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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.

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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

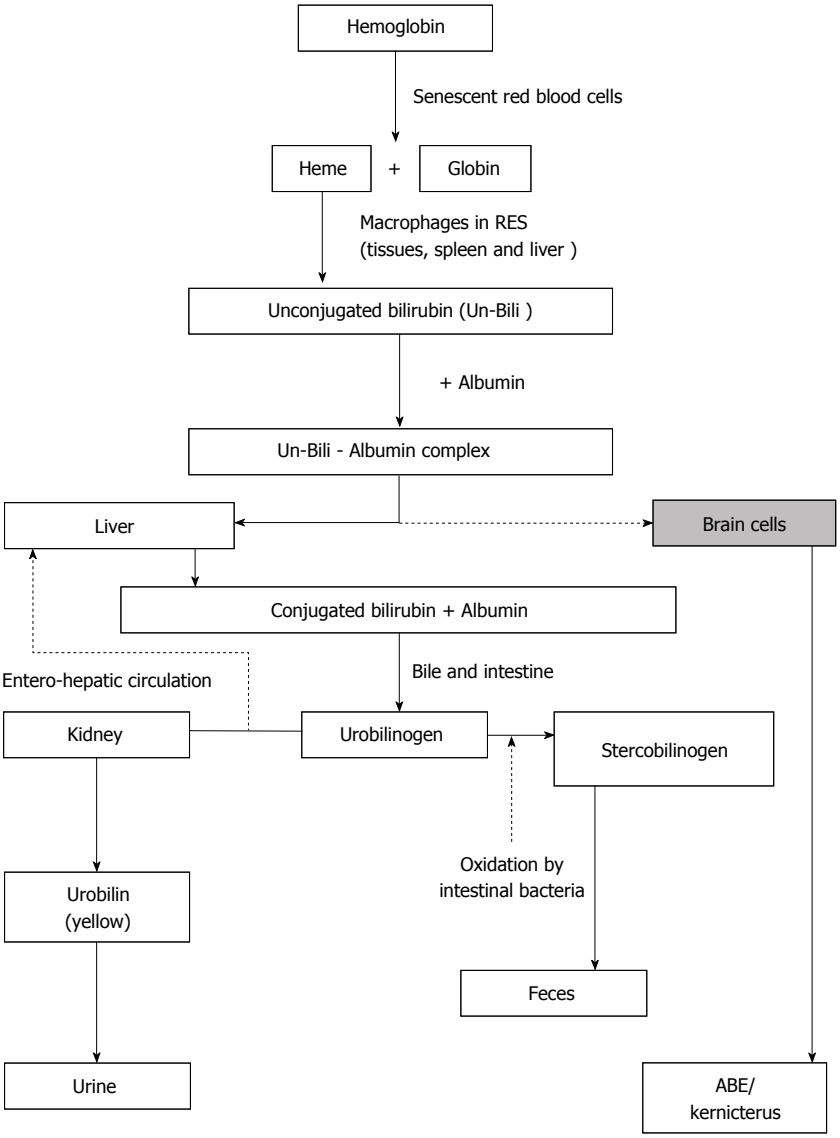

Figure 1 Metabolic pathway of bilirubin neurotoxicity. ABE: Acute bilirubin encephalopathy.

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-

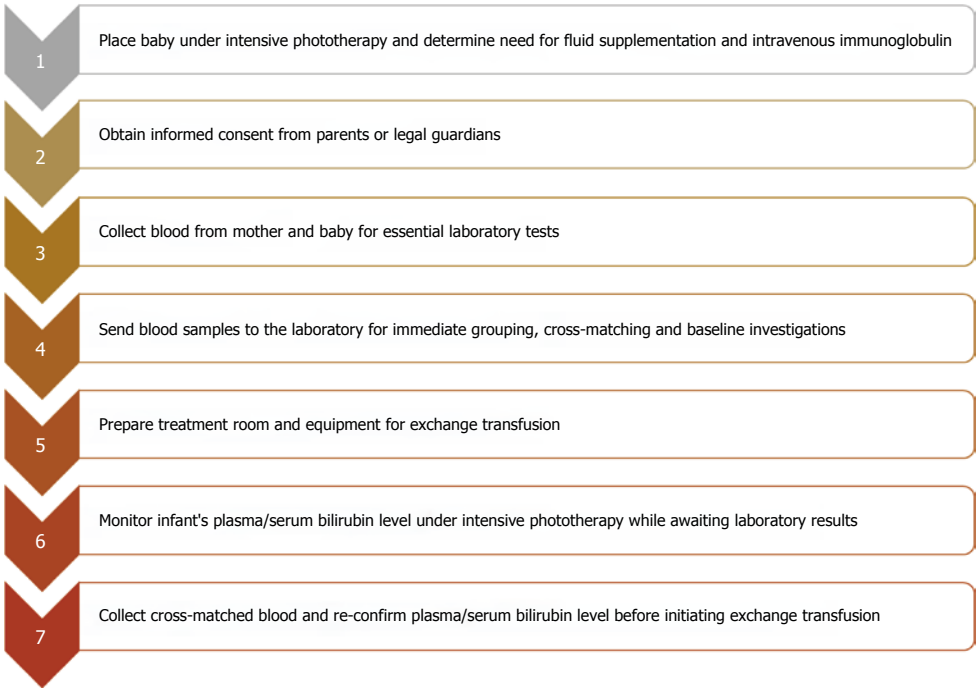

Figure 2 Sequence of events and sources of potential delays following the decision to initiate exchange transfusion.

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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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.

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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.

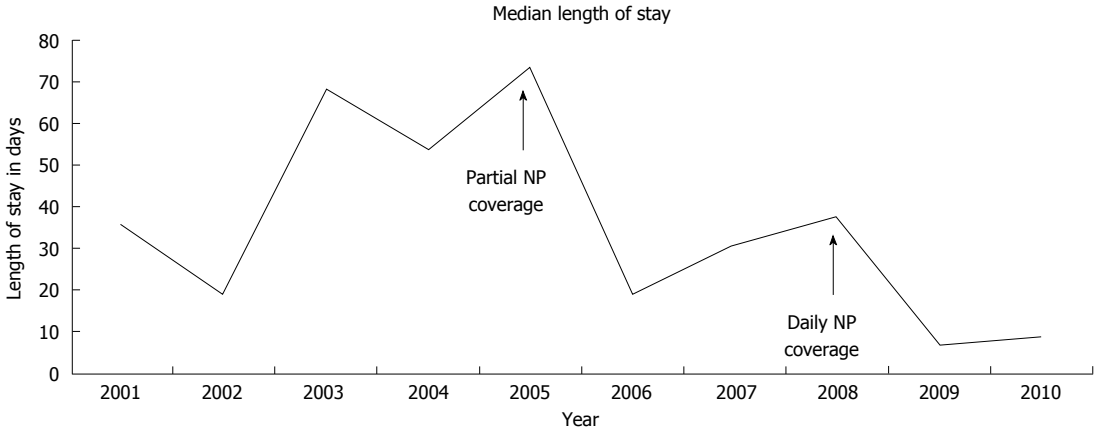

Figure 1 Median length of stay. In the figure above, the length of stay in days is plotted out over the course of the study from 2001 to 2010. The addition of partial NP coverage began in 2005 when the length of stay was highest. Daily NP coverage began in 2008. NP: Nurse practitioner.

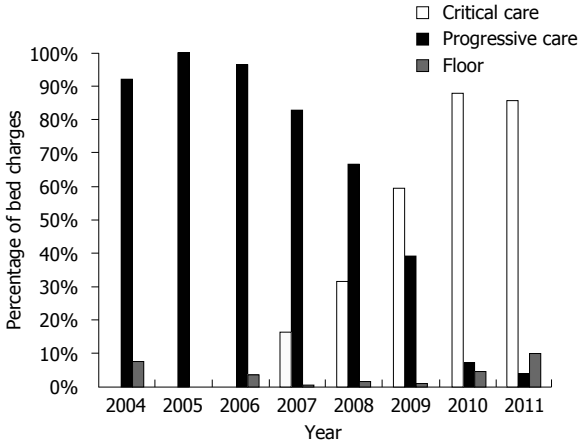

Figure 2 Percentage of bed charges during the length of the study. Over the course of our study, the average room charge per patient stay decreased as the dedicated NP was introduced into the PCVDU. The addition of the NP did not add specific charges as their services were bundled into the hospital and 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.

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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

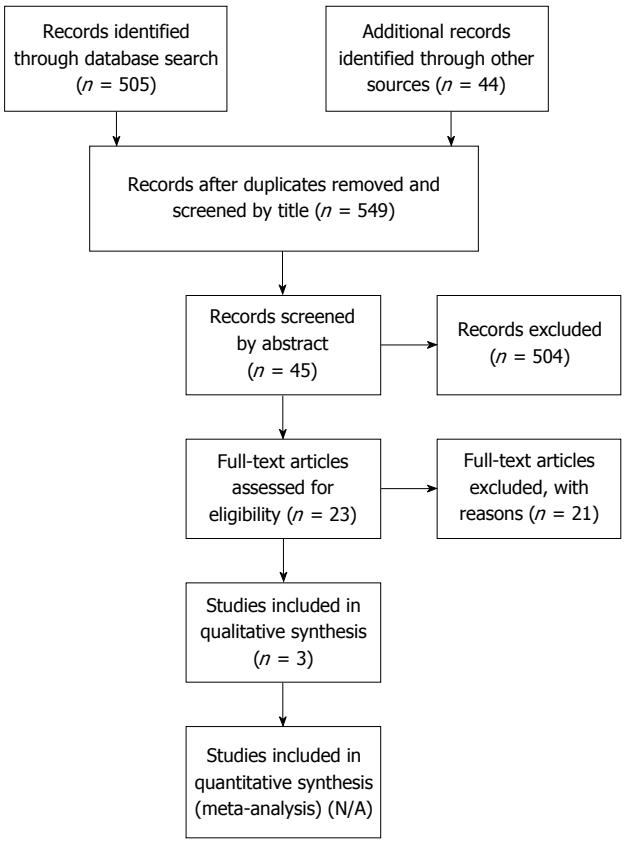

Figure 1 PRISMA flow diagram[12]. For search of PubMed and PSYCHINFO databases using mesh search terms for character development, chronic conditions, and childhood. N/A: Not applicable.

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.

Bhayat SI, Gowda HMS, Eisenhut M. Should dopamine be the first line inotrope in the treatment of neonatal hypotension? Review of the evidence. *World J Clin Pediatr* 2016; 5(2): 212-222 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i2/212.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i2.212

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]

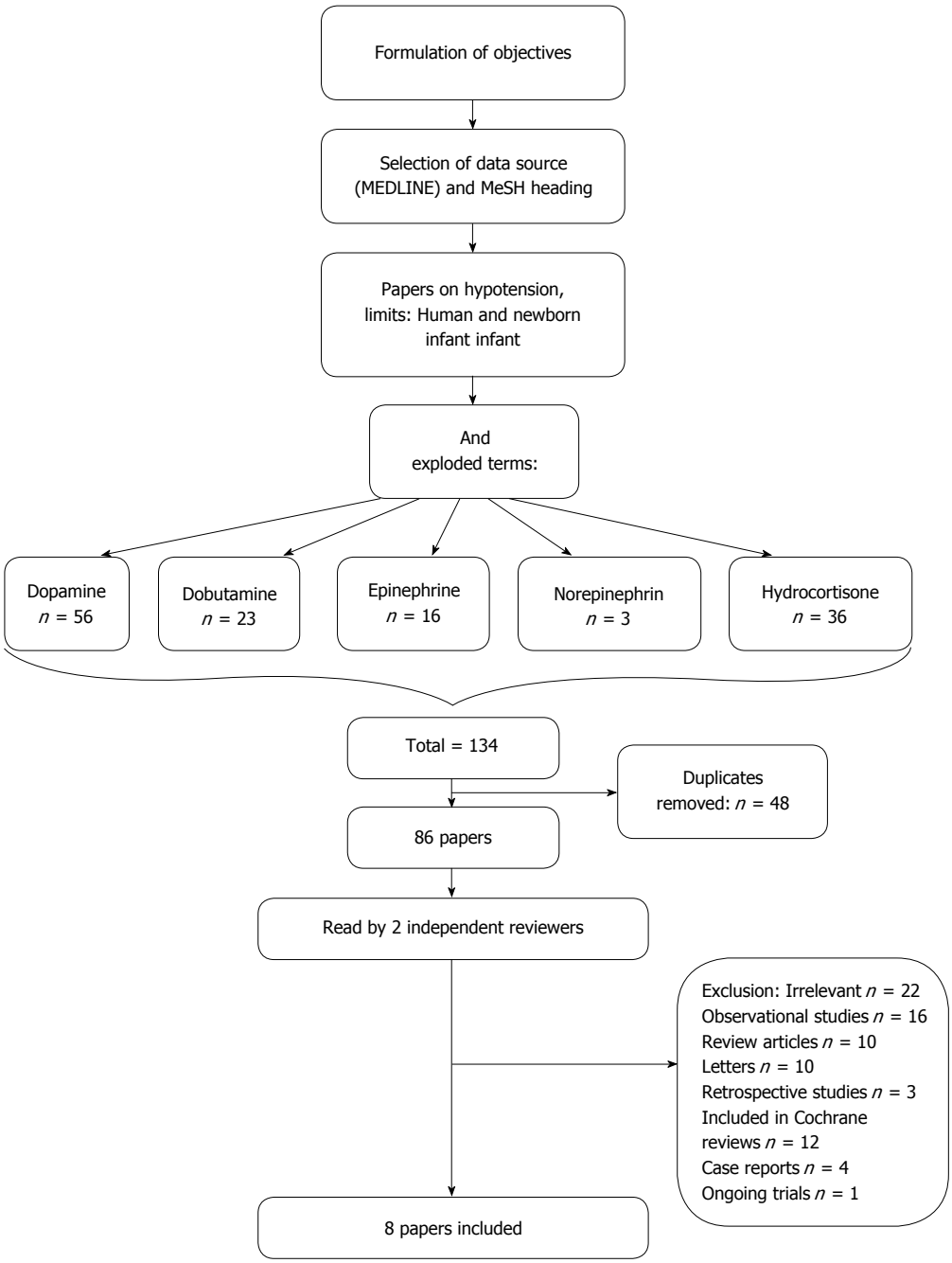

Figure 1 PRISMA flow chart of study selection comparing dopamine *vs* other inotropes in neonates.

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)

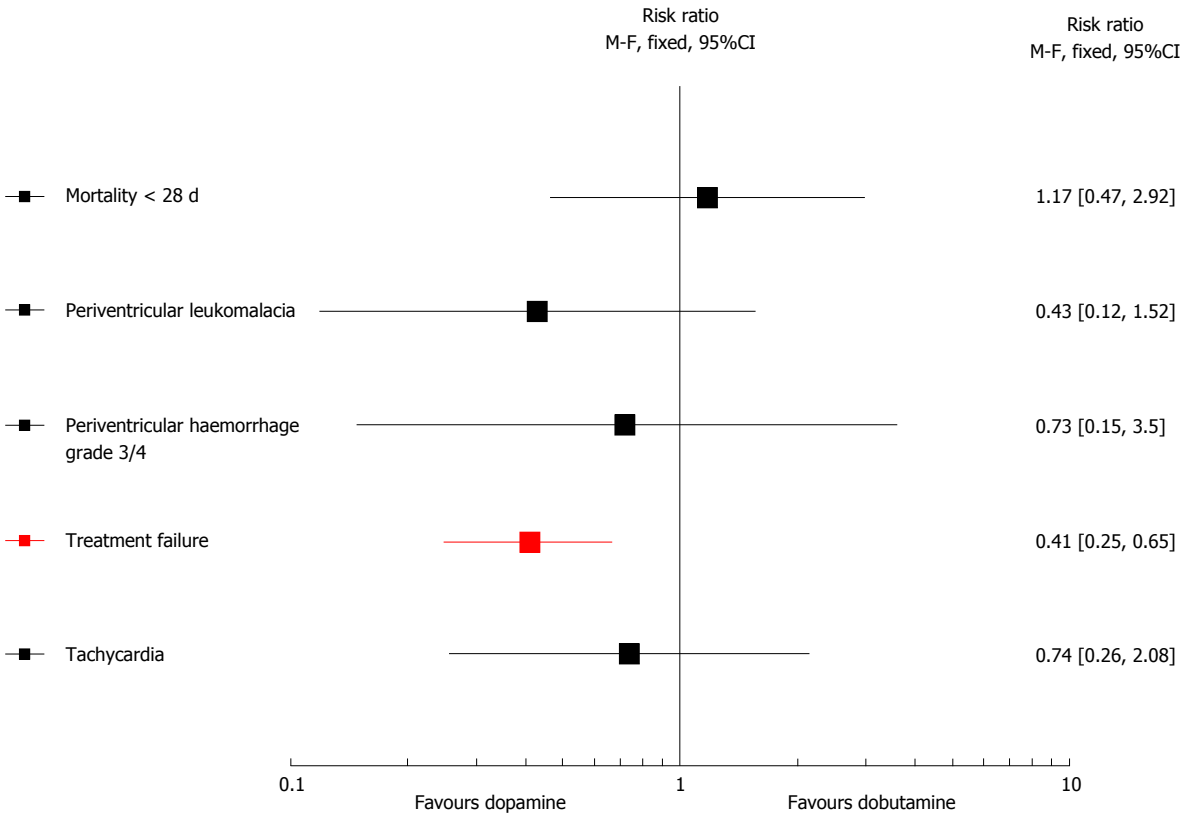

Figure 2 Outcomes of the Cochrane review comparing dopamine *vs* dobutamine in preterm infants.

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

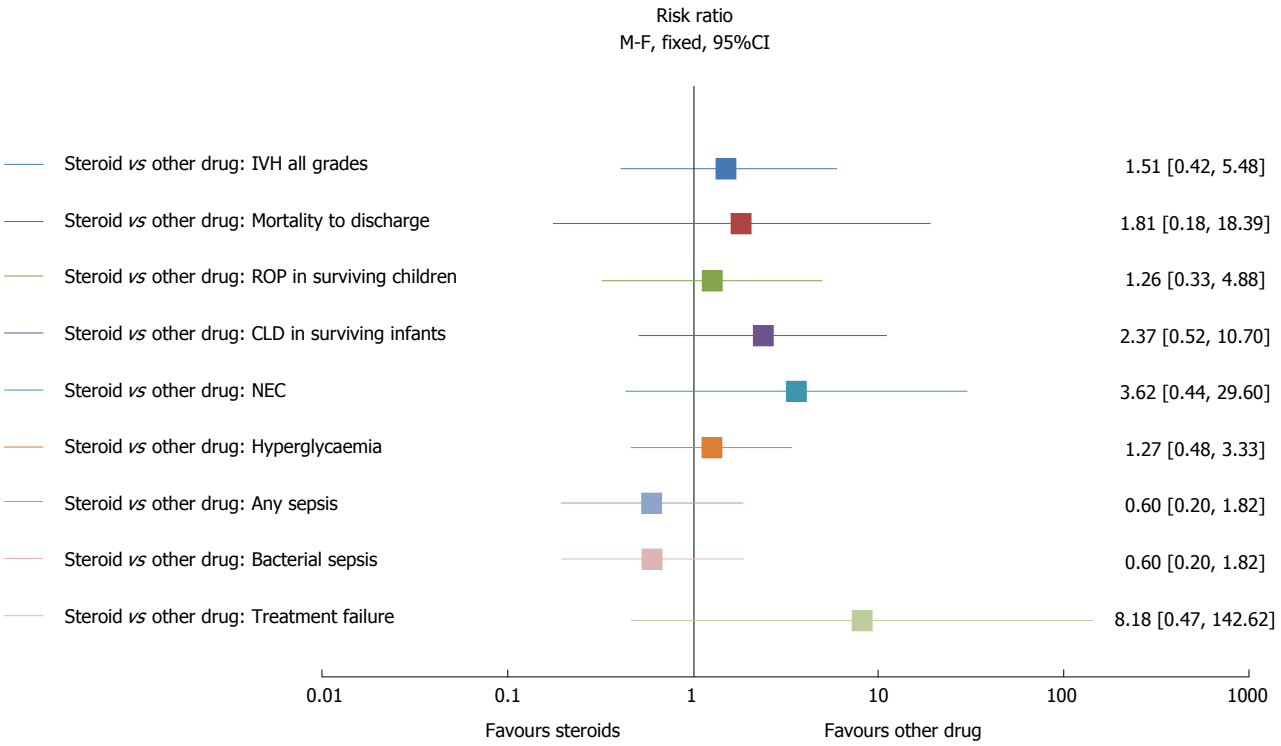

Figure 3 Outcomes of the Cochrane review comparing outcomes of steroids *vs* other drugs (only article included in the analysis compared dopamine to steroids).

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

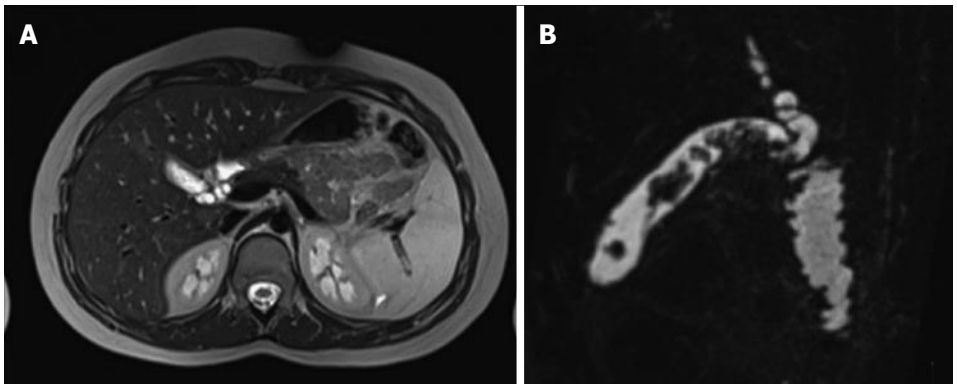

Figure 1 T2-weighted magnetic resonance imaging images confirming the irregular and diffuse thickening of gallbladder walls, more prominent in the body and in the fundus, suggestive of diffuse adenomyomatosis of the gallbladder (A and B). Nodular images with intraluminal protrusion were localized in the fundus and in the body of the gallbladder.

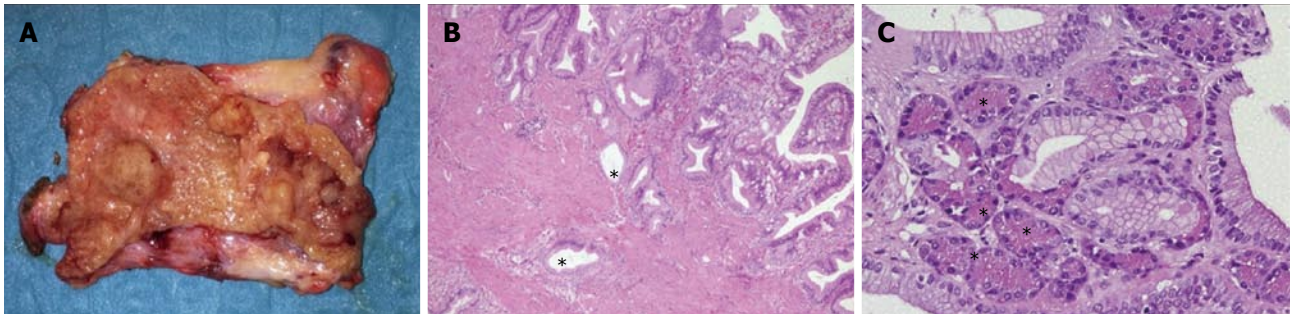

Figure 2 Intraoperative picture. A: Gallbladder specimen of 7 cm × 2 cm; B: Pathological examination showing the invagination of the gland (asterisks) into the muscular layer of the gallbladder, with the presence of glandular elements in the outer layers of the organ (hematoxilin-eosin, original magnification 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

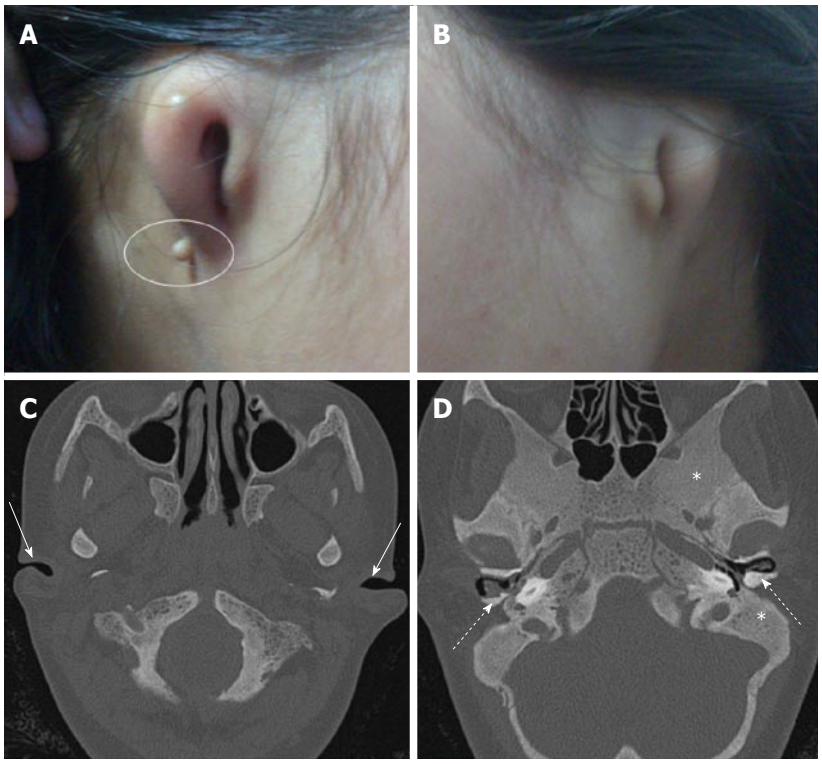

Figure 1 Bilateral dysplastic pinnae. Note preauricular skin tag on right side (circle). Axial HRCT (C and D) showing bilateral mild narrowing of cartilaginous EAC (arrows) and normal bony EAC (dotted arrow) with ear wax. Also seen are the thickened sclerotic calvarial bones with loss of normal medullary cavity (asterisk). EAC: External auditory canal.

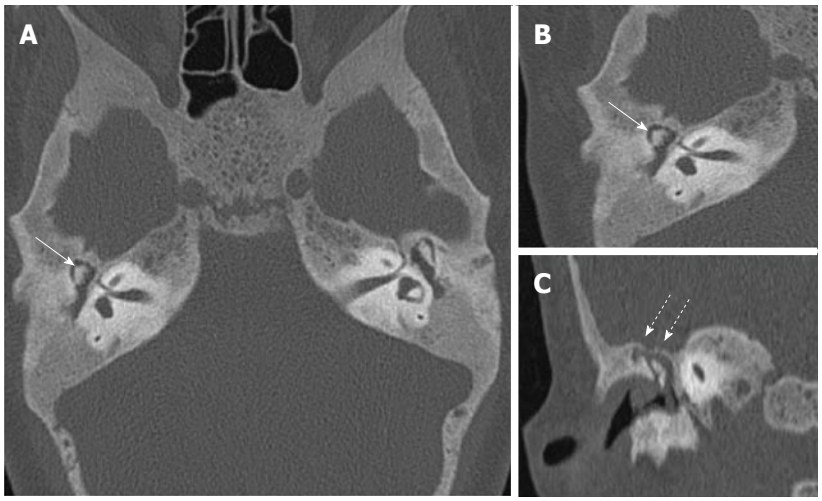

Figure 2 Axial high resolution computed tomography images. (A and B) showing soft tissue opacification in bilateral middle ears (A) with erosion of head of head of malleus (arrows). Coronal reformatted CT image (C) showing thinning and erosion of tegmen tympani (dotted arrows) secondary to cholesteatoma.

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

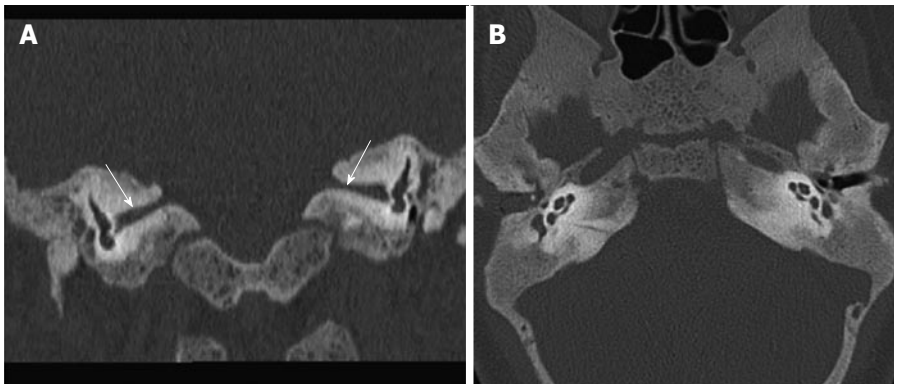

Figure 3 Coronal reformatted high resolution computed tomography. (A) image showing thickened sclerotic bones causing narrowing of bilateral internal auditory canal (arrows); normal cochlea and vestibule seen in both ears on axial high resolution computed tomography image (B).

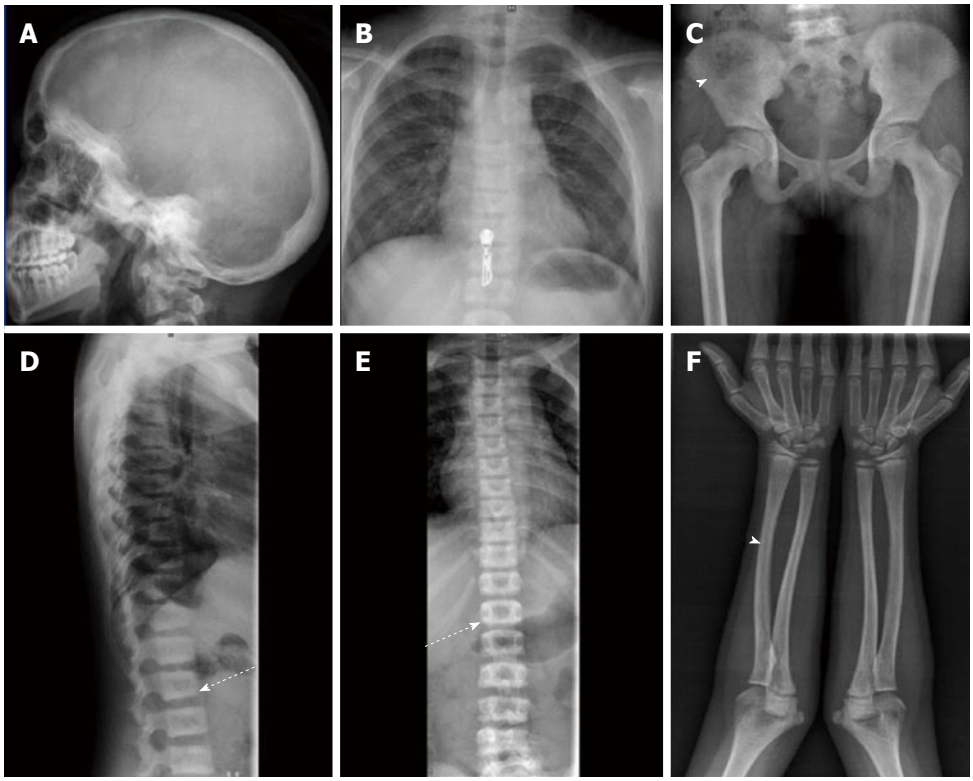

Figure 4 Skeletal survey. Note generalised increased bone density in all the radiographs (A to F). Calvarial bones as well as skull base are thickened (A), lung fields are normal with sclerotic ribs (B). No paraspinal masses to suggest extra medullary hematopoiesis. Sclerosis of pelvic bones with subtle 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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