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REVIEW

Modeling cardiac arrest and resuscitation in the domestic pig

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Abstract

Cardiac arrest remains a leading cause of death and permanent disability worldwide. Although many victims are initially resuscitated, they often succumb to the extensive ischemia-reperfusion injury inflicted on the internal organs, especially the brain. Cardiac arrest initiates a complex cellular injury cascade encompassing reactive oxygen and nitrogen species, Ca^{2+} overload, ATP depletion, pro- and anti-apoptotic proteins, mitochondrial dysfunction, and neuronal glutamate excitotoxity, which injures and kills cells, compromises function of internal organs and ignites a destructive systemic inflammatory response. The sheer complexity and scope of this cascade challenges the development of experimental models of and effective treatments for cardiac arrest. Many experimental animal preparations have been developed to decipher the mechanisms of damage to vital internal organs following cardiac arrest and cardiopulmonary resuscitation (CPR), and to develop treatments to interrupt the lethal injury cascades. Porcine models of cardiac arrest and resuscitation offer several important advantages over other species, and outcomes in this large animal are readily translated to the clinical setting. This review summarizes porcine cardiac arrest-CPR models reported in the literature, describes clinically relevant phenomena observed during cardiac arrest and resuscitation in pigs, and discusses numerous methodological considerations in modeling cardiac arrest/CPR. Collectively, published reports show the domestic pig to be a suitable large animal model of cardiac arrest which is responsive to CPR, defibrillatory countershocks and medications, and yields extensive information to foster advances in clinical treatment of cardiac arrest.

Key words: Acidemia; Asphyxia; Cardiopulmonary

resuscitation; Countershocks; Hyperoxia; Vasopressin; Ventricular fibrillation

Core tip: Cardiac arrest remains a leading cause of death worldwide, despite tremendous improvements in emergency medical care and increased public delivery of bystander cardiopulmonary resuscitation (CPR). But progress is being achieved, thanks to the joint efforts of biomedical scientists, physicians and emergency medical personnel to translate laboratory discoveries to the ambulance and hospital. The domestic pig has proven to be a superb preclinical model of cardiac arrest, yielding a wealth of mechanistic insights and practical strategies to refine the delivery of CPR and to test promising treatments. This review examines pivotal factors in modeling cardiac arrest and CPR in the pig.

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INTRODUCTION

Prior to 1960 cardiac resuscitation was administered by direct cardiac massage following thoracotomy. Based on animal experimentation a method of external cardiac massage administered by rapid, forceful compressions and passive recoil of the sternum was developed by Kouwenhoven *et al*[1]. Although over fifty years have passed since the inception of closed chest cardiac massage, and despite many refinements of this approach in the intervening decades, cardiac arrest remains a leading cause of death and persistent disability worldwide. All too often, victims who are initially resuscitated later succumb to extensive ischemia-reperfusion injury to their vital organs, especially the brain[2-5]. Further, many of the 10% of cardiac arrest patients who survive to hospital discharge experience persistent neurocognitive impairment which profoundly impacts their quality of life[3,6].

Although public health data and anecdotal evidence inform the refinement of cardiopulmonary resuscitation (CPR) protocols[7], knowledge of the complex mechanisms of internal organ damage, essential to foster development of effective pharmacological interventions, is incomplete. In the brain, ATP depletion, intracellular Ca^{2+} overload, excessive formation of reactive oxygen and nitrogen derivatives, inflammation and glutamate-induced excitotoxicity conspire to kill neurons and other cells and disrupt the blood-brain barrier. Currently there are no clinically effective pharmacological treatments to protect the brain during cardiac arrest and CPR[2], and therapeutic hypothermia is the only approved treatment in the United States[8]. Reliable preclinical models of cardiac arrest and resuscitation are essential to decipher the injury mechanisms and develop treatments to increase survival and improve quality of life after cardiac arrest.

Ischemia-reperfusion damage in the central nervous system is the result of a multifaceted injury cascade[9,10]. The structural complexity of the brain, which consists of integrated networks of different cell types including neurons, astrocytes, oligodendrocytes, microglia and vascular endothelium, presents fundamental challenges to developing neuroprotective treatments. The brain contains many functional regions which differ in their vulnerabilities to ischemia-reperfusion injury. Potential pharmacotherapeutic agents must first traverse the blood brain barrier, a significant permeability impediment to all but small, non-polar compounds, and act on multiple injury mechanisms, without producing untoward side effects.

Sophisticated animal models are required to model the composite structure and integrated function of the central nervous system and to evaluate the benefits and potential side effects of prospective treatments for ischemia and other brain disorders. Extensive research has established the domestic pig as an excellent animal model to study the impact of cardiac arrest, resuscitation, and therapeutic interventions on the brain and other internal organs. An impressive variety of swine cardiac arrest models are reported in the literature. By examining the features that distinguish these models, this article aims to assist the reader in evaluating the literature and in designing porcine cardiac arrest models appropriate to address specific research objectives.

ATTRIBUTES OF SWINE FOR MODELING CARDIAC ARREST AND RESUSCITATION

Several attributes make the domestic pig an ideal model for cardiac arrest research[11,12]: (1) a large mammal, the pig accommodates extensive instrumentation for blood sampling, monitoring of intravascular and intracardiac pressures, electrocardiography and intravenous administration of medications and experimental treatments; (2) pigs tolerate invasive surgical procedures and rapidly regain consciousness post-anesthesia; (3) resting heart rate, blood pressure, and serum chemistries of pigs and humans are very similar[13-15]; (4) pigs have sufficient blood volume to permit collection of multiple arterial and venous samples for analyses of blood gases and serum chemistry; (5) neurological examinations have been developed to evaluate neurobehavioral function

Table 1 Details of representative cardiac arrest protocols in pigs

Ref.	Lurie *et al*[93], 2002	Mayr *et al*[38], 2004	Tang *et al*[25], 2006	Li *et al*[94], 2008	Indik *et al*[95], 2009	Hang *et al*[96], 2014
Pre-anesthetic, induction anesthetic	Ketamine 20 mg/kg *im* Propofol 2.3 mg/kg *iv*	Ketamine 20 mg/kg *im* Propofol 1-2 mg/kg *iv* Piritramide 30 mg *iv*	Ketamine 20 mg/kg *im* Pentobarbital 30 mg/kg *iv*	Ketamine 20 mg/kg *im* Pentobarbital 30 mg/kg *iv*	5% isoflurane	Ketamine 15 mg/kg *im* Midazolam 0.5 mg/kg *im* Atropine 0.05 mg/kg *im* Propofol 1 mg/kg *iv*
Maintenance anesthesia	Propofol 10 mg/kg per hour *iv*	Isoflurane (1%-2%) in 65% nitrous oxide	Pentobarbital 8 mg/kg per hour *iv*	Pentobarbital 8 mg/kg per hour *iv*	1.5%-3% isoflurane	Propofol 9 mg/kg per hour *iv* Fentanyl 1 μg/kg per hour *iv*
Method of arrest	Electrical: 60 Hz, 140-160 V	Pharmacological: 5 mg/kg bupivacaine	Electrical: 1-2 mA	LAD balloon occluder	Steel plug in LAD	Asphyxiation: endotracheal clamping
Pre-CPR arrest	6 min	6 min	7 min	5 min	8 min	8 min
Precordial compressions (% of chest diameter)	Mechanical: 80/min (25%)	Manual: 100/min	Mechanical: 100/min (25%)	Mechanical: 100/min (Group 1 25%, Group 2 17.5%)	Manual: 100/min (*c.* 33%)	Manual: 100/min (*c.* 33%)
CPR duration	6 min	2 min	1 min	3 min	2 min	4 min
Ventilation during CPR?	F_{IO2} = 1.0; 5:1 compression: ventilation	F_{IO2} = 1.0	F_{IO2} = 1.0; 15:2 compression: ventilation	F_{IO2} = 1.0; 15:2 compression: ventilation	None	F_{IO2} = 1.0; 12 cycles/min; 10 mL/kg per cycle
Countershocks	1-3 x 200 J	3, 4, 6 J/kg	150-360 J	150 J	150 J	4 J/kg
CPR between countershocks	90 s	None	1 min/shock	3 min	2 min	2 min
Vasopressors to enhance CPR	EPI 0.045 mg/kg	AVP 0.4 or 0.8 U/kg ± EPI 45 or 200 μg/kg	None	None	EPI 0.02 μg/kg; 1-3 doses	EPI 0.02 μg/kg
Definition of ROSC	Systolic BP > 70 mmHg	Systolic BP ≥ 80 mmHg for ≥ 5 min	Mean aortic BP > 60 mmHg for ≥ 5 min	Mean aortic BP ≥ 60 mmHg for ≥ 5 min	Systolic BP > 50 mmHg for > 1 min	Systolic BP > 50 mmHg for > 10 min
ROSC duration	24 h	1 h	3 d	72 h	24 h	6 h
Pigs completing protocol	11/20	Placebo: 0/7; AVP: 5/7; EPI: 4/7; AVP + EPI: 7/7	36/44	Group 1: 6/6 Group 2: 0/6	11/15	ROSC: 8/16; Complete protocol: 3/16

AVP: Vasopressin; BP: Systemic arterial blood pressure; CPR: Cardiopulmonary resuscitation; EPI: Epinephrine; LAD: Left anterior descending coronary artery; ROSC: Recovery of spontaneous circulation.

in pigs[16,17]; (6) the pig's large chest accommodates forceful precordial chest compressions and application of transthoracic defibrillatory countershocks of electrical energies similar to those used clinically; and (7) pigs have the largest brains among the commonly studied laboratory animals, which provides ample tissue for extensive biochemical and histological analyses of specific brain subregions. Porcine models are especially well-suited to study cardiac arrest and CPR, because they are easily tailored to address specific research objectives.

FACTORS TO CONSIDER WHEN MODELING CARDIAC ARREST AND RESUSCITATION IN PIGS

The pathophysiological complexities of sudden cardiac death and cardiopulmonary resuscitation challenge the development of animal models that accurately replicate the clinical situation. The primary factors in developing suitable animal models are the study end points and objectives. However, the myriad variables in model design and experimental protocol, which mirror the complexity of cardiac arrest and its treatment, challenge the direct comparison of results obtained in different studies. This section summarizes several factors that must be considered in developing and reporting cardiac arrest-resuscitation protocols in pigs, including the anesthetic regimen, method of inducing ventricular fibrillation, the depth, frequency and duration of chest compressions, whether or not to ventilate during resuscitation and the fraction of inspired O_2 (F_{IO2}), the pattern and intensity of defibrillatory countershocks, the criteria taken to indicate recovery of spontaneous circulation (ROSC), the use of inotropic and/or vasoconstrictor support during ROSC, and strategies to correct post-arrest systemic acidemia. With multiple options for each component, it is critical that cardiac arrest-resuscitation protocols be designed carefully to address the study's specific

objectives. Table 1 summarizes and compares key features of representative cardiac arrest-resuscitation protocols in domestic swine.

Induction and maintenance of anesthesia

Invasive surgical procedures and ethical constraints require the induction and maintenance of an appropriate anesthetic plane. Anesthetics are infused intravenously or, in the case of volatile anesthetics, inhaled. The temporary or persistent effects of the anesthetic on study endpoints, *e.g*., cardiac function, cell death, inflammation or neurobehavioral recovery must be taken into account. For example, the cardiodepressant effects of some volatile anesthetics, *e.g*., halothane and isoflurane may produce hypotension[18-21], yet these anesthetics also exert cardioprotection[22,23]; thus, the anesthetic plane must be controlled carefully. Signs of inadequate anesthesia include increased jaw tension, limb withdrawal when the soft tissue between the hooves is pinched, wink reflex in response to delicate contact of the ocular canthus, spontaneous limb movements, and/or unexpected increases in heart rate and systemic arterial pressure.

Methods of inducing cardiac arrest

The major causes of clinical cardiac arrest are asphyxiation, electric shock and, most commonly, coronary artery occlusion and reperfusion. There are different methods of inducing cardiac arrest which model these clinical situations. The first and most common method of inducing ventricular fibrillation is the application of electrical current to the epicardium or, in closed-chest preparations, the left or right ventricular endocardium. Typically, a pacing wire is introduced into the external jugular vein and advanced into the right ventricle (Figure 1)[24-27]. While the wire is in contact with the right ventricular endocardium, a rapid train of impulses is transmitted which, within seconds, initiates ventricular fibrillation. The characteristic "torsades de pointes" pattern on electrocardiogram (*cf.* Figure 2), monophasic decline in aortic pressure and the absence of an arterial pulse confirm ventricular fibrillation. Aside from modeling electrocution-induced cardiac arrest, an important advantage of this method is the well-defined and reproducible time of ventricular fibrillation onset. Electrical induction of ventricular fibrillation does not impart substantial myocardial injury, which is advantageous if the study is examining other internal organs in which persistent cardiac insufficiency might be a confounding factor.

Myocardial ischemia imposed by coronary stenosis or occlusion is the leading cause of cardiac arrest. Porcine models of ischemia-induced ventricular fibrillation are available that accurately reproduce the pathophysiology of cardiac arrest. Porcine myocardium lacks significant coronary collateral vessels, so the ischemia imposed by occlusion of a major coronary artery, *e.g*., the left anterior descending coronary artery, is sufficiently severe to initiate ventricular fibrillation within several minutes of occlusion. Coronary occlusions may be imposed by introducing a balloon occluder (one used for percutaneous transluminal coronary angioplasty) and routing it, with the aid of fluoroscopy[28], into the target vessel before inflating it. An alternative approach is the use of an ameroid occluder around a coronary artery; however, this procedure requires invasive thoracotomy and pericardiotomy to permit placement of the occluder, necessitating post-surgical recovery of the animal before the cardiac arrest experiment. In either case, occlusion may be confirmed by arteriography[28,29]. A third method is advancement of a Teflon[30] or steel[31] plug into the coronary artery. Ventricular fibrillation typically ensues within 5-10 min of coronary occlusion[29,31]. The coronary occlusion may be released, *e.g*., release of the balloon or ameroid occluder upon defibrillation[28,29] or the intracoronary plug may be permanently installed, resulting in a myocardial infarct[30]. Because the onset of cardiac arrest is delayed to a variable extent while the artery is occluded, the severity of myocardial injury may vary considerably among experiments. The number and intensity of the countershocks required to restore sinus rhythm is greater in porcine models of ischemically-induced *vs* electrically-induced arrest, as is the incidence of post-resuscitation ventricular premature beats and recurrence of ventricular fibrillation[29,32,33]. Nevertheless, ischemia-induced cardiac arrest replicates the most common cause of cardiac arrest, affording ready translation of results to clinical settings.

Asphyxiation is the second most common cause of cardiac arrest and the leading cause in children. A facile method of producing asphyxia in anesthetized swine is to block the endotracheal tube while monitoring the electrocardiogram and arterial blood pressure[34-36]. Hypoxemia and hypercapnia progressively intensify until cardiac arrest ensues, typically within 10-15 min after blocking ventilation[37]. The principal advantages of asphyxia are its accurate modeling of a major cause of pediatric cardiac arrest and mortality, including the changes in blood gases and pH, and the noninvasive approach which obviates the introduction of pacing wires or occluders into the vasculature. Depending on the study endpoints and objectives, disadvantages may include the changes in blood gas chemistry[37] and the variable duration of asphyxiation before ventricular fibrillation, which imposes hypoxemia on the brain and other internal organs even before onset of cardiac arrest.

High dosages of certain chemicals, *e.g*., bupiva-

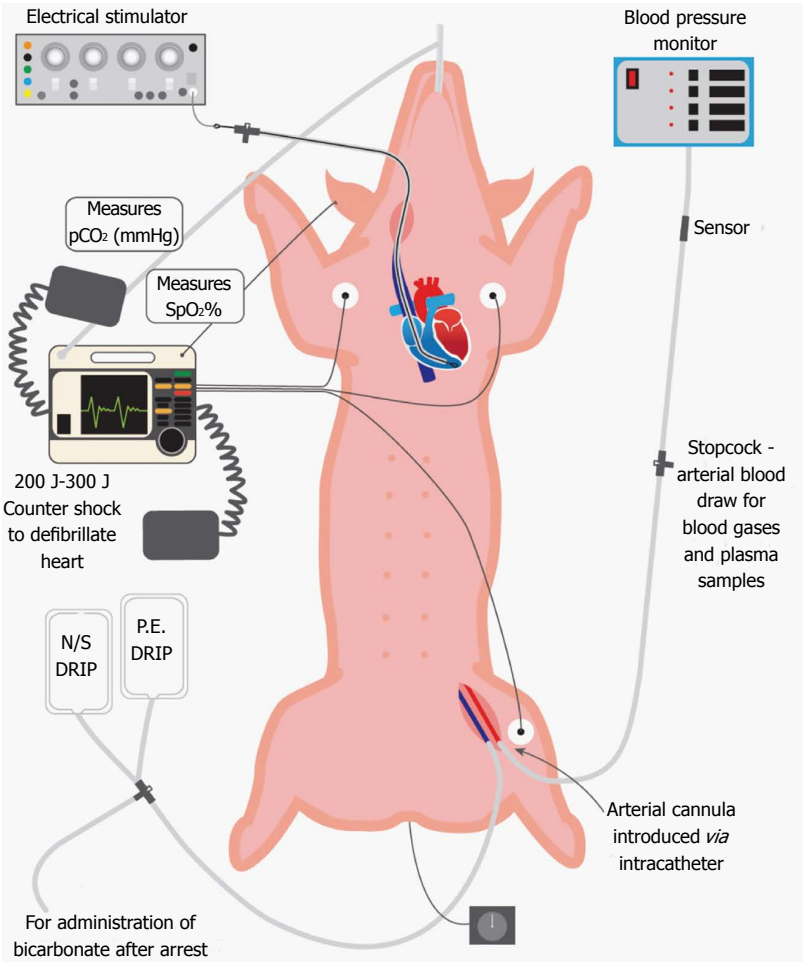

Figure 1 Porcine preparation for cardiac arrest-cardiopulmonary resuscitation studies. The pig is placed in supine recumbency and mechanically ventilated *via* an endotracheal tube, through which isoflurane anesthesia is administered. Hemodynamic function is monitored by a femoral arterial catheter connected to a pressure transducer, and electrocardiographic activity is monitored by standard limb lead Ⅱ electrocardiogram. Cardiac arrest is induced by a train of electrical impulses conducted by an intrajugular pacing wire from an electrical stimulator to the right ventricular endocardium. Body temperature is measured with a rectal probe, and end-tidal pCO_2 by a sensor placed in the endotracheal tube. Defibrillatory countershocks (200-300 J) are administered with external paddles. Intravenous treatments include normal saline (N/S), phenylephrine (PE), sodium bicarbonate and experimental resuscitative fluids. spO_2: Percentage oxyhemoglobin saturation.

caine[38], may be injected into the right atrium to arrest the heart, modeling cardiac arrest secondary to drug overdose. In such models the potential systemic side effects of the chemicals must be taken into account.

Duration of pre-CPR arrest

The duration of pre-intervention arrest is crucial; as this interval is prolonged, cardioversion, survival and good neurological recovery become progressively less achievable. The three-phase model of cardiac arrest[39] subdivides the pre-intervention period into three phases. The first 4-5 min constitute the electrical phase, during which countershocks are likely to achieve cardioversion even without pre-shock CPR. During the next 5-10 min, the circulatory phase, interventions to effect circulation, *e.g.*, chest compressions, are essential to ensure countershocks produce cardioversion. After 10-15 min arrest, the victim enters the *metabolic phase*, in which increasingly intense metabolic derangements result in protracted or permanent organ damage and severe neurological impairment even if cardioversion is achieved. If the study requires a high survival rate, the period of pre-intervention cardiac arrest may be limited to assure a high rate of defibrillation and ROSC.

Cardiopulmonary resuscitation: force, frequency and duration

By affording modest delivery of O_2 and metabolic fuels to the myocardium, precordial compressions may support enough myocardial ATP production to sustain ion transport and repolarize cardiomyocytes, enabling defibrillatory countershocks to restore spontaneous electrical rhythm. Indeed, in a canine cardiac arrest model, effective CPR afforded partial recovery of myocardial Gibbs free energy of ATP hydrolysis[40], the immediate energy source for cardiac electromechanical activity. Cardiopulmonary resuscitation protocols are readily customized to address the study end points. The frequency and depth of precordial compressions can profoundly influence outcome[41-44]. In some studies, CPR is administered by a pneumatic, piston-driven device (*e.g.*, Thumper®), which can be adjusted to deliver forceful compressions at a predetermined frequency and depth, ensuring consistency of frequency and depth of compressions across experiments[25]. Alternatively, precordial compressions can be administered manually, modeling the CPR given by a bystander responding to an out-of-hospital cardiac arrest. Current American Heart Association guidelines[45] recommend manual mid-sternal chest compressions be sufficiently forceful to compress the

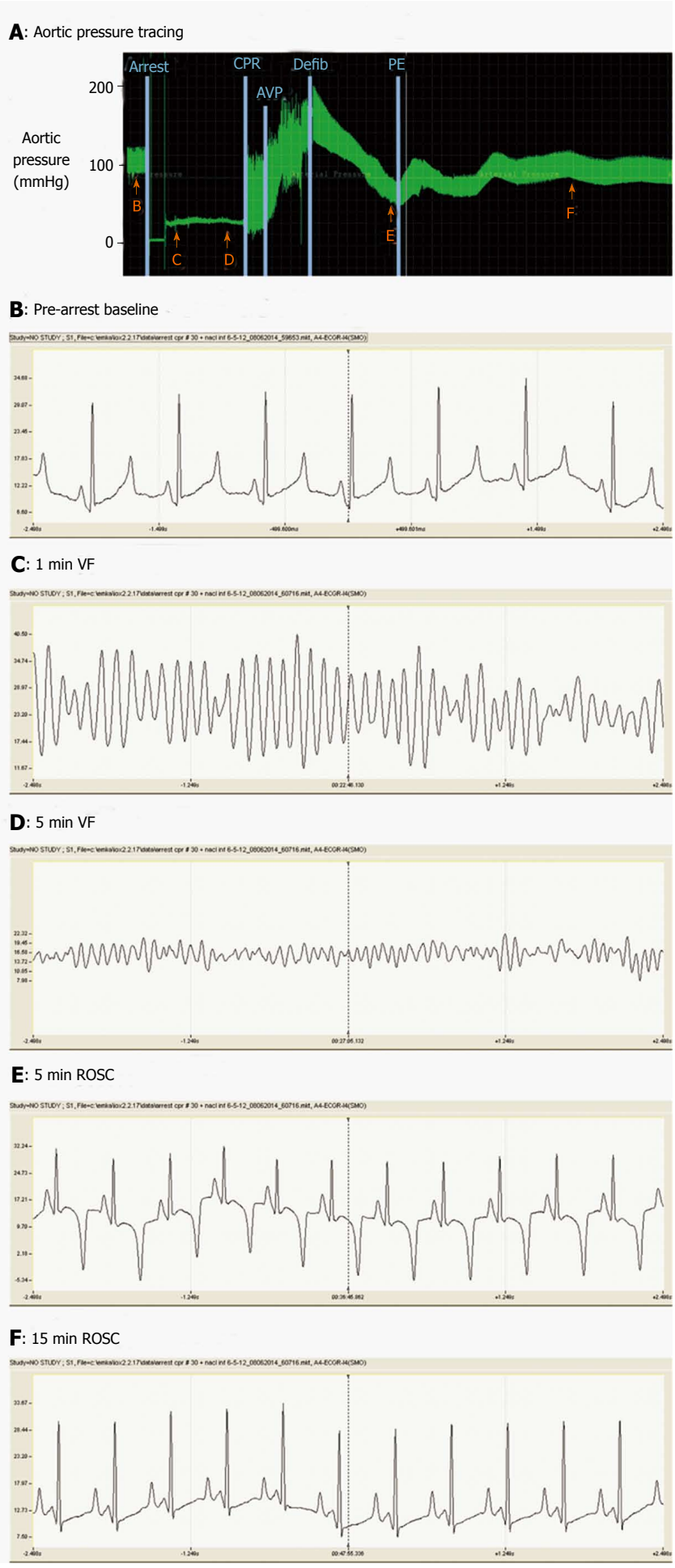

Figure 2 Aortic pressures and lead Ⅱ electrocardiogram during cardiac arrest, cardiopulmonary resuscitation and recovery of spontaneous circulation. A: Phasic aortic pressure tracing during the period from pre-arrest baseline to 20 min ROSC. Lettered arrows indicate times at which the electrocardiograms shown in panels B-F were obtained. Vertical lines indicate: (1) induction of ventricular fibrillation cardiac arrest; (2) commencement of precordial compressions (CPR); (3) injection of vasopressin (AVP); (4) defibrillation (Defib) by 200 J countershock; and (5) initiation of intravenous phenylephrine (PE; *c.* 2 μg/kg per minute) to stabilize systemic arterial pressure during ROSC. Mechanical ventilation was suspended during cardiac arrest and CPR. Panels B-F show 5 s electrocardiographic recordings. CPR: Cardiopulmonary resuscitation; ROSC: Recovery of spontaneous circulation; AVP: Vasopressin; PE: Phenylephrine.

chest by one-fourth of its antero-posterior diameter, followed by release and recoil, at a rate of 100 cycles/min.

The duration of CPR before defibrillatory countershocks is an important factor. Longer intervals model the protracted CPR given by bystanders before arrival of the ambulance team, but also lower the likelihood of post-arrest survival with good neurological outcome. Another important consideration is whether or not the animal will be ventilated during CPR and, if so, at what compression: ventilation ratio and FIO_2. Extensive clinical evidence demonstrates that assisted ventilation during CPR following witnessed cardiac arrest offers little or no neurological or survival benefit[26,46-49]. In accordance with current recommendations for bystander CPR[50], mechanical ventilation may be suspended for the duration of cardiac arrest and CPR, then resumed after confirming defibrillation to a productive sinus rhythm.

A systemic vasoconstrictor may be administered intravenously to increase the arterial pressures produced by the chest compressions, thereby increasing perfusion of brain and myocardium at the expense of peripheral organs and tissues. The most widely used vasoconstrictors include epinephrine, a physiological adrenergic agonist, and vasopressin, a non-adrenergic vasoconstrictor which may afford greater survival to hospital discharge than epinephrine, especially in patients with asystole[51,52].

Although epinephrine has been used in this manner for decades, its potentially detrimental effects, including increased physiological shunt compromising pulmonary gas exchange[53,54], intensified myocardial ATP consumption and oxygen demand[55], and the resultant post-resuscitation myocardial dysfunction[56] and ventricular arrhythmias[57,58] have raised concerns regarding its clinical application for CPR. Preclinical and clinical evidence has shown the non-adrenergic vasoconstrictor vasopressin to be at least as effective as epinephrine at augmenting arterial pressure during precordial compressions, but without epinephrine's untoward effects. In a porcine cardiac arrest model, vasopressin *vs* epinephrine produced greater myocardial and brain blood flows and mean arterial pressures during CPR[59]. Thus, vasopressin was associated with higher incidence of conversion to productive sinus rhythm[60], increased post-arrest cardiac function and decreased morbidity and mortality *vs* epinephrine. We have found[61] that vasopressin (*c.* 0.3 U/kg) injected into the right jugular vein at 60 s CPR improved markedly the quality of CPR, increasing the mean arterial pressures from 25-30 to *c.* 60 mmHg within 3 min (*cf.* Figure 1). Although epinephrine produced a more abrupt increase in arterial pressure following its injection, within 2 min vasopressin increased mean arterial pressure to a similar extent; during the first 15 min ROSC, the vasopressin-treated swine had less intense tachycardia and more moderate heart rate x arterial pressure product, a measure of myocardial energy expenditure, than their epinephrine-treated counterparts[61].

Defibrillation and cardioversion

The defibrillation protocol presents the investigator several options for model design. One choice is the sequence of defibrillatory countershocks, *i.e.*, whether the shocks will be administered singly, or in a sequence of multiple (often three) countershocks, before checking for cardioversion. The electrical energies of the countershocks must be considered, including that of the initial countershock, and, if the initial shock fails to achieve cardioversion, whether or at what progression the intensity will be increased for subsequent countershocks. It must be determined if and for how long CPR will be administered during the interval between an unsuccessful cardioversion and the next attempt. When pre-CPR arrest exceeds the electrical phase, bouts of CPR, including a minimum of 20-25 s of chest compressions following unsuccessful countershocks, are essential to ensure effective countershocks. A similar protocol of single shocks with intervening chest compressions increased post-arrest survival *vs* a conventional 3-shock protocol in a porcine model of ventricular fibrillation cardiac arrest[25].

The cardiocirculatory values that constitute ROSC, including the presence of an organized electrical rhythm and maintenance of arterial blood pressure above a predetermined target value for a minimum duration (*cf.* Table 1) must be specified. Core body temperature has a marked effect on post-arrest and neurological injury and mortality; indeed, moderate hypothermia is the only currently approved intervention consistently shown to produce significant clinical benefit[62-64]. Pigs do not thermoregulate effectively while under anesthesia, so typically the animal must be maintained on a heating pad during the cardiac arrest-resuscitation protocol to avoid the impact of hypothermia on study endpoints. Finally, the criteria for abandoning futile resuscitation efforts must be defined.

Post-resuscitation management

Because cardiac arrest imposes ischemia on the heart itself, cardiac mechanical function may be depressed for several hours of ROSC, a manifestation of reversible myocardial injury termed cardiac "stunning"[65]. As the period of ROSC progresses, interventions may be necessary to maintain adequate arterial pressure. Intravenous saline solutions may be infused to expand extracellular fluid volume. Vasopressor agents, *e.g.*, phenylephrine, may be administered, but it should be recognized that vasopressors may lose their efficacy over time due to desensitization of their membrane receptors[66] and, thus, may be unsuitable for long-

term maintenance of arterial pressure. Accordingly, the vasoconstrictor infusion can be tapered and ultimately discontinued as cardiac function recovers. It may be necessary to adjust tidal volume and frequency of ventilations or administer bicarbonate to compensate for post-arrest hypercapnia and/or acidemia. Isotonic saline (0.9% NaCl) may be infused *iv* to maintain extracellular fluid volume over the course of the protocol.

Inspired oxygen concentration

The oxygen concentration of medical gases used during resuscitation is an important consideration when designing a model of cardiac arrest-resuscitation. For decades, it has been recommended that patients be ventilated with 100% oxygen during resuscitation to increase oxygen delivery to ischemic tissues[67,68]. Recently, however, hyperoxic ventilation during resuscitation has been shown to intensify formation of reactive oxygen and nitrogen intermediates within tissues and, thus, exacerbate ischemia-reperfusion injury[69-75]. A recent meta-analysis of clinical trial data showed hyperoxia (PaO_2 > 300 mmHg) to be associated with increased in-hospital mortality following cardiac arrest[76]. Oxygen toxicity has been studied for years in a perioperative setting, but only recently has there been sufficient clinical evidence for the European Resuscitation Council to recommend that patients not be ventilated with 100% oxygen after cardiac arrest, but rather with room air supplemented with enough O_2 to maintain an oxyhemoglobin saturation (spO_2) of 94%-98%[77,78]. Thus, when designing a cardiac arrest model, the oxygen concentration used during resuscitation may be adjusted depending on whether the study aims to mimic the conventional approach of ventilation with 100% oxygen, or newly recommended strategies such as titration of oxygen administration to maintain a desired spO_2.

CHALLENGES TO MODELING CARDIAC ARREST IN PIGS

Pulseless electrical activity

Pulseless electrical activity (PEA) is a "non-shockable" cardiac electrical rhythm that does not produce ventricular contraction or forward movement of blood. Approximately 60% of out-of-hospital resuscitation attempts result in the development of PEA as the presenting rhythm[79]. Only 2%-5% of patients who present with PEA as their initial rhythm survive to hospital discharge[80-82], well below the 15%-40% survival rate of those presenting with ventricular fibrillation[83-85]. Even fewer patients in whom ventricular fibrillation converted to PEA following countershocks survive to hospital discharge[79,86]. In our porcine cardiac arrest model, PEA is an ominous finding; typically, even heroic efforts fail to convert PEA to a productive sinus rhythm. None of the 9 pigs developing PEA during resuscitative efforts survived for 4 h ROSC. This situation replicates the clinical setting of out-of-hospital cardiac arrest, where a much lower rate of survival to hospital discharge is achieved in cardiac arrest victims in which PEA is the initial rhythm *vs* patients with an initial electrocardiographic substrate of ventricular fibrillation[87].

Malignant hyperthermia

A small minority of pigs harbor a genetic lesion in the skeletal muscle sarcoplasmic reticular Ca^{2+} release channels[88,89] that predisposes them to develop malignant hyperthermia (*aka* porcine stress syndrome), often triggered by exposure to volatile anesthetics[90]. Malignant hyperthermia has no overt clinical phenotype detectable by routine screening. As post-arrest survival and neurobehavioral recovery are negatively correlated with body temperature, an episode of malignant hyperthermia, during which core body temperature may rise above 42 ℃, can have disastrous consequences, including systemic hypotension, acidemia, hypercapnia and hyperkalemia that are refractory to conventional interventions. Indeed, in our studies none of the five anesthetized pigs (4% of the total) that developed acute malignant hyperthermia survived to 4 h ROSC, despite aggressive measures including intravenous infusion of ice-cold saline and the K^+ chelator calcium gluconate.

Limitations of porcine models

An important limitation of many porcine cardiac arrest models is that juvenile, disease-free pigs are generally used. In clinical settings, patients who experience cardiac arrest typically are elderly and suffer from chronic disorders such as hypertension, atherosclerosis, congestive heart failure, diabetes, emphysema or end-stage renal disease. The Ossabaw swine, which is predisposed to develop metabolic syndrome when consuming a high fat diet[91,92], provides a unique, clinically relevant experimental model suitable for studying cardiac arrest and resuscitation superimposed on metabolic syndrome. Indeed, under anesthesia these swine develop severe arrhythmias, responsive to amiodarone, that may deteriorate into cardiac arrest (Johnathan D. Tune, personal communication).

Unlike most porcine preparations, human victims of out-of-hospital cardiac arrest are not anesthetized when they are stricken. Cardiac arrest is an unanticipated event, and when it occurs outside the hospital, the delays to effective treatments are variable, poorly defined and all too often lethal. Most preclinical cardiac arrest studies employ well defined protocols, such as those reviewed herein. The fundamental differences between these protocols

and the highly variable and exceedingly challenging clinical situation must be acknowledged.

CONCLUSION

Over the last few decades the collective efforts of many investigators have fostered the development of sophisticated porcine models of cardiac arrest, CPR and ROSC. The domestic pig provides an excellent large animal model of the human cardiovascular system and yields ample tissue for extensive analyses of mechanisms of injury and cytoprotection in the internal organs, such that each experiment generates a wealth of information. Although there is much to consider when constructing an experimental design, the swine model of cardiac arrest-resuscitation is easily tailored to accommodate the desired study end points. The swine model provides unparalleled translational value among current mammalian models of cardiac arrest and CPR, permitting an integrative approach to bridge the gap from bench to bedside.

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REVIEW

Antibiotic stewardship programmes in intensive care units: Why, how, and where are they leading us

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Abstract

Antibiotic usage and increasing antimicrobial resistance (AMR) mount significant challenges to patient safety and management of the critically ill on intensive care units (ICU). Antibiotic stewardship programmes (ASPs) aim to optimise appropriate antibiotic treatment whilst minimising antibiotic resistance. Different models of ASP in intensive care setting, include "standard" control of antibiotic prescribing such as "de-escalation strategies" through to interventional approaches utilising biomarker-guided antibiotic prescribing. A systematic review of outcomes related studies for ASPs in an ICU setting was conducted. Forty three studies were identified from MEDLINE between 1996 and 2014. Of 34 non-protocolised studies, [1 randomised control trial (RCT), 22 observational and 11 case series], 29 (85%) were positive with respect to one or more outcome: These were the key outcome of reduced antibiotic use, or ICU length of stay, antibiotic resistance, or prescribing cost burden. Limitations of non-standard antibiotic initiation triggers, patient and antibiotic selection bias or baseline demographic variance were identified. All 9 protocolised studies were RCTs, of which 8 were procalcitonin (PCT) guided antibiotic stop/start interventions. Five studies addressed antibiotic escalation, 3 de-escalation and 1 addressed both. Six studies reported positive outcomes for reduced antibiotic use, ICU length of stay or antibiotic resistance. PCT based ASPs are effective as antibiotic-stop (de-escalation) triggers, but not as an escalation trigger alone. PCT has also been effective in reducing antibiotic usage without worsening morbidity or mortality in ventilator associated pulmonary infection. No study has demonstrated survival benefit of ASP. Ongoing challenges to infectious disease management, reported by the World Health Organisation global report 2014, are high AMR to newer antibiotics, and regional knowledge gaps in AMR surveillance. Improved AMR surveillance data, identifying core aspects of successful ASPs that are transferable, and further well-conducted trials will be necessary if ASPs are to be an effective platform for delivering desired patient outcomes and safety through best antibiotic policy.

Key words: Antibiotic stewardship programme; Intensive care; Antimicrobial resistance; Antibacterial resistance; Antibiotic resistance

Core tip: Antibiotic stewardship programmes (ASPs) aim to optimise appropriate antibiotic treatment and minimise antimicrobial resistance (AMR). Multistrategic approaches must address challenges to future management of infectious disease. Models of ASP in intensive care unit, include "standard" control of antibiotic prescribing (*e.g.,* "de-escalation strategies") through to interventional approaches utilising biomarker-guided decisions. Protocolised ASPs using procalcitonin guided antibiotic-stop but not antibiotic-start alone decisions demonstrate reduced antibiotic and AMR rates, but not survival benefit. Immediate research needs include better AMR surveillance, early microbial diagnostic tests, and core transferable elements of ASPs.

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BURDEN OF INFECTION IN THE CRITICALLY ILL - MAJOR CHALLENGES TO PATIENT MANAGEMENT

The intensive care unit (ICU) is often regarded as an epicentre of infections, with sepsis being the second non-cardiac cause of mortality[1]. In two major cross-sectional studies of sepsis in the intensive care setting, Sepsis in European Intensive care units (EPIC Ⅱ)[2] and SOAP[3], 50% and 38% of all patients respectively had infections.

Mortality from Sepsis in the critically ill can approach 50%, with time to initiation of antibiotic treatment as the single strongest predictor of outcome. Each hour's delay increases mortality by 7.6%, over the first 6 h[4]. ICUs account for 5%-15% of total hospital beds but 10%-25% of total healthcare costs[5]. Sepsis increases patient-related costs six-fold[6]. In the United States, antibiotic-resistant infections are associated with 23000 deaths and 2 million illnesses per year, with estimated excess direct healthcare costs of $20 billion and $35 billion in lost productivity[7]. Resistant organisms can increase patient-related prescribing costs by $8000 to $30000[1]. Such empiric practice, deemed necessary at the point of care, due to uncertainty of causative organisms, is often ineffective and results in higher costs.

ANTIBIOTIC RESISTANCE IN ICU, ITS CONTRIBUTORS AND IMPACT

Antimicrobial resistance (AMR) is an increasing global healthcare phenomenon, with apocalyptic predictions of a post-antibiotic era where common infections and minor injuries may not be treatable by conventional antibiotics[8]. A WHO global report describes the majority of world regions with over 50% resistance of *Escherichia coli* (*E. Coli)* and *Klebsiella Pneumoniae* to 3rd generation cephalosporins and fluoroquinolones. The increasing prevalence of carbapenem-resistant organisms, and other multi-resistant strains such as Methicillin resistant *Staphylococcus aureus* (MRSA) as well as extended-spectrum beta-lactamase (ESBL) producers justifies these concerns. Specifically, AMR has a number of proposed causes. Data from United States National Nosocomial Infection Surveillance programme (NNIS) demonstrated 20%-30% increase in resistant isolates of *Pseudomonas*, *Staphylococcus aureus* and *Enterococcus* across a 5-year period[9]. In particular, fluoroquinolone-resistant *Pseudomonas* showed more than 50% increase during the period.

Intensive care units represent the heaviest antibiotic burden within hospitals. They are described albeit provocatively, as a factory creating, disseminating and amplifying antibiotic resistance[1]. In a European multi-centre cross-sectional prevalence study of academic ICUs, there were 14% of *Klebsiella* ESBL-producers, and nearly 25% of *Pseudomonas aeruginosa* isolates were carbapenem-resistant[10].

ICUs in emerging economies report notably higher prevalence of ESBL-producers[11-13] and carbapenem-resistant organisms[11-14]. Of note, the majority of multi-resistant *Acinetobacter* (MRA) isolates in these studies also demonstrates reduced susceptibility towards carbapenems[11-13].

The dynamics of antibiotic resistance are multifarious. Firstly, antibiotic usage in the animal and plant industry, to improve growth and productivity, is a major contributor to AMR[15]. The increasing prevalence of ESBL producers in animal products has been suggested. Furthermore, a link between antibiotic resistance in human clinical microbiological isolates and those from poultry has been raised[16]. On the contrary, other studies rule out such associations between chicken meat and colonisation of ESBL-producing *E. coli* in humans[17].

Within the ICU setting itself, causes of AMR may conveniently be categorised by procedure-related, management-related, and antibiotic-related factors. Procedure-related factors include central venous catheters[18,19] and endotracheal intubation for mechanical ventilation[20]. Management-related factors include poor adherence to infection control policy[20], lack of microbiological surveillance with delayed/failed recognition of resistant isolates[21], patient overcrowding[22,23], understaffing and implicit spread of AMR through human vectors[24,25], prolonged ICU length of stay[20,26], and pre-infection with resistant organisms at the time of ICU admis-

sion[26]. Antibiotic-related factors are related to the appropriateness and duration of treatment. Non-controlled usage[27] is well documented. Ceftriaxone for example, was shown to cause a rise in rates of vancomycin resistant *Enterococci* (VRE) rates[28]. The use of broad-spectrum antibiotics, often as the first step in therapy for patients with suspected infections, has accumulated considerable evidence regarding its association with the development of antibiotic resistance[20,26,29-32]. Similarly, the ease of access to certain antibiotic classes, either through their availability over-the-counter in certain countries (*i.e.,* penicillins, fluoroquinolones) or through unfounded clinician concerns of missing unlikely bacterial infection, leads to documented AMR, although causation proves difficult at an individual patient level. As such, the evidence behind the duration of treatment and AMR is comparatively lacking. In the PneumA trial, patients with ventilator-associated pneumonia (VAP), who had prolonged antibiotic treatment (15 d *vs* 8 d) developed higher rates of multi-resistant Pseudomonas isolates[33]. Clearly, one must be circumspect about distinguishing natural selection of antibiotic resistant bacteria through necessary antibiotic usage and judgements of inappropriate antibiotic usage as causation of AMR.

Although only shown in hospital wards rather than ICU, failure to de-escalate or discontinue therapy[34,35] is also a likely contributory factor to antibiotic resistance in ICU.

The exact impact of multidrug resistance (MDR) microbial organisms is difficult to quantify, depend as it does on, the causative microbe and its pathogenicity, patient populations, severity of illness and the appropriateness of therapy[36]. The association of increased ICU mortality and hospital length of stay (LOS) with MRSA, VRE, *Acinetobacter*, *Pseudomonas* and *Klebsiella* are well documented[37]. These mirror poor outcomes associated with such organisms in general ward settings[38]. From a financial perspective for instance, bloodstream infections caused by MDR organisms are estimated to increase treatment costs by 50%[39]. What effect such local outbreaks of MDR bacteria have on process of care within a hospital setting and outwith is dependent on effective surveillance, and links between infection control, Public health, and health policy makers. This data is all too often insufficient or not translated into effective intervention.

ANTIBIOTIC STEWARDSHIP PROGRAMMES IN ICU

Antibiotic stewardship programmes (ASP) are regarded as a keystone in tackling AMR in ICU. The intention is to reduce antibiotic resistance by minimising selection pressure, through optimising antibiotic therapy[40-44]. In Europe, the implementation of ASP follows a "top-down" model, with European council recommendations (*i.e.,* the Prague framework) and national-level guidance (*e.g.,* The Scottish Management of Antimicrobial Resistance Action Plan, ScotMARAP) informing delivery programmes at critical care network and individual unit levels[45,46]. In the context of these strategic initiatives, we have conducted the following systematic review of published ASPs in the ICU.

SUCCESS AND SHORTFALLS OF ASP IN THE ICU SETTING

Search strategy

To identify the eligible studies MEDLINE was searched from January 1996 to May 2014 using the following strategy: antibiotic and (stewardship programme or restriction or audit or decision support or education or guideline or policy or control or escalation or de-escalation) and (intensive care or critical care). The search was further refined by adding MeSH terms (intensive care unit or intensive care or critical care). Only human studies were included. The reference lists of all studies were reviewed to identify additional studies. Duplicate studies and conference abstracts were excluded.

Results

Forty three studies of ASPs in the ICU were identified. Thirty four were non-protocolised ASPs, and 9 studies of protocol-based ASPs. Their major findings are summarised in Table 1 and Table 2, respectively.

Out of the 34 non-protocolised ASPs, only 1 (3%) was a randomised controlled trial, whilst 22 (65%) were retrospective observational studies. Twenty nine (84%) studies comprised a single strategy, and 10 (29%) studies had a follow-up period of longer than one year. Antibiotic usage was the most common primary outcome measure (28 studies, 82%), followed by ICU LOS (19, 56%), mortality (15, 44%), antibiotic resistance (14, 41%) and antibiotics' cost (11, 32%). Twenty nine (85%) studies were regarded as positive studies, defined as achieving favourably in least one of the five aforementioned outcomes. Thirteen (38%) studies were conducted in specialist ICUs (purely medical, surgical, neonatal, paediatric or trauma). With respect to limitations, 8 (24%) had missing patient characteristics, whilst 4 (12%) studies had inconsistencies in patient characteristics between pre- and post-intervention arms.

Limitations of many of the non-protocolised ASP studies, particularly in regard to lack of consistency between the ASP and standard care arms are evident. Therefore, interpretation of the findings from these studies can at best be hypothesis-generating only. For instance, lack of standardised

Table 1 Non-protocolised antibiotic stewardship programmes

Kollef *et al*[18]	1997	9351601	Prospective cohort study Follow-up 6 mo	Incidence of VAP Incidence of bloodstream infection and sepsis Duration of mechanical ventilation LOS Mortality	680	Non-protocolised Components Rotating antibiotic schedule	1 Positive study 2 ↓ in resistant Gram negative organisms 3 ↓ in VAP incidence 4 No change to mortality 5 No change to LOS	1 No information on antibiotic usage 2 6 mo follow-up period only
Evans *et al*[91]	1998	9435330	Prospective observational study Follow-up 1 yr	Antibiotic use Antibiotic cost Cost of hospitalisation Number of adverse events caused by anti-infective agents No. of days of excessive antibiotic dosage LOS Mortality	1681	Non-protocolised Components Computerised decision support tool	1 Positive study 2 ↓ in total antibiotics cost 3 No change in DDD 4 ↓ in susceptibility-mismatch 5 ↓ in allergy-mismatch 6 ↓ of mortality 7 ↓ of LOS from 4.9 d to 2.7 d (4.9 to 8.3 d if overridden)	1 Less patients in post-intervention group 2 Young patients (mean age < 50 yr)
Price *et al*[84]	1999	10548192	Retrospective observational study Follow-up 1 mo	Antibiotic cost Antibiotic resistance LOS	321	Non-protocolised Components Antibiotic guideline	1 Positive study 2 77% ↓ in antibiotic cost 3 No change to LOS 4 No change to mortality	1 Surgical ICU only 2 1 mo FU follow-up 3 High compliance rate with guideline (95.6%) 4 High baseline APACHEII score (38.0-39.1)
Roger *et al*[64]	2000	11089498	Retrospective observational study Follow-up 2 mo	Antibiotic use Antibiotic cost	61	Non-protocolised Components ID specialist input	1 Positive study 2 ↓ in duration of treatment from mean 23 d to 13 d 3 ↓ in total antibiotic days from 596 d to 455 d 4 19% ↓ in total antibiotic cost 5 No change to mortality 6 No change to LOS	1 2 mo follow-up period
Fox *et al*[63]	2001	11712090	Retrospective observational study Follow-up 1 yr	Antibiotic use LOS Days on mechanical ventilation Days with fever No. of cultures performed Antibiotic resistance Antibiotic cost	295	Non-protocolised Components ID specialist input	1 Negative study 2 No change to antibiotic usage 3 57% ↓ in antibiotics cost 4 ↑ infection rate 5 No change in LOS	1 Trauma ICU only 2 Young patients (age < 35 yr)
Mullett *et al*[90]	2001	11581483	Retrospective observational study Follow-up 6 mo	Antibiotic cost Rate of anti-infective sub-therapeutic and excessive-dose days	1758	Non-protocolised Components Computerised decision support tool	1 Negative study 2 No change to total cost of antibiotics 3 ↓ of excessive dose days and sub-therapeutic days (*i.e.*, dose optimisation)	1 Paediatric ICU only 2 Significantly younger patients in post-intervention group
Dos Santos *et al*[61]	2003	14552737	Retrospective observational study Follow-up 1 yr	Antibiotic use Antibiotic cost	1473	Non-protocolised Components ID specialist input	1 Positive study 2 ↓ in cephalosporin, carbapenems and vancomycin usage 3 ↑ in penicillin usage 4 ↓ of cost by 37%	1 Limited patient characteristics 2 No information on antibiotic resistance 3 No information on LOS and mortality

Du *et al*[62]	2003	12682477	Prospective observational study Follow-up 1 yr	Antibiotic use Antibiotic resistance LOS	1205	Non-protocolised Components Antibiotic restriction Senior clinician input	1 Positive study 2 ↓ in 3rd generation cephalosporin usage 3 ↑ in cefepime usage 4 No change to resistance pattern 5 ↓ in LOS from 13.1 d to 9.3 d	1 Significant reduction in APACHEII scores and organ failure % in post-intervention group 2 High baseline Pseudomonas and *Acinetobacter* rate 3 No information on mortality
Geissler *et al*[82]	2003	12528022	Retrospective observational study Follow-up 4 yr	Antibiotic use Antibiotic resistance Antibiotic cost	1704	Non-protocolised Components *Antibiotic guideline*	1 Positive study 2 35% ↓ in antibiotic days 3 37% ↓ in antibiotics cost 4 Significant ↓ in total number of resistant isolates	1 High baseline mortality 2 No data on LOS
Micek *et al*[81]	2004	15136392	RCT Follow-up 14 mo	Antibiotic use Incidence of VAP LOS Mortality	290	Non-protocolised Components Antibiotic discontinuation policy	1 Positive study 2 ↓ of antibiotic treatment duration 3 No change to LOS 4 No change to mortality	1 Medical ICU only 2 Limited microbiology data
Aubert *et al*[80]	2005	15620440	Retrospective observational study Follow-up 1 yr	Antibiotic use Microbiological profile and antibiotic resistance	781	Non-protocolised Components Antibiotic restriction	1 Positive study 2 ↓ in fluoroquinolone usage by 75.8% 3 ↓ in usage of aminoglycosides and macrolides 4 ↓ of antibiotic resistance in *Pseudomonas* 5 No change to mortality 6 No change to LOS	1 No information on antibiotic usage
Sintchenko *et al*[89]	2005	15802478	Prospective observational study Follow-up 6 mo	Antibiotic use LOS Mortality	5176 patient-days	Non-protocolised Components Computerised decision support tool	1 Positive study 2 Significant ↓ in total DDD from 1925 to 1606, particularly vancomycin and beta-lactam resistant penicillins 3 ↓ of mean LOS from 7.15 to 6.22 d 4 No change to mortality	1 6 mo follow-up period 2 No information on antibiotic resistance
Bochicchio *et al*[88]	2006	16500251	Randomised pilot study Follow-up 6 mo	Antibiotic decision accuracy	125	Non-protocolised Components Computerised decision support tool	1 Positive study 2 ↑ in decision accuracy (verified by ID specialists)	1 No information on antibiotic usage 2 No information on antibiotic resistance
Brahmi *et al*[78]	2006a	16944257	Retrospective observational study Follow-up 2 yr	Antibiotic use	727	Non-protocolised Components Antibiotic restriction	1 Positive study 2 Significant ↓ in ceftazidime usage 3 ↓ in tazocin and imipenem resistance 4 ↑ resistance to penicillins	1 High baseline rate of VAP patients (63%-70%) 2 High baseline resistance rate among Pseudomonas (59% to tazocin, 58% to ciprofloxacin, 58% to imipenem, 47% to ceftazidime) 3 No info on mortality and LOS
Thursky *et al*[87]	2006	16415039	Prospective observational study Follow-up 6 mo	Antibiotic use Antibiotic susceptibility-mismatches Mortality	1060	Non-protocolised Components Computerised decision support tool	1 Positive study 2 ↓ of total DDD from 1670 to 1490 3 ↓ in usage of ceftriaxone, vancomycin and carbapenems 4 ↓ of susceptibility-mismatch 5 No change to mortality	1 6 mo follow-up period 2 High baseline mortality (19%) 3 Fewer isolates in intervention group 4 No information on LOS

Brahmi *et al*[79]	2006b	17027213	Prospective cohort study Follow-up 2 yr	Antibiotic use Antibiotic resistance	318	Non-protocolised Components Antibiotic guideline	1 Positive study 2 ↓ in duration of treatment from 14.1 to 11.9 d 3 ↓ in antibiotics cost 4 ↓ in LOS from 20.4 to 16.9 d 5 No change to mortality	
de Araujo *et al*[69]	2007	17625777	Retrospective observational study Follow-up 1 yr	LOS Days of parenteral nutrition Requirement for mechanical ventilation Antibiotic use	995	Non-protocolised Components Rotating antibiotic schedule	1 Positive study 2 ↓ in cefepime usage 3 ↑ in tazocin usage 4 No change to LOS	1 Neonatal ICU only 2 High baseline rates of *Pseudomonas* and *Klebsiella* 3 No information on mortality
Ntagiopoulos *et al*[77]	2007	17629680	Retrospective observational study Follow-up 6 mo	Antibiotic use Antibiotic resistance	147	Non-protocolised Components Antibiotic restriction	1 Positive study 2 ↓ of overall antibiotic usage by 55% 3 ↓ in resistance in Pseudomonas 4 ↑ in resistant strains of *Klebsiell*a and *Acinetobacter* 5 No change to mortality 6 No change to LOS	1 Male predominance 2 High baseline mortality 3 6 mo follow-up period 4 High baseline ceftazidime and fluoroquinolone resistance 5 90% policy compliance among clinicians
Ding *et al*[76]	2008	18493864	Retrospective observational study Follow-up 2 yr	Antibiotic use Rate of bacterial resistance	900	Non-protocolised Components Antibiotic guideline Staff education	1 Positive study 2 ↓ in usage of 3rd generation cephalosporin 3 ↑ in usage of beta-lactams 4 ↓ in antibiotics cost 5 No change to LOS	1 Paediatric ICU only 2 High baseline antibiotic utilisation (98.7% patients were on antibiotics) 3 High baseline resistance rate (> 60% to cefepime, for E coli and Klebsiella; > 20% to cefepime and imipenem, for *Pseudomonas*) 4 No information on mortality
Peto *et al*[60]	2008	19011742	Retrospective observational study Follow-up 2 yr	Antibiotic use Incidence of sepsis LOS Mortality	3403	Non-protocolised Components Senior clinician input	1 Positive study 2 ↓ of mean DDD from 162.9 to 101.3. 3 No change to LOS 4 No change to mortality	1 Surgical ICU only with > 60% neurological patients 2 Low baseline resistance rate 3 Increased patient turnover since intervention
Marra *et al*[59]	2009	18986735	Retrospective observational study Follow-up 10 mo	Antibiotic resistance	360	Non-protocolised Components ID specialist input	1 Positive study 2 ↓ of total DDD by 12.1% 3 ↓ of resistant strains of *Pseudomonas*, *Klebsiella* and *Acinetobacter*	1 High baseline resistance rate 2 Limited patient characteristics 3 Unknown sample size 4 No information on mortality and LOS
Meyer *et al*[74]	2010	19904488	Retrospective observational study Follow-up 3 yr	Mortality Antibiotic use	11887	Non-protocolised Components Antibiotic prophylaxis	1 Positive study 2 15% ↓ in total antibiotic usage primarily cefuroxime and co-trimoxazole 3 Sustained ↓ to antibiotic usage 4 No change to LOS 5 No change to mortality	1 Surgical ICU only 2 Limited resistance data

Yong *et al*[86]	2010	20215130	Retrospective observational study Follow-up 4.5 yr	Antibiotic susceptibilities of *Pseudomonas*, *Klebsiella*, *Acinetobacter* and *Enterobacteriaceae*	13295	Non-protocolised Components Computerised decision support tool	1 Positive study 2 No change to Abx usage 3 ↑ susceptibility to imipenem for *Pseudomonas*, *Acinetobacter* and *Enterobacter* 4 ↑ susceptibility to gentamicin for *Pseudomonas* and *Enterobacter* 5 No change to LOS	1 Limited patient characteristics 2 No information on mortality
Sharma *et al*[75]	2010	21206622	Retrospective observational study Follow-up 4 mo	Antibiotic use Antibiotic resistance	177	Non-protocolised Components Antibiotic restriction	1 Negative study 2 ↓ of carbapenem usage 3 ↑ in beta-lactam usage	1 Medical ICU only 2 No information on overall antibiotic usage 3 4 mo follow-up period 4 No pre-intervention arm 5 Male predominance 6 High baseline Acinetobacter isolates 7 High baseline resistance rate
Raymond *et al*[68]	2011	11395583	Prospective cohort study Follow-up 1 yr	Mortality Duration of treatment Antibiotic cost LOS	1456	Non-protocolised Components Rotating antibiotic schedule	1 Positive study 2 ↓ in infection rate by 25% 3 ↓ in infections caused by resistant organisms 4 ↓ in usage of aminoglycosides, vancomycin and antifungals 5 ↑ in usage of clindamycin 6 ↓ in mortality from 38.1% to 15.5% 7 No change to LOS	1 No information on overall antibiotic usage 2 High baseline mortality rate
Dortch *et al*[67]	2011	21091186	Retrospective observational study Follow-up 8 yr	Incidence of infection caused by MDR organisms Antibiotic use	20846	Non-protocolised Components Antibiotic guidelines Antibiotic prophylaxis Rotating antibiotic schedules	1 Positive study 2 Significant ↓ of total broad spectrum antibiotic usage 3 ↓ in total infection rate 4 ↓ in MDR Pseudomonas, Acinetobacter and Enterobacter isolates	1 Surgical ICU only 2 High baseline respiratory infection rate 3 High baseline Enterobacter infection rate 4 Concomitant infection control policy
Slain *et al*[57]	2011	21687626	Retrospective observational study Follow-up 7 yr	Antibiotic use Antibiotic resistance	N/A	Non-protocolised Components Prospective audits Antibiotic restriction Staff education Antibiotic guidelines Rotating antibiotic schedules	1 Positive study 2. Overall ↓ of DDD 3 Fluctuations due to resistance and change in protocols 4 ↑ in resistance to ciprofloxacin, tazocin, cefepime	1 Pseudomonas infections only 2 Limited patient characteristics 3 No information on mortality or LOS

Chiu *et al*[73]	2011	21085051	Prospective observational study Follow-up 1 yr	Antibiotic use	190	Non-protocolised Components Antibiotic guideline	1 Negative study 2 No change to overall antibiotic usage 3 ↓of vancomycin usage	1 Neonatal ICU only 2 Limited patient characteristics 3 Limited resistance data 4 No information on mortality and LOS
Sarraf-Yazdi *et al*[66]	2012	22445457	Retrospective observational study Follow-up 9 yr	Antibiotic use Antibiotic resistance	321	Non-protocolised Components Rotating antibiotic schedules	1 Positive study 2 No change in total antibiotic usage 3 ↓ in prescribed dosage of target antibiotics 4 ↓ in resistance against ceftazidime and tazocin	1 No LOS or mortality data 2 Limited patient characteristics
Sistanizad *et al*[72]	2013	24250656	Prospective cohort study Follow-up 9 mo	Antibiotic use Susceptibility of *P. aeruginosa*, *A. baumanni*, *K. pneumonia* and *E. coli*	N/A	Non-protocolised Components Antibiotic restriction	1 Positive study 2. 60% ↓ in imipenem use 3 ↑ in carbapenem sensitivity for Klebsiella and Pseudomonas	1 No mortality and LOS data 2 Limited patient characteristic data
Rimavi *et al*[58]	2013	23873275	Prospective cohort study Follow-up 3 mo	Antimicrobial use Treatment duration APACHEII score LOS Mechanical ventilation days Mortality rate	246	Non-protocolised Components ID specialist input	1 Positive study 2 Significant ↓ in overall antibiotic usage 3 ↓ of LOS 4 No change to mortality	1 Medical ICU only 2 Follow-up period of only 3 mo 3 Limited resistance data
Bauer *et al*[71]	2013	23571547	Retrospective cohort study Follow-up N/A	Duration of mechanical ventilation LOS Mortality	1433	Non-protocolised Components Intermittent *vs* extended dosing regimen of cefipime	1 Positive study 2. ↓ of mortality from 20% to 3% 3 ↓ of LOS 4 ↓ of antibiotic cost per patient by $23183 in extended dosing group	1 Pseudomonas infection only 2 No information on antibiotic resistance 3 No follow-up
Ramsamy *et al*[65]	2013	23725954	Retrospective observational study Follow-up 1 yr	Antibiotic use Antibiotic resistance	227	Non-protocolised Components Antibiotic restriction	1 Negative study 2 6.5% inappropriate broad- spectrum antibiotic usage	1 Trauma ICU 2 No pre-intervention arm 3 Limited patient characteristics 4 No information on mortality and LOS
Apisarnthanarak *et al*[98]	2014	24485368	Retrospective observational study Follow-up 1 yr	Rate of XDR *Acinetobacter* baumanni acquisition rate per 1000 patient days Rate of Acinetobacter baumanni infection or colonisation	1365	Not specified	1 Positive study 2 Significant ↓ in XDR Acinetobacter baumanni infection or colonisation rates	1 Type of ASP not specified 2 No information on antibiotic usage 3 Concomitant infection control policy (Use of disinfectant-detergent; Enhanced isolation; Active surveillance cultures for all ICU patients)

LOS: Length of stay; VAP: Ventilator-associated pneumonia; ICU: Intensive care units; ASP: Antibiotic stewardship programme; DDD: Defined daily dose; RCT: Randomised Controlled Trial; APACHE Ⅱ: Acute Physiology and Chronic Health Evaluation Ⅱ.

antibiotic treatment initiation triggers to reduce inter-clinician decision tree variability, or inadvertent variations in clinico-biochemical information provided to both arms. Patient or antibiotic selection bias are a few such confounders.

All 9 protocol-based studies were randomised controlled trials, 4 (44%) being multi-centred. Eight studies (89%) were procalcitonin-guided, and the remaining one (11%) was based on clinical scoring system. Only 1 (11%) study looked at the merit of PCT-guided ASP in both escalation and de-escalation of antibiotic treatment, whilst 5 (56%) and 3 (33%) studies, investigated its sole role in de-escalation or escalation, respectively. Six (67%) studies were

Table 2 Protocol-based antibiotic stewardship programmes

Ref.	Year	Pubmed ID	Study type	Outcome	No. of patients	Type of ASP	Major findings	Limitations/Confounding factors
Singh *et al*[54]	2000	10934078	RCT Follow-up N/A	1 LOS 2 Mortality 3 Proportion of patients with resolution of pulmonary infiltrate	81	Clinical Pulmonary Infection Score-based De-escalation	1 Positive study 2 ↓ in total antibiotic days from 9.8 to 3 d 3 ↓ of antibiotics cost by $381 per patient 4 ↓ in LOS from 14.7 to 9.4 d mean 5 Significant ↓ in total antibiotic resistance 6 No change to mortality	1 79% surgical patients 2 Mean APACHEII score of 42.7 in intervention group 3 Unknown follow-up period
Nobre *et al*[47]	2008	18096708	Single-centred RCT	1 Antiiotic Antibiotic use 2 28-d mortality 3 LOS 4 Incidence of clinical cure 5 Recurrence of infection 6 Incidence of nosocomial superinfection	79	PCT-based De-escalation	1 Positive study 2 ↓ in duration of treatment from median 9.5 to 6 d 3 ↓ in ICU LOS from 5 to 3 d 4 ↓ in hospital LOS 21 to 14 d 5 No change to mortality	1 Small study 2 Sepsis patients only 6 Infections by Pseudomonas, Acinetobacter *etc.* were excluded 7 Patients with chronic infections were excluded 8 Immunocompromised patients were excluded 9 Patients on antibiotics at time of admission were excluded
Hochreiter *et al*[48]	2009	19493352	Single-centred RCT	1 Antibiotic use 2 LOS 3 Mortality	110	PCT-based De-escalation	1 Positive study 2 ↓ in duration of treatment from median 7.9 to 5.9 d 3 ↓ in LOS from median 17.7 to 15.5 d 4 No change to mortality	1 Patients on antibiotics at time of admission were excluded 2 Sepsis patients only
Schroeder *et al*[49]	2009	19034493	Single-centred RCT	1 Antibiotic use 2 LOS 3 Mortality	27	PCT-based De-escalation	1 Positive study 2 ↓ in duration of treatment from 8.3 to 6.6 d 3 ↓ in antibiotic cost by 17.8% 4 No change to LOS 5 No change to mortality	1 Sepsis patients only
Stolz *et al*[55]	2009	19797133	Multi-centred RCT	1 No. of days without antibiotics at 28 d 2 Number of days without mechanical ventilation 3 ICU mortality 4 LOS 5 Incidence of VAP	101	PCT-based De-escalation	1 Positive study 2 27% ↓ in duration of treatment 3 No change to mortality 4 No change to LOS	1 VAP patients only
Bouadma *et al*[50]	2010	20097417	Multi-centred RCT (PRORATA trial)	1 28-d and 60-d mortality 2 Number of days without antibiotics at 28 d 3 Incidence of recurrence of infection or superinfection 4 Days of unassisted breathing 5 LOS 6 Antibiotic use 7 Incidence of MDR organisms	630	PCT-based Escalation/ De-escalation	1 Positive study 2 ↓ in duration of treatment from 13.3 to 10.3 d 3 No change to mortality 4 No change to LOS	1 Patients on antibiotics on admission were excluded 2 Patients with chronic infection were excluded 3 Immunocompromised patients were excluded 4 90% medical patients 5 Close to 50% respiratory/CVS failure, and > 30% CNS failure 6 70% pulmonary infection site 7 53% did not adhere to algorithm in PCT group

Jensen *et al*[51]	2011	21572328	Multi-centred RCT (PASS trial)	1 28-d mortality	1200	PCT-based Treatment escalation	1 Negative study 2 Significant ↑ in duration of tretment (Median: from 4 to 6 d), especially for tazocin and meropenem 3 ↑ in LOS from median 5 to 6 d 4 No change to mortality	1 Low resistance and antibiotic usage units 2 Incomplete adherence to PCT algorithm
Layios *et al*[52]	2012	22809906	Single-centred RCT	1 Antibiotic use 2 Accuracy of infectious diagnosis 3 Diagnostic concordance between intensive care unit physician and ID specialist	510	VAP -based Escalation	1 Negative study 2 No change in duration of antibiotic treatment 3 No change in DDD 4 No change to LOS 5 No change in mortality	1 41% surgery and trauma patients
Annane *et al*[53]	2013	23418298	Multi-centred RCT	1 Proportion of patients on antibiotics at day 5	62	PCT-based Escalation	1 Negative study 2 Premature termination	1 Poor clinician compliance with algorithm 2 Patients on antibiotics at time of admission were excluded

LOS: Length of stay; VAP: Ventilator-associated pneumonia; ICU: Intensive care units; ASP: Antibiotic stewardship programme; DDD: Defined daily dose; RCT: Randomised Controlled Trial; APACHEII: Acute Physiology and Chronic Health Evaluation II; PCT: Procalcitonin; CVS: Cardiovascular system; CNS: Central Nervous system; XDR: Extensively Drug-Resistant.

positive studies. The most commonly explored outcome measures were antibiotic usage (8 studies, 89%), ICU LOS (8 studies, 89%) and mortality (8 studies, 89%), followed by antibiotics' cost (2 studies, 22%) and antibiotic resistance (1 study, 11%). Clinician adherence was reported as a major issue in two (22%) studies.

In summary, 29 of 34 non-protocolised ASPs and 6 of 9 protocol-based ASPs were reported as positive studies. PCT guided prescribing, reduced antibiotic usage when used as a de-escalation/stop trigger[47-49], and in one study using PCT for escalation/de-escalation[50] It did not improve outcomes when used as an escalation trigger alone to reduce time-to-appropriate antibiotics[51-53]. PCT has also been effective in reducing antibiotic usage without worsening morbidity or mortality in ventilator associated pulmonary infection[54,55]. No survival benefit in the ICU has yet been demonstrated.

Discussion

Four basic principles of ASP have been described: Timeliness, appropriateness, adequacy and duration of antibiotic usage[56]. It represents a multifaceted approach that includes many components, and each individual ASP might encompass several, but not all, of them at a given time. These components include audits[57], infectious disease specialist or senior clinician input[58-64], or planned discontinuation/de-escalation of treatment in response to clinical and microbiological outcome data[65]. Other components include rotating antibiotic schedules[57,66-70] changes in prescribing policies involving antibiotic restriction, different dosing regimens or prophylaxis protocols[57,62,65,67,71-84] and a multi-disciplinary team (MDT) approach in treatment initiation and discontinuation, often emphasising feedback and non-punitive atmosphere among staff members[83,85]. Some programmes also encompassed staff education[57,74,76] and computerised decision support platforms[86-91]. Concomitant regional or national infection control campaigns, for example in the United Kingdom between 2003 and 2008, might serve as necessary adjuvants to the success of ASPs.

Additional input comes from ICU-based pharmacy support[92]. Pharmacists are significant drivers in ASPs, with roughly one-fifth of pharmacist intervention in an American trauma centre being ASP related[93]. The MDT approach itself seems to be more effective than purely its components. In a prospective study of Antibiotic stewardship comparing an MDT approach with a non-MDT (involving only the infectious disease physician and ICU pharmacist), the former, which also includes other affiliated healthcare professionals, led to superior outcomes of appropriate antibiotic selection and the rates of antibiotic resistance[94].

Protocol-based ASPs have recently gained popularity. Earlier programmes utilised clinical scoring systems in guiding antibiotic treatment[54], whilst PCT-based ASPs are increasingly being adopted in ICUs. PCT is regarded as a superior biomarker of sepsis compared with many others discovered over the decades, including white cell count, C-reactive protein and interleukin-6. It is relatively unhindered by the issues of slow kinetics and non-specificity faced by the latters[95-97]. Effective infection control and source control remain fundamental to successful ASPs[98]. As has been demonstrated by the systematic review, there is a clear signal

suggesting the potential benefits of ASP, even in non protocolised observational studies. This of course depends on the outcome measured, but in regards decreased antibiotic duration, and cumulative prescribed burden, the results are favourable when PCT is used to guide antibiotic stop decisions. These reductions in antibiotic use have been verified in many PCT guided protocol based RCTs, but not as an antibiotic escalation trigger alone[52,53,98]. Antibiotic reductions in these RCTs are demonstrated in the context of severe sepsis, critically ill surgical patients, single centre and multicentre trials, and in non microbiologically proven severe sepsis[47-51,55]. Moreover concerns regarding increases in AMR have not been borne out. However, the potential for AMR selection through reduced dosing regimens remains possible. Further studies need a common minimum universal standards of antibiotic prescribing practice, that adopt pragmatic core principles, which are adapted to local circumstances.

UNANSWERED QUESTIONS AND PROSPECTS FOR FUTURE WORK

Antibiotic usage and resistance represent an increasing global concern. The latest figures from the United Kingdom reveal that hospital-acquired infection costs GBP 1 billion annually[99], and USD 4.5 to 5.7 billions in the United States[100]. It is unsurprising that commentaries refer to "crisis" and "catastrophe" when describing possible worst case scenarios of uncontrolled AMR. The wording from the 2014 WHO global report of such a post-antibiotic era emphasises the need for action to prevent such a time. To tackle this increasing challenge, one might envisage a combined approach involving the development of next generation antibiotics (significant development times and costs), new innovations such as nanotechnology in infection control[101], together with strategies to optimise the effective use of currently available antimicrobials. Thus, ASPs involve a delicate interplay between economy, health and clinical evidence. To date the current high level evidence base for ASPs remains limited, with most of the reported studies being observational in nature. Those protocol based RCTs targeting de-escalation of antibiotics have demonstrated reduced usage, and on occasion reduced resistance patterns, length of stay but not manifested as survival benefit. Clinical decision support tools are of increasing interest in this regard.

Strategies to minimise antibiotic usage are multi-faceted. It remains uncertain whether the reported success in literature with regard to ASPs could be attributed to ASP alone, or confounders such as concurrent infection control policies. Should an ASP not by implication require an effective infection control policy? What would be the added value of the ASP? And what components should the ASP adopt? The role and impact of bed occupancy, staffing ratios and infection prevalence on antibiotic stewardship outcomes clearly require incorporation into study design. Further randomised controlled trials or indeed cluster studies, with staggered implementation of ASPs, where effective infection control policies are already in place may be required. Careful study design with appropriate components of the ASP, that could be implemented widely, would be desirable.

The dynamics of antibiotic resistance following the implementation of ASPs has been described as "balloon squeezing effect"[102]. It is believed that the development of antibiotic resistance towards one class of antibiotics, could lead to the emergence of resistance against another class, rendering multi drug resistance. The molecular mechanisms behind this concept remain unclear. However, the use of quinolones for *Pseudomonas aeruginosa* may be relevant. Quinolones selectively upregulate the bacterial membrane efflux system MexEF-OprN, and the loss of co-regulated porin OprD results in carbapenem resistance[103]. In a hypothetical situation where quinolones are routinely introduced empirically in favour of "targeted antibiotics" in a given ASP antibiotic regimen, resistance to both quinolones and carbapenems may develop.

Uncertainties around AMR in ICU being due to antibiotic selection pressure and distinguishing pathogenicity versus bystander effect of resistant organisms will remain a challenge for implementing fixed antibiotic protocols as part of ASPs. The lack of wholescale uptake of selective decontamination of the gut (SDD) or selective oral decontamination (SOD) to reduce rates of sepsis, is an example of this challenge[104,105]. Despite high level evidence for their efficacy, uptake is poor[106,107], with concerns regarding emergence of resistance being borne out in some settings[108].

Further evidence of practical difficulties in implementation of ASPs is the recent RCT of a PCT-based ASP. This was terminated prematurely due to poor clinician adherence to the algorithm[98]. Understanding the rationale behind clinician compliance and lack of it, specific to ASP antibiotic start and stop decisions will be important in designing future studies.

The culture positivity of microbiological isolates among ICU patients with suspected infections is generally low. EPIC II and SOAP studies reported culture positivity in only 51.4% and 60% of patients[2,3]. Furthermore, time required to identify the causative organism far exceed the clinical decision time. Until such time as rapid diagnostics can confidently rule out suspected infection within minutes, and the knowledge that delayed or inappropriate antimicrobials in sepsis equates with

higher mortality, even PCT-guided ASPs might not prevent clinician decision tree analysis based upon opinion. Thus, studies investigating its role in treatment escalation yielded relative limited information to this date. The prospect of novel rapid identification tools to enhance ASP programmes is another crucial facet of ASP[47]. The call here has been heeded, with the announcement of monetary prizes of up to $17 million, and $20 million from the NESTA foundation (a Uinted Kingdom organisation through the Longitude prize 2014), and the United States NIH/Biomedical Advanced Research Authority[7,109,110]. The US Administration also released its *National Strategy on Combating Antibiotic-Resistant Bacteria.* In addition, the President's Council of Advisors on Science and Technology (PCAST) is releasing a related report on *Combating Antibiotic Resistance.* The *National Strategy* provides a five-year plan for enhancing domestic and international capacity to prevent and contain outbreaks of antibiotic-resistant infections; maintain the efficacy of current and new antibiotics; and develop and deploy next-generation diagnostics, antibiotics, vaccines, and other therapeutics. The PCAST report provides recommendations from the President's Council and allied scientific and professional agencies,to act for the development of more effective ASPs[7].

The costs associated with ASP, have so far been limited to those of the prescribed antibiotics. Nonetheless, costs related to staff employment and education, as well as management and information technology, will require necessary health economic analysis.

It is said that, where ASP is today, is infection control programmes thirty years ago[111]. Thus the unanswered questions we encounter today might well hide the solution to the increasing burden of infection and AMR in ICUs and beyond. A multifaceted approach involving key stakeholders - healthcare, industry, technology, economy, security, government, charity and the public is warranted, to overcome AMR and perpetuate the future utility of antibiotics[112]. Refined and tailored Antibiotic stewardship programmes in (and outwith) ICU will be an important part of that partnership.

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REVIEW

Diagnosis of deep vein thrombosis, and prevention of deep vein thrombosis recurrence and the post-thrombotic syndrome in the primary care medicine setting anno 2014

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Abstract

The requirement for a safe diagnostic strategy of deep vein thrombosis (DVT) should be based on an overall objective post incidence of venous thromboembolism (VTE) of less than 1% during 3 mo follow-up. Compression ultrasonography (CUS) of the leg veins has a negative predictive value (NPV) of 97%-98% indicating the need of repeated CUS testing within one week. A negative ELISA VIDAS safely excludes DVT and VTE with a NPV between 99% and 100% at a low clinical score of zero. The combination of low clinical score and a less sensitive D-dimer test (Simplify) is not sensitive enough to exclude DVT and VTE in routine daily practice. From prospective clinical research studies it may be concluded that complete recanalization within 3-6 mo and no reflux is associated with a low or no risk of PTS obviating the need of MECS 6 mo after DVT. Partial and complete recanalization after 6 to more than 12 mo is usually complicated by reflux due to valve destruction and symptomatic PTS. Reflux seems to be a main determinant for PTS and DVT recurrence, the latter as a main contributing factor in worsening PTS. This hypothesis is supported by the relation between the persistent residual vein thrombosis (RVT = partial recanalization) and the risk of VTE recurrence in prospective studies. Absence of RVT at 3 mo post-DVT and no reflux is predicted to be associated with no recurrence of DVT (1.2%) during follow-up obviating the need of wearing medical elastic stockings and anticoagulation at 6 mo post-DVT. The presence or absence of RVT but with reflux at or after 6 mo post-DVT is associated with both symptomatic PTS and an increased risk of VTE recurrence in about one third in the post-DVT period after regular discontinuation of anticoagulant treatment. To test this hypothesis we designed a prospective DVT and postthrombotic syndrome (PTS) Bridging the Gap Study by addressing at least four unanswered questions in the treatment of

DVT and PTS. Which DVT patient has a clear indication for long-term compression stocking therapy to prevent PTS after the initial anticoagulant treatment in the acute phase of DVT? Is 6 mo the appropriate point in time to determine candidates at risk to develop DVT recurrence and PTS? Which high risk symptomatic PTS patients need extended anticoagulant treatment?

Key words: Deep Venous thrombosis; Ultrasonography; Post-thrombotic syndrome; ELISA VIDAS D-dimer; Medical elastic stockings; Anticoagulation

Core tip: A novel clinical concept for the assessment of acute deep vein thrombosis (DVT) and the post-thrombotic syndrome (PTS) by DUS in routine clinical practice at 1, 3 to 6 mo and at one year post-DVT will separates post-DVT patients in 4 groups: Group 1: rapid complete recanalization within 3 mo, no reflux at 6 mo post-DVT, and no PTS for which anticoagulation and medical elastic compression stockings (MECS) can be discontinued at 6 mo post-DVT. Group 2, no PTS with reflux of the deep venous system and no PTS when wearing MECS for which anticoagulation should be continued until re-evaluation at 1 year post DVT. Group 3 and 4 PTS with reflux and incomplete recanalization or obstruction at 6-12 mo post-DVT are candidates for long-term anticoagulation and MECS for at least 2 years or even longer to prevent DVT recurrence to prevent progression of PTS. A large scale prospective study is warranted to fine-tune and prove this concept.

Michiels JJ, Michiels JM, Moossdorff W, Lao M, Maasland H, Palareti G. Diagnosis of deep vein thrombosis, and prevention of deep vein thrombosis recurrence and the post-thrombotic syndrome in the primary care medicine setting anno 2014. *World J Crit Care Med* 2015; 4(1): 29-39 Available from: URL: http://www.wjgnet.com/2220-3141/full/v4/i1/29.htm DOI: http://dx.doi.org/10.5492/wjccm.v4.i1.29

DEEP-VEIN THROMBOSIS

The sequential use of compression ultrasonography (CUS), a sensitive ELISA VIDAS D-dimer test and clinical score to rule in and out deep vein thrombosis (DVT) and alternative diagnosis (AD) is safe and cost-effectieve (Figure 1)[1-10]. The general application of DVT exclusion by a negative SimpliRed (Simplify) by the combination of a negative CUS and low clinical score is not safe enough[5,9]. After a first negative CUS the prevalence of DVT is uniformly low, 2%-3%[8,9-14]. The combination of a first negative CUS and a D-dimer level of ELISA VIDAS < 1000, Tina-quant < 800 μg/mL or negative SimpliRed (Simplify) will exclude deep vein thrombosis with a NPV of more than 99% in 4 prospective outcome studies (Figure 1)[9,11-13]. A moderate to high probability in combination with a increased ELISA D-dimer (VIDAS > 1000 or Tinaquant > 800 μg/mL) or a positive qualitative D-dimer (SimpliRed or Simplify) should be followed by a second CUS of the legs after one week[12,13] to detect a thrombus in about 3% of patients (Figure 1)[8,9,11-14].

DEEP VEIN THROMBOSIS AND THE POST-THROMBOTIC SYNDROME

Recanalization of distal DVT is usually rapid and complete within one to three months without reflux and no or low risk of post-thrombotic syndrome (PTS) in an asymptomatic leg obviating the need to extend anticoagulation at 6 mo post-DVT. Recanalization of proximal DVT is usually delayed and may be completed after 3, 6 to 9 mo post-DVT with a high incidence of reflux, DVT recurrence and PTS (Figure 2)[15-17]. Loss of valve competence leading to ambulatory venous hypertension (AVP) and diversion of venous flow through incompetent perforans veins appear to play an important role in the development of late complications of the post-thrombotic syndrome (PTS)[15,16]. Anatomic studies have described the most distribution of venous valves to be a single valve in the common femoral vein (CFV) above the sapheno-femoral junction, a relatively constant deep valve just before its termination in the CFV, three to four valves in the superficial femoral vein with relatively constant locations at the mid-thigh and adductor canal, one or two valves in the popliteal vein (PPV) and one to two valves with the terminal 2-2 cm of the grater saphenous vein (GSV). Among the calf veins, the PPV appears to be of primary importance in the development of the post-thrombotic syndrome, by virtue of both its importance in the calf muscle pump and its communications with the posterior arch vein. Meissner *et al*[15] studied the relationship between complete recanalization (lysis time) and the development of reflux in patients with a first episode of DVT at 3 mo interval during the first year (Figure 2). Duplex criteria for complete occlusion were defined as the absence of detectable flow, either spontaneous or with augmentation, in an incompressible venous segment. Partial occlusion was defined as normal or diminished flow either spontaneous or with augmentation, in an incompletely compressible venous segment. Complete lysis of the leg vein clot (recanalization) was presumed to have occurred when spontaneous phasic flow returned and the vein was completely compressible[15]. For the PTVs, flow detected after distal augmentation in a completely compressible vein is accepted as evidence of complete recanalization (lysis of the leg vein clot). The median time from DVT to complete recanalization (lysis

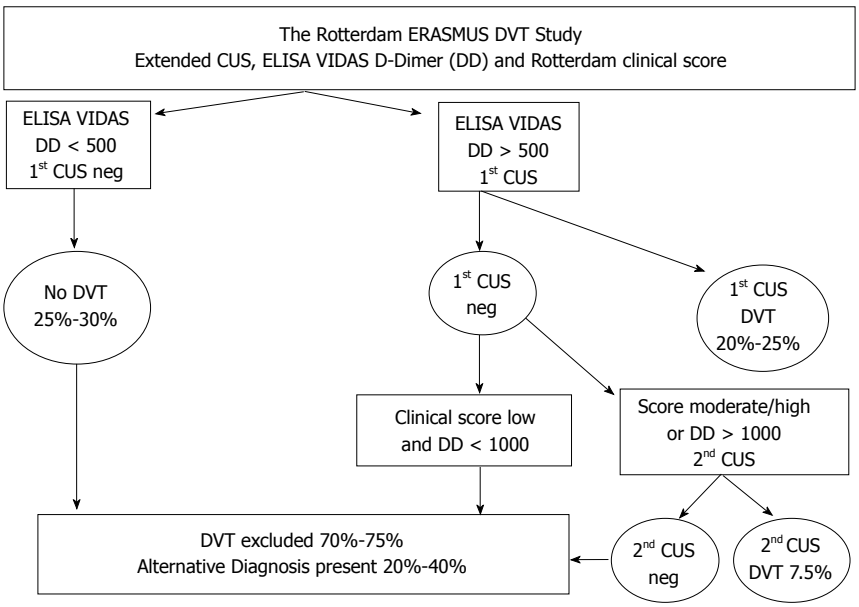


Figure 1 Rotterdam approach to safely exclude and diagnose deep vein thrombosis[8,9]. CUS: Compression ultrasonography; DVT: Deep vein thrombosis.

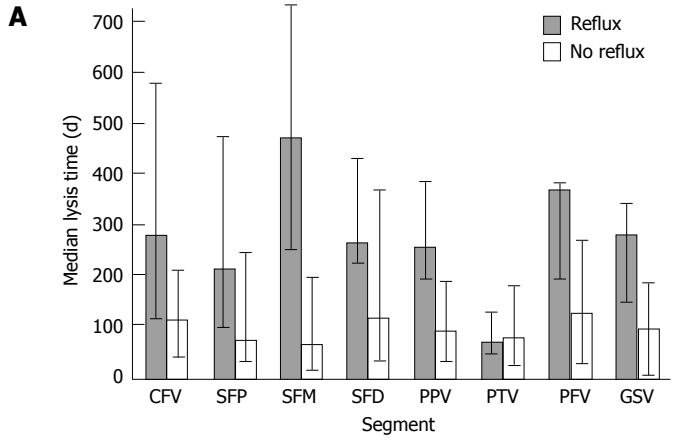
Table 1 Scoring system according to Brandjes for mild-to moderate and severe postthrombotic syndrome[24]

Subjective criteria			
Symptoms	**Score**	**Signs**	**Score**
For mild-to-moderate PTS: score > 3 of subjective and objective criteria			
Spontaneous pain in calf	1	Calf circumference ↑ by 1 cm	1
Spontaneous pain in thigh	1	Ankle circumference ↑ by 1 cm	1
Calf pain on standing/ walking	1	Pigmentation	1
Thigh pain on standing/ walking	1	Venectasia	1
Edema of foot/calf	1	Newly formed varicosis	1
Heaviness of foot/leg	1	Phlebitis	1
For severe PTS score > 4 of symptoms and signs			
Spontaneous pain	1	Calf circumference ↑ by 1 cm	1
Pain on standing/walking Edema calf	1	Pigmentation, discolouration, and venectasia	1
Impaiment of daily activities	4	Healed or active ulcer	1

time) was about 3 mo (100 d) for patients without reflux in all segments (Figure 2). In contrast, the median time from DVT to complete recanalization (lysis time) of all segments was about 9 to 12 mo (more than 6 mo) for DVT patients who developed reflux as the main determinant of PTS (Figure 2). In the study of 123 legs with DVT (107 patients) by Markel *et al*[16] about two third of the involved legs had developed valve incompetence. The distribution of reflux at the end of the first year follow-up in this study was the following: popliteal vein, 58%, superficial femoral vein, 37%, greater saphenous vein, 25% and posterior popliteal vein, 18%. Reflux appeared to be more frequent in the segments previously affected by DVT[16].

From these two prospective clinical research studies[15,16] it may be concluded that complete recanalization within 3 mo and no reflux is associated with a low or no risk of PTS obviating the need of medical elastic compression stockings (MECS) 6 mo after DVT (Table 1). On the other hand, partial and complete recanalization after 6-12 mo is usually complicated by reflux due to valve destruction. Consequently, reflux seems to be a main determinant for PTS and DVT recurrence, the latter as a main contributing factor in worsening PTS. This hypothesis is supported by the relation between the persistent residual vein thrombosis (RVT = partial recanalization) and the risk of VTE recurrence in two prospective studies[18,19]. In a prospective outcome study, RVT at 3 mo post-DVT was absent in 30%, which was associated with low recurrence of DVT (1.2% patient/years) during two years follow-up (Table 2, Figure 3)[18]. The presence of RVT at 3 mo post-DVT was associated with a DVT recurrence rate of 27% during two years follow-up after discontinuation of anticoagulant treatment (Table 2, Figure 3)[18]. The proportion of provoked *vs* unprovoked DVT was 64% and 36% in patients with complete recanalization within 3 mo and 23% *vs* 77% in the patient with RVT (incomplete recanalization) at 3 mo post-DVT indicating that the distinction provoked *vs* unprovoked DVT is artificial in terms of risk on DVT recurrence.

In a previous prospective study of 313 consecutive DVT patients, Prandoni *et al*[19] have shown that RVT at any time post-DVT is a risk factor for recurrent VTE. In this study, CUS of the common femoral and popliteal veins was performed at 3, 6, 12, 24 and 36 mo post DVT. The cumulative incidence of normal CUS (no RVT) was 39%, 58%, 69% and 74% at 6, 12, 24 and 36 mo post DVT respectively.



Segment	Reflux			No reflux			*P* value
	n	Median lysis time (d)	Interquartile range	*n*	Median lysis time (d)	Interquartile range	
CFV	10	278	104-577	14	111	37-208	0.14
SFP	15	214	95-474	18	73	30-245	0.086
SFM	10	474	245-736	16	65	15-199	0.002
SFO	7	268	230-433	13	118	34-371	0.15
PPV	10	260	187-388	20	93	29-190	0.006
PTV	8	72	49-130	38	80	28-182	0.85
PFV	6	375	289-388	10	130	30-275	0.04
GSV	5	287	145-348	7	98	4-191	0.11

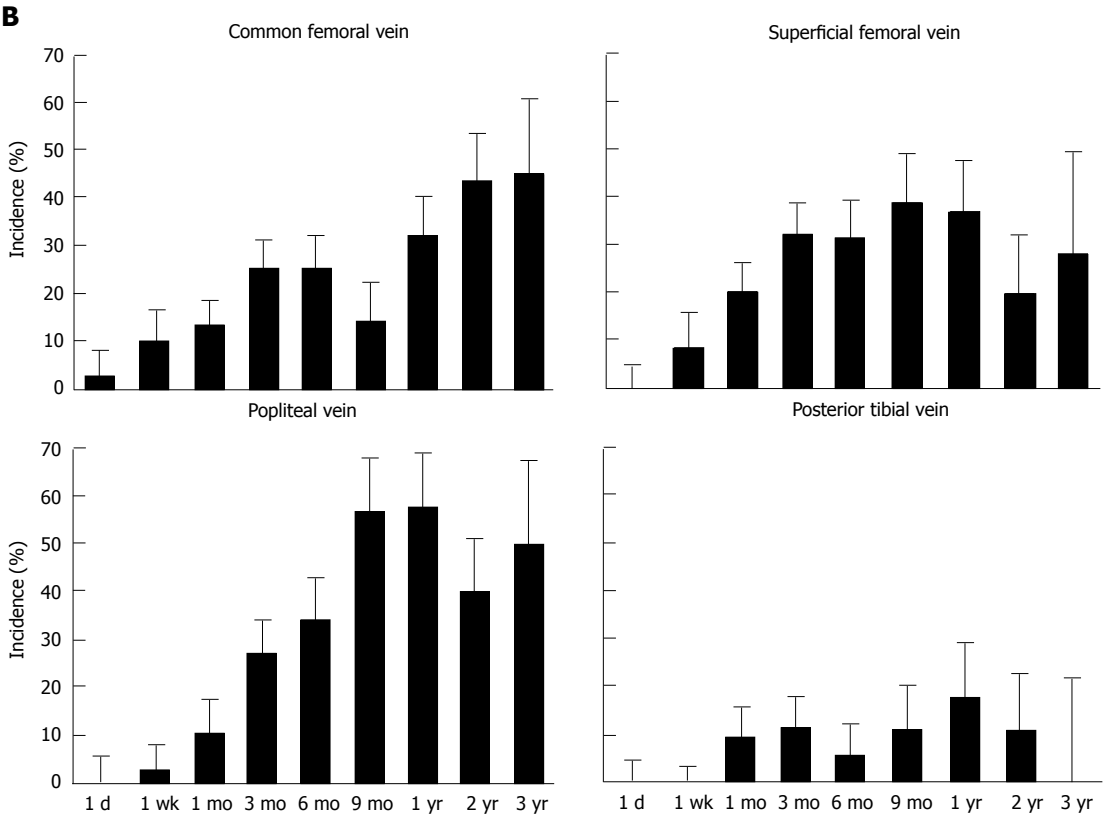
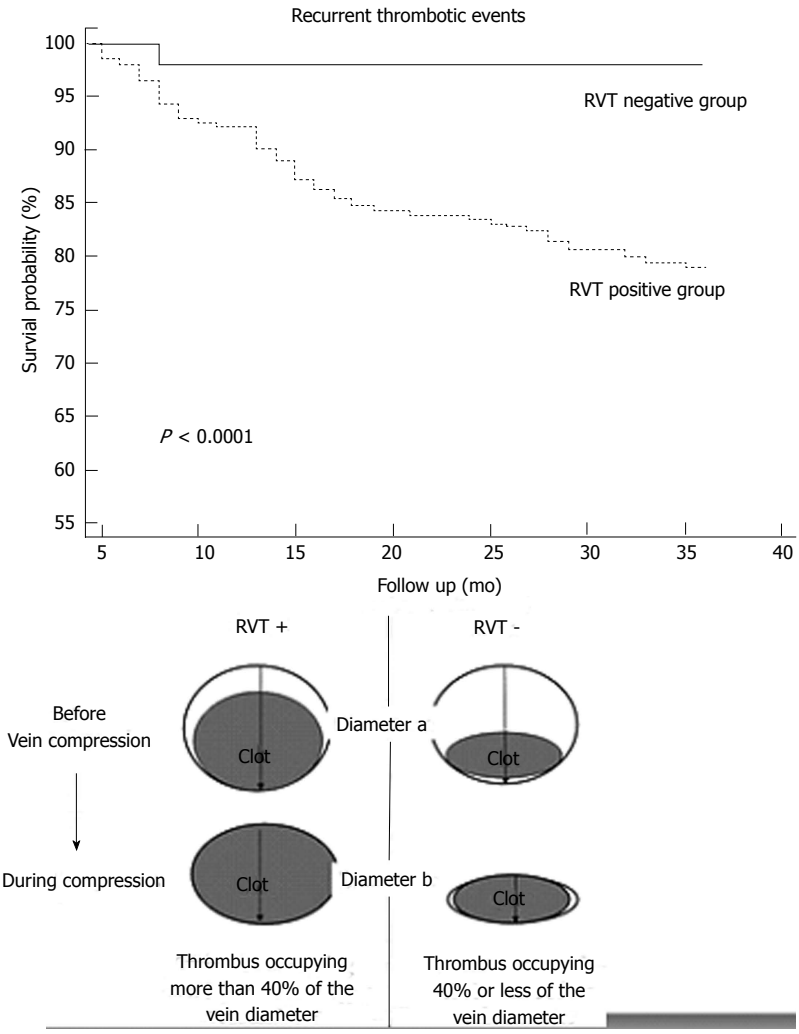


Figure 2 Recanalization of proximal deep vein thrombosis is usually delayed and may be completed after 3, 6 to 9 mo post-deep vein thrombosis with a high incidence of reflux, deep vein thrombosis recurrence and PTS. A: The relationship between the time of complete recanalization after deep vein thrombosis (DVT) (lysis time of leg vein thrombosis) appears to be 3 mo for those DVT patients who did not develop reflux, but appeared to be about 9 to 12 mo for those DVT patients who developed reflux as a main determinant for the development of PTS [Common femoral vein (CFV), superficial femoral vein (SFV), middle superficial femoral vein (SFM), distal superficial vein (SFD), popliteal vein (PPT), posterior tibial vein (PTV), greater saphena vein (GSV)][15]; B: Localization of reflux in patients with delayed recanalization (Figure 2A) of deep vein thrombosis[15].

Of 58 VTE recurrent episodes, 41 occurred at time of RVT. The hazard ratio for recurrent VTE was 2.4 with persistent RVT *vs* those with earlier complete vein recanalization[19].



Recurrence rate of DVT and PE = VTE
venous thromboembolism

without residual vein thrombosis: RVT neg (RVT⁻)

with residual vein thrombosis **RVT pos (RVT⁺)**

on DUS at 3 mo after an episode of proked or idiopathic deep vein thrombosis: DVT.

Siragusa *et al*[18] 2008

Figure 3 Event free recurrence rate of venous thromboembolism in 209 "low risk" DVT patients with no residual vein thrombosis at 3 mo post-DVT (RVT Neg in Table 3) as compared to 312 "high risk" DVT patients with RVT at 3 mo post-DVT (RVT Pos group in Table 3) after discontinuation of anticoagulation during 2 years follow-up in the prospective study of Siragusa *et al*[18] shown in Table 3. RVT: Residual vein thrombosis.

SCORING SYSTEMS FOR PTS

The fundamental pathophysiologic disturbance with severe leg symptoms or sign after distal and proximal DVT is sustained venous hypertension, which can be measured with invasive venous pressure measurement [ambulant venous pressure (AVP)]. AVP can be regarded as the gold standard, since it directly measures the pressure in the venous system of the lower extremity. This technique requires special equipment, is invasive, time consuming and cumbersome and therefore only suitable for basic research and scientific studies.

Identification of no, early and late PTS in patients after a first or recurrent DVT is not reflected by the clinical, etiological, anatomical and pathological (CEAP) classification and remains a challenge for clinicians and phlebologists. Several means of measuring and classifying the early clinical signs and symptoms of PTS and its long-term sequelae of PTS

Table 2 Scoring system according to Prandoni for the assessment of post-thrombotic syndrome in the early period 3 to 12 mo post-DVT known as the Vilalta score[29-31]

Subjective symptoms	Objective signs
Heaviness	Pretibial oedema
Pain	Induration of the skin
Cramps	Hyperpigmentation
Pruritus	New venous ectasia
Paraesthesia	Redness
Pain during calf compression	
Ulceration of the skin (= severe)	
Each sign or symptom is graded with a score as 0, 1, 2, or 3	
0 = absent, 1 = mild, 2 = moderate or interference with daily life and work, 3 = severe or invalidating	
The presence or absence of leg ulcer has to be noted	
Definition of post-thrombotic syndrome according to Prandoni(Vilalta)	
Absent	Score < 4
Mild-to-moderate	core between 5 and 14 at 2 consecutive visits
Severe	score > 15 at 2 consecutive occasions or ulcer at 1 occasion

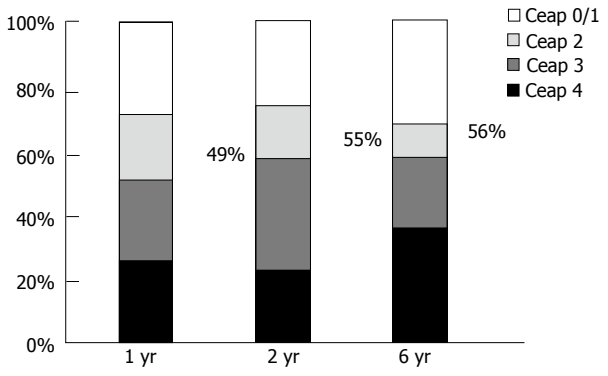


Figure 4 Incidence of the post-thrombotic syndrome according to the CEAP classification in patients with deep vein thrombosis during long-term follow-up[32].

Table 3 Clinical-etiology-anatomic-pathophysiologic classification for severity of chronic venous insufficiency[26]

Classification	Symptom
C0 (C = Clinical)	No visible varicose veins
C1	Spider or reticular veins
C2	Varicose veins
C3	Oedema
C4a	Pigmentetion or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C5	Skin changes with healed ulceration
C6	Skin changes with active ulceration
S	Symptomatic, including aches, pain, tightness, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction
A	Asymptomatic
C = Clinical symptom	Post-DVT
E = Etiology	Deep, perforator, or superficial vein, alone or in combination
A = Anatomic distribution	Reflux or obstruction, alone or in combination
P = Pathophysiologic dysfunction	

Table 4 Widmer classification for assessment of chronic venous insufficiency[27]

Classification	Symptom
I	Corona phlebotatica paraplantaris (ankle flare), subclinical mild oedema
II	Hyperpigmentation, lipo- and dermatosclerosis, atrophie blanche (white skin atrophy), oedema, eczema
III	Healed or active ulcer

exist. Most scoring systems for PTS are based on the presence or absence clinical signs and symptoms during the first year post-DVT and typical signs of CVI one or few years later. At least five definitions for early and/or late PTS exist for the early or long-term complications after an episode of documented DVT. For the prevention and management of PTS, it is crucial that the natural history and treatment outcome of the disease should be documented

Table 5 Venous clinical severity score system of PTS or chronic venous insufficiency[28]

Attribute	Absent = 0	Mild = 1	Moderate = 2	Severe = 3
Pain	None	Occasional, not restricting activity or requiring analgesics	Daily, moderate activity limitation, occasional analgesics	Daily, severe limiting activities or requiring regular use of analgesics
Varicose veins	None	Few, scattered: branch varicous veins	Multiple: GS varicose veins confined to calfor thigh	Extensive: thigh and calf or GSand LS distribution
Venous oedema	None	Evening ankle oedema only	Afternoon oedema, above ankle	Morning oedema above ankle and requiring activity change, elevation
Skin pigmentation	Non or focal, low intensity (tan)	Diffuse, but limited in area and old (brown)	Diffuse over most of gaiter distribution (lower 1/3) or recent pigmentation (purple)	Wider distribution (above lower 1/3) and recent pigmentation
Inflammation	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involves most of gaiter area (lower 1/3)	Entire lower third of leg or more
No. of active ulcers	0	1	> 2	> 2
Active ulceration, duration	None	< 3 mo	> 3 mo, < 1 yr	Not healed > 1 yr
Active ulcer, size	None	< 2 cm diameter	2 to 6 cm diameter	> 6 cm diameter
Compressive therapy	Not used or not compliant	Intermittent use of stockings	Wears stockings most days	Full compliance: stockings + elevation

GS: Greater saphenous; LS: Lesser saphenous.

by additional objective tools including residual vein thrombosis (RVT) on DUS, and reflux and/or obstruction on color ultrasonography (Table 1)[20-25]. At the baseline visit the clinicians should carefully examine the patient's leg to classify the clinical category and to assess the severity of early PTS or late CVI using the different scoring systems. The five scoring systems including the clinical classifications by Brandjes *et al*[24] and by Prandoni *et al*[25] (known as the Villalta score[25-28]) for early signs and symptoms of PTS during the first year post-DVT, and the CEAP, Widmer and VCS classifications to assess various degrees CVI as late onset sequelae of PTS are presented in Tables 1-5[29-31].

Two classifications for early PTS have been used

Table 6 2008 Rotterdam objective scoring system for grading the severity of PTS during the first two years post-DVT based on prospective studies[20-25]: therapeutic implications

Objective score	
Complete recanalization at 3 mo and no reflux	0
Incomplete recanalization at 3 mo	2
Complete recanalization after 6 mo and reflux	1
Incomplete recanalization after 6 mo and reflux	2
Obstruction after 1 year without or with reflux	3
Normal D-dimer after discontinuation of anticoagulant therapy	0
Increased D-dimer after discontinuation of anticoagulant thereapy	3
Clinical score	
Brandjes Prandoni score for PTS: Absent	0
Mild	1
Moderate	2
Total Rotterdam score 12	
Score	Therapeutic implication
Score 0 at 6 mo	No MECS and no ACT
Score 1 to 4 at 6 mo	MECS and discontinuation ACT
Score > 4 and normal D-dimer	MECS randomization ACT *vs* no ACT
Score > 4 and abnormal D-dimer	MECS and continuation of ACT according to the PROLONG Plus Study
Designed by Michiels	

ACT: Anticoagulant treatment.

by clinicians. The first clinical scoring system of Brandjes was developed in 1991 for early PTS during the first two years after DVT to assess the effect of wearing stockings. It had an equivalent system of subjective signs and objective symptoms, and both are graded as absent or present (Table 1)[24]. The Brandjes scoring system mild-to-moderate PTS as score 3 or more including one objective criterion. Severe PTS is assessed separately and consists of a score of 4 or more (Table 1). As the extension of the Brandjes scoring system, Prandoni developed a simplified clinical scoring system for PTS in a series of patients with overt PTS and patients without any sign and symptoms of PTS (Table 2), and validated his scoring system in prospective studies[29-31].

Three classifications for PTS have been used by dermatologists and phlebologist the CEAP (Clinical-Etiology-Anatomic-Pathophysiologic) (Table 3)[26] Widmer *et al*[27] (Table 4) and the venous clinical severity (VCS) score (Table 5)[28]. Clinical symptoms of PTS occurs in about half of the patients within one year post-DVT. A Dutch study prospectively evaluated the incidence and severity of PTS in 93 DVT patients under careful clinical survey using the CEAP classification and confirmed previous studies that half of DVT patients do develop PTS (Figure 4)[32]. The cumulative incidence of PTS increased from 49% after one year to 55% and 56% after 2 and 6 years, but class 5 and 6 (healed) ulcers did not occur while on treatment with MECS (Figure 4).

PREVENTION OF DVT RECURRENCE AND PTS

The incidence of DVT recurrence in the PROLONG and other studies in post-DVT patients with normal *vs* increased D-dimer levels one month after anticoagulation discontinuation was about 5% pt-years and 10%-5% pt/years respectively[20-22]. This difference was independent from other factors like thrombophilia or residual venous occlusion. In the PROLONG study, extended anticoagulation reduced the risk of DVT recurrence from 11% patient/years to less than 2% patient/years, whereas the incidence of DVT recurrence was still increased, 4.4% patient/years, in post-DVT patients with a normal D-dimer[23]. These data has to be interpreted in view of two other key observations: first the incidence of DVT recurrence after complete recanalization within 3 mo and no reflux is very low[15,16,18]. Second the incidence of PTS in the control arm of two randomized clinical trials was about 50% within 6 mo and did not significantly increase thereafter, whereas MECS decreased the incidence of PTS from around 50%-25% after two years follow-up[24,25]. This may implicate that DVT recurrence in those patients with either a normal or increased D-dimer do occur in those with incomplete or complete RVT after 6 mo with reflux (Table 1). The hypothesis in Table 6 that the Rotterdam scoring system for PTS will have therapeutic implications has to be tested by the use of objective measurements of RVT and reflux related to clinical score for PTS in prospective management and outcome studies.

Patients provoked and unprovoked DVT at time of diagnosis should be included in prospective studies on bridging the gap between DVT and PTS. All acute DVT patients are instructed to use medical elastic stockings for at least 3 to 6 mo (Figures 6 and 7). All DVT patients should be followed up by the combine use of the Prandoni (Vilalta) sclore and CEAP assessment for PTS at 1, 3, 6, 9 and 12 mo post-DVT. Patients with acute DVT should be followed up by CUS for the degree of recanilzation and PTS symptoms at 1, 3, and 6 mo post-DVT. About one third to half of the DVT patients do not develop PTS at 3 to 6 mo post-DVT and do not need to wear medical elastic compression stockings (Study arm 1 Figures 6 and 7)[33]. Rapid and complete recanalization of DVT with no residual vein thrombosis (RVT) at 3 mo post-dVT is followed by a very low risk of DVT recurrence after anticoagulant discontinuation (study arm 1, Figures 6 and 7), whereas a delayed recanalization of DVT with RVT at 3 mo post-DVT is associated with a high risk on DVT recurrence and PTS (Study arm 2, Figures 6

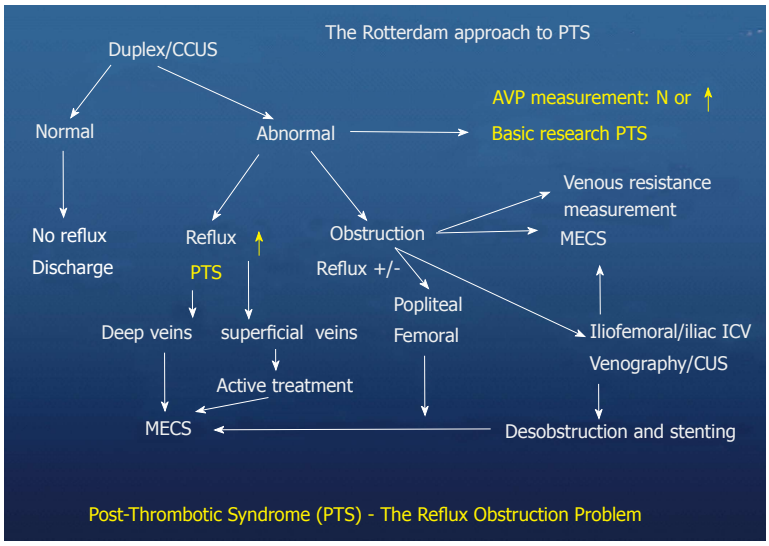


Figure 5 Rotterdam approach to the post-thrombotic syndrome according to Wentel *et al*[33]. PTS: Postthrombotic syndrome; MECS: Medical elastic compression stockings.

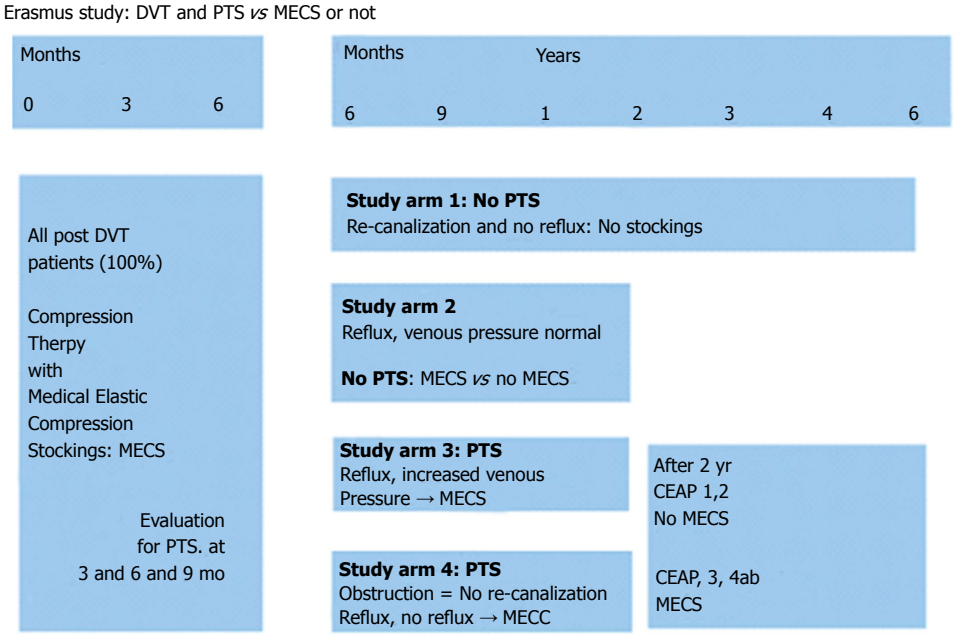


Figure 6 2007 Rotterdam Erasmus study design, time schedule, clinical score assessment and procedures for prospective evaluation of post-DVT venous thromboembolism-recurrence and postthrombotic syndrome. PTS: Postthrombotic syndrome; MECS: Medical elastic compression stockings.

and 7). If no pathological changes on DUS with complete recanalization, no reflux and no PTS at 3 to 9 mo post-DVT it is predicted that DVT recurrence rate and PTS remain low after anticoagulation discontinuation. Patients with PTS according to the prandoni (Villalta) score and/or CEAP assessment at 6, 9 and 12 mo post-DVT are candidates for continuation to wear MECS and the need to prolong anticoagulation for at least 24 mo to several years (Study arms 3 and 4, Figures 6 and 7).

ERASMUS STUDY DESIGNS TO PREVENT DVT RECURRENCE AND PTS WITH MECS

Study arm 1

Post-DVT patients with complete re-canalisation at 3 mo, no reflux, and asymptomatic (no PTS) will discontinue MECS and anticoagulant treatment (Figure 6).

Study arm 2

Post-DVT patients with reflux and no PTS will be randomized for MECS *vs* no MECS to address the question whether MECS is needed.

Study arm 3

MECS is recommended in symptomatic (PTS patients with delayed recanalization, reflux and increased ambulatory venous pressure for 2 years followed by randomization between continuation *vs* discontinuation of MECS for another 2 years.

Study arm 4

PTS patients with obstruction are candidates for MECS for 2 years followed by randomization between

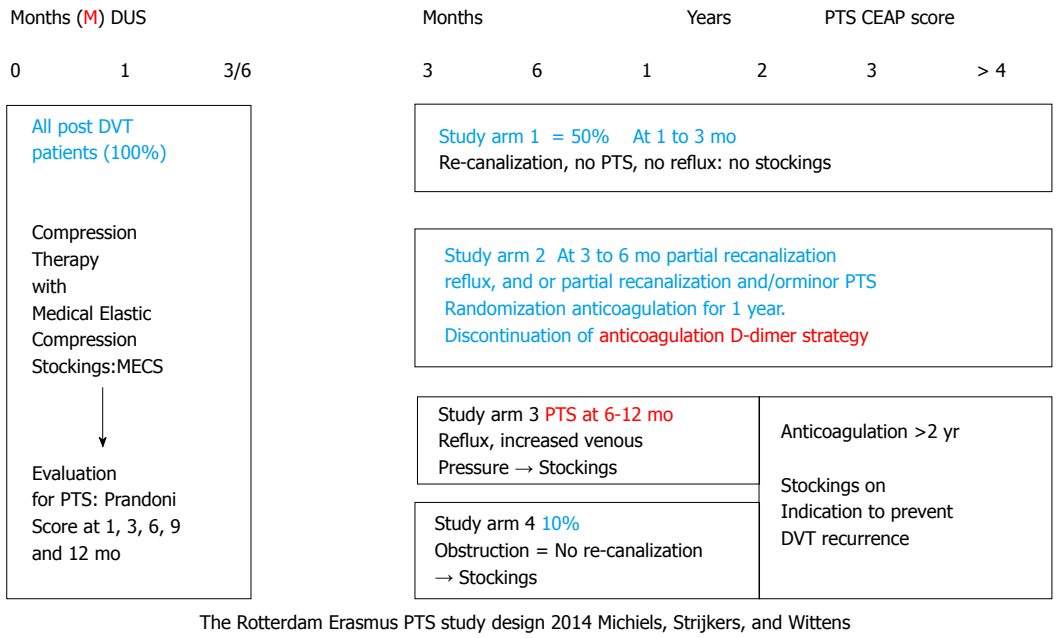


Figure 7 European DVT - postthrombotic syndrome Bridging the Gap study design 2014. MECS: Medical elastic compression stockings.

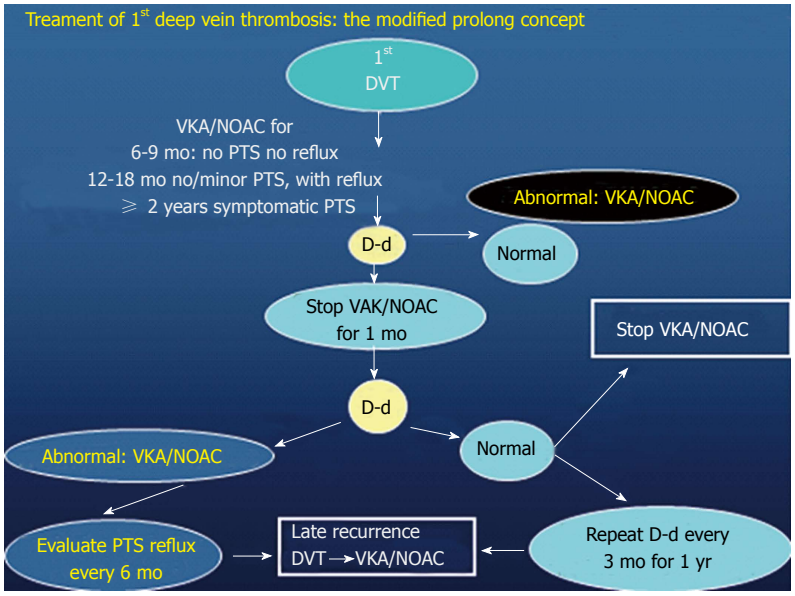


Figure 8 Algorith modification of the D-dimer strategy according to the modified PROLONG study 23 for the duration and extension of anticoagulant treatment in post-DVT patients on top of objective risk stratification in Figure 7.

continuation and discontinuation of MECS for at least another 2 years.

PTS patients in study arm 3 and 4 are in need for extended anticoagulationd according to the PROLONG study (Figures 7 and 8).

Evaluation procedures

At time of inclusion 1 mo and 3 mo after DVT: Evaluation of clinical findings and details of positive echogram for DVT from the records of various hospitals or medical diagnostic centers where the diagnosis of DVT was made. Blood collection (plasma, serum and DNA samples in deep freezer) for risk factor evaluation in retrospect.

Evaluation at time points 1 mo, 3 mo and 6 mo, 1 year, and 2 years post-DVT: (1) complete analysis for PTS according to subjective Prandoni (Vilalta) score and according to objective CEAP score; (2) DUS colour at 3 and 6 mo for assessment of the degree of recanilization, reflux and obstruction; (3) allocation of PTS patients at 6 mo to each of the four study arms; (4) randomization of study arm 2 at time point 6 mo into no MECS versus MECS; (5) at time point 2 years randomization of PTS patients arm 3 and 4 into MECS versus no MECS; and (6) repeat all measurements for PTS according to subjective Prandoni (Vilalta) score, and CEAP classification, and assess the degree of recanalization, reflux and obstruction by DUS and colour Doppler at 9, 12, 18 and 24 mo during follow-up.

Real life documentation of DVT patients and the need of extended anticoagulation: All patients with provoked and unprovoked DVT will be treated immediately with Direct Oral Oral Anticoagulants (DOACs) for 6 mo (Figures 6 and 7) and will undergo a complete evaluation for PTS at 3 and 6 mo post-DVT. Four groups of PTS at 6 mo post-DVT are distinguished depending on objective measurement criteria for PTS (Table 2) and allocated to the four study arms of the study design (Figures 6 and 7). Group 1: rapid and complete recanalization within 3 mo, no reflux at 6 mo post-DVT, and no PTS for which anticoagulation and MECS can be discontinued at 6 mo post-DVT. Group 2, no PTS with reflux of the deep venous system and no PTS when wearing MECS for which anticoagulation should be continued until re-evaluation at 1 year post DVT. Group 3 and 4 PTS with reflux and incomplete recanalization or obstruction at 6-12 mo post-DVT are candidates for long-term anticoagulation and MECS for at least 2 years or even longer to prevent DVT recurrence to prevent progression of PTS. A large scale prospective study is warranted to fine-tune and prove this concept.

Palareti *et al*[20] and other studies showed that normal versus increased D-dimer levels one month after anticoagulation discontinuation is related to a low versus high DVT recurrence rate of 5% patient-years *vs* 10%-15% patient/years respectively[20-23]. Such post-DVT patients with increased sensitive D-dimer after discontinuation surely belong to the group of symptomatic post-DVT patients at high risk to develop PTS (score $\geqslant$ 3, Table 1 integrated in the algorithm in Figures 7 and 8)[23,35]. In the prolong study, extended anticoagulation in post-DVT patients with increased D-dimer above the upper limit of normal will reduced the risk of DVT recurrence from 11% patient/years to less than 2% patient/years, whereas the incidence of DVT recurrence was still increased, 4.4% patient/years, in post-DVT patients with a normal D-dimer on month after discontinuation of regular anticoagulation[23,34]. This may implicate that DVT recurrence in those patients with either a normal or increased D-dimer very likely do occur in those with incomplete or complete recanalization of the leg veins after 6 mo with reflux score 3 or more (Table 6). This important observation has been confirmed by Latella *et al*[35] in a prospective study of 305 DVT patients selected for quantitative ELISA D-dimer (VIDAS) measurement 4 mo post-DVT. Of these 305 (46%) developed PTS (mild 25%, moderate 13%, severe 7%) and 54% did not during 24 mo follow-up. Mean D-dimer level measured 4 mo post-DVT were significantly higher in patients with PTS *vs* without PTS (712 *vs* 444 μg/L $P = 0.02$)[35]. At time of D-dimer measurement 213 were taken anticoagulants. The PROLONG study[23] demonstrated the need to continue anticoagulant treatment in post-DVT patients with increased D-dimer level during anticoagulant treatment and when D-dimer levels are above the upper level of normal one month after discontinuation of anticoagulant treatment (Figures 7 and 8)[34,35].

ACKNOWLEDGMENTS

The present report on DVT and PTS Bridging the Gap study was designed and written between 2007 and 2013 by Dr. Michiels in his position of Senior Investigator, Phlebology at the Department of Dermatology, Erasmus University Medical Center Rotterdam (Chief professor H.A. Martino Neumann).

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REVIEW

Treatment and prevention of gastrointestinal bleeding in patients receiving antiplatelet therapy

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Abstract

Antiplatelet therapy is the standard of care for the secondary prevention of acute coronary syndrome and ischemic stroke, especially after coronary intervention. However, this therapy is associated with bleeding complications such as gastrointestinal bleeding, which is one of the most common life-threatening complications. Early endoscopy is recommended for most patients with acute upper gastrointestinal bleeding. After successful endoscopic hemostasis, immediate resumption of antiplatelet therapy with proton-pump inhibitors (PPIs) is recommended to prevent further ischemic events. PPI prophylaxis during antiplatelet therapy reduces the risk of upper gastrointestinal bleeding. The potential negative metabolic interaction between PPIs and clopidogrel is still unclear.

Key words: Antiplatelet therapy; Aspirin; Clopidogrel; Gastrointestinal bleeding; Endoscopy; Proton-pump inhibitor

Core tip: Gastrointestinal bleeding (GIB) is a relatively common complication in patients receiving antiplatelet therapy and is associated with an increased risk of recurrent ischemic events and mortality. Early endoscopy is useful for both the diagnosis and the therapeutic management of GIB. Antiplatelet therapy should be resumed immediately after endoscopic hemostasis of GIB, unless the bleeding is life threatening. Prophylaxis with antisecretory drugs such as proton-pump inhibitors reduces the risk of GIB.

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INTRODUCTION

Antiplatelet therapy is widely used in the secondary prevention of acute coronary syndrome (ACS) and ischemic stroke, especially after interventional

therapy. Dual antiplatelet therapy (DAPT) with aspirin plus a thienopyridine derivative that inhibits the platelet $P2Y_{12}$ adenosine diphosphate (ADP) receptor is the standard treatment to prevent stent thrombosis after implantation of drug-eluting stents (DESs) in patients with symptomatic coronary artery disease[1,2]. The joint guidelines of the American College of Cardiology, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions recommend that aspirin therapy should be continued lifelong in all patients with ST-elevation myocardial infarction (MI)-ACS, and clopidogrel or prasugrel should be administered for at least 12 mo in patients receiving stents (bare metal stents or DESs) during percutaneous coronary intervention (PCI) for ACS[3,4]. Antiplatelet therapy is also used for both the management and the prevention of acute ischemic stroke. Aspirin is the most commonly used agent in this therapy. Long-term administration of clopidogrel in patients with ischemic stroke is also beneficial and induces a slightly lower frequency of gastrointestinal bleeding (GIB) than does aspirin administration[5].

Antiplatelet therapy is associated with bleeding complications such as GIB, which is one of the most common life-threatening complications of this therapy[6-9]. This review focuses on the management and prevention of upper GIB in patients receiving antiplatelet therapy.

ANTIPLATELET THERAPY AND GIB

Antiplatelet therapy causes GIB, especially in elderly patients. Usually, clinically important upper GIB is identified by hematemesis and/or melena and a decrease in hemoglobin level of at least 2 g/dL, and is confirmed by an endoscopic diagnosis of peptic ulcer lesions as the cause of bleeding. Antiplatelet therapy-related ulcers often occur without symptoms of dyspepsia. Aspirin and $P2Y_{12}$ inhibitors are the most common antiplatelet agents. Aspirin irreversibly inhibits cyclooxygenase-1 by acetylating a serine residue at position 530, thereby preventing the conversion of arachidonate to the prostaglandin PGH_2, which is converted to the platelet agonist thromboxane[10]. Several randomized trials (RCTs) have documented that patients with prior cardiovascular disease experience fewer cardiovascular events and deaths with the use of low-dose aspirin (LDA) therapy than without its use[11,12]. LDA is commonly defined as aspirin between 75 and 325 mg/d. A meta-analysis indicated that no additional benefit was observed with the use of a higher dose of aspirin (300 mg/d *vs* 50-100 mg/d[12]). LDA is an effective therapy for the secondary prevention of cardiovascular events and ischemic stroke.

Thienopyridines affect the ADP pathway by irreversibly blocking the ADP receptor $P2Y_{12}$, thereby inhibiting the activation of the glycoprotein Ⅱb/Ⅲa complex and platelet aggregation[10,13]. Ticlopidine, clopidogrel, and prasugrel are thienopyridine prodrugs that require conversion to an active metabolite. Ticagrelor belongs to a new family of antiplatelet agents, which directly and reversibly bind to the $P2Y_{12}$ receptor. The antiplatelet effects of the $P2Y_{12}$ inhibitor are additive to those of aspirin. The benefits of DAPT over aspirin alone in patients with ACS without ST-segment elevation were established in the Clopidogrel in Unstable Angina to Prevent Recurrent Events CURE trial[14]. Analysis of a subset of patients in the CURE trial also showed the efficacy of DAPT in PCI[15].

Incidence and risk factors of GIB

The reported risk factors for upper GIB include increasing age, female sex, major organ dysfunction (cardiac, respiratory, or hepatic), diabetes, hypertension, positive results for *Helicobacter pylori* infection, and hemostatic disorders[7,16,17]. A case-control study showed that the odds ratios (ORs) for upper GIB in patients receiving LDA were similar to those in patients regularly receiving nonsteroidal anti-inflammatory drugs[18]. A meta-analysis showed that there was an increased risk of major GIB with LDA use (OR = 1.55; 95%CI: 1.27-1.90[19]). The risk of upper GIB associated with the use of thienopyridine monotherapy is reported to be similar to[17] or greater than that associated with the use of aspirin alone[14]. The risk of major bleeding is reportedly increased in patients receiving DAPT compared with those receiving aspirin monotherapy[20]. In a population-based observational cohort study of elderly patients who survived MI, the rate of GIB was 1.5% per year with aspirin alone and 4.6% per year with aspirin plus clopidogrel or ticlopidine[21]. Several large RCTs[14,22-25] reported that 0.6% (28-d follow-up) to 4.8% (12-mo follow-up) of patients treated with DAPT experienced major bleeding, as compared with 0.6% (28-d follow-up) to 3.8% (12-mo follow-up) of patients treated with aspirin alone. An observational study reported that the 1- and 2-year cumulative incidences of upper GIB in patients who received DAPT without the use of an antisecretory drug [proton-pump inhibitor (PPI) or histamine-2 receptor antagonist (H2RA)] were 4.5% and 9.2%, respectively[9]. Of note, the first month after PCI is a high-risk period for upper GIB[9,17,26]. Further, the risk of GIB with triple therapy with warfarin, aspirin, and clopidogrel was reported to be as high as 5.1%[27].

Outcomes of GIB

Bleeding complications are associated with an increased risk of recurrent ischemic events and death[26,28]. In particular, GIB complicating PCI is associated with early mortality. In the Acute Catheterization and Urgent Intervention Triage Strategy trial, a large multicenter trial in patients

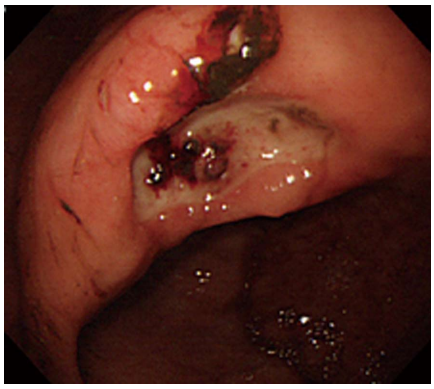

Figure 1 Peptic ulcer with an exposed vessel in a 68-year-old man 10 d after starting dual antiplatelet therapy after percutaneous coronary intervention for acute myocardial infarction.

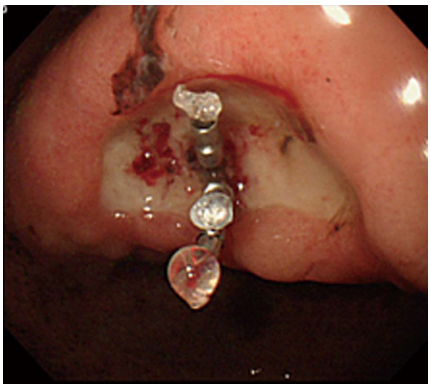

Figure 2 Successful endoscopic hemostasis using endoclips.

with moderate- and high-risk ACS, GIB occurred in 1.3% of the patients and was found to be associated with longer hospital stays and higher 30-d all-cause mortality rates (9.6% *vs* 1.4% in patients with no bleeding[29]). A retrospective study reported that the 30-d mortality rates were as high as 20.5% in patients with GIB, compared to 2.4% in those without GIB[30]. The mechanism underlying the high rates of early mortality in ACS patients with GIB may be multifactorial. The risk of ischemic events is further aggravated by the augmented release of endogenous catecholamines and increased platelet adhesiveness in ACS patients with bleeding complications. Importantly, GIB is a well-known cause of premature cessation of antiplatelet therapy, which poses a serious risk of ischemic events during hospital stay and after hospital discharge.

MANAGEMENT OF GIB IN PATIENTS RECEIVING ANTIPLATELET THERAPY

Impact of blood transfusion on mortality after PCI

Major GIB often requires red blood cell (RBC) transfusions. Although RBC transfusions are performed to augment oxygen delivery to avoid the deleterious effects of oxygen debt, these transfusions may have potential harmful effects[31]. Indeed, despite increased hemoglobin levels, RBC transfusion does not always increase tissue oxygenation. One possible explanation is that stored RBCs are low in 2,3-diphosphoglyceric acid; therefore, the hemoglobin will tend not to release oxygen to the tissues. In addition, RBCs mediate a nitric oxide-based hypoxic vasodilatory activity, which is impaired in banked blood, predisposing to vasoconstriction and ischemic insult[32]. Therefore, blood transfusion does not always provide beneficial effects in ACS patients[33]. A recent RCT in patients with acute upper GIB showed that a restrictive transfusion strategy (*i.e.,* transfusion when the hemoglobin level was < 7 g/dL) had significantly better outcomes than a liberal transfusion strategy (*i.e.*, transfusion when the hemoglobin level was < 9 g/dL[34]). Therefore, in patients with stable hemodynamic status, RBC transfusion is considered when the hemoglobin concentration falls below 7.0 g/dL in patients with stable angina and is 8-10 g/dL in those with ACS[35].

Endoscopic hemostasis of GIB in patients receiving antiplatelet therapy

In patients with GIB, early endoscopy is beneficial for decreasing the length of hospital stay and avoiding surgical intervention[36,37]. A case-control study reported that there were no serious complications of emergency endoscopy after MI[17]. During endoscopy, careful removal of clots in an ulcer bed is important to detect the exposed vessel. When active spurting or oozing bleeding or a nonbleeding visible vessel is observed, endoscopic therapy should be provided to patients[38]. Endoscopic hemostatic options include injection techniques using epinephrine or ethanol, ablative therapies such as use of a heater probe, coagulation with hemostatic forceps or argon plasma coagulation, and mechanical methods such as use of endoclips (Figures 1 and 2). Endoscopic treatment with a combination of epinephrine injection therapy and electrical coagulation or use of endoclips is also effective to achieve better outcomes. Routine second-look endoscopy is not recommended after successful endoscopic hemostasis with intravenous PPI therapy. Transcatheter arterial embolization can be considered for patients in whom endoscopic therapy has failed.

Continuation of antiplatelet therapy

GIB often causes premature cessation of antiplatelet therapy, which increases the thrombotic risk for cardiovascular and cerebrovascular events. A RCT in GIB patients receiving LDA therapy for the secondary prevention of cardiovascular disease showed that interruption of antiplatelet therapy is one of the most important determinants of fatal outcome. Although resumption of LDA therapy after endoscopic hemostasis was associated with a

50% increased risk of recurrent bleeding, the 8-wk mortality rate was significantly lower in the LDA group patients than in the placebo group patients (1.3% *vs* 12.9%[39]). Thus, antiplatelet therapy and PPI cotherapy should be resumed immediately after the successful endoscopic control of ulcer bleeding to avoid further ischemic events.

PREVENTION OF GIB IN PATIENTS RECEIVING ANTIPLATELET THERAPY

Optimal duration and dosage of antiplatelet therapy

Risks of GIB increase with the use of multiple antiplatelet or anticoagulant agents and an increase in the duration of medication use. The optimal duration of antiplatelet therapy after PCI is unclear when thrombotic and bleeding risks are both taken into consideration. Although the current guidelines recommend that DAPT should be continued for at least 12 mo in patients receiving DESs during PCI for ACS, the long-term use of DAPT is associated with a higher rate of bleeding events[40]. These guidelines are based on outcomes using first-generation DESs. Second-generation DESs, such as everolimus-eluting stents and zotarolimus-eluting stents, are now increasingly being used. Compared with first-generation DESs, second-generation DESs have equal or superior antirestenotic effects and lower stent thrombosis rates. Several studies have assessed the safety of a shorter duration of $P2Y_{12}$ inhibitor administration with second-generation DES use. A retrospective study reported that clopidogrel discontinuation before 1 year of therapy was associated with higher rates of stent thrombosis events for first-generation DESs but not for everolimus-eluting stents[41]. The Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice trial showed that in patients undergoing PCI with zotarolimus-eluting stent implantation, short-term (3 mo) DAPT was noninferior to long-term (12 mo) DAPT for the occurrence of death, MI, and stroke, without significantly increasing the risk of stent thrombosis[42]. Accordingly, DAPT duration could be potentially tailored to the type of stent used.

Prasugrel is a third-generation thienopyridine that provides more prompt, potent, and consistent platelet inhibition than does clopidogrel. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) trial demonstrated that prasugrel use (10 mg/d) resulted in significantly fewer ischemic events[43]; however, a higher incidence of bleeding was observed with prasugrel use than with clopidogrel use in ACS patients undergoing PCI. Recently, the PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI (PRASFIT-ACS) study in Japanese ACS patients undergoing PCI showed that a lower dose of prasugrel (3.75 mg/d) was associated with a low incidence of ischemic events, which is similar to the results of the TRITON-TIMI 38 trial, and with a low risk of clinically serious bleeding[44]. In particular, interethnic differences should be taken into consideration in the management of patients receiving DAPT.

If PCI is required in patients taking oral anticoagulants, DAPT with aspirin and clopidogrel is indicated, but such triple therapy increases the risk of serious bleeding[27]. Omission of aspirin may be advantageous in such patients. Recently, the What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing trial reported that the use of clopidogrel without aspirin was associated with a significant decrease in bleeding complications (2.9% *vs* 8.8%) without an increase in the rate of thrombotic events[45]. Therefore, triple therapy may be discouraged in such patients with an indication for oral anticoagulants after PCI.

PPI prophylaxis

In patients receiving antiplatelet therapy, the concomitant use of an antisecretory agent is associated with a reduced risk of upper GIB. In particular, PPI use is associated with a substantial decrease in the risk of upper GIB in both LDA and clopidogrel users[46]. Moreover, PPIs have been shown to be effective in preventing rebleeding after stabilization of upper GIB, which prevents the premature discontinuation of DAPT[47]. In patients receiving LDA therapy for the secondary prevention of cardiovascular disease, use of H2RAs was associated with a risk of mucosal erosion but not of ulcer development[48]. TAK-438, a novel potassium-competitive acid blocker, has also been shown to be as effective as PPIs in the prevention of aspirin-induced ulcer recurrence[49]. A population-based study from Sweden reported that the risk of gastrointestinal ulcers depended on PPI adherence in patients receiving LDA therapy[50]. After experiencing GIB, many patients stop receiving LDA therapy, which increases the risk of ischemic events. Therefore, physicians should encourage these patients to continue LDA therapy with PPI prophylaxis.

Potential metabolic interaction between PPIs and clopidogrel

Thienopyridine derivatives are prodrugs, which are metabolized into active forms through complex biochemical reactions involving several cytochrome P450 (CYP) isoforms including CYP2C19, which is also involved in the metabolism of PPIs. Several observational studies in clopidogrel recipients have shown a significant association between PPI use and cardiovascular events[51,52]. A meta-analysis showed that there was an increased risk (OR =

1.43; 95%CI: 1.15-1.77) of adverse outcomes in patients co-prescribed clopidogrel and a PPI[53]. Platelet studies have supported the use of PPIs with weaker inhibition of CYP2C19 (*e.g.*, rabeprazole or pantoprazole[54]. In contrast, in the Clopidogrel and the Optimization of Gastrointestinal Events trial of omeprazole *vs* placebo in coronary artery disease patients receiving aspirin and clopidogrel, no apparent cardiovascular interaction was observed between clopidogrel and omeprazole[55]. Taken together, the potential negative interaction between PPI therapy and clopidogrel use is still controversial. Prasugrel is as effective as clopidogrel in the prevention of ischemic events[43,44,56]. Of note, the platelet inhibitory activity of prasugrel is not affected by CYP2C19. Recently, the DOuble the dose of Clopidogrel or Switch to Prasugrel to Antagonize Proton pump inhibitor Interaction study reported that while the higher platelet inhibitory effect obtained by doubling the clopidogrel dose was completely neutralized by the coadministration of lansoprazole, this drug interaction was not observed with prasugrel[57]. Furthermore, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes study, which compared prasugrel with clopidogrel in patients with unstable angina or MI without ST-segment elevation[58], demonstrated that prasugrel was superior to clopidogrel in the subgroup of PPI users. The concomitant use of PPIs with prasugrel or ticagrelor may be beneficial for the prevention of upper GIB in patients receiving DAPT.

CONCLUSION

GIB is a relatively common complication in patients receiving antiplatelet therapy and is associated with an increased risk of recurrent ischemic events and mortality. Prophylaxis with antisecretory drugs such as PPIs reduces the risk of GIB. Early endoscopy is useful for both the diagnosis and the therapeutic management of GIB. Antiplatelet therapy should be resumed immediately after endoscopic hemostasis of GIB, unless the bleeding is life threatening.

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MINIREVIEWS

Noninvasive ventilation in trauma

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Abstract

Trauma patients are a diverse population with heterogeneous needs for ventilatory support. This requirement depends mainly on the severity of their ventilatory dysfunction, degree of deterioration in gaseous exchange, any associated injuries, and the individual feasibility of potentially using a noninvasive ventilation approach. Noninvasive ventilation may reduce the need to intubate patients with trauma-related hypoxemia. It is well-known that these patients are at increased risk to develop hypoxemic respiratory failure which may or may not be associated with hypercapnia. Hypoxemia in these patients is due to ventilation perfusion mismatching and right to left shunt because of lung contusion, atelectasis, an inability to clear secretions as well as pneumothorax and/or hemothorax, all of which are common in trauma patients. Noninvasive ventilation has been tried in these patients in order to avoid the complications related to endotracheal intubation, mainly ventilator-associated pneumonia. The potential usefulness of noninvasive ventilation in the ventilatory management of trauma patients, though reported in various studies, has not been sufficiently investigated on a large scale. According to the British Thoracic Society guidelines, the indications and efficacy of noninvasive ventilation treatment in respiratory distress induced by trauma have thus far been inconsistent and merely received a low grade recommendation. In this review paper, we analyse and compare the results of various studies in which noninvasive ventilation was applied and discuss the role and efficacy of this ventilator modality in trauma.

Key words: Acute respiratory distress syndrome; Noninvasive ventilation; Pulmonary contusion; Respiratory failure; Trauma

Core tip: The use of noninvasive ventilation is widely recognized as a suitable way to avoid intubation and its associated side effects. Noninvasive ventilation allows increased flexibility in the application and discontinuation of ventilator assistance and preserves airway defense mechanisms. The application of noninvasive ventilation may reduce the need to intubate patients with trauma-related hypoxemia, thereby potentially decreasing intensive care unit length of stay and preventing respiratory complications. In this review article, we summarize the results of various studies in which noninvasive ventilation was applied and discuss the role and efficacy of this ventilator modality in trauma.

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INTRODUCTION

Nearly one hundred and forty thousand traumatic deaths occur in the United States annually[1]. The most common cause of death in up to a quarter of patients with multiple system traumas is chest trauma[2]. Pulmonary contusion is particularly common occurring in approximately seventeen percent of patients with multiple traumas[3].

Previous studies[4,5] showed that posttraumatic respiratory failure was caused by an increased amount of interstitial and intraalveolar fluids and described the concept of the so-called "traumatic wet lung", and recommend positive airway pressure by mask to ensure adequate ventilation.

More recently, trauma management has been guided according to the mechanism of injury, its anatomic involvement, and the staging of the injury. Its main aims include pulmonary toilet, control of chest wall pain, surgical stabilization and fluid management. However, ventilator management has received little attention[6] and this is reflected by a low grade recommendation for the use of noninvasive ventilation in trauma patients by the British Thoracic Society guidelines[7] and "no recommendation" by Canadian Critical Care Trials Group/Canadian Critical Care Society Noninvasive Ventilation Guidelines Group[8] due to a lack of sufficient evidence.

There is a lack of randomized controlled trials on the use of noninvasive ventilation in the trauma population and therefore the efficacy of this treatment in the management of respiratory failure from trauma is for the most part unclear. This review will discuss the current evidence demonstrating the role and efficacy of noninvasive ventilation in trauma.

TRAUMA EPIDEMIOLOGY

The increasing number of high-velocity blunt traumas over the last few decades has caused a progressively higher incidence of chest injuries. As many as seventy to ninety percent of chest injuries in industrialized countries, are caused by blunt trauma, with eighty to ninety percent of cases associated with multiple injuries[9]. Typical causes of severe chest trauma include high-velocity traumas such as traffic accidents or falls from a height[10].

Flail chest involves the fracture of three or more ribs in two places or when there are multiple fractures associated with sternal fracture. The clinical significance of this condition varies, depending on the size and location of the flail segment and the extent of the underlying lung contusion. The respiratory insufficiency associated with flail chest has been shown to be due to the underlying pulmonary contusion rather than paradoxical respiration[11] and is in fact, the most common injury identified in blunt thoracic trauma.

In severely injured patients with accompanying chest injuries and pulmonary contusion, mortality is reported to be fifteen to sixty percent, depending on the overall severity of the injury[12]. In comparison, the mortality among patients with isolated chest injuries is low and ranges from zero to five percent in young patients and ten to twenty percent in elderly patients[13]. Furthermore, pulmonary contusions often occur in the absence of rib fractures[14].

Three mechanisms that are important in the etiology of pulmonary contusions have been reported[15]. The "inertial effect" occurs when low-density alveolar tissue is stripped from hilar structures as they accelerate at different rates whereas the "spalling effect" is due to bursting that occurs at the gas-liquid interface. Thirdly, the "implosion effect" involves the overexpansion of gas bubbles after a pressure wave passes and can tear the pulmonary parenchyma.

Pulmonary contusion promotes the development of acute lung injury (ALI), which may progress to acute respiratory distress syndrome (ARDS) secondary to elevated intrapulmonary shunting, ventilation-perfusion mismatching, increased lung water, pulmonary hemorrhage, loss of lung compliance, and the release of cytoactive modulators[14]. ARDS may develop in as much as five percent of patients with blunt trauma and the major predictors of its development have been shown to be pulmonary contusion and an Injury Severity Score higher than twenty five[16].

PATHOPHYSIOLOGICAL CONCEPTS OF TRAUMA

The likelihood of complications secondary to severe trauma are the consequences of the direct mechanical damage to the pulmonary parenchyma as well as the indirect systemic and pulmonary sequela. Furthermore, the severity of pulmonary contusion correlates with the development of pulmonary infections, respiratory failure, and mortality[17] despite the fact that some studies failed to demonstrate a correlation of pulmonary contusion with more severe ALI and ARDS[18]. This lung injury is an independent risk factor for ALI/ARDS and its severity has been shown to indicate the need for ventilatory support[16]. Two different forms of posttraumatic ALI/ARDS that have been described universally in trauma patients: (1) early ALI/ARDS which is attributed to hemorrhagic shock and capillary leak and develops within 48 h; and (2) late-onset ALI/ARDS that is associated with a higher incidence of pneumonia, often in conjunction with multiple organ failure[19].

The lung is exceedingly predisposed to the fracture of blood vessels as well as parenchymal laceration under briskly applied compressive or concussive loads such as those that occur in pulmonary contusions[14]. Mechanical injuries to the lung can occur through tissue tears when low-density alveolar tissue is stripped from the heavier hilar structures as they accelerate at different rates. The lung can also be damaged by bleeding into distant lung segments, direct laceration of the lung through displacement of fractured ribs and by chest wall compression. The combination of intraparenchymal hemorrhage, edema formation, direct mechanical damage to the lung parenchyma as well as additional indirect injuries, lead to post-traumatic ALI/ARDS.

The infiltration of the lung by polymorphonuclear leukocytes (PMNs) is the most characteristic feature of early post-traumatic ALI/ARDS[20]. This influx involves PMN retention, margination, and endothelial adhesion within the microvasculature, and migration into the alveolar space and pulmonary interstitium. Subsequently, when the PMNs are activated, they can release numerous cytotoxic products. Hoth *et al*[21] showed that the systemic levels of certain chemokines such as monocyte chemoattractant protein-1, macrophage inflammatory protein-2α (MIP-2α) and cytokine-induced neutrophil chemoattractant 1 (CINC-1) were significantly elevated at 3 h with all chemokines subsequently found to be significantly elevated at 24 h. Furthermore, the authors showed that pulmonary expression of elastase, CINC-1, tumor necrosis factor-α, interleukin-1β, intercellular adhesion molecule 1 and MIP-2α were increased and activated systemic neutrophils demonstrated increased cluster of differentiation molecule 11b. This indicates that the process of innate inflammation is activated both systemically and locally.

Ultimately, the combination of proteases, elastases and reactive oxygen species damage the alveolocapillary barrier, resulting in an increased permeability and in the accumulation of protein-rich alveolar and interstitial edema. This process destabilizes airspaces by inactivating the surfactant of alveoli and terminal airways whose production and function are already significantly impaired[22]. Eventually, this culminates in a combination of several different clinical phenomena including hypoxemia, ventilation-perfusion mismatching, raised intrapulmonary shunt, and reduced functional capacity.

EVIDENCE-BASED OVERVIEW FOR THE USE OF NONINVASIVE VENTILATION IN TRAUMA

Several systemic reviews and randomized controlled trials have shown the benefits of noninvasive ventilation (NIV) in patients with exacerbation of chronic obstructive pulmonary disease (COPD). These advantages are mostly due to avoidance of invasive mechanical ventilation (IMV) and its complications[23]. Therefore, NIV in COPD patients with hypercapneic acute respiratory failure (ARF) is now considered a first-line intervention ahead of endotracheal intubation and IMV, providing there are no contraindications to its use (Table 1).

Table 1 Contraindications to noninvasive ventilation

Trauma, deformity, facial or neurological surgery
Inability to protect airway or cooperate
High risk for aspiration and inability to clear secretions
Upper airway obstruction
Respiratory or cardiac arrest
Organ failure
Unstable cardiac arrhythmia/hemodynamic instability
Severe Encephalopathy (*e.g.*, GCS < 10)
Severe upper gastrointestinal bleeding

Adapted from ref.[46]. GCS: Glasgow Comma Scale.

Numerous studies have also shown that the use of NIV in patients with hypoxemic ARF is associated with fewer complications and reduced mechanical ventilation and length of intensive care unit stay[24]. Those patients who are at high risk of nosocomial infection such as patients with hematological malignancies, with chemotherapy induced neutropenia, organ transplantation recipients as well as the immunosuppressed are likely to benefit from the use of NIV. The Infectious Diseases Society of America and the American Thoracic Society have issued high grade evidence based recommendations in their most recent guidelines for the management and prevention of nosocomial infections thereby advocating the use of NIV whenever appropriate in the management of ARF[25].

There has been a scarcity of randomized controlled trials on ventilatory management of patients with posttraumatic hypoxemic respiratory failure. The British Thoracic Society has issued a low grade recommendation in its guidelines based on the available level C evidence for the use of NIV in multiple trauma patients[7]. Similarly, no recommendations were proposed by Canadian Critical Care Trials Group/Canadian Critical Care Society Noninvasive Ventilation Guidelines Group[8]. Two recently published systemic reviews[26,27] have confirmed the insufficiency of the available evidence on this area under discussion. We consequently aimed at investigating the available studies on the indications for NIV in trauma by selecting several major key topics related to pertinent methodological and technical issues.

Our search strategy included data from studies that enrolled adults who developed ARF as a consequence of trauma and who were admitted to the emergency department, trauma service or

Table 2 Tabulated summary of the most significant randomized control studies depicting the use of noninvasive ventilation in posttraumatic hypoxemic respiratory failure

Ref.	No. of Patients enrolled	Study intervention per patient group	Inclusion criteria	Exclusion criteria	Analgesia	Outcomes
Bolliger *et al*[32]	69	36 - CPAP 33 - CPPV	Chest trauma with > 3 rib fractures; Insufficient cough mechanism	PaO_2/FiO_2 < 200	Lumbar epidural catheter	Duration of treatment, ICU length of stay, complications, mortality
Tanaka *et al*[31]	59	25 - CPAP 11 - PSSB 44 - IMV/CMV	Blunt thoracic trauma with flail chest	Flail chest injury caused by CPR	Epidural analgesia	mortality, pulmonary complications
Ferrer *et al*[30]	105	51 - NIV 54 - High-concentration oxygen therapy	Chest trauma with acute respiratory failure	$PaCO_2$ > 45 mmHg; need for ETI; recent facial, esophageal, cranial trauma and surgery; ↓ GCS (≤ 11); hemo-dynamic instability; arrythmia/MI; > 1 organ system failure	Not defined	ICU mortality, rate of intubation, incidence of septic shock
Gunduz *et al*[33]	43	22 - CPAP 21 - IPPV	Flail chest; PaO_2/FiO_2 < 300; Acute respiratory distress	Need for ETI; hemo-dynamic instability; coma/confusion; Emergency surgery	PCA	ICU mortality, complications, improvement in oxygenation, ICU length of stay
Hernandez *et al*[34]	50	25 - NIV 25 - High flow oxygen mask	PaO_2/FiO_2 < 200 for > 8 h while receiving oxygen by high-flow mask	$PaCO_2$ > 45 mmHg; need for emergency ETI; standard contraindications for NIV (Table 1); severe traumatic brain injury	Epidural analgesia	Intubation rate Hospital length of stay, Survival

CPAP: Continuous positive airway pressure; CPPV: Continuous positive pressure ventilation; ICU: Intensive care unit; NIV: Noninvasive ventilation; PCA: Patient controlled analgesia; IPPV: Intermittent positive pressure ventilation; CPR: Cardiopulmonary resuscitation; CMV: Continuous mandatory ventilation; IMV: Intermittent mandatory ventilation; PSSB: Pressure support on spontaneous breathing; ETI: Endotracheal intubation; GCS: Glasgow Coma Scale; MI: Myocardial infarction; PaO_2: Partial pressure of O_2 in arterial blood; FiO_2: Inspired oxygen fraction; $PaCO_2$: Partial pressure of CO_2 in arterial blood.

intensive care unit and consequently treated with NIV. Studies in the pediatric population were excluded. We included randomized controlled trials, as well as observational studies, cohort, case-control and case series from previously published systematic reviews and meta-analyses in our search using MEDLINE and EMBASE, from inception until June 2014. We limited our search to studies on humans and those that were published in English. Our selected keywords were: non-invasive ventilation, continuous positive airway pressure, and trauma. These were cross-referenced with the following search terms: flail chest, pulmonary contusion, chest injury, blunt chest trauma, acute lung injury and acute respiratory distress syndrome. The following discussion is a summary of the most significant studies from our search, depicting the use of noninvasive ventilation in the setting of posttraumatic respiratory failure. Table 2 is a summation of the pertinent randomized controlled studies described below.

In a study by Trinkle *et al*[11], the possibility that obligatory mechanical ventilation for flail chest was not necessary was first discussed. Their small retrospective review with well-matched cohorts showed that the obligatory ventilation group had a longer hospital stay, a higher mortality and a higher complication rate as compared to a pulmonary contusion (PC) group treated conservatively. In addition, the PC group averaged only 0.6 ventilator days, indicating that the conservative management was often successful.

Another study by Schweiger *et al*[28] compared IMV to continuous positive airway pressure (CPAP) in three groups of pigs: a control group, flail chest injury group and pulmonary contusion/flail chest injury group. The authors showed that the use of ten to fifteen centimeters of CPAP was beneficial over IMV alone for correcting alveolar closure thereby minimizing shunt fraction and improving compliance significantly. The need for IMV was significantly reduced after the application of CPAP in all animals with this effect being more pronounced in the pulmonary contusion/flail chest injury group as opposed to the isolated flail chest injury group.

Antonelli *et al*[29] performed a multicenter survey in 2001, and showed that patients with posttraumatic hypoxemic respiratory failure responded favorably to NIV, with only a moderate failure rate of eighteen percent. The benefit of NIV was attributed to early inclusion of patients with hypoxemia within forty eight hours after trauma, the high prevalence of lung contusions as major underlying cause of hypoxia, and the extended length of NIV use. The authors concluded that in severe thoracic trauma-related hypoxia, early and continuous application of NIV is an effective means

for reducing the need for intubation and shortening the length of intensive care unit stay.

Ferrer *et al*[30] carried out a multicenter randomized trial in a mixed population of patients with acute hypoxemic respiratory failure. The authors compared the efficacy of NIV versus breathing with a conventional Venturi oxygen mask at a maximal concentration to avoid intubation and to improve survival. Patients with hypercapnia were excluded. Six patients with thoracic trauma were enrolled in the NIV group *vs* twelve in the control group. Only one out of six patients in the NIV group required endotracheal intubation *vs* five out of twelve patients in the control group. No mortality in the intensive care unit was observed in the NIV group as compared to three deaths in the conventional treatment group. Despite the small sample size, the authors did observe a nonsignificant trend in reduction of the intubation rate in patients with thoracic trauma treated with NIV.

In a prospective study by Tanaka *et al*[31], the use of CPAP in fifty nine patients with flail chest injury was investigated. The patients in the study were compared to historical controls treated for respiratory failure primarily with mechanical ventilation and the groups were well matched in terms of extent of chest wall injury and overall injury severity. The CPAP group had a lower rate of pulmonary complications and a significantly lower rate of invasive mechanical ventilation use.

Two major randomized controlled trials depicting the use of continuous positive airway pressure in patients with severe chest trauma include one for the prevention and one for treatment of respiratory failure in patients without endotracheal intubation at the time of presentation.

Bolliger *et al*[32] randomly allocated patients with multiple rib fractures to two groups in a prevention trial: (1) a CPAP group (thirty six patients) with lumbar epidural buprenorphine or an intercostal nerve block with bupivacaine; and (2) an endotracheal intubation and ventilation group (thirty three patients) with systemic morphine analgesia. Patients included in the study had all of the following: hospital admission within twenty four hours of injury; more than three rib fractures; and insufficient cough mechanism due to pain or pre-existing lung disease. As before, the use of CPAP was compared to intubation and mechanical ventilation. Although the group receiving noninvasive ventilation had a shorter length of stay in the intensive care unit and in hospital, the design of the study was flawed. It did not reflect current clinical practice since endotracheal intubation is not usually used prophylactically for patients similar to those as in this control group. Furthermore one of the exclusion criteria was severe lung contusion. Since no computed tomography chest images had been obtained, it is likely that patients with multiple rib fractures had underlying pulmonary contusion not detected by plain chest radiographs. On the whole, the two groups were similar at the five percent significance level except for injury severity score which was higher in the intubated group. The authors justified that this was due to the greater number of blunt abdominal injuries in the intubated group, and that the abdominal injuries were considered less severe than the chest injuries in both groups. It was deemed that the difference was not clinically significant.

Gunduz *et al*[33] executed a randomized comparison of mask CPAP to intermittent positive pressure ventilation *via* endotracheal intubation in fifty two patients in a treatment study. The results showed that CPAP led to a lower mortality (20% *vs* 33%, $P < 0.01$) and nosocomial infection rate (18% *vs* 48%, $P = 0.001$). However, a difference in the length of intensive care unit stay could not be demonstrated and the small number of patients enrolled as well as single-centre design raised concerns regarding generalizability.

Hernandez *et al*[34] investigated chest trauma-related hypoxemia and randomized patients to remain on high-flow oxygen mask (twenty five patients) or to receive NIV (twenty five patients) using bi-level positive airway pressure (BiPAP; Respironics Inc.; Murrysville, PA). Patients on oxygen by high-flow mask within the first forty eight hours after thoracic trauma with PaO_2/FiO_2 ratio less than or equal to two hundred for more than or equal to eight hours were included. The primary end point was intubation and secondary end points length of hospital stay and survival. The protocol utilized for the usage of bi-level positive airway pressure was well outlined, and the intubation criteria were similarly acceptably defined. The study findings showed that the Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ) score was higher in the NIV group ($P = 0.02$). It was nonetheless discontinued early due to a significant difference in the intubation rate, in terms of less frequent intubations ($P = 0.02$) and later intubations ($P < 0.01$) in the NIV group. It is therefore evident from the above discussion, that despite the application of NIV over last last several decades, there are still insufficient randomized control studies that support its use in trauma patients who have or are at risk for acute respiratory distress or failure.

APPLICATION OF NIV AS A VENTILATION STRATEGY

The diversity of the injuries to the trauma population means that they are especially at high risk of developing ALI/ARDS[35] and though the management of decreased alveolar ventilation is usually straightforward and is less challenging than that of posttraumatic ALI/ARDS, delayed or inappropriate management may still precipitate

complications.

One of the most important factors contributing to the development of posttraumatic pulmonary complications is atelectasis. Atelectasis causes ventilation-perfusion mismatch and hypoxemia refractory to supplemental oxygen when compensatory mechanisms such as hypoxic pulmonary vasoconstriction become insufficient. The pulmonary and extra-pulmonary damage can potentially lead to increased morbidity and mortality[36]. Atelectasis also interferes with the clearance of bacteria, such as Streptococcus pneumonia, Staphylococcus aureus and Klebsiella pneumoniae, which are frequent pathogens in early posttraumatic pneumonia[37,38]. Such a deleterious interaction together with the cyclic recruitment and derecruitment of lung units within atelectatic regions, partly explains why injured patients who frequently present with substantial atelectasis are so prone to develop early nosocomial pneumonia[39,40].

The identification of patients who should be managed with NIV is challenging, partly because there are few reliable selection criteria. According to the British Thoracic Society guidelines[7] and the findings of various studies discussed previously, a prudent approach is suggested, and it seems sensible to exclude patients who have multiorgan dysfunction or are poor candidates for NIV by virtue of inability to cooperate or protect the airway or because of excessive secretions (Table 1) . NIV should clearly be avoided in patients with shock, severe hypoxemia, or acidosis. A furtherissue is to agree on a threshold of severity for hypoxemia and acidosis beyond which NIV should be considered as being contraindicated. There are no clear recommendations on this dilemma, and the application of NIV in such patients with postraumatic ALI/ARDS should be limited to those that are mostly hemodynamically stable or alternatively who can be closely monitored in the intensive care unit, where endotracheal intubation would be promptly available.

The application of optimal levels of NIV can improve oxygenation, relieve dyspnea and dramatically reduce inspiratory muscle effort since patients with posttraumatic ALI/ARDS have diffuse alveolar damage and represent those with the most severe form of hypoxemic respiratory failure[41]. One has to balance NIV to improve oxygenation on the one hand and increase the pressure support above the CPAP to augment the tidal volume on the other. The clinical endpoints of all these effects are in the diminution of intubation rates.

A reasonable approach would be to use NIV judiciously in trauma patients. Although the optimal duration of the initial NIV trial remains uncertain, a reasonable expectation would be a response within 1 to 4 h of therapy initiation. Patients who are failing an NIV trial should be promptly intubated and mechanically ventilated as any delays in endotracheal intubation in patients managed with NIV have been associated with decreased survival[42].

An early conversion to more invasive mechanical ventilation is supported by the finding that the longer atelectasis is tolerated, the higher the transpulmonary pressures required to reinflate them will be. Furthermore, oxygenation goals accepted in some patient populations may not be acceptable in the trauma patient population. Hypoxemia on admission is an independent predictor of poor outcome in these patients which is in contrast to the results of the ARDS Network data. Thus tolerating borderline arterial oxygen tension values such as 55 mmHg can pose a serious threat to patients with cerebral injuries and intracranial hypertension or patients at risk of significant bleeding[43].

It has been shown that many of these patients deteriorate rapidly on the second or third posttraumatic day, and thus intubation and mechanical ventilation become necessary to ensure adequate oxygenation. This protracted respiratory decompensation corresponds to descriptions of the lateronset ALI/ARDS in trauma victims demonstrating how the coexistence of several predisposing factors may culminate in respiratory failure[19,44]. Early aggressive mechanical ventilatory support to prevent worsening of arterial oxygenation and progressive atelectasis is therefore recommended by several authors[12]. Controlled or assisted ventilatory modes can be chosen if patients need to be intubated and ventilated invasively. Putensen *et al*[45] described another concept focused on the maintenance of spontaneous breathing stating that diaphragmatic contractions will recruit dependent atelectatic lung regions and in so doing improve both the distribution of ventilation and ventilation-perfusion matching.

In conclusion, despite the heterogeneity of the studies on NIV for the treatment of respiratory failure associated with trauma and the scarcity of available randomized control data, recently published systematic reviews and meta-analysis[26,27] suggest that NIV could be useful in this setting. It can potentially be associated with a significant reduction in the incidence of overall complications, endotracheal intubation rate, length of intensive care unit stay and mortality. Therefore, the role of NIV in managing respiratory insufficiency associated with trauma may become significant if applied to the properly selected patient at an earlier stage of lung injury by appropriately trained and experienced personnel.

CONCLUSION

The use of NIV is widely recognized as a suitable way to avoid intubation and its associated complications and side effects. NIV allows increased flexibility in the application and discontinuation of ventilator assistance and preserves airway defense

mechanisms as well as speech and swallowing. Ventilatory management in the trauma population however is more challenging because of the difficulty in achieving a balance between the avoidance of further harm to the lungs and sufficient ventilation. Guidelines for the use of NIV in patients with trauma recommend continuous positive airway pressure in those patients who remain hypoxic despite regional anesthesia[7]. This recommendation is currently rated as low grade, mostly due to the lack of randomized controlled trials in this specific patient population[6,7]. Given the disappointing results of various trials and meta-analyses[8], selection of appropriate patients is crucial for optimizing NIV success rates and resource utilization. Extensive application of NIV in trauma-associated ALI/ARDS may otherwise be challenging. Thus, although it has become part of routine care for many patients with acute respiratory failure, implementing NIV for some of them may prove inadequate and may simply prolong the time to an inevitable endotracheal intubation. Close monitoring of its efficacy is therefore mandatory as delaying the time to endotracheal intubation often leads to further respiratory instability. Consequently, patients who do not respond to NIV are burdened by an increased mortality risk when intubation is delayed. The proper identification of patients who are likely to benefit from NIV and simultaneously avoiding the potential complications of a delayed endotracheal intubation remains a challenging issue.

Clinical trials are starting to appear, potentially signaling a reduction in mortality and pulmonary infections based on the less frequent intubations. More research is nonetheless required to determine the role of NIV in respiratory dysfunction stratification with the appropriate inclusion and exclusion criteria. The use of NIV represents one of the goals in investigating the role of ventilatory support to improve outcomes in trauma victims.

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MINIREVIEWS

Checklist for early recognition and treatment of acute illness: International collaboration to improve critical care practice

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Abstract

Processes to ensure world-wide best-practice for critical care delivery is likely to minimize preventable death, disability and costly complications for any healthcare system's sickest patients, but no large-scale efforts have so far been undertaken towards these goals. The advances in medical informatics and human factors engineering have provided possibility for novel and user-friendly clinical decision support tools that can be applied in a complex and busy hospital setting. To facilitate timely and accurate best-practice delivery in critically ill patients international group of intensive care unit (ICU) physicians and researchers developed a simple decision support tool: Checklist for Early Recognition and Treatment of Acute Illness (CERTAIN). The tool has been refined and tested in high fidelity simulated clinical environment and has been shown to improve performance of clinical providers faced with simulated emergencies. The aim of this international educational intervention is to implement CERTAIN into clinical practice in hospital settings with variable resources (included those in low income countries) and evaluate the impact of the tool on the care processes and patient outcomes. To accomplish our aims, CERTAIN will be uniformly available on either mobile or fixed computing devices (as well as a backup paper version) and applied in a standardized manner in the ICUs of diverse hospitals. To ensure the effectiveness of the proposed intervention, access to CERTAIN is coupled with structured training of bedside ICU providers.

Key words: Decision support systems; Critical care; Education; Checklists; Medical informatics

Core tip: Important barriers including limited access to educational resources, geographical distance, cost and lack of efficient global infrastructure greatly limit the feasibility of on site educational interventions. To overcome these barriers the international group of

intensive care unit (ICU) physicians and researchers developed a simple decision support tool: Checklist for Early Recognition and Treatment of Acute Illness (CERTAIN). CERTAIN is a systematic approach to error prevention with the use of checklists and electronic decision support algorithms. The effectiveness of CERTAIN to improve outcomes and reduce costs will be tested in a stepped wedge cluster before-after trial in ICUs with variable resources across five continents.

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INTRODUCTION

Incomplete knowledge of best practices by front-line health care providers and delayed, error-prone delivery processes can offset the potential benefits of critical care support. This is particularly important early in the course of critical illness, when errors and delays in appropriate care often lead to costly complications and poor outcomes, even in advanced hospitals[1,2]. Three major barriers prevent adequate delivery of care for critically ill patients: (1) provider (rather than patient)-oriented care delivery; (2) lack of access to standardized decision support; and (3) lack of an efficient global infrastructure. To overcome these barriers there is a need for standardized approach to evaluation and treatment of critically ill patients[3,4]. The systematic approach to error prevention with the use of checklists has been proposed to improve patient safety in surgical settings and in intensive care units (ICUs) in developed countries with encouraging results[5-9]. The expected benefit from a checklist approach to quality improvement process in various hospital settings including low-and middle-income countries is likely to be high. Indeed, the impact of surgical safety checklist was even more pronounced in the low-income country hospitals[5,10]. Our recent survey on critical care practices in resource limited settings showed that majority of these ICUs do not use any kind of checklist for acute resuscitation or rounding[11]. To address the third barrier, there is a need to establish an efficient interdisciplinary collaboration and robust infrastructure.

The advances in medical informatics and human factors engineering have provided possibility for novel and user friendly clinical decision support (CDS) tools that can be applied in a complex and busy hospital setting[12-14]. To facilitate timely and improved best-practice delivery and a reduction in preventable death and complications in critically ill patients compared to current practice international group of ICU physician and researchers developed a simple electronic decision support tool: Checklist for Early Recognition and Treatment of Acute Illness (CERTAIN)[15,16]. The central hypothesis is that health care provider access and training in CERTAIN will facilitate timely and accurate best-practice delivery and improve outcomes of critically ill patients.

OVERVIEW OF STUDY DESIGN

The Primary Objectives of the CERTAIN Study are: (1) to iteratively refine electronic decision support tool (CERTAIN); and (2) to implement CERTAIN into clinical practice in variable hospital settings and evaluate the impact of the tool on the care processes and patient outcomes.

The Secondary objective is to implement CERTAIN into educational settings as an interactive electronic educational tool.

The key outcomes of interest are related to better care, and better health at a lower cost (see below).

To ensure the effectiveness of the proposed intervention, access to the easy to use electronic checklist/decision support (CERTAIN) will be coupled with structured training of bedside ICU providers. CERTAIN will be uniformly available on either mobile or fixed computing devices (as well as a backup paper version). The proposed project consists of two phases.

PHASE 1 (TOOL REFINEMENT)

Description of the novel technology

CERTAIN is a web-based decision support tool displaying relevant clinical information incorporated with the knowledge about evidence-based best clinical practices, which are organized according to a systematic review of end user data needs and ergonomic workflow[17].

CERTAIN is a web based application suite hosting in a secured Platform as a Service (PaaS) environment with on-demanding scalability up to multiple Linux servers. Current main version graphical user interface (GUI) is developed by using Adobe ActionScript 3 which could be viewed through any web browser including flash player either from regular computer (desktop/laptop) or from mobile devices (tablet pc, smartphone). A mobile app version which is developed by HTML5 is also provided as a complementary part to extend CERTAIN availability and better user experience on the mobile device. A backup paper version is available in a case of problems with internet connection.

CERTAIN modules

CERTAIN consists of two modules, stabilization (admission/resuscitation) module [CERTAIN evaluation of life threatening emergencies (ELITE)] and

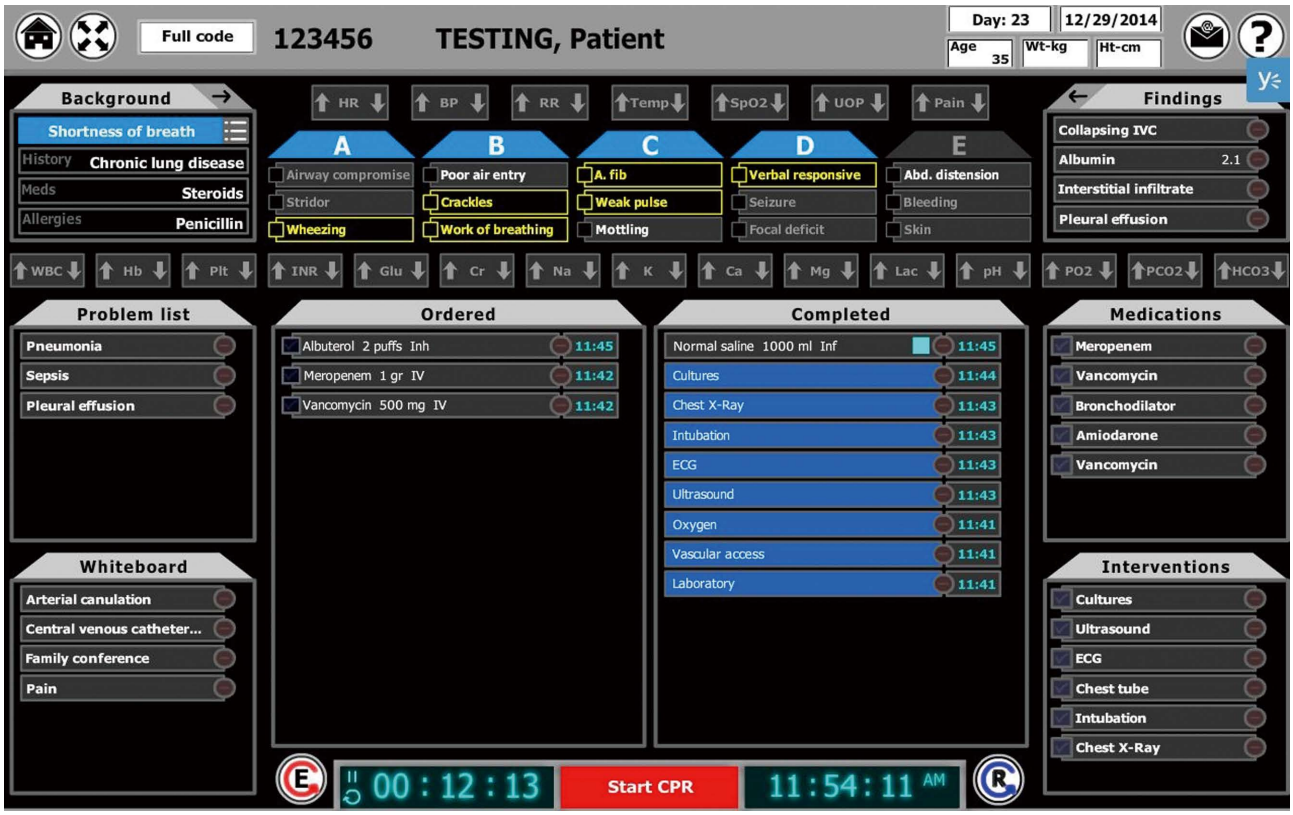

Figure 1 CERTAIN-ELITE (Evaluation of Life Threatening Emergencies) admission/resuscitation module. CERTAIN: Checklist for Early Recognition and Treatment of Acute Illness; ELITE: Evaluation of life threatening emergencies.

rounding module (CERTAIN Rounds), to help the clinicians with the routine recommended care processes which need to be assessed daily for every patient.

Stabilization (Admission/resuscitation) module

CERTAIN-ELITE (Figure 1) is designed as an electronic choreography for evaluation of life-threatening emergencies with embedded timer, checklist and decision support cards to facilitate error-free care of acutely deteriorating patient (ICU admission and subsequent emergencies).

In CERTAIN data elements are organized by considering how experts incorporate information into decision making mental models. Reading from up to bottom organizational elements are (1) primary (ABCDE) survey; and (2) secondary patient survey, and from left to right the key organizational elements are: (1) clinical context -reason for admission/patient problem list; (2) provider actions tracked in the status central panel; and (3) proposed medications and interventions.

Optimization (Rounding) module

CERTAIN Rounding module (Figure 2) is designed as a simple and efficient ICU rounding tool with embedded checklist and decision support cards to facilitate error-free day-to-day care in the ICU.

The key characteristics of CERTAIN are: (1) task specific, concept-oriented views of patient data -CERTAIN serves to organize appropriate data determined by a systematic review of end user data needs; (2) knowledge translation - evidence based checklists are incorporated; (3) collaborative workspace - real time plan of care with patient specific tasks, status checks and reminders which provide a location to communicate clearly the goals of care and their status to all members of the multidisciplinary team; (4) reports - scheduled and on demand unit/hospital level reports of quality metrics can be designed for local reporting; and (5) user interface - providers will interact with the system through secure fixed and mobile computer interfaces.

Supporting evidence base

Components of the evidence-informed ICU care practices incorporated in CERTAIN decision support cards are informed by a systematic, comprehensive search for published guidelines, clinical trials and cohort studies in multiple databases such as Medline, EMBASE, National Guideline Clearing House, and Cochrane Library. The guidelines and clinical studies are critically appraised to identify practices with the best evidence.

Utility of CERTAIN has been evaluated in high fidelity clinical simulation setting and has been shown to improve performance of clinical providers faced with simulated emergencies. Among 18 providers

Figure 2 Rounding module with system based plan of care and rounding checklists.

there was 14% absolute reduction in omissions of critical tasks with CERTAIN. Most providers (72%) felt better prepared during an emergency scenario when using the CERTAIN model[18].

Following initial development and alpha testing at Mayo Clinic simulation center the tool has been further refined by: (1) web-based survey of decision support needs in an international convenience sample of critical care practitioners from various backgrounds and settings. By directly requesting acute care providers to rank the importance of guidelines and information detailed in literature (from high to low priority), we defined and developed a card template. The detailed description of the development of card template can be found elsewhere[19]; and (2) a decision support card was made for each clinical problem, medication or intervention and was then validated through a modified Delphi process by multidisciplinary, international European Society of Critical Care Medicine/American Thoracic Society/ The United States Critical Illness and Injury Trials Group (ESICM/ATS/USCIITG) (ESICM/ATS/USCIITG) expert panel. Once the card was validated, each card is assigned expiration date for ensuring up to date medical knowledge.

PHASE 2 IMPLEMENTATION OF CERTAIN

Participant recruitment and enrollment

Settings: Following IRB approval the effectiveness of CERTAIN to improve outcomes and reduce costs will be tested in a stepped wedge cluster before-after trial of a total of 25-40 ICUs in hospitals with variable resources from five continents (Asia, Africa, Europe, America, Australia) (Figure 3). Total of 12000-15000 patients will be included in the study (Figure 4).

Study subjects: All adult (≥ 18 years) patients admitted for the first time to the participating ICUs will be included.

Not critically Ill, admitted for low risk monitoring, planned ICU admissions for routine postoperative surveillance for less than 24 h after uncomplicated surgery, readmission and transferred from outside ICU.

Data collection for outcome assessment: The pre-implementation phase consists of 3 mo full dataset, prospectively and 9 previous months of minimal outcome data, retrospectively baseline data collection (up to 250 patients per ICU). Data collection will include epidemiological data and daily assessment of processes of care, organ function and support. Length of ICU and hospital stay and outcome will be collected. The site research coordinators are instructed in the study protocol, outcome measures, and data collection process as soon as IRB approval is obtained.

Following pre-implementation phase and prior to the clinical implementation and testing, local champions resuscitation skills will be evaluated by

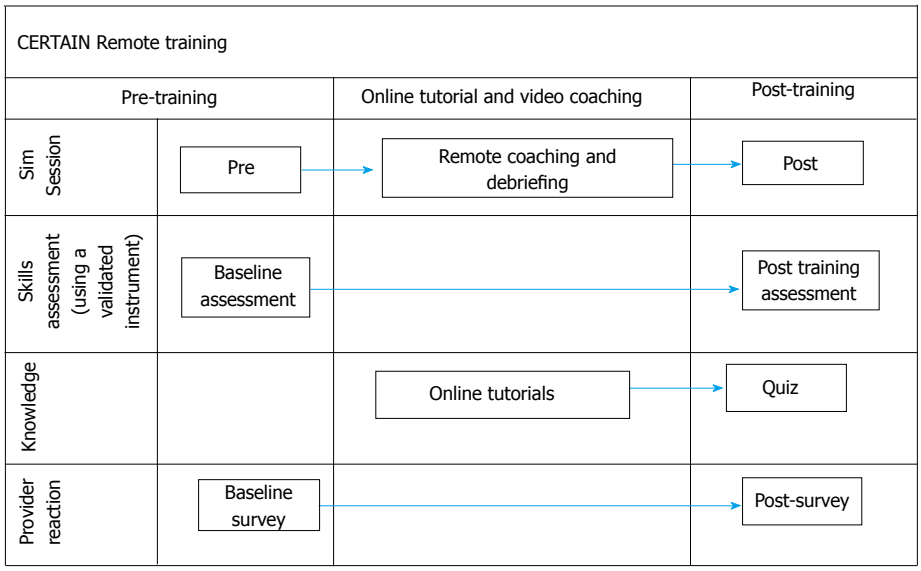

Figure 3 CERTAIN remote simulation training flow. CERTAIN: Checklist for Early Recognition and Treatment of Acute Illness.

remote online video simulation assessment (in a simulated acute care environment of all participating centers) (Figure 3). Each center has a baseline assesment with three physicians (Implementation team) who are given three admission and one rounding scenarios. Following baseline session, the participating centers will be given access to online CERTAIN tool and training materials. After 2-4 wk a follow up training session is performed during which we will test competency of the participants to use the CERTAIN tool. Again, the physicians are given 3 admission and one rounding scenario similar to the baseline session, but this time the physicians will use CERTAIN during all scenarios. These practice scenarios will be followed with remote debriefing to provide structured feedback to enhance learning experience. Following successful second skill assessment, the Implementation team will be certified and use the similar simulation procedure on site to train local staff with local languages. Once local physicians and nurses complete the training program the participating center will have a permission to proceed to clinical implementation and testing.

Bedside ICU providers (physicians and nurses) will be given access to and training in CERTAIN starting with the single ICU bed in a PILOT ICU with subsequent expansion to the whole unit followed by the step-wedge implementation in a similar manner across international ICUs. The participating site clinicians will be trained in the use of CERTAIN by the local Implementation teams. During the process, adoption feedback and suggestion will be collected by design team and make necessary customization for local hospitals. The local implementation experience will also be shared with whole CERTAIN investigators to facilitate subsequent implementation efforts in other centers.

Data collection on outcomes measures and compliance with each element of best practices will be done daily during the control period by trained research coordinators. It consists of 6 mo full dataset, and 6 more months of minimal outcome data; up to 250 patients per ICU. After implementation of CERTAIN during the post-intervention period, enrollment tracking, data cleaning, outcome assignment, outcome validation, and outcome tracking will be performed electronically. The site research coordinators will be trained in the study protocol, outcome measures, and data collection process *via* webinars conducted by the Outcomes group.

OUTCOME ASSESSMENT

We will track relevant outcomes to demonstrate better care, better health and lower costs in the objectives as outlined below: (1) with regards to better care: we expect to see an improvement in the processes of care, safety culture and patient and family satisfaction. Specifically we will measure: Compliance with timely and adequate antimicrobial therapy; Compliance with ventilator bundle (DVT prophylaxis, GI prophylaxis, sedation holidays, assessment of readiness to extubate); Compliance with lung-protective mechanical ventilation; Conservative blood product usage; (2) better health: we will examine the health outcomes of patients in a number of ways. Measures include: ICU, hospital and 28 d mortality, and discharge disposition (home *vs* other institution); and (3) lower costs - Resource utilization: ICU and hospital length of stay.

CONFIDENTIALITY OF SUBJECTS' DATA AND DATA SECURITY

All the cloud servers and database services used in CERTAIN project are secured by adopting Server

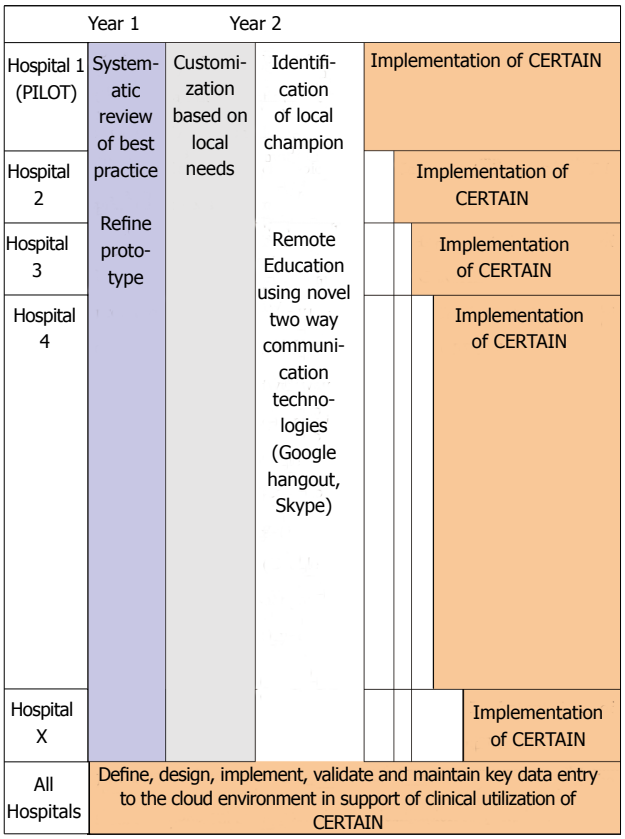

Figure 4 Overview of the proposed intervention. CERTAIN: Checklist for Early Recognition and Treatment of Acute Illness.

Name Indication (SNI) based Secure Sockets Layer (SSL) protocol. Every request to the server required to be authenticated by our SSL certificate. The data stored in the Database are encrypted based on security requirements and every hospital has its own separated logical space. Data backup is also planned and implemented by setting up scheduled jobs in the server side.

Each study subject will be assigned a unique study identification number linked to his or her medical record number at the respective home site. We will use existing procedures to ensure that individual patient identifiers are kept separate from analysis files and are available only to project personnel on a need-to-know basis. All identified patient data necessary to complete this research will be created and stored in secure computers to which only project team members will have access. Only project personnel directly involved in the study will have access to identified patient data and medical charts at their respective site. All project personnel with access to patient data will be trained in the proper handling of such data.

LIMITATIONS

Restricted availability of some medications and equipment in resource-limited settings may preclude delivery of best care practices and limit generalizibility of the study results. Nevertheless, we expect to see improvement in all proposed outcomes with the implementation of the CERTAIN tool. We overcame possible lack of internet access by providing paper version of the tool.

CONCLUSION

CERTAIN initiative directly addresses the major barriers to the consistent and timely delivery of error-free, evidence-informed clinical care to critically ill patients by: (1) organizing clinical information into vital components specific to the patient's condition and task at hand; (2) incorporating centralized CDS tools informed by evidence-based guidelines that are both patient and context appropriate to ensure that interventions are implemented at the right time for the right patients for the right conditions; (3) coupling the intervention with an interactive educational initiative to decrease the gap between knowledge and translation to clinical practice; and (4) providing centralized, timely and regular compliance and quality metrics feedback and auditing to empower institutions to implement and enact change. By providing ready solutions for major barriers - lack of collaboration, early recognition, prompting and support tools - we propose to be able to increase access to critical care knowledge at the point of care thereby minimizing diagnostic error, therapeutic harm and resulting preventable death, disability and cost.

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MINIREVIEWS

Has Stewart approach improved our ability to diagnose acid-base disorders in critically ill patients?

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Abstract

The Stewart approach-the application of basic physical-chemical principles of aqueous solutions to blood-is an appealing method for analyzing acid-base disorders. These principles mainly dictate that pH is determined by three independent variables, which change primarily and independently of one other. In blood plasma in vivo these variables are: (1) the PCO_2; (2) the strong ion difference (SID)-the difference between the sums of all the strong (*i.e.*, fully dissociated, chemically nonreacting) cations and all the strong anions; and (3) the nonvolatile weak acids (A_{tot}). Accordingly, the pH and the bicarbonate levels (dependent variables) are only altered when one or more of the independent variables change. Moreover, the source of H^+ is the dissociation of water to maintain electroneutrality when the independent variables are modified. The basic principles of the Stewart approach in blood, however, have been challenged in different ways. First, the presumed independent variables are actually interdependent as occurs in situations such as: (1) the Hamburger effect (a chloride shift when CO_2 is added to venous blood from the tissues); (2) the loss of Donnan equilibrium (a chloride shift from the interstitium to the intravascular compartment to balance the decrease of A_{tot} secondary to capillary leak; and (3) the compensatory response to a primary disturbance in either independent variable. Second, the concept of water dissociation in response to changes in SID is controversial and lacks experimental evidence. In addition, the Stewart approach is not better than the conventional method for understanding acid-base disorders such as hyperchloremic metabolic acidosis secondary to a chloride-rich-fluid load. Finally, several attempts were performed to demonstrate the clinical superiority of the Stewart approach. These studies, however, have severe methodological drawbacks. In contrast, the largest study on this issue indicated the interchangeability of the Stewart and conventional methods. Although the introduction of the Stewart approach was a new insight into acid-base physiology, the method has not significantly improved our ability to understand, diagnose, and treat acid-base alterations in critically ill patients.

Key words: Acid-base metabolism; Stewart approach; Base excess; Bicarbonate; Anion gap; Strong ion difference; Strong ion gap

Core tip: In this article, we comprehensively reviewed

the evidence that has been used to argue for the superiority of the Stewart approach over the traditional method for the analysis of acid-base metabolism in critically ill patients. The basic principles of the Stewart approach have severe weaknesses. In addition, the contribution of this method to the understanding of mechanisms is minor; furthermore, from a clinical standpoint, the Stewart approach has no advantage for diagnostic or prognostic purposes compared to the analysis based on bicarbonate, base excess, and albumin-corrected anion gap.

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INTRODUCTION

Acid-base disorders are usually found in critically ill patients. Thus, the understanding and identification of these derangements is crucial to the practice of critical-care medicine. Without a doubt, the Stewart approach is an appealing method to analyze acid-base metabolism. The so-called quantitative physicochemical approach has triggered opposing opinions that seem to be related more to passion than to science. The Stewart approach was conceived as a method to revolutionize our ability to understand, predict, and control what happens to hydrogen ions in living systems[1], whereas the method has instead been characterized as absurd and anachronistic[2].

The goal of this review is to comprehensively discuss the evidence supporting the conclusion that the Stewart approach, although innovative and attractive, does not significantly contribute to the diagnosis of acid-base abnormalities in critically ill patients.

APPROACHES TO ACID-BASE METABOLISM: THE TRADITIONAL AND THE STEWART APPROACHES

Acid-base disorders can conceivably be described by different methods: First, by a traditional approach, in which the metabolic component of acid-base physiology is based on the analysis of plasma concentrations of bicarbonate (HCO_3^-)[3]. This basis be further completed with the use of base excess (BE)[4]. Despite considerable argument over which parameter is better[5-9], both are usually employed in clinical practice, and all blood-gas analyzers include both calculations. Anion gap (AG) constitutes

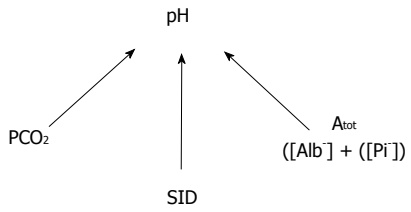

Figure 1 Independent determinants of pH according to the Stewart approach.

an additional diagnostic contribution[10], though hypoalbuminemia might preclude its usefulness. For this reason, many researchers have recommended to adjust AG to the albumin level ($AG_{corrected}$)[11-16].

An alternative approach is the application of basic physical-chemical principles of aqueous solutions to blood[1]. Some of the bases of this so-called Stewart approach are: (1) the protons of medium come from dissociation of the water to maintain electroneutrality; (2) the pH is determined by three parameters called "independent variables" because they change primarily and independently of each other (Figure 1). In blood plasma *in vivo* these variables are: (a) the PCO_2; (b) the "strong ion difference" (SID), *i.e.*, the difference between the sums of all the strong (fully dissociated, chemically nonreacting) cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) and all the strong anions (Cl^- plus other strong anions such as ketones and lactate); (c) the concentrations of nonvolatile weak acids (A_{tot}), that is, the sum of their dissociated and undissociated forms. Accordingly, neither the pH nor the bicarbonate (dependent variables) can be altered unless one or more of the independent variables change; and (3) The assessment of the metabolic component of acid-base physiology relies on the analysis of plasma SID and A_{tot}.

According to the Stewart approach, metabolic acidosis only occurs if the SID decreases or the A_{tot} increases. On the contrary, metabolic alkalosis develops only if the SID increases or the A_{tot} decreases.

In addition, the Stewart method allows the quantification of the magnitude of each acid-base disorder comparing actual values of the SID and the A_{tot} with normal reference values. Moreover, the approach also allows the computation of the effect of each individual component (Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, strong ion gap (SIG), albumin, and phosphate) on the SID and A_{tot}. The Stewart-approach supporters argue that the strength of the method lies in being essentially quantitative because the technique not only measures the magnitude of the deviation of all variables from the normal range but is also mechanistic, as it provides a clear idea of the causes of the acid-base disorders[1].

DRAWBACKS OF THE PRINCIPLES UNDERLYING THE STEWART APPROACH

Although the Stewart method constitutes an interesting analysis of acid-base metabolism, some of the underlying principles have been questioned:(1) Stewart stated that the protons of the environment come from the dissociation of the water. For example, low SID increases H^+ secondary to water dissociation. This concept, however, is controversial and lacks of experimental evidence; and (2) are the variables SID, PCO_2 and A_{tot} really independent of one another? An independent variable is defined as one that influences the system but is not influenced by the system. The term "system" here, refers to any single aqueous compartment (plasma, the interstitium, the intercellular, or cerebrospinal fluids). Within this scenario, PCO_2, A_{tot}, and SID fulfill the criteria for independent variables because those parameters directly influence the dissociation reactions that generate weak electrolytes, while they themselves are determined by distinctly separate control mechanisms[1]. The Stewart analysis, however, involves a single-compartment model and therefore does not take into account exchanges with red blood cells or with the interstitium as occurs when dealing with whole blood; the latter being considered as a tricompartmental model (intersititium, plasma, erythrocytes). In such a setting, PCO_2, SID and A_{tot} are not completely independent from each other[17-20], where this lack of independence is exemplified by the following situations: (1) PCO_2/SID interaction: The Hamburger effect or "chloride shift" is defined as the exchange between Cl^- and HCO_3^- caused by the addition to the venous plasma of CO_2 produced by the cellular metabolism[17-20]. In this condition, the increase in plasma PCO_2 and HCO_3^- is associated with the entrance of chloride in red blood cells, with the ensuing reduction in the plasma Cl^-. As a consequence of this process, the blood Cl^- becomes lower in the venous than in the arterial blood; (2) A_{tot}/SID: The loss of Donnan equilibrium describes the shift of chloride from the interstitium to the intravascular compartment. This change is produced in order to balance the decrease in A_{tot} secondary to an albumin transudation from the intravascular space in patients with capillary damage and thus an increased permeability[21]; and (3) the compensatory response to a primary disturbance in either independent variable: In these situations, an adjustment in other variables occurs. For example, hypercapnia causes an increased H^+, which is compensated by a decrease in Cl^-[22] along with an increase in the SID. On the other hand, the compensatory response to reduction in A_{tot} (hypoproteinemia) is a decrease in SID, secondary to an increase in Cl^-[23]. The net result of these complementary changes in these theoretically independent variables is an amelioration of the effect of the primary disorder on H^+.

In summary, contrary to the principles of Stewart approach, SID, PCO_2 and A_{tot} can be considered not completely independent from each other within certain particular settings (*e.g.*, blood plasma *in vivo*).

UNDERSTANDING THE MECHANISMS OF ACID-BASE ALTERATIONS

A relevant question has to do with an understanding of the mechanisms that underlie the development of hyperchloremic metabolic acidosis after fluid resuscitation with chloride-rich solutions. The traditional approach states that acidosis is caused by a dilution of plasma HCO_3^-[24-26]. This classical dilution concept regarding bicarbonate is rejected by the proponents of Stewart's approach, who highlight the mechanistic insight into acid-base physiology as the method's main strength and principal advantage over the traditional model. Therefore, the Stewart approach provides a "strong-ion"-based explanation for the mechanism of dilutional acidosis. They argue that dilutional acidosis is explained by a decrease in the SID[1,27-31].

This issue has been comprehensively studied by other researchers[32,33]. Based on simulations of dilution studies along with *in vitro* experiments, they tried to clarify the chemical mechanism responsible for dilutional acidosis. Consequently, they examined the effects of diluting normal extracellular fluid with different solutions both in a closed system (*i.e.*, a system not exchanging matter with the environment, such as venous blood before reaching the lung) and in a system open to gases (*i.e.*, one capable of equilibrating with the PCO_2). They observed that dilution of extracellular fluid did not lead to any detectable change in the H^+ when the system was closed. The explanation was that all the determinants of the H^+, SID, PCO_2 and A_{tot} were equally diluted so that their relative proportions did not change. In actuality, the decrease in the SID (leading to acidosis) was exactly balanced by the decrease in the CO_2 content and noncarbonic buffers (leading to alkalosis). As a consequence, the pH did not change. On the contrary, acidosis was only found when the system was open to the gases with normal PCO_2 (40 mmHg). In this situation, the CO_2 entered into the system because of the differing tensions between the gas phase and the diluted solution until the PCO_2 was equilibrated. Therefore, the excess of protons observed in this dilutional acidosis came from CO_2 hydration to carbonic acid (Figure 2). In other words, the chemical mechanism of the dilutional acidosis in blood plasma involves the dilution of an open CO_2/HCO_3^- buffer system, where the buffer base (*i.e.*, the HCO_3^-) is diluted but not the buffer acid (the CO_2).

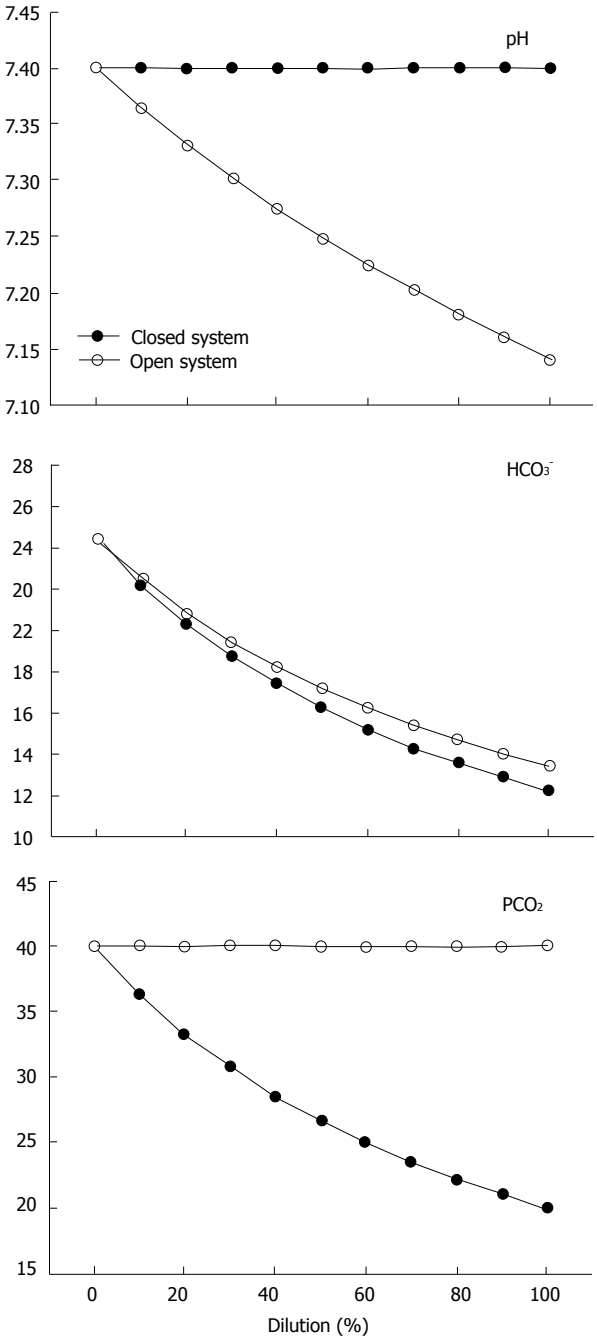

Figure 2 Behavior of pH (top), HCO_3^- (middle) and PCO_2 (bottom) in a closed system (black dots) and in an open system with a PCO_2 of 40 mmHg (withe dots), during stepwise dilution with 0.9% NaCl, as modified from Gattinoni *et al*[32].

Stated in brief, the Stewart and the traditional approaches may account for these results[32,33]: (1) according to Stewart's approach, since the SID and the A_{tot} remain unchanged after opening the system to gases, the only determinant of the decrease in the pH is the increase in PCO_2 or, more precisely, the increase in CO_2 content. Therefore, the change in the SID - it being merely a mathematical construct - is not the cause of dilutional acidosis, but rather a marker for the dilutional process. In addition, the increase in water dissociation is not the chemical mechanism of dilutional acidosis, and consequently the Stewart approach does not provide any mechanistic insight into acid-base disorders[33]; and (2) according to the traditional model, the acidosis is explained by the increase in the PCO_2 in the face of a dilution of the buffer's base.

CLINICAL USEFULNESS OF THE STEWART APPROACH IN CRITICALLY ILL PATIENTS

Although the principles of the Stewart approach have weaknesses and this method does not offer clear advantages for explaining mechanisms, several attempts have been made to show the superiority of that approach over conventional analysis in the diagnosis of acid-base alterations in critically ill patients.

The first question is if the SID is really different from the buffer base concentration (BB). The SID is actually equal to the buffer base described more than half a century ago. Consequently, the BE becomes the deviation of SID from its normal value. The SID and the BB are mirror images of each other[34].

Nevertheless, Fencl *et al*[35] studied a series of 152 critically ill patients and concluded that the Stewart approach allowed a detection and quantification of all the various individual components of even the most complex acid-base disturbances seen in critically ill patients[35]. In that study, the Stewart approach was able to detect metabolic acidosis in 20 patients with normal HCO_3^- and in 22 patients with normal BE. Low SID was unnoticed by changes in BE, because the low SID acidosis was masked by the alkalinizing effect of hypoalbuminemia. The $AG_{corrected}$, however, adequately identified all patients with elevated unmeasured anions. For this reason, a correct use of the traditional approach would have allowed a similar diagnosis. In addition, in normal volunteers, the SIG, the variable from the Stewart approach that quantifies unmeasured anions, was 8 mEq/L, which is an extremely high value. The expected values should have been close to zero. This finding suggests the presence of some methodological error.

In another study, Boniatti *et al*[36] concluded that their main result was the demonstration of a greater sensitivity on the part of physicochemical evaluation in identifying acid-base disorders in critically ill patients[36]. An evaluation according to the Stewart method allowed an additional diagnosis of a metabolic disorder in 34% of the cases, because of the greater sensitivity of the SID compared to BE. These results, however, might have been expected because of the methodological limitations of the study. The authors considered as normal BE values from -5 to 5 mmol/L, while the normal SID was arbitrarily defined as values from

Table 1 Examples of acid-base disorders

	Patient 1	Patient 2
Measured variables		
Sodium (mmol/L)	151	146
Potassium (mmol/L)	3.4	3.8
Calcium (mg/dL)	7.0	7.2
Magnesium (mmol/L)	2.0	1.8
Phosphate (mmol/L)	1.0	2.0
Albumin (g/L)	27.0	27.0
Chloride (mmol/L)	121	124
pH	7.48	7.43
$PaCO_2$ (mmHg)	29.0	30.2
Lactate (mmol/L)	2.0	1.3
Derived variables		
HCO_3^- (mmol/L)	21.5	20
BE (mmol/L)	-0.7	-3.8
AG (mmol/L)	12.4	6.3
SID (mmol/L)	29.9	28.8
SIG (mmol/L)	4.5	-1.4

BE: Base excess; AG: Anion gap; SID: Strong ion difference; SIG: Strong ion gap. Modified from Boniatti *et al*[36].

38 to 42 mmol/L. Consequently, the diagnosis of metabolic acidosis required a decrease in the BB of 5 mmol/L, when the BE was used as the criterion. In contrast, a reduction of only 2 mmol/L in BB identified the presence of metabolic acidosis when the SID was used. Therefore, the use of a more sensitive threshold for the diagnosis of metabolic acidosis by means of SID completely explained the results. This study has several other limitations - such as not measuring the arterial blood gases and electrolytes simultaneously, the negative values of SIG that were frequently found, the arbitrary choice of normal ranges, and the failure to evaluate the agreement between the acid-base variables of both approaches. Finally, the authors presented two cases to illustrate the diagnosis of metabolic acidosis by means of the Stewart approach (Table 1), but unfortunately those two were misinterpreted. Actually, the authors mistakenly chose patients with respiratory alkalosis instead of metabolic acidosis. The presence of the low SID was the result of the renal compensation for a respiratory alkalosis, which condition was the primary diagnosis of their cases, as indicated by the high pH and low PCO_2 values. As previously shown, the use of the Stewart approach, without consideration of the metabolic response to a primary respiratory disorder can lead to an incorrect diagnosis in 15% of the cases[37]. Indeed, the examples cited here adequately and definitively illustrate the very drawbacks of the Stewart approach, instead of its advantages.

Kaplan *et al*[38] performed a controlled study to show that the clinical use of the Stewart approach improved the accuracy of acid-base diagnosis and reduced the possibility of an inappropriate fluid loading. For this purpose, one-hundred consecutive trauma patients admitted to a surgical ICU were prospectively allocated to care by either one physician who was to use the Stewart approach or four other practitioners who would employ the conventional method. The diagnoses and interventions made by the "conventional physicians" were reviewed by the "Stewart physician". The results showed that the conventional approach missed a lot of diagnoses. Moreover, the acid-base balance normalized sooner (3.3 ± 3.4 d *vs* 8.3 ± 7.4 d) and fewer volume expansions were given through the use of Stewart approach. The ostensible conclusion was that the physician who used the Stewart approach more correctly diagnosed and treated the patients compared to the other four physicians who only utilized the conventional method. Nevertheless, the criteria used by these physicians were not presented in the study, and the Stewart physician himself determined what was right or wrong without any established definition. For example, 43 of the 50 patients treated by the physicians who used the traditional analysis were unnecessarily volume-expanded because of the presence of hyperchloremic metabolic acidosis. The Stewart approach, however, would not have been needed for that diagnosis. Consequently, the absence of a well-defined methodology precludes any conclusion from this trial.

Some studies have assessed SIG as a potential tool, not only for the measurement of anions but also as a surrogate of tissue hypoperfusion and a predictor of outcome. A theoretical advantage of SIG over AG is that the parameter remains stable and reliable, even in cases of extreme variations in the PCO_2 and pH[39].

Kaplan *et al*[40] studied the acid-base determinants of the outcome in trauma patients with major vascular injuries and concluded that SIG was a better predictor of mortality than AG[40]. Regrettably, these conclusions were not supported by the findings. The area under the ROC curve and the confidence intervals for SIG, BE and AG were quite similar. Therefore, these acid-base variables showed the same prognostic ability.

Other studies performed in pediatric critically ill patients came to similar conclusions[41,42]. The SIG was more strongly associated with mortality than traditional variables such as BE, AG, or lactate levels. Nevertheless, a proper evaluation of the unmeasured anions by the traditional method was not performed because the AG values were not corrected with respect to albumin levels.

A study by Funk *et al*[43] investigated the association between the SIG and the long-term outcome after cardiac arrest, in patients treated with therapeutic hypothermia[43]. The authors concluded that the SIG, measured 12 h after the return of spontaneous circulation, was an independent predictor of outcome. The AG and the SIG were strongly correlated, but the predictive capacity of the AG was not tested. Surprisingly, an editorial entitled

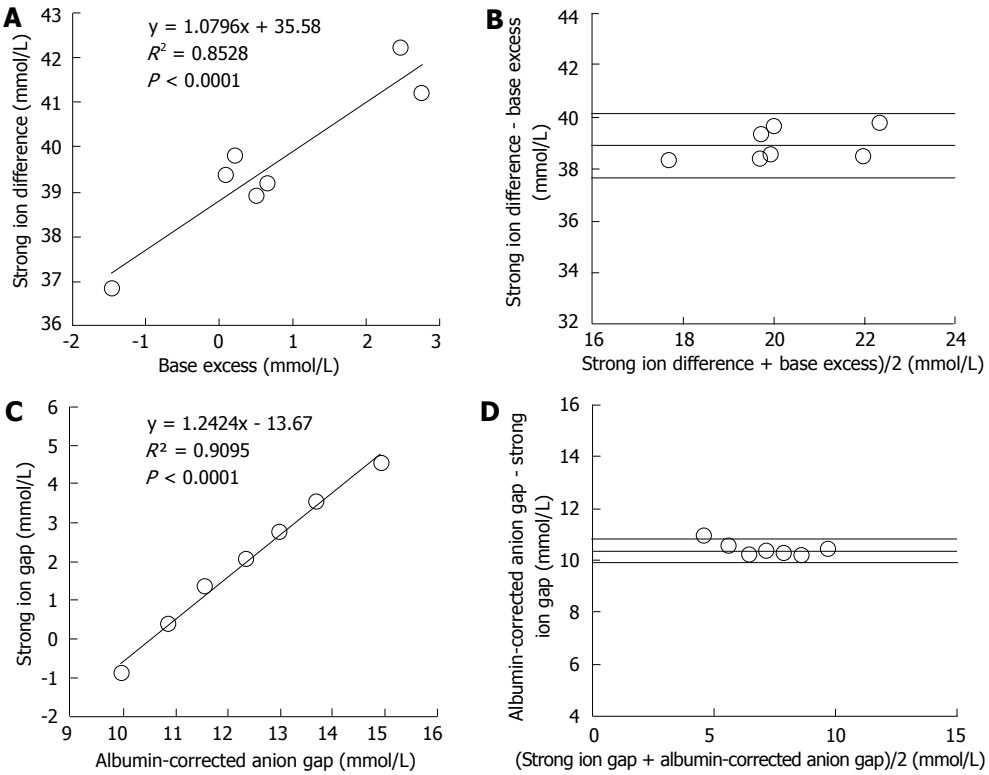

Figure 3 Regression and Bland and Altman analysis between metabolic parameters of different approaches in seven normal volunteers. A: Lineal regression between base excess and strong ion difference; B: Agreement between base excess and strong ion difference; C: Lineal regression between albumin-corrected anion gap and strong ion gap; D: Agreement between albumin-corrected anion gap and strong ion gap; Panel B and D display the relationship between the mean value and the difference of both measurements. The lines indicate the mean difference between both parameters (bias) ± 2 SD (95% limits of agreement). Modified from Dubin *et al*[37].

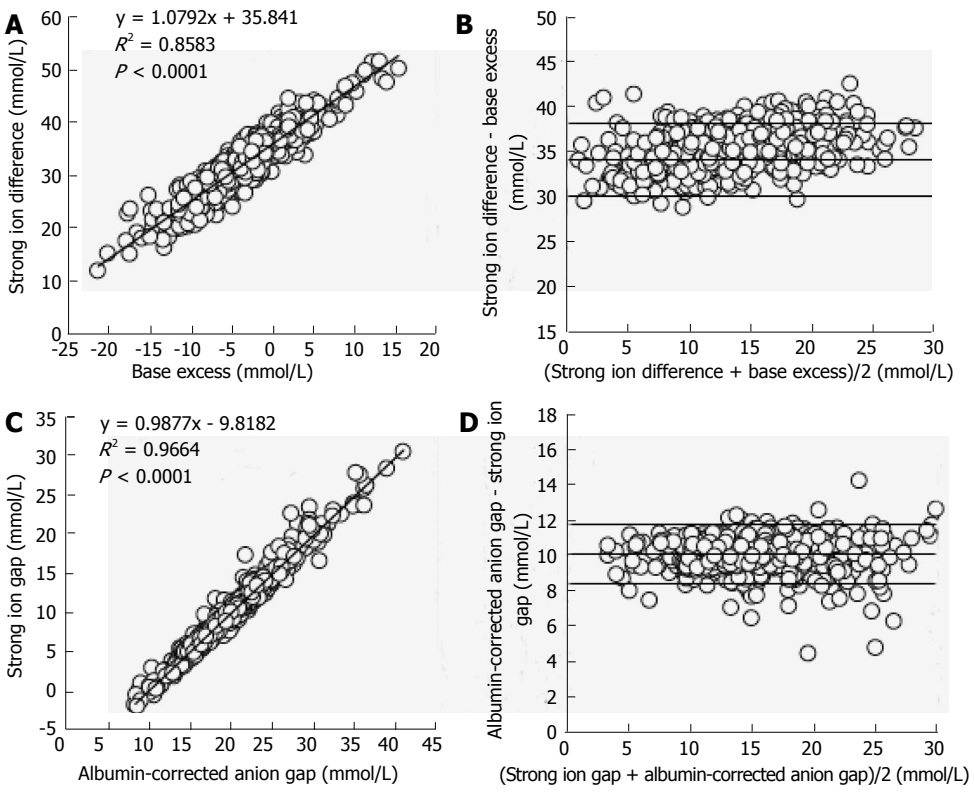

Figure 4 Regression and Bland and Altman analysis between metabolic parameters of different approaches in 935 critically ill patients. A: Lineal regression between base excess and strong ion difference; B: Agreement between base excess and strong ion difference; C: Lineal regression between albumin-corrected anion gap and strong ion gap; D: Agreement between albumin-corrected anion gap and strong ion gap. Panel B and D display the relationship between the mean value and the difference between both measurements. The lines indicate the mean difference between both parameters (bias) ± 2 SD (95% limits of agreement). Modified from Dubin *et al*[37].

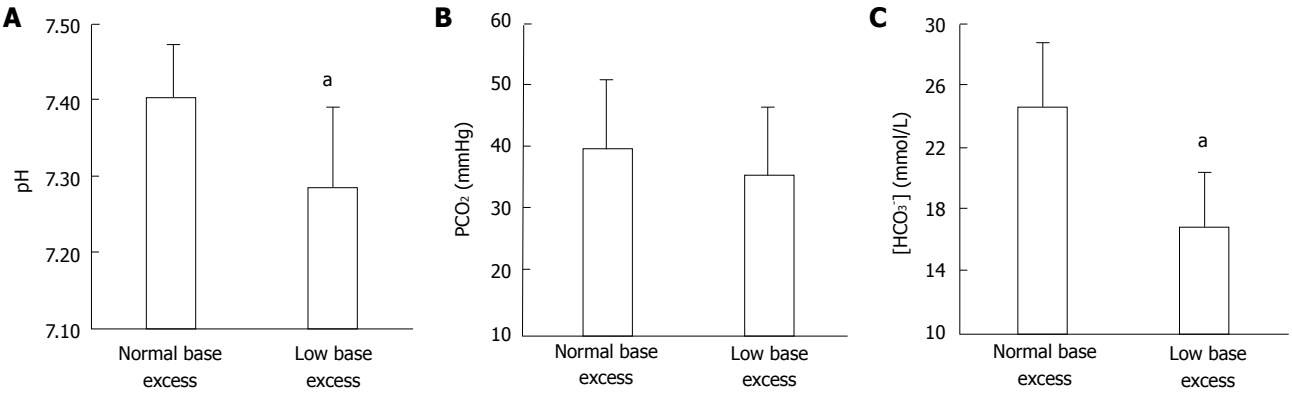

Figure 5 Arterial pH, and bicarbonate levels in patients with severe hyperlactatemia. Values for (A) arterial pH, (B) PCO_2, and (C) bicarbonate ($[HCO_3^-]$) in patients with severe hyperlactatemia, with normal or low base excess. $^aP < 0.05$ *vs* the other group.

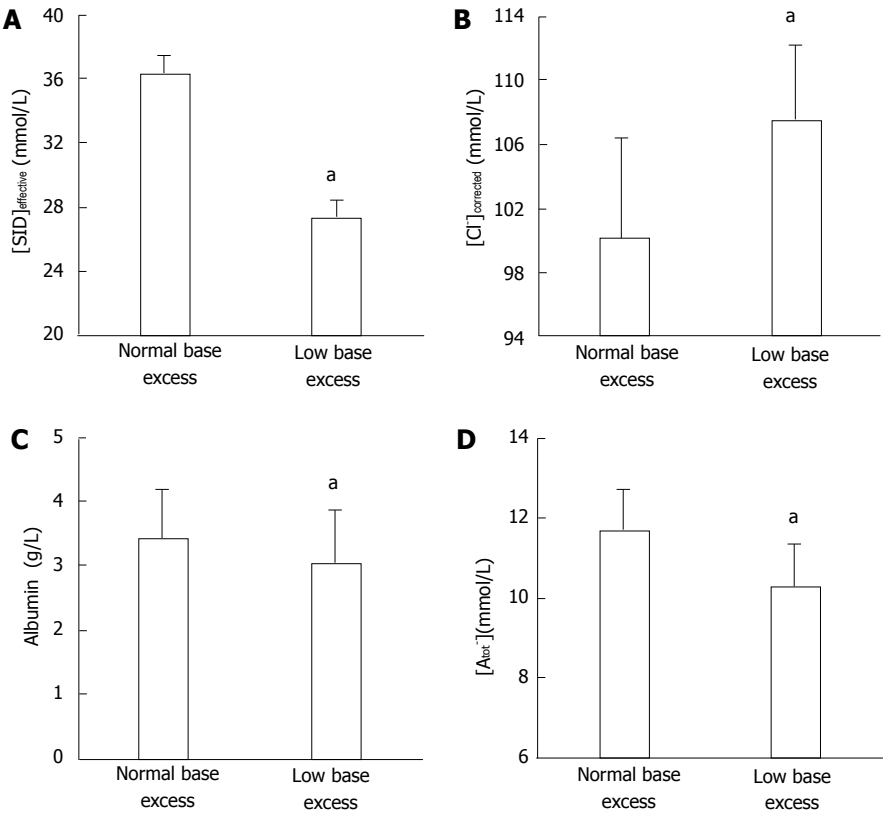

Figure 6 Strong-ion difference, sodium-corrected chloride, albumin, and nonvolatile weak acid levels in severe hyperlactatemia patients. Values for (A) the effective strong-ion difference ($SID_{effective}$), (B) sodium-corrected chloride levels ($Cl^-_{corrected}$), (C) the albumin concentration, and (D) nonvolatile weak acid (Atot) levels in patients with severe hyperlactatemia, with normal or low base excess. $^aP < 0.05$ *vs* the other group. $SID_{effective}$: Effective strong-ion difference.

"Another Nail in the Coffin of Traditional Acid-base Quantification" was published along with this same study[44].

We compared the traditional and Stewart approaches in a series of 935 critically ill patients and in 7 healthy volunteers in order to demonstrate that the Stewart approach does not offer any diagnostic or prognostic advantage[37]. With the use of an analysis based on HCO_3^-, BE and $AG_{corrected}$, only 1% of the patients with low SID acidosis were left undiagnosed. In contrast, diagnosis by the Stewart approach was normal in 2% of the patients in whom metabolic acidosis was identified by the criteria of decreased HCO_3^- and BE, and increased $AG_{corrected}$. Moreover, in normal volunteers, BE and SID, and $AG_{corrected}$ and SIG were strongly correlated, exhibiting narrow limits of agreement (Figure 3). Something similar occurred in the critically ill patients (Figure 4). In addition, the prognostic ability of the different acid-base parameters was similar. The results from this study suggest that the approaches are rather similar in terms of diagnostic and prognostic performance.

Another relevant issue with the Stewart approach

is the poor reproducibility with respect to the determination of its variables. A study analyzed 179 routine blood samples from consecutive patients over a 3-mo period. The determinations were performed by two automated blood-chemistry analyzers. An analysis of the agreement obtained indicated a lack of reproducibility among the simultaneous measurements as illustrated by the wide 95% limits of agreement: 10 mmol/L for SID and 12 mmol/L for SIG[45].

Finally, we demonstrated a similar diagnostic performance for the two approaches in a complex metabolic disorder[46]. Of the patients admitted to the ICU with severe hyperlactatemia (lactate levels $\geqslant$ 4 mmol/L), some 20% had normal pH, HCO_3^-, and BE - but also normal SID. This finding was explained by the simultaneous presence of hypochloremic metabolic alkalosis. Equimolar changes had occurred in the variables of the two approaches that had allowed the identification of the mixed metabolic alteration. The Stewart approach showed normal SID values together with a low chloride level, while the traditional analysis indicated an increase in the difference between the changes in AG and HCO_3^- (Figures 5 and 6). Consequently, the Stewart and conventional approaches were able to describe this complex acid-base disorder in a similar way.

CONCLUSION

The Stewart approach has allowed a new insight into acid-base physiology. Unfortunately, the introduction of that method did not result in relevant advantages, compared to the judicious use of HCO_3^-, BE, and $AG_{corrected}$ either for an understanding of the mechanisms of acid-base alterations or for diagnosis or prognosis. Furthermore, the Stewart approach is cumbersome, requires more determinations and calculations, and is more time-consuming and expensive. On the basis of the compelling evidence that we have discussed here, in order to improve acid-base evaluation we only need to continue with the proper use of the old tools.

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ORIGINAL ARTICLE

Observational Study

Serum bicarbonate may independently predict acute kidney injury in critically ill patients: An observational study

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Abstract

AIM: To explore whether serum bicarbonate at admission to intensive care unit (ICU) predicted development of acute kidney injury (AKI).

METHODS: We studied all patients admitted to our ICU over a 2 year period (February 2010 to 2012). The ICU has a case mix of medical and surgical patients excluding cardiac surgical, trauma and neurosurgical patients. We analysed 2035 consecutive patients admitted to ICU during the study period. Data were collected by two investigators independently and in duplicate using a standardised spread sheet to ensure accuracy. Ambiguous data were checked for accuracy where indicated. AKI was defined using the Kidney Disease Improving Global Outcomes criteria. Patients were divided into two groups; patients who developed AKI or those who did not, in order to compare the baseline characteristics, and laboratory and physiologic data of the two cohorts. Regression analysis was used to identify if serum bicarbonate on admission predicted the development of AKI.

RESULTS: Of 2036 patients 152 (7.5%) were excluded due to missing data. AKI developed in 43.1% of the patients. The AKI group, compared to the non-AKI group, was sicker based on their lower systolic, diastolic and mean arterial pressures and a higher acute

physiology and chronic health evaluation (APACHE) Ⅲ and SAPS Ⅱ scores. Moreover, patients who developed AKI had more co-morbidities and a higher proportion of patients who developed AKI required mechanical ventilation. The multi-regression analysis of independent variables showed that serum bicarbonate on admission (OR = 0.821; 95%CI: 0.796-0.846; P < 0.0001), APACHE Ⅲ (OR = 1.011; 95%CI: 1.007-1.015; P < 0.0001), age (OR = 1.016; 95%CI: 1.008-1.024; P < 0.0001) and presence of sepsis at ICU admission (OR = 2.819; 95%CI: 2.122-23.744; P = 0.004) were each significant independent predictors of AKI. The area under the ROC curve was 0.8 (95%CI: 0.78-0.83), thereby demonstrating that the predictive model has relatively good discriminating power for predicting AKI.

CONCLUSION: Serum bicarbonate on admission may independently be used to make a diagnosis of AKI.

Key words: Acute kidney injury; Bicarbonate; Mortality; Sepsis

Core tip: Metabolic acidosis is often associated with acute kidney injury (AKI) and can result in multiple complications, including cardiac dysfunction, hypotension and mortality. There is however, a paucity of data regarding the value of metabolic acidosis, especially serum bicarbonate, in making an early diagnosis of AKI in an intensive care unit (ICU) setting. We demonstrated that serum bicarbonate on admission may independently be used to make a diagnosis of AKI, in a mixed ICU setting. Our results are relevant since serum bicarbonate is inexpensive and easily available, which will enable initiate prompt treatment of AKI, for better outcomes.

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INTRODUCTION

Acute kidney injury (AKI) is defined as an abrupt decline in renal function, resulting in the inability to excrete metabolic wastes and maintain proper fluid, electrolyte and acid base balance. It results in multiple complications including hyperkalaemia, acidosis, volume overload, encephalopathy and anaemia[1]. Patients who develop AKI have worse long-term outcomes, especially in the immediate post-intensive care unit (ICU) period[2].

Metabolic acidosis, which is often associated with AKI, can result in cardiac dysfunction, hypotension, increased risk of infection and mortality. Hence clinical practice guidelines recommend initiation of alkali therapy when serum bicarbonate level is ⩽ 22 mmol/L[1] although a recent Cochrane review demonstrated the benefit of sodium bicarbonate in AKI management as equivocal[3].

A more thorough understanding of the impact and association of different risk factors with AKI is very important for designing predictive models of patients at high risk of developing this lethal condition, in order that preventative strategies may be created to benefit such a group. Predictive models for development of AKI already exist in cardiac-surgery critically ill patients[4-6]. There is however a lack of meaningful predictive models in mixed and medical ICUs. Most of the prediction models in these context have focused on the impact on mortality of AKI in ICU patients[7,8].

Multiple biomarkers including serum and urinary CysC, neutrophil gelatinase-associated lipocalin (NGAL) and interleukin-18 (IL-18) have been used to predict AKI[9]. The usefulness of these serum biomarkers in predicting the development of AKI appears to be evolving. Yet assay to assays to identify these biomarkers are expensive and not widely available.

There is however, a paucity of data regarding the value of metabolic acidosis, especially serum bicarbonate, in making an early diagnosis of AKI in an ICU setting. Measurement of serum bicarbonate is possible in most hospital settings and is not expensive. Hence we aimed to primarily assess the role of serum bicarbonate, measured during the first 24 h of ICU admission, in diagnosing AKI and identify other independent predictors of AKI.

MATERIALS AND METHODS

Ethics

The Human Research Ethics Committee of Peninsula Health reviewed the study protocol and waived the requirement for full ethics committee application, as the study was seen as a retrospective audit of data routinely collected for patient care and not experimental research.

Study design and setting

We studied all patients admitted to our ICU over a 2 year period (February 2010 to 2012). The ICU has a case mix of medical and surgical patients excluding cardiac surgical, trauma and neurosurgical patients. The study was undertaken at Frankston Hospital, the acute care hospital for Peninsula Health. The hospital is a tertiary referral centre that is affiliated with Monash University.

Clinical and laboratory features at admission and during ICU stay were collected from our ICU database (called STATIC), our hospital's pathology

Table 1 Comparison of demographical and clinical characteristics at the time of admission to intensive care

	NO AKI (*n* = 1006)	AKI (*n* = 877)	*P* value
Age (yr)	61.4 (18.8)	66.2 (16.6)	< 0.0001
Sex, M:F	1.1:1 (726:662)	1.1:1 (242:220)	0.978
Requirement for mechanical ventilation	46%	51.5%	0.01
Severity of illness			
APACHE Ⅲ	47.8 (25.3)	63 (35.7)	< 0.0001
SAPS Ⅱ	33.7 (13.8)	45.9 (17.6)	< 0.0001
Vital signs			
Heart rate (/min)	99 (22)	105 (23)	< 0.001
Respiratory rate (/min)	24 (6.6)	26 (7.5)	< 0.001
Temperature[1] (℃)	35.3 (0.9)	35.2 (1.2)	0.004
Systolic BP[1] (mmHg)	102.9 (16.8)	96.5 (169)	< 0.001
Diastolic BP[1] (mmHg)	55.8 (12.2)	52.3 (12.7)	< 0.001
MAP (mmHg)	71.3 (12.7)	67.0 (12.8)	< 0.001

[1]Lowest. Data are presented in mean ± SD; number of patients where data were available for analyses. SAPS Ⅱ: Simplified acute physiology score II; APACHE Ⅲ: Acute physiology age and chronic health evaluation Ⅲ; BP: Blood pressure; MAP: Mean arterial pressure.

database and the case records of the patients included in the study. Data were collected by two investigators independently and in duplicate using a standardised spread sheet to ensure accuracy. Ambiguous data were checked for accuracy where indicated.

Definition of parameters

Clinical and laboratory features at admission and during ICU stay were studied. AKI was defined using the Kidney Disease Improving Global Outcomes (KDIGO) Practice Guidelines[10]. As per the guidelines, a patient was considered to have AKI if there was an increase in serum creatinine by 26.5 μmol/L or more within 48 h, or an increase in serum creatinine to 1.5 times baseline or more within the last 7 d. Baseline renal function was defined as the lowest known serum creatinine during the preceding 3 mo prior to hospital admission. Patients with unknown baseline serum creatinine were excluded from the study. Patients were considered as having new AKI if they did not have AKI on ICU admission but subsequently met the KDIGO Guidelines during the first 48 h of ICU presentation. Metabolic acidosis was defined as pH < 7.35 and an arterial bicarbonate < 20 mmol/L.

Patient population and data collection

The patients were divided into two groups, the AKI and non-AKI groups, in order to investigate if there were differences in relation to all the studied parameters. Thereafter, the proportion of patients with metabolic acidosis in the AKI group was determined. The presence of hypertension, diabetes and peripheral vascular disease, as well as the length of ICU and hospital stays were analysed in all patients included in the study. The acute physiology and chronic health evaluation (APACHE) Ⅲ score[11] and simplified acute physiology score (SAPS) Ⅱ[12] were calculated for the first 24 h of admission. Physiological parameters during the first 24 h of ICU admission, including vital signs and partial pressures of oxygen and carbon dioxide were recorded. Serum urea and creatinine were recorded during the first 48 h of ICU admission, at 24 h-intervals, in all patients included in the study. The laboratory parameters consisted of serum bicarbonate, pH, lactate, albumin, urea, potassium, white cell count (WCC) and glucose levels.

Statistical analysis

Statistical analysis was performed by a biomedical statistician. Categorical data were assessed using Fisher's exact test. Student's *t* tests (for parametric data) or Mann-Whitney *U* (Non parametric) tests was used for continuously-scaled data.

Logistic regression analysis was used to distinguish independent predictors of hospital mortality. In regression analysis models data variables were entered using "Enter" method. The first model contained data variables including age, mean BP, serum lactate, pH, APACHE Ⅲ score, serum bicarbonate on admission, presence of sepsis at admission and the need for mechanical ventilation. Further models were constructed aiming for a parsimonious model. Every model constructed was assessed by Cox and Snell and Nagelkerke R square and Hosmer-Lemeshow goodness-of-fit statistic. Regression models were constructed using Wald statistic. The final model contained four variables including age, sepsis on admission, serum bicarbonate and APACHE Ⅲ score. A *P* value < 0.05 was considered to be statistical significant. Data analyses were performed using IBM SPSS statistics version 22.0 (SPSS Inc, Chicago, IL).

RESULTS

Over the two year study period 2035 patients were admitted to our ICU. We excluded 152 (7.5%) patients due to missing data on serum creatinine. 877 patients (43.1%) of the cohort developed AKI compared to 1006 patients (49.4%) who did not develop AKI in the first 48 h. Patient demographics and clinical parameters at the time of admission are shown in Table 1.

The AKI group was older than the non-AKI groups, and had a significantly higher proportion of hypertensive and diabetic patients (*P* = 0.003 and < 0.001 respectively). Other comorbidities such as peripheral vascular disease, ischemic heart disease and chronic obstructive airway disease were not significantly different (*P* = 0.58, 0.24 and 0.07 respectively). The AKI group, compared to the non-AKI group, was sicker based on the lower systolic, diastolic and mean arterial pressures and a higher APACHE Ⅲ and SAPS Ⅱ scores. Moreover, patients who developed AKI were more likely to require

Table 2 Comparison of laboratory characteristics at the time of admission to intensive care

	NO AKI (n = 1006)	AKI (n = 877)	P value
pH	7.4 (0.08)	7.3 (0.12)	< 0.001
$PaCO_2$ (mmHg)	41 (11.3)	40 (13.7)	0.005
PaO_2, (mmHg)	116 (85.4)	113 (79.7)	0.5
HCO_3 (mmol/L)	23.5 (3.7)	20.1 (5.3)	< 0.001
Sodium (mmol/L)	141 (4.2)	141 (5.3)	0.7
Potassium (mmol/L)	4.5 (0.6)	4.7 (0.8)	< 0.001
Urea (μmol/L)	6.2 (3.9)	14.4 (10.6)	< 0.0001
Baseline Creatinine (μmol/L)	72 (36.8)	180 (173.6)	< 0.001
Peak creatinine (μmol/L)[1]	76 (36.6)	196 (175.3)	< 0.001
Serum albumin (g/L)	35 (6.1)	34 (6.1)	0.001
Blood glucose (mmol/L)	8.9 (3.4)	11.1 (5.7)	< 0.001
Lactate (mmol/L)	2.1 (2.0)	3.4 (3.1)	< 0.001
White cell count ($\times 10^9$/L)	12.9 (9.6)	15.6 (10.8)	< 0.001
Hematocrit (%)	0.36 (0.057)	0.34 (0.061)	< 0.001

[1]During first 48 h of ICU admission. Data are presented in mean ± SD. ICU: Intensive care unit.

mechanical ventilation (51.5% *vs* 46.0%, P = 0.01). Patients who developed AKI were more acidotic with lower serum bicarbonate (20.1 mmol/L *vs* 23.5 mmol/L, P < 0.001) and higher lactate (3.4 mmol/L *vs* 2.1 mmol/L, P < 0.001) (Table 2).

The AKI group was sub-classified into 3 categories as per the grade of the renal impairment. Stage 1, 2 and 3 respectively had a serum bicarbonate of 20.8 ± 5.1, 18.2 ± 5.0 and 17.2 ± 6.3 mmol/L. There were however no significant differences in the death rates in ICU across the 3 groups.

In terms of morbidity and mortality, the AKI group had longer ICU and hospital duration and a higher ICU and hospital mortality (Table 3). The multi-regression analysis of independent variables showed that serum bicarbonate on admission (OR = 0.821; 95%CI: 0.796-0.846; P < 0.0001), APACHE Ⅲ (Odds ratio 1.011; 95% CI 1.007-1.015; P < 0.0001), age (OR = 1.016; 95%CI: 1.008-1.024; P < 0.0001) and presence of sepsis at ICU admission (OR = 2.819; 95%CI: 2.122-23.744; P = 0.004) were each significant independent predictors of AKI. The area under the ROC curve was 0.8 (Figure 1) confirming the discriminatory power of the model for predicting AKI.

DISCUSSION

Our study is amongst the first studies investigating whether serum bicarbonate predicts the development of AKI in unselected critically ill ICU patients, in whom AKI aetiology and timing are often unclear. We demonstrated that patients who developed AKI were more acidotic with a lower serum bicarbonate. Hence our study proved that in an ICU setting, serum bicarbonate on admission can be used to make an early diagnosis of AKI. Patients with more severe AKI were more acidotic, although the mortality across the sub-groups of AKI severity did not significantly differ. Also, serum lactate levels on ICU admission did not predict the onset of AKI. We also found that AKI significantly increased morbidity and mortality, hence highlighting the need for an early diagnostic tool.

Table 3 Comparison of outcomes

	NO AKI (n = 1006)	AKI (n = 877)	P value
Died in hospital (%)	30.9	69.1	< 0.001
Death in ICU (%)	57.0	43.0	< 0.001
Hospital length of stay (d)	12.6 (20.1)	14.5 (16.3)	0.02
ICU length of stay (d)	2.8 (4.1)	4.4 (5.7)	< 0.001

Data are presented in mean ± SD. ICU: Intensive care unit.

The rationale behind the association between AKI and low serum bicarbonate levels can be extrapolated from previous studies which have explored the benefits of sodium bicarbonate in reducing the risk of AKI[13-17]. Most of those have been performed in a cardiac surgery setting because of the ability to prospectively follow patients before and after a well-timed renal insult. Haase *et al*[15] designed a double-blind, randomized controlled trial in patients undergoing cardiac surgery, and found that sodium bicarbonate treatment was associated with an absolute risk reduction for AKI of 20% and with a significant attenuation in the postoperative increase of plasma urea, urinary NGAL and urinary NGAL/urinary creatinine ratio[15]. It is thought that sodium bicarbonate contributes to increasing oxygen delivery to the renal medulla, while reducing iron-mediated free radical formation due to neutralizing acidosis in this vulnerable region of the kidney[18]. Therefore, it can be argued that a lower serum bicarbonate level would increase the risk of ischemic injury to the kidneys, especially in a critical illness setting. This logic would support our findings and current model.

Of late, there has been a lot of interest in identifying novel serum and urinary biomarkers which would be more sensitive in predicting AKI. This is because serum creatinine has a poor predictive accuracy for renal injury, particularly in the early stages of AKI[19]. Our study supports the use of serum bicarbonate, an easily accessible parameter, usually readily available in all patients. Other markers which have been used as predictors of AKI are NGAL, kidney injury molecule-1, Cystatin C, IL-6, IL-8, IL-18, N-acetyl-glucosaminidase, glutathione transferases and liver fatty acid binding protein. However, there is still a lot of debate about their reliability. For example, a wide range of predictive value of NGAL has been only reported across observational cohort studies[20,21]. Also a clear cut off NGAL concentration for the detection of AKI has not yet been reported, whilst the predictive value of urinary Cystatin C should be interpreted with caution in pre-renal AKI[22]. More recently, a review

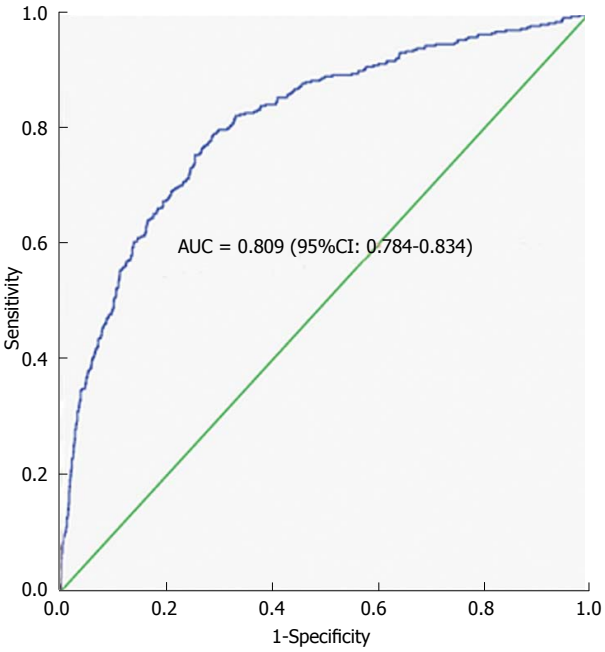

Figure 1 Receiver operating characteristic curve of the final model (including age, sepsis, serum bicarbonate and APACHE Ⅲ score) predicting acute kidney injury. AUC: Area under the curve.

emphasized on the cumbersome nature of these markers, especially in those settings where timing and aetiology of AKI are not well defined[23]. Hence, we support the use of serum bicarbonate as an inexpensive and potentially reliable predictor of AKI.

We do acknowledge the limitations of our study. It is a retrospective study with limitations on the selection of patients and the quality of the data. Nevertheless we aimed to include all patients admitted to ICU to reduce the selection bias and all data was collected by two investigators independently and in duplicate using a standardised spread sheet to ensure accuracy. Also, although 7.5% of our cohort had to be excluded from the study due to the unavailability of a baseline creatinine, they were not demographically different to the rest of the cohort.

This study showed that serum bicarbonate at admission may be a predictor of developing AKI in a mixed ICU setting. The current findings can allow timely patient management decisions, including withholding nephrotoxic agents, administration of putative therapeutic agents, and the initiation of RRT since a bicarbonate level is cheap and readily available.

COMMENTS

Background

Metabolic acidosis is often associated with acute kidney injury (AKI) and can result in multiple complications, including cardiac dysfunction, hypotension and mortality. There is however, a paucity of data regarding the value of metabolic acidosis, especially serum bicarbonate, in making an early diagnosis of AKI in an intensive care unit (ICU) setting.

Research frontiers

A more thorough understanding of the impact and association of different risk factors with AKI is very important for designing predictive models of patients at high risk of developing this lethal condition, in order that preventative strategies may be created to benefit such a group. Predictive models for development of AKI already exist in cardiac-surgery critically ill patients. There is however a lack of meaningful predictive models in mixed and medical ICUs.

Innovations and breakthroughs

Multiple biomarkers including serum and urinary CysC, NGAL and interleukin-18 have been used to predict AKI. The usefulness of these serum biomarkers in predicting the development of AKI appears to be evolving. Yet assay of these biomarkers are currently expensive and the facilities to assay these biomarkers are not widely available. There is however, a paucity of data regarding the value of metabolic acidosis, especially serum bicarbonate, in making an early diagnosis of AKI in an ICU setting.

Applications

The current study found that serum bicarbonate measured in the early phases of admission to ICU could be used to make an early diagnosis of AKI. Serum bicarbonate measurement is inexpensive and easily available, hence making it an easy test available to anticipate AKI, hence launch the necessary treatment promptly.

Peer-review

This study investigates the utility of serum bicarbonate as a marker of acute kidney injury.

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Utility of flexible fiberoptic bronchoscopy for critically ill pediatric patients: A systematic review

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Abstract

AIM: To investigate the diagnostic yield, therapeutic efficacy, and rate of adverse events related to flexible fiberoptic bronchoscopy (FFB) in critically ill children.

METHODS: We searched PubMed, SCOPUS, OVID, and EMBASE databases through July 2014 for English language publications studying FFB performed in the intensive care unit in children < 18 years old. We identified 666 studies, of which 89 full-text studies were screened for further review. Two reviewers independently determined that 27 of these studies met inclusion criteria and extracted data. We examined the diagnostic yield of FFB among upper and lower airway evaluations, as well as the utility of bronchoalveolar lavage (BAL).

RESULTS: We found that FFB led to a change in medical management in 28.9% (range 21.9%-69.2%) of critically ill children. The diagnostic yield of FFB was 82% (range 45.2%-100%). Infectious organisms were identified in 25.7% (17.6%-75%) of BALs performed, resulting in a change of antimicrobial management in 19.1% (range: 12.2%-75%). FFB successfully re-expanded atelectasis or removed mucus plugs in 60.3% (range: 23.8%-100%) of patients with atelectasis. Adverse events were reported in 12.9% (range: 0.5%-71.4%) of patients. The most common adverse effects of FFB were transient hypotension, hypoxia and/or bradycardia that resolved with minimal intervention, such as oxygen supplementation or removal of the bronchoscope. Serious adverse events were uncommon; 2.1% of adverse events required intervention such as bag-mask ventilation or intubation and atropine for hypoxia and bradycardia, normal saline boluses for hypotension, or lavage and suctioning for hemorrhage.

CONCLUSION: FFB is safe and effective for diagnostic and therapeutic use in critically ill pediatric patients.

Key words: Bronchoscopy; Critical illness; Pediatrics; Bronchoalveolar lavage; Pulmonary disease

Core tip: Flexible fiberoptic bronchoscopy (FFB) is effective and safe for diagnostic and therapeutic use

among critically ill pediatric patients. FFB led to change in management in 28.9% of patients, with a diagnostic yield of 82%. Bronchoalveolar lavage obtained during FFB may assist with identifying infectious organisms (25.7%) and optimizing antimicrobial therapy (19.1%). FFB had therapeutic benefit with removal of mucus plugs or resolution of atelectasis in 60.3%. The majority of reported adverse events were transient and included hypotension, hypoxia and/or bradycardia requiring minimal intervention.

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INTRODUCTION

Flexible fiberoptic bronchoscopy (FFB) is recognized as an essential tool to diagnose and treat pediatric pulmonary disorders. Even though the first published report on the utility of FFB in children was in 1978, rigid bronchoscopy by surgeons remained standard of practice for many years due to instrument size limitations[1,2]. With the advent of smaller-sized bronchoscopes, FFB use has increased in pediatric and neonatal patients[3-6].

In 1987, the first published FFB guideline for adults provided recommendations for the use of bronchoscopy for diagnosis and management of a broad spectrum of inflammatory, infectious, and malignant diseases[7]. Updated guidelines published by the British Thoracic Society further defined the indications, patient selection criteria, and potential adverse events in adult bronchoscopy[8]. However, the guidelines for adult FFB cannot necessarily be extrapolated to children given the smaller airways, differences in pulmonary diagnoses, and sedation needs for FFB in children. Guidelines about the use of FFB in pediatric patients are over a decade old[9,10]. Despite increased use of FFB by pediatric pulmonologists, intensivists and anesthesiologists, there are no current guidelines regarding the safety and utility of FFB in the pediatric critically ill population.

Our objective was to systematically review the published literature on the utility and safety of FFB in pediatric and neonatal intensive care settings. Our specific questions were: (1) what is the diagnostic yield of FFB; (2) what is the therapeutic efficacy of FFB; and (3) what is the rate of adverse events secondary to FFB?

MATERIALS AND METHODS

This systematic review was conducted according to PRISMA guidelines[11]. The protocol for our study was registered online at PROSPERO (CRD42014010801)[12]. The National Library of Medicine through PubMed was searched for "bronchoscopy" (MeSH and all fields) and "intensive care units" (MeSH and all fields) and English and "journal article" AND infant (MeSH) or child (MeSH) or adolescent (MeSH). In addition, we searched the following databases for the terms "bronchoscopy" and "intensive care unit" and (infant or child or adolescent) and "journal article" and English language: SCOPUS, OVID, and EMBASE. Our search strategy included studies published in English from database inception to July 20, 2014. References of identified articles were searched for additional relevant articles.

Articles eligible for inclusion were English-language manuscripts reporting either diagnostic, therapeutic or adverse events related to FFB performed on children (< 18 years old) in intensive care units (ICUs). Cohort, case control, or randomized controlled trials that reported either diagnostic, therapeutic, or adverse events related to FFB were included. Articles focusing on bronchoscopy in patients with foreign body aspiration were excluded, as rigid bronchoscopy is indicated for removal of foreign bodies[9]. For the purposes of this systematic review, we defined a positive diagnostic FFB as one identifying anatomic or functional airway abnormality, foreign body/obstruction, mucus plugging/atelectasis, hemorrhage, and/or airway inflammation.

One author (SM) screened article titles for initial inclusion. Two authors (SM and SL) independently screened abstracts in duplicate for inclusion. All authors (SM, SL, AF, VS and KN) piloted the standardized electronic data extraction form on two articles. Two authors independently assessed each article for study eligibility and extracted data. Data extracted included study design, participant demographics, and bronchoscopy outcomes (including diagnostic results, change in therapy, bronchoalveolar lavage (BAL) results, ICU length of stay, hospital length of stay, length of mechanical ventilation, rate of successful extubation, and adverse events). Risk of bias was not assessed. Discrepancies were resolved after joint article review and discussion. Results were presented as a narrative synthesis. Pooled estimates of diagnostic yield, therapeutic efficacy, and adverse events were estimated as weighted averages with weights proportional to study denominators from the relevant subpopulations, making the assumption that study-specific proportions are homogeneous. No formal tests for homogeneity were conducted in light of the wide variation in denominator counts, including very small studies[13].

Statistical analysis

The statistical methods of this study were reviewed by Daniel J. Tancredi, PhD, from the University of

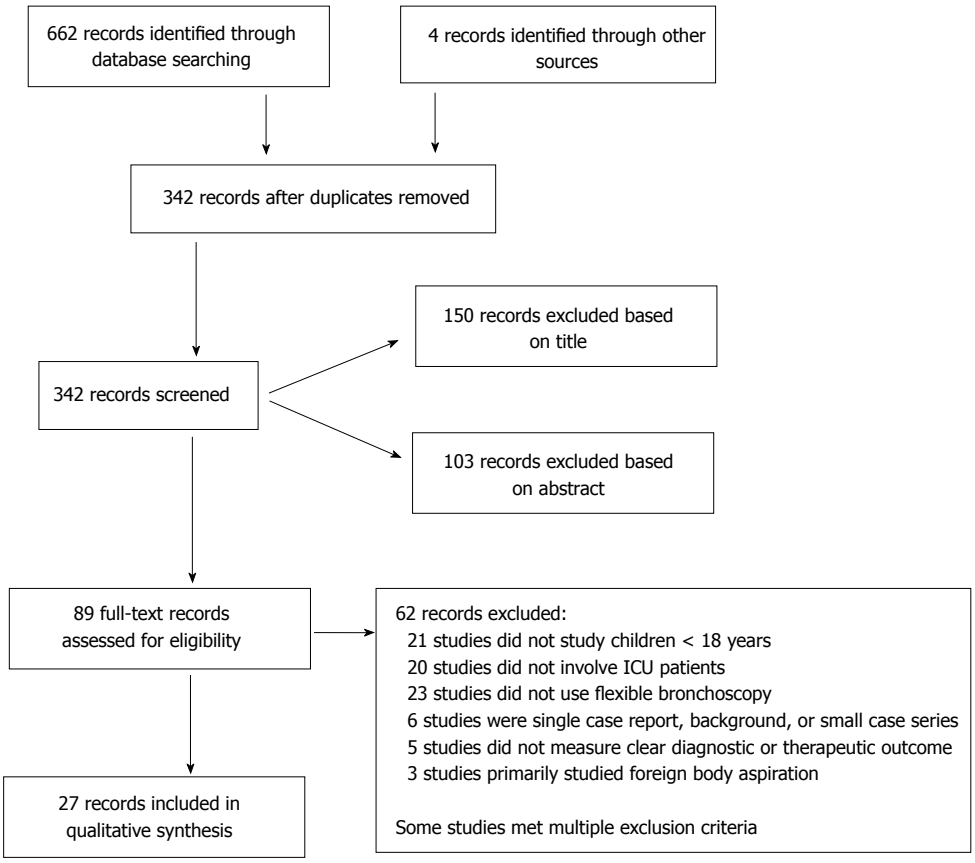

Figure 1 Flow diagram of the study selection process. ICU: Intensive care unit.

California Davis.

RESULTS

Study characteristics

We identified 666 studies, of which 89 full-text studies were screened for further review. Two reviewers independently determined that 27 of these studies met inclusion criteria (Figure 1).

Two-thirds of the included studies were retrospective cohort, the remainder consisted of case control or prospective cohort studies (Table 1). Sixteen studies (59%) investigated patients admitted to a pediatric intensive care unit (PICU), eight studies (30%) investigated neonatal intensive care Unit (NICU) patients, while three (11%) included both PICU and NICU patients. Almost all FFB were performed at the bedside, with the exception of routine evaluation for esophageal atresia, where the procedure took place in the operating room[14]. The patient populations undergoing FFB included patients evaluated for a spectrum of anatomic airway or intrinsic pulmonary abnormalities, including patients with congenital heart disease (CHD) (7/27; 26% studies) and patients on extracorporeal life support (ECLS) (4/27; 15% studies)[4,15-23]. FFB was performed multiple times on patients in 55% of the studies.

Diagnostic yield of FFB

Six studies reported a change in clinical management secondary to FFB in 28.9% (range 21.9%-69.2%; 157/540)[4,14-16,24]. Changes in clinical management included unanticipated surgical intervention, modification of surgical intervention, and alteration of endotracheal suctioning techniques. The change in clinical management due to FFB findings was similar for non-surgical patients (22.3%; range 18.5%-69.2%; 82/368) and lower for airway surgery patients (8.9%; range 3.4%-24.2%; 42/472). Atzori *et al*[14] reported that FFB was instrumental in delineating the type of tracheoesophageal fistula and altered surgical planning in 24.2% (15/62) of children with esophageal atresia[14]. De Blic *et al*[4] reported that in children with CHD, FFB findings of external compression of the airways by cardiovascular anomalies prompted earlier cardiac surgery in 50% (5/10)[4].

Twenty-one studies reported an overall diagnostic yield of 82% using FFB (range 45.2%-100%; 3791/4622)[3-5,14-18,20-33]. FFB was more likely to be positive in patients with suspected upper airway abnormalities (92.7%; range 73%-95.2%; 858/926) than in patients with suspected lower airway abnormalities (74.3%; range 11.3%-90.2%; 2274/3061). Upper airway findings included airway stenosis, compression or malacia, edema, foreign body, pseudomembrane,

Table 1 Indications, diagnostic, and therapeutic outcomes for flexible bronchoscopy in critically ill pediatric patients

Ref.	Population	Indications	Diagnostic yield	Diagnostic BAL findings	Therapeutic outcomes
Abu-Kishk *et al*[25], 2012	9 PICU: hemoptysis (age 2 mo-17 yr)	Hemoptysis	77.8% (7/9)		
Atzori *et al*[14], 2006	62 NICU: esophageal atresia (mean age 37.5 WGA)	Airway evaluation	24.2% (15/62): Change in surgical management 9.7% (6/62): Change in anatomic class 11.3% (7/62): Tracheomalacia		
Bar-Zohar *et al*[24], 2004	100 PICU: medical, non-airway surgery, and airway surgery groups (age 2 d-17 yr)	Airway evaluation; BAL; extubation failure	73% (65/89): Upper airway 56% (14/25): Lower airway 63.6% (28/44): Extubation failure 38.6% (44/114): Change in medical management 20% (11/31): Airway surgical re-exploration	46.7% (14/30) identified organism 50% (15/30) change in antimicrobials 40% (12/30) clinical improvement after change in antimicrobials 36.4% (4/11) concordance between BAL and blind tracheal aspirate	84.6% (11/13) extubated after lavage 74.3% (26/35) re-expanded collapsed lobe
Chapotte *et al*[18], 1998	72 PICU: CHD (age 1 d-14 yr)	Perioperative evaluation; respiratory symptoms; radiologic respiratory signs	70.8% (51/72) 48.6% (35/72) identified extra-luminal compression	33.3% (2/6) identified organisms in patients with mucosal inflammation	
Davidson *et al*[17], 2008	129 PICU: ECLS, CHD (age 2.9 mo-3 yr)	Airway evaluation; atelectasis; BAL; ETT position; respiratory distress	68.4% (78/114): Overall 46.3% (37/80): ECLS 60.3% (41/68): CHD identified extra-luminal compression	45.3% (53/117): Overall identified organism 53.8% (28/52): ECLS subgroup identified organism	82.1% (32/39) successful procedures: removed blood and mucous plugs, or instilled surfactant, placed endovascular stents
de Blic *et al*[4], 1991	33 NICU: CHD, lung disease and/or congenital malformations (age 2 d-9 mo)	Anatomic evaluation; atelectasis/ emphysema; respiratory distress	62.2% (23/37): Overall 52.8% (19/36): Change in management 13.9% (5/36): Change in surgical management 50% (5/10): CHD		
Efrati *et al*[16], 2009	319 PICU: CHD, oncology (age 1-22 yr)	Anatomic evaluation; BAL; trauma	79.3% (253/319): Overall 90.2% (46/51): CHD 83.3% (50/60): Oncology 21.9% (70/319): Change in management 3.4% (11/319): Change in surgical management	17.6% (56/319): Identified organism 12.2% (39/319): Change in antimicrobials 88% (22/25): Abnormal cytology consistent with infection	
Fan *et al*[26], 1988	87 PICU: (age 1 wk-18 yr)	Anatomic evaluation; decannulation; difficult intubation; respiratory symptoms; tracheostomy	94.8% (91/96)		87.5%(7/8) 100% (5/5): Difficult airways intubated 66.7% (2/3): Re-expanded collapsed lobe
Hintz *et al*[22], 2002	8 NICU: CDH on ECLS	Atelectasis			87.5% (7/8): Improved lung expansion after lavage
Kamat *et al*[19], 2011	79 PICU: ECLS (10 d-21 yr)	Atelectasis; BAL; anatomic evaluation; surfactant instillation		21.3% (33/155): Identified organism	76.1% (118/155): Atelectasis 15.4% (10/65): Improved CXR 2.6% (4/155): Surfactant
Kohelet *et al*[27], 2011	19 NICU: (age 1 d-8 mo)	Anatomic evaluation; atelectasis; BAL; difficulty weaning MV; respiratory symptoms	60% (15/25): Overall 100% (6/6): Wean from MV 52% (13/25): Abnormal anatomy	60% (6/10): Identified organism 50% (5/10): Change in antimicrobials	75% (6/8): Re-expanded collapsed lobe
Kolatat *et al*[28], 2002	45 NICU: (mean age 33 WGA)	Respiratory distress post-extubation	93.3% (42/45)		

Kotby *et al*[29], 2008	35 PICU: suspected pulmonary fungal infections (age 1-15 yr)	BAL		40% (14/35): Identified organism 77.1% (27/35): Diagnosed probable pulmonary fungal infection (+ BAL culture or + BAL fungal antigen)	
Maggi *et al*[36], 2012	44 PICU: status asthmaticus requiring MV (age 6 mo-18 yr)	Atelectasis; lavage; respiratory distress;			100% (29/29): Improved A-a gradient, shunt fraction, decreased FiO2, improved compliance. 37.9% (11/29): Extubated within 6 h 69% (20/29): Extubated within 12 h Reduced PICU LOS (3.06 d *vs* 3.4 d in control ($P < 0.05$)) Reduced length of time on MV [10 h *vs* 20.5 h ($P < 0.0005$)]
Manna *et al*[30], 2006	134 PICU: CHD (age 4 mo-6 yr)	Anatomic evaluation; atelectasis; BAL; extubation failure; hemorrhage	76.4% (113/148): Overall 84.4% (27/32): Upper airway 80% (56/70): Lower airway 18.6% (13/70): CHD identified extraluminal compression 90.5% (19/21): Extubation failure 44% (11/25): Pulmonary disease	35.3% (6/17): Identified organism	92.3% (24/26): Re-expanded collapsed lobe
Myer *et al*[30], 1988	10 NICU: (age 1 d-16 mo)	Atelectasis; hemorrhage; hypercarbia; hypoxia; hyperinflation; respiratory distress	50% (5/10): Overall 20% (2/10): Granuloma		60% (3/5): Re-expanded collapsed lobe 40% (2/5): Granuloma required rigid bronchoscopy
Nakano *et al*[5], 2004	16 NICU: esophageal atresia, Trisomy 21, CDH, hydrocephalus, Goldenhaar, and Kasabach-Merritt (age 3 d-8.5 mo)	Anatomic evaluation; extubation failure; hemorrhage; respiratory distress	66.7% (14/21)		23.8% (5/21): Removed obstruction (mucus plug, clot/local tissue) or altered suction practice
Nayak *et al*[21], 2012	30 PICU: CHD requiring mechanical ventilation prior to extubation (age 1 d-6 mo)	Anatomic evaluation; extubation failure	50% (15/30): Overall significant tracheobronchial narrowing 50% (4/8): Extubation failure		73.3% (22/30): Extubated
Nussbaum *et al*[31], 2002	2836 PICU: (age 1 d-15 yr)	Anatomic evaluation; atelectasis; BAL; hemorrhage; ETT position; intubation; tracheostomy evaluation; plastic bronchitis; respiratory distress	84.8% (2405/2836): Overall 95.2% (766/805): Upper airway 82.6% (1862/2254): Lower airway 47.9% (1358/2836): Inflammatory changes	24.1% (411/1705): Identified organism 41.7% (5/12): Transbronchial biopsy positive dyskinetic cilia syndrome 72.4% (21/29): Acute chest SCD plastic bronchitis	
Peng *et al*[32], 2011	358 PICU and NICU: (age 1 d-17.5 yr)	Anatomic evaluation; BAL; intubation; respiratory distress	87.2% (312/358): Overall 47.8% (171/358): Airway malacia 39.4% (141/358): Inflammatory changes		56.1% (201/358): Interventional FFB 71.4% (518/725): of all FFB were interventional
Pietsch *et al*[37], 1985	19 NICU: necrotizing tracheobronchitis (mean age 6.53 d)	Therapeutic removal of obstruction			66.7% (10/15): Survived after removal of debris

Prentice *et al*[23], 2011	7 PICU: ECLS (age 8 d-27 yr)	Persistent atelectasis	100% (7/7) 57.1% (4/7): Bronchus compression/ narrowing 71.4% (5/7): Mucus plugs	75% (3/4): Identified organism 75% (3/4): Change in antimicrobials	28.7% (2/7): Removed mucus plugs, ECLS subsequently weaned
Sachdev *et al*[35], 2010	30 PICU: clinical suspicion of VAP (age 1 mo-12 yr)	BAL		65% (26/40): Identified organism	
Soong *et al*[43], 2011	8 PICU and NICU: obstructive fibrinous tracheal pseudomembrane (age 2 mo-13 yr)	Therapeutic ablation			100% (8/8): Ablation of obstructive membrane
Soong *et al*[33], 1995	207 NICU and PICU: (age 1 d-10 yr)	Respiratory symptoms; intractable pneumonia	81.1% (172/212)		35.4% (75/212): Resolution of atelectasis, improved secretions
Tang *et al*[3], 2009	47 PICU: (age 1 d-13 yr)	Anatomic evaluation, BAL; therapeutic (FB, clot removal, hemoptysis, intubation)	80.9% (38/47)	36.8% (7/19): Identified organism 57.9% (11/19): Change in antimicrobials	87.0% (20/23): Re-expanded collapsed lobe. 44.8% (13/29): Extubated < 24 h after mucus plug, blood clot, FB removed
Ward *et al*[15], 1987	25 PICU: CHD (n = 7), (age 1 d-11 yr)	Anatomic evaluation; atelectasis; confirm ETT/tracheostomy position; hyperinflation; respiratory distress	64% (16/25): Overall 62.5% (5/8): Tracheostomy - change in management 80% (4/5): Hemoptysis - change in management 85.7% (6/7): CHD		

A-a gradient: Alveolar-arterial gradient; ARDS: Acute respiratory distress syndrome; BAL: Bronchoalveolar lavage; CDH: Congenital diaphragmatic hernia; CHD: Congenital heart disease; CXR: Chest X-ray; ECLS: Extracorporeal life support; ETT: Endotracheal tube; FB: Foreign body; FFB: Flexible fiberoptic bronchoscopy; F_{iO2}: Fractional of inspired oxygen; LOS: Length of stay; MV: Mechanical ventilation; NICU: Neonatal intensive care unit; PIC: Pediatric intensive care unit; SCD: Sickle cell disease; TEF: Tracheoesophageal fistula; VAP: Ventilator associated pneumonia; WGA: Weeks gestational age.

and vocal cord dysfunction[20,24,31]. Lower airway findings included airway stenosis, compression, malacia, mucus plugs, thrombus, and malpositioned endotracheal tube[3,14,15,17,18,20,21,23,24,31,32].

The diagnostic yield of FFB varied amongst different patient populations. The populations with the highest diagnostic yield of FFB were patients with extubation failure, patients with CHD, patients with hemoptysis, and patients undergoing ECLS. In patients with extubation failure, FFB identified a cause, such as mucus plugs, laryngotracheomalacia, laryngeal trauma/edema or compression, in 69.9% (range 50%-90.5%; 51/73)[3,16-21,24,27,31,32]. In children with CHD, the diagnostic yield of FFB was 57.5% (range 18.5%-90.2%; 177/308). External airway compression was the most commonly reported finding[15-18,20,21,34]. In patients with hemoptysis, FFB identified a cause in 56% of patients (range 20%-100%; 14/25)[5,15,25,30]. In patients receiving ECLS, 31% (range 21.5%-46.2%; 108/349) had a positive finding on FFB, including airway compression, abnormal bronchial anatomy, malpositioned or occluded endotracheal tube, or mucus plugging[17,19,22,23].

BAL was a common indication for FFB and findings were reported in 12 studies[3,16-20,23,24,27,29,31,35]. An infectious organism was identified in 25.7% (range 17.6%-75%; 631/2455) of all BALs performed. The highest yield of BAL was in immunocompromised patients, where 79.1% of BALs were found to be positive (range 42.9%-83.3%; 53/67)[16,20]. In ECLS patients, BAL identified an organism in 30.3% of procedures (range 21.3%-75%; 64/211)[17,19,23]. Five studies reported that BAL led to a change in antimicrobial therapy in 19.1% (range 12.2%-75%; 73/382) of patients[3,16,23,24,27]. Bar-Zohar *et al*[24] reported that in the 50% (15/30) of patients whose antibiotics were changed as a result of BAL findings, only 33% (10/30) of them improved clinically[24]. Concordance between BAL isolates and blind tracheal swab isolates was 47% (range 36%-67%; 8/17)[24,27]. In critically ill children, the use of BAL for non-infectious causes of pulmonary infiltrates was uncommon. Two isolated studies reported findings associated with aspiration in 67% (2/3) of cases and evidence of hemoptysis in 63% (5/8)[20,24].

Therapeutic efficacy

Therapeutic outcomes were reported in 17 of 27 studies. Overall, the therapeutic yield for FFB was 60.3% (range 23.8%-100%; 595/987). Interventions performed with FFB included lavage, removal of partial obstructions, and assistance with difficult intubations or failed extubations. An improvement in atelectasis after FFB was reported in 44.9% (range 15.4%-92%; 173/385)

of procedures[3,19,20,22,24,26,27,30,33]. In one study of 44 intubated children with status asthmaticus, FFB, compared to no FFB, was associated with decreased length of time on mechanical ventilation (20.5 h *vs* 10 h) and decreased PICU length of stay (3.4 d *vs* 3.1 d), but no change in total hospital length of stay[36]. In the three studies that examined the utility of FFB in assessing the etiology of extubation failure, FFB assisted in successful extubation in 69.9% of procedures (range 50%-90.5%; 51/73)[20,21,24] by removing mucus plugs or thrombus to assist with weaning from the ventilator. FFB was also used to identify patients with a normal exam who were ready for extubation[3,5,15,17,24]. Kohelet *et al*[27] found that in neonatal patients, therapeutic FFB in the NICU improved atelectasis in 75% (6/8) and decreased mechanical ventilation time.

Four studies reported the therapeutic yield of FFB in 174 patients receiving ECLS[17,19,22,23]. In these patients, repeat FFB to re-expand collapsed lobes was successful in 42.9% (range 15.4%-87.5%; 51/119). Furthermore, repeat therapeutic lavage was associated with decreased ventilator support, increased lung expansion and tidal volumes. Improved lung recruitment was associated with reduced ECLS support and, ultimately, separation from ECLS[17,19,22,23].

Adverse events

Sixteen studies that included 5060 bronchoscopies reported adverse events (Table 2). Overall, adverse events were reported in 12.9% (range 0.5%-71.4%; 654/5060) of FFBs performed. Serious adverse events requiring intervention were uncommon (2.1%; 108/5060). The most common adverse events were hypoxia, bradycardia, hypotension, and bleeding. Mild to moderate hypoxia (with oxygen saturations greater than 80%) was reported in 2.3% (range 0%-70.3%; 114/5060) of FFBs and usually resolved with removal of the FFB from the airway and/or supplemental oxygen[3,4,16,20,24,26,29,31,32]. In 6.1% (7/114) of patients with hypoxia, bag-mask ventilation was required for recovery. Bradycardia with hypoxia was reported in 0.4% (range 0%-4%; 21/5060) of FFBs performed[16,24,26,27,31-33]. A single study reported that 3.4% (11/319) of patients required atropine to treat bradycardia in addition to supplemental oxygen for hypoxia[16]. Hypotension occurred in 1.2% (range 0%-19.4%; 58/5060) of procedures performed, and a fluid bolus was given in 0.9% (46/5060) of all procedures[20,24,29]. Bleeding occurred in 4% (range 0%-37.5%; 198/5060) of overall procedures performed, and in most cases, resolved spontaneously or with suction[3,16,22,23,29,31,33]. In the 0.4% (range 0.4%-5.9%; 21/5060) of procedures that required intervention for hemostasis, saline or epinephrine lavage was sufficient to stop bleeding[16,19,23,31]. In patients receiving ECLS, who are at higher risk for bleeding secondary to systemic anticoagulation, 15.9% (range 0%-37.5%; 60/260) had bleeding after FFB[19,23]. Other reported complications included local trauma, such as pneumothorax or perforation (0.2%; 8/5060), stridor (0.3%; 14/5060), bronchospasm (0.5%; 24/5060), and fever (4.1%; 217/5060). Data on specific anesthetic risks were rarely reported. Three patients (0.1%; 3/2984), who received fentanyl in preparation for FFB, had rigid chest, and two of the three required intubation[20,23]. Two deaths were reported in high-risk neonates due to perforation of the mainstem bronchus. Both infants were subsequently found to have full thickness necrotizing tracheobronchitis[37].

DISCUSSION

FFB contributes to changes in clinical management, can assist in the diagnosis of upper and lower anatomic lesions of the respiratory tract, and is integral in identifying causes of respiratory distress and prolonged mechanical ventilation. Furthermore, FFB can be used for therapeutic interventions such as removal of obstructions and re-expansion of collapsed lung. Despite a consensus statement adopted by the American Thoracic Society in 1991, and guidelines by the European Respiratory Journal in 2003, there are no specific guidelines for FFB in critically ill pediatric and neonatal patients[9,10]. We have determined that there are populations for whom FFB is a high yield procedure and should be strongly considered (Table 3).

Change in clinical management is an important measure of the utility of FFB. We found that, in more than a third of cases, FFB was integral in changing patient care. This is similar to a study of adult ICU patients, in which 33% (29/87) of FFB led to a change in patient management[38,39]. We found that FFB significantly contributed to surgical planning in those without known respiratory anomalies, earlier surgical intervention in children with CHD, and change in the type of surgical intervention in children with esophageal atresia. FFB was also important in altering medical management, such as adjusting endotracheal suction techniques after identifying airway granulomas.

The overall diagnostic yield for FFB was 82%. While some studies included inflammation as a significant finding, even when these studies were excluded, the diagnostic yield was 75.2% (range 45.2%-100%; 1074/1428)[3,31,32]. This is higher than the 44% (44/87) diagnostic yield reported in critically ill adults[38]. The higher incidence of positive FFB in pediatric ICU patients may be secondary to the reluctance to perform early FFB in children, leading to severe and persistent symptoms prior to FFB. Specific populations in whom there was high diagnostic yield with FFB included children with CHD, children who failed extubation, and children with

Table 2 Adverse events reported with flexible bronchoscopy in critically ill pediatric patients

Ref.	Hypoxia	Bradycardia/ Hypoxia	Hypotension	Hemorrhage	Other
Bar-Zohar *et al*[24], 2004	0% (0/155)	0% (0/155)	19.3% (30/155) 12.9% (20/155) NS bolus	0% (0/155)	1.3% (2/155) intubated for mucus plug
Davidson *et al*[17], 2008				0% (0/200)	0.5% (1/200) patient "instability"
de Blic *et al*[4], 1991	70.3% (26/37) transient moderate hypoxia (SaO2 > 80)	0% (0/37)			
Efrati *et al*[16], 2009	6.6% (21/319), resolved - O_2 0.3% (1/319) - BMV 0.3% (1/319) required intubation	3.4% (11/319), resolved - O_2 and atropine		1.6% (5/319), resolved-saline lavage	1.6% (5/319) stridor resolved -steroids or epinephrine 0.9% (3/319) fever
Fan *et al*[26], 1988	2.3% (2/87), resolved - removal of scope or O_2	0% (0/87)			
Hintz *et al*[22], 2002				37.5% (3/8)	
Kamat *et al*[19], 2011				34.2% (53/155) mild to moderate blood tinged secretions 2% (3/155) placed on HFOV for increased bloody secretions	
Kohelet *et al*[27], 2011		Transient (number not reported)	0% (0/25)	0% (0/25)	4% (1/25) pneumothorax
Kotby *et al*[29], 2008	42.9% (15/35), transient		5.7% (2/35), transient	22.9% (8/35)	Decreased PaO_2
Manna *et al*[20], 2006	10.8% (16/148) transient; 16.7% (3/18) of ARDS patients		17.6% (26/148), NS bolus		0.6% (1/148) rigid chest after fentanyl
Nussbaum *et al*[31], 2002	0.7% (21/2836), of those 76.2% (16/21) resolved - removal of scope or O_2; 23.8% (5/21) emergency intubation; 2/5 apneic prior to FFB	Transient (number not reported)	0% (0/2836)	4% (113/2836) mild nasopharyngeal bleeding 0.4% (12/2836) bleeding after biopsy, resolved - epinephrine lavage	Transient stridor (number not reported) 0.6% (17/2836) laryngo/ bronchospasm, resolved - albuterol and O_2, BMV 9.5% (2/21) rigid chest after fentanyl
Peng *et al*[32], 2011	Transient (number not reported)	Transient (number not reported)			0.8% (6/725) laryngospasm, resolved - lidocaine spray and NIPPV 0.3% (2/725) pneumothorax 29.5% (214/725) fever
Pietsch *et al*[37], 1985					13.3% (2/15) death secondary to mainstem bronchus perforation 6.7% (1/15) pneumothorax - chest tube
Prentice *et al*[23], 2011				5.9% (1/17), resolved - epinephrine lavage	
Soong *et al*[33], 1995		4% (10/247) transient, resolved - removal of scope or O_2 1.2% (3/247) required BMV		Self-limited nasal bleeding (number not reported)	2% (5/247) stridor
Tang *et al*[3], 2009	20.8% (11/53), mild			3.8% (2/53), mild	1.9% (1/53) SVT 1.9% (1/53) pneumothorax 1.9% (1/53) bronchospasm

ARDS: Acute respiratory distress syndrome; BMV: Bag mask ventilation; FFB: Flexible fiberoptic bronchoscopy; HFOV: High frequency oscillatory ventilation; NIPPV: Noninvasive positive pressure ventilation; NS: Normal saline; O_2: Oxygen; PaO_2: Arterial partial pressure of oxygen; SVT: Supraventricular tachycardia.

concern for upper airway abnormalities. Therefore, we propose that FFB should be strongly considered in the early evaluation of patients with CHD, children who failed extubation, and children with suspected upper airway abnormalities (Table 3).

BAL was used to identify causative organisms

Table 3 Recommended indications for flexible bronchoscopy in critically Ill children

Recommend	Consider
Upper airway symptoms (*e.g.*, stridor)	CHD with persistent atelectasis
BAL in immunocompromised + respiratory distress	ECLS with persistent atelectasis
BAL in immunocompetent + respiratory distress AND + new/persistent fever AND infiltrate on chest X-ray on existing therapy	Prolonged mechanical ventilation
	Esophageal atresia
	Asthma intubated + persistent atelectasis

BAL: Bronchoalveolar lavage; ECLS: Extracorporeal life support; FFB: Flexible fiberoptic bronchoscopy; CHD: Congenital heart disease.

and tailor antibiotic management. The emergence of antibiotic resistant organisms requires that clinicians have the ability to tailor therapy. Thus, BAL may play a critical role in antibiotic stewardship. The 50% concordance of BAL with blind tracheal aspirates supports the use of BAL rather than blind tracheal aspirates in patients who are not improving on current antibiotic management. We found the highest yield of BAL culture was in patients who are immunocompromised (79%) or had a new fever with infiltrate on chest X-ray. Similar findings have been reported in critically ill adults, where BAL identified an organism in 24% (150/616) of procedures, with the highest yield (36%; 47/129) among immunocompromised patients[39]. Our findings support the use of FFB to obtain BAL in the immunocompromised host with respiratory insufficiency or in patients with pneumonia not responding to current antibiotic therapy (Table 3). Additional consideration should be given to FFB in the ECLS population[17,19,23]. In patients receiving ECLS, common clinical signs of infection may be obscured since body temperature is controlled *via* the ECLS circuit and systemic inflammatory response syndrome can be induced by ECLS. A high index of suspicion for infection is warranted in patients receiving ECLS who develop new infiltrates or have difficulty weaning from ECLS support. Therefore, FFB should be considered promptly in these patients.

FFB is an important therapeutic option for patients with respiratory compromise. Overall, greater than 50% of patients who underwent FFB for a therapeutic intervention achieved some benefit. This is similar to adult studies where 44% (range 22%-89%; 64/147) of patients received therapeutic benefit from bronchoscopy[38,40,41]. In pediatric studies, several specific populations appeared to derive the most benefit from therapeutic FFB. In a single study of patients with respiratory failure from asthma who underwent FFB, mucus plug removal was associated with improved oxygenation and lung expansion on chest X-ray, reduced ventilator support, and shorter PICU length of stay[36]. In patients receiving ECLS, FFB was associated with reduced need for ECLS support, particularly when bronchoscopy was performed multiple times. FFB may have the ability to decrease morbidity and mortality associated with prolonged ECLS support since FFB may improve respiratory mechanics and thus need for ECLS[42]. FFB has only recently become a treatment modality in the NICU with the advent of ultrathin bronchoscopes. An important consideration in this population is the impact of mechanical ventilation on premature and developing lungs. By treating atelectasis and decreasing time on mechanical ventilation, FFB in the NICU may ameliorate subglottic stenosis and chronic lung disease seen with prolonged ventilation. We suggest that therapeutic bronchoscopy be considered in intubated patients with asthma and atelectasis, patients receiving ECLS, and NICU patients with difficulty weaning from mechanical ventilation (Table 3). The recommendation to perform FFB in neonates to evaluate difficulty weaning from mechanical ventilation is in accord with the European Respiratory Journal guidelines, which support the use of FFB in neonates to evaluate for subglottic stenosis and other airway abnormalities. However, recommendations for FFB for asthmatic and ECLS dependent populations are not specified in either the European Respiratory Journal or the American Thoracic Society guidelines[9,10].

We found that 2.1% of pediatric patients who undergo FFB had adverse events that required a medical intervention, which is similar to the 2% (range 1.6%-4%; 17/814) reported in the adult populations[38,39]. Interventions were minor, including halting the procedure to allow spontaneous recovery from hypoxia, providing supplemental oxygen, and administering fluid boluses for hypotension. The patient populations with the highest proportion of complications were those receiving ECLS and immunocompromised patients. Patients receiving ECLS were systemically anticoagulated, and had more frequent bleeding complications requiring intervention with suctioning, saline lavage or local epinephrine. Whether the higher proportion of complications in immunocompromised patients is secondary to higher disease burden or directly related to the procedure itself is unclear. Nonetheless, adverse events requiring interventions including bag-mask ventilation and intubation were higher in this group. Due to insufficient data, we were not able to derive any meaningful interpretation regarding adverse events from sedatives used during FFB. In the studies that reported complications related to sedation, the most serious was rigid chest from fentanyl given pre-procedure in three patients who

were not intubated. In our review, studies reported a mix of intubated and non-intubated patients who underwent FFB. While there was not a reported difference in adverse events in those with a secured airway as compared to those with a natural airway, the considerations to undertake the procedure may be different. For example, sedation choices may vary, and consideration of bronchoscope size relative to airway becomes important when the approach is through the nares. Finally, there may be increased risk of adverse events in patients who undergo multiple FFBs, although this finding was not born out in our review.

Limitations

Our study has several limitations. We did not assess study quality in this review. Our inclusion criteria were broad to maximize our assessment of the available literature on the use of flexible bronchoscopy in critically ill children. Thus, the only studies excluded were case reports. We used standard methodology to identify papers to include in our review; however, it is possible that we may have missed publications. We limited our review to papers in English, and may have seen different results in non-English language publications. Included studies did not always distinguish between patients admitted to the ICU for procedural sedation and those that were critically ill. Thus, it is possible that not all patients included in this review were critically ill. Children with foreign body aspiration were excluded from our study because foreign body aspiration should be removed by rigid bronchoscopy.

Many of the included studies did not report quantitative outcomes after FFB, making it difficult to draw conclusions about specific risks or benefits of the procedure (*e.g.*, a study may have mentioned improvement in ventilator settings, but did not quantify this in a meaningful way). Some studies also reported normal examinations as part of their diagnostic yield. Furthermore, one of the concerns regarding the use of FFB in pediatric populations is the anesthetic risk in these patients. According to the pediatric guidelines by the American Thoracic Society, adverse reactions to medications account for at least half of complications associated with FFB[9]. In many of the included studies, it was difficult to differentiate anesthetic complications from procedural complications. Future studies should examine complications due to sedatives among patients who undergo FFB.

We have identified patient populations in whom FFB should be strongly considered. Given the overall high diagnostic and therapeutic yield, there is a rationale to perform FFB more frequently in critically ill children. Our data suggest that experienced bronchoscopists be readily available to evaluate and treat critically ill neonates and children. This begs the question: how will this demand be met? Currently, the majority of pediatric bronchoscopists are pulmonologists or otolaryngologists. Our data supports the need for pediatric intensivists to be trained in this procedure. Indeed, Kohelet *et al*[27] proposed that neonatologists be trained in bedside FFB, given the high incidence of respiratory pathology in the NICU[27]. Finally, more outcomes-based research regarding FFB and its impact on morbidity and mortality is needed in the NICU and PICU. Well-designed prospective, randomized multi-center trials to investigate clinical outcomes including mortality, length of mechanical ventilation, and length of ICU and hospital stay are needed. Furthermore, unlike in adults, the use of interventional FFB for procedures such as endobronchial stents, airway laser procedures, and endobronchial or transbronchial lung biopsies has received limited investigation in the pediatric population[32]. Further studies of the safety and efficacy of interventional FFB could have significant impact in reducing open surgical procedures in children.

Our study identified indications, as well as diagnostic and therapeutic utility for FFB in critically ill children. In this review, FFB was associated with very few complications. This study provides the foundation for guidelines for FFB in critically ill children. Randomized studies are needed to investigate the impact of FFB on clinical outcomes.

COMMENTS

Background

Flexible fiberoptic bronchoscopy (FFB) is used with increasing frequency in neonatal and pediatric populations. However, there are no recent guidelines regarding its use in these populations.

Research frontiers

The indications for use of FFB in critically ill children are not well delineated. Understanding the diagnostic yield, therapeutic efficacy, and rate of adverse events related to FFB in critically ill children will help determine the indications for use of FFB in critically ill children.

Innovations and breakthroughs

FFB led to a change in medical management in 28.9% of critically ill children, with a diagnostic yield of 82%. Bronchoalveolar lavage obtained during FFB may assist with identifying infectious organisms (25.7%) and optimizing antimicrobial therapy (19.1%). FFB had therapeutic benefit with removal of mucus plugs or resolution of atelectasis in 60.3%. The majority of reported adverse events were transient and included hypotension, hypoxia and/or bradycardia requiring minimal intervention.

Applications

FFB is effective and safe for diagnostic and therapeutic use among critically ill pediatric patients. In particular, FFB is recommended in patients with upper airway symptoms (*e.g.*, stridor), in immunocompromised patients with respiratory distress, and in immunocompetent patients with respiratory distress in addition to fever and/or persistent infiltrates on chest X-ray.

Terminology

FFB is a procedure that allows visualization of the upper and lower airways using a flexible bronchoscope. FFB can also be used to remove fluid or mucous plugs from the airways. Bronchoalveolar lavage is a procedure where fluid is squirted through the bronchoscope into the lungs and then recollected in order to diagnose lung disease.

Peer-review

A well written paper with good research of English literature.

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Thoracic epidural anesthesia: Effects on splanchnic circulation and implications in Anesthesia and Intensive care

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Abstract

AIM: To evaluate the currently available evidence on thoracic epidural anesthesia effects on splanchnic macro and microcirculation, in physiologic and pathologic conditions.

METHODS: A PubMed search was conducted using the MeSH database. Anesthesia, Epidural was always the first MeSH heading and was combined by boolean operator AND with the following headings: Circulation, Splanchnic; Intestines; Pancreas and Pancreatitis; Liver Function Tests. EMBASE, Cochrane library, ClinicalTrials.gov and clinicaltrialsregister.eu were also searched using the same terms.

RESULTS: Twenty-seven relevant studies and four ongoing trials were found. The data regarding the effects of epidural anesthesia on splanchnic perfusion are conflicting. The studies focusing on regional macro-hemodynamics in healthy animals and humans undergoing elective surgery, demonstrated no influence or worsening of regional perfusion in patients receiving thoracic epidural anesthesia (TEA). On the other hand most of the studies focusing on micro-hemodynamics, especially in pathologic low flow conditions, suggested that TEA could foster microcirculation.

CONCLUSION: The available studies in this field are heterogeneous and the results conflicting, thus it is difficult to draw decisive conclusions. However there is increasing evidence deriving from animal studies, that thoracic epidural blockade could have an important role in modifying tissue microperfusion and protecting microcirculatory weak units from ischemic damage, regardless of the effects on macro-hemodynamics.

Key words: Anesthesia; Epidural; Circulation; Splanchnic; Intestine; Microcirculation; Pancreatitis; Liver function tests

Core tip: Effects of thoracic epidural anesthesia on splanchnic circulation are still poorly understood. The influence on macro-hemodynamics seems to vary based on the metameric extension of the blockade, the volume repletion and the hemodynamic status of the patient. Thus epidural anesthesia could reduce regional blood flow to splanchnic organs and have detrimental effects on oxygen delivery. However, there is increasing

evidence, in particular deriving from animal studies, of a possible protective effect on microcirculation of the epidural blockade, especially in low flow states. In fact, despite reducing perfusion pressure, thoracic epidural anesthesia could foster perfusion of microcirculatory weak units and reduce local dysoxia.

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INTRODUCTION

Thoracic epidural anesthesia is a widely used anesthetic technique providing excellent intra and postoperative analgesia. In recent years there have been efforts to further understand the effects of the sympathetic blockade this technique produces, in particular on the vascular perfusion. These effects may have a role in protecting the intestinal mucosa from injury, and promoting tissue healing, both in surgery and in pathologic scenarios such as acute pancreatitis. However, the mechanisms of organ protection and splanchnic hemodynamic effects of epidural anesthesia are not entirely clear yet, and the available evidence is conflicting.

Aims of the review

This systematic review intends to evaluate the currently available evidence on the effects of thoracic epidural anesthesia on the splanchnic macro and microcirculation, in physiologic and pathologic conditions. Animal and human studies were taken into consideration.

MATERIALS AND METHODS

A PubMed search was conducted using the MeSH database. "Anesthesia, Epidural" was always the first MeSH heading and was combined by boolean operator and with the following headings: Circulation, Splanchnic; Intestines; Liver Function Tests; Pancreas; Pancreatitis.

EMBASE and Cochrane library were also searched using the same terms.

Finally ClinicalTrials.gov and clinicaltrialsregister.eu was also searched using the term "epidural anesthesia".

The abstracts were reviewed by three independent researchers and those not relevant to the search were excluded, only English language articles were taken into consideration. The quality of the studies was assessed using the Delphi List[1].

RESULTS

The search in Pubmed, EMBASE and Cochrane library produced a total of 245 results. Based on the review of the abstracts 219 were found not to be relevant and excluded. The full papers of the remaining 26 articles were independently reviewed by 3 researchers (Figure 1).

The Clinicaltrials.gov search produced a total of 420 studies, only 4 of these were relevant to our review. None of the trials found in clinicalregister.eu were relevant to the search terms (Figure 1).

Effects of epidural anesthesia on splanchnic circulation

The literature research found 26 studies related to splanchnic circulation, of these 17 were animal and 9 human studies.

Animal studies: Animal studies evaluating splanchnic regional macro-hemodynamics are synthesized in Table 1.

Three studies[2-4] used centrally injected radioactive or colored microspheres to determine cardiac output and regional blood flow. The regional flow could be estimated by measuring organ or regional arterial blood samples radioactivity, or by microscopy after autopsy.

Sivarajan *et al*[2] evaluated the effects of low (T10) and high (T1) epidural anesthesia on systemic hemodynamics and regional blood flow in anesthetized monkeys. The main findings of this study were that both CO and arterial blood pressure significantly decreased in both groups and more significantly in the high epidural T1 group. Low level epidural blockade did not significantly change absolute blood flow in splanchnic organs, while high blockade produced a significant reduction in hepatic blood flow.

Schäper *et al*[3] studied the influence of a continuous epidural lidocaine infusion in animal models of endotoxemia, induced by continuous *i.v.* infusion of *Escherichia Coli* lipopolysaccharide (LPS). The result showed that blood flow to the gastrointestinal organs (stomach and ileum) was significantly higher in the epidural group despite a lower Mean arterial pressure (MAP). Hepatic blood flow initially decreased after the onset of the epidural blockade, but was comparable to the one in control groups in the course of LPS infusion. Finally the decrease in pH and base excess induced by endotoxemia was partially blunted by epidural blockade.

Meissner *et al*[4] evaluated the effects of a thoracic epidural block on splanchnic blood flow in either awake or anesthetized dogs. No difference was found between the two groups, only an increase in liver perfusion when propofol was used as anesthetic agent.

Vagts *et al*[5] evaluated the effects of volume

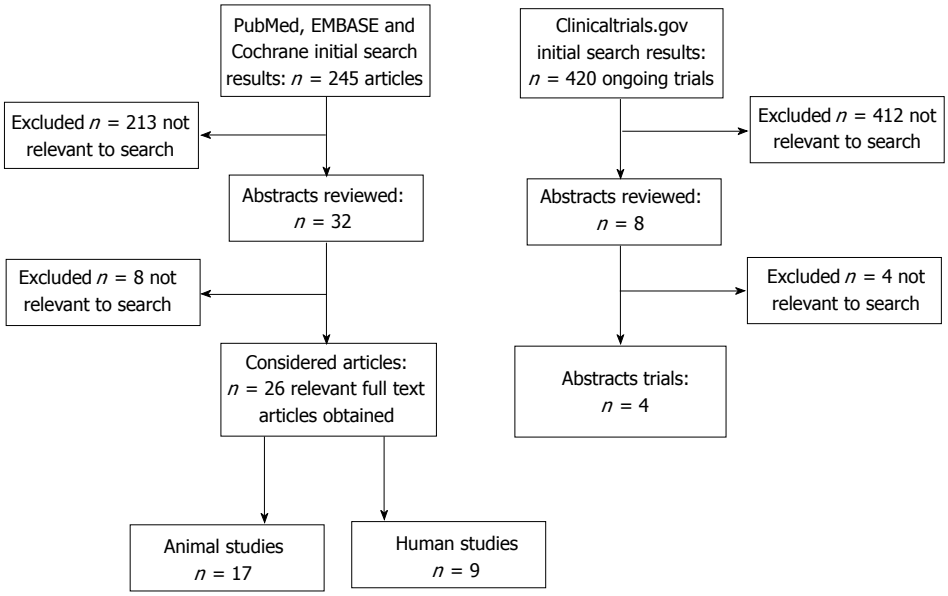

Figure 1 Floe chart showing selection of studies.

loading on hepatic perfusion in animals undergoing surgery with blended anesthesia. The hepatic flow measurement was obtained using perivascular flow-probes around the hepatic artery and portal vein; liver tissue PO_2, plasma disappearance rate of indocyanine green (PDR_{ICG}), total hepatic DO_2 and VO_2 were also recorded. The main finding of this study was that the reduction in MAP induced by thoracic epidural blockade, was not associated with a decrease in total hepatic blood flow, DO_2 and parenchymal PO_2. Volume loading could not modify macrohemodynamic parameters but significantly reduced portal venous oxygen content.

Ai *et al*[6] considered an animal model of systemic hypoxemia, finding that epidural blockade produced higher intramucosal and arterial pH, lower portal endotoxin and lower arterial lactate levels when compared to a control group. Portal blood flow remained stable during progressive hypoxia and was unaffected by epidural blockade.

Animal studies evaluating intestinal and pancreatic microhemodynamics are synthesized in Table 2.

Hogan *et al*[7,8], in two studies on rabbits, measured sympathetic efferent nerve activity, through surgically implanted electrodes in a postganglionic splanchnic nerve, and *in vivo* mesenteric vein diameter, to estimate venous capacitance.

The first protocol[7] compared the effects of a thoraco-lumbar epidural block using different lidocaine concentrations (T2-L5), with injection of i.m. lidocaine. The results showed a reduction in sympathetic efferent nerve activity, and an increase in mesenteric vein diameter in animals treated with epidural lidocaine.

The second study[8] investigated the different effects of a Thoracic (T4-L1) Thoracolumbar (T1-L4) and Lumbar (T11-L7) epidural block. The results showed that Thoracic and Thoracolumbar blocks reduced sympathetic tone and increased mesenteric vein diameter, whilst a lumbar block produced opposite effects.

Kosugi *et al*[9] investigated the effect of epidural analgesia on intestinal macro and microhemodynamics and the alterations in gut barrier function elicited by continuous endotoxin infusion in rabbits. The histopathological evaluation of the intestinal mucosa samples, showed that epidural anesthesia reduced injury. Moreover higher intramucosal pH, and reduced mucosal permeability, were recorded in animals treated with thoracic epidural blockade, despite a decrease in perfusion pressure and arterial oxygen content.

Intravital microscopy of the ileus was used as an indirect measure of splanchnic flow in 5 studies[10-14].

Sielenkämper *et al*[10] found, in anesthetized rats treated with epidural bupivacaine, an increase in arteriolar red blood cell velocity, expressing an increase in gut mucosal blood flow despite a lower MAP. Also, intercapillary area calculated for continuously perfused capillaries, was reduced in the TEA group, indicating a decrease in intermittent blood flow in the villus microcirculation.

Adolphs *et al*[11,12] investigated the effect of thoracic epidural anesthesia in hemorrhagic hypotension and normotensive endotoxemia in rats.

In the hemorrhagic hypotension model[12], the pH and base excess, and muscularis layer capillary perfusion, were significantly improved in the group receiving epidural anesthesia. Moreover, leukocyte rolling after resuscitation was attenuated in thoracic epidural anesthesia (TEA) group, indicating a reduction in postischemic tissue injury.

In the normotensive endotoxemia model[11], despite a lower MAP and an overall decrease in

Table 1 Animal studies evaluating macrohemodynamics and liver microhemodynamics

Subjects	Ref.	Year	Title	Type of study	Scenario	No. subjects	Sensory blockade	Surrogate measure of splanchnic flow	Findings
Monkeys	Sivarajan *et al*[2]	1976	Systemic and regional blood flow during epidural anesthesia without epinephrine in the rhesus monkey	Prospective randomized	Anesthetized animals, epidural catheter placed L1-L2	9 (4 low epidural aneshtesia - level T10 *vs* 5 high epidural anesthesia - level T1)	higher level T10 or T1	Radioactive microspheres and direct invasive monitoring of cardiac output	Low epidural - no difference in blood flow to major organs, while T1 epidural ↓ blood flow to liver, pancreas and gut (hepatic artery, portal vein)
Dogs	Meissner *et al*[4]	1999	Limited upper thoracic epidural block and splanchnic perfusion in dogs	Prospective observational	Induction of upper thoracic epidural in awake and anesthetized dogs and measurements of splanchinc perfusion	13 (6 anesthetized, 7 no)	T1-T5	Coloured microspheres injected in the aorta and then collected from tissue samples after autopsy	High TEA had no effect on sympathetic activity and splanchnic blood flow, nor in the awake nor anesthetized state. Propofol anaestehsia increased liver perfusion
Rabbits	Ai *et al*[6]	2001	Epidural anesthesia retards intestinal acidosis and reduces portal vein endotoxin concentrations during progressive hypoxia in rabbits	Prospective randomized	Progressive hypoxia in anesthetized animals	18 (9 TEA/ Lidocaine *vs* 9 TEA/NaCl 0.9%)	insertion point T12-L1 and 3-4 cm advancement	Portal blood flow, portal oxygen extraction ratio, portal pH, portal Lactate, intramucosal pH (pHi) of the ileum, portal endotoxin	pHi and pHart significantly higher and portal Endotoxin and Lactate significantly lower in TEA/Lido group. No diifferences in portal blood flow
Pigs	Vagts *et al*[5]	2003	The effects of thoracic epidural anesthesia on hepatic perfusion and oxygenation in healthy pigs during general anesthesia and surgical stress	Prospective randomized	Anesthetized and acutely instrumented pigs, assigned to 3 groups: control *vs* TEA plus basic fluid (BF) *vs* TEA plus VL	19 (3 CTRL; 8 TEA alone; 8 TEA + VL)	T5 to T12	Hepatic blood flow using ultrasonic transit-time perivascular flowprobes around the hepatic artery and portal vein; multiwire surface electrode placed onto the liver to measure tissue surface PO_2; PDR-icg	Despite a decrease in MAP, TEA had no effect on total hepatic blood flow, liver DO_2 and VO_2. Liver tissue PO_2 did not decrease. Lactate uptake and PDR-icg remained unchanged. Volume loading did not show any benefit with regard to hepatic perfusion, oxygenation, and function
Rats	Shäper *et al*[3]	2010	TEA attenuates endotoxin induced impairment of gastro intestinal organ perfusion	Prospective randomized	Sepsis model through infusion of LPS, evaluation of regional flow at 30', 60', 120'	18 (9 TEA *vs* 9 sham)	T4-T11 (methilen blue spread)	Fluorecent microspheres withdrawal technique, then evaluation of microspheres in brain, heart, ileopsoas muscle, liver pancreas gut segments; determination plasma cathecolamines	TEA ↑ blood flow to GIT organs under LPS effect
Studies evaluating liver micro hemodynamics									

Rats	Freise *et al*[17]	2009	Hepatic effects of TEA in experimental severe acute pancreatitis	Prospective randomized blinded image analysis	Animal model of acute pancreatitis induced by taurocholate injection or sham lesion	28 (7 sham + sham, 7 sham + TEA, 7 pancreat + sham, 7 pancreat + TEA) an additional 22 animals were assigned to the three group to asses hepatic apoptosis	catheter tip placed T6	Intravital microscopy of liver left lobe, cell adehesion to sinusoid wall (rollers and stickers), apoptosis of cells by Fas-L pathway	TEA ↑ diameter of sinusoids in pancreatitis, TEA ↓ the number of parenchymal apoptotic cells in pancreatitis (Fas-L pathway), TEA does not have much influence in sham groups
Rats	Freise *et al*[18]	2009	TEA reduces sepsis related hepatic hyperperfusion and reduces leucocyte adehesion in septic rats	Prospective randomized blinded image analysis	Sepsis model induced with cecal ligation and perforation	24 (8 sham + sham, 8 sepsis + sham, 8 sepsis + TEA); another 21 animals were assessed for liver failure and hemodynamics	catheter tip placed T6	Intravital microscopy of liver left lobe, cell adehesion to sinusoid and venules, serum transaminase activity, TNFα activity	TEA ↓ sinusoid dilation in sepsis by probably restoring hepatic arterial buffer response. TEA ↓ temporary adhesion to sinusoid wall but did not affect permanent adhesion. TEA did not affect transaminase or TNF activity. No differences in hemodynamics

↑: Increase; ↓: Decrease; VL: Volume loading; TEA: Thoracic epidural anesthesia; CTRL: Control; MAP: Mean arterial pressure; PDRICG: Plasma disappearance rate of Indocyanine Green; LPS: Lipopolysaccharide; GIT: Gastrointestinal tract; HR: Heart rate; PEEP: Positive end expiratory pressure; HES: Hydroxyethyl starch; PCO_2: Carbon dioxide partial pressure; LEA: Lumbar epidural anesthesia; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2 Animal studies evaluating intestinal and pancreatic microhemodynamics

Subjects	Ref.	Year	Title	Type of study	Scenario	No. subjects	Sensory blockade	Surrogate measure of splanchnic flow	Findings
Rabbits	Hogan *et al*[7]	1993	Effects of epidural and systemic lidocaine on sympathetic activity and mesenteric circulation in rabbits	Prospective randomized	Anesthetized animals receiving thoraco-lumbar epidural block with different anesthetic concentrations	32 (7 lidocaine 6 mg/kg *im vs* 5 lidocaine 15 mg/kg *im vs* 5 TEA lido 0.5% *vs* 8 TEA lido 1.0% *vs* 7 TEA lido 1.5%)	T2-L5	Mesenteric vein diameter, sympathetic efferent nerve activity (SENA) of post ganglionic splanchnic nerve	TEA ↑ splanchnic venous capacitance and ↓ SENA
Rabbits	Hogan *et al*[8]	1995	Region of epidural blockade determines sympathetic and mesenteric capacitance effects in rabbits	Prospective randomized	Anesthetized and non anesthetized animals receiving either a thoracic or lumbar block with special epidural catheters limiting anesthetic spread	26 (6 lidocaine 1% TEA *vs* 6 lido 1% LEA, *vs* 8 thoracolumbar anesthesia in spontaneous ventilation with lido 1% *vs* 6 thoracolumbar anesthesia with lido 1% in fully awake animals)	T11-L7 (LEA group), T4-L1 (TEA group), T1-L4 (thoracolumbar anesthesia)	Mesenteric vein diameter, sympathetic efferent nerve activity (SENA) of post ganglionic splanchnic nerve	↑ SENA and ↓ mesenteric vein diameter after lumbar epidural anesthesia while ↓ SENA and ↑ mesenteric vein diameter after thoracic epidural anesthesia
Rats	Sielenkämper *et al*[10]	2000	Thoracic epidural anesthesia increases mucosal perfusion in ileum of rats	Prospective randomized	Anesthetized and mechanically ventilated rats that underwent laparotomy to obtain access to the ileum	19: 11 bupivacaine 0.4% (TEA); 8 normal saline (CTRL)	Catheter tip placed T7-T9	Intravital microscopy on the ileum mucosa	TEA ↑ gut mucosal blood flow and ↓ the extent of intermittent flow in the villus microcirculation
Rats	Adolphs *et al*[12]	2003	Thoracic epidural anesthesia attenuates hemorrhage-induced impairment of intestinal perfusion in rats	Prospective randomized	Hemorragic shock model (PAM 30 mmHg for 60 min) induced by withdrawal of blood and subsequent retransfusion for resuscitation	32 (4 groups of 8); epidural lidocaine 2% (TEA) or normal saline (CTRL), muscolaris or mucosa evaluated	catheter tip placed T11-T12	Intravital microscopy with fluorescein (FCD = functional capillary density and erythrocyte velocity in the mucosa and muscularis of distal ileum)	TEA ↑ intestinal microvascular perfusion and ↓ hypotension-induced impairment of capillary perfusion in the muscularis, ↓ systemic acidemia during hypotension and ↓ leukocyte rolling after resuscitation

Rats	Adolphs *et al*[11]	2004	Effects of thoracic epidural anaesthesia on intestinal microvascular perfusion in a rodent model of normotensive endotoxaemia	Prospective randomized	Normotensive endotoxaemia model through LPS infusion in anesthetized animals	32 (8 no TEA *vs* 24 TEA) +/- *E.coli* LPS infusion +/- epidural lidocaine 2% or saline infusion, muscolaris or mucosa evaluated	catheter tip placed T11-T12	Intravital microscopy with fluorescein (densities of perfused and non-perfused capillaries and erythrocyte velocity in both the mucosa and the muscularis of the terminal ileum)	TEA ↓ MAP and HR, ↑ muscularis and ↓ mucosal microvascular perfusion
Dogs	Schwarte *et al*[15]	2004	Effects of thoracic epidural anaesthesia on microvascular gastric mucosal oxygenation in physiological and compromised circulatory conditions in dogs	Prospective randomized	Chronically instrumented and anaesthetized dogs. Animals were studied under physiological and compromised circulatory conditions (PEEP 10 cm H(2)O), both with and without fluid resuscitation	12 (6 lidocaine *vs* 6 saline)	catheter tip placed T10, thoracolumbar - paresis of the ocular nictitating membrane, sensory block up to the neck region, and motor block of the limbs	Gastric mucosal oxygenation by measuring microvascular haemoglobin oxygen saturation (μHbO2) using reflectance spectrophotometry	Under physiological conditions, TEA preserved gastric mucosal oxygenation but aggravated its reduction during impaired circulatory conditions, thereby preserving the correlation between gastric mucosal and systemic oxygenation. Fluid resuscitation completely restored these variables
Rabbits	Kosugi *et al*[9]	2005	Epidural analgesia prevents endotoxin-induced gut mucosal injury in rabbits	Prospective randomized	Normotensive endotoxaemia model through LPS infusion in anesthetized animals	PROTOCOL 1: 28 = 14 saline (C = CONTROL) *vs* 14 lidocaine (E = EPIDURAL); PROTOCOL 2: 20, into groups C or E (10 each group)	catheter placed *via* T11-T12 interspace	PROTOCOL 1: Measurements of systemic and splanchnic variables using catheter inserted through the mesenteric vein and perivascular probe attached around the portal vein. Intramucosal pH using tonometer catheter surgically inserted into the terminal ileum. Mucosal edema and microstructure of the terminal ileum using tissue sampling to determine wet-to-dry weight ratio and histological analysis (histopathological injury scores of gut mucosa). PROTOCOL 2: gut permeability using fluorescence spectrometry	The application of epidural analgesia in endotoxemic hosts attenuates the progression of intramucosal acidosis, the increase of intestinal permeability, and the structural alterations of intestinal villi, possibly throught the restoration of microcirculation, despite a significant decrease of perfusion pressure and arterial oxygen content

Rats	Freise *et al*[13]	2006	Thoracic epidural analgesia augments ileal mucosal capillary perfusion and improves survival in severe acute pancreatitis in rats	Prospective randomized	Animal model of acute pancreatitis (AP) induced by taurocholate injection or sham lesion	28 (4 groups of 7): sham + saline TEA (Sham) *vs* AP + saline TEA (PANC) *vs* AP + TEA (EPI) *vs* AP + delayed TEA (delayed EPI). Outcome protocol: (n = 30): 15 AP *vs* 15 TEA	catheter tip placed T6	Intravital microscopy of the ileal mucosa	TEA ↓ intercapillary area (↑ local perfusion) ↓ IL-6 and serum lactate and ↓ 66% mortality
Rats	Daudel *et al*[14]	2007	Continuous thoracic epidural anesthesia improves gut mucosal microcirculation in rats with sepsis	Prospective randomized, blinded image analysis	Sepsis model induced with cecal ligation and perforation (CLP)	27 (10 CLP/TEA *vs* 9 CLP/Control *vs* 8 sham laparotomy)	catheter tip placed T6	Intravital videomicroscopy performed on villi of ileum mucosa	Smaller intercapillary area hence ↑ villus perfusion in CLP/TEA *vs* CLP/Control. Diameter of terminal arterioles and red blood cell velocity didn't differ
Pigs	Bachmann *et al*[16]	2013	Effects of thoracic epidural anesthesia on survival and microcirculation in severe acute pancreatitis: a randomized experimental trial	Prospective randomized	Animal model of SAP induced by intraductal injection of glycodesoxycholic acid in the main pancreatic duct followed by closure	34: 17 bupivacaine *via* TEA after induction of SAP (TEA) *vs* 17 no TEA (control)	catheter introduced T7-T8 and advanced 2 cm (documented by epidurogram)	Continuous measurement of the tissue oxygen tension (tpO_2) using a flexible polarographic measuring probe placed in the pancreatic head and pancreatic microcirculation using Laser-Doppler imager during a period of 6 h after induction SAP. Histopathologic tissue damage (histopathologic severity score of acute pancreatis) by postmortem examination of the animals sacrificed after 7 d of observation	TEA improved survival as well as pancreatic microcirculation and tissue oxygenation resulting in reduced histopathologic tissue-damage

↑: Increase; ↓: Decrease. TEA: Thoracic epidural anesthesia; LEA: Lumbar epidural anesthesia; SAP: Severe acute pancreatitis.

mucosal functional capillary density, epidural infusion of lidocaine reduced the non-perfused capillaries in the muscularis layer after 120 min of continuous LPS infusion. Moreover, erythrocyte velocity decreased in the mucosa and muscularis layer during endotoxemia, but was not influenced by epidural blockade.

Freise *et al*[13] in a rodent model of acute pancreatitis, found a decrease in ileal mucosa intercapillary area, IL-6 and lactate levels, in animals treated with both immediate or delayed epidural injection of local anesthetic. These results indicate that a thoracic epidural block improved local perfusion. This group had also lower scores of pancreatic injury and a 66% decrease in mortality.

Daudel *et al*[14] induced sepsis by cecal ligation and perforation in rats, finding a significant decrease in intercapillary area in the group treated with TEA, without differences in terminal arterioles diameter and red blood cells velocity.

Schwarte *et al*[15] evaluated the effects on gastric mucosal oxygenation of epidural anesthesia and volume loading, in either normal or compromised circulation, in dogs. Hemodynamic failure was induced with high PEEP levels.

In healthy animals, TEA induced a reduction in MAP and DO_2, preserving gastric mucosal oxygenation. In compromised circulatory conditions, TEA aggravated the reduction of gastric mucosal oxygenation; volume loading restored both DO_2 and mucosal oxygenation. TEA maintained a constant relationship between gastric mucosal and systemic oxygenation.

Bachmann *et al*[16], evaluated a porcine model of acute pancreatitis finding that TEA enhanced

Table 3 Human studies

Ref.	Year	Title	Type of study	Scenario	No. subjects	Sensory blockade	Surrogate measure of splanchnic flow	Findings
Lundberg *et al*[19]	1990	Intestinal hemodynamics during laparotomy: effects of thoracic epidural anesthesia and dopamine in humans	Prospective observational	Patients undergoing abdominal aorto-bifemoral reconstruction	9	Catheter inserted T7-T8 or T8-T9 and advanced 2-3 cm	Superior mesenteric artery blood flow (SMABF) *via* electromagnetic flow probe, mesenteric arteriovenous oxygen difference mesenteric venous lactate	↓ SMABF and ↓ MAP only restored by dopamine infusion
Tanaka *et al*[23]	1997	The effect of dopamine on hepatic blood flow in patients undergoing epidural anesthesia	Prospective controlled	Patients ASA 1-2 undergoing elective gynecological surgery. Normotension maintained either with HES infusion or HES + dopamine	28 (7 no TEA *vs* 14 TEA + HES *vs* 7 TEA + HES + dopamine)	Upper T5	Hepatic blood flow using Plasma Disappearance Rate of indocyanine green (PDR-icg)	↓ PDR-icg in TEA + HES group, = PDR-icg in TEA + HES + dopamine group
Väisänen *et al*[25]	1998	Epidural analgesia with bupivacaine does not improve splanchnic tissue perfusion after aortic reconstruction surgery	Prospective randomized controlled	Patients undergoing elective aortic reconstruction surgery	20 (10 TEA *vs* 10 controls)	Catheter inserted T12-L1 and advanced 5 cm	Gastric and sigmoid mucosal PCO_2, pHi. Splanchnic blood flow direct invasive measure by cannulation of hepatic vein and dye diluition method (indocyanine green)	No differences
Spackman *et al*[26]	2000	Effect of epidural blockade on indicators of splanchnic perfusion and gut function in critically ill patients with peritonitis: a randomised comparison of epidural bupivacaine with systemic morphine	Double-blinded, prospective, randomised, controlled	Critically ill patients admitted in ICU with peritonitis (and systemic sepsis) and adynamic small bowel following abdominal surgery	21 (10 intravenous morphine *vs* 11 epidural bupivacaine)	Low thoracic or high lumbar epidural catheter insertion	Gastric tonometry: gastric intramucosal pH (pHig) and the intramucosal-arterial PCO_2 gradient (Pg-$PaCO_2$)	Significant improvements in gastric mucosal perfusion (a rise in Pg-$PaCO_2$ and a fall in pHig in the morphine group and a significant difference between groups in the Pg-$PaCO_2$ trends) and in the ultrasound appearance of the small bowel in the epidural group
Gould *et al*[20]	2002	Effect of thoracic epidural anaesthesia on colonic blood flow	Prospective observational	Patients undergoing elective anterior resection for rectal cancer	15	Cahteter inserted T9-T10	Doppler flowmetry for inferior mesenteric artery flow and Laser Doppler flowmetry for serosal red cell flux	↓ inferior mesenteric artery flow and ↓ serosal red cell flux significantly correlated to ↓ MAP reverted only by vasoconstrictors usage
Michelet *et al*[22]	2007	Effect of thoracic epidural analgesia on gastric blood flow after oesophagectomy	Prospective controlled	Patients undergoing elective radical oesophagectomy, postoperative evaluation	27 (18 TEA *vs* 9 controls)	C8-T11	Gastric mucosal blood flow (GMBF) measured using laser Doppler flowmetry at 1 and 18 h post surgery	↑GMBF in TEA group without correlation with MAP or CI

Kortgen *et al*[27]	2009	Thoracic but not lumbar epidural anaesthesia increases liver blood flow after major abdominal surgery	Prospective	Patients undergoing major abdominal surgery	34 (17 TEA *vs* 17 LEA)	Thoracic catheters between T5-T6 and T9-T10, lumbar catheters between L1-L2 and L4-L5	Blood lactate levels, central venous oxygen saturation ($ScvO_2$), PDR-icg	TEA but not LEA ↑ PDR-icg
Meierhenrich *et al*[21]	2009	The effects of thoracic epidural anesthesia on hepatic blood flow in patients under general anesthesia	Prospective controlled	Patients undergoing major pancreatic surgery	30 (15 TEA *vs* 5 TEA + Norepinephrine *vs* 10 no TEA)	T4-T11	Hepatic blood flow index and hepatic stroke volume index in the right and middle hepatic vein by use of multiplane TEE	↓ Hepatic venous blood flow. The combination of thoracic TEA with continuous infusion of NE seems to induce a further decrease in hepatic blood flow. CO was not affected by TEA
Trepenaitis *et al*[24]	2010	The influence of thoracic epidural anesthesia on liver hemodynamics in patients under general anesthesia	Prospective randomized	Patients undergoing upper abdominal surgery for carcinoma of the stomach, papilla of Vater, and pancreas	50 (40 TEA *vs* 10 controls)	T5-T12	Hepatic blood flow using Plasma Disappearance Rate of indocyanine green (PDR-icg)	↓ PDR-icg in TEA group, even if ephedrine was administered to correct hypotension. ↑ PDR-icg in patients receiving general anetshesia. CO was unaffected

↑: Increase; ↓: Decrease. HES: Hydroxyethyl starch; NE: Norepinephrine; TEA: Thoracic epidural anesthesia; TEE: Transesophageal echocardiography.

pancreatic microcirculation and oxygenation, and reduced histopathologic scores of tissue damage. Also, 7 d mortality was lower in animals treated with TEA.

Animal studies evaluating hepatic microhemodynamics are synthesized in Table 1.

Two studies by Freise *et al*[17,18] used intravital microscopy to assess hepatic microcirculation in different pathologic animal models.

In acute pancreatitis in rats[17], TEA prevented the vasoconstriction of sinusoids, but could not reduce the number of non perfused sinusoids. The number of parenchymal apoptotic cells was reduced by TEA, probably by inhibition of the Fas ligand pathway, without effects on leukocyte adhesion. In healthy animals, TEA did not exert any effect on the evaluated microcirculation parameters.

In a sepsis model induced by cecal ligation and perforation[18], TEA was able to normalize the increase in blood flow to the liver and to decrease temporary leucocyte adhesion to the venular endothelium, but not the vasoconstriction of hepatic vasculature and temporary sinusoidal leukocyte adhesion, both induced by sepsis.

Human studies: Human studies are synthesized in Table 3.

Of the 9 human studies taken into consideration, 4 evaluated splanchnic hemodynamics by direct measures of blood flow, 5 measured derived parameters such as gastric tonometry, intramucosal pH or PDR_{ICG}.

Three studies which used direct hemodynamic measures found a reduction in blood flow caused by TEA, even though different measuring techniques and different vessels were considered. One study showed that TEA improved microcirculatory parameters whilst worsening macro-hemodynamics.

Lundberg *et al*[19] measured superior mesenteric artery blood flow *via* an electromagnetic flow probe. In this study TEA reduced vascular resistance and blood flow in the superior mesenteric artery, with no change in measured CO. These hemodynamic changes were successfully corrected by dopamine infusion.

Gould *et al*[20] used doppler flowmetry to measure inferior mesenteric artery blood flow and laser doppler flowmetry to evaluate red cells flux. Results showed that TEA produced a reduction of blood flow and red cells flux in the inferior mesenteric artery, which was strictly correlated with the fall in MAP. The hemodynamic changes registered could be corrected by vasopressors infusion but not by goal directed fluid therapy.

Meierhenrich *et al*[21] used transesophageal echography to estimate blood flow in the hepatic veins, finding a reduction in estimated liver blood flow after the induction of a thoracic epidural blockade. The reduction in blood flow was resistant to the correction of hypotension using vasopressors.

Michelet *et al*[22] used doppler flowmetry to evaluate gastric mucosal blood flow in patients

Table 4 Delphi List for animal studies evaluating macrohemodynamics and liver microhemodynamics

	Hogan *et al*[7]	Hogan *et al*[8]	Sielenkämper *et al*[10]	Adolphs et al[12]	Adolphs *et al*[11]	Schwarte *et al*[15]	Kosugi *et al*[9]	Freise *et al*[13]	Daudel *et al*[14]	Bachmann *et al*[16]
Treatment allocation										
(1) Was a method of randomization performed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the treatment allocation concealed?	No	No	Yes	Yes	Yes	Yes	No	Yes	No	No
Were the groups similar at baseline regarding the most important progNostic indicators?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the eligibility criteria specified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Was the outcome assessor blinded?	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Was the care providor blinded?	No	No	No	No	No	No	No	No	No	No
Was the patient blinded?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Were point estimates and measures of variability presented for the primary outcome measures?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the analysis include an intention-to-treat analysis?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 5 Delphi list for animal studies evaluating gut and pancreatic microhemodynamics

	Lundberg *et al*[19]	Tanaka *et al*[23]	Väisänen *et al*[25]	Spackman *et al*[26]	Gould *et al*[20]	Michelet *et al*[22]	Kortgen *et al*[27]	Meierhenrich *et al*[21]	Trepenaitis *et al*[24]
Treatment allocation									
Was a method of randomization performed?	No	No	No	Yes	N/A	No	No	No	No
Was the treatment allocation concealed?	No	No	No	Yes	N/A	No	No	No	No
Were the groups similar at baseline regarding the most important progNostic indicators?	N/A	Yes	Don't know	Yes	N/A	Yes	No	Yes	Yes
Were the eligibility criteria specified?	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Was the outcome assessor blinded?	No	No	No	Yes	N/A	Don't know	Don't know	Yes	No
Was the care providor blinded?	No	No	No	No	N/A	No	No	No	No
Was the patient blinded?	No	Don't know	No	Yes	N/A	No	No	No	No
Were point estimates and measures of vari ability presented for the primary outcome measures?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the analysis include an intention-to-treat analysis?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 6 Delphi List for human studies

	Sivarajan *et al*[2]	Meissner *et al*[4]	Ai *et al*[6]	Vagts *et al*[5]	Shäper *et al*[3]	Freise *et al*[17]	Freise *et al*[18]
Treatment allocation							
Was a method of randomization performed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the treatment allocation concealed?	No	No	No	Yes	No	Yes	Yes
Were the groups similar at baseline regarding the most important progNostic indicators?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the eligibility criteria specified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Was the outcome assessor blinded?	No	No	don't kNow	No	Yes	Yes	Yes
Was the care providor blinded?	No	No	No	No	No	Yes	Yes
Was the patient blinded?	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Were point estimates and measures of variability presented for the primary outcome measures?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the analysis include an intention-to-treat analysis?	N/A	N/A	N/A	N/A	N/A	N/A	N/A

undergoing oesophagectomy. In this scenario TEA improved the microcirculatory perfusion of the gastric tube at 1 and 18 h after surgery, a result which did not correlate with the measured macro-hemodynamic parameters.

The six studies using surrogate hemodynamic parameters had conflicting results. Tanaka *et al*[23] used PDR-icg as indirect measure of hepatic blood

Table 7 Ongoing clinical trials

Title	Start year	Scenario	No. subjects	Current primary outcome measures	Current secondary outcome measures	Findings
Effect of Epidural Anesthesia on Pancreatic Perfusion and Clinical Outcome in Patients With Severe Acute Pancreatitis	July 2005	Acute pancreatitis with Ranson Criteria over 2, and/or CRP over 100, and or pancreatic necrosis on CT scan	35 (epidural anesthesia with carbostesin and fentanyl *vs* PCA with fentanyl)	Number of patients with adverse events related to epidural anesthesia, pancreatic perfusion measured by computerized tomography	Clinical outcome, Lenght of stay, admission to intensive care unit, need for surgery	n/d
Epidural Analgesia for Pancreatitis (Epipan Study)	April 2014	Patients admitted to the ICU for acute pancreatitis	148 (PCEA with Ropivacaine and sufentanyl *vs* conventional analgesia - acetaminophen, nefopam, tramadol, opidoids)	Ventilator-free days	Duration of invasive and/or non invasive mechanical ventilation, incidence of various complications, biological inflammatory response, cost analysis, incidence of intolerance to enteral feeding, effectiveness of pain management, duration of EA	n/d
Study of Effectiveness of Thoracic Epidural Analgesia for the Prevention of Acute Pancreatitis After ERCP Procedures	January 2008	Patients undergoing therapeutic ERCP for the first time without clinical signs of acute pancreatitis	491 (standard premedication + TEA *vs* standard premedication)	prevention of post-ERCP pancreatitis	Not provided	n/d
The Effects of Local Infiltration Versus Epidural Following Liver Resection 2 (LIVER 2)	December 2012	Patients undergoing open hepatic resection for benign or malignant conditions	100 (EA *vs* wound catheter)	Length of stay	Pain Scores, Molecular response to surgery, Central Venous Pressure, estimated Blood Loss, Operative field asessment, Pringle time, Quality of Life (EQ-5D), Morphine consumption, IV Fluid volume, Complications, Post-operative blood tests	n/d

flow, finding that TEA reduced blood flow to the liver, fluid resuscitation alone could not reverse this effect but had to be associated with dopamine infusion. Trepenaitis *et al*[24] found a reduction of PDR_{ICG} in patients undergoing upper abdominal surgery with TEA. This data was not associated with a fall in CO and could not be reversed by administration of vasopressors.

Väisänen *et al*[25] found no influence of TEA on gastric and sigmoidal PCO_2 gap in patients undergoing elective abdominal aortic surgery.

Spackman *et al*[26] evaluated the effects of TEA on a group of critically ill patients with surgically treated peritonitis, they found better pHi and PCO_2 gap in patients treated with epidural infusion of bupivacaine.

Kortgen *et al*[27] found an increase in liver blood flow measured with PDR_{ICG} in patients undergoing major abdominal surgery and treated with thoracic epidural anesthesia in addition to general anesthesia. This finding couldn't be replicated by using lumbar epidural anesthesia and general anesthesia as anesthetic technique.

The quality of animal and human studies assessed through Delphi List is synthesized in Tables 4-6.

The Animal studies considered in this review, in particular the most recent ones, are well designed; groups were homogeneous, methods were minutely described, and outcome assessors were frequently blinded. However, the high variability of surrogate measures used to estimate splanchnic blood flow in each study, is the biggest limit to the common interpretation of their results.

The quality of human studies was in general low. Most of the studies considered did not use randomization criteria, and the control groups were often composed by patients not eligible for epidural anesthesia, or who refused it. Patients were undergoing different surgical procedures, so that selection bias could not be excluded. Moreover, the outcome assessor was frequently not blinded. The outlined considerations limit the reliability of these studies, and underline the urgent need for well designed RCTs.

Ongoing clinical trials

Clinical trials search found 4 works of interest, which are synthesized in Table 7.

Two clinical trials are evaluating the effects of

thoracic epidural blockade on the clinical outcome of patients with acute pancreatitis.

One examines the hypothesis that thoracic epidural anesthesia for therapeutic ERCP could have a role in preventing post-ERCP pancreatitis.

Another study is comparing epidural anesthesia and the use of a wound catheter for post liver resection pain management. Amongst the secondary endpoints of this study are the molecular response to surgery, surgical and medical complications, and postoperative liver blood test results, which could all be modified by the microvascular effects of epidural blockade.

DISCUSSION

Splanchnic circulation and epidural blockade

Splanchnic blood flow is regulated by intrinsic and extrinsic mechanisms. Intrinsic factors include local myogenic and metabolic control, locally produced vasoactive substances and local reflexes. The main extrinsic factors are the sympathetic innervation and the circulating vasoactive substances.

Epidural blockade can interfere with all these factors, either by direct block of sympathetic efferents or by the systemic effects of circulating local anesthetics.

A thoracic epidural block influences the systemic hemodynamics by reducing the intestinal vascular resistance and the stimulation of the adrenal gland and the renin-angiotensin axis[28].

The extension of the blockade seems to be a key factor in determining the splanchnic circulation response to epidural anesthesia. In fact the sympathetic innervation to the celiac, superior and inferior mesenteric ganglia originates in the T5-T11 region of the spinal cord, hence a low epidural block could not ensure a sufficient spread of local anesthetic to include all the efferent sympathetic innervation to the gut. Moreover the sympathetic activity in the regions not involved by the epidural blockade could be increased[29]. For these reasons an epidural block limited to the upper thoracic region, could potentially result in splanchnic sympathetic hyperactivity and foster splanchnic ischemia. Meissner *et al*[4] tested this hypothesis and found no modifications in intestinal blood flow during epidural anesthesia extending to the T1-T5 metameres in dogs, indicating that other local or systemic mechanisms could counteract the sympathetic hyperactivity and maintain a normal blood flow.

The data available in current literature regarding the effects of thoracic epidural anesthesia on splanchnic perfusion are conflicting. Studies focusing on regional macro-hemodynamics in healthy animals[2,5] and humans undergoing elective surgery[19-21,23-25] demonstrated no influence or worsening of regional perfusion in subject receiving thoracic epidural anesthesia. On the other hand most of the studies focusing on micro-hemodynamics[7-12,17,18], especially those focusing on pathologic low flow conditions, suggested that TEA could foster microcirculation despite a reduction in mean perfusion pressure.

Intestinal microcirculation

The Gut receives its blood supply from three great vessels: the celiac artery, and the superior and inferior mesenteric arteries. The branchings of these three vessels result in a common set of mesenteric arteries evolving in two orders of arterioles, located in the superficial submucosa, forming a highly interconnected system to perfuse the small, third order arterioles.

Third order arterioles perfuse one or several villi, submucosal glands, crypt regions and the corresponding muscle layer, forming a mesh-like subepithelial capillary plexus. First and second order arterioles account for about 65% of the intestinal vascular resistance in rats, an additional 20% resistance resides in the capillaries and venules, so that terminal arterioles can govern only 15% of blood flow modifications[30]. One or two veins drain each villus. The parallel arrangement of these vessels produces a countercurrent mechanism that is the basis for the oxygen shunting phenomena that account for the extreme sensitivity of the apical region of the villi to hypoxia[31].

In low flow states, ischemia/reperfusion injury to the intestinal mucosa could damage the intestinal barrier and promote bacterial migration.

Intestinal circulation in sepsis

In sepsis and septic shock, both micro and macro-hemodynamics undergo profound alterations. However, the restoration of normal global hemodynamic and oxygen derived variables is not necessarily correlated to a correction of tissue dysoxia. This condition of oxygen extraction deficit could be correlated to metabolic disturbances or to regional hypoxia.

Microvascular flow distribution becomes highly heterogeneous during sepsis and septic shock, microcirculatory weak units can become hypoxic while other units can be overperfused.

These alterations are probably related to the presence of inflammatory mediators and microcirculatory emboli that impair microvascular autoregulation and increase oxygen shunting. This explains the finding of a venous PO_2 higher than regional capillary PO_2 (PO_2 gap) in sepsis models[32].

These observations are progressively changing the primary endpoint for resuscitation procedures: from global hemodynamic and oxygen derived variables, to microcirculatory oxygenation. In fact, administration of vasopressors, despite correcting macrohemodynamic and oxygen delivery, could have

counterproductive effects on microcirculation. This is the rationale for ongoing experimental therapies using vasodilators or oxygen carrying solutions to support dysoxic weak units[33].

Thoracic epidural blockade applied to animal[3,9,14] and human[26] models of sepsis appeared to be effective in fostering microvascular circulation or at least modify its distribution[11].

Regional sympathetic blockade could counteract the above mentioned mechanisms of heterogeneous flow distribution, restoring oxygenation to weak units, and thus contributing to the survival of the intestinal barrier[9,34].

Intestinal circulation in non septic low flow states

In non septic low flow states, the correction of the hemodynamic status appears to restore oxygenation if a damage to the microcirculation has not developed yet.

Epidural anesthesia in this context could help maintaining microvascular perfusion, reducing ischemia/reperfusion injury and inflammation, as demonstrated by Adolphs *et al*[12].

However, Schwarte *et al*[15] found that TEA produced a reduction in gastric mucosal oxygenation in dog models of hemodynamic dysfunction induced by high PEEP levels. In this study the extension of the epidural block was thoraco-lumbar, which produced a significant fall in blood pressure compared to the control group. This was not the case in the study by Adolphs *et al*[11], where hemodynamic disturbances were more limited. Overall TEA appears to have a protective role for intestinal microcirculation in hemorrhagic low flow states, until macro-hemodynamics are maintained.

Pancreatic microcirculation and acute pancreatitis

Pancreatic circulation is organized in a continuous network called insulo-acinar portal system. The pancreatic lobule is served by a single end artery, that first supplies blood to islets, and then continues as vasa efferentia to supply acini.

The autoregulation of this system is both hormonal and neural. The blood flow is strictly correlated to exocrine secretion, and modulated by various gastro-entero-pancreatic hormones.

This particular anatomy is very susceptible to ischemia, and it appears to have an important role in the development of acute pancreatitis[35].

During acute pancreatitis, microvascular perfusion is altered in accordance to the severity of the disease[36], and regional macro-hemodynamic blood flow appears not to correlate with microcirculation[37]. Pancreatic blood flow, red cell velocity, and functional capillary density all decrease; end artery vasoconstriction and increased shunts lead to ischemia, necrosis and circulatory stasis[38]. Moreover, local immune reaction and oxygen free radicals contribute to lobular and endothelial necrosis.

Animal models of acute pancreatitis treated with thoracic epidural blockade[13,16], showed reduced histologic signs of pancreatic necrosis and a restoration of continuous capillary perfusion and arteriolar blood flow, moreover, survival rate was significantly higher in both of the studies.

The microcirculatory effects induced by TEA could contribute in interrupting the ischemic injury involved in the beginning and progression of pancreatic lesions.

Nowadays TEA is increasingly used in humans as an effective analgesic technique for acute pancreatitis and it appears to be safe[39]. The currently ongoing clinical trials are expected to shed light on whether TEA can influence the prognosis of acute pancreatitis.

Liver circulation

Liver circulation is characterized by a double afferent flow from the portal vein and the hepatic artery. In physiologic conditions, the portal vein drains the digestive tract below the diaphragm, spleen, and pancreas and supplies approximately two thirds of the hepatic blood flow, whilst the hepatic artery supplies one third.

Regulation of this dual blood supply, is strictly regulated by the hepatic arterial buffer response (HABR). This mechanism is responsible for maintaining a constant total hepatic blood flow by adjusting the hepatic arterial flow in relation to the modifications of portal flow.

Mechanisms regulating HABR are not fully understood, adenosine seems to be an important mediator of hepatic artery resistance, and reduction in adenosine wash out consensual to a drop in portal blood flow could enhance arterial flow. However the mechanism appears to be more complex and other mediators could be involved[40].

The studies evaluating the effects of TEA on liver macro hemodynamics in normal conditions, found no difference[5], or a reduction[2], in total hepatic blood flow. It must be noted that, when comparing the results of these two studies, the extension of epidural blockade could have influenced the outcome. In fact Vagts *et al*[5] (cit) considered the effects of a T5-T12 block, while Sivarajan *et al*[2] (cit) compared two levels of sensory blockade, finding a reduction of total hepatic blood flow only in the high level sensory blockade group (T1).

Liver circulation in sepsis

Total liver blood flow in sepsis and septic shock is usually increased, proportionally to the cardiac output[41]. This is associated with a decreased oxygen hemoglobin saturation in the hepatic veins. The reasons behind these phenomena are probably an impairment of the HABR mechanism, and a mismatch between oxygen distribution and metabolic demand.

Microvascular circulation appears to be uncoupled from systemic circulation in this context. In fact, despite the hyperdynamic circulatory state, microvascular flow appears to be unchanged or even decreased[42,43].

Intrahepatic blood flow is redistributed, blood is channeled away from contracted to dilated vessels reducing the perfused sinusoidal area. Imbalances in nitric oxide production may be the origin of these modifications. Moreover, sinusoidal and Kupffer cells are activated by contact with leukocytes and toxins, and react by producing cytokines which further impair microcirculation[44,45].

The review of the literature found only one study[18] considering the effect of epidural blockade on liver circulation in septic animals. In this scenario of late sepsis, TEA appeared to ameliorate sinusoidal hyperflow and reduce temporary venular leukocyte adhesion.

The authors suggested that TEA could have a role in restoring the impaired HABR, reducing the immune activation, through a direct reduction in hepatic sympathetic activity, which seems to have a role in the regulation of liver immunity. Also TEA, by fostering intestinal barrier function, would have an indirect role in preserving liver microcirculation and function.

The data obtained in the animal studies on acute pancreatitis also suggest a protective effect of TEA on liver circulation[17]. In fact TEA prevented sinusoids constriction and reduced liver cells apoptosis.

In conclusion, epidural anesthesia has been increasingly used in the last decades as an effective analgesic technique. This method produces a central sympathetic blockade which has strong effects on macro and microcirculation, by reducing autonomic efference and modifying the endocrine profile.

In recent years there have been efforts to further understand the underlying mechanisms of this technique. The available studies to date are heterogeneous and show conflicting results, making it difficult to gather decisive conclusions. A recent review by Richards *et al*[46] investigated the effects of TEA on spanchnic blood flow, focusing in particular on its potential implications in abdominal surgery. Their analysis, which comprised some of the studies that have been taken into consideration in the present review, also found the results to be inconsistent when suggesting a protective or detrimental effect of TEA on splanchnic circulation.

Overall the studies we considered also suggest possible new therapeutic applications of TEA, especially if micro-hemodynamics are taken into consideration.

Thoracic epidural anesthesia appears to reduce regional blood flow in relation to its effects on the vascular resistance, but at the same time it seems to foster microcirculation, especially in pathologic low flow states, or in conditions involving a degree of microvascular dysfunction. In these scenarios epidural anesthesia seems to restore blood flow to microcirculatory weak units, ameliorating tissue dysoxia and resistance to hypoperfusion.

However, given the variable extension that the epidural blockade can have, a wide extension of the blockade could impair macro-circulation enough to reduce regional DO_2 under tissue requirements thus worsening hypoxia.

Human studies mostly evaluated macro-hemodynamics in patients undergoing surgery. Currently ongoing clinical trials could identify interesting applications in the prevention and treatment of acute pancreatitis, which have been strongly suggested by animal studies.

Further studies should investigate: (1) what is the extension of epidural blockade and local anesthetic concentration which can grant better micro-perfusion without significant hemodynamic impairment; (2) the effects on mortality and risk of catheter infection in septic animals treated with epidural anesthesia; (3) the effect of epidural blockade on the perioperative splanchnic organs function tests to assess whether epidural anesthesia can reduce perioperative organ injury or whether its macro-hemodynamic effects are relevant in inducing organ injury; and (4) the effect of epidural anesthesia on hepatic arterial buffer response, given the fact that this mechanism appears to be implicated in the constriction of the hepatic artery and the hemodynamic alterations developing after a liver resection, which could have a role in promoting Small for Size Syndrome[47].

COMMENTS

Background

Thoracic epidural anesthesia is a broadly used analgesic technique, however its eventual therapeutic effects in different fields are still matter of debate.

Research frontiers

Macro and microcirculatory effects that result from the interaction between the analgesic technique and the neuro-endocrine system are suggested to have some therapeutic effect in animal models, studies on humans are scanty and use different methods for measuring hemodynamic variables, hence a thorough comparison is difficult. The hotspot of this Systematic Review is to evaluate up to date literature considering macro and microcirculatory effects of thoracic epidural anesthesia on splanchnic circulation and their possible therapeutic implications.

Innovations and breakthroughs

This Review considered the peculiarities of each particular regional circulation of the abdominal organs in order to evaluate possible effects of thoracic epidural anesthesia in both physiologic and pathologic conditions, this could change the way we use this technique, making it glide into a more comprehensive therapeutic view of its usage in medical and surgical conditions.

Applications

This Review points out some research fields that would be of interest in everyday clinical practice. In fact, on the basis of some rodent models, it appears that epidural anesthesia could reduce the mortality of acute pancreatitis, so that it could be used as a simultaneously analgesic and therapeutic procedure for this pathology. Moreover it has profound effects on hepatic circulation that could influence the function of this organ when it is object of surgical interventions. At last, some interesting implications in abdominal sepsis conditions are discussed.

Peer-review

The study was well designed and carried out. The data and conclusions are convincing.

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