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. The aim of this review is to highlight current data on epidemiology, pathogenesis, and treatment of sepsis-induced ARDS.

Incidence, Mortality, and Risk Factors

The incidence of ARDS in adult patients with sepsis is about 6%–7% in Western countries. 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of the Korean Study Group on Respiratory Failure, the incidence of sepsis-induced ARDS is 6.8% (306/4,515) in Korea (unpublished data).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. 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. 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.

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. 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. 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. 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 hypoxic 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. 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. 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. 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$_2$O) is strongly advocated. Retrospective studies suggested that tidal volumes should be lowered even at plateau pressures <30 cm H$_2$O as lower plateau pressures associated with lower mortality rates. 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 recruited in patients with ARDS. 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, although a hyperinflammatory phenotype of ARDS with a higher prevalence of sepsis had lower mortality and less organ failure using high PEEP strategy.

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. 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, although the role of oxygenation improvement in reducing mortality became less clear. Prevention of ventilator-induced lung injury and improvement of hemodynamics 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. 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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 (ECCO\textsubscript{2}R) effectively reduces CO\textsubscript{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 ECCO\textsubscript{2}R may be limited in selected cases\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 unresolved ARDS, but a large multicenter trial showed that steroid administration after 14 days of ARDS onset could be harmful\textsuperscript{29}. Regarding to prolonged use of low-dose hydrocortisone in septic shock, the results of several meta-analyses are inconsistent\textsuperscript{30,31}. 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\textsuperscript{32}. In clinical studies, prehospital use of aspirin, with or without concomitant statins, significantly reduced the development and the mortality of severe sepsis and ARDS\textsuperscript{33}. 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\textsuperscript{34}.

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\textsuperscript{35}. However, a subsequent randomized controlled trial has failed to replicate the results\textsuperscript{36}, although discrepancies such as anti-coagulation 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\textsuperscript{37}. In a case report, intratracheal administration of umbilical cord blood-derived MSCs improved lung compliance, PF ratio, and chest radiography in ARDS\textsuperscript{38}. 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.

References

1. Stapleton RD, Wang BM, Hudson LD, Rubenfeld GD, Caldwell ES, Steinberg KP. Causes and timing of death in patients with ARDS. Chest 2005;128:525-32.
2. Gajic O, Dabbagh O, Park PK, Adesanya A, Chang SY, Hou P, et al. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. Am J Respir Crit Care Med 2011;183:462-70.
3. Mikkelsen ME, Shah CV, Meyer NJ, Gaieski DF, Lyon S, Miltiades AN, et al. The epidemiology of acute respiratory distress syndrome in patients presenting to the emergency department with severe sepsis. Shock 2013;40:375-81.
4. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
5. Menezes SL, Bozza PT, Neto HC, Laranjeira AP, Negri EM, Capelozzi VL, et al. Pulmonary and extrapulmonary acute lung injury: inflammatory and ultrastructural analyses. J Appl Physiol (1985) 2003;98:1777-83.
6. Caffee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med 2014;2:611-20.
7. O’Cróinin DF, Nichol AD, Hopkins N, Boylan J, O’Brien S, O’Connor C, et al. Sustained hypercapnic acidosis during pulmonary infection increases bacterial load and worsens lung injury. Crit Care Med 2008;36:2128-35.
8. Lee K, Kim MY, Yoo JW, Hong SB, Lim CM, Koh Y. Clinical meaning of early oxygenation improvement in severe acute respiratory distress syndrome under prolonged prone positioning. Korean J Intern Med 2010;25:58-65.
9. Guerin C, Reignier J, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med 2015;41:623-32.
10. Moretti M, Cilione C, Tampieri A, Fraccia C, Marchioni A, Nava S. Incidence and causes of non-invasive mechanical ventilation failure after initial success. Thorax 2000;55:819-25.
11. Meyer NJ, Li M, Feng R, Bradfield J, Gallop R, Bellamy S, et al. ANGPT2 genetic variant is associated with trauma-associated acute lung injury and altered plasma angiopoietin-2 isoform ratio. Am J Respir Crit Care Med 2011;183:1344-53.
12. Rubin DB, Wiener-Kronish JP, Murray JE, Green DR, Turner J, Luce JM, et al. Elevated von Willebrand factor antigen is an early plasma predictor of acute lung injury in nonpulmonary sepsis syndrome. J Clin Invest 1999;106:474-80.
13. Frat J, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372:2185-96.
14. Kang BJ, Koh Y, Lim CM, Huh JW, Baek S, Han M, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med 2015;41:623-32.
15. Merca...
23. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thala­nanany MM, et al. Efficacy and economic assessment of conven­tional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009;374:1351-63.

24. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Respir Crit Care Med 2014;189:1374-82.

25. Combes A, Brodie D, Bartlett R, Brochard L, Brower R, Conrad S, et al. Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. Am J Respir Crit Care Med 2014;190:488-96.

26. Cho WH, Lee K, Huh JW, Lim CM, Koh Y, Hong SB. Physiologic effect and safety of the pumpless extracorporeal inten­titional lung assist system in patients with acute respiratory failure: a pilot study. Artif Organs 2012;36:434-8.

27. Taylor RW, Zimmerman JL, Dellinger RP, Straube RC, Criner GI, Davis K Jr, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. JAMA 2004;291:1603-9.

28. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 2008;371:126-34.

29. National Heart, Lung, and Blood Institute ARDS Clinical Trials Network, Truwit JD, Bernard GR, Steingrub J, Matthay MA, Liu KD, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. Crit Care Med 2011;39:1343-50.

30. Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, et al. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. JAMA 2009;301:2445-52.

31. Payen DM, Guilhot J, Launey Y, Lukaszewicz AC, Kaaki M, Veber B, et al. Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial. Intensive Care Med 2015;41:975-84.

32. Kransnodembskaya A, Song Y, Fang X, Gupta N, Serikov V, Lee JW, et al. Antibacterial effect of human mesenchymal stem cells is mediated in part from secretion of the antimicrobial peptide LL-37. Stem Cells 2010;28:2229-38.

33. Chang Y, Park SH, Huh JW, Lim CM, Koh Y, Hong SB. Intra­tracheal administration of umbilical cord blood-derived mesenchymal stem cells is a patient with acute respiratory distress syndrome. J Korean Med Sci 2014;29:438-40.