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Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Critical Care Medicine
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: bpgoffice@wjgnet.com
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EDITORIAL

Rhabdomyolysis, compartment syndrome and thermal injury

Yusuf Kenan Coban

Yusuf Kenan Coban, Burn Unit and Department of Plastic Surgery, Inonu University Turgut Ozal Medical Centre, 44280 Malatya, Turkey
Author contributions: Coban YK solely contributed to this paper.
Correspondence to: Yusuf Kenan Coban, Professor, Burn Unit and Department of Plastic Surgery, Inonu University Turgut Ozal Medical Centre, 44280 Malatya, Turkey. ykenanc@yahoo.com
Telephone: +90-422-2374780 Fax: +90-422-2374780
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Abstract

Rhabdomyolysis (RML) after electrical burns and crush injuries is a well-known clinical entity, but its occurrence following thermal injury has not gained so much attention. Capillary leak syndrome and following polycompartmental syndrome are devastating end results of major thermal injuries. In the current review, polycompartment syndrome within the clinical picture of systemic oedema and its relationship to RML is discussed along with its management and prevention.

Key words: Capillary leak syndrome; Rhabdomyolysis; Thermal injury

Core tip: In the current review, polycompartment syndrome within the clinical picture of systemic oedema and its relationship to rhabdomyolysis is discussed along with its management and prevention.

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DEFINITION

Rhabdomyolysis (RML) is defined as muscle damage with dissolution of the skeletal muscle fibre and results in release of potentially toxic intracellular components into the systemic circulation. A classical triad of symptoms includes muscle pain, prostration and dark pigmented urine. Urine pigmentation only manifests itself when the renal threshold for myoglobulin (MB) is exceeded. In 1940-1941, RML syndrome was first described in patients with crush injury secondary to building destruction during wartime[1]. In later decades, it was understood that RML is not confined to crush injuries, but is also associated with thermal injuries and other medical causes. Although direct muscle injury remains the most common cause of RML, additional causes include toxins, endocrinopathies, malignant hyperthermia, neuroleptic malignant syndrome, electrolyte alterations, diabetic ketoacidosis, non-ketotic hyperosmolar coma, severe hypo- or hyperthyroidism and bacterial or viral infections. Generally speaking, RMLs can be divided into two categories as shown in Figure 1.

PATHOPHYSIOLOGY

The scenario is seen after severe crush and thermal or electric injuries in addition to direct muscle injury. In other words, there may be a combination of both direct muscle injury and compartment syndrome in the same clinical picture. On the other hand, the primary mechanism for position-related RML is reperfusion of damaged tissue after a period of ischaemia and the release of necrotic muscle material into the circulation after pressure is relieved. In severe burns, capillary leak syndrome leading to polycompartmental syndrome is also responsible for the development of RML *via* several mecha-

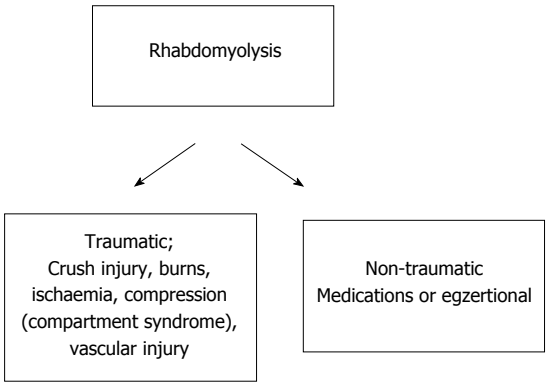

Figure 1 General classification of rhabdomyolysis.

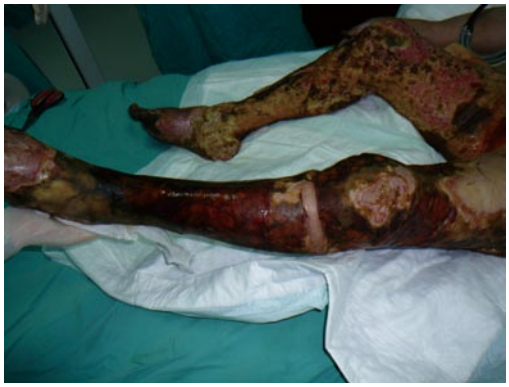

Figure 2 An example for full-thickness burns of both lower extremities.

nisms including loss of vasomotor tone of arterioles, collapse of thinner-walled veins, and the overall loss of the pressure gradient between the arterial and venous system. As the blood flow decreases, the tissues become progressively more ischaemic, thereby leading to further necrosis and oedema.

Muscle necrosis is triggered by derangements in oxidative or glycolytic energy production with resulting ATP depletion. In the presence of concomitant ATP depletion, free Ca^{2+} content in the myocyte increases due to failure of Ca^{2+} efflux mediated by the ATPase-driven Ca^{2+} pump. Influx from the extracellular compartment into muscle cells includes water, Na^{+}, Cl^{-} and Ca^{2+}. Muscle cells swell due to the accumulation of intracellular solutes and a reduction in active ion extrusion. Within minutes of trauma, intramuscular pressure may exceed arterial blood pressure within the intracompartmental space. Hypovolaemia develops, followed by haemodynamic shock, hypocalcaemia, and hyponatraemia in the context of trauma and burns. Progressive hypovolaemia is thought to contribute to the formation of casts that obstruct renal tubules and to renal vasoconstriction involving afferent glomerular arterioles and glomerular capillaries[2].

As the skeletal muscle (SM) is a principal actor that plays a major role in the pathophysiology of RML, its distribution within the body is worthy of mention. Subcutaneous muscle accounts for approximately 40% of total body mass for adult males and 29% for adult females. Depending on gender, age and health status, one-third and one-half of body protein resides within SM[3]. There is growing awareness of the importance of SM in many physiological and disease processes[4]. Janssen *et al*[5] studied skeletal muscle mass measurement in whole body distribution by magnetic resonance imaging. They found that the lower body had more SM mass than upper body regions in both sexes. As the lower extremity bears much of SM mass of total body SM mass, full-thickness burns of the lower extremity pose a higher risk for development of fatal RML (Figure 2). One might speculate that immobilization is more commonly seen after lower extremity full-thickness burns when compared to the upper body parts, and this may mean increased risk of RML for lower extremity burns.

LABRATORY DIAGNOSIS AND MORTALITY

The diagnosis of RML is based on the measurement of creatinine kinase (CK) in serum or plasma. Plasma and urine myoglobin CK measurement might be useful in the early stage of the syndrome[6]. Patient monitoring is pivotal (the mortality rate is as high as 8%) and should be aimed at preventing the detrimental consequences. Mortality for patients with RML secondary to flame burns seems to be high[7]. Stewart *et al*[8] studied percentage of full-thickness burns, percentage of total body surface area (TBSA) burned, injury severity score, peak CK and acute kidney injury (AKI) in burn patients. They found that the log peak CK correlated with stage of AKI[8]. Another study revealed that 28% of severely burned patients developed AKI during acute resuscitation[9]. In a retrospective study of 714 patients, eight were reported to have RML and these cases had poor survival[10].

THERMAL INJURY AND RHABDOMYOLYSIS

Several issues related to the subject are present. These are the role of albumin and fluid therapy, capillary leak syndrome and comorbid situations.

Albumin in severe burns

Lower albumin concentrations are commonly observed in older persons and are associated with worse health outcomes and mortality[11]. Albumin is a negative acute-phase protein that decreases with ongoing inflammation, and many of the reported associations with albumin may reflect this[12]. Serum albumin concentration $\leqslant$ 30 g/L was reported to be associated with a twofold increase in organ dysfunction[13]. The optimal resuscitation algorithm including albumin supplementation remains elusive for patients with large burn injuries. Park *et al*[14] compared the use of 5% albumin in the first 24 h with other protocols not using albumin solution. They found

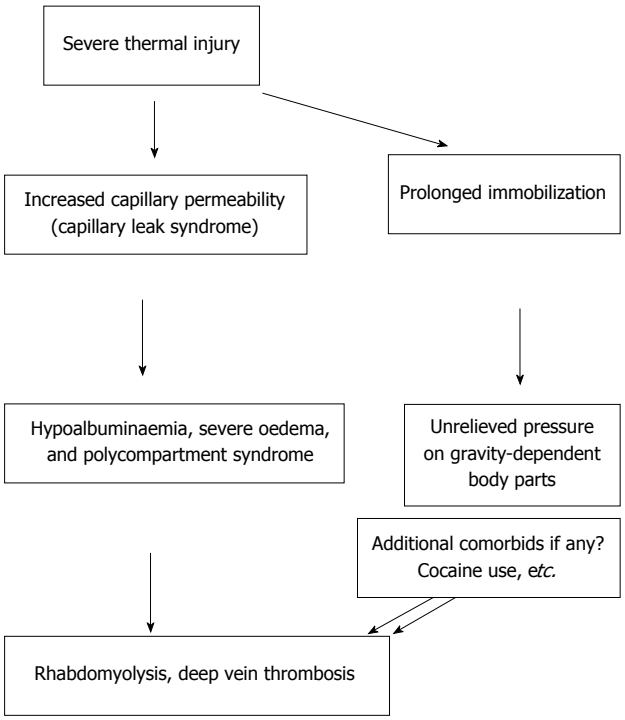

Figure 3 Pathogenic mechanisms for development of rhabdomyolysis in severe thermal injury.

that their new protocol decreased ventilator days and mortality, whereas another study revealed an opposite outcome. Currently, there is no consensus on using albumin replacement therapy for acute burn resuscitation[15]. The albumin molecule, being smaller (69 kDa) than the globulin molecule (90-156 kDa), will leak at a relatively earlier stage of the disease (with a moderate increase in capillary pore size) than globulin. This leads to albumin/globulin reversal. In cases with severe permeability changes related with rapid progression to larger pore size with simultaneous leak of both albumin and globulin, albumin/globulin reversal will not occur. Kumar's[16] study showed that patients with albumin protein values less than 5.0 g/dL showed higher mortality (95%) compared to those in other groups with more than 5.0 g/dL.

Capillary leak syndrome

Major burns are characterised by an initial capillary leak that requires fluid resuscitation for haemodynamic stabilization. The extensive capillary damage that follows thermal injury is responsible for massive plasma extravasation into burned tissues, with consequent hypovolaemia, abdominal hypertension and extremity compartmental syndrome necessitating fasciotomy, prolonged mechanical ventilation and hospital stay. Increased compartmental pressure poses a risk for RML. In local compartmental syndrome, the pathology is restricted to a unique body region and does not cause a life-threatening systemic condition. However, capillary leak syndrome, whether the cause is idiopathic or due to severe burns, causes hypovolaemic shock due to marked plasma shifts from the intravascular to the extravascular space. This presents as the characteristic triad of hypotension, haemoconcentration and hypoalbuminaemia. The reason is due to leakage of fluids and macromolecules (up to 900 kDa) into tissues. Systemic capillary leak syndrome is a transient event, and less than 150 cases have been reported. Systemic oedema causes multiple compartment syndrome, which needs emergency fasciotomies[17]. Hypoalbuminaemia always associates with the picture of systemic oedema and polycompartmental syndrome.

Direct damage to the striated muscle by high electrical voltage is well understood[18]. In thermal burns without direct muscle injury, the actual trigger for RML often remains unexplained. The majority of the publications on the subject are single case reports[19,20]. Prolonged immobilization following unconsciousness and repeated surgical procedures has been suggested to trigger RML in thermally injured patients. However, there may be several factors contributing to the development of RML in the context of severe thermal burns (Figure 3).

Ideal formulation of fluid therapy in burn shock

Less than 20% of burn injuries are associated with minimal fluid shifts and can generally be resuscitated with oral hydration. Current recommendations are to initiate formal intravascular fluid resuscitation when the surface area burned is greater than 20%. The ideal burn resuscitation is the one that effectively restores plasma volume, with no adverse effects. Isotonic crystalloids, hypertonic solutions and colloids have been used for this purpose, but every solution has its advantages and disadvantages. None of them is ideal, and none is superior to any of the others. Too vigorous resuscitative efforts may lead to severe protein depletion and further oedema accumulation into both burned and unburned tissues.

A condition of fluid unresponsiveness is present throughout the first 12 h of the post-burn period. The administration of supranormal volumes fails in the first 24 h to achieve normal preload volumes. The fluid creep started in the 1990s with an increasing proportion of the first 24 hours' fluid delivery above the 4 mL/kg TBSA% (Parkland formula). The first alerts were published under the form of case reports of increased mortality due to abdominal compartment syndrome and respiratory failure. While under-resuscitation was the major cause of mortality among burned patients until the 1980s, over-resuscitation has become an important source of complications[21]. Several studies have supported that patients who receive larger volumes of resuscitation fluid are at higher risk of injury complications such as pneumonia and extremity compartment syndrome. Hypertonic saline should be reserved for providers experienced in this approach. Plasma sodium concentrations should be closely monitored to avoid excessive hypernatraemia. Administration of high-dose ascorbic acid may decrease the overall fluid requirements, and is worthy of further study[22].

Resuscitation fluids influence the inflammatory response to burns in different ways and it may be possible

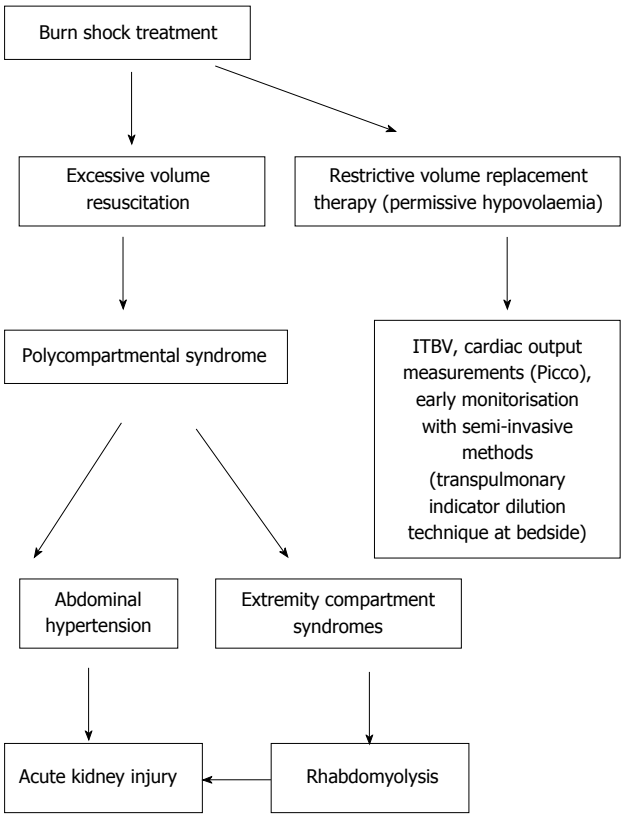

Figure 4 Possible scenarios during burn shock resuscitation. ITBV: Intrathoracic blood volume.

Table 1 Therapeutic goals of fluid resuscitation and therapeutic measures in thermal injury

Goal	Measure
Preventing hypovolaemia and shock	Fluid overloading (with rationing prehospital fluid delivery)
Improving organ perfusion	Mannitol, high dose vitamin C administration (avoiding early colloids)
Reducing capillary leak and oedema	Not known
Reducing inflammatory storm	Haemodialysis, plasmapheresis, *etc.*
Avoiding polycompartment syndrome	Permissive hypovolaemia

therefore to affect this response using appropriate fluid at the appropriate time[23]. Table 1 shows the goals of early fluid resuscitation in major burns.

Starches are effective volume expanders and early use of newer formulations may limit resuscitation requirements and burn oedema[24]. It has been shown that post-burn oedema is detrimental to organ function and that the deleterious effect is proportional to the amount of extravasated fluids[25]. Arlati *et al*[26] compared permissive hypovolaemia administered by a hemodynamic-oriented approach with Parkland formula resuscitation throughout the first 24 h period. They found permissive hypovolaemia allowed for less volume infusion, a reduced positive fluid balance and significantly lesser multiple organ dysfunction syndrome (MODS) score values than the Parkland formula.

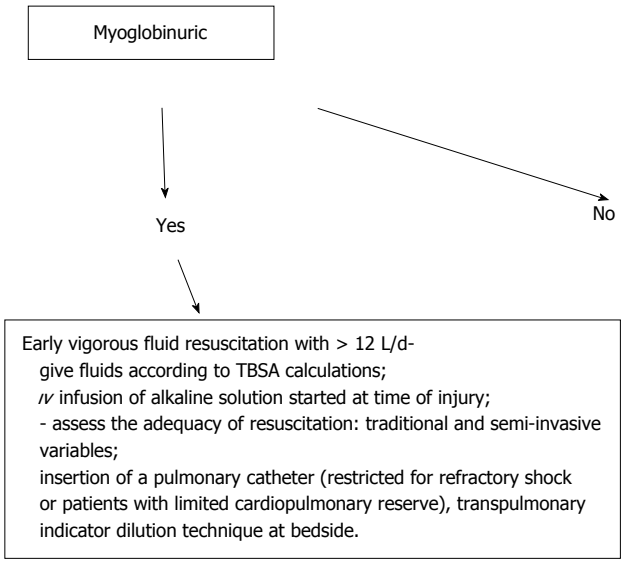

Figure 5 Algorithm for established clinical picture of rhabdomyolysis in burn victims. TBSA: Total body surface area.

Permissive hypovolaemia seems safe and well tolerated by burn patients. It seems effective in reducing multiple organ dysfunction due to induced oedema fluid accumulation and inadequate O_2 tissue utilization. It has been speculated that the insensitivity of cardiac preload to increase by even the most aggressive regimen might derive from the combination of both increased capillary permeability and higher hydrostatic pressure than most forms of hypovolaemic shock. A supranormal resuscitation volume might exacerbate post-burn oedema accumulation by unnecessarily increasing both the amount and length of fluid extravasation. The reduction of volume given was obtained throughout the period of maximum capillary damage. This would be impossible without the use of invasive haemodynamic monitoring as both intrathoracic blood volume (ITBV, as a cardiac preload indicator) and cardiac output measurements generated[26]. The PICCO system allows both ITBV and cardiac output measurements. ITBV and cardiac output measurement are earlier and more sensitive indicators of critical hypovolaemia than vital signs, hourly urine output and central venous pressure. A haemodynamic-oriented approach to burn shock resuscitation is gaining more acceptance for direct cardiac preload estimation nowadays (Figure 4).

Compartment syndrome

Burns and toxic causes may lead to polycompartment syndrome during fluid resuscitation if given at too high a dose. Compartment syndrome can be classified as primary (pathology within the compartment) and secondary (no primary pathology or injury within the compartment)[27]. SM compartments are especially susceptible to this type of injury. Thermal injuries, in particular full-thickness burns, cause secondary tissue constriction eschars and oedema. Fluid shifts associated with major burns adding to extravolume pressure may contribute to

Table 2 Risk factors for rhabdomyolysis

Risk factors for position-related rhabdomyolysis
Long-lasting surgery (more than 5-6 h) or prolonged immobilization (coma, unconsciousness)
Body weight more than 30% of ideal body weight
Pre-existing azotaemia
Diabetes
Hypertension
Uncontrolled extracellular volume depletion
Associated drug abuse (cocaine, *etc.*)

the development of compartment syndrome. The obtruded patient with prolonged limb compression, either during surgery or postoperative sedation, is at particular risk for development of an extremity compartment syndrome that may go unnoticed. In terms of the role of increasing CK levels and myoglobinuria, these are nonspecific signs of muscle necrosis and late signs of untreated irreversible compartment syndromes.

In most compartments, pressures > 30 mmHg critically compromise organ perfusion. According to the most recognised explanation of the syndrome, A-V gradient pressure theory, the perfusion of the intracompartmental tissues is hindered by the elevation of the interstitial fluid pressure above the level of the capillaries. The capillary pressure on the arterial end and the venous ends are 30 and 10 mmHg, respectively. Excessive volume resuscitation to prevent and treat burn shock may lead to intra-abdominal compartment syndrome, which is probably an underestimated contributor to the development of acute kidney injury after burn shock. The earliest effect of raising the intra-abdominal pressure (IAP) is to reduce visceral perfusion to organs. Subtle interactions with other noxious organ-damaging effects may be indistinguishable in a multifactorial setting. With higher IAP, more overt symptoms may be seen such as hypercarbic and hypoxaemic respiratory failure. Mortality rates of this clinical picture are between 70% and 100%.

Comorbid situations

The only cause of raised CK in thermal burns patients remains the involvement of muscles in deep burns. However, RML may occur in patients with superficial burns who had cocaine abuse[28]. Table 2 shows risk factors for development of RML. If any of these is present in the burn victim, RML may occur without the effect of presence of burn injury. Prolonged immobilization (*e.g.,* anaesthesia, coma, drug- or alcohol-induced unconsciousness) has been reported to induce RML due to unrelieved pressure on gravity-dependent body parts. Lateral decubitus, lithotomy, sitting, knee-to-chest and prone positions are reported to be the most common positions leading to RML. One of the risk factors for position-related RMLs was identified as having a bodyweight more than 30% greater than the ideal body weight .

RHABDOMYOLYSIS-INDUCED RENAL FAILURE

Leakage of intracellular contents such as myoglobulin (MB), CK, K, aldolase phosphate, lactate dehydrogenase, aspartate transaminase and urate into the extracellular space occurs in RML[29]. After complete sarcolemmal destruction, MB is released into the systemic circulation, leading to renal tubular obstruction. The extent of renal damage is dependent on the amount of volume deficit and renal ischaemia. When MB levels reach 100 mg/dL, dark, tea-coloured urine is seen. The principal goal is to prevent renal failure in cases of RML by aggressive fluid replacement and forced diuresis. If acute renal failure cannot be prevented by these measures, renal replacement therapy becomes mandatory. CK and MB levels must be routinely measured in all patients on admission.

In human patients, increased serum and perfusate levels of MB and CK during isolated limb perfusion have been shown for melanoma and sarcoma treatments[30]. Exertional muscle damage produced by eccentric exercise in healthy individuals has been shown to cause profound CK and MB elevations without renal impairment[31,32].

RML-induced renal failure is caused by the precipitation of myoglobin in the renal tubules. Early aggressive resuscitation with either normal saline or ringer lactate to maintain an adequate urine output is the most employed intervention in preventing the development of renal failure[33]. Therapeutic options include the correction of the hypovolaemia with sufficient fluid supply, the prevention of oliguria using loop diuretics, alkalinization of urine, normalization of serum electrolytes and decomposition of compartment syndromes. RML can be complicated by ARF occurring in 4%-33% of the patients[34]. Emerging data overwhelmingly suggest that fluid overload in critically ill patients may be associated with adverse outcomes. Over and under fluid resuscitation may endanger renal function in several ways. So, management of such patients should include a strategy of early resuscitation followed by a careful assessment of fluid status and early initiation of renal replacement therapy[35].

With increased pulmonary intestinal fluid during fluid administration, hypoxia is a frequent sequela in the context of systemic oedema. The septic patient with capillary leak syndrome is then diagnosed as having acute respiratory distress syndrome (ARDS) and placed on mechanical ventilation. Hyroxyethyl starch (HES) has negative effects on coagulation and causes an osmotic nephrosis that can lead to renal impairment. So, HES usage during fluid management of severe burn injuries may increase the risk of acute kidney injury (AKI)[36]. On the other hand, persistent fluid overload in AKI patients may lead to development of ARDS. Abdominal compartment syndrome (ACS) has been described with extensive abdominal fluid and impaired renal function[37]. ACS is associated with resuscitation volumes of 300

mL/kg per 24 h. Figure 5 shows possible negative consequences of over-resuscitation. Burn physicians must evolve their practices to avoid over-resuscitation or they should use more sensitive markers of organ perfusion than urine output.

Figure 5 proposes that myoglobinuric burn patients must be protected from AKI by *iv* infusion of alkaline solution. This regimen stabilizes the circulation and mobilizes oedema fluids sequestered in the injured muscles into the circulation, corrects hyperkalaemia and acidosis and protects against the nephrotoxic effects of myoglobulinuria and uricosuria[38].

Muscle injury as a consequence of burn injury may have led to elevation in serum creatinine concentrations by increased release of creatinine in circulation while glomerular filtration rate is unaffected. On the other hand, serum creatinine may already be increased on admission leading to a false low prevalence of AKI when defined as a relative increase of serum creatinine. Burn injury patients with AKI have a worse prognosis that is almost linearly correlated with severity of AKI. Although AKI with renal replacement therapy remains prevalent in populations with severe burn injury, the outcome improved[26,39].

CONCLUSION

RML is still one of the leading causes of fatality in major burns. Massive destruction of muscular tissue leads to RML, defined as CK elevation combined with organ damage, which requires immediate diagnostic and therapeutic intervention. It appears that RML following extensive full-thickness burns may be more common than previously suggested. So health professionals dealing with burn therapy must pay close attention against possible development of RML. Especially prolonged immobilization and surgeries in certain positions can be preventable, while health professionals are taking measures against these risk factors[40-42]. Judicious fluid resuscitation remains a basic, but potentially life-saving duty of all involved in the care of the severely burned patient. However, it is not known whether serious complications like secondary abdominal hypertension are iatrogenic or truly unavoidable in the most seriously burned patients. Our uncertainty regarding the basic pathophysiology of thermal injury and resuscitation may be the explanation. A number of alternative strategies have been explored in relatively small trials. Further advances may potentially arise from modulation of the inflammatory response through improved therapies and fluid or from new insights into the basic mechanism of cellular injury and its treatment.

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EDITORIAL

Iatrogenic pneumothorax related to mechanical ventilation

Chien-Wei Hsu, Shu-Fen Sun

Chien-Wei Hsu, Shu-Fen Sun, School of Medicine, National Yang-Ming University, Taipei 112, Taiwan
Chien-Wei Hsu, Intensive Care Unit, Department of Medicine, Kaohsiung Veterans General Hospital, Kaohsiung 813, Taiwan
Shu-Fen Sun, Department of Physical Medicine and Rehabilitation, Kaohsiung Veterans General Hospital, Kaohsiung 813, Taiwan
Author contributions: Hsu CW and Sun SF contributed to this paper, including designing, drafting and revising the article and giving final approval.
Correspondence to: Chien-Wei Hsu, MD, Assistant Professor, Intensive Care Unit, Department of Medicine, Kaohsiung Veterans General Hospital, 386, Ta-Chung 1st Road, Kaohsiung 813, Taiwan. cwhsu2003@yahoo.com
Telephone: + 886-7-342121-2081 Fax: +886-7-3420243
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Abstract

Pneumothorax is a potentially lethal complication associated with mechanical ventilation. Most of the patients with pneumothorax from mechanical ventilation have underlying lung diseases; pneumothorax is rare in intubated patients with normal lungs. Tension pneumothorax is more common in ventilated patients with prompt recognition and treatment of pneumothorax being important to minimize morbidity and mortality. Underlying lung diseases are associated with ventilator-related pneumothorax with pneumothoraces occurring most commonly during the early phase of mechanical ventilation. The diagnosis of pneumothorax in critical illness is established from the patients' history, physical examination and radiological investigation, although the appearances of a pneumothorax on a supine radiograph may be different from the classic appearance on an erect radiograph. For this reason, ultrasonography is beneficial for excluding the diagnosis of pneumothorax. Respiration-dependent movement of the visceral pleura and lung surface with respect to the parietal pleura and chest wall can be easily visualized with transthoracic sonography given that the presence of air in the pleural space prevents sonographic visualization of visceral pleura movements. Mechanically ventilated patients with a pneumothorax require tube thoracostomy placement because of the high risk of tension pneumothorax. Small-bore catheters are now preferred in the majority of ventilated patients. Furthermore, if there are clinical signs of a tension pneumothorax, emergency needle decompression followed by tube thoracostomy is widely advocated. Patients with pneumothorax related to mechanical ventilation who have tension pneumothorax, a higher acute physiology and chronic health evaluation Ⅱ score or PaO_2/FiO_2 < 200 mmHg were found to have higher mortality.

Key words: Barotrauma; Complication; Critical care; Mechanical ventilation; Pneumothorax

Core tip: Patients with pneumothorax related to mechanical ventilation (PRMV) have a high mortality rate. PRMV often occurs in the early stage of mechanical ventilation and it may recur on the other side of lung in a short period of time. Low compliance is associated with a high incidence of PRMV, with PRMV being more related to the underlying process than the ventilatory setting. PRMV patients with tension pneumothorax, higher acute physiology and chronic health evaluation score or PaO_2/FiO_2 < 200 mmHg have a higher mortality.

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INTRODUCTION

Pneumothorax, defined as the presence of air in the pleural space, is a serious complication of mechanical ventilation and is associated with increased morbid-

ity and mortality[1,2]. Pneumothorax can be categorized as primary, secondary, iatrogenic or traumatic according to etiology. Mechanical ventilation was found to be the common cause of iatrogenic pneumothorax in an intensive care unit (ICU)[3]. Pneumothorax is rare in intubated patients with normal lungs and most patients with pneumothorax related to mechanical ventilation (PRMV) have underlying lung diseases that range from primary obstructive lung disease to secondary pneumonia and acute respiratory distress syndrome (ARDS)[4-6]. In critical illness, pneumothoraces may be difficult to diagnose when they have different clinical presentations and their locations are atypical and complicated by other disease processes in unconscious patients[7,8]. Prompt recognition and treatment of pneumothorax is important to minimize morbidity and mortality[9] because if pneumothorax is not diagnosed quickly, once tension pneumothorax ensues, it usually has a malignant course leading to death if untreated[10]. Sudden fall in oxygen saturation followed by hypotension are often observed clinically in these patients[11,12]. Tension pneumothorax is more common in ventilated patients, occurring in 30%-97% percent of all pneumothoraces[13-17].

Pneumothorax was found to be an independent predictor of mortality during mechanical ventilation[18] and was associated with a significant increase in the ICU length of stay, hospital stay and mortality in all mechanically ventilated patients[3]. The mortality rates are high, ranging from 46% to 77% if barotrauma is a complication of mechanical ventilation[2,3,14,15,19-24].

EPIDEMIOLOGY

Patients who received mechanical ventilation have an approximate incidence of barotrauma of 4%-15%[4,13,19,25]. It has been reported that a 14%-87% incidence of pneumothorax occurs depending on severity and duration of ARDS and mode of ventilator for management[1,21,26]. A prior study found that the incidence rate of pneumothorax decreased after the implementation of protective lung strategies in pediatric patients with severe ARDS[27]. The incidence of barotrauma has been reported to be as low as 0.5% in postoperative patients[23].

DISEASE ASSOCIATED WITH PNEUMOTHORAX

Development of pneumothorax is most closely correlated with underlying lung disease[1,21]. Pneumonia is an important predisposing factor in the development of pulmonary barotrauma in mechanically ventilated patients[28]. Necrotizing bacterial pneumonia can cause air leaks into the pleura that result in development of pneumothorax[29].

Chronic obstructive pulmonary disease and asthma are also common underlying diseases associated with pneumothorax. High airway pressures are required to overcome severe bronchial obstruction. However, because of a variability of obstruction in the different airways, there is a mal-distribution of mechanical tidal volume, which promotes gas trapping and non-uniform alveolar distension. That is why these patients are at risk of pneumothorax[30].

PRMV is most closely correlated with ARDS[31], a heterogeneous disease in which the lung is physiologically small and with low compliance[32]. The dependent lung regions tend to be collapsed and the lung regions subject to high pressure overinflation and alveolar rupture are nondependent regions when positive end-expiratory pressure (PEEP) inflates and recruits some of collapsed regions during mechanical ventilation[33,34]. Subpleural and intrapulmonary air cysts occur in ARDS patients and the rupture of these air cysts may be a cause of pneumothorax[14]. Whether the pneumothorax in ARDS arises from overinflation of normal lung regions or from cyst rupture has not yet been conclusively established[21].

Other diseases such as lung cancer, tuberculosis, bronchiectasis, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, histiocytosis X, Marfan's syndrome, Ehlers-Danlos syndrome, lymphangioleiomyomatosis, rheumatoid arthritis and other connective tissue disease may predispose to the development of a pneumothorax[35].

PATHOPHYSIOLOGY AND RISK FACTORS FOR PRMV

An early investigation reported that peak airway pressure over 50 cm H_2O is associated with increased risk of alveolar rupture during mechanical ventilation[4]. There have also been correlations made between high peak airway pressure and the development of pneumothorax[15,36]. High PEEP had been reported to be associated with pneumothorax[1] but several studies have found no such relationship[15,17,23,28,37]. Increased pressure is not enough by itself to produce alveolar rupture, with some studies demonstrating that pneumothorax is related to high tidal volume[37]. In animal studies, there is evidence to conclude that lung overdistension rather than high airway pressure is the primary cause of alveolar and interstitial injury[38,39].

A clinical study showed that when plateau pressure was maintained lower than 35 cm H_2O, pneumothorax was unavoidable[40]. Although one study showed that the incidence of pneumothorax decreased after implementation of protective lung strategies[27], several recent studies comparing low tidal volume with conventional ventilation in ARDS failed to demonstrate any reduction in barotrauma when low tidal volumes were used[41-43]. Previous literature showed the incidence of barotrauma did not relate to the ventilatory settings[22,31,41,44] but a low compliance was associated with a high incidence of barotrauma, which suggested that barotrauma has been more related to the underlying process than the ventilatory setting[40].

CLINICAL MANIFESTATIONS OF PRMV

Pneumothorax is secondary to ruptured alveoli and dis-

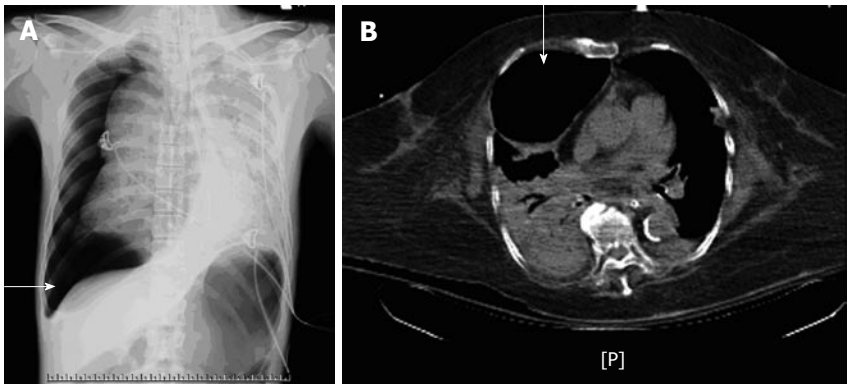

Figure 1 A chest radiograph demonstrates (A) and computed tomography (B) right pneumothorax (arrows). Air may lie in the costophrenic angle extending more inferiorly than usual (A, arrow).

section of air along the vascular sheaths passing to the mediastinum, subcutaneous tissue and retroperitoneum. Therefore, it may manifest as pulmonary interstitial emphysema, pneumomediastinum, pneumoperitoneum or subcutaneous emphysema[32]. Patients may present with tachycardia, chest pain, tachypnea, agitation, hypotension, cyanosis or consciousness change. Tachycardia is the most common finding.

It has been observed that the median time from mechanical ventilation to the development of pneumothorax was 4 d[3]. Anzueto *et al*[45] reported that 80% of their patients developed pneumothorax within the first 3 d of mechanical ventilation. Gattinoni *et al*[21] found that late ARDS (> 2 wk of mechanical ventilation) patients had an increased incidence of pneumothoraces when compared to early ARDS (less than 1 wk of mechanical ventilation) patients[21]. However, Gammon *et al*[31] reported that pneumothoraces occurred most commonly during the early phase of ARDS, with a declining risk over time.

Approximately 7.4%-10% of patients with first episode pneumothorax will develop second episode pneumothorax on the other lung during mechanical ventilation[3,31]. Clinically, we should take notice of these patients because the pneumothorax might attack the lung on the other side.

Tension pneumothorax is common in mechanically ventilated patients[13-17]. Mechanical ventilation will increase gas flow through pleura defects, allowing more air to pass per unit time, and resulting in a more rapid intrapleural pressure rise with earlier mechanical compressive effects and rapid progress to cardiorespiratory collapse and death[46].

DIAGONOSIS

The diagnosis of pneumothorax in critical illness is established from patients' history, physical examination and radiological investigation. The factors related to the underlying lung disease are important in the history. Examination of the respiratory and cardiovascular systems may help establish the diagnosis of pneumothorax. However, examination findings may vary according to the size of pneumothorax and presence of limited cardiorespiratory reserve[47], with patients with a small pneumothorax (one involving < 15% of the hemithorax) possibly having a normal physical examination. Careful inspection and repeated auscultation of the chest is therefore crucial. Contralateral tracheal deviation, hyperresonant percussion over the chest and decreased breathing sounds might be noted. Reduction in tidal volume during pressure controlled ventilation and increased airway pressure with volume controlled ventilation might be found from ventilators. A pulsus paradoxus on the arterial trace and increased central venous pressure from central venous catheterization may be observed[8,9,46,47].

It should be noted that many of the above findings are nonspecific and have not been a reliable indicator of pneumothorax given that dyspnea severity can be out of proportion to the size of the pneumothorax. The radiographic data thus remains the gold standard for the diagnosis of pneumothorax[8]. The chest radiograph may show radiolucent hemithorax with apparent lung edge and absent lung marking. Mediastinal emphysema was the initial manifestation of extra-alveolar air[1]. Although an erect posteroanterior chest radiograph may help to estimate the pneumothorax size[48], it is not practical in critical illness. However, the supine anteroposterior chest radiographs are available in the ICU, although the appearances of a pneumothorax on a supine radiograph may be different from the classic appearances on an erect radiograph. Air may lie in the costophrenic angle extending more inferiorly than usual (Figure 1A), which has been called deep sulcus sign[49]. Concurrent lung disease may lead to different distributions of free air in the pleural space than in relatively normal lungs[50] or it may lead to loculated gas collections if there is associated pleural disease[51]. Some radiographic findings that may be confused with pneumothorax are skin folds, visceral gas within the gas and emphysema bullae. A chest computed tomography (CT) examination, in contrast, can differentiate these diagnoses and is the gold standard test for both the diagnosis and sizing of pneumothorax (Figure 1B)[52]. CT is an excellent tool to differentiate bullous lung disease and prevent unnecessary drainage attempts that may result in the creation of a parenchymal-pleural fistula[53]. Chest radiographs may not distinguish between emphysematous bullae and pneumothorax, thus possibly resulting in potentially catastrophic insertion of intercostal chest drain into emphysematous bullae in mechanically ventilated patients. Unfortunately, it is not always practical or safe

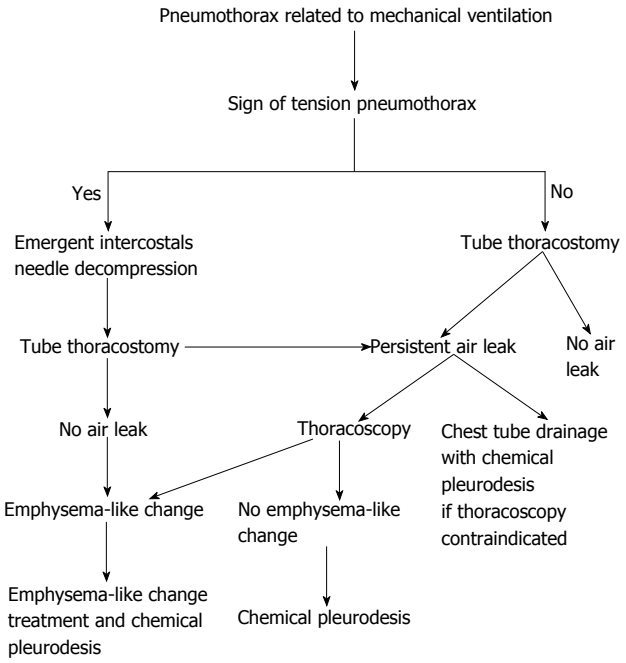

Figure 2 An algorithmic approach to treatment of pneumothorax related to mechanical ventilation.

to transport critically ill patients for a CT scan to exclude pneumothorax, particularly when the patient is hemodynamically unstable.

Transthoracic sonography is a diagnostic tool for pneumothorax[54-56]. There are several advantages of ultrasonography over standard chest radiography and CT scanning, including the lower radiation, portability, real-time imaging and the ability to easily perform dynamic and repeat evaluation. The main use of ultrasonography for assessment of pneumothorax lies in its capacity to rule out a pneumothorax. Respiration-dependent movement of the visceral pleura and lung surface with respect to the parietal pleura and chest wall can be easily visualized with real-time transthoracic sonography. This characteristic is known as lung sliding or gliding sign[56-58]. At the boundary between the pleura and the ventilated lung, intensive band-like reverberation echoes (comet-tail artifacts) are evoked during breathing movement[54,57]. M-mode images of patients without pneumothorax show breath-dependent movements as a single, thin comet-tail artifact. The presence of air in the pleural space prevents sonographic visualization of visceral pleura movements and the gliding sign and comet-tail artifacts disappear[57,58]. M-mode images of patients with pneumothorax show the immobility of these artifacts known as frozen echoes under breathing movement.

One study showed transthoracic ultrasound was more sensitive than chest radiography in the detection of pneumothorax[59]. Another study comparing ultrasonography to CT scan and chest radiographs for diagnosis of occult pneumothorax revealed that the use of ultrasonography detected 92% of occult pneumothoraces diagnosed with CT scan[60]. In trained hands, an ultrasound examination may obviate the need for empiric tube thoracostomy for suspected tension pneumothorax.

TREATMENT AND PREVENTION

Most mechanically ventilated patients with a pneumothorax require tube thoracostomy placement because of the high risk of tension pneumothorax[61]. The strategy of managing pneumothorax is shown in Figure 2. It is not advisable to wait for a radiograph if there are clinical signs of a tension pneumothorax. Emergency needle decompression followed by tube thoracostomy is widely advocated[46]. In critically ill patients with minimal pulmonary reserve, even a small pneumothorax can have adverse cardiopulmonary effects[62]. Positive pressure ventilation can exacerbate air leaks and prevent pleural healing, potentially causing a rapid increase in the size and severity of existing pneumothorax.

The traditional treatment for pneumothorax in mechanically ventilated patients has been chest tube thoracostomy[61], an image-guided small catheter whose size ranges from 7 to 10 Fr, to become an effective therapeutic option for pneumothorax[63]. A retrospective review of 62 ventilated patients who underwent small-bore chest tube drainage as the primary management of pneumothorax found a 68.6% success rate, defined as no residual air seen in the follow-up chest radiograph, and with no major complications[64]. These results compare favorably with previous data showing a success rate of 55% with the same definition for success as in the previous study with a large bore tube[20].

In patients with a persistent air leak or failure of the lung to expand, early thoracic surgical consultation is generally requested within 3-5 d[65]. Although surgical intervention is considered very effective and safe with a low recurrence rate, the studies reaching this conclusion do not include critically ill patients[66,67].

Muscle relaxants might be effective to decrease the incidence of pneumothorax for patients with ARDS. A recent study by Papazian *et al*[68] reported a significant reduction in pneumothoraces in patients with severe ARDS who received 48 h of paralysis.

OUTCOMES

Mechanically ventilated patients with pneumothorax had a significantly higher mortality rate than those without pneumothorax. de Lassence *et al*[3] reported that iatrogenic pneumothorax was associated with a greater than twofold increase in the risk of death. In terms of iatrogenic pneumothorax, the mortality rate of patients with ventilator-related pneumothorax was significantly higher than that of patients with procedure-related pneumothorax[20]. Ventilator-related pneumothorax patients with tension pneumothorax had a higher risk of death[20].

CONCLUSION

Pneumothorax is a medical emergency and a disease with a high mortality rate; it requires a careful awareness,

prompt recognition and intervention to reduce morbidity and mortality. Most patients with PRMV have underlying pulmonary diseases, the most common of which are pneumonia, ARDS and obstructive lung disease. Pneumothorax presentation and radiographic findings may be subtle or atypical. Whereas a CT scan is the gold standard for diagnosis, the use of ultrasonography has benefits in both diagnosis and management of pneumothorax. Most of the ventilated patients with a pneumothorax require immediate treatment with tube thoracostomy because of the high risk of progression to a tension pneumothorax. Small-bore catheters are now preferred in the majority of ventilated patients.

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REVIEW

Disaster preparedness, pediatric considerations in primary blast injury, chemical, and biological terrorism

Mitchell Hamele, William Bradley Poss, Jill Sweney

Mitchell Hamele, W Bradley Poss, Jill Sweney, Division of Pediatric Critical Care, Department of Pediatrics, School of Medicine, University of Utah, Salt Lake City, UT 84108, United States
Author contributions: Hamele M, Poss WB and Sweney J contributed equally to this manuscript.
Correspondence to: Mitchell Hamele, MD, Division of Pediatric Critical Care, Department of Pediatrics, School of Medicine, University of Utah, 295 Chipeta Way, Salt Lake City, UT 84108, United States. Mitchell.Hamele@hsc.utah.edu
Telephone: +1-801-5877572 Fax: +1-801-5818686
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Abstract

Both domestic and foreign terror incidents are an unfortunate outgrowth of our modern times from the Oklahoma City bombings, Sarin gas attacks in Japan, the Madrid train bombing, anthrax spores in the mail, to the World Trade Center on September 11th, 2001. The modalities used to perpetrate these terrorist acts range from conventional weapons to high explosives, chemical weapons, and biological weapons all of which have been used in the recent past. While these weapons platforms can cause significant injury requiring critical care the mechanism of injury, pathophysiology and treatment of these injuries are unfamiliar to many critical care providers. Additionally the pediatric population is particularly vulnerable to these types of attacks. In the event of a mass casualty incident both adult and pediatric critical care practitioners will likely be called upon to care for children and adults alike. We will review the presentation, pathophysiology, and treatment of victims of blast injury, chemical weapons, and biological weapons. The focus will be on those injuries not commonly encountered in critical care practice, primary blast injuries, category A pathogens likely to be used in terrorist incidents, and chemical weapons including nerve agents, vesicants, pulmonary agents, cyanide, and riot control agents with special attention paid to pediatric specific considerations.

Key words: Terrorism; Bioterrorism; Chemical terrorism; Blast injuries; Mass casualty incidents; Disasters; Pediatrics

Core tip: Terrorism and mass casualty events continue to increase on a global scale. Many injuries specific to terrorist incidents including blast injury, biological, and chemical casualties are unfamiliar to the critical care provider. We review the presentation, pathophysiology and care of these casualties. We give specific consideration to the pediatric population as they are a particularly vulnerable population and both adult and pediatric critical care specialists would be called upon to care for children in the event of a massive casualty terrorist event.

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INTRODUCTION

Terrorism is an unfortunate fact of life in current times. Children have been identified as a specific vulnerable population[1]. Additionally children have increased mortality when exposed to combat injury[2]. While these events have increased in frequency, exposure during medical training is limited. This review will cover those aspects of care of the pediatric victim of terrorist incidents that may not be familiar to the critical care provider. We will cover primary blast injury (PBI), biological weapons, and chemical weapons.

Table 1 Pediatric specific vulnerabilities to terrorist attacks

Vulnerability	Blast Injury	Biological agents	Chemical agents
Proximity to ground		Agents settle to the ground	Agents tend to pool in lower areas
Increased minute ventilation		Increased exposure to inhaled agents	Increased exposure to inhaled agents
Provider unfamiliarity with pediatric dosing of medications		Dosing of antibiotics different	No prepackaged store of antidotes in pediatric doses
Lack of knowledge or inability to flee danger	Either unaware or unable to flee from explosion Potentially curious about ordinance	Unlikely to recognize signs/ symptoms of biologic agents	Would not know to flee from strange odor or seek medical help with symptoms
Lack of stockpile of pediatric dosed antidotes and vaccines		Prepackaged stockpiles of vaccines and antidotes not dosed for small children[32]	Lack of guidelines for dosing of antidotes in children
Less blood volume/ physiologic reserve	More rapidly develop life threatening blood loss	Prone to dehydration with illness. Lower functional residual capacity	More prone to respiratory distress/ failure with nerve agents, vesicants, and pulmonary agents
Thinner skin			Faster absorbtion of agents
Increased BSA to mass ratio	Prone to hypothermia during triage, evacuation and treatment		Prone to hypothermia with decontamination
Developmental immaturity	Unable to follow mental status exam/communicate other injuries early	Present later in the course of biologic agents	Unable to promptly communicate symptoms
Increased head size compared to body	Increased head AIS when compared to adults[2]		

AIS: Abbreviated injury score; BSA: Body surface area.

High-order explosives (HE) were first available after dynamite was developed by Alfred Nobel in 1866. Since then several other HE have been developed and are used in up to 66% of terror attacks[3]. Biological warfare dates back to the Hittites driving diseased animals into enemy territories as early as 15th century BC. In 1346, Mongols hurled bodies of those killed by plague into Crimean city of Caffa, causing an epidemic resulting in their surrender. Chemical weapons were first used on a large scale during World War I where mustard, chlorine, and phosgene were used in the trenches[4]. In more recent times, Saddam Hussein and the Iraqi military used the nerve agent sarin against Kurdish villagers and the Iranian military during the Iraq-Iran War in 1988 with 75% of casualties being women and children. Sarin has been used on at least two occasions in the mid-1990s by the Japanese terror cult Aum Shinrikyo, including an incident in 1995 at a Tokyo subway station that killed 15 and injured over 5000. Among the injured were healthcare providers who were unprepared to deal with contaminated victims. Recent events in Syria have also clearly shown that chemical weapons are a threat we still face. Finally, chemical agents may be introduced into the food supply as was seen with the placement of a nicotine-containing insecticide into ground beef in Michigan, United States in 2002 that resulted in more than 40 children becoming ill.

As mentioned, children are identified as a vulnerable population. They have several specific physiologic, anatomic, and developmental differences from adults which make the particularly vulnerable (Table 1). In 2010 the National Commission on Children and Disasters reported that while children make up 25% of the United States population only 25% of EMS agencies and 6% of hospital emergency rooms have supplies and equipment to treat children[1]. This problem is likely more prevalent in the developing world where children make up a larger portion of the population. When planning and executing exercises and simulations of disaster events, including terrorist attacks, it is imperative that the unique aspects of treating children are taken into account[1].

PBI

Explosive charges can be divided into 2 types, HE, which cause a supersonic overpressure wave, or low-order explosives which are lower energy and do not cause an overpressure wave. Examples of HE include C-4, TNT, and ammonium nitrate, which was used in the bombing at the Murrah Federal Building in Oklahoma City.

Injuries caused by a blast can be divided into 4 categories; primary, secondary, tertiary, and quaternary. PBI is injury caused as a direct effect of overpressure caused by the blast wave itself passing through the tissues. Low-order explosives typically do not cause PBI due to the lack of an overpressure wave. Secondary blast injury is caused by fragments propelled by the explosion. These penetrating injuries are more easily identifiable and also more familiar to most physicians. Tertiary injuries are those injuries caused by displacement of the victim's body and are the result of impact on a surface such as fractures, traumatic brain injury (TBI), or abrasions. Quaternary injuries are burns and inhalation caused by the blast itself[5]. While we differentiate these 4 types of injury, injury in explosions is multi-mechanistic and can be difficult to determine individually[6]. We will focus on PBI as the penetrating, blunt, and thermal trauma associated with secondary, tertiary, and quaternary blast injuries are more familiar to the critical care physician. For pediatric

specific vulnerabilities in blast injury please see Table 1.

The overpressure wave that causes PBI does so through 2 mechanisms, stress and shear, which cause injuries by transmission of kinetic energy as the wave travels from tissue into air-filled organs[6,7]. Stress waves are longitudinal and cause "spalling", which can cause significant microvascular and tissue damage. Shear waves, are transverse and cause disruption of tissue attachments[7].

When explosions occur in closed environments, mortality is higher due to the blast wave reflecting off solid walls. In the Madrid subway bombings of 2004, 63% of patients who survived to intensive care unit admission were noted to have blast lung injury[8]. In a 1996 analysis of detonations in terrorist incidents in Israel, explosions occurring in enclosed spaces versus open air detonations had a higher rate of mortality (49.0% *vs* 7.8%) and higher incidence of primary blast injuries (77.5% *vs* 33.4%)[9].

Blast lung injury

Primary blast lung injury (PBLI) occurs in 3%-14% of blast survivors and is the most common fatal complication of initial survivors of blast injury[9,10]. Passage of the overpressure wave from tissue to the air filled alveoli causes disruption of the capillary alveolar interface resulting in pulmonary hemorrhage, pulmonary edema, pneumothorax, pulmonary fat embolus, or air embolus from arterio-venous fistulas[11]. The resultant clinical signs suggestive of PBLI are tachypnea, respiratory distress, cyanosis, and hemoptysis[7]. Chest radiographs may show bilateral central pulmonary infiltrates that are not always initially present on admission[12]. In a retrospective review from Israel all patients with PBLI had pulmonary infiltrates and hypoxia[12]. Thus PBLI should be strongly suspected in any patient with any of the above findings especially in the absence of evidence of other penetrating or blunt chest injury.

Treatment of PBLI should include maintaining patency of the airway, oxygenation, avoidance of overzealous fluid administration (which children are at increased risk of), and support of ventilation. Historically it has been taught that positive pressure ventilation should be avoided but in one series with excellent outcomes, 76% of patients required intubation and mechanical ventilation[12]. Additionally these patients are at high risk of pneumothoraces and prophylactic placement of chest tubes prior to intubation or transport should be considered[13]. Pulmonary hemorrhage should be treated with optimization of coagulation but if oxygenation cannot be maintained then positive pressure ventilation and selective ventilation of the non-involved lung is recommended. Permissive hypercapnia such as that used with acute respiratory distress syndrome has been recommended as a ventilatory strategy in PBLI patients[14]. Identification of air emboli by echocardiography, computed tomography (CT), or bronchoscopy is critical in PBLI as these are a frequently fatal. Thoracotomy on the affected side is the recommended treatment for non-traumatic air embolus but may not be effective in PBLI as there may be multiple sites of injury[15]. Therefore a more conservative approach would be to put the patient in a modified lateral decubitus position with the injured lung down or prone position.

Cardiovascular blast injury

The cardiovascular effects in victims of a blast can be complex. Secondary or tertiary injuries can cause cardiac contusion or tamponade. The stress of being in a blast can induce myocardial infarction in susceptible adults with pre-existing heart disease. Unique to blast injury is the observed phenomenon of bradycardia, apnea, and hypotension immediately following a blast[7]. Rat studies have demonstrated a similar response after a blast with a drop in systemic vascular resistance (SVR)[16]. The same authors found that when they performed a surgical vagotomy and administered atropine to rats subjected to blast that these effects were diminished suggesting a vagal response to the blast itself[17]. Some data indicate that atropine may be a useful adjunct in blast patients experiencing hemodynamic compromise[7]. Infants may be at increased risk of this vagally mediated bradycardia, apnea, and lack of compensatory increase in SVR due to immaturity of their sympathetic nervous system. Additionally, given the relative flexibility of the pediatric thoracic cage they are at increased risk for cardiac contusions.

Gastrointestinal blast injury

The pathophysiology of gastrointestinal (GI) tract PBI is similar to PBLI. It occurs when the overpressure wave passes from tissue into gas filled spaces causing microvascular damage and tearing across tissue planes. Incidence ranges from 3.0%-6.7% amongst initial survivors in a series of 1040 patients[18]. The regions most affected were the terminal ileum and cecum[18]. Solid organs can rupture although this occurs less frequently. Signs and symptoms include those typically seen with abdominal hemorrhage and perforation to include, abdominal pain, nausea, emesis, hematemesis, melena, hypotension, or signs of peritoneal irritation and may present several hours to days after injury[7].

Diagnosis is primarily clinical and accomplished through serial exams, which can be more challenging in the pediatric population. Adjunctive diagnostic tests such as plain abdominal radiograph can help in diagnosis. Abdominal CT scan is very effective at demonstrating solid organ injury but may not be as sensitive with intestinal injury. Diagnostic peritoneal lavage can be used as an adjunct if other studies or clinical exam are not conclusive[18]. The treatment of GI blast injury is similar to that of blunt or penetrating abdominal injury and indications for surgical intervention are similar[18]. It should be noted that GI blast injury typically develops over several hours to days and that treatment of PBLI, cardiac injury and other life threatening injuries should be stabilized prior to treatment of the GI injuries if they are not life threatening.

Blast TBI

While blast TBI (bTBI) is a common occurrence in explosions there is also a high incidence of closed TBI due to tertiary blast injury making it difficult to separate the

Table 2 Management of chemical agents

Agent	Pediatric dosing	Notes
Nerve agents	Atropine 0.05 mg/kg *iv* or *im* q 2-5 min (max 5 mg) Pralidoxime 25 mg/kg *iv* or *im* q 1 h (max 1 g *iv* or 2 g *im*) Benzodiazepines: Midazolam *im* 0.2 mg/kg (max 10 mg) (1st choice) Lorazepam *iv*/*im* 0.1 mg/kg (max 4 mg) Diazepam *iv* 0.3 mg/kg (max 10 mg)	Atropine should be repeated for persistent symptoms
Cyanide	Hydroxocobalamin 70 mg/kg (max 5 g) or sodium nitrate; 0.33mL/kg *iv* (max 10 mL) followed by sodium thiosulfate (25%) 1.65 mL/kg *iv* (max 50 mL)	Hydroxocobalamin may be repeated × 1 if needed

two[5]. Clinical findings in bTBI have a similar spectrum to injuries seen in the typical practice of critical care physicians and include edema, contusion, diffuse axonal injury, hematomas, and hemorrhage[5]. A study by Ling *et al*[19] based on the conflicts in Iraq in Afghanistan suggest that the pathophysiology in bTBI may be different with increased vasospasm and pseudoaneurysms as well as onset of cerebral edema much earlier in the course of bTBI than other TBI. Additionally they demonstrated early decompressive craniectomy in these patients may reduce mortality. With the exception of early craniectomy, current treatment strategies for bTBI do not differ from more common severe closed head injury[5]. Specific pediatric considerations include age appropriate equipment, assessment tools such as the pediatric Glasgow Coma Score, and recognition of the specific vulnerabilities of children to bTBI (Table 1).

Ophthalmologic and auditory blast injury

Significant ophthalmologic injury may occur in up to 10% of blast victims and may include a perforated globe, foreign body, air embolism, fractures, or globe rupture from the over pressure wave[13]. Auditory injury is also common in blast injury occurring in 9%-47% of victims[7]. While both ophthalmologic and auditory injuries are common and may require follow-up (such as globe rupture within 12 h) they should be addressed after life threatening injuries.

CHEMICAL AGENTS

There are estimated to be over 50 chemical agents that can be used as weapons, many of which have a high probability of injury. Children may often be the index case in the event of a chemical agent attack due to their inherent vulnerabilities (Table 1). Exposure to chemical agents is usually *via* either the respiratory system or skin with direct and systemic toxicity possible in either route.

Skin decontamination of suspected victims is imperative as it limits further absorption by the patient as well as preventing healthcare worker exposure. Decontamination ("The solution to pollution is dilution") is best done with 0.5% hypochlorite solutions or large amounts of soap and water after removal of all clothing and jewelry. Decontamination should be done by personnel in appropriate personal protective equipment[20]. Following this, the patient should be blotted dry instead of scrubbed dry as this can lead to increased cutaneous absorption through abrasions in the skin. Isolation is not required after thorough decontamination[21].

Nerve agents [Tabun (GA), Sarin (GB), Soman (GD), and VX]

Nerve agents can be absorbed, ingested, and inhaled (if in aerosolized form). Nerve agents are colorless liquids at room temperature and generally odorless and tasteless. Although they range in severity (VX is the most potent), all are organophosphate analogs and inhibitors of the enzyme acetyl cholinesterase, resulting in excessive acetylcholine stimulation of both nicotinic and muscarinic receptors.

Signs and symptoms depend on the form of the agent, concentration, and environmental variables. Aerosolized agents produce symptoms within minutes while cutaneous exposure symptoms may not develop for hours. Initial symptoms are often best remembered by SLUDGE (salivation, lacrimation, urination, defecation, GI upset, and emesis). More severe symptoms consist of respiratory (cough, wheezing with bronchorrhea, dyspnea, respiratory depression and cyanosis), cardiovascular (bradycardia, hypotension, and atrioventricular block), and central nervous system (muscle fasciculations, seizures, ataxia, and altered mental status including coma). It is important to note that children may not exhibit miosis to the same degree as adults but do exhibit a high incidence of weakness/hypotonia. Pediatric patients are at higher risk for severe toxicity than adults (Table 1).

The diagnosis of nerve agent exposure is generally made using presenting symptoms and response to antidotes. Although red blood cell or plasma acetyl cholinesterase levels can be measured, this test is not widely available on a rapid basis. In addition, nerve agent detection devices are available in certain settings (generally military and homeland defense) but not generally found in civilian healthcare settings. Decontamination (outlined above) is key to both treatment and prevention of contamination of providers.

Death, usually as a result of respiratory failure, can occur within 5-10 min of lethal dose exposure without proper treatment. Treatment consists of antidotes for both muscarinic (atropine) and nicotinic (pralidoxime chloride) with pediatric dosing provided in Table 2[22]. Atropine is indicated for all patients exhibiting signs/symptoms of nerve agent poisoning. Atropine should be

Table 3 Guidelines for the use of Mark I kits in pediatric patients

Pediatric patients	Mark I kits
3-7 yr (approximately 13-25 kg)	One Mark I kit as maximum dose
8-14 yr (approximately 26-50 kg)	Two Mark I kits as maximum dose
> 14 yr (approximately > 51 kg)	Three Mark I kits as maximum dose

Mark I kit: 2 mg atropine and 600 mg 2-PAM; PAM: Pralidoxime.

repeated every 2-5 min if symptoms persist[22]. Both pediatric intramuscular atropine (0.25, 0.5, 1 mg dosages) and adult (2 mg) auto injectors are available although pediatric ones may be less available in some settings. Patients with severe sign/symptoms should also be given pralidoxime chloride (2-PAM) and a benzodiazepine. 2-PAM is used to treat the nicotinic receptor blockage by binding to the nerve agent, thus "re-activating" the acetylcholinesterase which can now break down the excessive acetylcholine present, provided enzyme "aging" or inactivation has not occurred. Currently there are only adult auto injectors (600 mg of 2-PAM) which together with the 2 mg atropine adult autoinjectors (Mark- I kit) can be used in pediatric patients when necessary. The Pediatric Expert Advisory Panel of Columbia University's Program for Pediatric Preparedness at the National Center for Disaster Preparedness has published guidelines on the use of Mark I kits in pediatric patients (Table 3). There are newer types of kits that combine the two agents in to one syringe for easier administration. Benzodiazepines (with midazolam as the preferred treatment) are given concurrently with 2-PAM to both prevent as well as treat seizures.

Vesicants

Sulfur Mustard is a vesicant that forms blisters upon skin contact and has been used on occasion since World War I including against the Kurdish population in Iraq. Although other vesicants exist such as Lewisite, they are considered to be of less risk for weaponization[4]. Vesicants are alkylating agents that cause damage to rapidly reproducing cells. Although vesicants cause less morbidity than nerve agents, they can cause significant long-term morbidity with extensive damage to skin, respiratory system, eyes, as well as bone marrow suppression. Mortality is usually from respiratory failure. Pediatric patients again exhibit a greater vulnerability to these agents due to faster skin absorption and proximity to agents settling near the ground (Table 1). If ingested, vesicants can also cause extensive intestinal mucosal injury. Although extensive clinical symptoms may not present until hours after exposure, skin damage can occur within minutes unless prompt decontamination is done. In general care =is supportive (similar to traditional burn care except for not requiring high volume fluid administration as in traditional burns) except in the case of lewisite for which British Anti-Lewisite can be used (3 mg/kg *im* q 4-6 h)[20].

Pulmonary agents

Chlorine and phosgene are the classic pulmonary agents but there are other pulmonary agents that can cause significant injury such as methyl isocyanate which was accidentally released in Bhopal, India in 1984 causing over 3000 deaths. Pulmonary agents have an odor of newly cut hay or grass and symptoms start with eye and skin irritation[21]. Significant respiratory symptoms can be delayed up to 24 h[23]. Symptoms include airway irritation (coughing, wheezing) with subsequent pulmonary edema and respiratory failure. Injury can occur to both Type I and Ⅱ pneumocytes as well as alveolar macrophages with later release of prostaglandins and bradykinin producing vasodilatation and increased capillary permeability[23]. See Table 1 for pediatric specific vulnerabilities. Decontamination (moving to fresh air and supplying oxygen) is key to the management of these patients. Treatment for respiratory failure is similar to other causes of respiratory failure. Adjunct treatments that have been used but lack definitive recommendations include corticosteroids as well as in the case of phosgene, N-acetylcholine.

Cyanide

Cyanide is a potent toxin that disrupts cellular metabolism by inhibiting cytochrome oxidase with interruption of oxidative phosphorylation. Cyanide intoxication can be caused by inhalation, ingestion or transdermal absorption of vapor, solid, and liquid forms. Fortunately cyanide is difficult to formulate into a chemical weapon due to it being highly volatile and chemically unstable. The classic presentation of cyanide poisoning is hypoxia without evidence of cyanosis. Mild symptoms include tachypnea, dizziness, nausea, vomiting, and headaches. Significant exposure can cause seizures, coma, respiratory arrest, and cardiac arrest within minutes.

Cyanide poisoning should be suspected in patients with a sudden change in mental status and significant metabolic acidosis. Characteristically patients have a bitter almond odor with a cherry red appearance of the skin. Laboratory testing will reveal elevated serum lactate levels, a narrow arterial-venous oxygen saturation difference, and elevated blood cyanide levels.

Decontamination (soap and water) should be performed in the event of cutaneous exposure. Mild systemic symptoms generally resolve with fresh air. Severe symptoms (coma, respiratory distress, *etc.*) are an indication for administration of an antidote in addition to critical care support as indicated. Hydroxocobalamin is now recommended as first line treatment due to its improved safety profile as compared to traditional cyanide antidote kits (Table 2). Hydroxocobalamin's mechanism of action is binding with cyanide to form cyanocobalamin which is excreted renally[24]. Traditional cyanide antidote kits consist of sodium nitrite and sodium thiosulfate. A third component, amyl nitrite is no longer recommended due to questionable efficacy. Nitrite administration is now used as a second line treatment due to concerns of overproduction of methemoglobin which may compromise oxygen-carrying capacity, especially in young children, as well as hypotension that can be seen with nitrite infusions.

Riot control agents

Riot control agents are also known as lacrimators, "tear gas", and pepper spray. The most commonly used riot control agents are CS and CN. Although these agents produce mostly irritant symptoms to the eye they can be fatal as seen with a terrorist attack in Russia in 2002 where over 100 were killed. These agents are also alkylating but do not produce tissue damage similar to vesicants. In general they cause pain, conjunctival injection, blepharospasm, and lacrimation. In some cases respiratory symptoms may occur (laryngospasm and bronchospasm) and is the cause of fatalities. Treatment consists of eye and skin irrigation as well as supportive respiratory care, including bronchodilators, if needed.

BIOLOGIC AGENTS

The use of biologic weapons has been and continues to be a great threat to our population. The ability to recognize that an attack has occurred and the ability to differentiate this from a natural outbreak can be difficult as symptoms of these agents may be delayed days to weeks after the attack. It is imperative that physicians recognize patterns that could indicate the early manifestations of a bioterrorist attack. A sudden outbreak of an unusual illness or the diagnosis of a rare disease is likely to be the first indication. Epidemiologic surveillance systems have been set up for early detection with the goals of early institution of preventative measures such as vaccination, isolation, prophylaxis, and institution of other treatment modalities[25]. Children, like in previous sections, have particular vulnerabilities to biological attacks (Table 1).

The Soviet Union, United States, and Japan all developed biological weapons programs in the 20th century. It is suspected that Japanese planes dropped fleas carrying plague over China during World War Ⅱ. The Convention of the Prohibition of the Development, Production, and Stockpiling of Bacteriologic and Toxin Weapons was held in 1972, with over 140 countries signing[25]. Despite the signing of this document, the threat of biological warfare continues with the rise in terrorist groups. The release of anthrax spores through the United States postal system and the release of anthrax into the population following the September 11, 2011 terrorist attacks demonstrate that this is a continued threat. The United States continues to develop aggressive measure of surveillance and protection[26].

The Center for Disease Control (CDC) has categorized agents into three groups based on morbidity and mortality if used as a biological weapon. Category A agents pose the greatest risk due to their easy dissemination, high mortality rates, and require special action for public health preparedness. Category B agents are moderately easy to disseminate, result in high morbidity and low mortality and require enhancement of the CDC's surveillance. Category C agents include emerging pathogens that are engineered for mass dissemination in the future[27]. We will address the category A agents.

Anthrax

Anthrax is caused by a gram-negative, spore forming bacteria, *Bacillus anthracis* (*B anthracis*). It is naturally occurring in animals as they ingest spores from the soil Anthrax occurs in humans in 3 different forms: GI, cutaneous, and inhalational anthrax. Cutaneous and GI anthrax both occur naturally and are transmitted through breaks in the skin or ingestion of infected meat respectively. Inhalational anthrax rarely occurs naturally with no cases reported in the United States since 1978. Inhalational anthrax is thought to hold the most threat as it is expected to account for the most morbidity and mortality. Anthrax secretes two exotoxins, edema toxin and lethal toxin. These result in massive edema and a cytokine storm[28].

Papules form in cutaneous anthrax in 1-7 d following exposure. These papules then become vesicles that ulcerate and form a black eschar. Symptoms of inhalational anthrax typically occur 1-7 d after exposure but can occur as late as 60 d after exposure. Early symptoms are subtle, resembling a nonspecific upper respiratory infection. Later the child will develop a high fever, shock, and death. Autopsy studies of patients with inhalational anthrax show hemorrhagic thoracic lymphadenitis and mediastinitis with very few exhibiting signs of pneumonia. Up to 50% of patients will also develop meningitis[28,29].

Because diagnostic tests including enzyme-linked immunosorbent assay and polymerase chain reaction are only available at the national reference laboratories diagnosis of an outbreak could be delayed. Diagnosis on routine blood culture could be missed if the laboratory is not alerted to *B anthracis* being a possible cause. Antimicrobial treatment is outlined in Table 4. No widespread vaccine distribution is currently available, and person to person transmission has not been reported[29].

Plague

Yersinia pestis is a gram-negative bacillus, sometimes coccobacillus, known to cause plague. It occurs naturally in the forms of septicemia, bubonic and pneumonic forms. Pneumonic plague is the most likely to be seen in a bioterrorism as aerosolized forms would be easily disseminated. Pneumonic plague results in a multilobar, hemorrhagic and necrotizing bronchopneumonia. Unlike naturally occurring plague, plague following a biological attack will present with respiratory symptoms without the development of the buboes. Patients would likely develop fever and cough within 6 d of exposure and rapidly progress to severe bronchopneumonia. Untreated pneumonic plague has resulted in nearly 100% mortality[29]. An additional clue of intentional dissemination would be cases presenting in areas not known to have animal infection[30].

Large numbers of previously healthy patients presenting with severe pneumonia, hemoptysis, and sepsis would be the first signs of a biological attack with plague. There are no rapid tests available to detect *Y pestis*. A gram stain of blood or sputum may reveal a gram-negative bacilli 24-48 h after inoculation. Table 4 outlines a variety of treatment regimens available[29].

Table 4 Management of biologic agents

Agent	Pediatric dosing	Notes
Inhalational anthrax	Ciprofloxacin 10-15 mg/kg *iv* q 12 h (max 400 mg) or doxycycline 2.2 mg/kg *iv* q 12 h (max 100 mg) plus clindamycin 10-15 mg/kg q 8 plus penicillin G 400-600 k U/kg per day *iv* divided q 4 h prophylaxis for exposed contacts ciprofloxacin 15 mg/kg *po* q 12 h or doxycycline 2.2 mg/kg *po* q 12 h	Switch to oral therapy when patient shows signs of improvement At least one agent should have good CNS penetration Prophylaxis is for a 60 d course Amoxicillin or levofloxacin are second line
Plague	Gentamycin 2.5 mg/kg *iv* q 8 h or streptomycin 15 mg/kg *im* q 12 h (max 2 mg/d) or doxycycline 2.2 mg/kg *iv* q 12 h (max 200 mg/d) or ciprofloxacin 15 mg/kg *iv* q 12 h prophylaxis for exposed contacts trimethoprim/sulfa 4 mg/kg *po* q 12 h	Chloramphenical or Levofloxacin can also be used Prophylaxis should be continued for 5-7 d
Tularemia	Same as therapy for plague	
Botulism	Infants < 1 yr human-derived botulinum immunoglobulin children > 1 yr equine serum botulism antitoxin	In United States call 1-800-222-1222 or 770-488-7100 Outside United States contact local health agencies

CNS: Central nervous system.

Small pox

Any case of small pox, variola major, that is identified would be considered an act of terrorism. Small pox has been eradicated and no child has been routinely vaccinated against small pox since 1971. Small pox is highly contagious, with only a few viral molecules needed to induce disease. It is believed that the only remaining samples of this virus are kept secure at the CDC and in Russia, although there are some who believe other countries may have samples of it in their possession[29].

The incubation period of small pox is from 7-19 d after exposure. Initially symptoms are relatively nonspecific with fever, malaise, vomiting, headache and backache. Two to three days later the patient develops an erythematous macular rash that progresses to papules and then pustules, which spread centrifugally. Death occurs in the second week of illness with multi-organ failure due to overwhelming viremia.

Diagnosis of small pox will be clinical as there are no widely available assays. Initial suspicion should be reported immediately to the health department. Patients exposed to a case will need to be monitored for a minimum of 17 d on airborne and contact precautions in the hospital or isolated in their homes. They should remain isolated until they are ruled out (PCR assays are available at national laboratories) or when the vesicles have lost their scab. Vaccines obtained in the last 3 years are thought to provide full immunity. Treatment is supportive care. There are no FDA approved anti-virals although cidofovir has been shown useful in animal models. Vaccination 72-96 h after exposure provides good protection against developing disease and also decreases severity[25]. All close contacts will require vaccination and isolation.

Tularemia

Tularemia is caused by Francisella tularensis, a small, aerobic, gram-negative coccobacillus with extremely high virulence. It occurs naturally in the environment throughout North America and Europe. Humans are infected by insect bites, handling infected animal meat, or ingestion of contaminated water or food. An act of bioterrorism with tularemia would likely be in an aerosolized form, allowing for many to become ill with a single release[31].

In the event of an aerosolized tularemia attack, there would be an abrupt onset of patients presenting with flu-like symptoms and bronchitis 3-5 d post exposure. A large amount of those infected would present with severe cases of necrotizing hemorrhagic pneumonia, with or without bacteremia.

It is unlikely for tularemia to be identified with routine culture techniques. Rapid tests are primarily only run at research and reference laboratories. Serum antibody titers can be diagnostic but take 10 d to become positive. Standard precautions are all that is required as tularemia is not spread person to person. Patients have a significantly improved course with early initiation of the appropriate antibiotics (Table 4) and prophylaxis should be provided to others exposed to the attack[31].

Botulism

Botulinum toxin is produced by Clostridium botulinum, an anaerobic bacteria, and is the most lethal toxin known. Botulism can be spread naturally by three mechanisms: infantile botulism, wound botulism, and intestinal botulism. Botulinum toxin causes the inhibition of the release of acetylcholine at the nervous-skeletal muscle junction, thus producing a paralysis. Patients primarily die due to respiratory failure. Even with supportive care, recovery can take weeks to months as new axons must grow on each neuron[29].

In the event of a bioterrorism attack, the particles would likely be released and inhaled[32]. Symptoms can present within 12-24 h after exposure, with cranial nerve palsies presenting first, followed by descending paralysis progressing to respiratory failure. Clinical symptoms are constipation, ileus, dry mouth and mydriasis. The "gold standard" for diagnosis is a bioassay but treatment should not be delayed pending these results. Supportive care and ventilator support is the most important aspect of treatment. Antitoxin is available in two forms, bivalent human

Table 5 Viral hemorrhagic fever, virus and disease

Family	Virus	Disease
Arenaviruses	Lassa virus	Lassa fever
	Junin	Argentine hemorrhagic fever
	Machupo	Bolivian hemorrhagic fever
Bunyaviruses	CCHF	Cremiean-Congo hemorrhagic fever
	RVF	Rift Valley fever
	Hantavirus	Hemorrhagic fever with renal syndrome
Filoviruses	Ebola virus	Ebola hemorrhagic fever
	Marburg virus	Marburg hemorrhagic fever
Flavivirus	Yellow fever virus	Yellow fever
	KFD virus	KFD
	OHF virus	Omsk hemorrhagic fever
	DENV 1-4 viruses	Dengue hemorrhagic fever
Rhabdovirus	Bas-Congo virus	Bas-Congo hemorrhagic fever

CCHF: Crimean congo hemorrhagic fever; RVF: Rift valley fever; KFD: Kyasanur forest disease; OHF: Omsk hemorrhagic fever; DENV: Dengue hemorrhagic fever virus.

antiserum and equine heptavalent antitoxin, and should be administered at the first onset of symptoms. This will unlikely be available in massive quantities during a mass attack and will only shorten the course of illness. Prophylactic vaccination is reserved for at risk individuals, primarily laboratory workers[25].

Viral hemorrhagic fevers

The viral hemorrhagic fevers are produced by a variety of viruses originating from one of five virus families (Table 5). They are grouped by their ability to produce fever, shock, and bleeding. They are all spread by aerosolized particles, excluding dengue fever, which is blood-borne, and produce an illness with high morbidity and mortality.

All of the viral hemorrhagic fevers present with a nonspecific febrile illness including headache, myalgia and malaise. As they progress, the patient develops shock and hemorrhage. The cause of hemorrhage can vary depending on the causative agent. Most are multi-factorial in nature. Diagnosis should begin with a careful travel history to possible endemic areas as well as exposure to animals or animal feces. Patients have detectable viremia with most viruses identified through rapid enzyme immunoassays[25].

Supportive care is the mainstay for the hemorrhagic fevers. Vigorous fluid resuscitation and control of hemorrhage with platelets, red blood cells, and clotting factors will often require intensive care. Ribavirin is indicated only in Lassa fever but has been used experimentally in a few of the other viruses[29].

CONCLUSION

Terrorist incidents continue to occur and it is imperative that the critical care provider be familiar with signs, symptoms, and basic treatment of the injuries and illnesses caused by potential terrorist modalities. While these events are thankfully rare, the prompt recognition of a possible chemical or biological attack is crucial to limiting the damage caused by such an attack by instituting appropriate decontamination, treatment, and preventative measures. Familiarity with injuries specific to a blast should prepare the provider to anticipate and intervene appropriately when caring for these patients. For further information please refer to the agency for healthcare research and quality website at http://archive.ahrq.gov/research/pedprep/index.html.

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Controversies in fluid therapy: Type, dose and toxicity

Robert C McDermid, Karthik Raghunathan, Adam Romanovsky, Andrew D Shaw, Sean M Bagshaw

Robert C McDermid, Adam Romanovsky, Sean M Bagshaw, Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB T6G2B7, Canada
Karthik Raghunathan, Andrew D Shaw, Department of Anesthesiology, Duke University Medical Center/Durham VAMC, Durham, NC 90484, United States
Andrew D Shaw, Department of Critical Care Medicine, Duke University Medical Center/Durham VAMC, Durham, NC 90484, United States
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Correspondence to: Dr. Sean M Bagshaw, Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, 3C1.12 Walter C. Mackenzie Centre, 8440-122 ST NW, Edmonton, AB T6G2B7, Canada. bagshaw@ualberta.ca
Telephone: +1-780-4076755 Fax: +1-780-4071228
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Abstract

Fluid therapy is perhaps the most common intervention received by acutely ill hospitalized patients; however, a number of critical questions on the efficacy and safety of the type and dose remain. In this review, recent insights derived from randomized trials in terms of fluid type, dose and toxicity are discussed. We contend that the prescription of fluid therapy is context-specific and that any fluid can be harmful if administered inappropriately. When contrasting "crystalloid *vs* colloid", differences in efficacy are modest but differences in safety are significant. Differences in chloride load and strong ion difference across solutions appear to be clinically important. Phases of fluid therapy in acutely ill patients are recognized, including acute resuscitation, maintaining homeostasis, and recovery phases. Quantitative toxicity (fluid overload) is associated with adverse outcomes and can be mitigated when fluid therapy based on functional hemodynamic parameters that predict volume responsiveness and minimization of non-essential fluid. Qualitative toxicity (fluid type), in particular for iatrogenic acute kidney injury and metabolic acidosis, remain a concern for synthetic colloids and isotonic saline, respectively. Physiologically balanced crystalloids may be the "default" fluid for acutely ill patients and the role for colloids, in particular hydroxyethyl starch, is increasingly unclear. We contend the prescription of fluid therapy is analogous to the prescription of any drug used in critically ill patients.

Key words: Fluid therapy; Resuscitation; Critical illness; Peri-operative; Toxicity; Saline; Crystalloid; Colloid

Core tip: Fluid therapy is exceedingly common in acutely ill patients; however, numerous questions on the efficacy and safety of fluid therapy in terms of the type and dose remain. Fluid therapy prescription is context-specific and any fluid type can be harmful if administered inappropriately. When considering crystalloids versus colloids, differences in efficacy are modest but the risk of kidney toxicity and bleeding complications with hydroxyethyl starch appear more significant. The differences in chloride load across crystalloid solutions appears to have physiologic and clinically important effects, in particular for contributing to hyperchloremic metabolic acidosis, kidney injury and greater utilization of renal replacement therapy associated with 0.9% saline. Fluid therapy should be viewed as analogous to the prescription of any drug in acutely ill patients.

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INTRODUCTION

Intravenous (*iv*) fluid therapy is one of the most common interventions administered to acutely hospitalized patients; however, a number of fundamental questions about its efficacy and safety remain.

The origins of the administration of *iv* fluids for acute resuscitation date back to the cholera epidemic of the early 19th century, when Dr. Thomas A Latta first administered a warmed *iv* solution of "two drachams of muriate, two scruples of carbonate of soda to sixty ounces of water" to combat the profound dehydration in six patients hospitalized at the Leith Infirmary in Scotland[1]. With this non-sterile hypotonic solution, he was able to spare a few moribund patients from refractory hypovolemic shock. Impressive volumes of fluid (over 12 liters in some cases) were required to restore hemodynamics, and as described resulted in "...an immediate return of the pulse, and improvement in the respiration… [and in] the appearance of the patient [were] the immediate effects". Yet, even in 1832, an editorial subsequently published in the *Lancet* commented that "...the mass of the profession is unable to decide; and thus, instead of any uniform mode of treatment, every town and village has its different system or systems..." and that "...a suitable clinical investigation is required to resolve between such conflicting authorities…"[2]. As such, after nearly two centuries of advancements in the modern medicine, this editorial seemed to be remarkably familiar in many respects to our current state of knowledge regarding the optimal prescription of fluid therapy for acutely ill patients.

Fluid used in acute resuscitation should be viewed in the same context as any other drug administered to patients. Their prescription is certainly analogous to how drugs are prescribed (Table 1). This is relevant when considering that the vast majority of hospitalized acutely ill patients, including children, will receive *iv* fluid therapy, usually as some combination of crystalloids, colloids and/or blood products.

However, data have supported the notion that the form of fluid therapy prescribed is largely dependent on where medical care is provided (*i.e.,* country, region, hospital, care unit) and on the specialty of the clinician (*i.e.,* surgical, medical, anesthesia, emergency)[3,4]. There is wide variation in clinical practice with respect to the type and dose of fluid prescribed[3]. This variation in practice has historically been derived from a general lack of clarity in the literature on the principles of optimal fluid prescription (*i.e.,* efficacy and safety)-the idea of prescribing fluid therapy for "the right patient, at the right time, and in the right context". In the last few years, a number of large high-quality randomized trials have reported on the efficacy and safety intravenous fluid therapy for acute resuscitation in the critically ill[4-6]. These data are beginning to provide clarity to long-standing debates regarding fluid type and dose, during and following acute resuscitation and to better inform clinical practice to improve patient outcomes[7]. In this review, we discuss recent relevant evidence related to the type and dose of fluid therapy used in the resuscitation of critically ill patients.

Table 1 Overview of the analogy of prescribing fluid therapy and prescribing a drug

Steps for prescribing a drug	Prescribing an oral hypoglycemic medication	Prescribing fluid therapy
Define the clinical problem	Diabetes mellitus	Hypovolemia or other fluid responsive state
Specify the therapeutic objective	Lower blood glucose	Restore absolute/ relative fluid deficit
Verify the suitability of the drug	Class of oral hypoglycemic agent	Crystalloid, colloid or blood product
Write a prescription to start the drug	Order written by MD, verified and dispensed by pharmacy	Order written by MD, verified by pharmacy, blood bank or RN, administered by RN
Monitor therapeutic response of the drug	Blood glucose or hemoglobin A1C, evidence of adverse effect/ toxicity	Monitor hemodynamic profile and end-organ perfusion, evidence of dose-response toxicity
Write an order to discontinue	Order written by MD, verified by pharmacy	Order written by MD, administered by RN

Adapted from Raghunathan *et al*[58].

DOSE OF FLUID THERAPY

As aforementioned, *iv* fluid therapy is one of the most common and certainly may be one of the most important initial interventions in the resuscitation of acute ill patients. A key concept for dosing fluid therapy in critically ill patients is to actively address ongoing losses coupled with constant reassessment of need for further hemodynamic support. The routine practice of providing "maintenance" or replacement of unmeasured fluid deficits such as "third space losses" for most patients is questionable and often contributes unnecessary fluid accumulation. The optimal target endpoints for fluid therapy during resuscitation remain controversial. Recent data suggest static metrics of resuscitation, such as thresholds in central venous pressure (CVP), as currently recommended by the Surviving Sepsis Campaign[8], may not accurately correlate with restoration of intravascular volume and improvement in tissue oxygen delivery and may be associated with worse outcome[9]. Additional measures such as achieving a normalized central venous oxygen saturation (> 65%-70%) and rapid serum lactate clearance (> 20% in 2 h) in response to fluid resuscitation (± additional hemodynamic support) have been recommended and correlate with improve outcome, both of these endpoints also have important caveats to consider[9,10]. Rather, functional hemodynamic measures such as stroke volume variation, pulse pressure variation[11], bedside ultrasonic interrogation of cardiac output or respiratory variation in inferior vena cava diameter and additional novel dynamic metrics such changes in cardiac output associated with passive leg raising, changes in end-tidal CO_2 and end-expiratory endotracheal tube occlusion can better predict the hemodynamic response to fluid loading[12-15]. These

dynamic measures are superior to blood pressure, CVP, and urine output targets. Importantly, critically ill patients are heterogeneous and may vary considerably with respect to baseline susceptibilities, admission diagnoses and response to fluid loading. When conventional blood pressure or urine output targets are used to guide fluid loading in critically ill patients, often large doses of fluids are administered, and in these circumstances, colloids such as hydroxyethyl starch (HES) are associated with toxicity[7]. The use of fluid boluses in critically ill patients without integrating functional hemodynamic parameters may be associated with cardiovascular decompensation and worse outcome[5]. These observations would strongly support the need for individualized resuscitation goals that integrate functional hemodynamic measures rather than use of generic resuscitation endpoints.

TYPE OF FLUID THERAPY

For a given dose of fluid administered, toxicity may depend on the type and composition of fluid being administered and on patient susceptibilities and physiology. Both patient-specific and context-specific differences should be considered when selecting the type of fluid therapy to be administered.

The debate regarding the relative risks and benefits of colloid and crystalloid solutions has raged on for years. Although various forms of crystalloid solutions have been used in humans since the 1830s, it was approximately 100 years more before the technology to isolate albumin from serum was available. In World War Ⅱ, fractionated bovine albumin was first used on the battlefield as a resuscitation fluid. Synthetic colloids such as HES and gelatins have until recently been considered reasonable alternatives to albumin, due to their theoretical advantages such as mitigating the infectious risks of human blood products, improving blood rheology and microvascular flow, and modulating neutrophil aggregation. The choice of fluid type; however, has largely been a matter of individual clinician preference rather than being specifically directed by high-quality data from clinical trials.

In 1998, the crystalloid/colloid controversy came to a head with the publication of a systematic review that suggested that the use of human albumin was associated with one additional death for every 17 patients treated[16]. Despite this review having methodological misgivings, a political firestorm ensued when the Cochrane Injuries Group urged politicians to "take action" six weeks before the article was published by the *BMJ*. Unfortunately, the lay media reported the findings prior to peer review and publication, resulting in statistically-questionable, poorly-supported inflammatory news headlines such as "300 die as health chiefs dither"[17]. The director of the United Kingdom Cochrane Center went so far as to suggest that he would sue any doctor who gave him an infusion of albumin[15,16].

Due to this ongoing narrative, interest in the patterns of clinical use of crystalloid and colloid solutions for fluid resuscitation in the intensive care unit (ICU) has increased. An international study of 391 ICUs across 25 countries observed that colloid therapy was the primary fluid used in 48% of instances for acute resuscitation, whereas crystalloid and blood products were used in 33% and 28% of instances, respectively[3]. However, the variation in the type of fluid administered was six-fold different between countries. These data suggested that local factors, such as "unit protocols" and commercial marketing played an important role in guiding clinicians' choice of fluid type for resuscitation. These data also recommended better evidence in the form of high-quality randomized trials were needed along with appropriate mechanisms to translate new knowledge from such data into bedside practice.

Several studies have repeated provided a physiological rationale for the preferential use of a colloid (with an emphasis on HES) over crystalloid therapy for resuscitation in septic shock and other in states of acute stress such as peri-operatively. HES solutions have been shown to attenuate the acute inflammatory response[18-21], mitigate endothelial barrier dysfunction and vascular leak[18,22], and preserve intestinal barrier function[17]. Small clinical trials have suggested superiority of HES solutions for resuscitation of the microcirculation in sepsis[22]. Small randomized clinical trials have also shown that early fluid resuscitation with HES solutions results in more rapid hemodynamic stabilization and shock reversal (*i.e.,* greater efficacy) compared with crystalloids, and require significantly less fluid to restore intravascular volume[23,24].

Several more recent randomized trials have specifically evaluated the "colloid/crystalloid" hypothesis for fluid resuscitation in critically ill patients. The SAFE[25] (4% albumin in 0.9% saline *vs* 0.9% saline), CHEST[6] (6% HES in 0.9% saline *vs* 0.9% saline) and 6S[7] (6% HES in Ringer's acetate *vs* Ringer's acetate) trials were specifically designed to evaluate the effectiveness of colloids against corresponding crystalloids. These trials have shown that the efficacy of volume expansion of colloids over crystalloids (*i.e.,* the ability to increase plasma volume) is greater for colloids (ratio 1.2-1.4:1 for crystalloid:colloid about 20%-40% enhanced effect with colloids); however, less than conventional teaching and evidence generated in experimental models[5-7,25]. This may be accounted for by the collapse of the classical "Starling model" based understanding of fluid movement across capillary membranes in critically ill states, where vascular endothelia is disrupted and hydrostatic (*i.e.,* systemic venous hypertension/endothelial injury) and oncotic (*i.e.,* hypoproteinemia) forces are deranged. Moreover, this also highlights that these issues are dynamic during the coarse of critical illness and that variable fluid types are expected to have heterogeneous effects that will depend upon: (1) the relative chloride load (*i.e.,* strong ion difference); (2) the presence of colloid (*i.e.,* HES or albumin); and (3) the underlying/evolving severity in patients pathophysiology.

The ideal electrolyte solution is yet undiscovered; however, for resuscitation may be one that reasonably parallels the plasma (chloride) and has a strong ion difference that is greater than zero (0.9% saline) but less

Table 2 Summary of studies comparing isotonic saline to balanced crystalloid solutions

Study	Design	Population	Solutions	Outcome
McFarlane *et al*[59]	RCT	Elective hepatobiliary/ pancreatic surgery	0.9% saline *vs* PL-148	Iatrogenic metabolic acidosis with 0.9% saline
Wilkes *et al*[47]	RCT	Major abdominal surgery	0.9% saline *vs* Hartmann's (in HES)	Iatrogenic metabolic acidosis with 0.9% saline
O'Malley *et al*[48]	RCT	Kidney transplant recipients	0.9% saline *vs* RL	Iatrogenic metabolic acidosis and hyperkalemia with 0.9% saline
Yunos *et al*[56]	Prospective before-and-after	Critically ill patients	Chloride-rich *vs* chloride-poor fluid strategy	More acidosis with chloride-rich; more alkalosis and reduced cost with chloride-poor
Chowdbury *et al*[26]	RCT (cross-over)	Healthy volunteers	0.9% saline *vs* PL-148 (2 L infusion)	↑ Δ [Cl⁻]; ↑ Strong ion difference; ↓ RBF; ↑ weight gain; ↑ extravascular volume; ↑ time to micturation
Chua *et al*[49]	Retrospective	Critically ill with DKA	0.9% saline *vs* PL-148	More rapid resolution of acidosis with PL-148
Shaw *et al*[55]	Retrospective	Major abdominal surgery	0.9% saline *vs* PL-148	↑ Major infection; ↑ composite of complications; ↑ blood transfusions; and ↑ RRT with 0.9% saline
Yunos *et al*[57]	Prospective before-and-after	Critically ill patients	Chloride-rich *vs* chloride-poor fluid strategy	↑ AKI (KDIGO stage Ⅱ / Ⅲ); ↑ RRT with chloride-rich strategy

Adapted from Raghunathan *et al*[58]. RCT: Randomized clinical trial; 0.9% saline: Normal saline; PL: Plasmalyte; RL: Ringers lactate; RBF: Renal blood flow; DKA: Diabetic ketoacidosis; AKI: Acute kidney injury; HES: Hydroxyethyl starch; RRT: Renal replacement therapy; KDIGO: Kidney disease improving global outcomes; FO: Fluid overload; FB: Fluid balance.

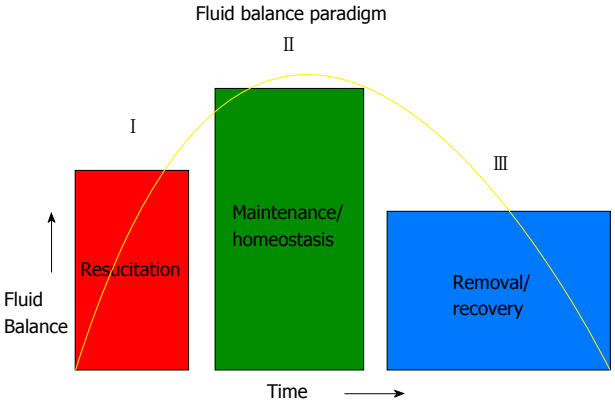

Figure 1 Fluid balance paradigm. The management of fluid therapy in critical illness can be conceptually viewed across three broad phases differentiated according to clinical status of the patient. During the "resuscitation" phase, the goal is restoration of effective intra-vascular volume, organ perfusion and tissue oxygenation. Fluid accumulation and a positive fluid balance may be expected. During the maintenance phase, the goal is maintenance of intravascular volume homeostasis. The broad aim here would be to mitigate excessive fluid accumulation and prevent unnecessary fluid loading. During the recovery phase, passive and/or active fluid removal would correspond to organ recovery.

than plasma during resuscitation[26]. Clinically important outcomes differ when comparing physiologically balanced crystalloids with isotonic saline solution. In the past year, a study at a single ICU[27] and another in patients undergoing major abdominal surgery[28], compared outcomes based on "chloride load". Consistent with earlier preclinical and human studies[25-28], chloride restriction was found to be beneficial (Table 2). However, even large volume resuscitation with balanced crystalloid solutions is capable of inducing mild metabolic acidosis due to hemodilution of weak acids and relative changes in strong ion difference. The challenges with many balanced crystalloid solutions is that they contain small concentrations of calcium and additional electrolytes that theoretically increase the risk for precipitation or clot formation during co-administration with citrated blood products when compared with saline. However, 0.9% saline is non-physiologic and the high (chloride) and a lower strong ion difference compared to plasma (0.9% saline: 0 mmol/L *vs* plasma: 40 mmol/L), directly contributes to iatrogenic hyperchloremic metabolic acidosis. Indeed, the use of balanced crystalloid resuscitation in patients with diabetic ketoacidosis, despite the added (potassium) content [(K^+) 5.0 mmol/L], was associated with more rapid correction of base deficit when compared to 0.9% saline[49]. Recent data have also clearly shown high (chloride) solutions contribute to renal vasoconstriction, decreased glomerular filtration, greater interstitial fluid accumulation[29-34] along with increased risk of acute kidney injury (AKI) and utilization of renal replacement therapy (RRT)[35].

A CONCEPTUAL FRAMEWORK FOR FLUID MANAGEMENT

A novel conceptual framework for fluid management in critical illness introduces the idea of interrelated phases of fluid management differentiated according to the clinical status of the patient with evolving goals for fluid need[33] (Figure 1). The model proposed for the epidemiology of fluid balance in AKI may be extended across the spectrum of critical illness with caveats: (1) In the initial phase of acute resuscitation-the objective is restoration of effective circulating blood volume, organ perfusion and tissue oxygenation. Fluid accumulation and a positive fluid balance may be expected; (2) In the second phase of resuscitation-the goal is maintenance of intravascular volume homeostasis. The objective during this phase is to prevent excessive fluid accumulation and avoid unnecessary fluid loading; and (3) In the final stage, the objective centers around fluid removal and the concept of active "de-resuscitation" corresponding to a state of physiologic stabilization, organ injury recovery and convalescence. During this phase, unnecessary fluid accumulation may contribute to secondary organ injury and adverse events.

Table 3 Studies in critically ill patients describing the association with fluid overload and worse outcome

Study	Design	Population	Exposures	Outcomes
Pediatric Studies				
Goldstein *et al*[33]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↑ mortality
Foland *et al*[60]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↑ organ dysfunction + mortality
Sutherland *et al*[31]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↑ mortality
Arikan *et al*[30]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↓ lung function
Adult Studies				
Payen *et al*[61]	Post-hoc prospective	Adult critically ill septic patients	FB	↑ FB associated with ↑ mortality
Murphy *et al*[62]	Retrospective	Adult critically ill ALI patients	AIFR + CLFM	↑ Survival for ↑ AIFR + ↑ CLFM
Bouchard *et al*[63]	Post-hoc prospective	Adult critically ill AKI patients	% FO > 10%	↑ FB associated with ↑ mortality
Wiedemann *et al*[36]	RCT	Adult critically ill with ALI	Conservative *vs* liberal fluid management strategy	↑ MV-free days; ↑ ICU-free days with conservative strategy
Fulop *et al*[64]	Retrospective	Adult critically ill starting CRRT	VRWG	↑ VRWG associated with ↑ mortality
Boyd *et al*[65]	Post-hoc analysis from VASST	Adult critically ill septic patients	Quartiles of FB + CVP at 12 h and 4 d	↑ FB at 12 h and 4 d associated with ↑ mortality; CVP < 8 at 12 h ↓ mortality
Grams *et al*[66]	Post-hoc FACCT	Adult critically ill with ALI + AKI	FB + diuretics	↑ FB associated with ↑ mortality
Heung *et al*[67]	Retrospective	Adult critically ill starting CRRT	% FO	↑ % FO associated with ↓ kidney recovery
Bellomo *et al*[68]	Post-hoc RENAL	Adult critically ill with AKI	FB	↑ FB associated with ↑ mortality

Adapted from Raghunathan *et al*[58]. ALI: Acute lung injury; AIFR: Adequate initial fluid resuscitation; CLFM: Conservative late fluid management; VRWG: Volume-related weight gain; AKI: Acute kidney injury; CVP: Central venous pressure; ICU: Intensive care unit; RCT: Randomized clinical trial.

Numerous studies in peri-operative and critical care settings support this concept of "ebb and flow" in fluid loading, fluid accumulation and removal. Indeed, these phases of resuscitation likely exist on a continuum and the observed variability in fluid balance is understood to be a dynamic process, does not necessarily follow a fixed temporal pattern or time scale and is likely highly individualized. For example, in septic patients with acute lung injury, the balance between early goal-directed therapy aimed at adequate initial fluid resuscitation coupled with downstream diuretic use and "de-resuscitation" (*i.e.,* conservative late fluid management) can improve outcomes[37,38]. Similarly in pediatric septic shock, outcome improved with early appropriate fluid therapy[39]. Such phasic need for fluid and then need for active fluid removal has also been demonstrated in peri-operative settings[40]. Inappropriate fluid therapy, regardless of fluid type, may disrupt compensatory mechanisms and worsen outcome[5].

QUANTITATIVE TOXICITY

Fluid therapy is a critical aspect of initial acute resuscitation in critically ill patients. Following the acute resuscitative phase (*i.e.,* achievement of immediate resuscitation goals and after hemodynamic stabilization), excessive fluid accumulation has been associated with worse clinical outcome, across a range in clinical settings, particularly in AKI[37] (Table 3). In patients with sepsis-associated AKI, continued fluid loading in the setting of apparent optimal systemic hemodynamics was shown not to improve kidney function, but worsen lung function and oxygenation[30]. Similar observational data in critically ill adults with sepsis-associated AKI has found fluid accumulation to be a predictor of 60-d mortality (HR = 1.21/L per 24 h, 95%CI: 1.13-1.28, $P < 0.001$)[37]. Additionally, although the FACCT trial did not demonstrate a mortality difference between a liberal and a more conservative fluid management strategy in the setting of acute lung injury, the conservative strategy was associated with improved lung function, reduced length of stay in ICU and a trend for lower utilization of RRT[36]. Increasing severity of fluid accumulation among both pediatric and adult patients with AKI at the time of initiation of RRT has been associated with higher mortality and reduced likelihood of recovery of kidney function[42-45]. For each 1% increase in percentage fluid overload (% FO, as calculated below) at RRT initiation, risk of death increased by 3%[31]. % FO = [(total fluid in-total fluid out)/admission body weight × 100].

Failure to appreciate these phases of fluid management following resuscitation may underscore the observed phenomenon of "fluid creep", first identified in the burn literature in response to the overwhelming enthusiasm for aggressive and sustained fluid resuscitation[29,32]. These observations highlight the importance of monitoring fluid balance in critical illness, in particular after the initial phase of resuscitation, where obligatory fluid intake (*i.e.,* medications, nutrition, blood products) may greatly exceed output (*i.e.,* relative oliguria), leading to rapid fluid accumulation[34]. In these circumstances, there should be effort to minimize or avoid all non-essential fluid administration. However, data on fluid accumulation in critically ill patients is almost entirely post-hoc, associative and not causal. Very few prospective interventional studies, with the exception of the FACCT trial and selected studies of conservative peri-operative fluid regimens have informed on the optimal fluid management strategies for critically ill patients and evaluated their association with organ function, adverse events, and survival[35,36]. This represents an important knowledge gap in our understanding of how to optimally manage-

Table 4 Summary of randomized trials of hydroxyethyl starch resuscitation in severe sepsis/septic shock and kidney outcomes

Ref.	RCT type	*n* (HES/CON)	Population (*n*)	HES fluid	Control fluid	Kidney parameters	RRT (OR; 95%CI)
Schortgen *et al*[50]	Multi-centre	129 (65/64)	Severe sepsis/ septic shock	6% (200/0.62)	3% gelatin	↑ AKI ↑ oliguria, ↑ peak SCr	1.20 (0.5-2.9)
Molnár *et al*[69]	Single centre	30 (15/15)	Septic shock	6% (200/0.60)	3% gelatin	NR	NR
McIntyre *et al*[70]	Multi-centre	40 (21/19)	Septic shock	6% (200/0.50)	0.9% NS	No difference	3.00 (0.3-31.6)
Brunkhorst *et al*[42]	Multi-centre	537 (262/275)	Severe sepsis/ septic shock	10% (200/0.5)	RL	↑ AKI	1.95 (1.3-2.9)
Guidet *et al*[23]	Multi-centre	196 (100/96)	Severe sepsis/ septic shock	6% (130/0.4)	0.9% NS	No difference	NR
Perner *et al*[6]	Multi-centre	798 (398/400)	Severe sepsis/ septic shock	6% (130/0.42)	Ringer's acetate	↑ AKI	1.35 (1.01-1.8)
Myburgh *et al*[5]	Multi-centre	7000 (3315/3336)	Sepsis (27.4%) (1921/7000)	6% (130/0.4)	0.9% NS	↑ RRT	1.21 (1.00-1.45)

RCT: Randomized clinical trial; HES: Hydroxyethyl starch; CON: Control; NS: Normal saline; RL: Ringer's lactate; AKI: Acute kidney injury; RRT: Renal replacement therapy; NR: Not report.

ment fluid beyond the initial resuscitation for acutely ill patients.

QUALITATIVE TOXICITY

Colloid solutions

The saline *vs* albumin fluid evaluation (SAFE) trial, in which nearly 7000 critically ill patients were randomized to either 4% human albumin or saline for resuscitation was the first large scale high-quality trial to show no overall difference in mortality, ICU length of stay, need for mechanical ventilation or RRT, or hospital length of stay. However, subgroup analyses founds trends for higher mortality in trauma patients, predominantly with head injury (OR = 1.36, $P = 0.06$) and lower mortality in sepsis (OR = 0.87, $P = 0.09$)[37]. Subsequently, a post-hoc longer-term follow-up study of patients enrolled in the SAFE trial who had suffered traumatic brain injury was performed, confirming the initial trends to suggest a higher mortality in head-injured patients receiving albumin (OR = 1.88, $P < 0.001$)[38].

While HES solutions, including newer starches, appear equally or more efficacious (*vs* older starches or crystalloids in certain situations) for restoration of intravascular volume in acute resuscitation, data continues to accumulate to suggest harm in critical illness (Table 4). Small clinical trials have suggested HES solutions are also superior for resuscitation of the microcirculation in sepsis and contribute to more rapid hemodynamic stabilization and shock reversal, and require significantly less fluid to restore intravascular volume. There has been suggestion of an improved safety profile for HES solutions with a lower molecular weight and lower degree of molar substitution, in terms of bleeding complications and AKI; however, these findings have been inconsistent. Prior to VISEP, 6S and CHEST, the literature had largely been dominated by small lower quality randomized trials that precluded a clear appraisal of potential survival benefit and the risk of toxicity[39,40]. In addition, wide scale retractions have followed reporting of fraud in research evaluating the safety of HES[41,46]. Accrued data from large randomized trials have now raised serious concerns about potential for dose-associated kidney toxic effects of HES[5,6,42,43]. Experimental data have shown even newer generation HES solutions can still accumulate in tissues within hours of administration, including in the liver, kidney, lung, spleen and lymph nodes[69]. In the VISEP trial, pentastarch (10% HES 200/0.5) was compared to Ringer's lactate for fluid resuscitation in ICU[42]. The trial was stopped early due to the increased incidence of AKI (34.9% *vs* 22.8%, $P = 0.001$) and a trend towards increased mortality (41% *vs* 33.8%, $P = 0.09$). These results were corroborated in the CHEST and 6S trials[5,6]. The CHEST trial evaluated the use of Voluven® (6% HES 130/0.4 in 0.9% saline) compared to 0.9% saline for acute resuscitation in ICU[5]. While there was no difference in mortality, there was an increase in the utilization of RRT (7.0% *vs* 5.8%, $P = 0.04$) in those receiving HES. In the 6S trial, Tetraspan® (6% HES 130/0.42 in Ringer's acetate) was compared to Ringer's lactate for acute resuscitation in severe sepsis[7]. Both the incidence of AKI (22% *vs* 16%, $P = 0.04$), and mortality (51% *vs* 43% at 90 d, $P = 0.03$) were significantly higher with HES. These data imply an increased risk for harm associated with HES solutions and have lead the European Society of Intensive Care Medicine to recommend against the use of HES in patients with severe sepsis or those at risk for AKI and has further suggested a moratorium on the use of HES except in the context of a clinical trial[49]. In addition, the United States Food and Drug Administration has recently issued black Boxed warning against their use in critically ill patients due to the increased risk of AKI and death[44]. However, there remains continued controversy on whether the use of HES in recent randomized trials was appropriate, such as only being used early and in limited volumes for the acute resuscitation of critically ill hypovolemic patients[45].

All HES solutions are carried in crystalloid. In the 6S trial, both arms received balanced crystalloid solution (*i.e.,* Ringer's acetate); whereas in the CHEST trial, both groups received 0.9% saline. It is biologically plausible there may be considerable interaction between the ad-

verse effects of HES and the chloride-rich 0.9% saline. When considering high chloride load is associated with adverse effects and worse outcome, it is therefore plausible that the harm associated with HES is exaggerated when used with 0.9% saline compared with a balanced crystalloid carrier.

In the 6S trial[6], patients were less likely to achieve shock reversal (*i.e.,* failure to clear lactate); whereas, in the CHEST trial[5], shock was reversed (*i.e.*, lactate cleared) with less total fluid administered in the HES group. These data imply that while HES may be more efficacious for shock resolution when compared to crystalloid; if there is delayed or failure to reverse shock, there may be greater toxicity and harm associated with HES; and this hazard may not be immediately apparent (*i.e.,* risk of harm is delayed several days to weeks).

The use of hyperoncotic colloid solutions for acute resuscitation remains controversial. In a large multi-centre European study of 822 critically ill adults with shock receiving fluid resuscitation, use of hypertonic natural and synthetic colloids was associated with a several fold increased risk for AKI and death[50]. A recent systematic review found divergent findings for use of hyperoncotic colloids for resuscitation and subsequent risk of AKI[51]. In this meta-analysis of 7 trials including 1220 patients, hyperoncotic albumin was associated with reduced risk (OR = 0.24, $P < 0.001$); whereas hyperoncotic HES solutions were associated with increased risk for AKI (OR = 1.92; 95%CI: 1.31-2.81, $P < 0.001$). These data seem to further infer the kidney toxicity may be a class effect associated with HES solutions.

Crystalloid solutions

The *iv* solution used in 1832 by Dr Thomas Latta for the treatment of cholera would today be considered a balanced salt solution: 134 mmol/L Na^+, 118 mmol/L Cl^-, 16 mmol/L HCO_3^-[52]. Surprisingly, it was not until 1888 that a reference to *normal* or *physiologic saline* is found in the medical literature, and not until 1896 that 0.9% saline is described[53,54]. Despite the fact that 0.9% sodium chloride is not isotonic to serum, it is believed that *in vitro* experiments comparing the freezing points of various solutions to serum led to the belief that this solution was "physiologic". Perhaps it was for simplicities' sake that solutions containing mixtures of anions were avoided in favor of the addition of table salt to water.

However, data are accumulating to suggest chloride-rich solutions are problematic. As aforementioned, the high (chloride) and a lower strong ion difference compared to plasma (0.9% saline: 0 mmol/L *vs* plasma: 40 mmol/L), directly contribute to iatrogenic hyperchloremic metabolic acidosis, which may mask, simulate and/or precipitate adverse effects[55,56]. In a randomized crossover trial of healthy volunteers, renal blood flow and renal cortical perfusion decreased significantly following the bolus administration of 2 L of 0.9% saline compared to plasma-lyte 148[30]. The use of chloride-rich solutions in critically ill patients is not only associated with increased costs and laboratory utilization[57], but also increased incidence of AKI and RRT utilization[27].

These observations are supported from a recent interrogation of the Premier perspective comparative database of patients undergoing elective or emergent open general surgical operations evaluating the rate of adverse events associated with receiving either balanced or isotonic saline solutions on the day of surgery[28]. In this study, patients who received exclusively a calcium-free balanced salt solution (plasma-Lyte A or plasma-Lyte 148) were matched on a 3:1 basis with those receiving exclusively 0.9% saline. Although there were no statistically significant differences between the two groups at baseline, the differences in outcome were dramatic: significantly fewer postoperative infections ($P = 0.006$), less dialysis ($P < 0.001$), fewer blood transfusions ($P < 0.001$), fewer electrolyte disturbances ($P = 0.046$), fewer acidosis investigations ($P < 0.001$) and interventions ($P = 0.02$) were all associated with the use of balanced salt solutions compared with 0.9% saline. While these data are not a randomized comparison of balanced *vs* 0.9% saline solutions, randomized trials are ongoing.

CONCLUSION

Despite its ubiquitous use in critical care, further carefully performed, transparent research on fluid resuscitation in critical illness is desperately needed. Context appears to be crucial when prescribing fluid and any fluid can be harmful if dosed incorrectly. Differences in immediate efficacy between crystalloid and colloid solutions are modest at best, but the differences in longer-term safety appear more significant. Qualitative toxicity for colloids (even with newer lower molecular weight, less substituted HES solutions) and isotonic saline remain a concern. The observed differences in chloride load and strong ion difference in the various crystalloid solutions appear to be clinically important. We contend that physiologically balanced crystalloids may be the best "default" fluid for acutely ill patients, and that the role of colloids is unclear. Optimal dosing of any resuscitation fluid mandates an understanding the dynamic nature of fluid resuscitation, and future investigations will hopefully allow for the development of better tools to guide therapy.

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META-ANALYSIS

Ulinastatin for acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis

Yu-Xin Leng, Shu-Guang Yang, Ya-Han Song, Xi Zhu, Gai-Qi Yao

Yu-Xin Leng, Shu-Guang Yang, Xi Zhu, Gai-Qi Yao, Department of Intensive Care Unit, Peking University Third Hospital, Beijing 100191, China
Ya-Han Song, Library of Peking University Third Hospital, Beijing 100191, China
Author contributions: Leng YX and Yang SG contributed to literature search and study selection; Leng YX and Song YH contributed to data extraction, analysis and interpretation; Yao GQ, Zhu X and Yao GQ contributed to study conception and design; Leng YX drafted the article; Yao GQ revised the article critically for important intellectual content.
Correspondence to: Gai-Qi Yao, MD, PhD, Associate Professor, Department of Intensive Care Unit, Peking University Third Hospital, A 49 North Garden Rd., Haidian District, Beijing 100191, China. yaogaiqi@yeah.net
Telephone: +86-10-82267280 Fax: +86-10-82267281
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Abstract

AIM: To investigate the efficacy and safety of ulinastatin for patients with acute lung injury (ALI) and those with acute respiratory distress syndrome (ARDS).

METHODS: A systematic review of randomized controlled trials (RCTs) of ulinastatin for ALI/ARDS was conducted. Oxygenation index, mortality rate [intensive care unit (ICU) mortality rate, 28-d mortality rate] and length of ICU stay were compared between ulinastatin group and conventional therapy group. Meta-analysis was performed by using Rev Man 5.1.

RESULTS: Twenty-nine RCTs with 1726 participants were totally included, the basic conditions of which were similar. No studies discussed adverse effect. Oxygenation index was reported in twenty-six studies (1552 patients). Ulinastatin had a significant effect in improving oxygenation [standard mean difference (SMD) = 1.85, 95%CI: 1.42-2.29, $P < 0.00001$, $I^2 = 92\%$]. ICU mortality and 28-d mortality were respectively reported in eighteen studies (987 patients) and three studies (196 patients). We found that ulinastatin significantly decreased the ICU mortality [$I^2 = 0\%$, RR = 0.48, 95%CI: 0.38-0.59, number needed to treat (NNT) = 5.06, $P < 0.00001$], while the 28-d mortality was not significantly affected ($I^2 = 0\%$, RR = 0.78, 95%CI: 0.51-1.19, NNT = 12.66, $P = 0.24$). The length of ICU stay (six studies, 364 patients) in the ulinastatin group was significantly lower than that in the control group (SMD = -0.97, 95%CI: -1.20--0.75, $P < 0.00001$, $I^2 = 86\%$).

CONCLUSION: Ulinastatin seems to be effective for ALI and ARDS though most trials included were of poor quality and no information on safety was provided.

Key words: Ulinastatin; Acute lung injury; Acute respiratory distress syndrome; Mortality; Oxygenation index

Core tip: Currently, many studies highlight the advantages of ulinastatin in lung protection, which is likely because acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) share a common pathogenesis with sepsis. We tried to provide more specific evidence on this practice by performing a meta-analysis. In our study (29 clinical trials included), we found that though all the studies were of low quality, ulinastatin might improve oxygenation and mortality and be truly effective in patients with ALI/ARDS.

Leng YX, Yang SG, Song YH, Zhu X, Yao GQ. Ulinastatin for acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis. *World J Crit Care Med* 2014; 3(1): 34-41 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i1/34.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i1.34

INTRODUCTION

Ulinastatin, also known as human urinary trypsin inhibitor, can be found in urine, plasma and all organs[1]. It is a glycoprotein marketed as an experimental medication for acute pancreatitis and septic shock in Asia for its involvement in suppressing the systemic inflammation and proteolytic process[2-5]. Currently, many animal studies and clinical trials highlight its advantages in lung protection[6-38], which is likely because acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) share a common pathogenesis with sepsis, which is systemic inflammatory response syndrome. However, it remains uncertain whether ulinastatin can be recommended as a standard medication for ALI and ARDS. Without the support of large-scale, high-quality trials, it is difficult to draw a definite conclusion. Therefore, we perform a systematic review to evaluate the efficacy and safety of ulinastatin for ALI and ARDS to provide more specific evidence.

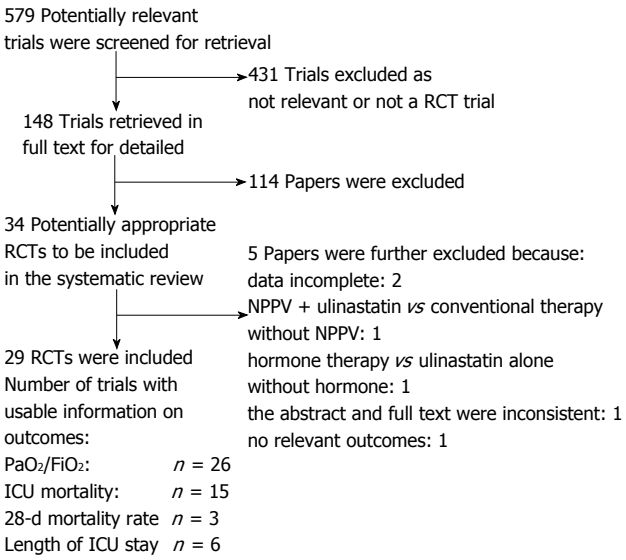


Figure 1 Flow chart of reviewed articles. RCT: Randomized controlled trial; NPPV: Noninvasive positive-pressure ventilation; ICU: Intensive care unit.

MATERIALS AND METHODS

Search strategy

We searched the published randomized controlled trials (RCTs) (from 1st January 2006 to 20th August 2012) from eight databases including Pubmed, Medline (Ovid SP), The Cochrane Library, Wanfang Database, China Biology Medicine Database, Chinese Periodical Database, China Knowledge Resource Integrated Database and Chinese Clinical Trial Registry with the following search terms: "Ulinastatin" or "Protease-Inhibitors" or "Glycoprotein" and "Acute Respiratory Distress Syndrome" or "ARDS" or "Acute Lung Injury" or "ALI". There were no language restrictions on inclusive studies. All potentially relevant papers based on titles and abstracts were retrieved for full text screening. We also collected relevant articles by checking the references of the retrieved papers.

Study selection

Both the study selection (Leng YX, Song YF) and data extraction processes (Leng YX, Yang SG) were performed by two authors independently. Disagreements were resolved by group discussion. Figure 1 showed the flow chart of study selection process.

We included the RCT studies comparing ulinastatin plus routine treatment (treatment group) versus routine treatment alone or placebo plus routine treatment (control group) for ALI and ARDS. ALI and ARDS were diagnosed as: acute onset; pulmonary artery wedge pressure $\leqslant$ 18 mmHg or absence of clinical evidence of left atrial hypertension; bilateral infiltrates on chest radiography; ALI is present if PaO_2/FiO_2 ratio is $\leqslant$ 300; ARDS is present if PaO_2/FiO_2 ratio $\leqslant$ 200. Any dose and duration of ulinastatin were permitted. The outcomes included intensive care unit (ICU) mortality rate or PaO_2/FiO_2 ratio.

Data extraction and quality assessment

The following parameters were extracted from each inclusive study: (1) first author and year of the publication; (2) patients' characteristics and study design; and (3) clinical outcomes (ICU mortality, 28-d mortality, PaO_2/FiO_2 ratio, length of ICU stay and adverse effect). The quality of all selected articles was evaluated according to the Jadad scale[39], which bases on the random assignment, double blinding, and flow of patients. The range of score is 0 (bad) to 5 (good).

Statistical analysis

Meta-analysis was conducted using RevMan 5.1 software. For dichotomous variables (ICU mortality, 28-d mortality) we estimated the pooled risk ratios (RRs) and 95%CI. For continuous variables (PaO_2/FiO_2 ratio and length of ICU stay), we calculated the estimation of standard mean difference (SMD). Heterogeneity was explored by the I^2 test. If $I^2 < 50\%$, the fixed-effect model (Mantel-Haenszel) was employed, otherwise the random-effect model (DerSimonian and Laird) was used. The significance of pooled RR was determined by Z test. $P < 0.05$ was considered statistically significant. Funnel plots were used to detect the potential publication bias if more than ten studies were included. The sensitivity analysis was conducted by taking each single study away from the total and re-analyzing the remainder.

RESULTS

Study characteristics

After full text screening, 34 potentially relevant studies were identified. Among these studies, five were excluded because there were incomplete data (1 study), other interventions besides ulinastatin were included (2 studies), the abstract and full text were inconsistent (1 study), and no relative outcomes were reported (1 study) (Figure 1). Finally, 29 studies involving 1726 participants were included[10-38], the basic conditions of which were similar. The conventional therapy included mechanical ventila-

Table 1 Quality and characteristics of all included studies

Ref.	Yr	Jadad score	Design	Sample size	Gender (male/female)	Age (yr, mean or range)	Dosage	Frequency	Duration (d)	Outcomes
Chen *et al*[10]	2006	1	NRCT	70	40/30	36.6	200000	*bid*	2-7	Oxygenation index
Gu *et al*[11]	2011	1	NRCT	120	65/55	56.2	100000	*tid*	5	Oxygenation index
Hu *et al*[12]	2009	1	NRCT	54	39/15	41.2	300000	*tid*	7	Oxygenation index Length of ICU stay 28-d mortality rate
Huang *et al*[13]	2010	1	NRCT	80	41/39	49	100000	*tid*	5	Oxygenation index Length of ICU stay ICU Mortality rate
Jiang *et al*[14]	2006	1	NRCT	57	32/25	58.1	200000	*qd*	7-10	Oxygenation index ICU Mortality rate
Liang *et al*[15]	2011	1	NRCT	62	36/26	38.8	200000	*bid*	7	Oxygenation index Length of ICU stay
Liang *et al*[16]	2008	1	NRCT	76	42/34	57	200000	*bid*	6	Oxygenation index ICU Mortality rate
Lu *et al*[17]	2008	1	NRCT	60	42/18	39.7	50000	*qd*	3	Oxygenation index
Ou *et al*[18]	2008	1	NRCT	36	24/12	63.7	200000-300000	*bid*	5-7	Oxygenation index ICU Mortality rate Incidence of MODS
Pi *et al*[19]	2009	1	NRCT	40	25/15	37	200000-	*bid*	5-7	Incidence of MODS ICU Mortality rate
Qian *et al*[20]	2009	1	NRCT	48	35/13	48	200000	*qid*	6	Oxygenation index ICU Mortality rate Length of ICU stay
Qin[21]	2007	1	NRCT	60	40/20	35	300000	*bid*	3	Oxygenation index
Shang *et al*[22]	2008	2	RCT	60	48/12	14-72	200000	*tid*	7	Oxygenation index ICU Mortality rate
Shi *et al*[23]	2011	1	NRCT	50	34/16	59.4	300000	*bid*	7-10	Oxygenation index ICU Mortality rate
Wang *et al*[24]	2011	1	NRCT	52	32/20	55.4	200000	*tid*	10	ICU Mortality rate
Wang *et al*[25]	2011	1	NRCT	60	44/16	18-60	200000	*bid*	5	Oxygenation index
Xiang *et al*[26]	2011	1	NRCT	72	46/26	46.8	200000	*tid*	7	Oxygenation index
Xiong[27]	2008	1	NRCT	50	28/22	35	300000	*bid*	7	Oxygenation index
Yang *et al*[28]	2011	1	NRCT	40	NA	NA	200000	*tid*	10	Oxygenation index
Yang *et al*[29]	2006	2	NRCT	80	58/22	14-72	300000	*bid*	7	Oxygenation index ICU Mortality rate
Zhang *et al*[30]	2009	1	NRCT	34	22/12	9-61	200000	*tid*	10	Oxygenation index ICU Mortality rate
Zhang *et al*[31]	2011	1	NRCT	82	43/39	18-65	200000	*bid*	7	Oxygenation index 28-d mortality rate
Zhang[32]	2010	2	RCT	60	45/15	43.3	300000	*bid*	7	Oxygenation index
Zhang *et al*[33]	2010	1	RCT	60	30/30	55.7	500000	*bid*	7	Oxygenation index Length of ICU stay 28-d mortality rate
Zhang *et al*[34]	2009	1	NRCT	61	54/7	61.9	200000	*bid*	7	Oxygenation index
Zhao *et al*[35]	2012	2	RCT	56	37/19	46.2	200000	*bid*	4	Oxygenation index
Zhao *et al*[36]	2007	1	NRCT	37	29/8	42.6	100000	*bid*	5	Oxygenation index ICU Mortality rate
Zheng *et al*[37]	2011	1	NRCT	60	42/18	40.2	50000	*qd*	3	Oxygenation index ICU mortality rate
Zhou *et al*[38]	2011	1	NRCT	40	NA	40.2	600000	*qid*	5	Length of ICU stay Oxygenation index ICU Mortality rate

NA: Not available; NRCT: Non-randomized controlled trial; RCT: Randomized controlled trial; ICU: Intensive care unit.

tion, low dose hormone, nutritional support, treatment of primary diseases, *etc*. Of the included studies, no one discussed the adverse effect of ulinastatin. Oxygenation index was reported in 26 studies (1552 patients). Eighteen studies (987 patients) and three studies (196 patients) analyzed the ICU mortality and 28-d mortality, respectively. The length of ICU stay was reported in six studies (364 patients). Although all the trials announced the randomization, only four studies mentioned the allocation concealment without detailed description of mechanisms. Table 1 displays the quality and characteristics of these studies.

Oxygenation index

The basal oxygenation indexes in all studies were similar. After treatment with standard strategy or ulinastatin, the patients' oxygenation indexes were improved in all studies. The effect of ulinastatin was more significant (Figure

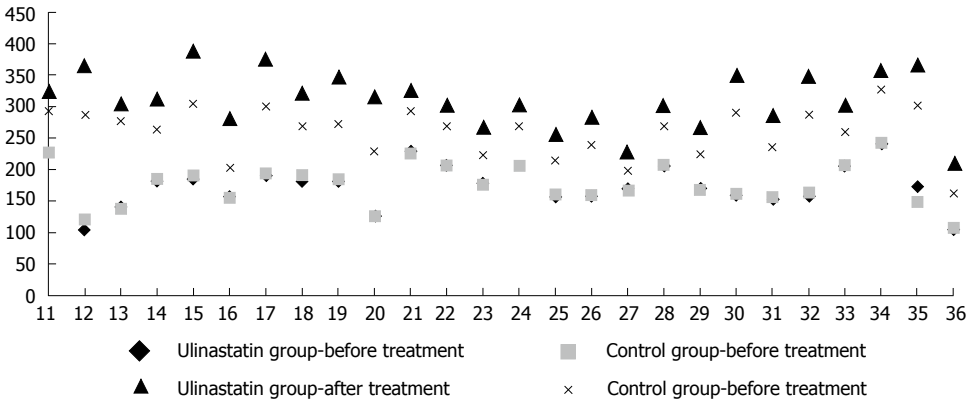


Figure 2 Oxygenation indexes of different groups before and after treatment. The horizontal axis, number of references.

2), which was confirmed by the meta-analysis (SMD = 1.85, 95%CI: 1.42-2.29, $P < 0.00001$, $I^2 = 92\%$, Figure 3A).

Mortality rate

Most studies (15/18) reported that the ICU mortality rate was not significantly different between ulinastatin treatment and conventional treatment. The 95%CI crossed 1.00. Nevertheless, the result of meta-analysis indicated that ulinastatin actually reduced the patients' ICU mortality rate, and the pooled RR was 0.48 (95%CI: 0.38-0.59, $I^2 = 0\%$, Figure 3B). The number needed to treat (NNT) was 5.06. However, the 28-d mortality was not significantly different between the two groups (RR = 0.78, 95%CI: 0.51-1.19, $I^2 = 0\%$, Figure 4A), and the NNT was 12.66.

Length of ICU stay

Five of the six studies reporting the length of ICU stay suggested that compared with conventional therapy, ulinastatin significantly decreased the length of ICU stay, which was confirmed by the result of meta-analysis (SMD = -0.97, 95%CI: -1.20--0.75, $P < 0.00001$, $I^2 = 86\%$, Figure 4B).

Publication bias and sensitivity analysis

Funnel plots of ICU mortality and oxygenation index are shown in Figure 5, which indicated that the publication bias did exist. The language bias may be the main bias because all the inclusive studies were written in Chinese. The sensitivity analysis showed that exclusion of any single study from the meta-analysis did not alter the overall conclusion. Though I^2 of the oxygenation index and ICU stay were larger than 50%, we considered that those heterogeneities were probably related to great difference among studies.

DISCUSSION

ARDS is a common severe lung complication with direct and indirect causes in ICU. In the past 20 years, the mortality rate decreased from 40%-70% to 30%-40%. This survival improvement is considered to be partly related with the better understanding and treatment of sepsis[40]. Since ulinastatin is marketed as an experimental medication for septic shock, the probable efficacy of ulinastatin for ALI and ARDS gains more and more attention.

It is reported that ulinastatin inhibits pathogenic changes in animal models of ALI/ARDS induced by many factors (including scald, seawater, LPS, phosgene)[6-9]. Immunoregulation and the mitigation of excessive inflammatory reaction might be involved. Downregulation of the human major histocompatibility complex class I chain-related antigen A (MICA), mitigation of lipid peroxidation and apoptosis may play important roles. Upregulation of MICA in scald induced lung injury can be ameliorated by ulinastatin[6]. Moreover, ulinastatin treatment can reduce the level of cytokines like serum E, P-selectin and VCAM-1, which are considered to be critical in the development of inflammatory responses[41]. Nevertheless, the effect of ulinastatin on pulmonary injury and the molecular mechanism(s) by which ulinastatin exerts its organ-protective activity remain obscurely studied. In addition, clinical trials also recommended application of ulinastatin for ALI/ARDS though no high quality evidence was reported. Only one meta-analysis on ulinastatin for ALI/ARDS was reported till now[42], in which only Chinese databases were detected. Accordingly, we yet have no enough evidence to support the recommendation of ulinastatin for ALI/ARDS. We performed this meta-analysis to evaluate the existing clinical trials objectively and to provide more specific evidence for ulinastatin selection for ALI/ARDS.

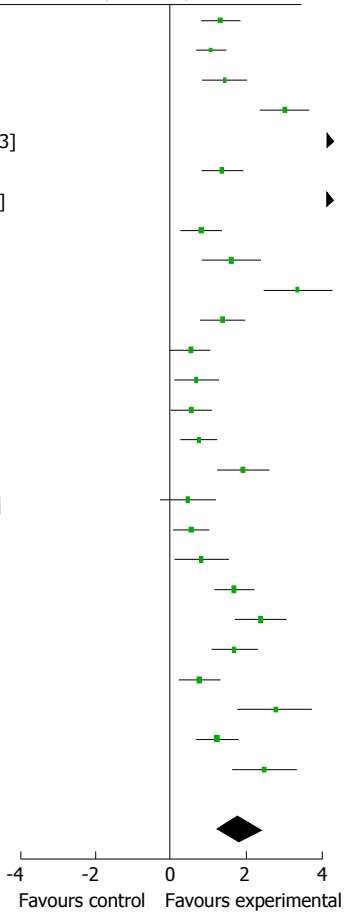
Our results seem to be inspiring. Compared with routine treatment alone, ulinastatin plus routine treatment significantly improved the oxygenation index (SMD = 1.85, 95%CI: 1.42-2.29, $P < 0.00001$) and reduced the ICU mortality rate (RR = 0.48, 95%CI: 0.38-0.59, NNT = 5.06, $P < 0.00001$) and the length of ICU stay (SMD = -0.97, 95%CI: -1.20--0.75, $P < 0.00001$). Nevertheless, the validity of this meta-analysis to some extent is limited. No studies reported the adverse effect. Most of the clinical trials were of poor quality without description of randomization and allocation mechanisms. Meanwhile, the language bias is introduced in this review, because all the included trials were published in Chinese. Then, how should we interpret these clinical trials and the systematic review based on these trials? Should the clinical

A

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. mean difference IV, Random, 95%CI
Chen HD 2006	326	25	35	294	23	35	4.1%	1.32 [0.80, 1.84]
Gu ZY 2011	364.42	56.21	60	286.56	86.54	60	4.2%	1.06 [0.68, 1.44]
Hu MH 2009	305.67	18.31	29	276.93	21.23	25	4.0%	1.44 [0.83, 2.04]
Huang YP 2010	309	16	40	263	14	40	4.0%	3.03 [2.38, 3.68]
Jiang XQ 2006	389.59	5.77	29	305.28	4.95	28	1.4%	15.45 [12.46, 18.43]
Liang DS 2011	282.08	53.43	31	203.34	60.83	31	4.1%	1.36 [0.80, 1.91]
Liang QX 2008	378	6.92	39	300	7.82	37	2.5%	10.47 [8.71, 12.24]
Lu WH 2011	322.63	56.71	30	267.82	75.66	30	4.1%	0.81 [0.28, 1.34]
Ou SQ 2008	347.75	48.56	18	272.62	42.77	18	3.8%	1.61 [0.84, 2.37]
Qian HB 2009	311.9	18.4	24	228.3	29.2	24	3.7%	3.37 [2.47, 4.27]
Qin XW 2007	327.03	24.98	30	293.28	22.95	30	4.1%	1.39 [0.82, 1.96]
Shang GJ 2008	303.25	57.64	30	269	68.92	30	4.1%	0.53 [0.02, 1.05]
Shi QJ 2011	265.78	65.95	25	223.58	57.26	25	4.1%	0.67 [0.10, 1.24]
Wang KM 2011	303.85	57.6	30	268.98	68.82	30	4.1%	0.54 [0.03, 1.06]
Xiang JF 2011	256	58	36	214	51	36	4.1%	0.76 [0.28, 1.24]
Xiong SS 2008	286.15	21.23	25	238.96	26.78	25	3.9%	1.92 [1.24, 2.60]
Yang JB 2011	228.55	67.56	15	198.23	56.78	15	3.9%	0.47 [-0.25, 1.20]
Yang K 2006	303.3	57.6	40	269	68.9	40	4.2%	0.53 [0.09, 0.98]
Zhang BM 2009	266.5	45.7	17	224.4	55.3	17	3.9%	0.81 [0.11, 1.51]
Zhang CQ 2010	352.1	38.8	42	291.2	31.6	40	4.1%	1.70 [1.19, 2.21]
Zhang RW 2010	288.1	19.1	30	236.1	23.4	30	4.0%	2.40 [1.73, 3.08]
Zhang YL 2009	350.2	40.1	31	287.4	32.2	30	4.0%	1.70 [1.11, 2.29]
Zhao HQ 2012	304.27	53.54	28	259.09	61.72	28	4.1%	0.77 [0.23, 1.32]
Zhao RG 2007	356.45	10.92	18	327.08	9.57	16	3.6%	2.78 [1.81, 3.76]
Zheng JM 2011	362.42	40.57	30	302.25	55.37	30	4.1%	1.22 [0.67, 1.78]
Zhou MH 2011	206.78	17.68	20	161.06	18.2	20	3.7%	2.50 [1.65, 3.34]
Total (95%CI)			782			770	100.0%	1.85 [1.42, 2.29]

Heterogeneity: Tau^2 = 1.13; χ^2 = 325.20, df = 25 (P = 0.00001); I^2 = 92%

Test for overall effect: Z = 8.36 (P = 0.00001)



B

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95%CI
Hu MH 2009	5	29	6	25	3.5%	0.72 [0.25, 2.07]
Huang YP 2010	10	40	20	40	10.7%	0.50 [0.27, 0.93]
Jiang XQ 2006	7	29	20	28	10.9%	0.34 [0.17, 0.67]
Liang DS 2011	2	31	7	31	3.8%	0.29 [0.06, 1.27]
Liang QX 2008	10	39	22	37	12.1%	0.43 [0.24, 0.78]
Ou SQ 2008	3	18	9	18	4.8%	0.33 [0.11, 1.03]
Pi Y 2010	3	20	9	20	4.8%	0.33 [0.11, 1.05]
Qian HB 2009	6	24	8	24	4.3%	0.75 [0.31, 1.83]
Shang GJ 2008	4	30	11	30	5.9%	0.36 [0.13, 1.01]
Shi QJ 2011	2	25	8	25	4.3%	0.25 [0.06, 1.06]
Wang CB 2011	3	26	7	26	3.8%	0.43 [0.12, 1.48]
Yang K 2006	4	40	11	40	5.9%	0.36 [0.13, 1.05]
Zhang BM 2009	2	17	5	17	2.7%	0.40 [0.09, 1.78]
Zhang CG 2011	10	42	12	40	6.6%	0.79 [0.39, 1.63]
Zhang CQ 2010	11	30	14	30	7.5%	0.79 [0.43, 1.44]
Zhao RG 2007	5	19	8	18	4.4%	0.59 [0.24, 1.47]
Zheng JM 2011	1	23	3	22	1.6%	0.32 [0.04, 2.84]
Zhou MH 2011	2	18	4	16	2.3%	0.44 [0.09, 2.11]
Total (95%CI)		500		487	100.0%	0.48 [0.38, 0.59]
Total events	90		184			

Heterogeneity: χ^2 = 10.13, df = 17 (P = 0.90); I^2 = 0%

Test for overall effect: Z = 6.76 (P = 0.00001)

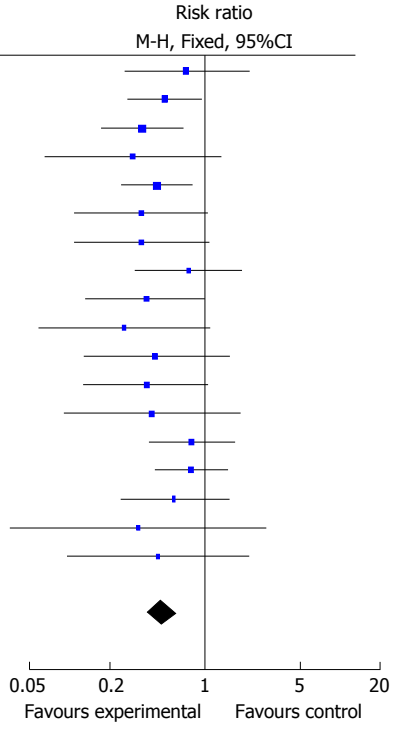


Figure 3 Meta-analysis of patients' oxygenation index (A) and intensive care unit mortality rate (B) after treatment with conventional therapy *vs* with ulinastatin (random effects). A: Random effects model; B: Fixed effects model.

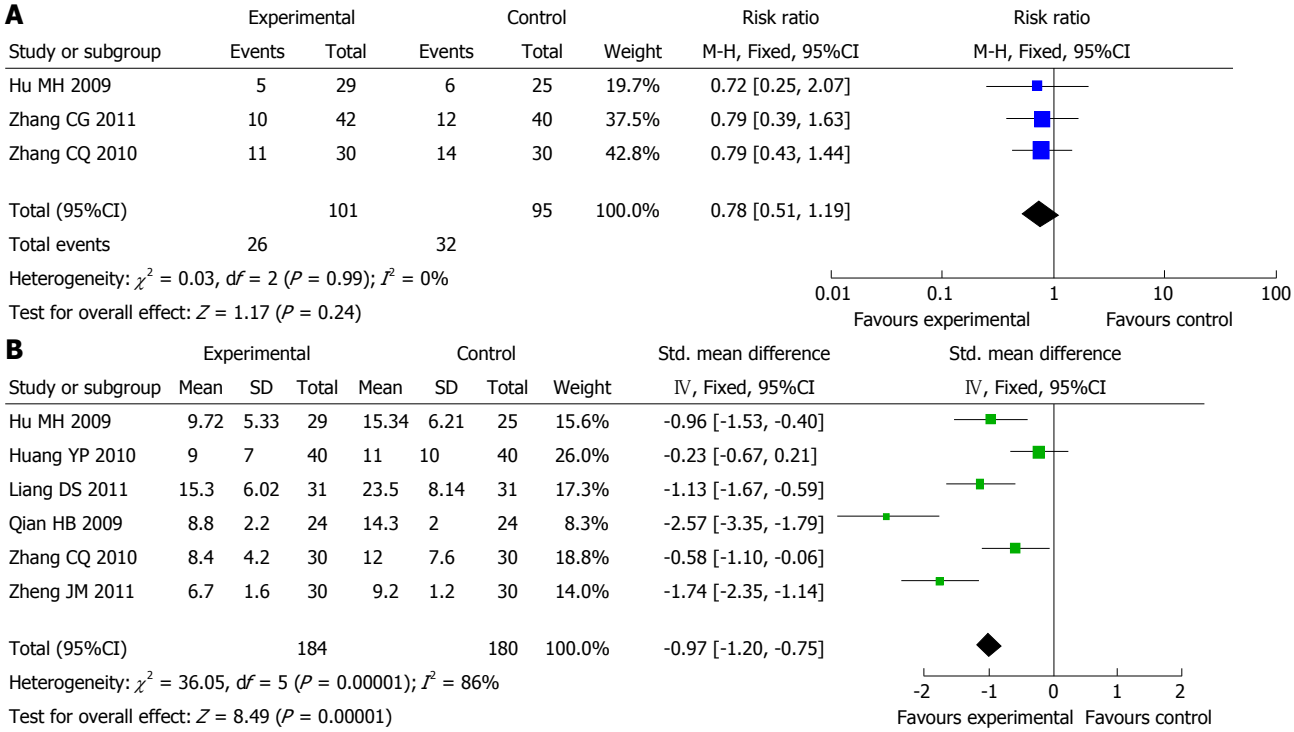


Figure 4 Meta-analysis of 28-d mortality rate (A) and length of intensive care unit stay (B) between treatment with conventional therapy and with ulinastatin. A: Fixed effects model; B: Random effects model.

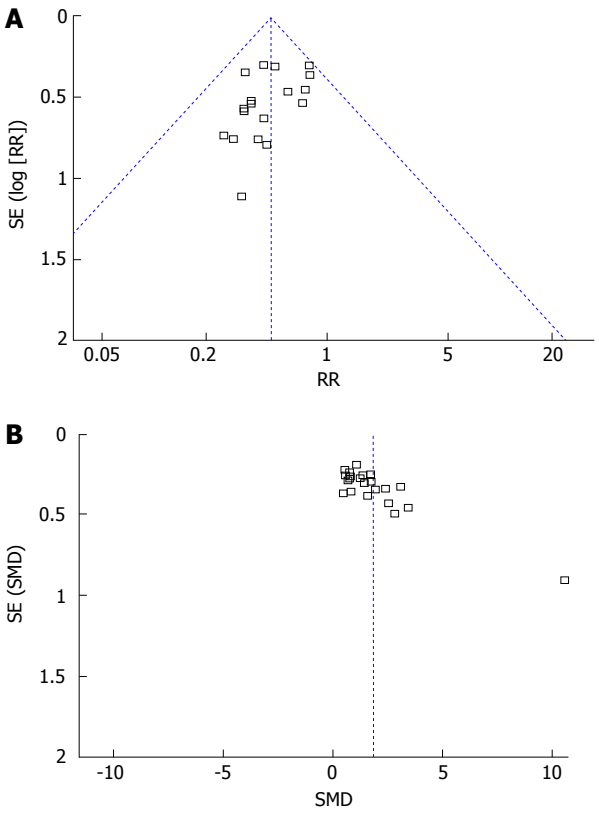


Figure 5 Funnel plots of intensive care unit mortality (A) and oxygenation index (B). SMD: Standard mean difference.

practitioners consider ulinastatin as a first-line treatment? Obviously, we can not draw a definite conclusion right now. Although ulinastatin seems to be effective for ALI/ARDS, high-quality RCTs discussing the efficacy and safety are needed in the future.

COMMENTS

Background

Ulinastatin is marketed as an experimental medication for septic shock in Asia for its involvement in suppressing the systemic inflammation and proteolytic process. Currently, many studies highlight its advantages in lung protection, which is because acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) share a common pathogenesis with sepsis. However, it remains uncertain whether ulinastatin can be recommended as a standard medication for ALI and ARDS.

Research frontiers

No large-scale randomized controlled trials (RCTs) studies or high quality meta-analysis on ulinastatin for ALI and ARDS were performed till now. Whether the application of ulinastatin in ALI and ARDS is appropriate remains unclear.

Innovations and breakthroughs

To provide more specific evidence for clinical practice, the authors performed a meta-analysis on ulinastatin for ALI and ARDS.

Applications

This study indicated that ulinastatin might be truly effective for ALI and ARDS though most RCT studies included were of poor quality.

Peer review

The authors conducted a systematic review and meta-analysis of the retrieved studies on the effects of ulinastatin on ALI and ARDS. The paper is essentially well written, and provides some information.

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CASE REPORT

Failure of lorazepam to treat alprazolam withdrawal in a critically ill patient

Gaurav Sachdev, Gail Gesin, A Britton Christmas, Ronald F Sing

Gaurav Sachdev, Gail Gesin, A Britton Christmas, Ronald F Sing, The F H Sammy Ross, Jr Trauma Center, Department of Pharmacy, Carolinas Medical Center, Charlotte, NC 28023, United States
Ronald F Sing, Department of Surgery/MEB 601, Carolinas Medical Center, Charlotte, NC 28203, United States
Author contributions: Sing RF planned the study and was responsible for the design, collection of data, and initial draft of the manuscript; Sachdev G was responsible for author coordination, data interpretation, and final drafting of the manuscript; Gesin G and Christmas AB helped draft the manuscript; all authors read and approved the final manuscript.
Correspondence to: Ronald F Sing, DO, Department of Surgery/MEB 601, Carolinas Medical Center, 1000 Blythe Boulevard, Charlotte, NC 28203,
United States. ron.sing@carolinashealthcare.org
Telephone: +1-704-3553176 Fax: +1-704-3555619
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Abstract

Management of sedation in the critical care unit is an ongoing challenge. Benzodiazepines have been commonly used as sedatives in critically ill patients. The pharmacokinetic and pharmacodynamic properties that make benzodiazepines effective and safe in critical care sedation include rapid onset of action and decreased respiratory depression. Alprazolam is a commonly used benzodiazepine that is prescribed for anxiety and panic disorders. It is frequently prescribed in the outpatient setting. Its use has been reported to result in a relatively high rate of dependence and subsequent withdrawal symptoms. Symptoms of alprazolam withdrawal can be difficult to recognize and treat in the critical care setting. In addition, other benzodiazepines may also be ineffective in treating alprazolam withdrawal. We present a case of alprazolam withdrawal in a critically ill trauma patient who failed treatment with lorazepam and haloperidol. Subsequent replacement with alprazolam resulted in significant improvement in the patient's medication use and clinical status.

Key words: Alpralazom; Lorazepam; Withdrawal; Pharmacokinetics; Pharmacodynamics

Core tip: Withdrawal from drugs and alcohol is a common phenomenon in the intensive care unit. Benzodiazepines are commonly used for both alcohol and benzodiazepine withdrawal. The pharmacokinetics and pharmacodynamics among drugs within this class vary. The failure of lorazepam to treat withdrawal of alprazolam is demonstrated in this case study.

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INTRODUCTION

Benzodiazepines have been commonly used as sedatives in critically ill patients and also used extensively in the treatment of depression, anxiety, and panic disorders[1]. Key pharmacokinetic and pharmacodynamic properties of benzodiazepines include a rapid onset of action, decreased respiratory depression, higher ratio of lethal dose to effective dose, and a greater therapeutic dose margin between anxiolysis and sedation.

Alprazolam is a commonly used benzodiazepine for anxiety and panic disorders. It has been reported to have a relatively high occurrence of dependence and withdrawal symptoms[2,3]. Symptoms of alprazolam withdrawal can be difficult to recognize and treat in the critical care setting. In addition, other benzodiazepines may be

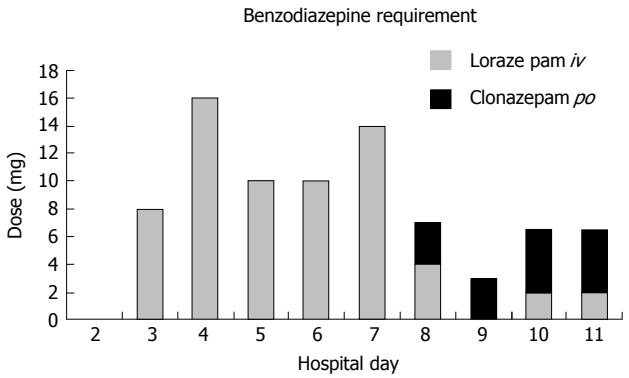

Figure 1 Dosages of lorazepam and clonazepam: hospital days 2-11.

ineffective in treating alprazolam withdrawal. We present a case of alprazolam withdrawal in a critically ill trauma patient who failed treatment with lorazepam.

CASE REPORT

A 28-year-old male was involved in a motor vehicle crash. After assessment and stabilization in the trauma bay he was noted to have an altered level of consciousness, mild traumatic brain injury with small subarachnoid hemorrhage, grade Ⅱ splenic laceration and ethanol level of 221 mg/dL. The patient required emergent splenic artery embolization for a decreasing hematocrit. Subsequently, he was admitted to the trauma intensive care unit and started on an alcohol withdrawal protocol which included lorazepam administered on an as needed symptom-directed schedule.

By hospital day 3, the patient became extremely agitated requiring multiple doses of intravenous lorazepam (2 mg times four doses) (Figure 1). Over the next 5 d, the patient required escalating doses of lorazepam to control his agitation (2 mg 6-7 times per day). Symptoms necessitating pharmacologic intervention included tachycardia, hypertension, confusion, slurred speech and pulling of his catheter and naso-enteric feeding tube.

On hospital day 8, a family member reported that the patient takes alprazolam 1 mg by mouth three times daily as a home medication. Following discussion with the clinical pharmacist member of the multi-professional critical care team, the patient was immediately started on clonazepam 1 mg three times a day. Following the first dose of clonazepam at noon, the patient received only one as needed dose of lorazepam that evening. On hospital day nine, no *as needed* lorazepam doses were required and only one was administered on hospital day 10. Despite an improving mental status, the patient remained confused. Thus, lorazepam was discontinued and the clonazepam dose was increased to 1.5 mg three times daily. On hospital day eleven, the patient again became acutely agitated and received lorazepam and multiple doses of haloperidol. By hospital day thirteen, his clonazepam was increased to 2 mg three times a day. The patient was less agitated and was transferred to an intermediate care unit.

Although improved, the patient remained restless and intermittently agitated. He required haloperidol 3 mg three times a day to control his agitation. Over the next 2 wk, the patient did not require any as needed benzodiazepines or haloperidol for acute agitation. The scheduled haloperidol was tapered and discontinued by discharge at hospital day 25. The clonazepam dose was tapered by 50% each week, and the patient was discharged to a rehabilitation facility on clonazepam 0.5 mg twice daily.

DISCUSSION

In comparison to other benzodiazepines, alprazolam may be associated with a higher propensity for addiction and result in more severe withdrawal symptoms. The prevalence of rebound anxiety is higher with benzodiazepines that have a short to intermediate half-life compared to those with a long half-life[4,5]. The effectiveness of other benzodiazepines at treating alprazolam withdrawal has been studied. The triazole ring found in alprazolam may have a significantly greater binding affinity for a subgroup of benzodiazepine receptors in areas of the brain that are not generally influenced by other benzodiazepines[6]. A review of eight case reports of alprazolam withdrawal published between 1984 and 1986 combined with six unpublished cases reported to the manufacturer provide early evidence of unique properties related to this agent. Chlordiazepoxide and diazepam were both found to be ineffective in preventing withdrawal symptoms in two separate cases. This review has been cited as providing clinical evidence to suggest that there is incomplete cross-tolerance between alprazolam and other benzodiazepines[7]. More recent review has shown that despite over prescription of benzodiazepines, withdrawal and dependence can be reduced by shorter duration prescriptions and withdrawal can be prevented by judicious weaning[8].

Differentiating withdrawal symptoms from pre-hospital substance use from those associated with the physiologic response to trauma can be difficult in critically ill patients since they are similar. In this patient, confusion, slurred speech, restlessness, and hypertension were thought to be related to alcohol withdrawal and tachycardia was presumed to be a presenting sign of a splenic bleeding. Although the patient was appropriately started on a symptom-directed alcohol withdrawal protocol at the time of admission, lorazepam was not effective in abating his agitation.

Lorazepam was clearly ineffective in treating this patient's alprazolam withdrawal. This is consistent with a previous report of a critically ill patient who exhibited alprazolam withdrawal despite large doses of lorazepam and diazepam[9]. Initiation of clonazepam on hospital day eight was associated with a reduction in lorazepam requirements (Figure 1). Although clonazepam was used, it is likely that alprazolam would have also been effective as a rapid response is often observed with reinstitution of the drug[4,5]. Clonazepam was chosen because it has an intermediate to long half-life ranging from 17-60 h and is associated with less rebound anxiety and withdrawal symptoms in comparison to shorter acting agents such as

alprazolam[4,5]. Furthermore, it has been used successfully for the management of alprazolam detoxification. This substitution in alprazolam-dependent patients has been shown to be safe and effective[5,10].

Given the unique characteristics and pharmacodynamics properties of alprazolam, reinstitution of this medication or substitution with clonazepam on a milligram per milligram basis are the preferred management strategies for trauma patients admitted with a history of pre-hospital alprazolam use to prevent withdrawal. Furthermore, consideration should be given to the high potential for therapeutic failure of other benzodiazepines in this patient population. This approach may prevent confusion with physiologic responses to injury and reduce the overall benzodiazepine requirement. This report highlights the need for obtaining an accurate medication history, as well as recognizing the physiologic effects related to injury, substance withdrawal, and medication administration. As such, we recommend a multi-professional approach with input from physicians, nurses, and clinical pharmacists to optimize these processes.

COMMENTS

Case characteristics

The authors present a case of alprazolam withdrawal in a critically ill trauma patient who failed treatment with lorazepam and haloperidol.

Clinical diagnosis

After assessment and stabilization in the trauma bay he was noted to have an altered level of consciousness, mild traumatic brain injury with small subarachnoid hemorrhage, grade Ⅱ splenic laceration and ethanol level of 221 mg/dL.

Differential diagnosis

The patient required emergent splenic artery embolization for a decreasing hematocrit.

Treatment

The patient was admitted to the trauma intensive care unit and started on an alcohol withdrawal protocol which included lorazepam administered on an as needed symptom-directed schedule.

Related reports

It has been used successfully for the management of alprazolam detoxification. This substitution in alprazolam-dependent patients has been shown to be safe and effective.

Experiences and lessons

This report highlights the need for obtaining an accurate medication history, as well as recognizing the physiologic effects related to injury, substance withdrawal, and medication administration.

Peer review

The authors well explained the failure of lorazepam to treat alprazolam withdrawal. This manuscript reports a case report on failure of lorazepam to treat alprazolam withdrawal in a critically ill trauma patient. The reason for this was well explained. Clonazepam was effective in the patient.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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