REVIEW

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Sepsis and Acute Respiratory Distress Syndrome: Recent Update

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Severe sepsis or septic shock is characterized by an excessive inflammatory response to infectious pathogens. Acute respiratory distress syndrome (ARDS) is a devastating complication of severe sepsis, from which patients have high mortality. Advances in treatment modalities including lung protective ventilation, prone positioning, use of neuromuscular blockade, and extracorporeal membrane oxygenation, have improved the outcome over recent decades, nevertheless, the mortality rate still remains high. Timely treatment of underlying sepsis and early identification of patients at risk of ARDS can help to decrease its development. In addition, further studies are needed regarding pathogenesis and novel therapies in order to show promising future treatments of sepsis-induced ARDS.

Keywords: Sepsis; Shock, Septic; Acute Respiratory Distress Syndrome; Biomarkers; Treatment; Review

Introduction

Severe sepsis and septic shock are major healthcare problems that affect millions of patients globally each year. An excessive response to infectious pathogens by inflammatory mediators is implicated in pathogenesis, and mortality from septic shock is high. Acute respiratory distress syndrome (ARDS) is a devastating complication of severe sepsis. Sepsis and ARDS have similar underlying mechanisms, characterized by inflammation and endothelial dysfunction. In addition, severe sepsis is the most common etiology of ARDS, and patients with sepsis-induced ARDS have higher case fatality rates than patients with other risk factors of ARDS[1]. The aim of this review is to highlight current data on epidemiology, pathogenesis, and treatment of sepsis-induced ARDS.

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Incidence, Mortality, and Risk Factors

The incidence of ARDS in adult patients with sepsis is about 6%–7% in Western countries[2,3]. According to data of the Korean Study Group on Respiratory Failure, the incidence of sepsis-induced ARDS is 6.8% (306/4,515) in Korea (unpublished data). In patients with sepsis, the progression to ARDS is rapid and is associated with an increased risk of in-hospital mortality[2,3]. On the other hand, early goal-directed therapy in patients with severe sepsis or septic shock reduced a proportion of the patients received mechanical ventilation[4]. These findings indicate that the incidence of sepsis-induced ARDS is relatively low, but treatment of underlying sepsis and identification of patients at risk of ARDS development is of great importance. To date, few studies have evaluated the risk factors of developing ARDS in severe sepsis population. The Lung Injury Prediction Score, initial serum lactate level, and microbiologically proven infection were factors associated with increased risk of ARDS in patients with severe sepsis[3].

Pathogenesis

ARDS is a heterogeneous syndrome characterized by increased permeability of pulmonary capillary endothelial cells

and alveolar epithelial cells. The cause of injury may be either direct (e.g., pneumonia and gastric aspiration) or indirect to the lung (e.g., non-pulmonary sepsis and trauma), although distinguishing direct from indirect injury may be difficult in some cases (e.g., pneumonia sepsis). Preclinical models have suggested that direct lung injury begins with an insult to the lung epithelium, but indirect lung injury originates with systemic endothelial damage due to inflammatory mediators[5]. Several studies have demonstrated differences of these two phenotypes in humans using a panel of plasma biomarkers. For instance, the levels of surfactant protein, which is a matrix of amphipathic lipoproteins and phospholipids used to prevent alveolar collapse, were significantly higher in direct ARDS patients[6]. On the other hand, the levels of angiopoietin and Von Willebrand factor, which are both dysregulated in endothelial injury, were significantly increased in indirect ARDS by trauma and non-pulmonary sepsis[6-8]. A biomarker panel which includes biomarkers of lung epithelial and vascular endothelial injury may be useful in understanding the pathogenesis of sepsis-induced ARDS, and for selecting patients in trials of new therapies targeted to the lung epithelium and vascular endothelium.

Treatment

At present, there is no specific treatment for sepsis-induced ARDS. The overall treatment strategies of ARDS are not different for patients with sepsis-induced ARDS, and adequate delivery of oxygen to tissue is a primary goal.

1. High-flow nasal cannula and noninvasive ventilation

High-flow nasal cannula (HFNC) is a novel oxygen device that can deliver up to 100% heated and humidified oxygen via a wide-bore nasal cannula at a maximum flow rate of 60 L/min. In a recent multicenter trial, the use of HFNC in acute hypoxemic respiratory failure significantly decreased the intensive care unit (ICU) and 90-day mortality in overall, and the intubation rate in patients with PaO_2/FiO_2 (PF) ratio ≤200 mm Hg[9]. However, this study did not include patients with hemodynamic instability. In addition, HFNC failure with late intubation (>48 hours after HFNC initiation) was associated with higher overall ICU mortality and poorer extubation success in acute respiratory failure[10]. Noninvasive ventilation (NIV) may be effective for patients with chronic obstructive pulmonary disease and cardiogenic pulmonary edema. However, it is less likely to be helpful in patients with hypoxemic respiratory failure. Similar to HFNC, late NIV failure (>48 hours after NIV initiation followed by invasive mechanical ventilation) was associated with high mortality and poor prognosis[11]. Therefore, the use of HFNC or NIV should be carefully considered in sepsis-induced ARDS patients in whom the benefits are thought to outweigh the risks.

2. Invasive mechanical ventilation

The lung protective ventilation strategy (tidal volume of 6 mL/kg of predicted body weight and plateau pressure less than 30 cm H_2O) is strongly advocated. Retrospective studies suggested that tidal volumes should be lowered even at plateau pressures <30 cm H_2O, as lower plateau pressures associated with lower mortality rates[12,13]. On the other hand, a recent study suggests that the lung protective ventilation is beneficial only if associated with decreases in driving pressure (plateau pressure minus positive end-expiratory pressure [PEEP]), indicating the importance of lung recruitability in patients with ARDS[14]. To enhance gas exchange and to avoid atelectotrauma, PEEP can be applied. Large multicenter trials using higher levels of PEEP in conjunction with low tidal volumes did not show survival benefit[15], although a hyperinflammatory phenotype of ARDS with a higher prevalence of sepsis had lower mortality and less organ failure using high PEEP strategy[16].

Permissive hypercapnia, in conjunction with limiting tidal volume and minute ventilation, is an important component of lung protective ventilation strategy. In contrast, hypercapnia may increase the severity of lung injury by prolonging pneumonia. The possible underlying mechanism seems to involve prolonged immune suppression and subsequent increase of bacterial load[17]. Nevertheless, current opinion recommends the use of permissive hypercapnia in treatment of sepsis-induced ARDS.

3. Prone positioning

In sepsis-induced ARDS with severe refractory hypoxemia, rescue therapies can be considered. Prone positioning could be an effective modality. Prolonged prone positioning (≥16 hours) in patients with PF ratio ≤100–150 mm Hg showed positive results in patients with ARDS[18,19], although the role of oxygenation improvement in reducing mortality became less clear. Prevention of ventilator-induced lung injury[20] and improvement of hemodynamics[19] may be alternative mechanisms explaining clinical benefits of prone positioning in ARDS, and further studies are required.

4. Neuromuscular blockade

A multicenter trial showed that early continuous infusion of neuromuscular blocking agent (NMBA) for 48 hours in patients with severe ARDS (PF ratio <150 mm Hg) was associated with improved outcomes without increased muscle weakness[21]. Although the disease severity was lower than previous studies, an analysis found that early treatment with NMBA showed lower in-hospital mortality among patients with severe sepsis and respiratory infection in mechanical

ventilation[22]. These data suggest that early short-term use of NMBA, if indicated, may be helpful in patients with sepsis-induced ARDS.

5. Extracorporeal life support

Extracorporeal membrane oxygenation (ECMO) can be used to treat refractory hypoxemia when patients fail to improve with traditional management. Recent large-volume trials in severe ARDS have shown positive results of ECMO treatment[23]. The initiation of ECMO may be individualized according to the diagnosis of respiratory failure and associated infection. For instance, according to the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score[24], a patient with pneumonia sepsis would receive three additional points (more indicated); whereas three points would be deducted in a patient with non-pulmonary sepsis (less indicated). In addition, the experience using ECMO for pandemic influenza A (H1N1)–ARDS identified that many centers initiated ECMO protocols without much experience, and the outcomes were variable[25]. ECMO should be considered in centers with expertise and experience with its use due to procedure-related complications and challenges in interhospital transfers. Extracorporeal carbon dioxide removal (ECCO2R) effectively reduces CO_2 tension and permits lung protective ventilation in patients with ARDS. Due to its inability to correct severe hypoxemia and hypotension, however, the use of ECCO2R may be limited in selected cases[26].

6. Other rescue therapies

Recruit maneuvers are available to permit extra gas exchange, but blood pressure and oxygenation should be carefully monitored. Inhaled nitric oxide (NO) attenuates alveolar-capillary membrane injury and sepsis-induced pulmonary inducible NO synthase activity, however, clinical trials of inhaled NO in ARDS have not shown survival benefit[27].

7. Supportive care

Several clinical trials have demonstrated that protocolized sedation followed by a prompt spontaneous breathing trial reduces duration of mechanical ventilation, ICU and hospital length of stay, and even long-term mortality[28]. There is no definite fluid management strategy in sepsis-induced ARDS. The landmark study showed that a conservative fluid strategy to minimize fluid administration in patients with ARDS led to fewer days of mechanical ventilation and ICU stay without compromising end-organ perfusion[29]. In this study, however, active attempts to reduce fluid volume were withheld during the periods of shock. Current guidelines recommend a conservative fluid strategy for patients with sepsis-induced ARDS who do not have tissue hypoperfusion.

8. Anti-inflammatory therapy

The role of corticosteroid in sepsis and ARDS is inconclusive despite many studies for many decades. Small studies suggested benefits of steroid for patients with unresolving ARDS, but a large multicenter trial showed that steroid administration after 14 days of ARDS onset could be harmful[30]. Regarding to prolonged use of low-dose hydrocortisone in septic shock, the results of several meta-analyses are inconsistent[31,32]. Current guidelines recommend against using corticosteroid unless shock is refractory.

Platelets play an important role in the pathogenesis of sepsis-induced lung injury, and preclinical models have shown that aspirin, the platelet inhibitor, can prevent or treat ARDS by derecruitment of neutrophils, deactivation of inflammatory cascade, and reduction of platelet sequestration in the lungs[33]. In clinical studies, prehospital use of aspirin, with or without concomitant statins, significantly reduced the development and the mortality of severe sepsis and ARDS[34]. Statins also reduce inflammation and have been shown to prevent ARDS, but a recent multicenter trial showed no mortality benefit in patients with sepsis-induced ARDS[35].

Recently, hemoperfusion has gradually developed for use in treatment of sepsis and acute lung injury. Polymyxin B hemoperfusion (PMX-HP) is a device that reduces endotoxin levels in sepsis, and a recent randomized controlled trial showed survival benefit and improvement of other clinical outcomes in severe sepsis and septic shock of intra-abdominal origin[36]. However, a subsequent randomized controlled trial has failed to replicate the results[37], although discrepancies such as anticoagulation regimen and microbiological data exist between the two studies. There is no hard evidence yet for PMX-HP, and we should wait for the results of ongoing clinical trials (EUPHRATES, NCT01046669; EUPHAS-2).

9. Experimental trials

Cell therapies offer promise for treatment of sepsis and ARDS. In ARDS, mesenchymal stem/stromal cells (MSCs) may restore epithelial and endothelial functions by differentiating into these cells or secretion of paracrine factors. In addition, preclinical models show that MSCs directly attenuate bacterial sepsis via increased bacterial clearance and secretion of antimicrobial peptide[38]. In a case report, intratracheal administration of umbilical cord blood-derived MSCs improved lung compliance, PF ratio, and chest radiography in ARDS[39]. Several clinical trials of cell therapies for ARDS are underway (UCMSC-ALI, NCT02444455; START, NCT02097641; NCT01902082).

Conclusion

Sepsis-induced ARDS is associated with high mortality in critically ill patients, although the incidence is relatively low. The evaluation of risk factors of developing ARDS in patients with severe sepsis is of the utmost importance. Sepsis and ARDS share similar mechanisms, although differentiating the indirect injury from the direct injury using a panel of biomarkers may be useful in understanding of sepsis-induced ARDS and for selecting patients in trials of new therapies. Lung protective mechanical ventilation is the mainstay of treatment for these patients. In patients with refractory hypoxemia, high PEEP strategy, prone positioning, administration of NMBA, and ECMO are available for use. Hemoperfusion, anti-inflammatory therapy, and other experimental trials can be considered, yet more studies are required to evaluate their efficacy and safety.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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