERIALS AND METHODS

Data source and case definition

We conducted a retrospective descriptive analysis by obtaining data from the National Notifiable Diseases Surveillance System (NNDSS), Australia. IPD has been a notifiable disease in Australia since the year 2001. Laboratories, medical practitioners and allied health providers are required to report IPD cases to the health authorities. De-identified data on notified cases are reported by authorities electronically to NNDSS.

A case of IPD is defined as an identification of SPn through culture or nucleic acid testing from any normally sterile body site. The onset date is considered as the date of diagnosis. Demographic and clinical information including Indigenous status, age, vaccination status and serotype of the isolated pneumococci were collected from each case of IPD. According to the Australian NIP, all cases $\geqslant$ 2 mo old were presumed to receive dose one of DTPa. The VT-IDP was defined as the isolation of one of the serotypes contained in 7vPCV (4, 6B, 9V, 14, 18C, 19F and 23F). Isolation of other serotypes was defined as non-vaccine type-IPD (NVT-IDP). Eligibility criteria of IPD cases for analysis were non-Indigenous, infant (aged $\leqslant$ 12 mo) of both genders with no documented underlying pre-existing medical conditions.

We undertook the following comparisons: (1) the first analysis in this paper compares the number of VT-IPD within two weeks after a single carrier primed dose of 7vPCV with that occurred during 2-9 wk; (2) the second analysis compares the number of VT-IPD cases *vs* NVT-IPD cases after a single carrier primed dose of 7vPCV during and two weeks after vaccination; (3) the third analysis compares the number of VT-IPD cases after a single carrier primed dose of 7vPCV with the number of VT-IPD cases after non-carrier-primed dose of 7vPCV during and two weeks after vaccination; and (4) the final analysis explores herd immunity after the introduction of 7vPCV to assess the herd effect during the transitional period (when most of the analysed cases occurred). Herd immunity was explored by detecting numbers of VT-IPD among infants < 2 mo before, during and after the introduction of 7vPCV.

Ethics approval

Permission to access NNDSS data for the study was granted by the data custodian Communicable Disease Network Australia of the Australian Department of Health. Australian Capital Territory Health Human Research Ethics Committee approval was obtained as a prerequisite for data access (Reference number ETHLR.13.318).

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 22 software program (SPSS, Inc., Chicago, IL, United States) was used to carry out descriptive data analyses. Categorical variables were compared by using the one-sided fisher's exact test. A P value $\leqslant$ 0.05 was considered statistically significant.

RESULTS

A total of 23632 IPD cases were identified and scanned for study eligibility. The number of cases included in the study was 184 among non-Indigenous Australian children who developed IPD after at least one dose of 7vPCV and were born between 1st January 2001 (when 7vPCV became available in the private market) until 31st December 2006 (when the 7vPCV catch up program ended). Of these, 108 (58.7%) were males. The majority of cases were from New South Wales [61 (33.2%)], Victoria [50 (27.2%)] and Queensland [42 (22.3%)]. Serotype was determined in 174 cases (94.5%). Final analysis in this study included 22 IPD cases with median ages as shown in Figure 1.

While examining a carrier-priming protective effect after one dose of 7vPCV, we found that four VT-IPD cases (serotypes: 23F, 4, 14 and 19F) occurred within two weeks after one carrier primed dose of 7vPCV. We did not expect the vaccine to work effectively for two weeks; we found that only one case (serotype 19F) occurred 2-9 wk later (Figure 2), indicating that one carrier primed dose could provide a substantial protection after two weeks.

Further analysis revealed that two NVT-IPD cases (serotypes: 6C and 22F) occurred within two weeks after the first carrier primed dose of 7vPCV whereas seven NVT-IPD cases (serotypes: 35B, 38 and five 10A) were reported 2-9 wk after vaccination (Figure 3). Compared to the number of VT-IPD cases after the carrier primed dose, this suggests a protective effect (P = 0.06) against VT-IPD occurring after only one carrier primed dose (Table 1).

Upon further comparison with the non-carrier primed VT-IPD cases, two VT-IPD cases (serotypes: 18C and 14) occurred within two weeks after the first dose of 7vPCV while six VT-IPD cases (serotypes: 18C, 14, 23F, 6B and two 19F) occurred 2-9 wk after vaccination (Figure 4); which although not quite significant, may indicate that protection ensued (P = 0.08) (Table 2). However, age would be a confounder in the latter comparison as the primed cases were older with possibly more mature immunity.

Considering the fact that most of the cases included in our analysis took place during the transitional years

Table 1 Contingency table comparing the numbers of vaccine type invasive pneumococcal disease and non-vaccine type invasive pneumococcal disease cases 9 wk after single carrier primed dose of the 7-valent pneumococcal conjugate vaccine among non-Indigenous Australian infants (2001-2006)

	Two weeks after carrier primed dose of 7vPCV	2-9 wk after carrier primed dose of 7vPCV
Number of VT-IPD cases	4	1
Number of NVT-IPD cases	2	7
[1]*P* value	0.06	

[1]One-sided fisher's exact test. 7vPCV: 7-valent pneumococcal conjugate vaccine; VT-IPD: Vaccine type invasive pneumococcal disease; NVT-IPD: Non-vaccine type invasive pneumococcal disease.

Table 2 Contingency table comparing the numbers of vaccine type invasive pneumococcal disease cases 9 wk after carrier primed and non-carrier primed dose of the 7-valent pneumococcal conjugate vaccine among non-Indigenous Australian infants (2001-2006)

	Two weeks after dose of 7vPCV	2-9 wk after dose of 7vPCV
Number of VT-IPD cases after carrier primed 7vPCV	4	1
Number of VT-IPD cases after non-carrier primed 7vPCV	2	6
[1]*P* value	0.08	

[1]One-sided fisher's exact test. 7vPCV: 7-valent pneumococcal conjugate vaccine; VT-IPD: Vaccine type invasive pneumococcal disease.

of 2005-2006, we explored herd immunity during this transitional period to evaluate its effect. The trends shown in Table 3 and Figure 5 demonstrate little evidence of clinical protection (herd immunity) among young infants aged < 2 mo (before first vaccine dose). This suggests that herd immunity was unlikely to have contributed to the protection of young infants against IPD during observation period of our study. Therefore, the explanation for protection is likely to be the direct effect of one PCV dose enhanced by prior carrier priming.

DISCUSSION

Our analysis suggests that infants may receive some protection even from a single dose of 7vPCV if conjugate vaccines are offered after DTPa vaccination; this could be attributed to enhanced protection through a carrier priming effect even after one dose of vaccine. This is consistent with other incidental findings among infants, adults and even in animal models where prior exposure to DTPa or one of its components was shown to enhance the immunogenicity of subsequent PCV[6,10-13]. There is evidence from other settings that children who had not carrier primed would still be susceptible to IPD at 2-8 wk after one dose of 7vPCV (unpublished Danish IPD data, Z Harboe personal communication). It has been shown elsewhere that one dose of 7vPCV provides

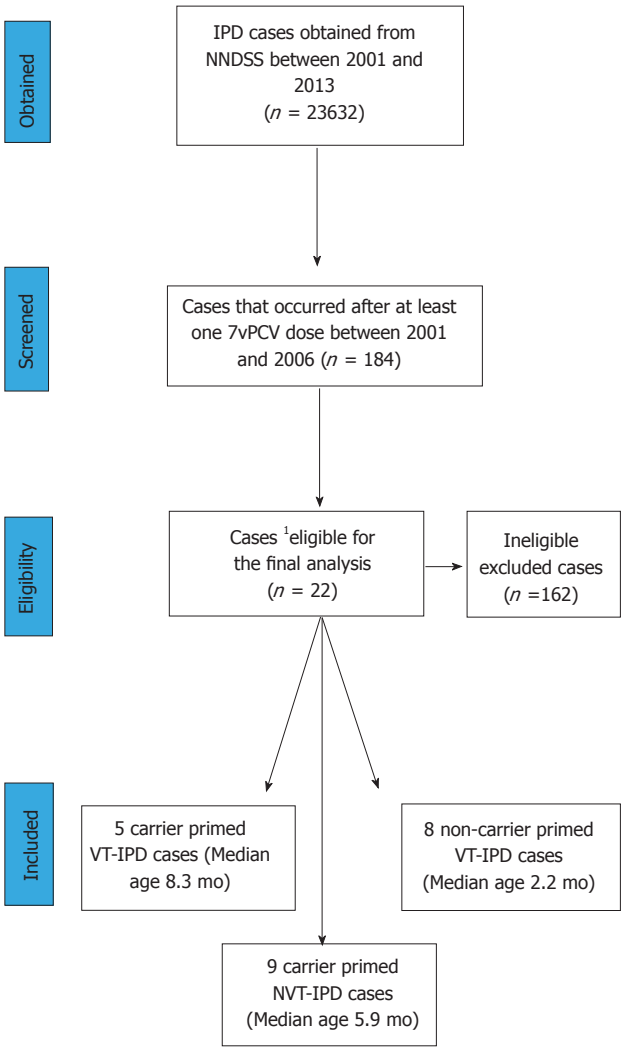

Figure 1 Flowchart showing the selection process of analysed cases and their median ages. [1]Australian non-Indigenous immunocompetent infants with receipt of first dose of 7vPCV after diphtheria, tetanus and acellular pertussis vaccine. NNDSS: National Notifiable Diseases Surveillance System; 7vPCV: 7-valent pneumococcal conjugate vaccine; VT-IPD: Vaccine type invasive pneumococcal disease; NVT-IPD: Non-vaccine type invasive pneumococcal disease.

no significant protection to young infants in the absence of carrier priming effect[14].

Our limited data suggested that herd protection in infants was not prominent in the first two years of vaccine introduction which is not surprising as the impact on carriage takes some years, and the proportion of infants and children that were vaccinated was still low[15].

PCV is highly effective, but it is also one of the most expensive vaccines on the routine paediatric schedule, at about USD $100/dose[16]. Among Australian children < 5 years of age there were approximately 700 cases of IPD and 16 associated deaths in the year prior to universal 7vPCV introduction. In 5 years of 7vPCV use IPD due to VT declined by 97% and total IPD by 68% in these children[17]. The percentage of the world's birth cohort living in countries with PCV in their NIPs rose from 1% in 2000 to 58% in 2014[7]. This suggests that efforts to increase PCV use globally are succeeding;

Table 3 Invasive pneumococcal disease cases among non-Indigenous Australian children < 6 mo (2001-2010)

	Year	2001-2002			2003-2004			2005-2006			2007-2008			2009-2010		
	Age	< 2 mo	2 mo-< 4 mo	4 mo-< 6 mo	< 2 mo	2 mo-< 4 mo	4 mo-< 6 mo	< 2 mo	2 mo-< 4 mo	4 mo-< 6 mo	< 2 mo	2 mo-< 4 mo	4 mo-< 6 mo	< 2 mo	2 mo-< 4 mo	4 mo-< 6 mo
VT-IPD	Vaccinated	0	1	0	0	2	0	0	7	2	1	0	0	0	1	4
	Not vaccinated	7	14	26	7	19	37	12	2	0	3	2	1	1	2	0
NVT-IPD	Vaccinated	0	0	0	0	0	0	0	5	8	2	9	14	2	8	18
	Not vaccinated	8	7	13	14	6	13	13	3	3	7	3	5	14	3	4

VT-IPD: Vaccine type invasive pneumococcal disease; NVT-IPD: Non-vaccine type invasive pneumococcal disease.

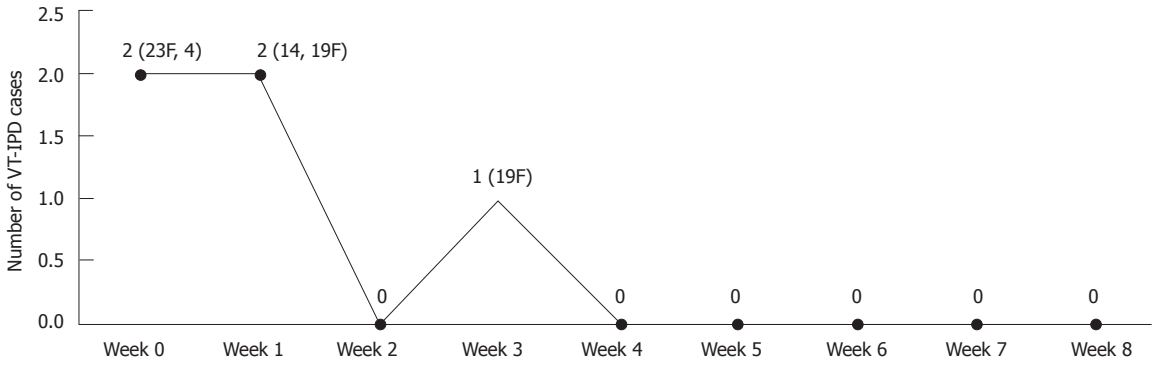

Figure 2 Number of vaccine type invasive pneumococcal disease cases 9 wk after a single carrier primed dose of the 7-valent pneumococcal conjugate vaccine among non-Indigenous Australian infants (2001-2006). VT-IPD: Vaccine type invasive pneumococcal disease.

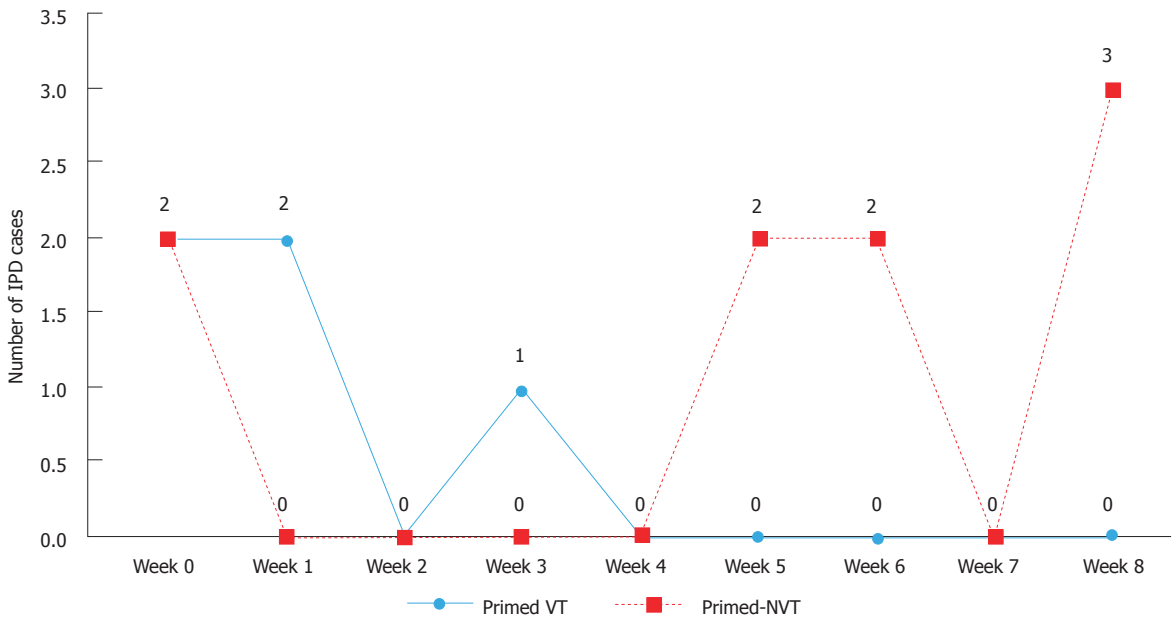

Figure 3 Number of vaccine type invasive pneumococcal disease compared to non-vaccine type invasive pneumococcal disease cases 9 wk after single carrier primed dose of 7-valent pneumococcal conjugate vaccine among non-Indigenous Australian infants (2001-2006). IPD: Invasive pneumococcal disease; VT: Vaccine type; NVT: Non VT.

however, important gaps in PCV introduction remain, notably in the World Health Organization South-East Asia Region that includes several countries with large birth cohorts but limited financial capacities to purchase these costly vaccines[18].

The implication of carrier priming raises hope for developing countries where IPD is still a major cause of morbidity and mortality[19,20]. The serotypes in the current PCV formulations account for 49%-88% of deaths in Africa, Asia and Latin America where IPD morbidity

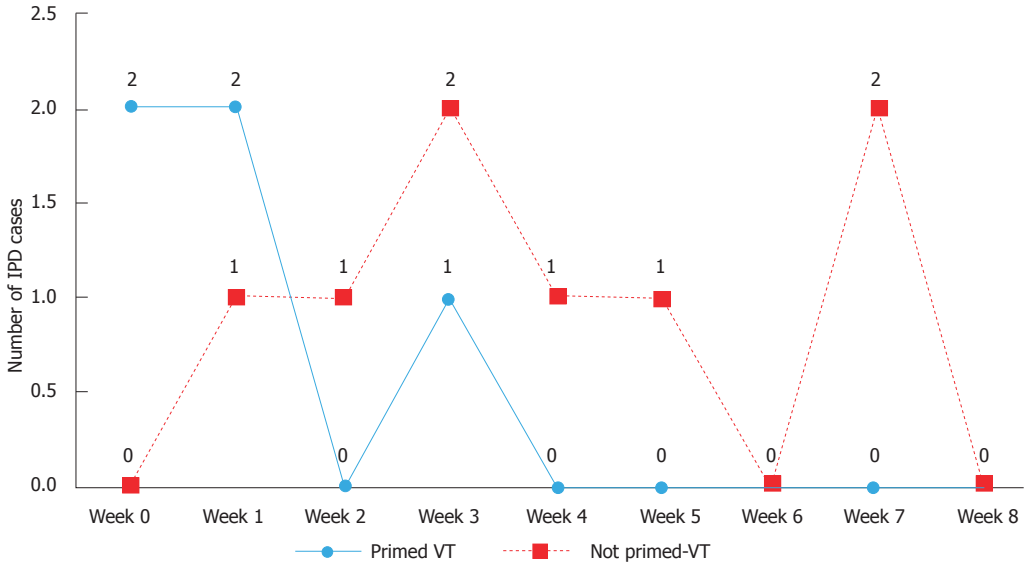

Figure 4 Number of vaccine type invasive pneumococcal disease cases 9 wk after a single carrier primed dose of 7-valent pneumococcal conjugate vaccine compared to the vaccine type invasive pneumococcal disease cases after non-carrier primed single 7-valent pneumococcal conjugate vaccine dose among non-Indigenous Australian infants (2001-2006). IPD: Invasive pneumococcal disease; VT: Vaccine type.

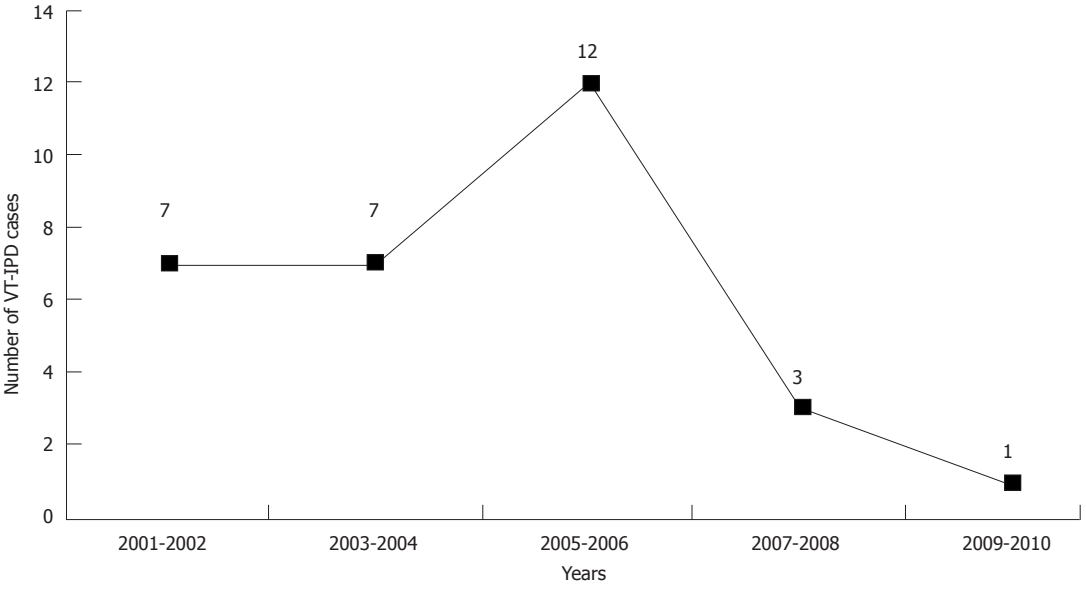

Figure 5 Number of vaccine type invasive pneumococcal disease cases among non-Indigenous Australian in children aged < 2 mo (2001-2010). VT-IPD: Vaccine type invasive pneumococcal disease.

and mortality are the highest, yet many children do not have access to these vaccines[21]. Achieving sufficient immunity against pneumococcal disease in spite of sparing a dose of vaccine could be of great value to these countries.

Simply minimizing the number of doses of PCV would not likely to be beneficial unless the carrier priming effect is also harnessed. A study in Fiji by Russell *et al*[22,23] was conducted to explore the immunogenicity of the reduced dose schedule of 7vPCV in order to determine optimal pneumococcal vaccination strategy for poor settings. They found that the immunogenicity of three PCV doses is better than two doses with potentials for a two dose PCV primary series to offer similar protection as provided by three doses for most serotypes. They also noted that a significant protection from one dose of PCV would not continue for children throughout the highest risk period for IPD and an early booster at 6 or 9 mo of age ("1 + 1" schedule) deserves a further investigation for use in the developing world[22,23]. However, in their variable schedules/methods, they only administered DTPa with the first dose of PCV, and missed the chance to examine the effect of carrier priming.

This paper sheds light on the need for further RCTs designed specifically to detect/provide conclusive evidence of the positive impact of carrier priming. If priming occurs, there is a possibility in the third world that if DTPa vaccine is given first, at anywhere between

2 and 6 wk of age, a subsequent single dose of PCV may be at least partially protective, and a second dose 4 wk later highly protective so that a third dose may not be required, either making a substantial saving in vaccine cost or allowing the third dose of PCV to be used at a more strategic time, *e.g.*, between 9 and 12 mo of age. We believe that this theory is applicable to other conjugate vaccines, *e.g.*, Hib and meningococcal conjugate vaccines, irrespective of the carrier protein. Furthermore, carrier-priming phenomenon could be implemented to reinforce immunisation schedules in resource-poor settings.

We are currently investigating this innovative concept of carrier priming by RCT among adult travellers to mass gathering, where we offer DTPa before, with and after conjugate vaccines to examine the effect.

A limitation of the study is that it is retrospective and observational with a limited number of cases included in the final analysis. Additionally, the exact dates of receipt of DTPa were not accessible as the NDDS system registers only the vaccines related to the disease, in this case PCV. However, the Australian surveillance data indicated that the coverage of DTPa was ⩾ 90% during that time[24]. This is the first established descriptive analysis looking at clinical evidence of carrier priming for prevention of pneumococcal disease.

In conclusion, these data suggest a favourable level of evidence of the effectiveness of one dose of PCV; this could be attributed to enhanced immunity through a carrier priming effect. If priming really occurs, an adjusted 2-dose schedule (where the first PCV is given following DTPa) may be sufficient and more cost-effective for vulnerable populations, particularly those that have used PCV for several years so that herd immunity is also operating.

COMMENTS

Background

Conjugate vaccines such as pneumococcal conjugate vaccine (PCV) have a carrier protein to enhance its immunogenicity. These carrier proteins have some similar antigens to the contents of diphtheria, tetanus and pertussis vaccine (DTP). This similarity may bring a potential interaction between PCV and DTP. This occurs as upon administering DTP before PCV which leads to development of carrier-specific T-cells resulting in an enhance immunogenicity of PCV, a phenomenon called carrier priming.

Research frontiers

Invasive pneumococcal diseases carry substantial morbidity and mortality particularly in developing countries and among vulnerable populations. Currently, infants are required to receive at least three doses of (the expensive) PCV. In this analysis, the authors propose investigating the use of carrier priming to enhance the immunogenicity of PCV in order to spare one of the three doses.

Innovations and breakthroughs

Most studies exploring conjugate vaccine interactions, examine concurrent co-administration. This unique analysis examines sequential administration and its effect on the protectiveness conjugate vaccines.

Applications

If carrier priming used judicially to enhance the immunogenicity of PCV, an adjusted 2-dose schedule (where the first PCV is given after DTPa) may be sufficient and cost-effective.

Terminology

Invasive pneumococcal disease (IPD): Infection confirmed by the isolation of pneumococci from a normally sterile body site, such as the blood stream, cerebrospinal fluid and joint fluid. Vaccine type invasive pneumococcal disease (VT-IPD): IPD caused by one of the pneumococcal serotype that is included in the pneumococcal vaccine. Non-vaccine type invasive pneumococcal disease (NVT-IPD): IPD caused by one of the pneumococcal serotype that is not included in the pneumococcal vaccine. Carrier priming: Enhanced antibody response to a glycoconjugate vaccine when an individual has been previously primed with the carrier protein. Carrier primed IPD case: IPD case that occurred after one dose of PCV that was administered at least one dose of DTP vaccine. Non-carrier primed VT-IPD cases: IPD case that occurred after one dose of PCV without previous exposure to at least one dose of DTP vaccine.

Peer-review

This is an interesting descriptive analysis investigating evidence for clinical protection in infants after one dose of the 7-valent PCV as a result of possible prior carrier priming from Tdap vaccine administration. It provides evidence for efficacy of reduced PCV schedule if administered following Tdap vaccination. This is valuable especially for developing countries as saving cost.

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ORIGINAL ARTICLE

Observational Study

Single institution experience with the Ladd's procedure in patients with heterotaxy and stage I palliated single-ventricle

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Abstract

AIM: To investigate and describe our current institutional management protocol for single-ventricle patients who must undergo a Ladd's procedure.

METHODS: We retrospectively reviewed the charts of all patients from January 2005 to March 2014 who were diagnosed with heterotaxy syndrome and an associated intestinal rotation anomaly who carried a cardiac diagnosis of functional single ventricle and were status post stage I palliation. A total of 8 patients with a history of stage I single-ventricle palliation underwent Ladd's procedure during this time period. We reviewed each patients chart to determine if significant intraoperative or post-operative morbidity or mortality occurred. We also described our protocolized management of these patients in the cardiac intensive care unit, which included pre-operative labs, echocardiography, milrinone infusion, as well as protocolized fluid administration and anticoagulation regimines. We also reviewed the literature to determine the reported morbidity and mortality associated with the Ladd's procedure in this particular cardiac physiology and if other institutions

have reported protocolized care of these patients.

RESULTS: A total of 8 patients were identified to have heterotaxy with an intestinal rotation anomaly and single-ventricle heart disease that was status post single ventricle palliation. Six of these patients were palliated with a Blaylock-Taussig shunt, one of whom underwent a Norwood procedure. The two other patients were palliated with a stent, which was placed in the ductus arteriosus. These eight patients all underwent elective Ladd's procedure at the time of gastrostomy tube placement. Per our protocol, all patients remained on aspirin prior to surgery and had no period where they were without anticoagulation. All patients remained on milrinone during and after the procedure and received fluid administration upon arrival to the cardiac intensive care unit to account for losses. All 8 patients experienced no intraoperative or post-operative complications. All patients survived to discharge. One patient presented to the emergency room two months after discharge in cardiac arrest and died due to bowel obstruction and perforation.

CONCLUSION: Protocolized intensive care management may have contributed to favorable outcomes following Ladd's procedure at our institution.

Key words: Congenital heart disease; Heterotaxy; Single-ventricle; Pediatrics; Ladd's procedure; Congenital heart disease

Core tip: Babies born with congenital heart disease consisting of a functional single-ventricle present a complicated subset of patients to care for. When these patients also have heterotaxy and an intestinal rotational anomaly combined with their heart defect, determining when and how to safely perform a Ladd's procedure is challenging for clinicians involved in their care. Having experienced practitioners involved and using protocolized care may help reduce surgical morbidity and mortality in these patients.

Piggott KD, George G, Fakioglu H, Blanco C, Narasimhulu SS, Pourmoghadam K, Munroe H, Decampli W. Single institution experience with the Ladd's procedure in patients with heterotaxy and stage I palliated single-ventricle. *World J Clin Pediatr* 2016; 5(3): 319-324 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i3/319.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i3.319

INTRODUCTION

Heterotaxy syndrome is a relatively rare phenomenon with an incidence of approximately 1 in 10000 live births. It accounts for about 3% of cases of congenital heart disease[1]. Heterotaxy is synonymous with "visceral heterotaxy" and "heterotaxy syndrome" and is defined as an abnormality where the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right access of the body. The heterotaxy syndrome is typically associated with complex cardiovascular malformations. These malformations can vary from relatively common defects such as ventricular septal defects to complex anatomy not amenable to complete repair and resultant single ventricle physiology[2].

Intestinal rotation and fixation abnormalities (IRA) are commonly associated with heterotaxy syndrome. Normal intestinal rotation and fixation occurs between days 32 and 56 in the human fetus[3]. IRA is a spectrum of disease that depends on the stage of intestinal rotation or fixation that was interrupted. IRA occurs in 40%-90% of children with heterotaxy syndrome[4,5]. Practice among institutions pertaining to IRA is extremely variable and ranges from observation and conservative management for asymptomatic patients to surgical intervention with a Ladd procedure early in life.

A Ladd procedure may be performed in patients with IRA in an attempt to reduce the risk of bowel ischemia and infarction. During the Ladd procedure, peritoneal bands (Ladd's bands) are divided, and the mesentery of the small bowel is widened. An appendectomy is performed and the bowel is rearranged to a nonrotated state with the small bowel on the right side of the peritoneal cavity and the colon on the left.

The decision of whether or not to perform an elective Ladd procedure in a patient with heterotaxy syndrome becomes more complicated when the patient has complex cardiac anatomy resulting in the need for single ventricle palliation. These patients are at risk for complications such as hypoxia, shunt thrombosis, bowel ischemia and coronary ischemia to name a few. This physiology may increase the risk of morbidity and mortality, particularly in the young infant age group. As such, procedures including major abdominal surgery carry an increased risk of complications and instability.

Our institutional approach to patients with heterotaxy sydrome, IRA and functional single ventricle has been to perform a Ladd procedure if: (1) there are signs of bowel obstruction or ischemia; or (2) there is feeding intolerance and the patient requires a gastrostomy or jejunostomy tube, then a Ladd procedure is performed at the same time.

Substantial morbidity and mortality has been reported in these complex patients[4-7]. Over a period of several years, we have attempted to protocolize as much as possible our pre-operative and post-operative approach to all stage I single ventricle palliated patients, in hopes of minimizing morbidity and mortality. We report our experience with 8 patients carrying a diagnosis of heterotaxy syndrome, IRA and functional single ventricle status post stage I palliation who underwent Ladd procedure at the time of nissen fundoplication and gastrostomy tube or jejunostomy tube placement. The purpose of this paper is to share our current protocol and experience as well as to

retrospectively determine if complications occurred during or after the Ladd's procedure.

MATERIALS AND METHODS

Following approval by the Arnold Palmer Medical Center institutional review board, we conducted a retrospective chart review. We searched our surgical database for all patients with heterotaxy syndrome and functional single ventricle who underwent a cardiac procedure at Arnold Palmer Hospital for Children between January 2005 and March 2014. For the subset of patients who were diagnosed with an IRA and underwent a Ladd procedure, we collected data including patient sex, age at the time of Ladd procedure, cardiac and segmental anatomy, type of gastrointestinal surgery, intraoperative or post-operative complications from the Ladd procedure and mortality associated with the procedure. We also reviewed each patient's hospital records and clinic notes to ascertain their most up to date feeding status, evidence of post-operative bowel obstruction, or need for further gastrointestinal (GI) procedures.

RESULTS

A total of 8 patients were identified with heterotaxy, IRA and functional single ventricle. All 8 patients had undergone first stage single ventricle palliation. Two patients underwent stenting of the ductus arteriosus. The remaining 6 patients underwent placement of systemic-pulmonary artery shunts. Four of the patients who underwent shunt placement also underwent repair of total anomalous pulmonary venous connection. Each of the 8 patients had an upper GI series with small bowel follow through confirming IRA. Two patients had modified barium swallows showing aspiration. Seven of the 8 patients underwent placement of gastrostomy tube as well as nissen fundoplication at the time of the Ladd procedure. The other patient underwent Roux-en-Y jejunostomy at the time of the Ladd procedure. None of these patients experienced intraoperative complications. One patient had mild postoperative hypotension upon immediate arrival to the cardiovascular intensive care unit, which was responsive to fluid resuscitation. One patient had transient oxygen desaturation upon arrival to the cardiovascular intensive care unit which was found to be mucous plugging and responded immediately to manual bag mask ventilation and suctioning. Neither of these events were considered complications of the procedure as neither of these events recurred and additionally, these can be seen as common, postoperative events in any patient undergoing a procedure.

All eight patients survived to discharge. One patient died as an outpatient. She presented 2 mo after discharge to the emergency department in cardiopulmonary arrest and was found to have bowel perforation and hemodynamic collapse, likely secondary to bowel obstruction. Six patients are currently free from bowel obstruction. One patient had continued feeding intolerance and had suspicion of partial bowel obstruction but was managed conservatively and is currently tolerating full feedings by gastrostomy tube and did not require additional surgery. One patient is feeding entirely per oral, three entirely by gastrostomy tube and the remaining 3 are fed by a combination of oral and gastrostomy tube. Table 1 shows the details for each of the 8 patients with heterotaxy syndrome.

DISCUSSION

Children born with complex cardiac anatomy resulting in a functional single ventricle present a challenging group of patients. Their unstable physiology and typically unbalanced circulation puts all single ventricle patients at risk for morbidity and mortality after stage Ⅰ palliation. This mortality has improved over the years, however it has still been reported between 10% and 25%[6,7]. Patients with heterotaxy syndrome and functional single ventricle have been reported to have a mortality rate as high as 41%[8]. For this reason, procedures and exposures to general anesthesia should be minimized.

Patients with heterotaxy syndrome have an incidence of IRA between 40% and 90%[4,5,9]. It is understood and agreed upon that patients with heterotaxy and IRA who develop feeding intolerance need immediate evaluation for IRA. However, there is no consensus on whether or not to evaluate asymptomatic patients with heterotaxy for IRA. Additionally, significant institutional variance remains on whether or not to perform an elective Ladd procedure if an IRA is discovered in an asymptomatic patient and if so, the appropriate timing of the procedure. This decision becomes even more complicated when the patient has a functional single ventricle and unbalanced circulation.

In 2013, Pockett *et al*[10] described their institutional experience of performing elective Ladd procedure in all heterotaxy patients with IRA. They reported a high rate of serious complications (57%) after Ladd procedure in patients with heterotaxy syndrome. They felt that it was likely the limited cardiopulmonary reserve that shunt-dependent and single-ventricle patients have that led to the high rate of complications[10].

In 2013, Sharma *et al*[11] reported significant morbidity and mortality in patients undergoing Ladd procedure both prior to and after stage Ⅰ palliation. Two patients had Ladd procedure prior to stage Ⅰ palliation. One had recurrent necrotizing enterocolitis and died. Two patients had Ladd procedure after stage Ⅰ palliation, both of whom developed shunt thrombosis, one of which died. They also reported no mortalities in 5 asymptomatic patients who underwent elective Ladd procedure after second-stage palliation.

Our programmatic approach to heterotaxy syndrome with functional single ventricle is to evaluate for IRA in all patients with heterotaxy. However, we have chosen to intervene surgically only in those patients who develop signs of bowel obstruction or feeding intolerance. All 8 patients described above had feeding

Table 1 Heterotaxy patients

Reason for GI surgery	Studies	Segmental anatomy	Cardiac anatomy	Visceral abnormality	Cardiac procedure	GI surgery	Age at ladd	Intra/postop Complications	Outcome	Current GI status
Poor PO intake, severe GE Reflux	UGI/SBFT	I, D, D	Unbalanced CAVC, PA, LSVC	IRA	PDA stent	Ladd, Roux-en-Y jejunostomy	6 wk	None	Alive	At 5 yr had jejunal perforartion resulting in laparotomy and Nissen. Feeds PO and Gtube
Poor PO intake, severe GE Reflux	UGI/SBFT	A, D, D	Unbalanced CAVC, TAPVR, PA, RPA stenosis	IRA	3.5 mm central shunt placement, TAPR repair, RPA plasty	Ladd, Nissen/ Gtube	6 wk	None	Alive	No obstruction or GI surgeries. Feeds PO and Gtube
Severe GE Reflux, Vocal cord paralysis with aspiration	UGI/SBFT Mod. Barium Swallow	I, D, S	Dextrocardia, TA, Unbalanced CAVC, Coarctation	IRA	Norwood with 3.5 mm Modified BT shunt	Ladd, Nissen/ Gtube	8 wk	None	Alive	No obstruction or GI surgeries. Gtube is removed and now eats entirely PO
Poor PO intake, severe GE Reflux	UGI/SBFT	A, L, D	Unbalanced CAVC, TAPVR, PA	IRA	3.5 Modified BT shunt, TAPVR repair, PA plasty	Ladd, Nissen/ Gtube	8 wk	None	Outpatient death from bowel perforation	N/A
Poor PO intake, TE Fistula repair, severe GE Reflux	UGI/SBFT	S, D, D	DORV, right atrial isomerism, BLSVC, CAVC, PS	IRA	PDA stent	Ladd, Nissen/ Gtube	5 wk	None	Alive	No obstruction or further GI surgeries. Gtube fed only
Poor PO feeding, GE Reflux,	UGI/SBFT	I, D, D	Dextrocardia, Unbalanced CAVC, TAPVR, PA	IRA	3.5 mm central shunt, TAPVR repair, PA plasty	Ladd, Nissen/GT	6 wk	None	Alive	No obstruction or GI surgeries. Feeds PO and Gtube
Poor PO intake, feeding intolerance, GE Reflux	UGI/SBFT	I, D, D	Unbalanced CAVC, Pulmonary atresia	IRA	3.5 mm Modified BT shunt	Ladd, Nissen/ Gtube	6 wk	None	Alive	No obstruction or GI surgeries, All feeds *via* Gtube
Poor PO feeding, GE reflux, aspiration	UGI/SFT, Modified barium swallow	A, L, L	Unbalanced CAVC, TAPVR, Pulmonary atresia	IRA	4.0 mm Modified BT shunt, TAPVR repair	Ladd, Nissen/ Gtube	5 wk	None	Alive	No obstruction or GI surgery. All feeds *via* Gtube

PA: Pulmonary atresia; BT: Blaylock-Taussig; CAVC: Complete atrioventricular canal; TAPVR: Total anomalous pulmonary venous return; GI: Gastrointestinal; GT: Gastrostomy tube; GE: Gastroesophageal; PO: Per oral; TA: Tricuspid atresia; IRA: Intestinal rotation and fixation anomaly; UGI/SBFT: Upper GI with small bowel follow through; DORV: Double outlet right ventricle.

intolerance and were found by upper GI series with small bowel follow through to have IRA. All patients had a Ladd procedure at the time of gastrostomy or jejunostomy tube placement. As a program, we maintain a philosophy of not performing prophylactic Ladd procedures in asymptomatic patients and we would prefer to wait until after the stage two palliation to perform a Ladd's procedure, when the circulation is more balanced. However, all 8 patients had feeding difficulties resulting in the need for an alternate source of enteral feeding. We have maintained the philosophy that if the patient requires GI surgery for an alternate feeding source that we will perform the Ladd's procedure at that time. To date all patients have required an alternate feeding source and therefore underwent successful Ladd's at that time. To date we have not encountered any patients with heterotaxy syndrome, functional single-ventricle and IRA who developed bowel obstruction requiring urgent Ladd procedure.

At our institution over a period of several years, we have protocolized the pre-operative and post-operative management of patients with functional single-ventricle, status post stage I palliation who are to undergo general anesthesia for any procedure. All patients have preopera-

tive labs performed to evaluate for signs of infection and to monitor hemoglobin, assuring adequate oxygen carrying capacity pre-operatively. All patients get a pre-operative echocardiogram 1-2 d prior to the procedure to evaluate shunt patency and systolic function of the systemic ventricle and all patients regardless of echocardiographic findings, are placed on a milrinone infusion at a dose of 0.5 mg/kg per minute 24 h prior to the procedure and it is continued during the surgery and for 24 h following surgery in an attempt to support the ventricular function during the stress of anesthesia and a major gastrointestinal surgery. Aspirin is not stopped prior to surgery. We have chosen to accept some risk of bleeding in order to have continued antiplatelet affect and avoid any period without some anticoagulation affect in hopes of preserving shunt patency. All patients receive aggressive intraoperative and postoperative fluid resuscitation in addition to maintenance fluids regardless of hemodynamic data to replace assumed fluid losses from gastrointestinal surgery and to prevent intravascular depletion in hopes of minimizing risk of shunt thrombosis. All patients receive a minimum of one 20 mL/kg fluid bolus upon arrival to the cardiac intensive care unit. All patients are placed on postoperative antibiotics for a minimum of 48 h. Anesthesia is performed by experienced cardiac anesthesiologists. The surgery is performed by experienced pediatric surgeons and the patients recover in our dedicated cardiovascular intensive care unit with 24 h in-house attending physician coverage.

While there is still no consensus on the need for evaluation of heterotaxy patients for the presence of IRA and the need for elective Ladd procedure in asymptomatic patients, there will continue to be a need for Ladd procedure in patients with heterotaxy syndrome. As an institution, we do agree with previous reports that suggest waiting until completion of the second stage of palliation to undergo elective Ladd's procedure. However, we feel that if a gastrointestinal surgery, such as gastrostomy tube, is necessary during the stage I palliated phase, that our practice of doing a Ladd's procedure at the same time is acceptable.

It is important to realize that Ladd procedure does not guarantee that a patient will free of partial or complete bowel obstruction later in life as is suspected in our only patient who died following bowel perforation as an outpatient 2 mo after discharge.

While the 8 patients we have presented is a small number, we believe that it does show that a protocolized pre-operative and post-operative management strategy may improve morbidity and possibly survival in this complex patient population. This subset of patients is extremely challenging and each institution must weigh the risk and benefit of the procedure with their own experiences and resources available to care for these patients. While our protocol and results appear satisfactory, we fully recognize that this is a very small group of patients and to say that this strategy is entirely safe and that it would work for every program is not possible. The combination of heterotaxy syndrome, functional single-ventricle and IRA describes a relatively unique and rare subset of patients. For this reason, further research containing larger cohorts of patients in this field is needed and will likely require data sharing and multi-institution studies.

Our paper does have significant limitations including the fact that it is a retrospective, single institution review and additionally it contains a small cohort of patients.

COMMENTS

Background

Heterotaxy, while rare is often associated with heart defects. When these defects result in single-ventricle physiology and are associated with intestinal rotational anomalies. A Ladd's procedure can carry a high rate of morbidity and mortality in the complex subset of patients and should be undertaken with caution and with the appropriate expertise to care for these patients.

Research frontiers

To our knowledge, no paper has described a protocolized approach to the care of this complicated care of patients undergoing a Ladd's procedure.

Innovations and breakthroughs

The major conclusion from this paper is that with an experienced providers and protocolized approach to the Ladd's procedure in this patient population, morbidity and mortality may be reduced.

Applications

With the current literature reporting high rates of morbidity and mortality when performing the Ladd's procedure in stage I palliated, functional single-ventricle patients, a protocolized approach may improve outcomes.

Terminology

Heterotaxy is defined as an abnormality where the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right access of the body.

Peer-review

An interesting article that provides a different perspective in the management of patients with heterotaxy, intestinal rotation anomaly and single-ventricle undergoing the Ladd's procedure.

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ORIGINAL ARTICLE

Observational Study

Significant variations in nutritional supplementation amongst neonates in the United Kingdom

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Abstract

AIM: To ascertain United Kingdom adherence to European society of Paediatric Gastroenterology, Hepatology and Nutrition guidance (ESPGHAN).

METHODS: A national cross sectional questionnaire study of neonatal units across England was completed between January and March 2014. All 174 units in the country were attempted to be contacted to complete a telephone survey. This included all level 1, 2 and 3 units. They were initially contacted by phone and asking any senior member of the team about their current practice and procedures. The first ten telephone interviews were completed with two researchers present to ensure consistency of approach. If no response was received or no details were available, one further attempt was made to contact the unit. The results were recorded in a proforma and then collated and entered into a spreadsheet for analysis. Comparison to United Kingdom adherence to ESPGHAN guidance was completed.

RESULTS: Response rate was 53%. There was variation in use of all supplements. The survey collected data from 91 neonatal units (53% response rate). It was found that 10% of neonatal units had no fixed policy on supplements. The protocols regarding supplementation involved predominantly folic acid, vitamin A, vitamin D

and iron, with much variation in doses and regimens. The criteria for prescribing supplements was largely based on age (47%) with only 7% using a weight targets to initiate supplements. Summary data regarding the appropriateness of each nutritional supplement for a variety of different weights are presented, as well as comparison to ESPGHAN guidance which suggests issues with both underdoing of Breast Fed infants and overdosing of infants on several artificial formulas which already contain significant amounts of these nutritional elements.

CONCLUSION: There is significant heterogeneity in neonatal policies when prescribing supplements to neonates. National policies which take international guidance into account are recommended.

Key words: Neonatal; Nutritional additives; Preterm nutrition; Term nutrition; Iron

Core tip: Nutritional supplementation in neonates is common in neonatal units, but there is no clear United Kingdom guidance. This study set out to ascertain United Kingdom practice with a national cross-sectional study with reference to European society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) nutritional guidance. Fifty-five percent of the 174 units in the country were contacted. There was variation in use of all supplements. Comparison to ESPGHAN guidance suggests issues with both underdoing of Breast Fed infants and overdosing of preterm infants on several artificial formulas which already contain significant amounts of nutritional elements. National policies which take international guidance into account are recommended, with similar research needed in other countries.

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INTRODUCTION

Nutritional needs of both preterm and term neonates are not the same as older children and are subject to rapid changes. A number of nutritional supplements have been studied in relation to prematurity, notably vitamin A, D, iron and folic acid - these form the basis of supplementation recommendations in neonates. Preterm infants have higher nutrient requirements than term infants but inappropriate or absent supplementation can be detrimental to their health[1]. Preterm infants have a low vitamin A status at birth[1]. Evidence shows vitamin A supplement significantly reduces the risk of chronic lung disease and reduces mortality, however excessive levels can lead to symptoms[2].

Preterm infants are susceptible to developing iron deficiency, particularly more premature infants and those being exclusively breastfed without supplementation. As iron plays a role in various tissue functions this would support the need supplementation in preterm infants[3]. Vitamin D is needed for bone health and low levels can cause rickets and seizures secondary to low calcium[4]. Folic acid is used for the prevention of anaemia of prematurity. Levels are high at birth but fall rapidly in the first few weeks of life more notably in the lowest birthweight neonates[5].

Nutritional supplements are almost ubiquitous for infants admitted to United Kingdom neonatal units. Compositions of vitamin supplements vary, for example, Dalavit and Abidec are both commonly used, but Dalavit contains nearly 4 times the amount of vitamin A[1] as Abidec. Doses of supplements should be adjusted according to the type of milk the infant is receiving. Breast milk is best for preterm and low birth weight babies - better long term health outcomes have been well documented, but higher doses of supplements or the addition of fortifiers is required in order to reach the recommended daily intake of vitamins and minerals.

There are currently no national guidelines on nutritional supplementation, but local protocols exist based on growth and nutrition studies and guidance provided by expert groups[6]. The aim of this study was to establish current practices in neonatal supplementation in neonatal units across England[6] and to compare these dosing regimens to guidance provided by European society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[7].

MATERIALS AND METHODS

A national cross sectional questionnaire study of Neonatal units across England was conducted between January and March 2014[6]. This included all level 1, 2 and 3 units. They were initially contacted by phone and asking any senior member of the team about their current practice and procedures. Eligible staff included senior nurses, advanced neonatal nurse practitioners and senior medical staff.

Firstly, the existence of a local policy was established. Then, details of the supplements used, their brands, dosing, criteria for initiation and the impact of gestational age, weight and feeding type were recorded.

The first ten telephone interviews were completed with two researchers present to ensure consistency of approach and then further interviews were conducted by either researcher. If no response was received or no details were available, one further attempt was made to contact the unit.

The results were recorded in a proforma and then

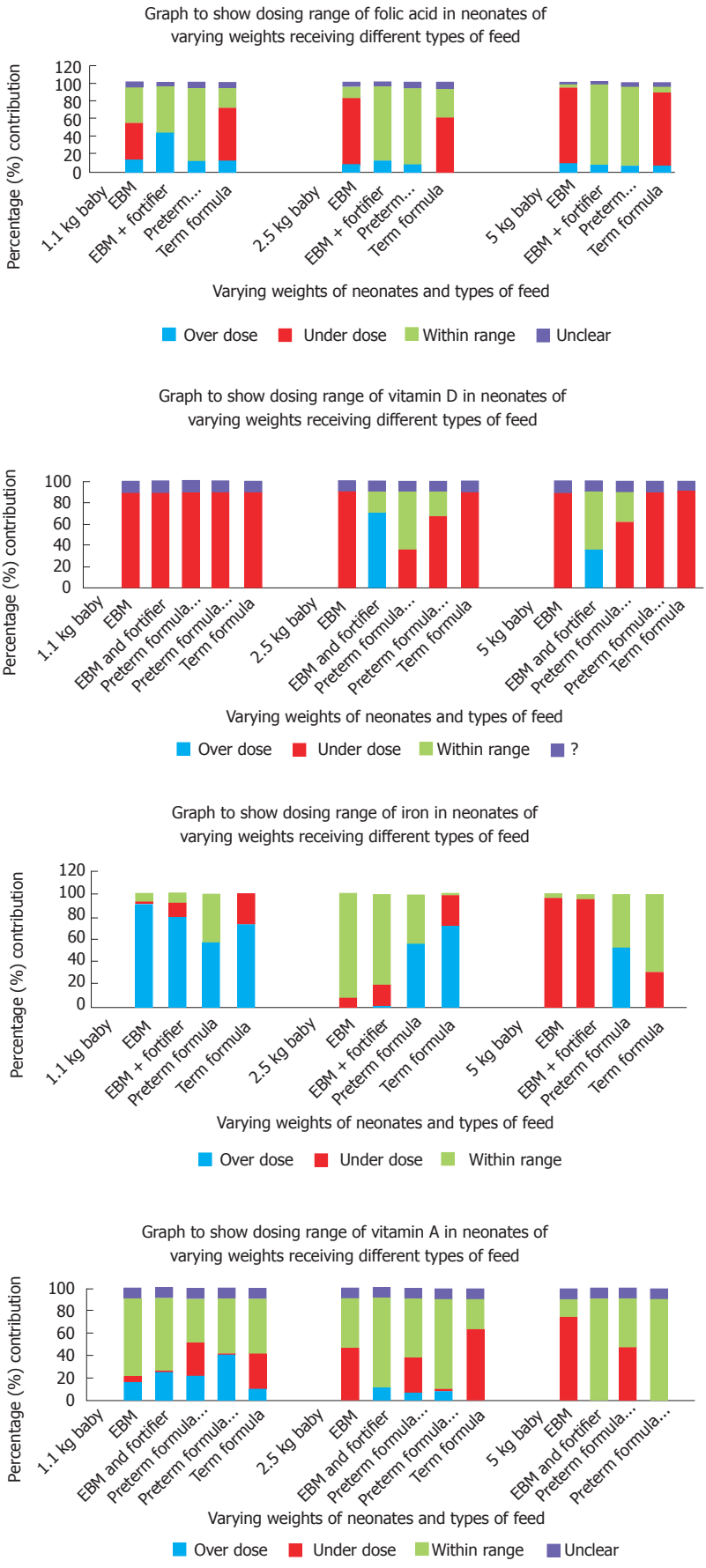

Figure 1 Dosing range results for various nutritional supplements. EBM: Expressed breast milk.

Table 1 Nutritional content of breast milk and artificial formulae (brand names of United Kingdom formula preparations used)[5]

Type of feed (based on 180 mL of feed)	Vitamin A (μgRE)	Vitamin D (μg)	Folic acid (μg)	Iron (mg)
EBM	104	0.07 μg/kg per day	9	0.126
EBM + 2 × 2.2 g Nutriprem (C and G) Breast Milk Fortifier	522	9.1 μg/kg per day	63	Neg
EBM + 2 × 2 g SMA BMF	486	13.68 μg/kg per day	54	Neg
SMA gold Prem 1	333	6.1 μg/kg per day	52	2.5
SMA Gold Prem 2	180	2.7 μg/kg per day	27	2.16
C and G Nutriprem 1	650	5.4 μg/kg per day	63	2.9
C and G Nutriprem 2	180	3.06 μg/kg per day	36	2.16
C and G 1	97.2	2.16 μg/kg per day	23.4	0.954
Aptamil 1	97.2	2.16 μg/kg per day	23.4	0.954
SMA 1	119	2.2 μg/kg per day	19.8	1.2
HiPP 1	126	2.16 μg/kg per day	18	0.9
Neocate LCP	100.8	2.16 μg/kg per day	15.84	1.8
ESPGHAN recommendation	400-1000 μg RE/ kg per day	20-25 μg/d	35-100 μg/kg per day	2-3 mg/kg per day (from 2-6 wk)

EBM: Expressed breast milk.

collated and entered into a spreadsheet for analysis. Comparison to ESPGHAN guidance was completed.

RESULTS

The survey collected data from 91 neonatal units (53% response rate), with a representative sample of hospital size and level of neonatal care achieved[6]. It was found that 10% of neonatal units had no fixed policy on supplements. The protocols regarding supplementation involved predominantly folic acid, vitamin A, vitamin D and iron.

In regards to folic acid, when supplementing expressed breast milk (EBM), 36% of hospitals prescribed 50 μg of folic acid daily, whilst 37% of units prescribed no folic acid. For remaining units, the dose varied from 50 μg daily to 1 mg weekly of folic acid.

Similar results were obtained when looking at the vitamins A and D data. Dalavit and Abidec doses varied in each hospital. Two units had no fixed regime and was based on which supplement (Dalavit or Abidec) was available at the time of prescribing.

When considering iron supplementation[7], over 65% of units prescribed iron supplementation with various feeds types whereas 27% did not supplement with iron at all. Doses across the different units varied between 0.5 mL sytron once daily to 2.5 mL twice daily. Forty-six percent of units recognised that no additional iron supplementation is needed for babies receiving preterm formula. The criteria for prescribing supplements was largely based on age (47%) with only 7% of units interviewed using a weight based set of criteria to initiate supplements. A small number of hospitals had no fixed criteria, and certain hospitals (24%) used both age and weight.

Summary data regarding the appropriateness of each nutritional supplement for a variety of different weights are presented in Figure 1. Table 1 demonstrates the amount of each of the supplements that are delivered purely through feeding with breast milk, fortified breast milk and with a variety of artificial milks.

DISCUSSION

Dosing of all nutritional additives varied greatly across the country[6]. Only a small proportion of units actually achieved dosing within ESPGHAN recommended limits in all supplements[7]. More than 80% of units are in-fact overdosing smaller infants iron potentially causing toxicity.

In general, overdosing of supplements was seen in smaller babies. Larger babies are more commonly receiving doses within the recommended limits. However, the criterion was seen to be based on either birth weight, gestational age or both. ESPGHAN recommends that the infant's dry weight should be used when calculating the dose of supplements[5]. This would mean weighing the baby on a regular basis and adjusting doses accordingly. This practice was not being done in any unit surveyed; doses calculated from birth seem to remain static until discontinued.

Whilst there is clearly no national policy on this issue, there are local networks that carry guidance. Whilst it was outside the scope of this study to investigate these in great detail, the local network in Greater Manchester included a total of 8 units surveyed. Not only did the dose of vitamin A vary but units were also using different brands. Supplementing with folic acid was completely absent in one hospital but the use of iron was consistent. This highlights that current practice is clearly leading to massive variations in both strategy and outcome for babies. With such wide variation in dosing and differing criteria for initiation there is great potential for causing harm to infants, from either insufficient or excessive supplementation. Consistent dosing and one policy for all feed types are also not ideal and can put smaller babies in particular at risk.

Table 1 highlights certain dosing issues that could become tenants of a national policy. It is clear that neonates on preterm formula generally do not need

further vitamin A, folic acid or iron supplementation, but require vitamin D. Neonates on EBM will require all additional supplementation, but those on fortifier will only require iron supplements. It seems that iron supplementation is not indicated for any babies on artificial formulas, as changing requirements have been considered in the changing constituents of preterm *vs* term formulations. It is also important to assess whether the supplements need to continue on discharge as both requirements and content of formulas change with age.

These principles and the huge variation in practical prescribing that have been highlighted by this study support the need for a standardised supplementation regime based on available evidence, with arrangements to update regular to consider changes in artificial formulas and fortification. This will allow the nutritional needs of infants to be met in an appropriate and safe manner. Further research is indicated to assess if similar problems exists in other countries.

There is significant heterogeneity in neonatal policies when prescribing supplements to neonates. National policies which take international guidance into account are recommended. Further research is indicated to assess if similar problems exists in other countries.

COMMENTS

Background

Nutritional requirements amongst preterm and term neonates differ from older infants and change rapidly. Preterm infants have higher nutrient requirements than term infants but inappropriate or absent supplementation can be detrimental to their health.

Research frontiers

There are currently no national guidelines on nutritional supplementation, although there is international guidance from ESPGHAN.

Innovations and breakthroughs

This study confirms that despite international guidance that is evidence informed, practice across the country does not align to this or any prescribed guidance. Indeed, practice varies significantly and this potential means neonates may be under or overdosing on supplements.

Applications

It is advised that readers consider the evidence base of their local guidance and how this compares to national and international guidance.

Terminology

ESPGHAN: European society of Paediatric Gastroenterology, Hepatology and Nutrition.

Peer-review

In the paper, the authors present a useful and interesting study regarding nutritional supplementation in preterm babies in the United Kingdom.

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ORIGINAL ARTICLE

Observational Study

Hypothesis on supine sleep, sudden infant death syndrome reduction and association with increasing autism incidence

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Abstract

AIM: To identify a hypothesis on: Supine sleep, sudden infant death syndrome (SIDS) reduction and association with increasing autism incidence.

METHODS: Literature was searched for autism spectrum disorder incidence time trends, with correlation of change-points matching supine sleep campaigns. A mechanistic model expanding the hypothesis was constructed based on further review of epidemiological and other literature on autism.

RESULTS: In five countries (Denmark, United Kingdom, Australia, Israel, United States) with published time trends of autism, change-points coinciding with supine sleep campaigns were identified. The model proposes that supine sleep does not directly cause autism, but increases the likelihood of expression of a subset of autistic criteria in individuals with genetic susceptibility, thereby specifically increasing the incidence of autism without intellectual disability.

CONCLUSION: Supine sleep is likely a physiological stressor, that does reduce SIDS, but at the cost of impact on emotional and social development in the population, a portion of which will be susceptible to, and consequently express autism. A re-evaluation of all benefits and harms of supine sleep is warranted. If the SIDS mechanism proposed and autism model presented can be verified, the research agenda may be better directed, in order to further decrease SIDS, and reduce autism incidence.

Key words: Autism; Autism spectrum disorder; Incidence; Prevalence; Prone sleep; Sudden infant death syndrome; Supine sleep; Time trends

Core tip: An earlier article presents evidence that supine sleep is a stressor, with sympathetic arousal that protects infants with defects in auto-resuscitation from sudden infant death syndrome. This article argues that a possible side-effect in the population being subjected to supine sleep is an increase in the expression of features contributing to diagnosis of autism spectrum disorder. In a literature search, five countries were identified (Denmark, United Kingdom, Australia, Israel, United States) with published time trends of autism, and with change-points coinciding with supine sleep campaigns. The stressor hypothesis for both conditions are amenable to testing, a better understanding of both is likely to improve outcomes.

Bergman NJ. Hypothesis on supine sleep, sudden infant death syndrome reduction and association with increasing autism incidence. *World J Clin Pediatr* 2016; 5(3): 330-342 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i3/330.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i3.330

INTRODUCTION

Supine sleep campaigns have successfully achieved global reductions in sudden infant death syndrome (SIDS), which is well documented in 13 countries[1]. In all these countries the reduction was fairly immediate and in proportion to the population uptake of supine sleep following the public health messages. Reductions achieved a plateau, somewhat higher in the United States than in Scandinavia[2]. Continued intensive supine sleep messages have not lowered mortality further. Indeed, in the United States unexplained infant deaths appear to have increased[3]. The underlying mechanism for SIDS has not been explained, nor the mechanism whereby prone sleep exerts a potentially harmful effect. That prone sleep is harmful has indeed been the assumption, since the association was so clear.

This author has recently presented a hypothesis for the mechanisms of SIDS and the protective mechanism of supine sleep[4]. Briefly, this hypothesis elaborates on the Triple Risk Model for SIDS[5], the three aspects being an underlying vulnerability, a critical developmental period, and an exogenous stressor or risk factor. The key element of this model is that there is an underlying defect: The great majority of SIDS cases have identified brainstem abnormalities, which have not yet been found in controls[5,6]. This author proposes that these defects are specific to various stages of auto-resuscitation[7], and it is the failure of these which is the proximal or immediate cause of SIDS. Tobacco specifically augments defects in the gasping mechanism that initiates auto-resuscitation[8]. However, at an intermediate level of causation, auto-resuscitation is a necessary response to "adverse autonomic events" (AAE), whereby the autonomically immature organism responds in a primitive reptilian autonomic defence style, through a purely parasympathetic discharge orchestrated by the ventrolateral periaqueductal gray matter[9]. This is not compatible with mammalian physiology, therefore a robust auto-resuscitation mechanism is activated. Distal mechanisms include those that induce the AAEs, or conversely reduce them, along with the critical period and the risk factors of the Triple Risk Model. In healthy infants without defect, such AAE's appear to be common, and auto-resuscitation is robust. REM sleep processes negative emotions[10], and is likely the key period of SIDS risk[11,12] with increasing frequency of AAEs. In SIDS subjects, neural gliosis suggests that there have been repeated episodes of "near-misses" with hypoxic damage, prior to a lethal event[13]. It is possible that the same defects in serotonin metabolism identified in SIDS cases may contribute also to sleep disruption, increased REM sleep and decreased quiet sleep has been documented in such cases. Further, serotonin is also involved in anxiety and autonomic arousal[14], which may contribute further to increased AAE.

The association with prone sleep has made it the focus of research as to mechanisms of harm. No such harmful effects have been ascertained. This author argues from a biologically based developmental paradigm, that prone sleep is in fact the normal and healthy form of sleep[4], as a near universal mammalian phenomenon (exceptions include bats and sloths). Supine sleep in human infants qualifies as a stressor in a number of respects, primarily in producing a raised level of state organisation, and autonomic arousal[4]. This is indeed protective for such infants that have a brainstem defect, the effect may be due to decreased frequency of REM sleep, but perhaps more through an element of sympathetic autonomic stressor arousal, that counteracts the primitive parasympathetic dissociation defence mechanism[4].

The defect has not been found in post-mortem control cases[6], and SIDS qualifies as a "rare disease"[15]. The lethality of the defect is clearly not absolute, otherwise it would not be responsive to supine sleep. Conjecture can be based on existing data: in the United States neonatal mortality has halved, this would fit a population with a defect prevalence of 1.0/1000 with a 50% lethality. Sweden had a mortality around 1.0/1000, this has fallen to 0.25/1000; perhaps a 5/1000 defect prevalence with a 20% lethality reduced to 5% by supine sleep. The number needed to treat from such a "treatment" is high, perhaps above 1000. Clearly, current information does not allow an exact figure, but this is likely the order of magnitude, or else controls with defect would be found.

Consideration should then be given to potential side-effects of such an intervention applied to a whole population. Plagiocephaly was identified early[16], occurring in 1 of 60 supine sleeping infants, but will only

rarely have long lasting major impact. More importantly, supine sleep in the first months of life leads to delayed motor development at 6 mo and up to a year[4,17]. Recent developments in epigenetics and developmental neuroscience have relevance here. Prolonged stressor effects result in elevated cortisol levels that mediate gene methylation changes during sensitive periods of early development. "Perinatal life is a critical time for DNA methylation and for susceptibility to environmental factors"[18], methylation generally down-regulates genes, with adverse effects[18]. Sleep cyclicity is another factor essential for the development of healthy neuronal circuits[19]. Supine sleep may therefore have two separate mechanisms that disrupt early development, as evidenced by delayed motor development.

The first two months of life are a critical period for socio-emotional development[20]. This entails neural circuitry from the amygdala and associated limbic structures (emotional brain) to the medial and orbito-prefrontal cortex and executive function, also called the social brain[20]. The establishment of early resilience requires that social oxytocin circuits are connected also to reward-related dopamine circuits[21], a likely consequence of early bonding and secure attachment. A predictable consequence of such disruption is autism spectrum disorder (ASD), from here just "autism". Autism has recently been redefined in the DSM-5[22], encompassing persistent deficits in social communication and interaction, along with restricted and repetitive patterns of behaviour, beginning in early childhood and impairing everyday functioning. The emotional social deficit has been attributed to methylation of oxytocin receptors[18,23], and repetitive behaviours may be attributable to dopamine pathway disruption[24,25].

There has been extensive debate in the literature, with some arguing that the increase in autism is due to diagnostic changes and other factors[26,27]. These include methodological variations in conducting surveys[26,28], definitions of autism displaying variability[29] (including new definition in DSM-5, predicted by some to decrease the identified incidence[30,31], or make little difference[32-34]), broadening of diagnostic concepts[27], increased awareness[35-37], diagnostic substitution[38,39], and altered ranking of co-morbidities[28,40]. This debate has led to some relevant reflection: Hrdlicka and Dudova[41] argue there is a need for a "broader model of social disorders". While "autism" as a diagnosis may be welcomed by parents seeking economic support for care of a challenged child, autism could be seen as a smaller piece of a broader group of "social inhibition disorders"[41], all of which require support without discrimination[28,40,42].

The above notwithstanding, "a significant portion of the time trend remains unexplained"[43], an actual increase cannot be ruled out[43-47]. Keyes *et al*[48] analysed Californian data by birth cohorts, showing a consistent increase over time, with no evidence of an characteristic factor contributing to increase. The Autism and Developmental Disabilities Monitoring Network (ADDM)[49] likewise reports on birth cohorts, using a standardised approach in case finding and diagnosis for self-selected sites in the United States, incidence has risen from 6.6 to 14.7 (1994 to 2002 birth cohorts).

The hypothesis presented in this paper assumes that a portion of the increased incidence of autism is real, and proposes that supine sleep is contributing to that real increase. Since supine sleep campaigns have been introduced in many countries, with measurable change in infant sleeping position in the community, such change should according to this hypothesis be reflected in change points in the incidence of autism, attributable to "change in risk factor prevalence"[50]. Further, only susceptible infants will express such autism, therefore an incidence plateau should be achieved within a time period that matches the sleeping behaviour change in the community. Establishing this requires accurate data based on birth cohorts. Most cases are believed to be diagnosed by the age of 8 years[49], although current trends do show that additional cases are diagnosed in the teen years[51].

MATERIALS AND METHODS

A literature search was undertaken for published incidence or prevalence data on autism for countries with clear dates for supine sleep campaigns, and with time line series that straddle a period before and after such campaigns. The focus period was the decade before supine sleep campaigns (1980's), through the campaign decade, and for the decade after (2000's), allowing for full expression of incidence. Data on actual sleep position in community over time are scarce[42], as reported in author's previous paper[4], aligning to such data would be preferable otherwise. Search was conducted through PubMed, using terms "autism" or "ASD", with "incidence", "prevalence" and "trends". This was followed up in Google Scholar, and subsequent internet searches on key words found in articles. Data were collated in Excel in country-specific graphs. Statistical analysis was not undertaken, merely identification of change points aligned to supine sleep campaigns.

Based on the putative insight that supine sleep is a stressor, a mechanistic hypothesis for increase in autism was generated. This integrates genetics, epigenetics, stress biology and developmental neuroscience with current theories and understanding of ASD.

RESULTS

Epidemiological findings

Data for autism incidence from five countries are presented in Table 1 and Figure 1, with incidence time series straddling supine sleep campaigns.

There is a broadly consistent temporal relationship

Table 1 Countries with time series prevalence data on supine sleep and autism

Country	Campaign	Supine sleep data	Ref.
Denmark	1990	-	[1]Madsen *et al*[45] Parner *et al*[109]
United Kingdom	1991	Gilbert *et al*[42]	[1]Taylor *et al*[52] Blaxill[64] Smeeth *et al*[112]
Australia	1991	-	[1]Nassar *et al*[53] Atladottir *et al*[51] Parner *et al*[109]
Israel	1993	Inbar *et al*[115] Tauman *et al*[116]	[1]Gal *et al*[55]
United Sates	1994	Willinger *et al*[65]	Blaxill[64] Boyle *et al*[56] [1]MMWR[49] Keyes *et al*[48]

[1]References provide data used in Figure 1. MMWR: Morbidity and Mortality Weekly Report.

between supine sleep campaigns and the change-points for autism increase for Denmark in 1990[45], United Kingdom in 1991[52], Australia in 1991[53], Israel in 1993[54,55], and the United States in 1994[49,56]. Note the data for Israel are as reported from a national database for medical insurance cover, so rather than the usual 8 years, the mean age at diagnosis was 39 mo[54], providing a close match of change-point with supine sleep campaign date. Uptake of supine sleep following launch of campaigns[42] correlates with rates of later autism increase. The change-points span a five-year period in five separate countries, making any other extrinsic or secular factor less likely.

The quality of supine sleep data is poor[42], but where such exists there is an improved correlation, since population supine sleep increase started before actual campaigns in the United States, United Kingdom and Australia. Norway has long term supine sleep data, the only data known to author that precedes safe sleep campaigns, based on a retrospective survey of parent recall conducted in 1992 and going back 25 years[57]. This showed a correlation of decreasing supine sleep with increasing SIDS, and a corresponding decrease of SIDS following supine sleep campaign[58]. Autism data from earlier years was not found, published data does not cover the putative change-point[59-61], a comment from such later reports is that this represents a "tenfold increase in all ASD" compared to previous reports[59].

McDonald and Paul[62] "used data sets from Denmark, California, Japan, and a worldwide composite of studies" on autism, seeking change-points that may assist in identifying an "exposure to controllable exogenous stressors". They identified a worldwide change-point around 1988-1989. They identify Japan as being alone in having no change-point, this may reflect the patchy uptake of supine sleep from independent prefectures[63], with no standardised denominators for comparisons. Blaxill[64] provides a detailed review of

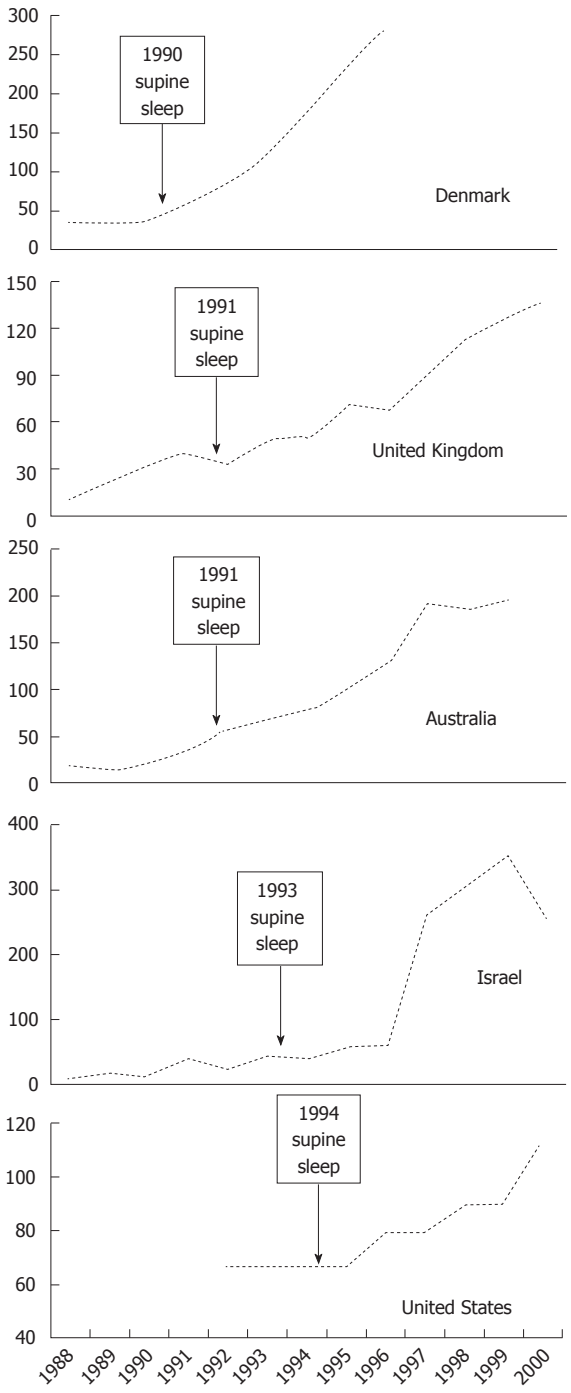

Figure 1 Epidemiological associations with autism rates (dashed line, rate per 10000) and supine sleep campaigns (block arrows). Autism incidence plotted by reported year of birth cohort, except Israel which is reported from year of insurance claim for infants average 39 mo old (source references in Table 1).

time trends in autism prevalence in the United Kingdom and the United States. These results show slight increases preceding the formal campaigns, which may reflect population uptake of supine sleep prior to formal campaigns, or other factors. For the United Kingdom, Gilbert *et al*[42] shows change before 1990, for the United States this can be seen in the NISP data for sleeping position[65] and CDC data for SIDS[66]. Note however

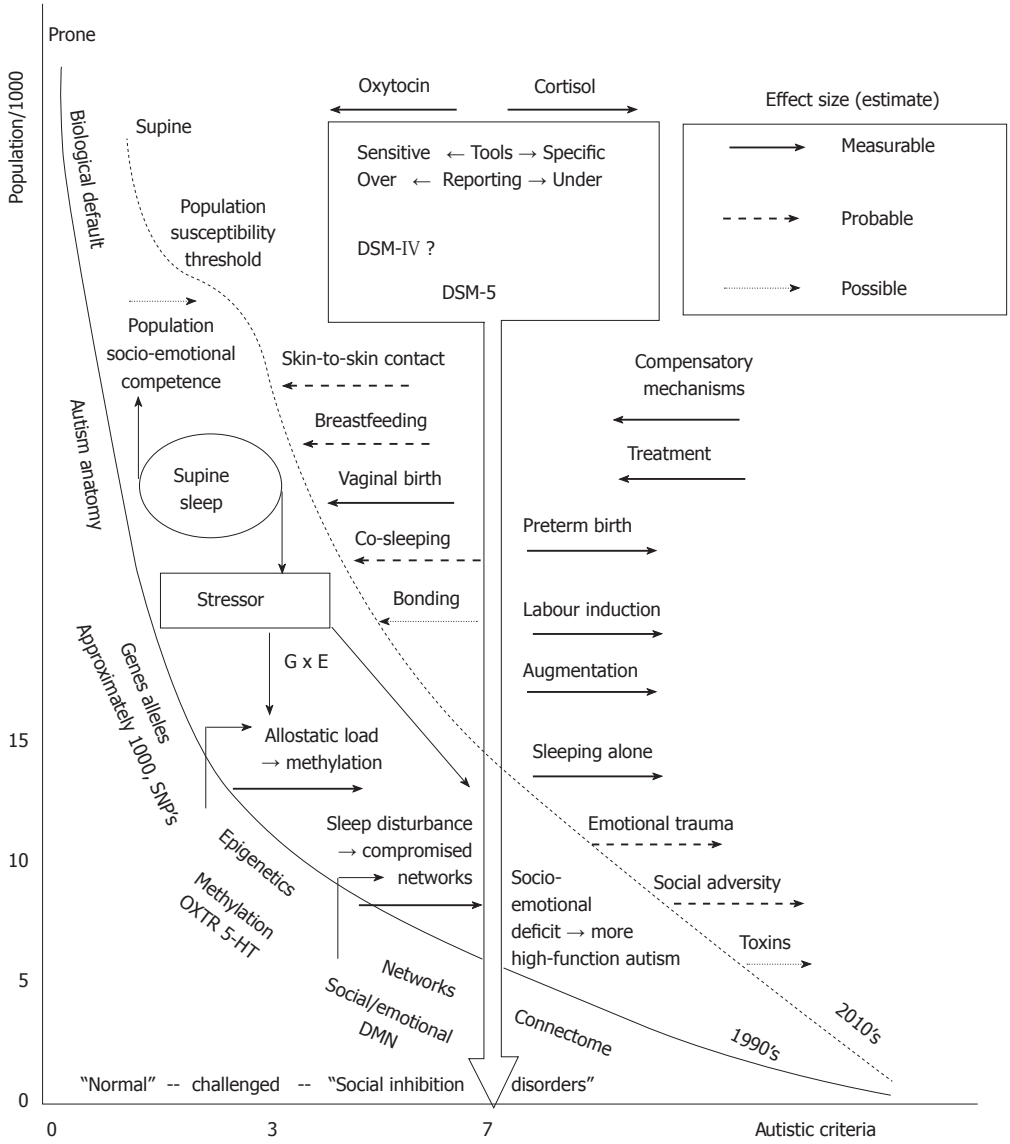

Figure 2 Model for proposed mechanisms of impact of supine sleep on expression of autistic criteria in a population. Autism diagnosis according to DSM-5 is indicated by block arrow, issues debated concerning real incidence in arrow box. Solid black line represents "1990's" incidence of 8 years old final and actual criteria, dashed black line represents the rightward shift that supine sleep is proposed to have made to current time ("2010's"), with mechanisms indicated between the curves, see text for details. Autism incidence increases by right shift of the curve along the X axis, as reflected on Y axis. Other factors identified that increase and decrease expression of autistic criteria are to the right of the dashed curve. 5-HT: Serotonin; DMN: Default mode network; DSM: Diagnostic and Statistical Manual; G x E: Gene environment interaction; OXTR: Oxytocin receptor.

that countries with clear change-points all had supine sleep campaigns with launch dates.

Resulting model for hypothesis on supine sleep and autism

It is acknowledged that the quality of this data leaves much to be desired. However, the original case for association with prone sleep and SIDS was based on similar quality data. In either case, an epidemiological association requires a biologically plausible hypothesis of causation, which in turn can be tested. The hypothesis for supine sleep's effect on autism incidence is presented as an integrated mechanism model in Figure 2. The "busyness" of the model is commensurate with the complexity of the subject. The population incidence is on the Y axis, plotted against the sum of individual symptom criteria of autism on the X axis. The majority of the population may have one or no autistic feature. However numbers of "healthy" people may have autistic features[67], but are coping well and without "impaired everyday functioning" (criteria D, DSM-5). Some may have impaired functioning and have some autistic features, perhaps part of another "social inhibition disorder"[41]. Given the high heritability and variable expression of "autism genes", relatives of confirmed cases are likely to be clustered to the right of the larger population, closer to the diagnostic cut-off[68].

The DSM-5 does not provide diagnostic cut-off as a numeric, nor any sense of severity, but an arbitrary score of 7 is here marked by the blocked arrow as the

diagnostic cut-off point for autism. The diagnostic cut-off line can be (administratively) shifted separately from the reality in the population. The new DSM-5 is believed to decrease the incidence[30], and is therefore more to the right than the DSM-Ⅳ cut-off. Diagnostic and screening tools, and new International Classification of Diseases editions, with various sensitivity and specificity, may be to the left or right of the block arrow. This could be depicted as a zone, and even be quantified, but makes little difference to the hypothesis presented here.

The curves represent the "population autistic criteria", but could equally be seen as the "population emotional and social competence curves"; the focus of this paper is however on the extreme right of the curve where autism is diagnosed. Aligning with the ADDM, the model is regarded as applying to 8 years old, assuming all cases of autism are expressed or diagnosed by this age. The solid curve represents the "true" or real incidence of "population autistic criteria" in the population in the early 1990's, the dashed line the real incidence in the 2010's. Prior under-diagnosis would provide incidence to the left of solid line curve, later over-diagnosis provides figures to the right of the dashed curve. For realistic scale the curves are approximately aligned to the DSM-5 diagnostic cut-off with reported ADDM incidence data of 1992 and 2002 birth cohorts[49]. The curves should however be seen as a generic and conceptual model. Effectively this presents autism as having doubled in incidence during this period, conveyed by a right shift of the "population autistic criteria" curve. Note this is a modest increase in comparison to other data sources, factoring in secular artefactual increases, as described in the introduction.

To the left of the solid curve are itemised basic components of autism etiology and pathology. Space precludes a description of these, review references are provided on "autism anatomy"[69], "genes and alleles"[70-74], "epigenetics"[18,23], "networks"[75], and the "connectome"[76,77]. The latter suggests that autism is a neural network disease, providing a unifying view of the genes, epigenes, effects of environment, hormones and receptors and all the anatomical parts identified. Underlying genetic defects are necessary, and in some cases sufficient, to "cause" autism[72,78].

Right shift - exacerbating factors

To the right of the block arrow are external factors other than the hypothesised effect of supine sleep that are known or believed to increase autism incidence (right shift of curve, dashed line). This hypothesis does not address prenatal adverse factors.

Being born preterm exposes the developing brain to an environment that makes profound changes to a broad range of genes, even in children who do not go on to develop autism[79], and even those born late preterm[80]. The incidence of preterm birth has increased in the ten year period depicted, but so have also efforts to improve the quality of care: Preterm birth may therefore account for a small portion of the increase depicted.

In a population sample (North Carolina) a significant effect on autism was found following induction and augmentation of labour[81]. Caesarean birth can for similar reasons be included in this argument[82]. Though of relatively short duration, these interventions directly disrupt key oxytocin circuits of the connectome in autism[83,84]. These interventions may interfere with the normal pulsatile function of oxytocin[85]. Oxytocin administration has been in use for many years preceding 1994, only in so far as the use has increased after 1994 may this have made a minor contribution to the observed increase. In terms of gene-environment interaction[86], induction and augmentation involve approximately a one day "adversity dose". A single anaesthetic and surgical procedure for an infant does not appear to be enough "adversity dose" to impact the curve[87]. Schieve *et al*[50] review evidence on factors associated with autism as above, and have quantified the possible impact the above factors may have had on the increase in autism, concluding their contribution has been negligible.

"Toxic stress" as defined in early childhood development[88] would also produce a right shift. However, much of the underlying etiology of autism begins in the uterine and early birth period[78]. Even in great adversity, if the early uterine environment and the early perinatal period was "good-enough", some resilience will be in place. The contribution to increasing autism may thus be relatively small, even if many other developmental and social ills follow. This hypothesis requires that "toxic stress" be expressed early to increase the incidence of autism. Repeated emotional and social traumas during the first year of life have been linked to autism[89]. Toxic stress during the First 1000 Days will certainly further exacerbate early changes that took place[90], and so the sum contribution of childhood adversity to right shift is at most moderate, but more likely mild as other factors preceded.

A large number of environmental factors and toxins have been proposed as contributing to the increase in autism. Many of them are plausible in so far as they can impact on epigenetic mechanisms and neurodevelopmental processes. However none of them can easily be linked to the increase since the early 1990's. A possible contributor is advancing parental age[91], which may be acting through increased genetic and allelic changes.

Left shift - protective factors

To the left of the block arrow are protective factors. Skin-to-skin contact and breastfeeding support oxytocin networks[92], so shift the curve to the left. The paradigm could however be that they represent the basic biologically normal condition of the original and normative curve for "population autistic criteria" (prone sleep, solid curve), in which autism is infrequently caused

solely by adverse genomic phenomena. Prone sleep can be regarded as part of a package of normal biological expectation of human reproduction. Co-sleeping is controversial, but is an integral part of human life course sciences[93]. In the context of preterm birth, and perhaps family history of autistic features, consciously increasing the dose of leftward factors (enhancing oxytocin) may be an informed choice for some parents. Higher maternal intake of folate and some other nutrients may lower autism risk[94]. In the ecobiodevelopmental model presented by Shonkoff *et al*[88], "life science theory" is presented as a key concept alongside epigenetics and neuroscience. In the model, all of the protective factors listed are in fact directly out of "life science theory". This encompasses a holistic approach to reproduction, where no single factor acts in isolation.

Compensatory mechanisms develop in the majority of autism cases later in life[95], but some may be apparent and effective at 8 years, and provide a left shift to the curve. Successful treatment likewise, if only by accomplishing everyday functioning: It appears the underlying neurology does not change that much[96].

Biological rationale for hypothesised impact of supine sleep

The hypothesis that supine sleep produces rightward shift, *i.e.*, increases autism incidence, is depicted between the solid and dashed curves. Supine sleep can be seen as a population-wide novel environmental factor introduced in the early 1990's, before which the solid line of the model represents the baseline "population autism criteria".

Supine sleep may bring two separate and distinct stressor disruptions to early development. In the context of the current public health recommendations, it does so over an extended and critical period, more so than many of the "right shifting" factors described above. First is the autonomic stressor effect, sufficient to cause motor developmental delay[17]. High sympathetic tone elevates cortisol and other mediators, which may lead to gene methylation[90,97]. Oxytocin receptor gene methylation has been measured accurately[89], showing a correlation with autism severity, with methylation reported as percentages[98]. Changes may be acute or act over time, as described in the allostasis and allostatic load concept[86]. The Developmental Origins of Health And Disease concept clarifies that developmental disruptions caused by stressors occur at critical periods during development, impacting only the specific developmental goal of that time[99]. One result of stress in the period from 0-2 mo may be disruption of socio-emotional networks, and other parts of the connectome implicated in autism[76]. The default mode network is implicated in autism, this may likely be disturbed antenatally[72,78,100], but could be further dysregulated by the stress of supine sleep.

Second, good quality sleep cycling is necessary for consolidation of memory in adults[101], and even more for neurodevelopment in infants and children[19]. Supine sleep disturbs sleep architecture, with autonomic effects equivalent to anxious arousal and with adverse effect on normal sleep cyclicity[102]. The consolidation and integration of diverse neural networks is necessary for developing the capacities required for Theory of Mind[103]. Oxytocin is core to developing emotional and social networks, and future Theory of Mind[104]. Birth itself and early bonding are highly reliant on oxytocin, which is critical to the parturition process, to early breastfeeding and to bonding[105,106]. Breastfeeding and early bonding are maintained by skin-to-skin contact, which in and of itself supports oxytocin, and the neurobiological processes associated with oxytocin. Continued contact allows mother to be sensitive and attuned to her infant's cues[107], and the infant to establish a trajectory toward a secure attachment.

Ecologically, supine sleep may be part of a package that acts synergistically to disrupt development. Supine sleep and swaddling often go together, the latter per se increases stress, even when practised only the first day there is a measurable adverse impact one year later[108]. Life sciences theory affirms infants should never sleep alone, and maternal-infant separation has been shown to increase autonomic arousal[102]. Other co-factors do undoubtedly exist, but for the current paper, supine sleep is identified as a likely contributor to developmental disruption leading to the increase in autism.

Supine sleep does not "cause" autism in and of itself, the model proposes it as one of many external risk factors, operating during a critical period, and requiring underlying vulnerability (genetic susceptibility), analogous to the Triple Risk Model for SIDS. In the model therefore, it is proposed that supine sleep is exerting at least a moderate effect in shifting the curve to the right, thereby increasing the incidence of autism.

DISCUSSION

This hypothesis is consistent with the changing profile of the autism spectrum in the last two decades. The actual numbers of cases with lower IQ and profound developmental disruption has stayed approximately the same[109,110], but the proportion with high functioning and high IQ has increased[48,53]. The first four months are a critical period for socio-emotional development, not IQ. This is also consistent with the observation that many cases are only diagnosed after some years, despite public health efforts at "early diagnosis". The Theory of Mind concept comes with a prolonged "latent" period[103], and when the primary stressor only starts after birth, as opposed to early and midfetal life[72,78], the expression and recognition of autism may be similarly delayed.

Denmark[45] and Japan[110] are countries that have

specifically studied autism in relation to vaccines, demonstrating no effect of the latter. Both however document similar increase in autism incidence (after thimerosal cessation), and in contexts where similar diagnostic criteria have been used consistently. The Danish data is robust, being based on total population inpatient and outpatient psychiatric records, with the population register as denominator. Incidence prior to 1990 was stable, after which there was an increase[45], such an increase may indeed be caused by increased community awareness. Hansen *et al*[111] attribute 60% of increase in Denmark to change in diagnostic criteria in 1994 and inclusion of outpatients in 1995. In Yokohoma Japan, in a defined catchment with dedicated mental health services and standardised tools, reported incidence increased from 40/1000 between 1988 and 1992, to 117.2 for those born in 1996[110]. Robust data also come from the United Kingdom (United Kingdom General Practice Research Database)[112], showing a five-fold increase from 1988 through to 2001, after which "incidence and prevalence rates in 8-year old children reached a plateau… and remained steady through 2010"[52]. This appears to apply also for Israel and Australia, showing a levelling off of the autism increase[52-54], possibly also in the United States since 2001[113], with supine sleep rates remaining stable. This is consistent with the hypothesis presented in that the population dose of supine sleep cannot increase much more (96% in 1996 in the United Kingdom)[42], and the full effect of susceptibility from this one proposed contributory factor is maximised. The hypothesis presented here for autism may equally apply to all or some of social inhibition disorders.

In parallel to autism, SIDS reduction reached a plateau in the United States and elsewhere. Apart from the finite stressor dose effect, another reason for this may be that for both SIDS and autism there are rare underlying genetic susceptibilities. Under the most ideal conditions of low environmental risk factors, both autism and SIDS would therefore still occur, though rarely. Expression of autism and SIDS genes are exacerbated by adverse environments. In autism, supine sleep thereby exerts an epigenetic and developmental mechanism that disrupts the connectome. In SIDS, supine sleep is working as a protective mechanism on already disrupted neural networks. Since supine sleep is a stressor, and is acting at an intermediate level of causation, it is an imperfect intervention, and can only prevent a finite portion of SIDS mortality, hence the plateau. In the absence of new risk factor changes, it is likely that all current increase in autism is secular, as presented for Sweden[28].

Implications and future directions

In presenting this integrated mechanism review as a hypothesis to this readership, the intention is not to make any kind of public health recommendation, this would be premature, and beyond the scope of this paper. The implications are however considerable, and merit urgent attention: A reassessment is warranted[114]. The epidemiological arguments presented should be scrutinised in data sources globally, with respect to sleep position, autism and SIDS. The proposed model identifies some of the complexity involved, in that exacerbating factors over and above supine sleep need to be teased out, as well as protective factors.

The primary contention that supine sleep is a stressor is amenable to testing. Current clinical and physiological studies already provide ample evidence that supine sleep causes autonomic arousal, and other stressor effects, but this finding has been interpreted as healthy. It may be interpreted as harmful if methylation of specific receptors related to autism could be correlated to supine sleep position. A purely epidemiological approach could be to select cohorts that complied or did not comply to supine sleep recommendations, and compare autism rates, first retrospectively, and then perhaps prospectively. Ethically the latter might be possible if the prone cohort had additional protective measures against SIDS. Genome-wide sequencing for methylation, and focusing on methylation of specific genes identified (*e.g.*, for oxytocin receptors), could establish presence or absence of harmful stress. Other measures of stress or allostatic load, and socio-emotional outcome measures, may confirm or refute the hypothesis. The prevalence of SIDS defects and autism genes should be quantified. This may allow a new perspective on the risk benefit ratio in terms of quantifying SIDS decrease against possible autism increase. More research could focus on practical methods to identify neonates with SIDS and autism susceptibility, allowing for differentiated care options.

In conclusion, it is proposed that there may be an association between supine sleep and autism incidence increase. No other potential stressor than supine sleep is known to have been introduced globally in widely separated regions, nor one that matches the temporal patterns described here. The biological rationale proposed is that supine sleep may be a stressor, increasing gene methylation in, and disrupting needed sleep cyclicity for developing socio-emotional neural circuits. As stated above, it would be premature to offer any kind of clinical or parenting advice based on this hypothesis. Rather, the SIDS mechanism proposed and autism model presented should be urgently examined and researched, then the future research agenda may be better directed, toward better care and advice to parents and health departments in order to further decrease SIDS, and reduce autism incidence.

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COMMENTS

Background

Autism has increased since the early 1990's. Sudden infant death syndrome (SIDS) decreased only to level off after supine sleep campaigns in the 1990's. Currently supine sleep for neonates and infants is very strongly encouraged by public health authorities. However, the mechanism whereby supine sleep achieves SIDS reduction is totally unknown. This article suggests that supine sleep achieves SIDS reduction through a stressor mechanism, which will have the unintended side-effect of increasing autistic criteria in sensitive individuals of the population. The relevance of this article is that a re-evaluation of the fields of both SIDS and autism may lead to research that improves outcomes for both.

Research frontiers

Current research into SIDS includes identifying the mechanism of harm from prone sleep; this article suggests such research is fruitless. In terms of autism, a more fruitful direction of research suggested by this study is developmental stress biology.

Innovations and breakthroughs

The major innovative thinking of this article lies in its re-appraisal of prone sleep as the healthy physiological sleep. This can be seen as an application of "rare disease epidemiology". For example, the rare side-effects of vaccines given to the whole population are accepted since the risks of those are greatly outweighed by the benefits. In the case of supine sleep campaigns, the potential risks have not been properly evaluated. Increasing autistic criteria in the population should be regarded as a major risk factor, which requires urgent and accurate quantification in order to properly balance benefit and risk of supine sleep.

Applications

These findings emphasise that for both conditions, rare underlying genetic susceptibility is fundamental, and this will be a fruitful direction of research. The mechanistic model published previously on SIDS, and the model in this article on autism, allow more focused preventive and therapeutic application. In SIDS for example, a cardiorespiratory based physiological screening test is a possibility. In autism, genetic screening could identify a smaller part of the population for which family counselling allowing may result in advice to provide prone sleep, based on "informed choice".

Terminology

The term autism is used for brevity, where the correct terminology is autism spectrum disorder. This is currently best understood as a "connectome" disorder, this term refers to brain networks and their interactions, shared areas of high neural network traffic are referred to as hubs.

Peer-review

The topic is really interesting and the manuscript is clear and well organized.

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ORIGINAL ARTICLE

Observational Study

Solitary rectal ulcer syndrome: Is it really a rare condition in children?

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Abstract

AIM: To evaluate the clinicopathologic characteristics of the children with solitary rectal ulcer.

METHODS: Fifty-five children with a confirmed diagnosis of solitary rectal ulcer were studied in a period of 11 years from March 2003 to March 2014. All data were collected from the patients, their parents and medical records in the hospital.

RESULTS: From 55 studied patients, 41 were male (74.5%) and 14 female (25.5%). The mean age of the patients was 10.4 ± 3.7 years and the average time period from the beginning of symptoms to diagnosis of solitary rectal ulcer was 15.5 ± 11.2 mo. The most common clinical symptoms in our patients were rectal bleeding (n = 54, 98.2%) and straining during defecation or forceful defecation (n = 50, 90.9%). Other symptoms were as follows respectively: Sense of incomplete evacuation (n = 34, 61.8%), mucorrhea (n = 29, 52.7%), constipation (n = 14, 25.4%), tenesmus and cramping (n = 10, 18.2%), diarrhea (n = 9, 16.4%), and rectal pain (n = 5, 9.1%). The colonoscopic examination revealed 67.3% ulcer, 12.7% polypoid lesions, 10.9% erythema, 7.3% both polypoid lesions and ulcer, and 1.8% normal. Most of the lesions were in the rectosigmoid area at a distance of 4-6 cm from the anal margin. Finally, 69.8% of the patients recovered successfully with conservative, medical and surgical management.

CONCLUSION: The study revealed that solitary rectal ulcer is not so uncommon despite what was seen in previous studies. As the most common symptom was rectal bleeding, clinicians and pathologists should be familiar with this disorder and common symptoms in order to prevent its complications with early diagnosis.

Key words: Rectal bleeding; Children; Solitary ulcer; Colonoscopy; Forceful defecation

Core tip: What is known? (1) solitary rectal ulcer is considered a rare condition in children; (2) there is a small number of case report and small case series in pediatric age group in the literature; and (3) this disorder has not been well known in children, so, their symptoms can be confused with other more common diseases. What is new? (1) this study reveals that solitary rectal ulcer is not so uncommon in children; (2) to the best of our knowledge it is the largest pediatric series in the world; and (3) high index of suspicious is needed to think about and diagnosis of this disorder.

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INTRODUCTION

Solitary rectal ulcer has been defined as an infrequent but benign disorder of rectal and sigmoid region which is diagnosed on the basis of clinical symptom and histologic findings[1,2]. Although solitary rectal ulcer is a relatively common disorder in adults, it has been reported as a rare disease in children, so it can be misdiagnosed and troublesome in pediatric cases[3].

The exact cause is not known, but several causes such as trauma, rectal prolapse, ischemia, behavioral disorders such as excessive straining during defecation and rectal manipulation, sexual abuse and disharmony of the pelvic floor muscles during defection may be involved. Patients with this disorder exhibit a range of symptoms; however, a small number of patients can be asymptomatic[2,4-6].

The clinical symptoms in children are similar to adults, but since this disorder has not been well known in children, their symptoms can be confused with more common diseases. For instance, the obstructive symptoms can be viewed by parents as constipation, rectal bleeding may be related to the anal fissure or causes such as juvenile polyps or tenesmus and also rectal bleeding, may be incorrectly diagnosed as inflammatory bowel disease[3].

Colonoscopic findings are not specific and can be similar to other disorders of the rectal and anal area[2]. The histological study of solitary rectal ulcer has a distinct diagnostic appearance including thickening of the mucosal layer with disrupting crypts structure, infiltration of the lamina propria with fibroblasts, muscle and collagen fibers that lead to hypertrophied and disrupted muscularis mucosa which look like fibromuscular obliteration. Diagnosis of solitary rectal ulcer is usually based on the clinical history and histopathological changes from the rectal biopsy.

Before treatment, it is very important to differentiate solitary rectal ulcer from other disorders of the rectum including cancer, Crohn's disease, granulomatous diseases like lymphogranuloma venereum using laboratory facilities[7].

Many treatments have been tried so far, but there is no strong evidence for their effects[7]. It seems that the medical and surgical treatments are not very effective due to the high incidence of recurrence[8].

The first step of treatment is conservative therapy including dietary fiber, fluid intake, behavioral adaptation and use of laxative, which has not been proven to have long term benefits[2,5].

Enema with sucralfate can cover the wounds and act as a protection against harmful substances to heal the wound. Injection of sclerosing agents into the submucosa or rectal space has been useful for the treatment of rectal prolapse in some cases, but the benefits of long term uses need further investigation[5].

Most patients with solitary rectal ulcer have a satisfactory prognosis with treatments such as behavior change in their childhood. Follow up of these patients is necessary in order to improve and sustain treatment method to prevent morbidity and recurrences which lead to the disease progresses to adulthood[3]. The aim of this study was to assess the children diagnosed with solitary rectal ulcer in Southern Iran.

MATERIALS AND METHODS

All of the children including 55 (14 females and 41 males) with final diagnosis of solitary rectal ulcer in Pediatric Gastroenterology Section of Nemazee Hospital affiliated to Shiraz University of Medical Sciences from March 2003 to March 2014 were studied.

The diagnosis of solitary rectal ulcer in our patients was based on the clinical history, colonoscopic and histopathological findings of rectosigmoid biopsies.

The colonoscopies were done under general anesthesia and biopsies were taken from normal and abnormal looking mucosa and all lesions of the rectum and sigmoid colon in all patients. Histopathologic evaluation of all biopsy samples was done by a gastrointestinal pathologist (BG).

After confirming the diagnosis, their information including age and sex, clinical presenting symptoms, colonoscopic and histopathologic findings and also therapeutic modalities and responses to their treatment were retrieved from their registered medical records

and also by phone calls. All of the information obtained from patients' records was registered into the designed collecting data forms; then the analysis of data, was performed according to their age and sex, presenting symptoms, colonoscopic and histopathologic findings and treatment outcome.

This study was approved by the Research Ethics Committee of Shiraz University of Medical Sciences and informed consent was obtained from all the parents or legal guardians.

RESULTS

In these 11 years, 55 children with the final diagnosis of solitary rectal ulcer were evaluated. The mean age of the onset of symptoms in the patients was 9.2 ± 3.4 years. The mean age of the patients at diagnosis was 10.4 ± 3.7 years. The average time from the onset of symptoms to final diagnosis was 15.5 ± 11.2 mo. The youngest and oldest patients at the onset of symptoms were 1.5 and 17 years, respectively. From 55 patients, 14 were female (25.5%) and 41 male (74.5%).

The first clinical finding in all patients except one was rectal bleeding. One patient presented with a history of passing of mucoid stool and had no history of rectal bleeding during the illness.

The most common presenting clinical symptoms of the patients was rectal bleeding (n = 54; 98.2%) and then straining during defecation or forceful defecation (n = 50; 90.9%). Sense of incomplete evacuation was reported in 34 patients (61.8%) and 29 cases had a history of passing mucoid stool (52.7%). Change of bowel habits was seen in some patients as 14 patients were suffering from constipation (25.4%) and 9 patients had a history of diarrhea (16.4%). Although abdominal pain is not an obvious symptom of the disease, 18.2% of the patients were suffering from this problem. Three patients (5.4%) had a history of anal manipulation with fingers, 1 had a history of sexual abuse, and 4 patients (7.3%) had a history of rectal prolapse and the sensation of a mass during defecation.

The colonoscopic studies of 55 patients as recorded in their charts were examined. Colonoscopy was normal in 1 of the patients and showed no specific findings (1.8%). Colonoscopy of 37 patients showed ulcers (67.3%). Among the ulcers, 3 were superficial (8.1%), 1 was circumferential (2.7%), 1 was reported as linear (2.7%), and 1 of them was clean based (2.7%). The others (83.8%) were white based ulcers with erythematous borders and exudates. Seven patients had polypoid lesions (12.7%) which were pedunculated in 3 patients (42.8%). Four patients had both ulcers and polypoid lesions (7.3%). Colonoscopy of 6 patients only showed erythema (10.9%) and there was no obvious ulcer. In colonoscopy of 37 patients only one lesion was seen (67.3%), 7 patients had two lesions (12.7%) and 10 patients showed more than two lesions (18.2%).

The ulcers were registered with different sizes. Most of them were 5-15 mm in diameter.

Table 1 Different treatment protocol and response rate in children with solitary rectal ulcer

Treatment protocol	Number	Percent
Conservative treatment	11	21.6%
Asacol suppositories	23	45.1%
Sucralfate enema	9	17.6%
Alcohole injection	2	3.9%
Methylprednisolone injection	1	1.9%
Rectopexy	5	9.8%

All of the ulcers were localized in the rectosigmoid region. The distance of most of them from the anal margin was 4 to 6 cm, but it was about 13 cm in one of the patients and 20 cm in another one.

The histology findings of patients included ulcer, granulation tissue, inflammation, increasing collagen bands and fibrosis in lamina propria, and sometimes elongation of the crypts, fibrosis, reduction in goblet cells and hyperplastic changes.

The therapeutic information of 51 patients was provided from their reports and by phone calls. Different treatments were offered for different patients based on the severity of the symptoms. Conservative measures including avoidance from excessive straining during defecation, use of high fiber diets and fluids, and use of laxatives (if they had constipation) were recommended to all patients. Eleven patients (21.6%) became completely symptom free with only recommended conservative treatments. In 23 patients (45.1%) who had not responded to the conservative treatments, the use of Asacol suppository was recommended. Nine patients (17.6%) were treated with Sucralfate enema.

The alcohol injection was carried out for 2 patients (3.9%) who had rectal prolapse. Methylprednisolone was injected around the lesion in 1 of the patients. Five patients (9.8%) with persistent solitary rectal ulcer and rectal prolapse were finally treated with laparoscopic ventral rectopexy (Table 1).

From 55 patients, 43 were followed by medical reports and also with phone calls. Thirty patients (69.8%) showed a significant improvement during the follow-up and their symptoms disappeared. Most of these patients (28 patients) had responded to the conservative treatments, Asacol suppositories, and Sucralfate enema and 2 patients were treated with rectopexy. Thirteen patients had still their symptoms (30.2%) at the time of the study.

DISCUSSION

Solitary rectal ulcer is an unusual and uncommon disorder of rectosigmoid region which is mostly seen and reported in adults and is less common in children. This disorder is diagnosed with clinical findings, colonoscopy findings and histology changes[2].

In this study, 55 children with the final diagnosis of solitary rectal ulcer were evaluated in 11 years, and to the best of our knowledge it is the largest pediatric

series in the world.

Most of the patients (74.5%) were male in this study which is similar to other studies and reports on the children with solitary rectal ulcer. In the study by Perito *et al*[9], 9 out of 15 patients were male. Five of 6 children were male in Urganci *et al*[8] study and 9 out of 12 patients were also male in Dehghani *et al*[10] study, but in Blackburn *et al*[3] study, from 8 affected children, 4 were female and 4 were male. However, this predominance in males is only in the pediatric age group and the prevalence of disorder between male and female is the same in adults. It has been even mentioned in some articles that it has more prevalence in the women; so that, from 68 studied patients in Madigan and Morson[7]'s study, 33 were male and 35 were female.

In this study, the youngest and oldest patients were 1.5 and 17 years at the onset of the symptoms. The mean ± SD of the patients was 10.4 ± 3.7 years and the average of time from the beginning of symptoms to diagnosis of solitary rectal ulcer was 15.5 ± 11.2 mo, these results are similar to Blackburn *et al*[3] study in which the mean age of children was 9.87 years and the average time from the onset of the symptoms to diagnosis was 1.73 years. In Urganci *et al*[8] study, the average of time from the onset of symptoms to the diagnosis of disease was reported as 4.7 years; this is longer than this study. In Suresh *et al*[11] study, the age of the youngest patient studied was 1.5 years which is similar to this study.

In this research, the first presenting symptom in most patients was rectal bleeding (98.2%) and then excessive straining during defecation (90.9%). Other problems in order of their prevalence included the sense of incomplete evacuations, mucoid stools, constipation, abdominal pain and tenesmus, diarrhea, and rectal pain. In the study by Suresh *et al*[11] the most common clinical finding of the patients have also been reported as rectal bleeding which has been seen in all 22 patients, but it is expressed that need for blood transfusions in this disorder is low. In another study by Madigan and Morson, the most common clinical symptoms were bleeding from the anus (91%), then mucorrhea, rectal pain, diarrhea and lower abdominal pain[7]. In another study by Blackburn *et al*[3] all of the patients had the history of straining on defecation and 7 of 8 patients had rectal bleeding history. Other symptoms in order of frequency were sense of incomplete evacuation, tenesmus, mucus excretion, constipation, diarrhea and manipulation of the anus for defecation, respectively[3]. According to this study and other related studies, it seems that rectal bleeding is the most common symptom; other less common symptoms were mucorrhea and straining during defecation which can be easily obtained from the patient's history.

The main causes of this disorder are still unknown. In previous studies, it has been concluded that several factors lead to this disorder. In most of the previous studies, it has been stated that the main mechanism of this disorder is mostly excessive straining during defecation which leads to increased intra-abdominal pressure which in turn causes protrusion of the anterior wall of the rectum into the anal canal and puborectalis muscle contraction and continuation of this state leads to trapping the mucus membrane of the anterior wall of the rectum, edema and hyperemia and finally hypoperfusion, ischemia and ulceration[12]. In the present study, more than 90% of patients had excessive straining during defecation which can confirm this problem. In addition to these, 3 patients had the history of anal manipulation with fingers, 1 had the history of sexual abuse and 4 patients had the history of rectal prolapse and sensation of a mass during defecation which is considered as causes of this disorder due to mucosal trauma.

De la Rubia *et al*[1] have reported ischemia as the etiology of this disorder because of the lack of trauma in the studied patients and histologic changes in the course of the disease and have suggested that continuous contraction of the puborectalis muscle during defecation can cause hyperemia, edema, necrosis and ulcer in the mucous membrane of the rectum. Womack *et al*[13] also concluded that the combination of rectal prolapsed and high pressure during defecation cause instability between intra-abdominal pressure and into the rectum which leads to ruptured submucosal vessels and mucosal necrosis[13]. In Dehghani *et al*[10] study, traditional way of defecation has been proposed as the cause of solitary rectal ulcer, which leads to protrusion of the anterior wall of the rectum into the anal canal and then hyperemia, edema and ulcer.

Therefore, according to these studies and the results of the present study, it can be concluded that the combination of high rectal pressure during defecation, the hidden prolapse and insufficient contraction of the puborectalis muscle in addition to trauma which cause direct damages, leads to hyperemia, ischemia, and finally ulceration of the rectal wall and the traditional way of defecation in our geographic region in Iran, can intensify these factors; it is the reason for high prevalence of this disease. It has been recommended that defecography and anorectal manometry should be performed in all children with solitary rectal ulcer to define the primary pathophysiological abnormality and to select the most appropriate treatment protocol. These evaluations were not performed in this work.

In the present study, the most common findings in the colonoscopic examination of the patients were ulcer (67.3%), polypoid lesions (12.7%), and mucosal redness and erythema (10.9%). Four patients had both ulcer and polypoid lesions (7.3%) and 1 colonoscopy failed to show any specific finding (1.8%). Most of the patients had one lesion (67.3%) and the size of many ulcers was 5-15 mm and most of them were in 4-6 cm of the anal margin. There were one ulcer in 13 cm and the other one in 20 cm of the anal margin. In the study by Madigan *et al*[7], most of the patients had one ulcer (70%). The size of most of the ulcers was about 2 cm

and their distance from the anus was between 3 and 15 cm, but most of them were in 7-10 cm of the anal margin. It is stated in this study that there is one stage of disease in which there is no ulcer and it can be seen at the local inflammation of the rectum[7]. It seems that there were some patients in this stage that did not show any specific findings in colonoscopy or only showed redness and inflammation. In the study by Dehghani *et al*[10] 11 out of 12 patients had between 1 to 4 superficial ulcers which was in 7 cm of rectosigmoid area and only 1 patient had polypoid lesion. In the study by Perito *et al*[9] it is mentioned that the lesions of patients are mostly at the end part of rectum and in 10 cm of the anal margin. From 10 registered colonoscopy report, there were redness and inflammation in 8 patients and there was polypoid lesions in 4 of them.

According to the studies conducted so far, it seems that polypoid lesions are rare in the pediatric age group and most of the lesions are ulcers, erythema and inflammation; this has been reported in previous studies[14].

All of the patients evaluated in this study, were initially treated with conservative treatments, recommendation to avoid straining during defecation and also dietary changes. Only the patients who did not respond to this method were treated with Sucralfate enema, Asacol suppository and also methylprednisolone injection around the lesion and finally 5 patients who did not also respond to these treatments, were treated with laparoscopic ventral rectopexy. During the follow-up, the symptoms of 69.8% of patients were recovered. Only 2 of these non-responsive patients were treated with rectopexy and the others with conservative treatments and use of Sucralfate enema and Asacol suppository.

In the study by Dehghani *et al*[10] conservative treatments, and behavioral and dietary changes were recommended as the preliminary treatment. In that study, 58.3% of the patients (7 out of 12 patients) had the complete recovery of symptoms after treatment with Sucralfate enema and concluded that this is a suitable treatment for children. One of their patients responded to Salicylate enema, 1 to corticosteroid enema, 2 to corticosteroid injection and 1 of the patients were finally treated with rectopexy[10].

In the study by Martín de Carpi *et al*[15] which was conducted on 3 affected patients, 2 patients were treated with budesonide enema and 1 patient with only a dietary change. The symptom of all the 3 patients was recovered. In the study by Blackburn *et al*[3] changing the behavior and encouraging children not to strain on defecation were recommended and the stool softeners were only used for the patients who had rigid stool; improvement was seen in all patients except for a patient who was not able to cooperate due to autism. This study indicated that most of the patients responded to behavioral change methods like biofeedback therapy[3]. In another study by Urganci *et al*[8] the patient's treatment began with Mesalazine enema, Sucralfate and steroid enema.

These and other similar studies reveal that a comprehensive study has not been conducted so far to determine the best therapeutic procedures, so determining suitable treatment requires more and more complete examinations. But it seems that the treatment method without complications like trying to change diets and bowel habits is the best treatment in children; also, it is better to consider medical treatment and use of laxatives and enema with different substances as the second line of treatment[2,9].

There are also different studies about the medical management in the children and most of the surgical cases have been conducted in patients with polypoid lesions or rectal prolapse and patients who were still symptomatic after trying several medical treatment[14,16,17].

Bonnard *et al*[17] have published the first successful rectopexy with laparoscopic method in a 12-year-old child who became asymptomatic in the next follow up and his colonoscopy became normal. In Godbole *et al*[16] study, polypoid lesions and hidden rectal prolapse were diagnosed in the examinations for 1 of the 2 studied patients. Polypectomy through the anus and then ablation of the remained granulation were performed for this patient. The second patient had a large prolapse and was treated with rectopexy and the symptoms of both patients were recovered in the next follow-ups.

According to this and other similar studies, it seems that this disorder is not so rare in children in spite of what had been said about its rarity before and the reason of its low reporting is low familiarity of physicians with this disorder and its similarity with other common diseases of the anal canal and rectosigmoid. Therefore, the physicians should be aware of this disorder and thus prevent the late diagnosis of the disease and prevent its long term complications.

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COMMENTS

Background

Solitary rectal ulcer is defined as an infrequent but benign disorder of rectal and sigmoid colon which is diagnosed on the basis of clinical symptoms and histologic findings. The clinical symptoms in children are similar to adults, but since this disorder has not been well known in children, their symptoms can be confused with more common diseases of the rectum and sigmoid. It is very important to differentiate solitary rectal ulcer from other disorders of the rectum and sigmoid before starting treatment. Follow-up of these patients is necessary

in order to improve and sustain treatment method to prevent morbidity and recurrences which lead to the disease progresses to adulthood.

Research frontiers

Solitary rectal ulcer is diagnosed as a cause of rectal bleeding in children in Pediatric Gastroenterology Section of Nemazee Hospital affiliated to Shiraz University of Medical Sciences and its frequency become increasing during the last years. However, there are very few English language literatures sources from Iran and other countries concerning the diagnosis and treatments of solitary rectal ulcer in children. The research hotspot is to introduce these real things happening to this population and to help other peers understand these backgrounds and trends in Iran.

Innovations and breakthroughs

In recent years, the number of children with rectal bleeding who diagnosed as of solitary rectal ulcer has been increasing in Shiraz, Iran. The present study represents the largest pediatric series of solitary rectal ulcer in the world. On the other hand, the current data also suggested that this disorder is not so rare in children in spite of what had been said about its rarity before and the reason of its low reporting is low familiarity of physicians with this disorder and its similarity with other common diseases of the rectosigmoid. Therefore, the physicians should be aware of this disorder and thus prevent the late diagnosis of the disease and prevent its long term complications.

Applications

The data in this study suggested that solitary rectal ulcer is not so rare in children and conservative and medical management for solitary rectal ulcer could yield relatively favorable outcomes. Furthermore, this study also provided readers with important information regarding the clinical and colonoscopic findings in these patients.

Terminology

Solitary rectal ulcer is a benign and chronic disorder well known in young adults and less in children. It is often related to prolonged excessive straining or abnormal defecation and clinically presents as rectal bleeding, copious mucus discharge, feeling of incomplete defecation, and rarely rectal prolapse. Solitary rectal ulcer is diagnosed based on clinical symptoms and endoscopic and histological findings. The current treatments are suboptimal.

Peer-review

Available papers concerning pediatric solitary rectal ulcer are scarce. The authors in this study analyzed the characteristics and outcomes of children with solitary rectal ulcer based on a large single-center series. This study showed that solitary rectal ulcer is not so rare in children. The results were interesting and provided important information concerning the background and trends of various treatments for solitary rectal ulcer in children.

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ORIGINAL ARTICLE

Prospective Study

Factors affecting breastfeeding duration in Greece: What is important?

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Abstract

AIM: To investigate factors associated with breastfeeding duration (BD) in a sample of mothers living in Greece.

METHODS: Four hundred and twenty-eight mothers (438 infants) were initially recruited in a tertiary University Hospital. Monthly telephone interviews (1665 in total) using a structured questionnaire (one for each infant) were conducted until the sixth postpartum

month. Cox regression analysis was used to assess factors influencing any BD.

RESULTS: Any breastfeeding rates in the first, third, and sixth month of the infant's life reached 87.5%, 57.0% and 38.75%, respectively. In the multivariate analysis, maternal smoking in the lactation period [hazard-ratio (HR) = 4.20] and psychological status (HR = 1.72), and the introduction of a pacifier (HR = 2.08), were inversely associated, while higher maternal education ($HR_{university/college\ vs\ primary/high\ school}$ = 0.53, $HR_{master's\ vs\ primary/high\ school}$ = 0.20), and being an immigrant (HR = 0.35) were positively associated with BD.

CONCLUSION: Public health interventions should focus on campaigns against smoking during lactation, target women of lower educational status, and endorse the delayed introduction of pacifiers.

Key words: Breastfeeding; Exclusive; Formula feeding; Duration; Greece

Core tip: This was a prospective study investigating the factors which are associated with breastfeeding duration (BD) in a sample of mothers living in Greece. Maternal smoking during lactation, the respective psychological status, and the introduction of a pacifier, were inversely associated, while higher maternal education and maternal immigrant status positively associated with BD. Public health interventions should focus on campaigns against smoking during lactation, target women of lower educational status, and endorse the delayed introduction of pacifiers.

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INTRODUCTION

Breastfeeding is the natural way to feed infants and young children ensuring optimal growth and development[1-5], while exclusive breastfeeding is recommended for the first six months of life[5]. Nevertheless, breastfeeding is not fully protected and supported as expected, and a number of important international public health initiatives were endorsed by the World Health Organization and United Nations International Children's Emergency Fund in order to protect and support breastfeeding[6-8].

Although some slight improvements have been recorded in breastfeeding rates during the last decade, they continue to fall short of global recommendations, and many mothers, who initially chose to breastfeed, shift to formula-feeding, and finally cease breastfeeding[9-12].

A variety of factors influence and determine breastfeeding initiation and duration, including personal and socio-cultural characteristics of the mother, the child and the family, aspects of the health care system, public health and social policies, as well as advertising and promotion of alternative feeding methods[13]. Some of these factors, such as maternal education and employment, may act on the opposite direction in different populations[11]. The identification of the determinants that influence breastfeeding duration (BD) across countries may provide useful information, which could be used to improve breastfeeding rates at national levels and worldwide.

The aim of the present study is to investigate the factors which are associated with BD in a sample of mothers living in Greece, a typical Southern European country, and explore further how modifiable these factors are.

MATERIALS AND METHODS

Study population and data collection at baseline

Four hundred and twenty-eight mothers, who had given birth to 438 live infants, were recruited in the maternity ward of a tertiary University Hospital between February and December 2009. The hospital provides gynaecological and maternity services to women residing in the Prefecture of Attica, where the capital of Greece, Athens is located, and monitoring of high-risk pregnancies at a nationwide level.

The study design and characteristics of the study population have been described in more detail elsewhere[14]. In brief, during the aforementioned 10-mo period, women, who had delivered a child and were permanent inhabitants of Greece with basic understanding of the Greek language, were approached by the first author after 24 h from delivery, and asked to participate in the study. The mothers were expected to be in good condition to withstand an interview at that time, taking also into account that the average nationwide in-patient stay in the maternity ward is four days.

The study protocol was approved by the Ethics Committee of the Medical School of University of Athens. All participants were asked to sign an informed consent form before being enrolled in the study.

At recruitment, baseline information about medical, lactation-related, and socio-demographic characteristics was collected through a structured baseline questionnaire, by means of an interview conducted by the first author. The baseline questionnaire consisted of five sections: (1) a section associated with the lactation status of the specific newborn/s (seven items); (2) a section associated with the gestation/childbirth of the specific newborn/s (eight items); (3) a section related

to the past medical/gynaecological history of the mother (two items); (4) a section for general information (three items); and (5) socio-economic characteristics (12 items).

The selection of the variables included in each section was based on prior knowledge derived from respective studies which had investigated a similar research hypothesis, as well as on our intention to explore further the respective parameters in the Greek setting. The questionnaire included both open-ended and closed questions and the baseline interviews typically lasted for about 30 min. Pre-pregnancy body weight and height were self-reported.

Data collection during follow-up

Telephone interviews for the collection of information about the duration of breastfeeding and/or alternative feeding methods were conducted by the first author with the use of an itemized follow-up questionnaire. The respective phone calls were made every month during the first six months following the child's birth. In total, 1665 interviews took place within a 14-mo period. The first interview wave involved 400 infants yielding a participation rate of 91.3%.

The follow-up questionnaire, consisting of closed-ended questions, collected information which was grouped in the following sections: (1) topics relating to the infant (number of items 5); (2) issues associated with the mother (number of items 7); (3) approaches of health professionals (number of items 1); and (4) alterations influenced by social/economic factors (number of items 4). The duration of the follow-up interview was approximately 15 min.

Infant feeding definitions

Exclusive breastfeeding comprised of giving breastmilk (or expressed breastmilk) only to the infant, precluding the use of any other liquid or solid food, except vitamin syrups/drops, medication, or mineral supplements. Formula-fed babies were given liquid food from a bottle with a nipple/teat, while no breastmilk was provided[15]. Any other combination of breastmilk with formula and/or additional liquids, or the administration of food and food-based fluids (such as weaning foods) was classified as partial breastfeeding[16].

A mother was considered to be continuing either exclusive or partial breastfeeding when she replied positively to the respective question, during the follow-up phone call.

Statistical analysis

Initial analysis included descriptive statistics. Categorical variables are presented as relative and absolute frequencies. The main variable of interest was BD (exclusive and partial together, henceforth referred as any breastfeeding). BD is a quantitative variable demonstrating right censoring. We employed Cox proportional hazard models to explore the parameters which were associated with any BD, after ascertaining that the respective prerequisite assumptions were met. Univariate models were initially run, in order to detect any potential association between BD (in weeks) and each of the covariates of interest. Potential confounding was addressed with the use of multivariate models. The final multivariate model included all covariates demonstrating a *P* value of less than 0.1 in the univariate analysis, as well as, a small set of covariates inserted in the model based on prior knowledge from the pertinent literature. These covariates comprised the age of the mother, the pre-pregnancy body mass index (BMI), and the employment status. Maternal age was additionally tested for correlation with the period of active lactation by applying Spearman's correlation coefficient. Pre-pregnancy BMI was calculated by dividing the weight of the mother (in kilogram) by the square height (in meters).

Available data were processed by using the IBM SPSS Statistics 21.0. Statistical importance was accepted at a level of 0.05 and lower.

Table 1 Main socio-demographic characteristics of the mothers at recruitment

Characteristics	% (*n*)
Maternal age	
Mean (SD)[1]	32.0 (4.7)
Country of origin	
Greece	71.0 (304)
Other	29.0 (124)
Marital status[2]	
Married	96.2 (403)
Not married	3.8 (16)
Educational status	
Primary school	1.8 (8)
Secondary/high school	37.0 (158)
University/college	54.4 (233)
Postgraduate studies	6.8 (29)
Employment status[3]	
Employed	73.4 (311)
Public sector	18.6 (79)
Private sector	45.1 (191)
Self-employed	7.8 (33)
Other	1.9 (8)
Domestically occupied	20.5 (87)
Unemployed	6.1 (26)

[1]In years; [2]Missing cases $n = 9$; [3]Missing cases $n = 4$. *n*: Absolute numbers.

RESULTS

Approximately 70% of recruited mothers had Greek nationality, while the mean age was 32 years (min 19, max 44) (Table 1). A high percentage of the mothers were university or college graduates (54.4%) and employed (73.4%). The vast majority of mothers were also married. The mean maternal BMI was 23.4 kg/m^2 at the beginning of gestation and 28.6 kg/m^2 before delivery. Almost one third of the mothers (30.8%) were smokers before pregnancy. Previous breastfeeding

Table 2 Characteristics of the infant population at recruitment

Characteristics	% (*n*)
Gender	
Female	45.7 (200)
Male	54.3 (238)
Birth weight	
Mean (SD)[1]	3215 (493)
Delivery mode	
Vaginal delivery	49.0 (218)
Caesarean section	51.0 (220)
Multiplicity	
Singletons	95.4 (418)
Twins	4.6 (20)
Prematurity (< 37 wk)	
No	91.0 (399)
Yes	9.0 (39)
Newborn health problems[2]	
No	80.5 (350)
Yes	19.5 (86)

[1]In grams; [2]Missing cases *n* = 2. *n*: Absolute numbers.

Table 3 Partial and exclusive breastfeeding rates during the follow-up period by postpartum month

Postpartum month	Partial breastfeeding *n*[1] (%)	Exclusive breastfeeding *n* (%)
1	175 (43.75)	174 (43.50)
2	125 (31.25)	154 (38.50)
3	92 (23.00)	136 (34.00)
4	75 (18.75)	118 (29.50)
5	58 (14.50)	106 (26.50)
6	57 (14.25)	98 (24.50)

[1]Absolute numbers.

experience was reported in 44.5% of women, whilst the present birth was the first in 50.0% of recruited mothers.

With regard to baseline characteristics related to the infant (Table 2), the percentage of babies being delivered *via* caesarean section was remarkably high (51.0% of all deliveries), although in most cases the reason was a previous caesarean. The majority of infants were full-term (91.0%), had normal birth weight (94.0%), and were born without any health problem (80.5%). A far as the maternity hospital practices were concerned, rooming-in was implemented in 47.0% of newborns and breastfeeding was encouraged by health professionals and/or family in 89.7% of them.

Any breastfeeding initiation rate was high (92.1%), while almost half of the mothers (44.4%) practiced exclusively breastfeeding. Any breastfeeding rates were 87.5% for the first, 57.0% for the third and 38.8% for the sixth postpartum month. Exclusive breastfeeding at the first, third and six month reached 43.5%, 34.0% and 24.5%, respectively (Table 3). The percentages of formula-feeding were 12.5%, 36.5% and 57.3%, for the aforementioned monthly periods, respectively. With respect to BD, the mean duration was 15.3 (± 8.6, min 1 and max 24) wk.

Table 4 Reasons for breastfeeding cessation in the postpartum period as reported by mothers (percentages only refer to mothers who have stopped breastfeeding)

Reason for breastfeeding cessation	Percentage of mothers (%)
Not enough milk	48.5
Other[1]	29.3
Other medical reason[2]	13.5
Return to work	4.2
Sore/traumatized nipples	2.4
Mastitis	1.5
Obstructed mammary ducts	0.6

[1]Includes fatigue, ablactation, general breastfeeding problems; [2]Includes health problems of the infant, maternal health problems, medications received by the mother.

Commonly reported problems which led to breastfeeding discontinuation are shown in Table 4. Almost half of the mothers (48.5%), who stopped breastfeeding, reported that the main reason for the cessation of breastfeeding was the production of inadequate milk volume. In addition, a noteworthy percentage of mothers reported "other" (29.3%) (*i.e.*, fatigue, ablactation, general breastfeeding problems), or "other medical" (13.5%) (*i.e.*, health problems of the infant, maternal health problems, medications received by the mother) reasons for breastfeeding cessation.

Exclusive breastfeeding percentage is also presented, as it evolves during the follow-up period, when the monthly samples of the interviewed mothers are examined individually (*i.e.*, a given sample of mothers who continue to breastfeed is compared to the previous or the next interview). The progress of exclusive breastfeeding for each monthly sample is depicted in Figure 1. The percentage of exclusively breastfed babies in the overall population of breastfed babies of each monthly interview was, hence, noted. Exclusive breastfeeding practice, when studied under this approach, demonstrated an increasing trend throughout follow-up, up until the fifth postpartum month (saturation period), after which the respective rates started to fall (Figure 1).

Table 5 presents the fully adjusted Cox regression-derived hazard ratios for any BD by specific characteristics of the mother or the infant. Mothers who smoked during the follow-up period were 4.2 times more likely (95%CI: 2.57-6.89) to stop breastfeeding earlier within the first 6 mo after delivery, compared to women who did not smoke during follow-up ($P < 0.001$). On the other hand, maternal smoking before pregnancy was not associated with any BD ($P = 0.124$) in the multivariate analysis, in contrast to the results of the univariate analysis, where it was found to be inversely associated (HR = 2.16, 95%CI: 1.67-2.80) (data not shown).

The nationality of the mother was found to be important, as immigrant mothers had 0.35 times (95%CI: 0.21-0.58) less chance for earlier breastfeeding discontinuation in comparison with Greek

Table 5 Adjusted hazard ratios and 95%CI for any breastfeeding duration

Characteristic	HR	95%CI	*P* value
Maternal age (per year)	1.01	0.97 to 1.05	*P* = 0.779
BMI before pregnancy (per kg/m^2)	1.01	0.97 to 1.05	*P* = 0.600
Maternal educational status			
High school graduate or lower	1.00		
University/college education	0.53	0.37 to 0.76	*P* = 0.001
Postgraduate degree	0.20	0.09 to 0.43	*P* < 0.001
Maternal employment status			
Unemployed/domestically occupied	1.00		*P* = 0.213
Employed	0.76	0.50 to 1.17	
Maternal nationality			
Greek	1.00		
Immigrant	0.35	0.21 to 0.38	*P* < 0.001
Smoking before pregnancy			
No	1.00		
Yes	0.49	0.20 to 1.22	*P* = 0.124
Smoking during follow-up			
No	1.00		
Yes	4.20	2.57 to 6.89	*P* < 0.001
Maternal psychological problems			
No	1.00		
Yes	1.72	1.23 to 2.41	*P* = 0.002
Previous breastfeeding experience			
No	1.00		*P* = 0.069
Yes	0.69	0.46 to 1.03	
Breastfeeding encouragement			
No	1.00		
Yes	0.98	0.60 to 1.58	*P* = 0.916
Multiparity			
Singleton	1.00		
Twins	1.83	0.89 to 3.74	*P* = 0.099
Prematurity			
Full-term	1.00		*P* = 0.088
Premature	1.65	0.93 to 2.93	
Pacifier introduction			
No	1.00		
Yes	2.08	1.40 to 3.08	*P* < 0.001

mothers (*P* < 0.001).

A similar trend was observed regarding the maternal educational status. In addition to having a postgraduate study degree (*P* < 0.001), which had also been identified as important in the univariate analysis, increased duration of any breastfeeding was also found to be more likely among university/college graduates, compared to mandatory education and high school graduates (*P* = 0.001). Indeed, having a university/college diploma was associated with a lower risk of earlier breastfeeding cessation (HR = 0.53, 95%CI: 0.37-0.76), and having a postgraduate study degree with an even lower risk of earlier weaning (HR = 0.20, 95%CI: 0.09-0.43), compared with mandatory or high school education.

The psychological status of the mother, reflecting the prevalence of related psychological problems postpartum (including swinging mood, easy change of disposition, bad disposition, anxiety, and easy crying), was inversely associated with the duration of any breastfeeding (*P* = 0.002). The presence of such problems carried a 1.72 (95%CI: 1.23-2.41) times higher risk of earlier breastfeeding cessation.

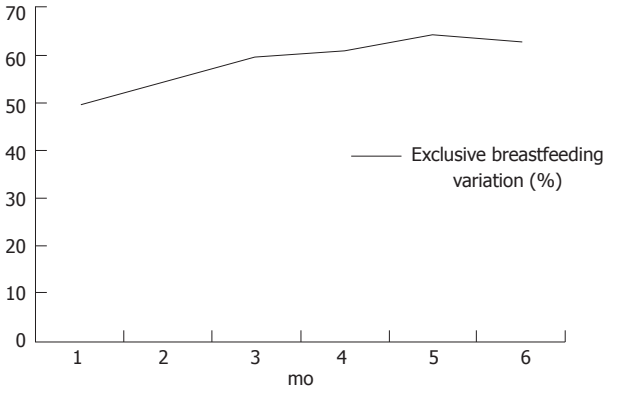

Figure 1 Exclusive breastfeeding evolvement during the postpartum period (monthly samples).

Finally, the use of a pacifier was found to affect any BD in a negative manner (*P* < 0.001, HR = 2.08, 95%CI: 1.40-3.08), a result also observed in the univariate analysis (HR = 2.87, 95%CI: 2.05-4.00).

Previous breastfeeding experience and lack of home support, immigrant status of the father, and low birth weight/prematurity, or multiplicity of the newborns, although found significant in the univariate analysis, did not remain significant in the final multivariate model. In addition, maternal age was neither associated with the duration of breastfeeding in the univariate analysis (*P* = 0.689), nor was it correlated with the period of active lactation after applying Spearman's correlation coefficient (ρ = 0.013, *P* = 0.783).

DISCUSSION

The present study sample comprising mothers, who were recruited in a maternity ward of a tertiary University Hospital, indicated that maternal smoking during the postpartum period was associated with higher risk for the cessation of any breastfeeding, whereas maternal education and immigrant status were positively associated with increased duration of any breastfeeding. The adverse maternal psychological status and the introduction of a pacifier affected the continuation of any breastfeeding in a negative manner.

The initiation of any breastfeeding among the interviewed mothers was high, with almost half of them practicing exclusive breastfeeding. Any breastfeeding rates gradually declined during the follow-up period, reaching 38.75% at the sixth postpartum month, while exclusive breastfeeding exhibited a similar trend and was practiced by the one quarter of the study sample at the sixth postpartum month.

It is interesting to note however, that if we examine each monthly sample of interviewed mothers separately as they evolve during the follow-up period, the progress of exclusive breastfeeding rate for each sample demonstrates an increasing trend throughout the follow-up period, up until the fifth postpartum month (saturation period), after which the respective

rates started to fall (Figure 1). That means, in effect, that every month until the fifth postpartum month, the proportion of exclusively breastfed babies in the remaining population increased. In other words, more babies who were partially breastfeeding stop being breastfed, compared to their exclusively breastfed counterparts, from the first until the fifth postpartum month (Table 3). This, in turn, might suggest that promoting exclusive breastfeeding may be a good strategy to avoid early weaning.

Exclusive and any BD rates were also reported in previous Greek studies, but the respective percentages were lower[17-19]. The lack of breastfeeding-friendly hospital practices has been consistently identified as detrimental for BD[18,19]. However, Bakoula *et al*[18] concluded that women in Greece seemed capable of overcoming formula supplementation in the hospital environment and could revert to exclusive breastfeeding at home. Hence, it can be postulated that mothers, who choose to continue breastfeeding in this study, possess the determination to overcome the related obstacles. The finding that any BD was not affected by previous information about breastfeeding, maternal employment status, or paid leave of absence, may, therefore, not be unrelated.

It should also be mentioned that the majority of mothers in the present study (48.5%) reported that the main reason for the cessation of breastfeeding was the production of inadequate milk volume. This belief is erroneous from a scientific point of view, as various studies have determined that less than 5% mothers do not seem able to meet the goals regarding the appropriate weight gain of their infant, because of inadequate milk production[20-23]. Thus, the length of BD may further increase, if mothers receive appropriate guidance from health professionals[24].

Drawing on the factors, which positively influenced the continuation of any breastfeeding, higher educational level of the mother was positively associated with BD. University/college graduates had about half the risk of premature weaning during the first six months, compared to mandatory education and high school graduates, whereas Master degree holders less than one fifth of that risk. Similar findings were reported by Flacking *et al*[25] in a prospective population-based cohort study in Sweden. Mothers of term infants with mandatory or upper secondary education in that study had more than twice the risk of premature discontinuation of breastfeeding within the first six postpartum months, compared with mothers of higher educational level. It should be mentioned that the educational level measured in the present analysis was the level of formal education, rather than education about breastfeeding. Further research might discern which aspects of maternal education play the most important role in breastfeeding, and such information may be used in school educational programs.

Immigrant mothers were also more likely to demonstrate increased duration of any breastfeeding. This finding has been previously reported in multi-cultural societies (*i.e.*, United States, United Kingdom), in which lower breastfeeding rates were consistently associated with acculturation[26-29]. It is possible that the association identified in this study, reflects the fact that immigrant mothers in Southern Europe come from families and communities, where breastfeeding is by far the predominant infant feeding method[30]. Moreover, even in societies with multi-cultural backgrounds there seems to be a stark contrast in of breastfeeding by ethnicity[26,27], which, in turn, suggests that different public health approaches need to be adopted in order to increase BD. In contrast, paternal immigrant status was not found to be significant in this study.

Focusing on the factors which adversely affected the continuation of any breastfeeding, smoking during follow-up was found to be important. In particular, mothers who reverted to regular smoking after delivery had a fourfold risk of stopping breastfeeding earlier within the first 6 postpartum months, compared to women who did not smoke. An early weaning risk of similar magnitude was also reported by Rattner *et al*[31] in a secondary analysis of data from a randomized controlled trial involving 228 women, who had stopped smoking before pregnancy, but reverted to daily smoking thereafter. In contrast, in a retrospective questionnaire-based national survey of a random sample of 24438 Norwegian women, Haug *et al*[32] reported that women who did not smoke were twice as likely to continue to breastfeed at 6 mo, compared with women who smoked. In addition, the adjusted odds ratio for breastfeeding continuation of more than 6 mo in women who had stopped smoking in pregnancy was 3.7 in the study of Giglia *et al*[33]. Further to the potential biological mechanisms associated with smoking and lactation[34-36], women who smoke may wean prematurely because of being unsure whether it is still safe to breastfeed. These women may be reluctant to seek the advice of health professionals, or even help for breastfeeding problems, as they could be wary of their reactions[37].

The adverse psychological status of the mother during the first postpartum month proved significant and affected the duration of any breastfeeding in a negative manner. The related postpartum problems which were examined included swinging mood, easy change of disposition, bad disposition, anxiety, and easy crying. As a whole the appearance of such problems postpartum carried a 1.72 times higher risk of earlier breastfeeding cessation. Hence, not only true depression, but also other forms of postnatal distress seem to influence the duration of breastfeeding, and timely identification and intimate knowledge of these factors could assist in recognizing women at risk for early weaning, and constructing programs capable of increasing the length of BD. The importance of psychological factors in predicting BD was also stressed in the study of O'Brien *et al*[38].

The introduction of a pacifier was found to negatively affect the duration of any breastfeeding. Similar

results were reported by Howard *et al*[39], who had associated the introduction of a pacifier by the sixth week with a significant decline in BD, in a prospective cohort study of 265 breastfeeding mother-infant dyads. However, the duration of breastfeeding up to 3 mo was not affected by the early introduction of a pacifier in that study. In addition, Scott *et al*[40], in a prospective study of 587 Australian mothers, found that the introduction of a pacifier after 10 wk did not significantly affect the duration of breastfeeding, whilst its use in the first 10 wk increased the risk for the cessation of full breastfeeding by 6 mo and overall breastfeeding by 12 mo. It has been suggested that the decreases in BD associated with pacifier use may be a consequence of less frequent breastfeeding among women who introduce pacifiers to their infants[27]. The reasons for introducing a pacifier in the first place need to be determined. There is also a need to determine whether breastfeeding problems associated with the use of pacifiers precede or follow their introduction. In the former case women need to be advised on how to prevent, identify, and manage breastfeeding problems, as a means of reducing the need for the use of pacifiers. In the latter case, however, women need to be discouraged from introducing pacifiers in order to reduce the risk of breastfeeding problems, and increase the duration of breastfeeding[28].

Limitations

The present study was conducted in a single-centre setting, which may result to the study sample not being strictly representative of the Greek population. Nevertheless, the study population was recruited in the maternity ward of a tertiary University hospital, which is not only serving the Prefecture of Attica, but also accepting referrals of high-risk pregnancies from the entire Greek territory. Hence, the validity of the associations found between BD and various factors under study is not likely to have been affected.

In conclusion, the results of the present study revealed the importance of maternal education and immigrant status regarding the duration of any breastfeeding. In addition, maternal smoking during lactation, as well as the use of a pacifier, were inversely associated with the duration of any breastfeeding. Post-partum psychological status was also found to be inversely associated with any BD in this study sample.

Public health interventions in order to protect, support and promote breastfeeding should include campaigns against smoking during lactation, as a means of increasing BD, as well as, endorsing the delayed introduction of pacifiers. Interventions should also focus on women of low educational status, which obviously consist a high risk group for early breastfeeding cessation.

Findings of this study could also prove useful for comparing factors which are responsible for BD across countries, and providing information that could be used as a tool for the promotion of practices and programs that encourage breastfeeding.

It is becoming increasingly important that public health authorities and health professionals need to identify the factors that influence BD across countries, and aim at creating socio-cultural and economic settings that encourage the continuation of breastfeeding.

COMMENTS

Background

Breastfeeding is the natural way to feed infants and young children ensuring optimal growth and development, while exclusive breastfeeding is recommended for the first six months of life. Although some slight improvements have been recorded in breastfeeding rates during the last decade, they continue to fall short of global recommendations, and many mothers, who initially chose to breastfeed, shift to formula-feeding, and finally cease breastfeeding. A variety of factors influence and determine breastfeeding initiation and duration, including characteristics of the mother, the child and the family, aspects of the health care system, public health and social policies, advertising and promotion of alternative feeding methods. The identification of the determinants that influence breastfeeding duration (BD) across countries may provide useful information, which could be used to improve breastfeeding rates at national levels and worldwide.

Research frontiers

Maternal smoking during the postpartum period is associated with higher risk for earlier breastfeeding discontinuation, as also the adverse maternal psychological status and the early introduction of a pacifier to the infant. Maternal education and immigrant status, on the other hand, are positively associated with increased BD.

Innovations and breakthroughs

In the present study, the authors additionally examined each monthly sample of interviewed mothers separately, as they evolved during the follow-up period. The progress of exclusive breastfeeding rate for each sample demonstrated an increasing trend throughout the follow-up period, up until the fifth postpartum month (saturation period), after which the respective rates started to fall. That means, in effect, that every month until the fifth postpartum month, the proportion of exclusively breastfed babies in the remaining population increased. In other words, more babies who were partially breastfeeding stop being breastfed, compared to their exclusively breastfed counterparts, from the first until the fifth postpartum month. This, in turn, might suggest that promoting exclusive breastfeeding may be a good strategy to avoid early weaning.

Applications

Public health interventions in order to protect, support and promote breastfeeding should include campaigns against smoking during lactation, as a means of increasing BD, as well as, endorsing the delayed introduction of pacifiers. Interventions should also focus on women of low educational status, which obviously consist a high risk group for early breastfeeding cessation. Findings of this study could also prove useful for comparing factors which are responsible for BD across countries, and providing information that could be used as a tool for the promotion of practices and programs that encourage breastfeeding.

Peer-review

In this paper, authors investigated factors associated with BD in a sample of mothers living in Greece. The results of the present study revealed the importance of maternal education and immigrant status regarding the duration of any breastfeeding. Furthermore, authors also found that maternal smoking during lactation and the use of a pacifier, were inversely associated with the duration of any breastfeeding. This is a well written and well conducted study.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Serial physical examinations, a simple and reliable tool for managing neonates at risk for early-onset sepsis

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Abstract

AIM

To investigate whether serial physical examinations (SPEs) are a safe tool for managing neonates at risk for early-onset sepsis (EOS).

METHODS

This is a retrospective cohort study of neonates (≥ 34 wks' gestation) delivered in three high-volume level Ⅲ birthing centres in Emilia-Romagna (Italy) during a 4-mo period (from September 1 to December 31, 2015). Neonates at risk for EOS were managed according to the SPEs strategy, these were carried out in turn by bedside nursing staff and physicians. A standardized form detailing general wellbeing, skin colour and vital signs was filled in and signed at standard intervals (at age 3, 6, 12, 18, 36 and 48 h) in neonates at risk for EOS. Three independent reviewers reviewed all charts of neonates and abstracted data (gestational age, mode of delivery, group B streptococcus status, risk factors for EOS, duration of intrapartum antibiotic prophylaxis, postpartum evaluations, therapies and outcome). Rates of sepsis workups, empirical antibiotics and outcome of neonates at-risk (or not) for EOS were evaluated.

RESULTS

There were 2092 live births and 1 culture-proven EOS (*Haemophilus i*) (incidence rates of 0.48/1000 live births). Most newborns with signs of illness (51 out of 101, that is 50.5%), and most of those who received postpartum antibiotics (17 out of 29, that is 58.6%) were not at risk for EOS. Compared to neonates at risk, neonates not at risk for EOS were less likely to have signs of illness (51 out of 1442 *vs* 40 out of 650, $P = 0.009$) or have a sepsis workup (25 out of 1442 *vs* 28 out of 650, $P < 0.001$). However, they were not less likely to receive empirical antibiotics (17 out of 1442 *vs* 12 out of 650, $P = 0.3$). Thirty-two neonates were exposed to intrapartum fever or chorioamnionitis: 62.5% ($n = 20$) had a sepsis work-up and 21.9% ($n = 7$) were given empirical antibiotics. Among 216 neonates managed through the SPEs strategy, only 5.6% ($n = 12$) had subsequently a sepsis workup and only 1.9% ($n = 4$) were given empirical antibiotics. All neonates managed through SPEs had a normal outcome. Among 2092 neonates, only 1.6% ($n = 34$) received antibiotics; 1.4% ($n = 29$) were ill and 0.2% ($n = 5$) were asymptomatic (they were treated because of risk factors for EOS).

CONCLUSION

The SPEs strategy reduces unnecessary laboratory evaluations and antibiotics, and apparently does not worsen the outcome of neonates at-risk or neonates with mild, equivocal, transient symptoms.

Key words: Sepsis; Group B streptococcus; Intrapartum antibiotic prophylaxis; Newborn; Prevention

Core tip: The management of asymptomatic neonates at-risk for early-onset sepsis (EOS) remains a challenge. Algorithms based on the threshold values of risk factors result in a large number of uninfected newborns being evaluated and treated. In a 4-mo, multicenter retrospective cohort study, we evaluated a strategy based on serial physical examinations (SPEs) instead of sepsis workup. We studied 2092 neonates. Among 216 neonates initially managed through SPEs, only 12 (5.6%) had subsequently a sepsis workup; only 4 (1.9%) were given empirical antibiotics. All neonates had a normal outcome. SPEs is a simple and reliable tool for managing neonates at risk for EOS.

Berardi A, Buffagni AM, Rossi C, Vaccina E, Cattelani C, Gambini L, Baccilieri F, Varioli F, Ferrari F. Serial physical examinations, a simple and reliable tool for managing neonates at risk for early-onset sepsis. *World J Clin Pediatr* 2016; 5(4): 358-364 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i4/358.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i4.358

INTRODUCTION

Infections are a leading cause of neonatal mortality. Exposure to neonatal infection is a large contributor to cerebral injury and long-term disabilities in survivors, especially in the case of preterm neonates[1-4]. Early-onset sepsis (EOS) is transmitted (during delivery or shortly before) from a mother who is colonized at the genital site[2,5]. EOS may be diagnosed on the basis of nonspecific clinical signs and the isolation of a pathogen from sterile sites. EOS is typically defined as sepsis occurring within the first 3 or 7 d after birth[3]. Seven days is typically used for Group B streptococcus (GBS) sepsis[6,7], that remains a leading cause of EOS[1,2]. Universal screening for GBS in late pregnancy and the administration of intrapartum antibiotic prophylaxis (IAP) have led to a striking decline in GBS EOS (from 1.8 cases per 1000 live births in 1990 to 0.25 in 2013 in the United States)[8,9].

The initial symptoms of sepsis are often subtle, but the clinical course may be fulminant, so that neonatologists often initiate antibiotic treatment as soon as there is the slightest clinical suspicion of EOS. There is currently no diagnostic test that can confirm or rule out neonatal sepsis with an acceptable sensitivity and specificity[10,11]. Evidence-based recommendations have been insufficient to date, and neonatal management remains challenging. Guidelines often recommend administering empirical antibiotics to well-appearing neonates at risk of EOS (WAARNs)[12-14]. Algorithms are usually based on the assumption that the presence of maternal risk factors (RFs) implies a higher neonatal risk of EOS. However, most data regarding RFs for EOS have been obtained before the era of IAP. As clinical signs are a sensitive indicator of neonatal sepsis[15]. The 2010 revised Centers for Disease Control and Prevention guidelines recommend observation (instead of laboratory testing) for WAARNs born full term. A sepsis workup is recommended for neonates born after prolonged membrane rupture ($\geqslant$ 18 h) and inadequate IAP (duration shorter than 4 h prior to delivery). A sepsis workup and empirical antibiotics are recommended for chorioamnionitis-exposed neonates[7]. However, concerns have arisen that unnecessary antibiotics contributes to the development of antimicrobial resistance. A selective use of antibiotics in the highest risk patients is now a universal goal[16]. With the aim of further reducing unnecessary testing and antibiotics, some authors have more recently proposed alternative approaches (based on physical examination) to managing WAARNs[17-20].

In Emilia-Romagna (Italy) a GBS Prevention Working Group was set up in 2003 and active GBS surveillance was started. An efficient antenatal screening strategy for the prevention of EOS has been successfully implemented over the years[21,22].

Since 2009 clinicians have managed WAARNs by relying on serial physical examinations (SPEs) rather than on laboratory tests[23,24]. Since its introduction, this strategy has apparently been safe, so that an increasing number of infants at a higher risk of EOS (*i.e.,* late preterm neonates, or neonates born with chorioamnionitis) have been gradually managed through the SPE strategy.

The purpose of this retrospective study was to

confirm that the SPE approach was safe for all WAARNs and was not associated with unnecessary antibiotics. Current data concerning SPEs in WAARNs are limited, especially in neonates exposed to chorioamnionitis at birth, and further data supporting this strategy are needed.

MATERIALS AND METHODS

This is a retrospective cohort study of infants delivered during a 4-mo period (from September 1, to December 31, 2015) at three high-volume, level Ⅲ, regional centres (Azienda Ospedaliero Universitaria Policlinico, Modena; Azienda Ospedaliero Universitaria Policlinico, Parma; and Arcispedale S.M. Nuova, Reggio Emilia) in Emilia-Romagna (an Italian region with about 40000 live births/year). In this region, prevention of GBS infections have led to a decline in the incidence of GBS EOS, which in recent years has decreased to 0.19/1000 live births[23].

Definitions

Inadequate IAP refers to ampicillin or cefazolin given less than 4 h prior to delivery. Risk factors for EOS: These include GBS bacteriuria identified during the current pregnancy, a previous GBS-infected newborn, preterm birth (< 37 wks' gestation), rupture of membranes ≥ 18 h, intrapartum fever ≥ 38 ℃, that is a surrogate of chorioamnionitis[7]. Well-appearing refers to neonates with risk factors for EOS without any clinical symptom of sepsis at age 0-6 h. At-risk newborn is defined as an infant whose mother is GBS colonized or has risk factors for EOS. Culture-proven EOS: Isolation of a pathogen from a normally sterile body site (blood or cerebrospinal fluid) within 72 h of birth and clinical signs and symptoms consistent with sepsis[2,3]. Suspected EOS is defined as the presence of clinical signs and symptoms consistent with sepsis[1-3] plus an abnormal complete blood count and/or elevated C-reactive-protein levels in the absence of a positive blood culture. Ruled out sepsis: Neonates with signs of illness who rapidly recover without antibiotic treatment.

Antenatal screening and management of neonates, before and after the introduction of the SPE strategy

In accordance with the Centers for Disease Control and Prevention guidelines[7,13], women with prenatal GBS colonization or risk factors (see below) should be given IAP. Up to 2008, WAARNs underwent a limited laboratory evaluation (complete blood count - CBC - with differential, blood culture and C-reactive protein)[13]. Since 2009 a new strategy (SPE) for managing WAARNs has been implemented[23,24]. A standardized form detailing information on vital signs and general wellbeing was included in the medical records of WAARNs managed through the SPE strategy (see below). Three independent reviewers reviewed all charts of neonates (≥ 34 wk gestation) delivered in the 3 participating centres and abstracted data (gestational age, mode of delivery, GBS status, risk factors for EOS, duration of IAP, postpartum evaluations, therapies and outcome). The results of standardized forms detailing SPEs were also reviewed. To maintain patient confidentiality, the spreadsheets submitted to the principal investigator did not include any data that would have allowed identification of patients or caregivers.

SPE strategy

Full-term and late preterm WAARNs who received inadequate or no IAP are managed through SPEs, without any laboratory evaluations. This strategy is carried out in turn by bedside nursing staff, midwives and physicians. It is based on the relief of simple vital signs, these may be easily detected by medical and non-medical staff. Each examiner fills in and signs a standardized form (detailing general wellbeing, skin colour - including perfusion and the presence of respiratory signs) at standard intervals (at age 3-6-12-18-36-48 h) (Figure 1). The standardized form is then included in the records of the newborn. Nursing staff and midwives give notification to clinicians when signs of illness develop. As we experienced in our clinical practice, every evaluation requires a maximum of 1 to 2 min. SPE has proven very sensitive for the early detection of all cases of EOS, not only for GBS sepsis.

Neonates with mild or equivocal symptoms during the first hours of life (*i.e.,* neonates born by caesarean section with mild tachypnea that resolves spontaneously within a few hours) are closely observed, but do not necessarily undergo a sepsis workup or receive empirical antibiotics. Antibiotics are given after the collection of blood samples and (when possible) cerebrospinal fluid cultures. WAARNs are not discharged home before age 48 h.

From 2009 to 2012, SPEs were performed on WAARNs ≥ 35 wks' gestation. However, intrapartum fever/chorioamnionitis-exposed neonates or neonates with ≥ 2 risk factors underwent sepsis workup and were given empirical antibiotics[24]. Because of its apparent safety, in 2013 this SPE strategy was extended to all WAARNs ≥ 34 wks' gestation, regardless of RFs.

Statistical analysis

Analyses were performed using STATA/SE 11.2 for Windows; continuous variables were expressed as the mean ± standard deviation or median and range; categorical data were expressed as numbers (percentages). Statistical analyses were performed using the χ^2 test and Mann-Whitney test for independent samples, when appropriate. A P value < 0.05 was used as a threshold for statistical significance.

RESULTS

During the study period there were 2092 newborns with ≥ 34 wks' gestation; the median gestational age was 39 wk (25^{th}-75^{th} IQ range 38-40) and median birth weight was 3920 g (25^{th}-75^{th} IQ range 2980-3590).

Demographics

Table 1 shows the demographics of neonates according

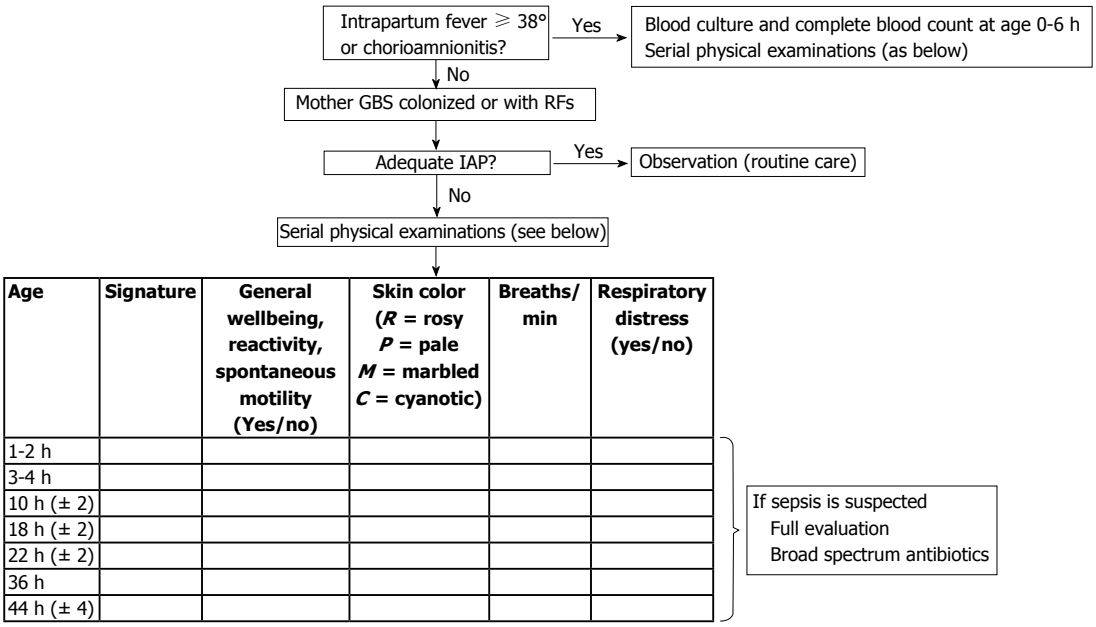

Figure 1 The neonatal management approach for neonates at risk for early-onset sepsis. Full evaluation includes blood culture and complete blood count, C-reactive protein, chest X ray and lumbar puncture. GBS: Group B streptococcus; IAP: Intrapartum antibiotic prophylaxis; RFs: Risk factors.

Table 1 Demographics from the sample of 2092 birth records

Mothers	*n* = 2092
Antenatal screening, *n* (%)	1923 (91.9)
GBS culture-positive, *n* (%)	392 (20.4)
Mothers with risk factor, *n* (%)	578 (27.6)
GBS bacteriuria during pregnancy, *n* (%)	116 (5.5)
Previous infant with GBS disease, *n* (%)	1 (0.05)
Preterm delivery (34 to 36 wks' gestation), *n* (%)	123 (5.9)
Intrapartum fever ⩾ 38 ℃, *n* (%)	32 (1.5)
Membrane rupture ⩾ 18 h, *n* (%)	254 (12.1)
Vaginal delivery, *n* (%)	1507 (72)
IAP administration, *n* (%)	771 (36.8)
IAP given more than 4 h prior to delivery, *n* (%)	470 (61.0)
IAP given to culture-positive women, *n* (%)	341 (87.0)
Gestational age, weeks, median, (IQ)	39.0 (38-40)
Birth weight, g, median (IQ)	3290 (2980-3590)

IAP: Intrapartum antibiotic prophylaxis; GBS: Group B streptococcus; IQ: Interquartile range 25th-75th.

to maternal colonization, risk factors, and IAP administration. Approximately 27% of neonates had at least 1 risk factor for EOS, and 20% were born to mothers with a positive GBS screening. The vast majority of them received IAP (which in most cases was given more than 4 h prior to delivery).

Neonates exposed to intrapartum fever/chorioamnionitis

Thirty-two neonates were intrapartum fever/chorioamnionitis-exposed. Seven of 32 had signs of illness (of which 4 at age 0-6 h and 3 at age 7-24 h). Twenty out of 32 (62.5%) had a sepsis workup, but only 7 (21.9%) were given empirical antibiotics. All had a normal outcome and none of them had culture-proven sepsis.

Neonates at risk and not at risk for EOS

Figure 2 presents data for neonates at risk (or not) for EOS and details of neonates with signs of illness, sepsis workup and empirical antibiotics. Most newborns with signs of illness, and most of those who received postpartum antibiotics were not at risk. However, compared to neonates at risk, neonates not at risk for EOS were less likely to have signs of illness (51 out of 1442 *vs* 40 out of 650, $P = 0.009$) or have a sepsis workup (25 out of 1442 *vs* 28 out of 650, $P < 0.001$), but not less likely to receive empirical antibiotics (17 out of 1442 *vs* 12 out of 650, $P = 0.3$). Among 18 at-risk neonates with signs of illness at age 0-6 h, 9 had mild, equivocal and transient symptoms and were kept under observation without further evaluation; the remaining 9 neonates underwent a sepsis workup.

WAARNs and SPEs

Among the 2092 newborns, 216 (10.3%) initially WAARNs were managed through SPEs; only 12 of 216 (5.6%) had a sepsis workup (because of respiratory signs in most cases) and 4 of 216 (1.9%) were given antibiotics. Sepsis was ruled out in the remaining 8 neonates who had a sepsis workup (as neonates recovered promptly without any antibiotic treatment).

Neonates treated with antibiotics

Postpartum antibiotics were given to 34 (1.6%) of the 2092 neonates, of whom 5 (0.2%) were asymptomatic (they were given antibiotics because of risk factors for EOS) and 29 (1.4%) had signs of illness (respiratory signs in 23 out of 29 neonates). Nine required oxygen support (chest X-rays were consistent with pneumonia in 4 cases), none received nasal CPAP or mechanical ventilation. Twelve of the 29 neonates (41.4%) presented with symptoms at age 0-6 h. One of them had culture proven sepsis (caused by *Haemophilus i.*) The baby was born at 35 wks' gestation to a GBS-negative mother

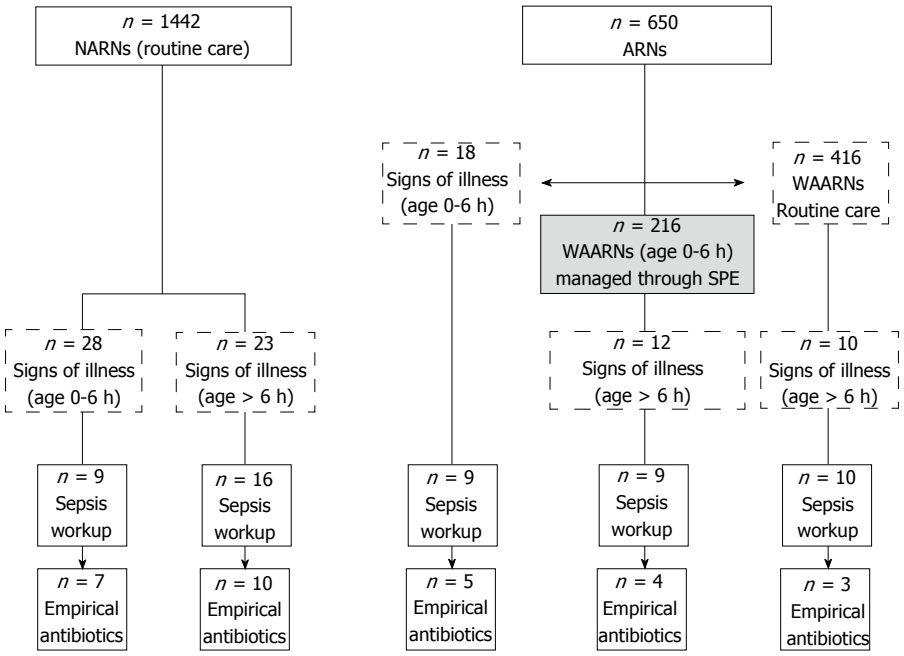

Figure 2 Neonates at risk or not at risk for early-onset sepsis: Signs of illness, sepsis workup and empirical antibiotics. Neonates delivered *via* a planned caesarean section are included among NARNs. ARNs: Neonates born to GBS-positive mothers or with risk factors; NARNs: Neonates born to GBS-negative mothers without risk factors; SPE: Serial physical examinations; WAARNs: Well-appearing at-risk neonates; GBS: Group B streptococcus.

and was given no IAP. Seventeen of the 29 (58.6%) presented with symptoms at age 7 to 63 h. Four of these 17 neonates had been managed initially through the SPE strategy (Figure 2).

All 34 neonates who were given postpartum antibiotics had a sepsis workup before treatment (all had blood culture obtained; 11 underwent also lumbar puncture), and all had a normal outcome, without brain lesions at ultrasound scanning (when performed).

DISCUSSION

Since IAP has become a standard of care, the management of WAARNs has remained a challenge for clinicians. Laboratory tests currently available have poor specificity, low positive predictive value and lack sufficient accuracy for guiding the decision as to whether neonates should be treated with antibiotics[10]. Most guidelines for neonatal management rely on studies carried out prior to the era of IAP. However, IAP leads to a substantial reduction of the risk of EOS. Recent studies show that algorithms based on the threshold values of risk factors may result in a large number of uninfected newborns being evaluated and treated; or they may fail to identify many newborns who require early treatment[11,18,19]. Therefore, new data are necessary in order to develop alternative approaches.

More recently, methods to stratify the risk of EOS by combining different maternal RF groups and clinical examination of newborns have been devised[25]. It is however unclear what impact these methods have on preventing the occurrence of sepsis or what impact they have on the number of asymptomatic newborns unnecessarily treated with antibiotics. Such methods still recommend empirical antibiotics for some WAARNs. A recent study aimed at evaluating the impact of this strategy among 2094 newborns found that 5.3% of full-term neonates were given empirical antibiotics, but more than 40% of them were asymptomatic[26].

A second controversial issue concerns the management of chorioamnionitis-exposed neonates. Early studies reported that most failures of IAP (up to 90% of cases) occur in such neonates[27]. However, recent data show that less than 50% of failures of IAP are tied to chorioamnionitis[28] and the risk of EOS is strongly dependent on gestational age[11]. Because most asymptomatic chorioamnionitis-exposed neonates are born full term, the number of neonates to be evaluated and treated empirically (number needed to treat) in order to prevent one infection may be high (60-1400 newborns) and antibiotic treatment might not be justified for full-term neonates[29].

In the current study, the low incidence of culture-proven EOS (0.48/1000) was the result of high rates of maternal prenatal screening and IAP. No cases of GBS-EOS occurred in the study period. This finding is consistent with regional data, which clearly show a continuous decline in GBS-EOS over the years, thanks to the implementation of the prevention strategy[23].

Most newborns had symptoms at birth or in the first few hours of life, and most had apparently no risk factors for EOS. Under our approach, neonates with mild or equivocal, initial symptoms or asymptomatic neonates with risk factors for EOS underwent SPEs without sepsis workup. Furthermore, only approximately 2/3 of neonates exposed to intrapartum fever or chorioa-

mnionitis had a sepsis workup and only 21% (neonates with signs of illness) were given antibiotics. We could not calculate the number needed to treat, as we had no cases of EOS among initially asymptomatic neonates managed through SPEs.

This less invasive approach has resulted in very few infants (1.6%) treated with antibiotics. Nevertheless, no cases of EOS were missed, as all neonates had a sepsis workup (including blood culture) prior to administering antibiotics. Furthermore, none of the newborns had complications or a worse outcome because of this strategy. By providing strong assurance that frequent examinations actually are performed, this strategy seems safe, reliable and easy to perform.

This study has major limitations, firstly the small sample size of neonates in study. EOS has become rarer than in the past, therefore larger population is required in order to better define neonatal risks. This is especially true for intrapartum fever/chorioamnionitis-exposed newborns, who represent approximately 1% in our population. However, starting from 2003, we recommended an SPE-based approach for the entire region, but the GBS-EOS surveillance network has to date reported no cases of delayed diagnosis. Moreover, our study addresses neonates aged 0-72 h, and we could not exclude that some newborns have fallen ill after the first days of life. However, our approach does not seem to increase the risk of subsequent complications[24].

In conclusion, our study suggests that the SPE strategy may reduce unnecessary laboratory evaluations and antibiotics, apparently without worsening the outcome. However, larger studies are needed to validate this strategy.

COMMENTS

Background

There are insufficient evidence-based recommendations for managing well-appearing neonates at-risk for early-onset sepsis (EOS). Algorithms based on the threshold values of risk factors may result in a large number of uninfected newborns being evaluated and treated; or they may fail to identify many newborns who require early treatment.

Research frontiers

New data are necessary in order to develop alternative approaches.

Innovations and breakthroughs

In this 4-mo, multicenter retrospective cohort study, we studied 2092 neonates, of which > 30% were at-risk for EOS; 216 neonates were initially managed through a strategy based on serial physical examinations (SPEs) instead of sepsis workup. Only 12 (5.6%) had subsequently a sepsis workup and only 4 (1.9%) were given empirical antibiotics. All neonates managed through SPEs had a normal outcome. Among 2092 neonates, only 1.6% (n = 34) were given antibiotics (all but 5 had clinical symptoms consistent with sepsis). Most of them were not at risk for EOS.

Applications

A strategy based on SPEs reduces unnecessary sepsis workup and antibiotics, and does not worsen the outcome.

Terminology

SPEs are carried out in turn by bedside nursing staff, midwives and physicians. at standard intervals (at age 3-6-12-18-36-48 h). A standardized form (detailing general wellbeing, skin colour - including perfusion and the presence of respiratory signs) filled in and signed by the staff is then included in the records of the newborn.

Peer-review

The reviewed article raises important topic of newborn babies potentially at risk of early infection (EOS) because of maternal Group B streptococcus colonization or the existence of other risk factors or the presence of non-specific signs of infection. At the same time, as the authors point out, the real risk for a newborn - in the era of intrapartum antibiotic prophylaxis - is not so common in the group of term and late preterm infants. Driven by concern about the excessive use of antibiotics, as well as exposing the infant to pain when performing laboratory tests, the authors propose a clinical observation in the form of repeated physical evaluation every few hours in the first days of life. It is well-written.

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ORIGINAL ARTICLE

Retrospective Study

Packed red blood cell transfusions as a risk factor for parenteral nutrition associated liver disease in premature infants

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Author contributions: D'Souza A and Valencia G provided the neonatal clinical care in the nursery assisted in the collection of the data and critically reviewed the manuscript after completion; Algotar A created some of the figures, participated in writing of the final manuscript and critically reviewed the manuscript after completion; Pan L collated all of the data collection and organization, created some of the figures, and participated in writing an earlier draft of the manuscript; Schwarz SM assisted in the analysis of the data, performed the statistical analysis, supervised the creation of the figures and critically reviewed the manuscript after completion; Treem WR designed the study, supervised the collection of the data and participated in the analysis of the data, and had input into the final draft of the manuscript, he also critically reviewed and edited the manuscript after completion; Rabinowitz SS reanalyzed the data and wrote the final draft of the manuscript, he oversaw the entire completion of the project.

Institutional review board statement: This study was approved by the Institutional Review Board of SUNY Downstate Medical Center.

Informed consent statement: As this was a retrospective chart review, informed consent was waived by the institutional review board.

Conflict-of-interest statement: None of the authors involved in this study have any conflicts of interest.

Data sharing statement: No additional data are available.

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Abstract

AIM

To determine if packed red blood cell transfusions contribute to the development of parenteral nutrition associated liver disease.

METHODS

A retrospective chart review of 49 premature infants on parenteral nutrition for > 30 d who received packed red blood cell (PRBC) transfusions was performed. Parenteral nutrition associated liver disease was primarily defined by direct bilirubin (db) > 2.0 mg/dL. A high transfusion cohort was defined as receiving > 75 mL packed red blood cells (the median value). Kaplan-Meier plots estimated the median volume of packed

red blood cells received in order to develop parenteral nutrition associated liver disease.

RESULTS

Parenteral nutritional associated liver disease (PNALD) was noted in 21 (43%) infants based on db. Among the 27 high transfusion infants, PNALD was present in 17 (64%) based on elevated direct bilirubin which was significantly greater than the low transfusion recipients. About 50% of the infants, who were transfused 101-125 mL packed red blood cells, developed PNALD based on elevation of direct bilirubin. All infants who were transfused more than 200 mL of packed red blood cells developed PNALD. Similar results were seen when using elevation of aspartate transaminase or alanine transaminase to define PNALD.

CONCLUSION

In this retrospective, pilot study there was a statistically significant correlation between the volume of PRBC transfusions received by premature infants and the development of PNALD.

Key words: Packed red blood cell transfusion; Neonatal intensive care unit; Parenteral nutrition associated liver disease

Core tip: The etiology of parenteral nutrition associated liver disease (PNALD), a commonly encountered morbidity in the neonatal intensive care unit (NICU) remains unknown. Potentially hepatotoxic packed red blood cell (PRBC) transfusions are routinely administered in this setting. Whether PRBC transfusions increase the prevalence of PNALD is a clinical question that has not been systematically investigated. This pilot study demonstrated that in a cohort of NICU infants who received greater volumes of PRBC, there was a significantly higher prevalence of PNALD. Further investigations to define the exact risk are warranted to minimize NICU stays, costs, and future liver damage.

D'Souza A, Algotar A, Pan L, Schwarz SM, Treem WR, Valencia G, Rabinowitz SS. Packed red blood cell transfusions as a risk factor for parenteral nutrition associated liver disease in premature infants. *World J Clin Pediatr* 2016; 5(4): 365-369 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i4/365.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i4.365

INTRODUCTION

Preterm infants are among the most highly transfused patient populations, in part because of the presumption that packed red blood cells (PRBC) improve oxygen delivery[1]. Approximately 38000 premature neonates receive more than 300000 transfusions annually[2]. PRBC transfusion guidelines are based on expert opinion, rather than evidence-based data, and vary among practitioners, institutions and clinical situations[3,4]. The increased susceptibility of neonatal intensive care unit (NICU) patients to develop anemia requiring blood transfusions is attributable to multiple factors. These include prematurity itself, nutritional deficiencies, iatrogenic blood loss, and other medical conditions commonly seen in the NICU such as sepsis, hemolysis, bleeding disorders, and surgery[5].

Although PRBC transfusions are believed to be helpful in the NICU[6], they have been implicated in the development of bronchopulmonary dysplasia, acute lung injury, necrotizing enterocolitis (NEC), intraventricular hemorrhage, and retinopathy of prematurity[7,8]. Multiple transfusions may result in iron deposition leading to dysfunction in the liver, heart and other organs[9-14]. Because RBC life span in preterm infants is shorter, accelerated cell breakdown results in even greater degrees of hepatic iron deposition. Efforts to decrease transfusion requirements in low birth weight infants include utilizing erythropoietin in the first 48 hour of life[15]. This hematopoietic agent has been suggested to have a neuroprotective effect in newborns[16].

Parenteral nutrition (PN) is another recognized risk factor contributing to hepatobiliary dysfunction in newborn infants[17-20]. The clinical spectrum of parenteral nutrition-associated liver disease (PNALD) encompasses cholestasis, cholelithiasis, elevated transaminases, steatosis, fibrosis, biliary cirrhosis, portal hypertension and, potentially, hepatic failure[18]. Although PNALD's pathogenesis may be multifactorial, omega-6 fatty acids in PN regimens now appear to be the primary etiologic agent[19]. Additional risk factors include prematurity, other nutrient excesses or deficiencies, sepsis from the central line, decreased enterohepatic circulation, intestinal stasis, and bacterial overgrowth[20].

The published literature most often defines PNALD in this setting as a direct bilirubin (db) > 2.0[20,21]. As this was a pilot study to provide preliminary data on predicting hepatobiliary disease in the premature infant, transaminase values were also examined. While alanine transaminase (ALT) has been considered a more specific marker for liver dysfunction, aspartate transaminase (AST) has recently been employed as part of a derived AST/platelet ratio index, to predict liver pathology in infants with intestinal failure[22] and biliary atresia[23].

Most low birth weight infants, especially sicker babies, are unavoidably exposed to multiple risk factors associated with hepatobiliary dysfunction, including PN and PRBC transfusions. This retrospective study was conducted to determine if there was any preliminary evidence suggesting that the volume of PRBC transfusions received was associated with the subsequent development of PNALD in this population.

MATERIALS AND METHODS

This retrospective chart analysis was performed as part of a study of 49/51 premature infants maintained on PN

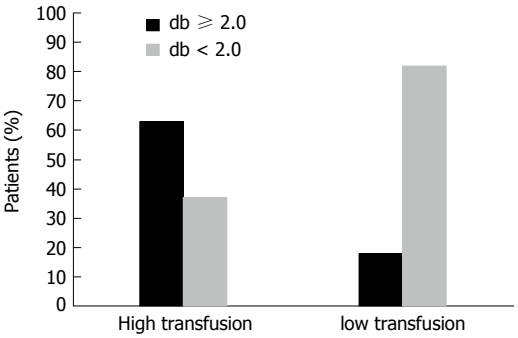

Figure 1 The number of patients that reached peak direct bilirubin ⩾ 2.0 (black bar) or direct bilirubin < 2.0 (grey bar). They are shown for both the low transfusion (total PRBC volume < 75 mL) and the high transfusion (total blood volume ⩾ 75 mL) groups (high transfusion *vs* low transfusion $P < 0.01$). db: Direct bilirubin.

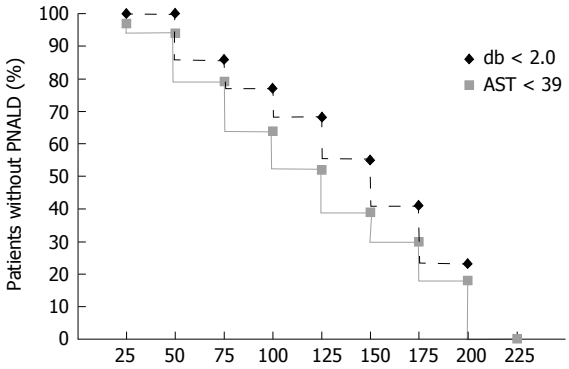

Figure 2 Kaplan-Meier plots tracking the onset of parenteral nutrition associated liver disease by the direct bilirubin and aspartate transaminase criteria as a function of total packed red blood cell transfused. PNALD: Parenteral nutrition-associated liver disease; db: Direct bilirubin; AST: Aspartate transaminase.

> 30 d, at the Children's Hospital at Downstate, State University New York, Downstate Medical Center. Two patients, one with cystic fibrosis and one with Hirschsprung disease (disorders independently associated with cholestasis), were excluded from analysis. In these 49 infants, we assessed the timing and volume of PRBC transfusions, and PNALD was primarily defined as a db level > 2.0 mg/dL[20,21].

One of the authors, SMS performed all of the biomedical statistics. Kaplan-Meier plots estimated the amount of PRBC transfused to attain PNALD onset by this db criterion. Similar analyses were performed for elevation of AST and ALT as alternative markers of PNALD. Proportional hazards regression analysis used age at PNALD onset as the dependent variable, and cumulative RBCs as the time dependent predictor of interest. Potential confounders were cumulative days on TPN (time-dependent) and birth weight. Odds ratios, hazard ratios (HR) and confidence intervals (CI) are reported. This study was approved by the Institutional Review Board of SUNY Downstate Medical Center.

RESULTS

In this cohort of 49 NICU infants, 21 (43%) reached the endpoint of PNALD, defined by a db > 2.0 mg/dL. To analyze any potential role of PRBC transfusions in the development of PNALD, the study population was subdivided into high and low transfusion groups. The subgroups were defined by the median volume transfused in this study cohort, specifically transfusion volumes of ⩾ 75 mL (high) or < 75 mL (low). Employing this cut off value, 27/49 (55%) infants were in the high transfusion group and 22/49 (45%) were in the low transfusion cohort.

Figure 1 shows the relationship between transfusion volume and PNALD, as defined by a db > 2.0 mg/dL. Among the 27 high transfusion infants, 17 (64%) developed PNALD, while PNALD was seen in only 4/22 infants (18%) in the low transfusion group. Further, among all infants who developed PNALD, 17/21 (81%) received PRBC ⩾ 75 mL while only 10/28 (36%) received < 75 mL PRBC volumes ($P < 0.001$). The calculated odds ratio for developing PNALD, based on being in the high verses low transfusion group, was 7.6 (95%CI: 2.01-29.1).

Kaplan-Meier plots provide another perspective on the relationship between PRBC transfusions and PNALD (Figure 2). With cumulative transfusion volumes of 126-150 mL, the prevalence of db > 2.0 mg/dL reached 50%. All infants who were transfused > 200 mL PRBC demonstrated PNALD. Regression analysis showed neither birth weight nor cumulative time on TPN were significant predictors of these endpoints, when used as linear covariates (data not shown). However, cumulative PRBCs were a significant predictor of db ⩾ 2.0 with an estimated HR associated with each additional 15 mL/kg transfused of 1.09 (95%CI: 1.00-1.19). After controlling for birth weight and PN duration, PRBC volume transfused remained a predictor of reaching the primary end point of db ⩾ 2.0. The HR related to incremental PRBC transfused volumes approached significance for each 15 mL/kg (HR = 1.11, 95%CI: 1.00-1.23, $P = 0.053$). However, when the NEC cases were excluded, the transfusion effect on db ⩾ 2.0 became statistically significant ($P = 0.026$).

Five of the 49 infants in our study developed NEC. Of these five infants, three also had culture proven sepsis, and two of these three exhibited PNALD. Of the two infants with NEC but without sepsis, both demonstrated PNALD. Overall, 11/17 study subjects with culture proven sepsis demonstrated PNALD. Employing elevated transaminases, AST and ALT, to define PNALD yielded results similar to those based on db ⩾ 2.0. PNALD was seen in 67% of the cohort based on AST elevations and in 41% based on ALT elevations. Of the 33 infants with AST-defined PNALD, 70% were in the high transfusion and 30% were in the low transfusion cohorts. Similarly, among the cohort of 20 infants with PNALD defined by elevated ALT, 75% were in the high transfusion and 25% were in the low transfusion groups. Similarly to db PNALD, the odds ratio for developing PNALD based on high *vs* low PRBC transfusion was 6.9 (95%CI: 1.78-26.7) if defined by AST, and was 4.2 (95%CI: 1.21-14.9) if

defined by ALT.

DISCUSSION

Although potentially lifesaving, blood transfusions are associated with risks in the NICU[7,8]. Several studies have attempted to better define indications for transfusion in NICU babies[24,25]. Previous investigations have sought to develop transfusion protocols, to achieve an acceptable balance between the risks and the benefits of transfusing preterm infants[1,7,25]. The PINT trial concluded that a higher hemoglobin threshold for transfusions in the NICU resulted in a greater number of transfusions without any added benefit, when compared to a restricted hemoglobin threshold[26]. In the present review of 49 premature infants on TPN, transfusion of $\geqslant$ 75 mL PRBC represented a significant risk factor for developing PNALD. If this relationship is confirmed in larger studies, the potential benefits of PRBC transfusions could be balanced with the associated risk of developing liver disease.

The pathogenesis of hepatotoxicity secondary to both PRBC transfusions and PN includes injury secondary to the generation of hepatic reactive oxidative stress (ROS)[26-30]. Since no effective mechanisms allow for excretion of parenteral iron, repeated transfusions can yield secondary Iron overload[27]. The primary sites for iron overload toxicity are those tissues where iron is stored, with liver being the main target[28]. One of the most important recognized mechanisms of liver injury in this setting is free radical mediated oxidative damage[29]. Preterm infants are especially vulnerable to this insult, as a higher proportion of their iron remains unbound to transferrin, leading to increased ROS[30]. Malonylaldehyde (MDA), a byproduct of hepatic ROS, has been employed as a marker of oxidative stress. Elevations of this compound are associated with chronic transfusion states, such as thalassemia and sickle cell disease[31]. Emerging evidence has also implicated oxidative damage as a factor in PNALD[32,33]. Animal models of PNALD using weanling rat[32] and infant rabbit[33] have correlated severity of liver injury and hepatic MDA content with time on PN.

Several important limitations are associated with this pilot study. This retrospective analysis involved a relatively small number of representative NICU patients. Additionally, the cohort was heterogeneous, as subjects were included over a wide range of gestational ages. Other potential comorbidities, previously identified as PNALD risk factors, were unable to be controlled. If this small study group were to be further subdivided, the numbers would not provide meaningful data. Finally, because this is a small cohort, the higher PRBC transfusions volumes associated with PNALD may actually be secondary to coexisting conditions which are the true primary risk factors for this condition.

In conclusion, our pilot study supports the hypothesis that repeated PRBC transfusions increase the risk of PNALD in NICU infants. This preliminary observation is being presented to stimulate further studies employing larger NICU databases. Access to this information could yield a series of well-defined PRBC transfusion recommendations and/or guidelines based on specific characteristics in this vulnerable cohort.

COMMENTS

Background

Parenteral nutrition is commonly associated with liver disease in the neonatal intensive care unit (NICU). There are a variety of factors that have been described as risk factors for this problem including prematurity, time on parenteral nutrition, sepsis, prolonged periods without enteral nutrition and necrotizing enterocolitis. Packed red blood cells transfusions which can generate reactive oxygen species especially in the livers of premature neonates are a potential trigger for this morbidity.

Research frontiers

Whether the transfusion of packed red blood cells is an actual contributor to the incidence of cholestatic liver disease in the NICU infant receiving parenteral nutrition has not been systematically investigated.

Innovations and breakthroughs

This retrospective pilot study compared a cohort of NICU infants on parenteral nutrition who had received more than the median volume of packed red blood cell transfusions to a second cohort from the same nursery at the same time who received less than the median value. Higher volumes of transfusion led to a statistically significant increase in the prevalence of liver disease in this study as defined by elevated direct bilirubin, by elevated aspartate transaminase and by elevated alanine transaminase.

Applications

This preliminary observation should now be investigated in larger cohorts of NICU infants. If these results are confirmed, then guidelines addressing the safety of packed red blood cell transfusions in the NICU can be developed.

Terminology

NICU: Neonatal intensive care unit; PRBC: Packed red blood cells; PNALD: Parenteral nutrition associated liver disease.

Peer-review

A small and succinct study, while it has some limitations, which are well acknowledged by the author. There are some interesting and statistically significant within this study.

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ORIGINAL ARTICLE

Retrospective Study

Clinical profile and outcomes of pediatric endogenous endophthalmitis: A report of 11 cases from South India

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Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision, editing, and final approval of the final version.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Aravind Eye Hospital.

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Abstract

AIM

To study the clinical profile and outcomes of pediatric endogenous endophthalmitis from a tertiary eye hospital in South India.

METHODS

A total of 13 eyes of 11 children presented to us with varied symptoms and presentations of endogenous endophthalmitis, over a five-year period from January 2010 to December 2015 were studied. Except for two eyes of a patient, vitreous aspirates were cultured from all 11 eyes to isolate the causative organism. These eleven eyes also received intravitreal injections. All patients were treated with systemic antibiotics.

RESULTS

Two cases had bilateral endophthalmitis. Ages ranged from 4 d to 11 years. Five cases were undiagnosed and treated, before being referred to our center. Ten of the 13 eyes underwent a core vitrectomy. The vitrectomy was done at an average on the second day after presenting (range 0-20 d). Five of the 11 vitreous aspirates showed isolates. The incriminating organisms were bacteria in three and fungus in two. An underlying predisposing factor was found in seven patients. At a mean follow-up 21.5 mo, outcome was good in 7 eyes of 6 cases (54%), five eyes of four cases (38%) ended up with phthisis bulbi while one child died of systemic complications.

CONCLUSION

Endogenous endophthalmitis is a challenge for ophtha-

lmologists. Early diagnosis and intervention is the key for a better outcome.

Key words: Pediatric; Endogenous endophthalmitis; Outcomes; South India; Fungal

Core tip: It was a retrospective study of 13 eyes of 11 children with endogenous endophthalmitis, where a detailed evaluation of the clinical profile including the presenting symptoms, signs, incriminating organisms and outcomes were studied.

Murugan G, Shah PK, Narendran V. Clinical profile and outcomes of pediatric endogenous endophthalmitis: A report of 11 cases from South India. *World J Clin Pediatr* 2016; 5(4): 370-373 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i4/370.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i4.370

INTRODUCTION

Endogenous endophthalmitis is a rare, but highly destructive infection of the eye, in which the pathogenic organisms reach through the systemic circulation. Studies have shown that endogenous endophthalmitis accounts for 2% to 8% of all endophthalmitis cases[1,2]. It is even rarer in children, and constitutes only 0.1% to 4% of all endogenous endophthalmitis cases[2,3]. In children it may masquerade as uveitis, pre septal orbital cellulitis, congenital glaucoma, conjunctivitis or retinoblastoma. It can also occur as a rare complication of neonatal sepsis. In a particular series in India from a tertiary hospital for every 1000 live births, 1 case of endophthalmitis was seen[4]. The incidence of neonatal endophthalmitis from the United States is about 4.42 cases per 100000 live births[5]. The reasons for the high incidence of endophthalmitis in Indian population may be because of more immunocompromised, poor hygiene and high rates of infection secondary to antibiotic resistant microbes[4]. We report a series of 11 chidren presenting with endogenous endophthalmitis at our institute over a period of five years.

MATERIALS AND METHODS

This is a retrospective study of 13 eyes of 11 children who presented at Aravind Eye Hospital, Coimbatore with signs and symptoms of endogenous endophthalmitis. After taking a detailed history from all the patients, a through ocular examination was done. Visual acuity was taken for all cooperative cases. This was followed by through anterior examination using slip lamp biomicroscopy. Fundus examination was done with indirect ophthalmoscopy. B scan ultrasonography was done for all cases with a hazy media. Short general anesthesia was administered to children who very not cooperative for a through ocular examination. Cases with severe infection were immediately posted for vitreous biopsy with or without core vitrectomy with intravitreal antibiotic injections. All were given systemic antibiotics. All vitreous aspirates were cultured at the microbiology department of Aravind Eye Hospital, Coimbatore. A thorough systemic examination was undertaken with the help of a paediatrician to look for any precipitating factors. A good outcome was defined as maintenance of ocular anatomy with functional vision at the end of treatment.

RESULTS

Two cases had bilateral disease. There were 5 females and 6 males. The mean age was 43 mo (range 4 d to 132 mo). Ten cases (91%) presented with swelling, pain and redness in the eyes. Ten of the 13 eyes underwent a vitreous biopsy with core vitrectomy and intravitreal antibiotics injection. One patient underwent only a vitreous tap with lens aspiration for a lens abscess with intravitreal antibiotics. Two eyes of another patient who suffered from a multifocal retinochoroidal infiltrate secondary to septic arthritis recovered with systemic antibiotics alone. Eleven vitreous aspirates were cultured to isolate the causative organism. The mean time from the onset of symptoms to presentation was 11 d (range 3-30 d). Five cases were undiagnosed by the treating ophthalmologist, before being referred to our center. Of these two were being treated as uveitis, two as conjunctivitis and one as suspected retinoblastoma. There did not seem to be a prediliction for either eye with an almost equal distribution of 5 left and 4 right eyes. Both the eyes were affected in two patients. Five of the 11 vitreous taps showed isolates. The incriminating organisms were fungi in two and bacteria in remaining three (Table 1). Core vitrectomy was done in 10 eyes at a mean of second day after presentation (range 0-20 d).

A positive blood culture was seen only in case 8 which grew pseudomonas in blood, vitreous and also from the hand abscess. An underlying predisposing factor was found in seven patients. Case 1, who developed endophthalmitis secondary to broncho pneumonia and meningitis, the vitreous tap and the cerebrospinal fluid both tested positive for Aspergillus. This child met a fatal end within two weeks of presenting to us due to his systemic condition. Case 5 was referred with a suspected diagnosis of retinoblastoma. Child had multiple small yellowish retinal lesions over posterior pole and periphery in both eyes with a history of septic arthritis. The ocular lesions resolved completely with systemic antibiotics only (Figure 1). Good outcome was seen in 7 eyes of 6 cases (54%), of which final visual acuity of $\geqslant$ 6/9 was seen in 5 eyes and $\leqslant$ 6/36 in 2 eyes. Five eyes of 4 cases ended up with phthisis bulbi and one child died of systemic complications.

DISCUSSION

Detection of endogenous endophthalmitis is based on a through history and a good ocular examination.

Table 1 Baseline characteristics and outcome of all cases

Case	Age (mo)	Sex	Eye	Vitreous growth	Systemic affection		Follow-up (mo)	Final outcome
					Focus	Growth		
1	24	M	LE	Aspergillus flavus	Broncho pneumonia, meningitis with cerebral abscess	Aspergillus flavus	1	Death
2	132	M	LE	Nil	-	-	48	Good
3	48	M	LE	Neisseria meningitides	Fever	-	44	Good
4	36	F	RE	Nil	URI		7	Phthisis bulbi
5	1	F	BE	-	Knee arthritis	-	26	Good
6	7	M	LE	Candida	Pre term		9	Phthisis bulbi
7	48	F	RE	Staphylococci	Fever with cough		24	Good
8	4[1]	M	BE	Pseudomonas aeruginosa	Hand abscess	Pseudomonas aeruginosa	48	Phthisis bulbi
9	108	M	LE	Nil	-	-	9	Good
10	24	F	RE	Nil	-		18	Good
11	48	F	RE	Nil	Fever with URI		3	Phthisis bulbi

[1]In days. LE: Left eye; RE: Right eye; BE: Both eyes; URI: Upper respiratory tract infection; M: Male; F: Female.

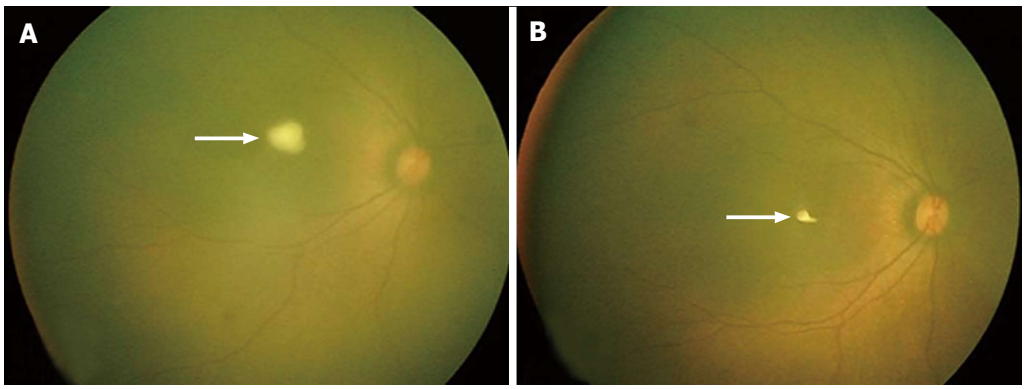

Figure 1 Retcam fundus image showing reduction of retino-choroidal abscess pre and post treatment. A: Fundus picture of right eye showing yellowish lesion over fovea (white arrow) suggestive of active chorio-retinitis; B: Fundus picture of same eye showing dramatic reduction in the size of the lesion (white arrow), 1 wk after systemic antibiotics.

Early detection of endophthalmitis in children is really challenging because they may not be able to identify or express their symptoms. On top of that, it is usually not easy to carry out a thorough ocular examination. Though there have been innumerable studies on adult onset endogenous endophthalmitis there is limited literature in pediatric group. In the study by Basu *et al*[4] six premature infants with extremely low birth weight developed endogenous endophthalmitis. They reported Klebsiella pneumoniae and Pseudomonas aeruginosa in two cases each and Candida albicans and Methicillin resistant *Staphylococcus aureus* in one case each. Three of the 6 cases died in their series and remaining 2 infants retained good vision and one ended up with phthisis bulbi. Our study had two neonates of which one was proven to be pseudomonas. There was one death in our study and 5 (38%) eyes went for phthisis bulbi.

Wrong diagnosis at the time of referral is reportedly seen in 16% to 63% of cases, thus delaying the proper treatment[6,7]. In our study 5/11 cases (45%) were referred to us with a wrong diagnosis, which were, two as uveitis, two as conjunctivitis and one as retinoblastoma. Common sources of infection in endogenous endophthalmitis in children include distal wound infection, meningitis, which was seen in one case each in our study, intravenous catheters, endocarditis and urinary tract infections[8,9]. In United States, the rate of endogenous endophthalmitis from septicemia declined from 8.71 cases in 1998 to only 4.42 cases per 100000 live births in 2006, which is a 6% decrease per year[5]. This may be due to the improvement in neonatal care and the advent of effective broad spectrum antibiotics in the treatement of septicemia. A major review of pediatric infectious endophthalmitis by Khan *et al*[8] found *Streptococcus* and *Staphylococcus* species as the most common cause of post-traumatic and post-operative endophthalmitis and Candida albicans for endogenous endophthalmitis. We had two cases with fungal infection in our study.

In conclusion, endogenous endophthalmitis in children is a diagnostic and therapeutic challenge for ophthalmologists. It can occur at any age, and in either sex. Since there is a usually a septic foci, systemic antibiotics seem to play a much definitive role in treatment. Inspite of early diagnosis and treatment, 1/3rd of patients can still have a dismal outcome.

COMMENTS

Background

Pediatric endogenous endophthalmitis is a devastating infection of the eye

which can lead to permanent blindness.

Research frontiers

Although a blinding condition, early diagnosis and treatment can save the eye and vision.

Innovations and breakthroughs

Finding the source of infection is important as this may lead to a quicker recovery. Apart from systemic antibiotics, core vitrectomy with intravitreal antibiotic injections by a retinal surgeon may improve the prognosis, as seen in the present study.

Applications

The study results suggest that prompt and correct diagnosis and treatment can lead to better outcome.

Terminology

Endogenous endophthalmitis is a severe and serious infection of the eye where the source of infection is from a distal organ. The infective organisms reach the ocular tissues *via* the blood stream.

Peer-review

This study has valuable data that would be of interest if published. It is well written and comprehensive.

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ORIGINAL ARTICLE

Observational Study

Pandemic influenza 2009: Impact of vaccination coverage on critical illness in children, a Canada and France observational study

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Abstract

AIM

To study the impact of vaccination critical illness due to H1N1pdm09, we compared the incidence and severity of H1N1pdm09 infection in Canada and France.

METHODS
We studied two national cohorts that included children with documented H1N1pdm09 infection, admitted to a pediatric intensive care unit (PICU) in Canada and in France between October 1, 2009 and January 31, 2010.

RESULTS
Vaccination coverage prior to admission to PICUs was higher in Canada than in France (21% *vs* 2% of children respectively, $P < 0.001$), and in both countries, vaccination coverage prior to admission of these critically ill patients was substantially lower than in the general pediatric population ($P < 0.001$). In Canada, 160 children (incidence = 2.6/100000 children) were hospitalized in PICU compared to 125 children (incidence = 1.1/100000) in France ($P < 0.001$). Mortality rates were similar in Canada and France (4.4% *vs* 6.5%, $P = 0.45$, respectively), median invasive mechanical ventilation duration and mean PICU length of stay were shorter in Canada (4 d *vs* 6 d, $P = 0.02$ and 5.7 d *vs* 8.2 d, $P = 0.03$, respectively). H1N1pdm09 vaccination prior to PICU admission was associated with a decreased risk of requiring invasive mechanical ventilation (OR = 0.30, 95%CI: 0.11-0.83, $P = 0.02$).

CONCLUSION
The critical illness due to H1N1pdm09 had a higher incidence in Canada than in France. Critically ill children were less likely to have received vaccination prior to hospitalization in comparison to general population and children vaccinated had lower risk of ventilation.

Key words: Vaccine; Children; Intensive care; Critical care; Influenza; Pandemic

Core tip: This article is on a two national cohorts study from Canada and France of critically ill children during influenza pandemic and reports that: (1) critically ill French children were much less likely to have received vaccine prior to hospitalization against influenza A(H1N1)pdm09 in comparison to children in the Canadian populations; and (2) in Canada, where vaccination rate was higher, the risk of severe respiratory failure was less among those critically ill children receiving vaccine.

Fléchelles O, Brissaud O, Fowler R, Ducruet T, Jouvet P, the Pediatric Canadian Critical Care Trials Group H1N1 Collaborative and Groupe Francophone de Réanimation et Urgences Pédiatriques. Pandemic influenza 2009: Impact of vaccination coverage on critical illness in children, a Canada and France observational study. *World J Clin Pediatr* 2016; 5(4): 374-382 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i4/374.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i4.374

INTRODUCTION

By March 2009, pandemic influenza A(H1N1)pdm09 had begun to spread from Mexico across the globe. The epidemiology of the first pandemic wave in Canada revealed that A(H1N1)pdm09 affected both young healthy patients and patients with underlying conditions. The severity of illness among children was high, predominantly due to severe hypoxic respiratory failure, resulting in prolonged pediatric intensive care unit (PICU) length of stay and mechanical ventilation, in comparison with seasonal influenza[1]. Countries from the Southern Hemisphere also reported early patterns of severity of illness including higher mechanical ventilation rate and higher mortality than previously observed with seasonal influenza[2,3].

To limit the impact of the pandemic influenza A(H1N1)-pdm09 especially on children[4-6], a vaccination campaign was conducted just before the second wave. However, different vaccine coverage across countries was observed, especially between Canada and France[7-10]. In order to study the impact of pandemic influenza H1N1 vaccination prior to hospitalization on critical illness, we conducted a bi-national observational study in 42 centers across Canada and France on pandemic influenza A(H1N1)-associated critically illness in children, the most sensitive population affected by the pandemic. We originally hypothesized that the higher rate of vaccination coverage in children in Canada and previous exposure to influenza A(H1N1)pdm09 would have protected Canadian children from critical illness in the Fall of 2009.

MATERIALS AND METHODS

Ethical considerations

The participating institutions' research ethics boards approved study procedures in the two countries (Sainte-Justine IRB and Bordeaux IRB). The need for informed consent was waived given the non-interventional study design.

Study design

We studied pandemic influenza A(H1N1)pdm09 incidence and severity in children in Canada and France using two multicenter national databases designed for pandemic surveillance. A key difference between the two countries was that 54% of children in Canada and 18% in France had been vaccinated[7-10]. On the other hand, Canada and France are two similar industrialized countries with a gross domestic product par capital ranking, 15th and 23rd rank in the world, respectively - with similar per capita health expenditures[11,12]. Their climates during autumn are similar (average temperatures (low/high) are 0 ℃ to 15 ℃ in Canada and 5 ℃ to 20 ℃ in France). France and Canada have similar health care systems in that they are based on social health insurance to provide near universal coverage to the adult and pediatric populations. Family practitioners provide primary health care in each country and most vaccine delivery does not require out-of-pocket payment. The number of PICU is also similar (2.9 bed/100000 children under 15 years in Canada and 2.5 beds per 100000 children in France)[9,13]. During the pandemic, treatment recommendations were the

same, those of the World Health Organization. Although oseltamivir was not prescribed initially to children under two years of age in Canada, and under one year of age in France, as of October 27, 2009 in Canada and December 10, 2009 in France, these restrictions were abolished[14,15]. Vaccination campaigns were organized in the two countries with the same priority groups and guidelines[16-18]. The campaigns started on October 18, 2009 in Canada and October 20, 2009 in France[19].

Data collection was prospective in all Canadian PICUs (n = 17). In France, data collection was both prospective and retrospective in 25 of 29 French PICUs. Four French PICUs did not participate to the study. All children admitted to a participating PICU in Canada and France, with documented A(H1N1)pdm09 infection between October 1 2009 and January 31 2010, were included. During this second wave of pandemic influenza A(H1N1)pdm09, all children admitted to PICU with clinical symptoms of H1N1 infection or strong epidemiologic link to patients with known H1N1 infection were tested for H1N1, in both countries. Proven A(H1N1)pdm09 corresponded to World Health Organization criteria in both countries: Any specimen yielding influenza A(H1N1)-pdm09 by polymerase chain reaction and/or viral culture[20]. Variables in common between both databases were identified.

Data collection and outcomes

The data collected in both cohorts included demographic characteristics, vaccination history, comorbid conditions, admission severity of illness according to the Pediatric Logistic Organ Dysfunction (PELOD)[21] and Pediatric Index of Mortality 2 (PIM2)[22] scores, and intensive care management conditions. The geographic area of 17 Canadian PICUs corresponded to a pediatric population of almost 6 millions children[23] and the 25 French PICUs cover a pediatric population of almost 11 millions children[24]. We also collected data on infection severity including acute respiratory distress syndrome (ARDS) that is characterized by an acute hypoxemia due to lung inflammation[1] in reaction to viral infection or secondary bacterial infection, nosocomial infection that could result from invasive treatments and seizures.

The study's primary objective was to assess whether vaccination prior to hospitalization protects against critical illness. The secondary outcomes were A(H1N1)pdm09 incidence, the timing of the epidemic peak and the epidemic duration, PICU mortality, the incidence and duration of invasive mechanical ventilation, PICU length of stay between the two countries. Mechanical ventilation was considered invasive if delivered through an endotracheal tube or a tracheostomy. The duration of each episode of mechanical ventilation was defined as the time from intubation to final extubation or death. Mechanical ventilation was considered non-invasive if delivered through a nasal or facemask interface. Total duration of ventilation corresponded to the sum of the periods of both invasive and non-invasive ventilation.

Statistical analysis

Descriptive statistics included counts and proportions, means (and standard deviations), medians (and inter-quartile ranges) as appropriate. Incidence and incidence curves were calculated using as a denominator, the number of susceptible patients in the population in each country from Statistics Canada and the "Institut National de la Statistique et des Etudes Economiques" in France. We compared the two countries using bi-variate analysis including Pearson's χ^2 test or Fisher's exact test for categorical variables. Student's t-test, Wilcoxon rank-sum test or the log-rank test, were used for continuous variables. To assess associations between patient or country factors and outcomes, we performed a multivariate logistic regression for invasive ventilation risk and Cox proportional hazards modeling for time-dependent variables such as length of stay and invasive ventilation duration. Because data came from two different cohorts, there was heterogeneity in data distributions, requiring country-specific analyses for many variables. Variables used in final multivariate models met the following criteria: Factors of clinical interest or possibly associated with the outcomes ($P < 0.1$ in univariate analysis), more than 3 cases per group and per country, and with few (< 5%) missing values in each country. All variables were tested for excessive (> 0.80) co-linearity. For Cox regression modeling, variables respected the proportional hazards assumption. Analyses were considered statistically significant at $\alpha < 0.05$. SPPS version 19 was used for all analyses. The statistical methods of this study were performed by a biomedical statistician (Thierry Ducruet from Sainte-Justine Hospital, co-author).

RESULTS

Epidemiologic data

In total 285 children were included, 160 in Canada and 125 in France. The rate of admission to PICU due to A(H1N1)pdm09, calculated using the estimated population studied (see methods), was 2.63 per 100000 children in Canada and 1.15 per 100000 children in France (Table 1). The incidence curves showed a higher peak (41 *vs* 17 admissions per week, both during week 45) but shorter pandemic period (6 wk *vs* 11 wk) in Canada compared to France (Figure 1).

Baseline characteristics and health status on admission (Table 1)

The sex ratios and age distribution of critically ill children were similar in Canada and in France. After vaccination program start (Figure 1), vaccination coverage prior to hospitalization of children admitted to PICU was higher in Canada than in France (21% *vs* 2% of children respectively, $P < 0.001$), and in both countries, this vaccination coverage was substantially lower than that of the general pediatric population ($P < 0.001$, using conservative estimates of 54% in children in Canada and 18% in

Table 1 Characteristics of critically ill children with influenza A(H1N1)pdm09 virus at admission to the pediatric intensive care unit in two countries

	Canada (*n* = 160)	France (*n* = 125)	OR (95%CI) Canada/France	*P* value
Incidence rate (/100000 children)	2.6	1·1	2.3 (1.8-2.9)	< 0.001
Age, mean (SD), yr	6.6 (0.40)	5.5 (0.48)	NA	0.09
Weight, mean (SD), kg	25.9 (1.62)	20.1 (1.45)	NA	0.01
Female gender, *n* (%)	68 (42)	56 (45)	0.91 (0.57-1.46)	0.70
Vaccination H1N1, *n* (%)	34 (21)	2 (2)	16.6 (3.90-70.6)	< 0.001
Underlying chronic conditions, *n* (%)				
Any underlying conditions	102 (64)	93 (74)	0.60 (0.36-1.01)	0.05
Infant < 1 years old	21 (13)	32 (25)	0.44 (0.24-0.81)	0.007
Lung disease	65 (40)	29 (23)	2.26 (1.34-3.82)	0.002
Asthma	42 (26)	16 (13)	2.40 (1.29-4.56)	0.005
Chronic lung disease	33 (20.6)	14 (11.2)	2.06 (1.05-4.05)	0.03
Cystic fibrosis	0 (0)	2 (2)	NA	NA
BPD	4 (2)	4 (3)	0.78 (0.19-3.16)	0.73[1]
Tracheostomy	5 (3)	1 (1)	4.00 (0.46-33.3)	0.24[1]
Congenital heart disease	24 (15)	3 (2)	7.18 (2.11-24.4)	< 0.001
Neurological disease	31 (19)	19 (15)	1.33 (0.71-2.50)	0.36
Seizure disorder	19 (12)	5 (4)	3.23 (1.18-9.09)	0.02
Immunosuppressive disorder	11 (7)	9 (7)	0.95 (0.38-2.37)	0.91
Diabetes mellitus	6 (3.8)	0 (0)	NA	0.04[1]
Renal insufficiency	7 (4)	1 (1)	5.56 (0.69-50.0)	0.08[1]
Others diseases	32 (20)	28 (22)	0.87 (0.95-1.54)	0.62
PELOD score, mean (SD)[2]	6.67 (0.82)	7.80 (1.47)	NA	0.47
PIM2 score, mean (SD)[3]	8.47 (1.05)	9.74 (2.77)	NA	0.67
Clinical presentation at admission				
Lower respiratory infection, *n* (%)	101 (63)	90 (72)	0.67 (0.40-1.10)	0.11
CNS infection	2 (1)	7 (6)	0.21 (0.04-0.99)	0.04
Shock	13 (8)	6 (5)	1.75 (0.65-4.76)	0.26
Other	48 (30)	35 (29)	1.10 (0.67-1.85)	0.90
Bacterial infection at admission	22 (14)	27 (22)	0.58 (0.31-1.07)	0.08

[1]Fisher's exact test; [2]Missing values PELOD: 42.4% in France, 1.9% in Canada; [3]Missing values PIM2: 37.6% in France, 0% in Canada. Chronic lung disease = chronic restrictive lung syndrome and chronic upper airway disease and tracheo/bronchomalacia and obstructive sleep apnea and recurrent aspiration into lungs and others; Immune deficit = oncologic disorder and HIV and hemoglobinopathy. CI: Confidence interval; NA: Not applicable; BPD: Broncho-pulmonary dysplasia; PELOD: Pediatric logistic organ dysfunction; PIM2: Paediatric index of mortality revised version; OR: Odds ratio; SD: Standard deviation.

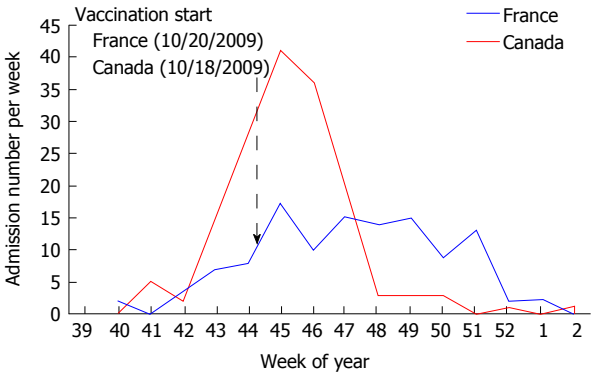

Figure 1 Admission number per week in pediatric intensive care units in Canada (red line) and France (blue line). In Canada, the decrease in incidence starts 2 wk after vaccination campaign start.

France[7-10]). Co-morbid conditions were common in both Canada and France but individual distributions were different.

Clinical presentation and hospital course

The most common reason for PICU admission was lower respiratory infection in both Canada (63%) and France (72%) and clinical presentations at admission were similar between the two countries (Table 1). The mean organ dysfunction score (PELOD score) at day one and mean predicted mortality score (PIM2 score) were similar. During hospitalization, there was a higher rate of severity of illness in France: ARDS, nosocomial infection, nosocomial pulmonary infection, and seizures (Table 2).

Outcomes

Mortality rate (4.4% *vs* 6.5%, *P* = 0.45) and rate of invasive mechanical ventilation (49% *vs* 40%, *P* = 0.14) were similar in Canada and France (Table 2). The duration of invasive mechanical ventilation (median, 4 d *vs* 6 d, *P* = 0.02) and total (invasive and non-invasive) mechanical ventilation (4 d *vs* 5 d, *P* = 0.07) was shorter in Canada than in France (Table 2). The mean PICU length of stay was shorter in Canada (5.7 d *vs* 8.2 d, *P* = 0.03) but median PICU length of stay was not different (3 d *vs* 2.9 d).

Among Canadian patients, independent multivariate analyses showed that H1N1 vaccination and asthma were associated with an almost four-fold decrease risk of invasive ventilation: (OR = 0.3, 95%CI: 0.11-0.83, *P* = 0.02) and (OR = 0.23, 95%CI: 0.09-0.64, *P* = 0.004), respectively (Table 3). This multivariate analysis did not include French patients because there were only 2

Table 2 Hospital course of critically ill children with influenza A(H1N1)pdm09 infection in two countries

	Canada (n = 160)	France (n = 125)	OR (95%CI), difference	P value
Time-dependent variables, median (25th 75th percentile), d				
PICU length of stay	2.9 (2.1-3.6)	3.0 (1.8-4.2)	0.1	0.03
Duration of mechanical ventilation	4.0 (2.8-5.2)	5.0 (3.2-6.8)	1	0.07
Duration of invasive ventilation	4.0 (2.9-5.1)	6.0 (4.6-7.4)	2	0.02
Categorical variables, n (%)				
Mortality	7 (4.4)	8 (6.5)	0.67 (0.24-1.90)	0.45
Respiratory dysfunction				
ARDS	29 (18)	40 (32)	0.48 (0.27-0.81)	0.007
Mechanical ventilation	86 (54)	66 (53)	1.04 (0.67-1.67)	0.87
Invasive ventilation	78 (49)	50 (40)	1.43 (0.91-2.50)	0.14
Pneumothorax	19 (12)	10 (8)	1.17 (0.67-3.33)	0.32
ECMO	3 (2)	8 (6)	0.28 (0.07-1.07)	0.05
Neurologic dysfunction				
Seizures	2 (1)	9 (7)	0.16 (0.03-0.13)	0.01
ADEM	3 (2)	7 (6)	0.32 (0.08-1.26)	0.09
Renal dysfunction				
Dialysis/hemofiltration	10 (6)	4 (3)	2.00 (0.63-6.67)	0.24
Nosocomial infections				
Nosocomial infection	15 (9)	26 (21)	0.39 (0.20-0.78)	0.006
Ventilator-associated pneumonia	9 (6)	21 (17)	0.29 (0.13-0.67)	0.002
Antiviral treatment				
Oseltamivir	148 (93)	111 (89)	1.55 (0.69-3.49)	0.28
Oseltamivir within 48 h	102 (63)	99 (79)	0.46 (0.27-0.79)	0.004

A bivariate analysis compared mortality, organ dysfunction, nosocomial infection and anti-viral treatment between the two countries. OR: Odds ratio; CI: Confidence interval; PICU: Pediatric intensive care unit; ARDS: Acute respiratory distress syndrome: ECMO: Extracorporeal membrane oxygenation; ADEM: Acute demyelinating encephalo-myelitis or demyelinating disorder.

Table 3 Critically ill patient-based factors associated with risk of invasive ventilation in Canada

Included variables	n = 157	OR	95%CI	P value
PIM2 > 7.5	39	6.26	2.43-16.4	< 0.001
Age, years < 1	21	1.88	0.51-6.94	0.35
1-4	52	1.50	0.51-4.35	0.46
5-9	46	2.42	0.45-6.93	0.10
> 10	38	1	(Ref)	
H1N1 vaccine	32	0.30	0.11-0.83	0.02
Asthma	41	0.23	0.09-0.64	0.004
Lung diseases (not asthma)	22	0.99	0.32-3.08	0.99
Neurologic diseases	31	2.51	0.92-6.90	0.07
Cardiologic diseases	28	1.13	0.43-2.97	0.76
Others diseases	47	0.87	0.37-2.05	0.76
Oseltamivir within 48 h	102	1.02	0.47-2.24	0.95

H1N1 vaccine, children vaccinated against H1N1; lung diseases, chronicle lung diseases without asthma; Neurologic disease, neurologic and muscular disorder; Cardiologic diseases, cardiologic diseases before admission; other diseases, all comorbities without lung, cardiologic or neurologic diseases. OR: Odd ratio; CI: Confidence interval; PIM2: Paediatric index of mortality revised version.

children in the vaccine group (Table 1).

DISCUSSION

Key findings

In this bi-national observational study of pandemic influenza A(H1N1)-associated critically illness in children, we found that pandemic influenza A(H1N1) vaccination prior to hospitalization was less common among critically ill children when compared to the general paediatric population, and that history of vaccination was not associated with a clinically relevant difference in PICU length of stay (0.1 d). However, in Canada, with higher vaccine coverage among critically ill patients, the PICU course seems less severe (shorter duration of invasive mechanical ventilation and PICU stay, lesser development of ARDS, and fewer subsequently acquired bacterial infections) (Table 2).

Despite a higher vaccine coverage and potential previous exposure to the virus in Canada during the first pandemic wave in the Spring of 2009[1], the incidence of admission of critically ill children to intensive care due to Influenza A(H1N1)pdm09 during the Fall of 2009 was twice as high in Canada as in France (2.6 per 100000 children *vs* 1.1 per 100000 children). However, the mortality rate for these critically ill children was similar between the two countries.

We originally hypothesized that the higher child vaccination coverage in Canada (> 50% *vs* 18% in France) and previous exposure to influenza A(H1N1)-pdm09 would have protected Canadian children from critical illness in the Fall of 2009. We did not observed such a protection. This hypothesis was based on the following arguments: (1) previous exposure to influenza A(H1N1)pdm09 would have increased herd immunity; (2) adjuvant pandemic vaccine has an efficacy up to 97%[25-27]; (3) an influenza vaccination coverage rate above 45% reduces influenza transmission[28]; and (4) modeling studies suggested that the vaccination campaign was associated with a decrease in mortality and morbidity of 20% and 18% respectively[29]. Other factors previously identified as contributing to outbreak

spread such as proximity to the first infectious focus, human mobility, reproduction number, generation time, population susceptibility, age pyramid, school calendar, and climate[30] were similar between the two countries and the underlying characteristics of the children were similar (Table 1). Given that the difference in incidence of PICU admission was the opposite of what was expected, our study suggests that additional national, geography-specific, and/or further unappreciated factors likely exhibit substantial residual influence on the incidence of pandemic influenza in differing regions of the world.

It has also been shown that the virulence of influenza A(H1N1)pdm09 strains virulence can vary considerably in animals and in humans[31-35]. Some specific strains were associated with severe disease in Canada and France but the proportion of these virulent strains in Canada and France is incompletely reported. Differing virulence could have contributed to the increased incidence of critical illness in Canada, as well as to the higher mortality observed in Argentina and Turkish pediatric cohorts when compared with those in North America, Europe and Australia and New Zealand[36-39].

Despite the higher incidence of critical illness in Canada when compared to France, our study provides some arguments on the positive impact of vaccine on influenza critical illness in children, even when the vaccine is given when pandemic second wave has already started (Figure 1). Our study showed that: (1) the second wave ended earlier than in France, which had a lower vaccine coverage; (2) vaccination coverage was substantially lower in the PICU population than in the general pediatric population; (3) total duration of mechanical ventilation was shorter in Canada; and (4) vaccination was associated with a decreased risk of invasive mechanical ventilation (Table 3). As expected, asthma was also associated with a decreased risk of invasive ventilation. This is consistent with previous findings of a low rate (4.6%) of invasive mechanical ventilation in PICU patients admitted for acute asthma[40]. The significant association between vaccination coverage and reduction in invasive mechanical ventilation is remarkable considering that the rate of invasive mechanical ventilation in children without a diagnosis of asthma diagnosis in this study was > 40%.

Strengths and weaknesses of the study

This study has several strengths: (1) It represents the largest pediatric cohort of critically ill H1N1 infection yet described in Canada and France; (2) the evolution of new H1N1 cases per week in PICUs (Figure 1) was similar to the consultations rates for influenza-like illness in the general population of Canada and France[41,42]; and (3) there was a large difference in vaccine coverage. This difference in coverage may be attributed to differences in perception of risk amongst the population such as awareness of the public health issues, the risk of being infected by the virus, the risk of severe illness if infected, and the risk of harm from a pandemic vaccine[43,44].

Our study has several limitations that should be noted. First, the suspected difference in virulence between the two countries could have created a bias on the analysis of pandemic vaccine impact. However, the analysis of critically ill children in Canada only provided an association between vaccine delivery and reduction in the risk of invasive ventilation (Table 3); second, admission criteria in PICUs are not standardized across countries and this can impact the incidence of PICU admission and inferred critical illness. However, several arguments suggest that admission criteria between Canada and France are similar, including: (1) the similar number of PICU beds per capita; and (2) patients displayed similar organ failure score (PELOD score) and predicted risk of mortality (PIM2) on admission to PICU (Table 1). Interestingly, this difference in ICU admission rate was also observed in adult intensive care units, with a rate of A(H1N1)pdm09-associated admission of 3.5/100000 population in Canada and 2.1/100000 population in France (OR = 1.7)[45,46]. Another limitation is that the two national cohorts used similar but not identical case report forms. Therefore, we needed to compare similar variables that may have been collected in slightly different ways in order to compare the two cohorts. In order to address this point for future outbreaks and pandemics, a number of national critical care research consortia initiated the International Forum of Acute Care Trialists which seeks to improve the care of acutely ill patients around the world by harmonizing case report forms and definitions[47]. This goal has been further advanced by the creation of International Severe Acute Respiratory and Emerging Infection Consortium.

In conclusion, the critical illness due to H1N1pdm09 had a higher incidence in Canada than in France. In both Canada and France, critically ill children were much less likely to have received vaccination against influenza A(H1N1)pdm09 prior to hospitalization when compared with children in the general population. In Canada, with higher vaccine coverage among critically ill patients, the PICU course seems less severe and the risk of invasive mechanical ventilation was lower amongst Canadian critically ill children receiving prior vaccination. There is a need for further studies to confirm our observations as numerous and still uncertain factors influence differences in pandemic influenza incidence and severity in different regions of the world, even in countries with similar population characteristics, access to health care resources and response systems.

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COMMENTS

Background

By March 2009, pandemic influenza A(H1N1)pdm09 had begun to spread from Mexico across the globe. The epidemiology of the first pandemic wave in Canada revealed that A(H1N1)pdm09 affected both young healthy patients and patients with underlying conditions. To limit the impact of the pandemic influenza A (H1N1)pdm0 especially on children, a vaccination campaign started when the second wave occurred. A lot of discussions criticized the vaccination campaign policy.

Research frontiers

Nowadays, Bird flu could combine with human flu to create a virulent kind of super-flu that can spread worldwide. The information gathered from previous pandemic (including the authors' study) are helpful to predict the spread and severity of such a risk.

Innovations and breakthroughs

This study report data on: (1) the incidence of critically ill children with pandemic influenza A (H1N1)pdm09 infection that was not known in Europe and Canada; (2) on mortality rate were higher in South American and Turkish studies; and (3) a positive impact of vaccination, even if started at second wave start, was not previously described in critically ill children.

Applications

According to the results, in case of pandemic, it is recommended to perform the flu vaccination as soon as the vaccine is available to potentially decrease disease severity.

Terminology

H1N1pdm09 infection: Flu pandemic; PICU: Pediatric intensive care units; ARDS: An acute hypoxemia due to lung inflammation.

Peer-review

The study is well designed with detailed methodology to assess the impact of vaccination status on severity of infection and mortality rates.

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SYSTEMATIC REVIEWS

Zinc supplementation as an adjunct to standard therapy in childhood nephrotic syndrome - a systematic review

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Data sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author at rrdas05@gmail.com.

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Abstract

AIM

To evaluate the role of zinc as add on treatment to the "recommended treatment" of nephrotic syndrome (NS) in children.

METHODS

All the published literature through the major databases including Medline/Pubmed, Embase, and Google Scholar were searched till 31st December 2015. Reference lists from the articles were reviewed to identify additional pertinent articles. Retrieved papers concerning the role of zinc in childhood NS were reviewed by the authors, and the data were extracted using a standardized data collection tool. Randomized trials (RCTs) comparing zinc *vs* placebo was included. Effect of zinc was studied in both steroid sensitive and steroid dependent/frequent relapsing NS. The primary outcome measure was the risk of relapse in 12 mo. The secondary outcome measures were mean relapse rate per patient in 12 mo, mean relapse rate per patient in 6 mo, risk of infection associated relapse in 12 mo, cumulative dose of steroids in two groups, mean length of time to next relapse, adverse effects of therapy, and change in serum zinc levels.

RESULTS

Of 54 citations retrieved, a total of 6 RCTs were included. Zinc was used at a dose of 10-20 mg/d, for the duration that varied from 6-12 mo. Compared to placebo, zinc reduced the frequency of relapses, induced sustained remission/no relapse, reduced the proportion of infection episodes associated with relapse with a mild adverse event in the form of metallic taste. The GRADE evidence generated was of "very low-quality".

CONCLUSION

Zinc may be a useful additive in the treatment of childhood NS. The evidence generated mostly was of "very low-quality". We need more good quality RCTs in

different country setting as well different subgroups of children before any firm recommendation can be made.

Key words: Nephrotic syndrome; Pediatric; Relapse; Zinc; Micronutrient

Core tip: Relapses in nephrotic syndrome (NS) increase morbidity and mortality. Studies have shown that zinc deficiency is common in NS. Zinc deficiency might lead to down-regulation of T-helper 1 (Th1) cytokines, a relative T-helper 2 (Th2) bias, and an increased risk of infection. The later commonly associated with relapse in NS. Zinc supplementation restores Th1-Th2 imbalance and may decrease relapse. The primary aim of this review is to evaluate the efficacy of zinc in preventing relapses in childhood NS (steroid sensitive and steroid dependent/ frequent relapsing). The secondary aim is to evaluate the safety of zinc supplementation in this regard.

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INTRODUCTION

Nephrotic syndrome (NS) is a chronic childhood illness characterized by heavy proteinuria, hypoalbuminemia and oedema. About 80%-85% of the patients with NS shows initial response to corticosteroids and labeled as steroid sensitive nephrotic syndrome (SSNS). Remaining 15%-20% of the patients, who do not respond to steroid therapy are labeled as steroid resistant nephrotic syndrome (SRNS)[1]. About 40%-50% of patients with SSNS have either frequent relapses (FRNS) or steroid dependent (SDNS) courses leading to prolonged course of illness. Relapses are associated with an increased risk of complications such as sepsis, thrombosis, dyslipidemia and malnutrition[2]. Although, relapses can be successfully treated with corticosteroids, repeated usage of high dose corticosteroids lead to significant side-effects like avascular necrosis of hip, hypertension, diabetes and behavioral disorders[3].

Relapses of NS often follow minor infections of the upper respiratory (URI) or gastrointestinal tracts, and the estimated frequency is around 50%-70% among children in developing countries[4,5]. Other infections such as urinary tract infection, diarrhea, peritonitis and skin infections have also been implicated as triggers for relapse[6]. Several theories like cytokine release, immune dysfunction, increased glomerular permeability, and podocytopathy are proposed, but none of them is conclusive[4,7-9].

A number of interventions have been tried to prevent/ decrease relapses in NS. Relapses are significantly reduced when daily corticosteroids are given during onset of viral URIs[10,11] or when the maintenance doses of corticosteroids are increased at the onset of viral URIs[12]. Studies have shown that zinc supplementation reduces relapses in children with SSNS[5,13]. It is proposed that zinc deficiency might lead to down-regulation of T-helper 1 (Th1) cytokines, a relative T-helper 2 (Th2) bias, and an increased risk of infection[14,15]. As a result, zinc supplementation augments the gene expression for IL-2 and IFN-γ, thereby restoring the Th1 immune response[16]. Since, the Th1-Th2 cytokine imbalance is also believed to result in relapses of SSNS, it was proposed that the benefits of supplementation in these patients may be associated with its ability to rectify the immune defect[5]. In the present systematic review, we tried to found the role of zinc supplementation as an adjunct to standard therapy in childhood NS. To evaluate the efficacy and safety of zinc in preventing relapses in childhood NS, steroid sensitive and steroid dependent/ frequent relapsing.

MATERIALS AND METHODS

The review has been registered at the PROSPERO register: CRD42015026456.

Types of studies

Randomized controlled trials (RCTs) and quasi RCT's comparing zinc with placebo or no additional intervention with ⩾ 80% follow-up (to reduce the risk of attrition bias in the included studies in case intention-to-treat analysis has not been done).

Types of participants

Children of 1 to 18 years of age with frequently relapsing or steroid dependent NS were included. Studies including children with first episode NS, secondary NS, impaired renal function, SRNS, congenital NS, serious (peritonitis, Pnumonia, cellulitis) or active infections, leucopenia, thrombocytopenia, and severe anemia were excluded.

Types of intervention

The intervention group received oral zinc supplementation regardless of the dosage and type and the control group received standard therapy alone or an oral supplementation without zinc in adjunct to standard therapy for NS.

Types of outcome measures

Steroid sensitive NS.

Primary outcomes: Frequency of relapses in 12 mo.

Secondary outcomes: Frequency of relapses in 6 mo; risk of relapse per year; risk of infection associated relapse per year; cumulative dose of steroids in two groups; mean length of time to next relapse; adverse

effects of therapy; change in serum zinc levels.

Steroid dependent/frequent relapsing NS
Primary outcomes: Frequency of relapses in 12 mo.

Secondary outcomes: Frequency of relapses in 6 mo; risk of relapse per year; risk of infection associated relapse per year; cumulative dose of steroids in two groups; mean length of time to next relapse; adverse effects of therapy; change in serum zinc levels.

Steroid sensitive: Remission is achieved within 4 wk of steroid therapy.

Relapse: It is defined as urinary protein excretion 3+/4+ on reagent strip or proteinuria > 40 mg/m^2 per hour for 3 consecutive days in patient who had previously been in remission (urine albumin trace or nil or proteinuria < 4 mg/m^2 per hour for 3 consecutive days). Frequent relapse is defined as ⩾ 2 relapses in 6 mo of initial response or > 3 relapses in 12 mo. For the treatment of relapse, the patient is initially put on daily corticosteroids till remission and then on alternate day steroids.

Steroid dependent: Two consecutive relapses while on alternate steroids or within 14 d of its discontinuation.

Frequent relapse: ⩾ 2 relapses in 6 mo of initial response or > 3 relapses in 12 mo.

Search methodology
Following major databases were searched systematically: Cochrane Central Register of Controlled Trials, PubMed/MEDLINE, Google Scholar, and EMBASE till 31st December 2015. Following search terms were used: [("zinc"/exp or "zinc" or "zinc phosphate"/exp or "zinc phosphate") and ("child"/exp or "infant"/exp or "school child"/exp or "preschool child"/exp or "toddler"/exp) and ("NS"/exp or "congenital NS"/exp or "kidney disease"/exp)] and ("randomized controlled trial"/exp or "controlled clinical trial"/exp or "clinical trial"/exp).

We also searched the major Pediatric nephrology scientific meetings and contact the authors involved in previous studies for any unpublished work. To identify unpublished trial results, we searched the United Stated National Institutes of Health, Department of Health and Human Services trials registry (http://www.clinicaltrials.gov/) and the WHO International Clinical Trials Registry Platform trial registry (http://www.who.int/ictrp/en/). No language restriction was applied. Two reviewers reviewed the search results to identify relevant original human clinical trials.

Data extraction
Data extraction was done using a pilot tested data extraction form. Two authors independently extracted data including author, year, study setting, type of population, exposure/intervention (dose of steroid, duration), results (outcome measures, effect, significance), and sources of funding/support. Any disagreement in the extracted data was resolved through discussion with the third author.

Risk of bias (quality) assessment
Two review authors independently assessed the methodological quality of the selected trials by using Cochrane risk of bias tool[17].

Grade of evidence
For assessment of the quality of evidence we used GRADE Profiler software (version 3.2)[18]. The software uses five parameters for rating the quality of evidence. The parameters used were - limitations to design of randomized controlled trials, inconsistency of results or unexplained heterogeneity, indirectness of evidence, imprecision of results, and publication bias. The rating was done as - no, serious, and very serious limitation.

Statistical analysis
The data from various studies was pooled and expressed as mean difference (MD) with 95%CI in case of continuous data, and odds ratio with 95%CI in case of categorical data. *P*-value < 0.05 was considered significant. Assessment of heterogeneity was done by I^2 statistics. If there is a high level heterogeneity (> 50%), we tried to explore the cause. A fixed effects model was initially conducted, and if significant heterogeneity existed between the trials, potential sources of heterogeneity were considered and where appropriate, a random effects model was used. RevMan (Review Manager) version 5.2 was used for all the analyses.

RESULTS

Description of the studies
Of 56 citations retrieved, full text of 7 articles were assessed for eligibility (Figure 1). Out of these, a total of 6 RCTs were included[5,13,19,20], actually 2 RCTs evaluated both SSNS/FRNS, and SSNS/SDNS[5,19]. Out of these, 2 were conference abstracts[19,20]. We contacted the authors of these abstracts for providing the details but no reply was given, so we included data given in the abstracts only. The detailed characteristics of trials have been described in Table 1. Out of the 4 trials, 2 were conducted in India, 1 in Pakistan, and 1 in Philippines. Five trials included a total of 256 children [SSNS = 2 trials (100 children); SDNS/FRNS = 4 trials (156 children)] of 1 to 18 years age (excluding neonates < 1 mo). The dose of zinc used was 10 mg/d for a period of 12 mo in one trial[5], and 6 mo in another trial[13]. In other 2 trials, one used 20 mg/d zinc for 2 wk starting at the onset of an episode of acute infection[19], and another used zinc at the recommended daily allowance dose[20].

Risk of bias in included studies
Effect of Interventions: (1) steroid sensitive NS: Primary outcome measure: Frequency of relapses in 12 mo: This was reported in 1 out of the 2 trials[5]. The

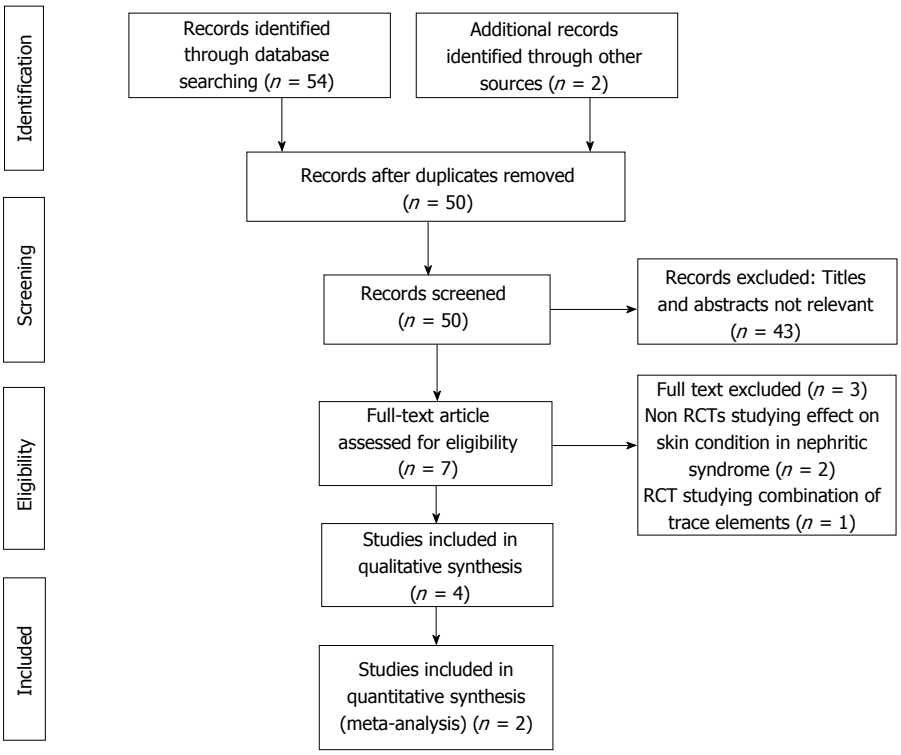

Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram. RCTs: Randomized controlled trials.

mean relapse rate was lower in the zinc group (1.0 ± 1.16) compared to the placebo group (1.2 ± 1.11), the pooled effect size showing 20% reduction that was not significant (MD = 0.2; 95%CI: 0.71-0.31); (2) secondary outcome measure: Frequency of relapses in 6 mo: This was reported in two trials[5,20]. The result could not be pooled as the data was not provided in 1 trial[19]. In one trial, the mean relapse rate was lower in the zinc group (0.49 ± 0.79) compared to the placebo group (0.68 ± 0.92), the pooled effect size showing 19% reduction (MD = 0.19; 95%CI: 0.57-0.19; $P > 0.05$). In another trial, there was significant decrease in the frequency of relapse in the zinc group[20]; risk of relapse per year: This was reported in 1 out of the 2 trials[5]. The zinc group had a 31% lower risk of relapse (RR = 0.69, 95%CI: 0.45-1.07; $P > 0.05$) compared to the placebo group; risk of infection associated relapse in 12 mo: This was reported in one trial, but the data was not provided; cumulative dose of steroids in two groups: This was not reported in any of the trials; mean length of time to next relapse: This was reported in one trial[5]. There was a non-significant decrease in the length of time (mo) to next relapse in the zinc group compared to the placebo group (7.9 *vs* 6.4; $P > 0.05$); adverse effects of therapy: A mild adverse event in the form of metallic taste was reported in three subjects in one trial[5]; change in serum zinc levels: One trial provided this information[5]. At enrollment, 5 children (zinc = 2; placebo = 3) were zinc deficient, but at 12 mo none was zinc deficient.

Steroid dependent/frequent relapsing NS: (1) primary outcome measure: Frequency of relapses in 12 mo: This was reported in 3 trials[5,13,19], however the result could be pooled from 2 trials[5,13]. There was decreased frequency of relapses in the zinc group compared to the placebo group (MD = 0.17; 95%CI: 0.39-0.04; $P = 0.11$) (Figure 2); (2) secondary outcome measure: Frequency of relapses in 6 mo: This was reported in 2 trials[5,19]. The result could not be pooled as the data was not provided in 1 trial[19]. In one trial, the mean relapse rate was lower in the zinc group (0.52 ± 0.0) compared to the placebo group (0.68 ± 0.8), the pooled effect size showing 16% reduction (MD = 0.16; 95%CI: 0.6-0.3; $P > 0.05$). In another trial, there was significant decrease in the frequency of relapse in the zinc group[19]; sustained remission/no relapse: This was reported in 2 trials[5,13]. The zinc group had a higher chance of going into sustained remission/no relapse compared to the compared to the placebo group (RR = 1.42; 95%CI: 0.99-2.05; $P = 0.06$) (Figure 3); proportion of infection episodes associated with relapse: This was reported in one trial[19]. The risk was lower in the zinc group (0.16) compared to the placebo group (0.33) ($P = 0.012$); cumulative dose of steroids in two groups: This was not reported in any of the trials; mean length of time to next relapse: This was not reported in any of the trials; adverse effects of therapy: A mild adverse event in the form of metallic taste was reported in three subjects in one trial[5], and in 10% of children in another trial[13]; change in serum zinc levels: Two trials provided this information[5,19]. None were zinc deficient at 12 mo.

Table 1 Characteristics of included studies

Ref.	Setting, country	Participants	Intervention	Outcomes measured	Comments
Arun *et al*[5]	Hospital (out-patient), India	Number: 81 [Frequent relapse = 52 (zinc = 26; placebo = 26); Infrequent relapse = 29 (zinc = 14; placebo = 15)] Age: 1-16 yr Inclusion: SSNS with infrequent relapses or FRNS with prednisolone requirement ⩽ 0.75 mg/kg on alternate days	Dose: Zinc sulfate 10 mg/d (1 h before or 2 h after meal) Duration: 12 mo	Frequency of relapses, number of relapses (mean), time to first relapse, adverse drug affects, proportion of infection associated relapses, and change in serum zinc level	Double blind placebo-controlled trial. ITT analysis not done. Small sample size (underpowered to show significant differences in the groups). Inclusion of infrequent relapsers may have diluted the significance of the findings. Authors proposed testing of a higher zinc dose along with immunological correlation
Sherali *et al*[12]	Hospital (out-patient), Pakistan	Number: 60 (zinc = 30; placebo = 30) Age: 2-15 yr Inclusion: FRNS	Dose: Zinc sulfate 10 mg/d Duration: 6 mo	Frequency of relapses, number of relapses (mean), episodes of infections, adverse drug affects, and change in serum zinc level	Double blind placebo-controlled trial. ITT analysis not done. Small sample size. Allocation concealment not clear. Post-supplementation zinc level was not measured in all subjects. Authors proposed testing of a higher zinc dose in a larger cohort
Afzal *et al*[18]	Hospital (out-patient), India	Number: 30 (zinc = 16; placebo = 14) Age (mean ± SD): 6.45 ± 2.92 yr Inclusion: FRNS (*n* = 24) and SDNS	Dose: Zinc 20 mg/d Duration: 2 wk starting at the onset of an episode of infection (for 12 mo)	Frequency of relapses, number of relapses (mean), episodes of infections, adverse drug affects, and change in serum and hair zinc level	Open label trial. ITT analysis not clear. Small sample size. Post-supplementation. Authors proposed testing of a higher zinc dose in a larger population
Pardillo *et al*[19]	Hospital (out-patient), Philippines	Number: 34 Age: Not clear (only children included) Inclusion: SSNS (majority) and SDNS	Dose: RDA Duration: 6 mo	Frequency of relapses, number of relapses (mean), episodes of infections, and adverse drug affects	Double blind placebo-controlled trial. ITT analysis not clear. Small sample size. Authors proposed testing of a higher zinc dose in a larger population

SSNS: Steroid sensitive nephrotic syndrome; FRNS: Frequently relapsing nephrotic syndrome; SDNS: Steroid dependent nephrotic syndrome; ITT: Intention-to-treat analysis; SD: Standard deviation; RDA: Recommended daily allowance.

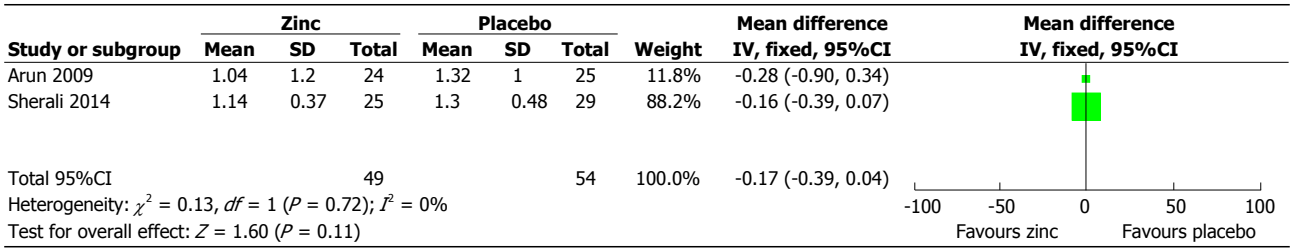

Figure 2 Frequency of relapses in 12 mo in case of frequent relapses/steroid dependent. IV: Inverse variance.

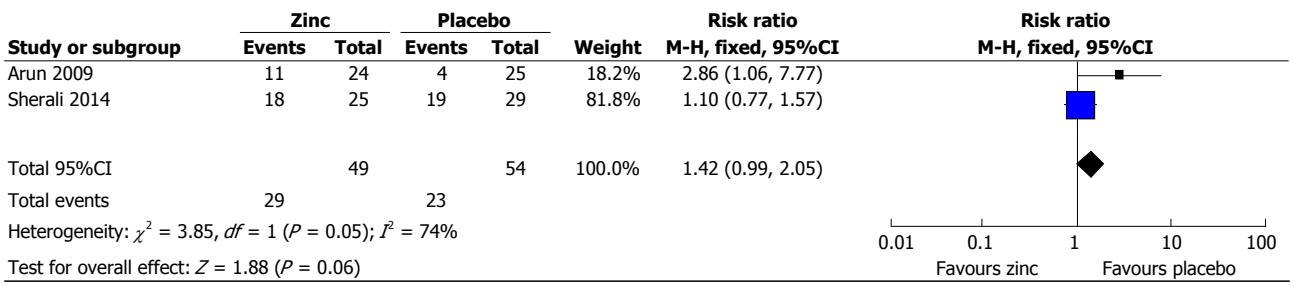

Figure 3 Sustained remission/no relapse in case of frequent relapses/steroid dependent. M-H: Mantel-Haenszel.

Table 2 Zinc for nephrotic syndrome (steroid sensitive nephrotic syndrome)

Patient or population: Patients with nephrotic syndrome Settings: Hospital setting Intervention: Zinc					
Outcomes	Illustrative comparative risks[3] (95%CI)		Relative effect (95%CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Zinc			
Frequency of relapses in 12 mo Follow-up: 12 mo	The mean frequency of relapses in 12 mo in the control groups was 2%	The mean frequency of relapses in 12 mo in the intervention groups was 0.2 lower (0.71 lower to 0.31 higher)		81 (1 study)	Very low[1,2]
Frequency of relapses in 6 mo Follow-up: 12 mo	The mean frequency of relapses in 6 mo in the control groups was 19%	The mean frequency of relapses in 6 mo in the intervention groups was 0.19 lower (0.57 lower to 0.19 higher)		81 (2 studies)	Very low[1,2]
Risk of relapse per year Follow-up: 12 mo	725 per 1000	500 per 1000 (326 to 776)	RR = 0.69 (0.45 to 1.07)	78 (1 study)	Very low[1,2]
Mean length of time to next relapse Follow-up: 12 mo	The mean length of time to next relapse in the control groups was 1.5 mo	The mean length of time to next relapse in the intervention groups was 1.5 higher (0 to 0 higher)		78 (1 study)	Very low[1,2]

[1]Single trial; [2]Small sample size; [3]The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI). CI: Confidence interval; RR: Risk ratio; GRADE: Working Group grades of evidence; high quality: Further research is very unlikely to change our confidence in the estimate of effect; moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: We are very uncertain about the estimate.

Publication bias

We could not assess publication bias in the included trials because of fewer numbers.

Grade of evidence

The evidence generated was of "very low quality" for following outcomes under SDNS/FRNS the result of which could be pooled: Frequency of relapses in 12 mo, and sustained remission/no relapse (Tables 2 and 3).

DISCUSSION

Summary of evidence

After an extensive search of the literature we could find 6 trials to be eligible for inclusion. Our result indicates that, for steroid sensitive NS, zinc reduces the frequency of relapses in 12 mo and 6 mo, risk of relapse per year, mean length of time to next relapse with a mild adverse event in the form of metallic taste. For steroid dependent/frequent relapsing NS, zinc reduces the frequency of relapses in 12 mo and 6 mo, induces sustained remission/no relapse, reduces the proportion of infection episodes associated with relapse with a mild adverse event in the form of metallic taste. When we constructed the GRADE of evidence from the available evidence, it was found to be of "very low quality".

The mechanism by which zinc is helpful as an adjunct in the treatment of childhood NS is not clear. The pathogenesis of childhood NS (*e.g.*, SSNS, SDNS, FRNS) and the basis for relapses triggered by various infections are also unclear. There is evidence from the literature that a perturbed immune dysfunction (*e.g.*, elevated levels of IgE and up-regulation of IL-4 and IL-13 suggest a Th2 cytokine bias[14,15]. There have been studies that show a lower blood level of zinc in childhood NS[21]. Moreover, children from developing country setting are more prone for zinc deficiency. Zinc deficiency might lead to down-regulation of Th1 cytokines, a relative Th2 bias, and increased risk of infections[14,15]. Data from various reports suggest that zinc has a therapeutic role in diarrhea and respiratory infections[22,23]. As infections are most common inciting condition leading to relapse in childhood NS, it is believable that that zinc supplementation would reduce the frequency of infections and thereby relapses. The present evidence is also in accordance with this.

Limitations

Most outcomes were reported in single trials, so result could not be pooled except from few. The evidence generated was of "very low quality" (the result could be pooled for only two outcomes, high chance of publication bias, some trial also having moderate to high risk of bias because of the methods of blinding/allocation concealment). As the dose range varied among the trials, we could not determine an optimal therapeutically effective dose of zinc. No trial was conducted in a developed country setting, so it is difficult to make any generalized recommendation to all parts of the world.

Future area of research

More trials including a larger sample of children with FRNS or SDNS are needed in order to strengthen the evidence. A uniform dose of zinc as well different dose should be studied to find any optimal therapeutic benefit. Trials should also report about the cost-benefit ratio. The therapeutic effect of zinc in different subgroups of children should also be studied. The effect of zinc supplementation should be correlated with the immunological markers to strengthen the evidence or recommendation in this regard.

Table 3 Zinc for nephrotic syndrome (frequent relapses/steroid dependent)

Patient or population: Patients with nephrotic syndrome Settings: Hospital setting Intervention: Zinc					
Outcomes	Illustrative comparative risks[4] (95%CI)		Relative effect (95%CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk Zinc			
Frequency of relapses in 12 mo Follow-up: 12 mo	The mean frequency of relapses in 12 mo in the control groups was 17%	The mean frequency of relapses in 12 mo in the intervention groups was 0.17 lower (0.39 lower to 0.04 higher)		103 (2 studies)	Very low[1,2,3]
Frequency of relapses in 6 mo	The mean frequency of relapses in 6 mo in the control groups was 16%	The mean frequency of relapses in 6 mo in the intervention groups was 0.16 lower (0.6 lower to 0.3 higher)		50 (2 studies)	Very low[1,2]
Sustained remission/no relapse Follow-up: 12 mo	426 per 1000	605 per 1000 (422 to 873)	RR = 1.42 (0.99 to 2.05)	103 (2 studies)	Very low[1,2,3]
Proportion of infection episodes associated with relapse Follow-up: 12 mo	The mean proportion of infection episodes associated with relapse in the control groups was 17%	The mean proportion of infection episodes associated with relapse in the intervention groups was 0.17 lower (0 to 0 higher)		30 (1 study)	Very low[1,2]

[1]Single trial; [2]Small sample size; [3]Allocation concealment not clear in one study; [4]The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI). CI: Confidence interval; RR: Risk ratio; GRADE: Working Group grades of evidence; high quality: Further research is very unlikely to change our confidence in the estimate of effect; moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: We are very uncertain about the estimate.

In conclusion, zinc may be a useful additive in the treatment of childhood NS. The evidence generated mostly was of "very low-quality". We need more good quality RCTs in different country setting as well different subgroups of children and disease subtype before any firm recommendation can be made.

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COMMENTS

Background

Relapses in childhood nephrotic syndrome (NS) increase morbidity and mortality. Studies have shown that zinc supplementation reduces relapses in children with steroid sensitive NS. It is proposed that zinc deficiency might lead to down-regulation of T-helper 1 (Th1) cytokines, a relative T-helper (Th2) bias, and an increased risk of infection. The later commonly leading to relapse in childhood NS. Zinc supplementation restores Th1-Th2 imbalance and may decrease relapse. The primary aim of this review is to evaluate the efficacy of zinc in preventing relapses in childhood NS (steroid sensitive and steroid dependent/frequent relapsing). The second aim is to evaluate the safety of above intervention in the prevention of relapses in childhood NS.

Research frontiers

About 80%-85% of children with NS shows initial response to corticosteroids (SSNS), and remaining 15%-20% who do not steroid resistant NS. About 40%-50% of patients with SSNS have either frequent relapses or steroid dependent courses leading to prolonged course of illness. Relapses often follow infections (*e.g.*, respiratory, gastrointestinal, urinary infections). Several theories like cytokine release, immune dysfunction, increased glomerular permeability, and podocytopathy are proposed, but none of them is conclusive. A number of interventions have been tried to prevent/decrease relapses. Studies have shown that zinc supplementation reduces relapses in childhood NS.

Innovations and breakthroughs

Zinc supplementation has been shown to reduce relapses in childhood NS. It is proposed that zinc deficiency might lead to down-regulation of Th1 cytokines, a relative Th2 bias, and an increased risk of infection. Zinc supplementation probably corrects the underlying immune imbalance and decreases relapse. Retrieved papers (clinical trials) concerning the utility of zinc were reviewed by the authors, and the data were extracted using a standardized collection tool.

Applications

This review suggests that zinc may be a useful additive in the treatment of childhood NS. The evidence generated mostly was of "very low-quality". We need more good quality randomized trials in different country setting as well different subgroups of children and disease subtype before any firm recommendation can be made.

Terminology

Steroid sensitive NS: Remission is achieved within 4 wk of steroid therapy. Relapse is defined as urinary protein excretion 3+/4+ on reagent strip or proteinuria > 40 mg/m^2 per hour for 3 consecutive days in patient who had previously been in remission (urine albumin trace or nil or proteinuria < 4 mg/m^2 per hour for 3 consecutive days). Frequent relapse is defined as ⩾ 2 relapses in 6 mo of initial response or > 3 relapses in 12 mo. For the treatment of relapse, the patient is initially put on daily corticosteroids till remission and then on alternate day steroids. Steroid dependent NS: 2 consecutive relapses while on alternate steroids or within 14 d of its discontinuation. Frequent relapse NS: ⩾ 2 relapses in 6 mo of initial response or > 3 relapses in 12 mo.

Peer-review

In this systematic review, the authors have presented a thorough and critical analysis of the utility of zinc supplementation in prevention/decrease of the frequency of relapses in childhood NS.

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SYSTEMATIC REVIEWS

Middle East respiratory syndrome coronavirus disease is rare in children: An update from Saudi Arabia

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Abstract

AIM

To summarize the reported Middle East respiratory syndrome-coronavirus (MERS-CoV) cases, the associated clinical presentations and the outcomes.

METHODS

We searched the Saudi Ministry of Health website, the World Health Organization website, and the Flutracker website. We also searched MEDLINE and PubMed for the keywords: Middle East respiratory syndrome-coronavirus, MERS-CoV in combination with pediatric, children, childhood, infancy and pregnancy from the initial discovery of the virus in 2012 to 2016. The retrieved articles were also read to further find other articles. Relevant data were placed into an excel sheet and analyzed accordingly. Descriptive analytic statistics were used in the final analysis as deemed necessary.

RESULTS

From June 2012 to April 19, 2016, there were a total of 31 pediatric MERS-CoV cases. Of these cases 13 (42%) were asymptomatic and the male to female ratio was 1.7:1. The mean age of patients was 9.8 ± 5.4 years. Twenty-five (80.6%) of the cases were reported from the Kingdom of Saudi Arabia. The most common source of infection was household contact (10 of 15 with reported source) and 5 patients acquired infection within a health care facility. Using real time reverse transcriptase polymerase chain reaction of pediatric patients revealed that 9 out of 552 (1.6%) was positive in the Kingdom of Saudi Arabia.

CONCLUSION

Utilizing serology for MERS-CoV infection in Jordan and

Saudi Arabia did not reveal any positive patients. Thus, the number of the pediatric MERS-CoV is low; the exact reason for the low prevalence of the disease in children is not known.

Key words: Pediatric; Middle East respiratory syndrome-coronavirus; Children; Respiratory tract infection

Core tip: The number of the pediatric Middle East respiratory syndrome-coronavirus (MERS-CoV) is low and the exact reason for the low prevalence is not known. A total of 31 pediatric MERS-CoV cases were reported since June 2012. Of all the cases 13 (42%) were asymptomatic and the male to female ratio was 1.7:1. The mean age of patients was 9.8 ± 5.4 years. The most common source of infection was household contact followed by infection within a health care facility. Using real time reverse transcriptase polymerase chain reaction of pediatric patients revealed that 9 out of 552 (1.6%) was positive in the Kingdom of Saudi Arabia.

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INTRODUCTION

Middle East respiratory syndrome-coronavirus (MERS-CoV) was first isolated in 2012 from a patient in the Kingdom of Saudi Arabia (KSA)[1]. As more cases were reported, the case fatality rate changed to 40% from 60%[2-5]. In addition, initially there was a predominance of males; later this ratio decreased[2,6]. MERS-CoV is characterized by three different patterns of disease: Sporadic cases, intra-familial transmission[7-9] and health care associated infection[2,3,10-16]. Despite the increased number overtime and the multiple health care associated outbreaks[17], the number of pediatric cases remained low during the study period[18]. The initial description of 47 cases included only a 14-year-old child[4]. The first pediatric case was a 2-year-old child reported from Jeddah, KSA on June 28, 2013[19]. Later an additional three asymptomatic children were reported[4]. The largest report of childhood MERS-CoV cases included eleven, of which two patients were symptomatic and nine were asymptomatic[18]. The exact reason for this low prevalence of the disease in children is not known. In this study, we summarize the reported MERS-CoV cases and the associated clinical presentation and the outcome.

MATERIALS AND METHODS

We searched the Saudi Ministry of Health website[20], the World Health Organization website[21], the Flutracker website[22], the medical literature and the retrieved published studies for any childhood MERS-CoV infections. We searched MEDLINE and PubMed for the keywords Middle East respiratory syndrome-coronavirus, MERS-CoV, in combination with pediatric, children, childhood, infancy and pregnancy from the initial discovery of the virus in June 2012 until April 19, 2016. The retrieved articles were also read to find other relevant articles.

Statistical analysis

Relevant data were placed into an excel sheet and analyzed accordingly. Descriptive analytic statistics were used in the final analysis as deemed necessary, including mean and standard deviation when applicable and frequency. The statistical review of the study was performed by a biomedical statistician. Statistical review is performed before the submission of the manuscript.

RESULTS

Summary of pediatric cases

From June 2012, to April 19, 2016, there were a total of 31 pediatric MERS-CoV cases as shown in Table 1. Of all the cases, thirteen (13) or 42% were asymptomatic, and there were 17 males, 10 females and 4 unreported (a male to female ratio of 1.7:1). The mean age of patients was 9.8 + 5.4 (0.75-17) years. Twenty-five cases (80.6%) were reported from KSA; the other patients were in Jordan, United Arab Emirates and the Republic of Korea (Table 1). The most common source of the infection was household contact (10 of 15 with reported source), and 5 patients acquired the infection within a health care facility. About one half of the cases were reported in 2014, and 29% were reported in 2013 and 22.6% in 2015 (Table 2).

Screening of pediatric patients for MERS-CoV

Screening of pediatric patients for MERS-CoV infection using real time reverse transcriptase polymerase chain reaction showed that only 9 out of 552 (1.6%) were positive in KSA[23]. However, serologic testing of pediatric patients admitted with lower respiratory tract infection in Jordan and Saudi Arabia revealed no positive tests[24,25] (Table 3).

Pregnancy associated MERS-COV

The effect of MERS-CoV infection on the fetus was described in eight cases[26-29] as summarized in Table 4. The mean age of the mothers was 32.25 + 3.4 years, and the mean gestational age was 28.4 + 6.3 wk. Death of the fetus was observed in 3 (37.5%) of the 8 fetuses.

DISCUSSION

Despite the total number of MERS cases increasing, especially in KSA, the number of pediatric cases remained low during the study period. Initially, the

Table 1 Summary of reported pediatric Middle East respiratory syndrome cases

Age	Gender	Country	Sample source	Year of reporting	Symptoms	Co-morbidity	Signs	Sample type	Viral load ct value	Imaging	Intensive care	Death	Ref.
2	Male	KSA	Hospital inpatient	2013	Fever, respiratory distress	Cystic fibrosis	Chest: Bilateral fine crepitation	NPS	36	Bilateral diffused infiltrate	+	Yes	[18]
14	Female	KSA	Hospital inpatient	2013	Fever	Down's syndrome		NPS	37	Bilateral diffused infiltrate	No	No	[18]
7	Female	KSA	Family contact	2013	Asymptomatic	None	None	N + T	37	ND	No	No	[18]
15	Female	KSA	Family contact	2014	Asymptomatic	None	None	NPS	35	ND	No	No	[18]
14	Male	KSA	Family contact	2014	Asymptomatic	None	None	NPS	34	ND	No	No	[18]
12	Female	KSA	Family contact	2014	Asymptomatic	None	None	NPS	35	ND	No	No	[18]
16	male	KSA	Family contact	2013	Asymptomatic	None	none	NPS	36	ND	No	No	[18]
7	Female	KSA	Family contact	2014	Asymptomatic	None	none	NPS	37	ND	No	No	[18]
3	Female	KSA	Family contact	2013	Asymptomatic	None	none	NPS	38	ND	No	No	[18]
13	Female	KSA	Contact	2014	Asymptomatic	None	none	NPS	34	ND	No	No	[18]
14	Female	KSA	Family contact	2013	Asymptomatic	None	none	NPS	36	ND	No	No	[18]
0.75	Male	KSA	Not known	2014	ICU	Nephrotic syndrome	Respiratory distress	Tracheal aspirate	NA	Diffuse bilateral haziness	Yes	Yes	[35]
4	Male	KSA	NA	2013	Mild respiratory symptoms	None	NA		NA	ND	No	No	[36]
8	Male	KSA	NA	2013	Mild respiratory symptoms	None	NA		NA	ND	NA	No	[37]
17	NA	KSA	Contact	2014	Asymptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
11	NA	KSA	Contact	2014	Asymptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
16	NA	KSA	NA	2014	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
13	M	KSA	NA	2014	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
10	M	KSA	Hospital contact	2014	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[20,22]
2	NA	KSA	NA	2014	Symptomatic	Congenital anomalies	NA	NA	NA	NA	NA	NA	[20,22]
11	M	KSA	Hospital contact	2014	Symptomatic	Brain tumor	NA	NA	NA	NA	NA	NA	[20,22]
17	M	KSA	NA	2014	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[20,22]
16	M	South Korea	Hospital contact	2015	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
2	M	KSA	Hospital contact	2015	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[20,22]
16	M	KSA	contact	2015	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[20,22]
7	F	Jordan	Contact	2015	Asymptomatic	None	NA	NA	NA	NA	NA	NA	[22]
0.8	F	Jordan	Contact	2015	Symptomatic	None	NA	NA	NA	NA	NA	NA	[22]
14	M	KSA	Contact	2015	Symptomatic	None	NA	NA	NA	NA	NA	NA	[20,22]
4	M	UAE	NA	2014	NA	NA	NA	NA	NA	NA	NA	NA	[22]
8	M	UAE	Family contact	2013	NA	NA	NA	NA	NA	NA	NA	NA	[22]
11	M	UAE	Family contact	2015	Asymptomatic	None	NA	NA	NA	NA	NA	NA	[22]

NPS: Nasopharyngeal swab; N + T: Nasal and tracheal aspirate; ND: Not done; KSA: Kingdom of Saudi Arabia; UAE: United Arab Emirates; ICU: Intensive care unit; NA: Not available.

testing in KSA was directed towards hospitalized patients with severe pneumonia. In 2015, the Saudi Ministry of Health added a specific case definition for MERS-CoV infection in children[30]. The definition includes those $\leqslant$ 14 years, meets the adult case definition and has either a history of exposure to a confirmed or suspected MERS-CoV in the proceeding 14 d or a history of contact with camels or camel products in the proceeding 14 d[30]. The case definition also includes children with unexplained severe pneumonia[30]. The 2015 change in the case definition does not account for the low rate of childhood MERS-CoV infection as 33% of the cases were reported in 2014 before the case definition was changed. One of the reasons for an increased number of cases in 2014 during the Jeddah outbreak was increased testing of asymptomatic and mildly symptomatic patients[11].

Table 2 Summary of the demographic characteristics of pediatric Middle East respiratory syndrome-coronavirus

	No.	%
Male:female	17:10 (1.7:1)	63 *vs* 37
Saudi	20	83.3
City		
Jeddah	7	29.2
Riyadh	7	29.2
Hafr al-Batin	3	12.5
Symptomatic	12	50.0
Death	8	33.3
Year of report		
2013	9	29
2014	15	48.4
2015	7	22.6

Table 3 Summary of different studies examining Middle East respiratory syndrome-coronavirus infection in children

Country	Testing method	Population	Positive *n* (%)	Yr	Ref.
KSA	rRT-PCR	Screening of children	9/552 (1.6)		[23]
KSA	Neutralizing antibodies testing	Serum samples from children hospitalized for lower respiratory tract infections	0/158 (0)	May 2010-May 2011	[25]
Jordan	rRT-PCR	Hospitalized children < 2 yr of age	0/2427 (0)		[24]

rRT-PCR: Real time reverse transcriptase polymerase chain reaction; KSA: Kingdom of Saudi Arabia.

Table 4 Summary of pregnancy associated Middle East respiratory syndrome-coronavirus infection

Age of the patient (yr)	Gestational age	Fetal outcome	Diagnostic test	Country	Ref.
39	5 mo	Still birth	Antibody by EIA	Jordan	[26]
33	32 wk	Healthy infant	PCR	Saudi Arabia	[27]
32	32 wk	Healthy	PCR	United Arab Emirates	[28]
34	34 wk	Died	PCR	Saudi Arabia	[29]
32	38 wk	Survived	PCR	Saudi Arabia	[29]
31	24 wk	Died	PCR	Saudi Arabia	[29]
27	22 wk	Survived	PCR	Saudi Arabia	[29]
30	23 wk	Survived	PCR	Saudi Arabia	[29]

PCR: Polymerase chain reaction; EIA: Enzyme immunoassay.

The pattern of MERS-CoV pediatric cases was similar to the 2003 SARS outbreak. Children were less affected than adults and children less than 2 years of age had milder disease[31]. In the largest screening of contacts, the rate of MERS-CoV positive children (1.6%, 9/616) compared to 2.2% (99/4440) in adults (P = 0.23)[23]. Thus, in this study utilizing MERS-CoV PCR the positivity rate did not differ in children and adults.

In adults with MERS-CoV infections, three patterns of transmissions were observed: Sporadic (primary) cases presumed to be due to animal exposure (mainly camels), household contacts or health care associated infections[32]. In KSA, the majority (45%) of cases were health care-associated infections, 38% were primary cases, and 13% were household contacts[32]. In contrast, in the majority of pediatric cases that reported source of acquisition (66.7% of the 15 with reported source), the disease was acquired through household contact. This pattern indicates a low exposure of children to animals and a higher rate of health care associated infections in adult wards. The male to female ratio (2.8:1 and 3.3:1) was initially high[3,4]. This apparent male predominance could be explained by the nature of hospital outbreaks[2]. Eventually the male to female ratio was reduced to 1.3:1 to 1.8:1[5,6]. Consistent with these studies, the male to female ratio in children with MERS-CoV was 1.7:1 and may indicate similar exposure of children to index cases in the household settings and differential host factors.

Possible explanations for the lower number of pediatric cases compared to adults include differential testing of adult patients and milder diseases in children; although, serologic testing of pediatric patients in KSA and Jordan did not reveal any positive cases[24,25]. In the largest sero-epidemiologic survey in KSA, the study did not include children and thus it is difficult to establish the rate of sero-positivity in children[31].

The MERS-CoV infection rate in children remains low and possible explanations include: A milder disease in children, asymptomatic infection, or the presence of yet to be identified factors. The development of a shorter duration of MERS in children is another possible explanation. If this is the case, it may limit the development of a positive serology. In one study, delayed antibody responses as measured with the neutralization test was associated with severe diseases[33]. The longevity of antibodies in MERS-CoV cases might be limited as was the case with SARS[33,34]. The only study of serology among children was done among hospitalized pediatric cases who presented with lower respiratory tract infections[25]. There is no systematic screening of exposed children using serologic testing; this limited the interpretation of available serologic studies.

Little data also exist regarding the effect and the likelihood of MERS-CoV in pregnancy. Eight cases were reported[26,27,29]. The outcome was favorable in the majority of cases. The exact prevalence of MERS-CoV antibodies and exposure of pregnant women to MERS-CoV is not known.

In conclusion, the number of MERS-CoV infections in pediatric patients remains low. Possible explanations include low exposure, presence of asymptomatic, mildly symptomatic patients or the presence of yet to be identified factors. The immune system predisposing to severe disease and to fatal outcome remains unknown. An exploration of the virus-host interaction may add

to the understanding of the low prevalence in this age group.

COMMENTS

Background

Middle East respiratory syndrome-coronavirus (MERS-CoV) was first isolated in 2012 from a patient in the Kingdom of Saudi Arabia (KSA). Despite the increased number of MERS-CoV cases overtime, the number of pediatric cases remained low. The exact reason for this low prevalence of the disease in children is not known. The aim of this study is to summarize the reported MERS-CoV cases and the associated clinical presentation and the outcome.

Research frontiers

The first pediatric case was a two-year-old child reported from Jeddah, KSA on June 28, 2013. Later an additional three asymptomatic children were reported. The largest report of childhood MERS-CoV cases included eleven, including nine asymptomatic cases.

Innovations and breakthroughs

The number of MERS-CoV infections in pediatric patients remains low. Possible explanations include low exposure, presence of asymptomatic, mildly symptomatic patients or the presence of yet to be identified factors. The immune system predisposing to severe disease and to fatal outcome remains unknown. An exploration of the virus-host interaction may add to the understanding of the low prevalence in this age group.

Applications

Despite the low number of pediatric MERS-CoV cases, it is important to continue to monitor the development of this disease in this age group and to understand the risk factors.

Terminology

MERS-CoV is a new emerging virus that was first isolated in 2012.

Peer-review

This complication of all known pediatric cases is a useful contribution to the medical literature, and knowing it is possible but rare is important.

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Can language acquisition be facilitated in cochlear implanted children? Comparison of cognitive and behavioral psychologists' viewpoints

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Abstract

AIM

To study how language acquisition can be facilitated for cochlear implanted children based on cognitive and behavioral psychology viewpoints?

METHODS

To accomplish this objective, literature related to behaviorist and cognitive psychology prospects about language acquisition were studied and some relevant books as well as Medline, Cochrane Library, Google scholar, ISI web of knowledge and Scopus databases were searched. Among 25 articles that were selected, only 11 met the inclusion criteria and were included in the study. Based on the inclusion criteria, review articles, expert opinion studies, non-experimental and experimental studies that clearly focused on behavioral and cognitive factors affecting language acquisition in children were selected. Finally, the selected articles were appraised according to guidelines of appraisal of medical studies.

RESULTS

Due to the importance of the cochlear implanted child's language performance, the comparison of behaviorist and cognitive psychology points of view in child language acquisition was done. Since each theoretical basis, has its own positive effects on language, and since the two are not in opposition to one another, it can

be said that a set of behavioral and cognitive factors might facilitate the process of language acquisition in children. Behavioral psychologists believe that repetition, as well as immediate reinforcement of child's language behavior help him easily acquire the language during a language intervention program, while cognitive psychologists emphasize on the relationship between information processing, memory improvement through repetitively using words along with "associated" pictures and objects, motor development and language acquisition.

CONCLUSION

It is recommended to use a combined approach based on both theoretical frameworks while planning a language intervention program.

Key words: Language; Cochlear implantation; Behavior; Child; Cognition

Core tip: Cognitive and behavioral theoretical frameworks are not in opposition to one another, at least when translated to practice. So, an intelligent practitioner in the field of speech therapy may make practical benefit of both theories simultaneously in a combined approach, by planning to promote the child's cognitive and motor development and his ability for information processing, accompanied by appropriate reinforcement for his correctly imitated or spontaneous responses. This of course needs experimental research for verification of enhanced effectiveness.

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INTRODUCTION

Communication is an important way by which information and idea is transferred between people. Getting in touch with others through language is the well-known method of communication all over the world[1]. Although language is the best means of communication, it cannot be totally acquired in hearing impaired children. Hearing impaired children usually suffer from different kinds of language disorders which include disabilities in comprehension, speech processing and writing. They usually experience one or more of the phonological, syntactic, semantic and pragmatic types of disorders that cause them to be highly in need of systematic rehabilitation programs for language acquisition[2].

Before cochlear implants innovation about 35 years ago, children with profound hearing impairment could only rely on hearing aids for receiving the slightest degrees of auditory stimuli. However, nowadays cochlear implants have effectively replaced older means of speech and language acquisition in children who suffer from sensorineural hearing loss. Based on the evolution from use of hearing aids to cochlear implantation, it is also expectable to see significant changes in language treatment procedures of hearing impaired children. Also, these days' researches on cochlear implants are taking new path and direction. More and more research is focusing on pre-linguistically cochlear implanted children, that is, those who have noticeably gained benefit in language acquisition post-cochlear implantation[3]. Due to the importance of the cochlear implanted child's language performance, the authors have turned their efforts to respond to a rather basic question: How can language acquisition programs be facilitated and their effects maximized for cochlear implanted children. Different studies up to now have indicated that the cochlear implanted child's success in language acquisition is significantly related to certain factors including the age at which deafness occurred, length of hearing loss and the age at which the child underwent cochlear implantation[4,5]. However, if the above-mentioned demographic variables were kept controlled, would the outcome of cochlear implantation be influenced by any other variables? In other words, is there any other remaining factor affecting language acquisition and performance in this group of children? The authors speculate that language acquisition is highly correlated with some cognitive and behavioral factors which have been mostly ignored over the years, especially regarding hearing impaired children, and specifically in the case of those who have underwent cochlear implantation.

Evidently, hearing impaired children encounter significant delay and disorders of speech and language development[6,7]. Such children have much difficulty in communication and social adjustment. These problems will still be prevalent among hearing impaired children after cochlear implantation. It is now well-known that cochlear implantation with no language intervention following it cannot be much helpful to the acquisition of language by the child[8-10].

There are different language treatment protocols all over the world, most of which have indicated the importance of timely language intervention for language disordered children or those at risk of it. However, they differ in terms of the theories, concepts and principles underpinning their intervention strategies. Each of these different treatment protocols may have proven effective for different target groups but to our knowledge, no study has proposed the best treatment strategy for hearing impaired children who have undergone cochlear implantation. With the growing number of these children and the usually limited period of golden time remaining for their language training, it seems quite necessary and urgent that we figure out the best strategies fitting

Table 1 Levels of evidence in medical research

Level of evidence	Study design
Level Ⅰ	Systematic review (with homogeneity) of RCTs
	RCT with statistically significant difference or narrow confidence intervals
Level Ⅱ	Low quality RCT (*e.g.*, < 80% follow-up)
	Cohort study or other Prospective comparative study
	Systematic review of cohort studies
Level Ⅲ	Case-control study or other Retrospective comparative study
	Systematic review of case-control studies
Level Ⅳ	Case series
	Poor quality case-control studies
Level Ⅴ	Expert opinion
	Narrative reviews

Adopted from URL: http://www.cebm.net. RCT: Randomized control trial.

their specific state of health.

As a small step towards this goal, in this article we plan to explain behavioral psychologists' and cognitive psychologists' theories and viewpoints, mainly based on expert-opinion type literature relevant to language acquisition and to compare and discuss them in order to find clues for facilitating language acquisition in cochlear implanted children.

MATERIALS AND METHODS

In order to study literature related to behaviorist and cognitive psychology prospects about language acquisition, some relevant books as well as Medline, Cochrane Library, Google scholar, ISI web of knowledge and Scopus databases were searched. While screening titles and abstracts, the authors excluded any duplicates, case reports and articles written in languages other than English. Studies accessed only in abstract form were also excluded.

At first 25 articles were selected, but only 11 met the inclusion criteria and were included in the study. The inclusion criteria consisted of review articles, expert opinion studies, non-experimental and experimental studies that clearly focused on behavioral and cognitive factors affecting language acquisition in children.

After collecting relevant articles, they were appraised according to guidelines of appraisal of medical studies (Table 1)[11].

RESULTS

The 11 studies that met the inclusion criteria are described below in Table 2.

Behavioral psychologists' point of view regarding language acquisition

A number of single subject studies which have specifically focused on the language responses of language impaired children have demonstrated diverse language behaviors in this group of children[12,20].

Behavioral psychologists usually emphasize on a noticeable relationship between child's encouragement and language acquisition. They believe that as well as any other behavior, language acquisition might happen through operant conditioning. In addition, they suggest that immediate reinforcement of child's language behavior causes him to acquire the language as fast as he can. So, learning language has a positive relationship with visual and auditory reinforcements that the child receives when making improvements. Based on this theory, language acquisition is not dependent on complex mental development but the most critical variable in language acquisition is functional feedback[12]. Hence, teaching a new behavior with step by step reinforcements is the effective way of acquiring that behavior.

Also, in behavioral psychology, repetition and modeling a word or a verb are recommended to facilitate language acquisition. Therefore, the clinician is asked to model an appropriate response to help the child imitate it.

The behavioral theory is the basis of most conventional language treatment programs for various language disordered children, including those with hearing impairment who have undergone cochlear implantation[18]. Actually, the first step in auditory verbal training of cochlear implanted children is to help them be aware of the verbal and non-verbal sounds by conditional responses. The normal process in such programs is that first, every correctly imitated response is encouraged. After 4-5 times of encouragement, the reinforcements are reduced to once for every 2-3 correct responses in a fixed rate. Finally, the child cannot predict the exact time of receiving prizes because of the variant rate of reinforcements. By this method the number of child's correct responses will increase dramatically[8,18].

Cognitive psychologist's point of view in language acquisition

Cognitive psychologists emphasize that the complexity of language structures in a child indicates his level of cognitive development and *vice versa*[8,15]. Although it seems that young language learners acquire language simply by exposure to their mother's tongue in a natural trend[9], the process is actually more complex than it appears. In fact, a young child's language acquisition is based on a series of perceptual and cognitive skills. Language in humans is acquired in unique ways that require information processing. As a result, early sensory deprivation, especially hearing loss will cause impairments in language acquisition that may last a life time[5].

Information processing generally refers to a complex set of mental processes that include perception, cognition and thought. It is concerned with many functions that are themselves based on cognition, such as object recognition, perceptual learning, memory development, and language processing skills like speech perception and production. In fact, different aspects of information processing such as sensation, perception, memory, thought, language processing and problem-solving are

Table 2 Study characteristics and outcomes

Ref.	Yr	Study design	Evidence level	Sample	Result
Hegde *et al*[12]	1979	Case-control	Ⅲ	Normal children Language disorder children	Behaviorist Language learning is limited to what is trained especially in language disordered children Reinstatement and generalization are very rare
Elger *et al*[13]	1997	Low quality RCT	Ⅱ	Temporal lob impaired patients	Cognitive based There is a relationship between temporal lobe structures for memory and language acquisition
Kutas *et al*[14]	2000	Systematic review of case-control studies	Ⅲ	Normal children	Cognitive based The organization of semantic memory has an effect on word processing
Pisoni[15]	2000	Expert opinion	V	Cochlear implanted children	Cognitive based Promotion of cognitive development, information processing and language acquisition are the most important results of early cochlear implantation
Bloom[8]	2000	Narrative review	V	Normal children	Cognitive based Acquiring language is the result of cognitive abilities that include the abilities to acquire concepts and understanding of the mental status of other people
Iverson *et al*[16]	2004	Low quality RCT	Ⅱ	Normal children	Cognitive based There is an age related increase in frequency of vocal motor coordination in children A temporal pattern similar to that is seen in adult gestures and speech coordination
Clark[9]	2004	Narrative review	V	Normal children	Cognitive based Conceptual and linguistic representations for talking about experience provide the starting point for language from the age of 12 mo
Pulvermüller[17]	2005	Expert opinion	V	Normal children	Cognitive based Motor development prompts cognitive development The neuronal connection between systems for action and language perception is seen
Yu *et al*[18]	2007	Single subject studies	V	Normal children	Cognitive based and behaviorist Child's social cognitive capacities like joint attention, prosody and intention reading help him acquire the meaning of words. In other word, a combination of cognitive and behavioral development play important role in language development
Behrens *et al*[19]	2011	Systematic review of case-control studies	Ⅲ	Normal children Language disorder children	Cognitive based and behaviorist There is a relationship between motor and language development
Hegde *et al*[20]	2013	Prospective study	Ⅱ	Learning disabled children	Behaviorist Reinforcement, imitation and modeling facilitate language acquisition Reinstatement and generalization are very rare

RCT: Randomized control trial.

all part of a spectrum and are all related to cognitive processing and cannot be considered independently and separately[15]. Appreciation of one requires understanding and consideration of the others[21]. Also, the more complex aspects of information processing that appear at older age are hierarchically dependent on the more simple aspects that have occurred earlier[13,15,22].

The information processing approach helps better understand the cognitive and language development in language impaired children[15].

Based on the cognitive psychologists' point of view, one of the preconditions of language acquisition is memory and memory improvement. In fact, it is said that separation of the process that supports language perception from that which supports memory is impossible. When a word is produced, the meaning is derived from a life-long storage of knowledge, experience and memory in the brain. Evidence has shown that this storage of knowledge is organized in different dimensions and can be used flexibly[14].

For young children to understand the meaning of a new word among the various word-referent pairs in their environment, it is commonly presumed that this needs the repeated accompanying of auditory stimuli in the form of a word with a simultaneous extra-linguistic stimulus such as seeing and experiencing an object or an action[18]. This mechanism of word learning is called "associationism" and usually starts with the most familiar objects and actions in a child's environment[5,8,9]. "Association" improves memory and helps the child keep

visual and auditory stimulations in his mind.

As with any other young language learner, perception and production of intelligible speech in a cochlear implanted child needs to have a structured system for symbolizing and coding sounds in the brain[9,21-23]. According to cognitive psychologists' point of view, this is actually what happens among cochlear implanted children during the process of language acquisition[18]. So, cognitive psychologists suggest that one of the best methods of language treatment in cochlear implanted children is to strengthen memory *via* repetitively using words along with "associated" pictures and objects[24].

In addition, one other precondition for language acquisition that is often overlooked and thus requires additional attention is the child's motor development. The impact of this developmental domain on the child's language acquisition is an issue that requires further attention.

In human beings, movement and thought have always been correlated. Nowadays, research has shown that movement in human life occurs with other intentions than movement itself[19]. The main reason that causes the psychologists to believe in interrelationship between motor and language development is derived from the idea that infant's motor development encourages him to explore his surrounding as much as he can[16]. The children's locomotion ability enable them to achieve new experiences by investigation of the environment and object manipulation. These new experiences provide an opportunity to develop communication skills. According to these finding, psychologists and other scientists need to explore the link between motor development and language acquisition furthermore[17,19].

Locomotion and object-manipulation are two important components of motor movement that facilitate language acquisition in children, especially those with language impairment. This finding has resulted from research on monkeys' brains which have shown connections between their motor cortex and that part of their cortex which is similar to the human language cortex. So, it can be assumed that faster information processing is the consequence of correlating language and action[17,19].

DISCUSSION

The review of literature regarding theoretical frameworks of behaviorists' and cognitive psychologists' prospects in language acquisition, indicates some key points which might facilitate language acquisition in language impaired children, especially those with hearing loss who have undergone cochlear implantation.

In behavioral methods of language training, expansion and generalization of the trained element is reached by repetition of the items that are being taught. Accordingly, a gradual increase of training trails will similarly cause enhancement of generalization. However, it should be noted that generalization occurs with different number of newly trained items in the case of a pronoun for example, than in the case of a verb. So, training in each modality is not influenced by training in other modalities[20].

Furthermore, according to behavioral theories the parents' response to a child by smiling, hugging or imitation of what they have heard when the child makes a sound or produces a word or a phrase, are the best means of communication and encouragement for language acquisition. Such environmental reinforcements are the basic of behavioral treatment protocols in language impaired children[12,20].

On the other hand, according to cognitive theories there are a number of cognitive factors that are necessary to be taken into consideration, while planning a language training program[8,9,13-17,19].

The two main cognitive principles of language acquisition are memory development and motor movement training. As a result, cognitive psychologists believe that it is necessary to focus on a child's cognitive improvement and his understanding of the association between words and meaning while planning a language intervention program. Also, including motor movement training in a language intervention program may facilitate language acquisition in a child by promoting investigation of his surroundings[16,17]. Since movement allows the child to find and focus attention on new objects of interest, he is more likely to learn new words associated with the new objects.

Given that the two theoretical frameworks are not in opposition to one another, at least when translated to practice, the authors speculate that a practitioner in the field of speech therapy can intelligently make benefit of both theories simultaneously and in a combined approach. For example, in order to help cochlear implanted children develop language, based on their cognitive as well as their behavioral development, it can be proposed that a combination of visual and auditory stimuli accompanied by memory exercises using pictures, objects and asking the child to repeat and imitate the words that are being heard, be utilized[13-15]. This of course should be followed by positive response and reinforcement from the therapist and the family. Also, making use of language exercises that somehow include actions related to different parts of the body in semantic terms, can be eventually added to the training process to facilitate the process of language acquisition through previously mentioned mechanisms activated by movement. Once the child's attention is directed towards a newly discovered object, the caregiver can then provide input. This input may be words referring to certain characteristics of the new object, along with positive reinforcements (*e.g.*, "Yes dear, that's a cup!").

Finally, the authors suggest that this combined approach for children, especially those with hearing impairment who have undergone cochlear implantation, be put to trial by researchers and compared with training interventions based on each of the theoretical frameworks independently.

In conclusion, given that the two theoretical frameworks are not in opposition to one another, at least when translated to practice, the authors speculate that a practitioner in the field of speech therapy can

intelligently make benefit of both theories simultaneously and in a combined approach by planning to promote the child's cognitive and motor development and his ability for information processing, accompanied by appropriate reinforcement for his correctly imitated or spontaneous responses. This of course needs experimental research for verification of enhanced effectiveness.

COMMENTS

Background

Hearing impaired children usually suffer from one or more of the phonological, syntactic, semantic and pragmatic types of disorders that cause them to be highly in need of systematic rehabilitation programs for language acquisition. Although cochlear implantation is now considered to be one of the most effective interventions for children with sensori-neural deafness in terms of language acquisition, cochlear implantation with no language intervention following it cannot be much helpful to the acquisition of language by the child. There are different language treatment protocols all over the world. However, no study has proposed the best treatment strategy for hearing impaired children who have undergone cochlear implantation.

Research frontiers

Due to the importance of the cochlear implanted child's language performance, one of the current research hotspots in the field of cochlear implantation, is to figure out the best strategies for language acquisition in this group of children.

Innovations and breakthroughs

There are different language treatment protocols all over the world, most of which have indicated the importance of timely language intervention for language disordered children or those at risk of it. Each of these different treatment protocols may have proven effective for different target groups but to our knowledge, no study has proposed the best treatment strategy for hearing impaired children who have undergone cochlear implantation. According to this study, in a language intervention program for cochlear implanted children, the two theoretical frameworks can be used in a combined approach by planning to promote the child's cognitive and motor development and his ability for information processing, accompanied by appropriate reinforcement for his correctly imitated or spontaneous responses.

Applications

Since the two theoretical frameworks are not in opposition to one another at least when translated to practice, the authors suggest that practitioners in the field of speech therapy intelligently make benefit of both theories simultaneously by planning to promote the child's cognitive and motor development and his ability for information processing, as well as by providing appropriate reinforcement for his correct responses.

Terminology

A cochlear implant is an electronic device which functions similar to how the inner ear functions and is used to transfer sound signals to the brain in patients who suffer from hearing loss because of damaged inner ear. Rehabilitation is a word most commonly used to facilitate language acquisition following cochlear implantation.

Peer-review

The authors are writing down a well written narrative review related to behaviorist and cognitive psychology prospects about language acquisition for cochlear-implanted children.

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