Review Article

Early identification and diagnosis, pathophysiology, and treatment of sepsis-related acute lung injury: a narrative review

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Background and Objective: Sepsis is a life-threatening organ dysfunction, and the most common and vulnerable organ is the lungs, with sepsis-related acute respiratory distress syndrome (ARDS) increasing mortality. In recent years, an increasing number of studies have improved our understanding of sepsis-related ARDS in terms of epidemiology, risk factors, pathophysiology, prognosis, and other aspects, as well as our ability to prevent, detect, and treat sepsis-related ARDS. However, sepsis-related lung injury remains an important issue and clinical burden. Therefore, a literature review was conducted on sepsis-related lung injury in order to further guide clinical practice in reducing the acute and chronic consequences of this condition.

Methods: This study conducted a search of the MEDLINE and PubMed databases, among others for literature published from 1991 to 2023 using the following keywords: definition of sepsis, acute lung injury, sepsis-related acute lung injury, epidemiology, risk factors, early diagnosis of sepsis-related acute lung injury, sepsis, ARDS, pathology and physiology, inflammatory imbalance caused by sepsis, congenital immune response, and treatment.

Key Content and Findings: This review explored the risk factors of sepsis, sepsis-related ARDS, early screening and diagnosis, pathophysiology, and treatment and found that in view of the high mortality rate of ARDS associated with sepsis. In response to the high mortality rate of sepsis-related ARDS, some progress has been made, such as rapid identification of sepsis and effective antibiotic treatment, early fluid resuscitation, lung-protective ventilation, etc.

Conclusions: Sepsis remains a common and challenging critical illness to cure. In response to the high mortality rate of sepsis-related ARDS, progress has been made in rapid sepsis identification, effective antibiotic treatment, early fluid resuscitation, and lung-protective ventilation. However, further research is needed regarding long-term effects such as lung recruitment, prone ventilation, and the application of neuromuscular blocking agents and extracorporeal membrane oxygenation.

Keywords: Sepsis; sepsis-related acute respiratory distress syndrome (sepsis-related ARDS); pathophysiology; risk factors; early diagnosis

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Introduction

Sepsis is a syndrome of physiological, pathological, and biochemical abnormality caused by infection. Sepsis is a common, deadly, and costly disease worldwide. According to statistics, more than 30 million people are affected by sepsis every year, and it is one of the main causes of death for critically ill patients (1). In cases of sepsis, the body's immune system releases a large number of inflammatory mediators (such as cytokines) that help fight infection but can also cause extensive tissue damage. The lungs are one of the organs most commonly affected by sepsis and are the first target organ affected by sepsis (2), which often manifests as acute respiratory distress syndrome (ARDS). ARDS is a syndrome characterized by noncardiogenic pulmonary edema, hypoxemia, and the need for mechanical ventilation and is associated with a mortality rate of up to 30–40% (3). Treating sepsis and the lung damage it causes usually involves controlling the underlying infection, using antibiotics, providing supportive treatment (such as oxygen or mechanical ventilation), and applying treatments that target the inflammatory response. The treatment focus for sepsis-associated ARDS is protective lung ventilation, and there is currently no mature and specific drug therapy available. As the long-term prognosis of patients with this disease is being increasingly recognized as a critical research goal, the early identification and further understanding of the pathogenesis of sepsis-associated ARDS have been identified as the main research directions through treatment methods can be improved. We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/jtd-24-1191/rc).

Methods

To explore the association between sepsis and ARDS, a search of the MEDLINE and PubMed databases, among others, was conducted for literature published from 1991 to 2023 using the following keywords: definition of sepsis, acute lung injury, sepsis-related acute lung injury, epidemiology, risk factors, early diagnosis of sepsis-related acute lung injury, sepsis, ARDS, pathology and physiology, inflammatory imbalance caused by sepsis, congenital immune response, and treatment (*Table 1*).

Results

Definition

Definition of sepsis

The term sepsis was first proposed by Hippocrates and refers to the process of organic matter decay or decomposition (4,5). Subsequently, inflammation was coined to describe a condition characterized by redness, swelling, fever, pain, and loss of function (5,6). In the early 20th century, it was discovered that sepsis was a host system response caused by excessive systemic inflammation induced by pathogenic microorganisms in the bloodstream (7). Before the early 1990s, consensus definitions for systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock had been proposed by the American

Table 1 The search strategy summary

Item	Specification
Date of search	01/01/2024
Databases and other sources searched	PubMed, MEDLINE
Search terms used	Definition of sepsis, acute lung injury, sepsis-related acute lung injury, epidemiology, risk factors, early diagnosis of sepsis-related acute lung injury, sepsis, ARDS, pathology and physiology, inflammatory imbalance caused by sepsis, congenital immune response, and treatment
Timeframe	1991 to 2023
Inclusion and exclusion criteria	All English-language, full-text literature related to our topic was in the database, while literature in other languages was excluded
Selection process	All retrieved literature was discussed and selected by three associate chief physicians or researchers in the research group

ARDS, acute respiratory distress syndrome.

College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) from the perspective of clinical and laboratory indicators of abnormalities (namely sepsis 1.0), which emphasizes the continuity of acute inflammatory response syndrome and organ dysfunction (8). Although these definitions are crucial for the clinical work and basic research of sepsis, they also have certain limitations. Research has shown that 87% of patients who meet the diagnostic criteria for SIRS meet the criteria for intensive care unit (ICU) transfer and that the incidence of infection in long-term ICU patients is 100% while that of SIRS is 93% (9). Another study showed that there was no significant difference in mortality between infected patients who did not meet the SIRS diagnostic criteria and those who met the SIRS diagnostic criteria (10). These findings point to a controversy over the sensitivity and specificity of SIRS. In 2001, SCCM, ACCP, and the European Society of Intensive Care Medicine (ESICM) launched the "Battle to Save Sepsis" [Surviving Sepsis Campaign (SSC)] and revised sepsis 1.0 to develop sepsis 2.0, proposing new diagnostic criteria including infection or suspected infection, inflammatory response, organ dysfunction, hemodynamics, or tissue perfusion indicators (11).

In 2016, the 45th edition of the Society of Intensive Care Medicine unanimously adopted the third definition of sepsis (sepsis 3.0) with sepsis now referring to "life-threatening organ dysfunction caused by host dysregulation of response to infection" (12). This definition eliminates the notion of SIRS and severe sepsis, emphasizes the mechanisms and severity of organ dysfunction caused by infection, and requires timely identification and intervention in clinical treatment (13). The new definition also includes a revised definition of organ dysfunction based on changes in Sequential Organ Failure Assessment (SOFA) scores; meanwhile, septic shock, which greatly increases the mortality rate, refers to sepsis that requires vasoactive drugs to maintain a mean arterial pressure ≥65 mmHg and concentration of lactate level >2 mmol/L despite sufficient fluid resuscitation (12). The diagnostic criteria for sepsis differ between ICU patients and non-ICU patients. For ICU patients suspected of or already infected, diagnosis is possible when the SOFA score is ≥2 points; for non-ICU patients suspected of infection or already infected, a diagnosis can be made when two or more positive quick SOFA (qSOFA) scores (systolic blood pressure ≤100 mmHg, respiratory rate ≥22 beats/min, change in consciousness) appear (11,13,14). However, since the release of the qSOFA score, the qSOFA score has been criticized as being too sensitive, having low specificity, and being potentially responsible for the overdiagnosis of sepsis. Therefore, neither SIRS, SOFA, nor qSOFA can be considered an independent or uniform definitions of sepsis. In order to achieve more accurate diagnosis and treatment, new standards and models are gradually being studied (15-17). The 2021 SSC treatment guidelines for sepsis and septic shock do not recommend the use of qSOFA scores alone to screen for sepsis and septic shock and rather encourage clinical doctors to comprehensively evaluate and diagnose patients based on their condition (18).

Definition of ARDS

ARDS is a respiratory failure that endangers illness and is one of the main causes of death in critically ill patients (3,19). As with sepsis, understanding the epidemiology, pathophysiology, and treatment of lung injury should be based on a consensus definition.

Due to the existence of similar clinical and imaging standards, acute lung injury (ALI) as clinical terms were defined together in the 1994 North American European Consensus Classification, and were specifically described as acute onset, decreased fraction of inspiration O_2 [partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2)] ratio, and bilateral pulmonary infiltrative shadows that cannot be explained by cardiogenic factors. ALI and ARDS are distinguished by the PaO_2/FiO_2 ratio, with ALI having a PaO_2/FiO_2 ratio <300 mmHg and ARDS having a PaO_2/FiO_2 ratio <200 mmHg (20). ALI/ARDS is mainly characterized by noncardiogenic pulmonary edema, mainly due to the increased protein permeability of the pulmonary endothelial and alveolar epithelial cell barriers (3,21). In 2012, the term ALI was abolished, and the definition of adult ARDS was updated to the Berlin definition, with ARDS being classified into mild, moderate, and severe based on the oxygenation index (22,23).

However, due to factors such as the treatment environment and regional economies, some scholars believe that the Berlin definition cannot be used to identify patients with ARDS under conditions of limited resources, including the inability to obtain mechanical ventilation, arterial blood gas diagnosis, and chest X-ray examination (23,24). In 2016, Riviello *et al.* proposed the Kigali version of the ARDS definition through research, which removed the requirement for positive end-expiratory pressure (PEEP) based on the Berlin definition and replaced PaO_2/FiO_2 ratio with SPO_2/FiO_2. When the ratio of arterial oxygen partial pressure to fractional inspired oxygen (SPO_2/FiO_2) ratio is less than 315, hypoxemia is

considered to be present, and bilateral lung turbidity is determined according lung ultrasound or chest X-ray (25). Although the widespread application of the Kigali version of the ARDS definition still needs to be validated, it has undoubtedly prompted researchers to rethink and develop definition standards that are applicable to all regions.

Definition of sepsis-related ARDS

Many patients meet the consensus criteria for both sepsis and ARDS and are considered to have sepsis-related ARDS (26,27). Severe acute inflammation plays a crucial role in sepsis-related ARDS (28). Sepsis causes irreversible damage to the lungs by preventing the inflammation of the lungs from subsiding (29). Sepsis-related ARDS can occur on any side, including direct lung injury caused by lung epithelial injury and indirect lung injury caused by endothelial cell injury (30,31).

Epidemiology

Accurately estimating the incidence and trend of ARDS secondary to sepsis involves certain challenges. Although screening procedures and data technology can help improve our ability to define ARDS associated with sepsis, it remains difficult to strictly identify ARDS attributed to sepsis due to the complexity of critically ill patients.

Research shows that in the past 40 years, the incidence rate of sepsis has increased significantly due to the substantial aging of the population. The latest research in the United States, Europe, and the United Kingdom shows that the incidence rate of sepsis is between 0.4/1,000 and 1/1,000 of the population (32). In contrast, the in-hospital mortality rate of sepsis patients is decreasing (33). A comprehensive review of the number of inpatients in the United States over the past 20 years found that the incidence rate of sepsis increased from 82.7/100,000 to 240.4/100,000 while the mortality rate decreased from 27.8% to 17.9% (33). Another study, which collected data from most ICU inpatients in Australia and New Zealand from 2000 to 2012, corroborates this trend (34). Overall, epidemiological studies indicate that sepsis is becoming increasingly common but that its lethality is decreasing.

In 2014, the LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) study analyzed data from 29,144 patients in 459 ICUs across 50 countries and found that the prevalence of ARDS was 10% among ICU patients and 23% among all patients using ventilators in the ICU (35). This study also reported that according to the Berlin diagnostic criteria, the mortality rates of mild, moderate, and severe ARDS were 34.9%, 40%, and 46.1%, respectively (35). A study has shown that the 90-day in-hospital mortality rate for patients with moderate-to-severe ARDS is 43% (36). In the follow-up analysis of the LUNG SAFE study, it was found that 21% of patients with ARDS had impaired immune function, and the mortality rate of these patients was much higher than that of the non-immunocompromised patients (37). Therefore, it is unclear to what degree the mortality rate reported for ARDS can be attributed to ARDS rather than underlying comorbidities. More importantly, the study also showed that clinical doctors have a low recognition rate for ARDS and that the related treatment is not standardized (35). These results indicate that ARDS is common in critically ill patients but is not commonly fully recognized or treated.

Although the mortality rate attributed to ARDS itself has always been difficult to ascertain, the mortality rate associated with sepsis in ARDS is 27–37% (38). Sepsis is the main indirect cause of ARDS in the ICU (35), and the lungs are the first and most vulnerable organ affected by sepsis (2). sepsis-related ARDS can be divided into indirect lung injury caused by extrapulmonary infection and direct lung injury caused by intrapulmonary infection (35). Research has shown that the mortality rate of ARDS caused by sepsis is higher than that caused by other factors (39).

Risk factors

The most common risk factors for ARDS are pneumonia (bacteria, viruses, fungi) and sepsis from non-pulmonary sources (including the abdomen, ureter, soft tissue, skin, etc.), followed by inhalation of gastric contents (35,40). Risk factors such as trauma and blood transfusion have become less common in modern ARDS with the development of ventilator therapy and blood transfusion management (35,41); however, it has been shown that the use of e-cigarettes, a relatively novel product, can lead to the occurrence of e-cigarette or vaping use-associated lung injury (EVALI) (42,43). Undoubtedly, identifying the risk factors for ARDS is a key therapeutic goal in improving the prognosis of those with ARDS (44).

A study has also shown that drinking alcohol increases the risk of sepsis, related organ failure, and mortality (45). It is widely acknowledged that smoking is a risk factor for ARDS, and research suggests a significant correlation between smoking and sepsis (46). Smoking not only increases the risk of invasive pneumococcal pneumonia but also increases the

incidence of septic shock and 30-day mortality. In addition, a 2013 meta-analysis found that vitamin D deficiency increases the risk of sepsis (47), but whether supplementation can reduce the risk remains unclear (48). Finally, it has also been demonstrated that vaccination can reduce the incidence rate of sepsis caused by specific pathogens (49).

ARDS is independently associated with ICU patient mortality, length of hospital stay, ICU length of hospital stay, and days without ventilation. The occurrence of ARDS in ICU patients with sepsis increases the risk of sepsis and hospitalization mortality in ICU patients (38).

Early identification and diagnosis of sepsis-related ARDS

Since sepsis and ARDS are independently associated with increased incidence rate, mortality, and hospital length of stay, early detection is critical to providing the opportunity for successful treatment (38,50). This is especially critical for ARDS, as it only occurs in a small number of patients with risk factors, but there is currently no evidence or consensus to screen patients for ARDS. In addition, once ARDS emerges, it progresses rapidly and generally occurs within 12–48 hours of hospitalization (44).

Early screening and diagnosis of sepsis

Sepsis is a serious disease characterized by the triggering of a systemic inflammatory response being. With the goal of identifying and diagnosing sepsis earlier, in addition to the diagnosis of sepsis based on sepsis 3.0, an increasing number of biomarkers are being discovered and studied, with inflammation-related markers being the most prominent (1,8). Procalcitonin (PCT) is a precursor of the calcitonin hormone secreted by thyroid C cells, an acute phase protein, or a monocyte chemokine secreted by cytokines and lipopolysaccharides (LPS) under endogenous and exogenous stimuli (51). During sepsis, PCT appears earlier than do other inflammatory factors, significantly increases in abundance within 2–6 hours, and reaches its peak within 6–24 hours (52). In a meta-analysis, PCT value was identified as being statistically significant for the prognosis of sepsis but not for the prognosis of septic shock (53). In a comprehensive analysis of all biomarkers relevant to inflammatory response, PCT was considered the most predictive biomarker (54,55). With the goal of improving rational drug use and reducing bacterial resistance, another study indicated that discontinuing antibiotics when serum PCT <0.25 ng/mL is a reference indication (56,57). C-reactive protein (CRP) is an acute phase protein synthesized by liver cells when the human body is invaded by microorganisms or tissue damage, and it is the most studied inflammatory marker (58). Research has shown that CRP has a moderate diagnostic value for patients with sepsis. During sepsis, CRP levels increase within 6–8 hours and peak after 36–50 hours. CRP levels can be used to help evaluate the response of patients with sepsis to the initiation of antimicrobial therapy and can serve as a marker for early infection. Therefore, during sepsis, CRP contributes to prognosis and treatment monitoring, with the level of CRP potentially being related to the severity of infection (59).

In addition to the application of inflammatory markers, early screening for sepsis can also be combined with the comprehensive application of SIRS standards, vital signs, infection signs, qSOFA or SOFA standards, the National Early Warning Score (NEWS) or the Modified Early Warning Scores (MEWS), etc., to make a diagnosis based on actual clinical symptoms (60,61).

The latest guidelines from the 2021 SSC state that patients suspected of having sepsis should have their serum lactate levels dynamically measured (18). The definition of sepsis 3.0 includes elevated lactate (13), and the correlation between lactate levels and mortality has been confirmed. Previous studies have shown that lactate can be used to screen for the presence of sepsis in clinically suspected (but undiagnosed) patients with sepsis (62-64). However, lactic acid itself is neither sensitive nor sufficiently specific to be used alone for diagnosis or exclusion (18).

Early screening and diagnosis of ARDS

The most widely used score for predicting ARDS in high-risk patients is the Lung Injury Prediction Scale (LIPS), which relies on available clinical data on susceptibility risk factors, comorbidities, and acute physiological variables to generate risk scores. The higher the score is, the higher the risk of ARDS (65). A related study has shown that the negative predictive value of LIPS score is considerably high, while the positive predictive value is considerably low (66). Another score related to ARDS, the Early Acute Lung Injury (EALI) score, is mainly aimed at identifying lung injury before the occurrence of ARDS. Compared with that of the LIPS score, the negative predictive value of the EALI score is still higher (67).

In terms of biomarkers, analysis has shown that angiopoietin 2 and interleukin 8 (IL-8) are elevated in patients before the onset of ARDS, while angiopoietin 2 increases the positive predictive value of LIPS (68). Another study has shown that soluble receptor for advanced

glycation end-products (RAGE) can also predict the occurrence and development of ARDS (69).

Despite the continued development and refinement of the Berlin definition, the accurate diagnosis of ARDS remains challenging. Researchers have confirmed that the interpretation of ARDS chest X-rays is subjective and that the diagnostic results are directly related to the experience and level of the readers (45). This suggests that there are certain difficulties in distinguishing pulmonary edema caused by ARDS from pulmonary edema caused by heart failure or volume overload in clinical practice. According to the Berlin definition, echocardiography can be used to evaluate new functions in the absence of risk factors (22). With the development of related technologies and the accumulation of research, other methods are emerging than can aid in distinguishing between the types of pulmonary edema. These approaches include B-type natriuretic peptide (BNP) elevation indicating cardiac dysfunction, vascular widening on chest X-ray indicating volume overload, and the ratio of pulmonary edema fluid to plasma albumin. If the ratio of pulmonary edema fluid to plasma albumin is less than 0.65, this indicates cardiogenic pulmonary edema, and if the ratio is greater than 0.65, this indicates increased alveolar capillary permeability (70). For patients who have already undergone mechanical ventilation, we can use the oxygenation index for the diagnosis of ARDS. However, in situations where resources are insufficient and advanced detection techniques and treatment methods are not readily available, the diagnosis of ARDS will be further hindered. Therefore, in 2016, an alternative standard for diagnosing ARDS without chest X-ray, mechanical ventilation, or blood gas analysis was proposed, which is the Kigali-modified version of the Berlin standard (25). In addition, it should also be noted that in the early stages, attention should be paid to distinguishing diseases that require specific treatment and have similar clinical manifestations to those of ARDS, such as interstitial pneumonia, diffuse alveolar hemorrhage, and acute heart failure (3). The risk factors of ARDS, such as sepsis and pneumonia, are also key factors for the early diagnosis of ARDS. Bronchoscopy combined with bronchoalveolar lavage and cell counting can help aid in achieving a differential diagnosis. If the cause is still unclear after bronchoscopy and the examination results directly change the treatment method, lung biopsy can be considered.

Pathology and physiology

The pathogenesis of sepsis is extremely complex and includes imbalanced inflammatory response, immune dysfunction, mitochondrial damage, coagulation disorders, abnormal neuroendocrine immune network, endoplasmic reticulum stress, autophagy, and other pathological and physiological processes that ultimately lead to organ dysfunction (1).

In undamaged lungs, the selective barrier to liquids and solutes is composed of adhesive and tight junctions in endothelial cells. The barrier of the alveolar epithelium is composed of flat alveolar type I (AT I) cells and cubic alveolar type II (AT II) cells. AT II cells secrete surfactants that can reduce surface tension, keep alveoli open, and promote gas exchange. In addition, under normal circumstances, AT I and AT II cells can excrete excess fluid absorbed from the air through ion channels.

In ARDS, the permeability of pulmonary endothelial cells to fluid and proteins increases, leading to pulmonary interstitial edema. Due to the destruction of the alveolar epithelial barrier, the edema fluid further transfers to the alveoli, increasing the permeability of alveolar capillaries to fluid, proteins, neutrophils, and red blood cells, which is a characteristic of ARDS. Due to the increased permeability of alveolar capillaries, there is an imbalance in the ventilation-to-blood flow ratio and an increase in alveolar dead space, resulting in severe hypoxemia in clinical manifestations (3). We generally believe that diffuse alveolar damage (DAD) is a characteristic pathological manifestation of ARDS, which manifests primarily as the eosinophilic deposition of the transparent membrane. However, recent studies have shown that DAD only exists in a small proportion of patients with clinical ARDS, but its occurrence and mortality are positively correlated, with there being no difference in the severity of hypoxemia and SOFA score among patients (71-73).

In sepsis-related ARDS, pathogens activate the innate immune response of epithelial cells and alveolar macrophages, which is followed by the migration and aggregation of neutrophils and monocytes and the inflammatory factors tumor necrosis factor-α (TNF-α) and IL-1β. The release of IL-6 disrupts the integrity of the alveolar capillary barrier, increasing permeability and leading to sepsis-related ARDS (74).

Inflammatory imbalance caused by sepsis

Inflammatory imbalance is the basis for the pathogenesis of sepsis and pervades the entirety of the sepsis process. Pathogens that cause inflammatory reactions include bacteria, fungi, parasites, and viruses. The initial acute

response of the host to invading pathogens usually leads to macrophages engulfing the pathogen and producing a series of proinflammatory cytokines, triggering a cytokine storm and activating the innate immune system (75). The activation of the innate immune system is mediated by pattern recognition receptors (PRRs), which initiate a series of immune cell activations by detecting damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), thereby upregulating the expression of inflammation-related genes (76). In the immune response to sepsis, exogenous factors from pathogens (such as LPS) and endogenous factors released by damaged cells [such as high mobility group box-1 protein (HMGB-1)] can interact with various PRRs, such as toll-like receptors (TLRs), C-type lectin receptors (CLRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs). Among these receptors, TLRs have been the most extensively studied (76,77). TLRs induce interactions with their ligands through the TIR domain, activate related signaling pathways, stimulate inflammatory cytokines (IL-1, IL-6, TNF-α), and generate AP-1, among other effects (78). In addition, some NLRs are involved in the formation of protein complexes in inflammasomes, which cleave caspase-1 precursors into active caspase-1. Activated caspase-1 interacts with IL-1β and IL-18 precursor, releasing cytokines IL-1β and IL-18 (78). Dectins, as part of the CLR family, induce the production of reactive oxygen species (ROS) and activate inflammatory responses through Src and Syk kinases.

Both exogenous PAMPs and endogenous DAMPs can activate PRRs. Related studies have shown that in the case of endogenous sepsis, liver cells release a large amount of HMGB-1, which binds with bacterial endotoxins (LPS). LPS is then transported to the cytoplasm through RAGE receptors expressed on endothelial cells and macrophages, leading to caspase-11-mediated cell pyroptosis, shock, multiple organ failure, and death (79,80).

Congenital immune response of the lungs in sepsis-related ARDS

The lungs are not only important organs for gas exchange but are also the primary immune organs that protect the host from diseases caused by the inhalation of pathogens, allergens, and foreign objects during the respiratory process. Pulmonary epithelial cells, intrinsic lymphocytes, alveolar macrophages, and other lung immune cells are essential for maintaining a stable state in the lungs (26). Neutrophil infiltration is crucial in this process, and the recruitment of neutrophils in the lungs depends on the expression of E-selectin (CD62E, ELAM-1, or ELAM-2). In sepsis-induced lung injury, E-selectin is not expressed on unstimulated endothelial cells, but under the influence of pro-inflammatory cytokines, its expression on pulmonary vascular endothelial (VE) cells increases and induces neutrophil infiltration.

Pulmonary epithelial cells

The production of proinflammatory factors and sustained hypoxia disrupt the pulmonary epithelial barrier during sepsis-induced ARDS (81,82). This damage to lung epithelial cells alters their barrier function, leading to fluid and protein infiltration into the alveolar cavity. Studies have shown that damage to type I and type II alveolar epithelial cells can be evaluated by biomarkers in plasma and alveolar lavage fluid (81,83). The damage and increased permeability of pulmonary epithelial cells in sepsis are related to changes in actin tissue (84). Research has shown that in sepsis-related ARDS, lung epithelial cells exhibit integrin α, integrin V, and integrin β. The increase of these three integrins can increase the permeability of endothelial cells, leading to ARDS (85,86). The expression of C3a receptor and C5a receptor in bronchial epithelial cells increases during sepsis (87). During sepsis, C5a levels in the lungs also increase, leading to severe ARDS via the binding of the C3a and C5a receptors, resulting in increased infiltration of neutrophils into the lungs and cytokine storms (88,89). Neutrophils infiltrating the lungs during sepsis-associated ARDS have a unique phenotype and antiapoptotic ability. Studies have shown that neutrophil apoptosis is reduced in the lungs of patients with sepsis-associated ARDS (90,91). Another study found that during sepsis-associated ALI, CDK inhibitors called AT7519 can enhance apoptosis of infiltrating neutrophils and act as mediators for initiating inflammation resolution (92). Therefore, during sepsis-related ARDS, the mechanisms that cause ARDS and the resolution of inflammation occur simultaneously. However, the inflammatory imbalance process that leads to ARDS is stronger than is the inflammatory resolution process, causing irreversible damage in the process of Gram-negative bacteria-induced sepsis, which manifests as the aggregation of antiapoptotic neutrophils in lung tissue and the elevation of pro-inflammatory cytokine level in alveolar lavage fluid (29). In the later stage of ARDS caused by sepsis, due to mitochondrial ROS and HIF-1α, the transformation of epithelial cells into fibroblasts can be observed.

Alveolar macrophages

The proinflammatory mediators released by alveolar

macrophages play a crucial role in sepsis-related ARDS by inducing neutrophil infiltration into the alveoli (26). The establishment of interstitial vascular permeability gradient promotes the migration of neutrophils within alveoli and blood vessels. During sepsis, alveolar macrophages are activated, and neutrophils infiltrate into the alveoli through pulmonary endothelial cells. The activation of NADPH oxidase in pulmonary endothelial cells produces superoxide anions in response to alveolar macrophage activation, which plays a crucial role in the migration of neutrophils across endothelial cells during sepsis-associated ALI. In addition, these infiltrating neutrophils block the microcirculation of the lungs due to their long-term retention in capillaries, leading to the formation of dead spaces, which further exacerbates sepsis-related ARDS (93). The release of IL-10 during sepsis impairs the phagocytic function of alveolar macrophages, further increasing the incidence and severity of sepsis-related ARDS. IL-1β can reduce cyclic adenosine monophosphate (cAMP) and transcription factor cAMP responsive element binding (CREB) in pulmonary endothelial cells, which can block the transcription of VE cadherin, leading to damage to pulmonary VE cells and exacerbating pulmonary vascular leakage and sepsis-related ARDS (94). The activation of SIRT1 during sepsis can prevent sepsis-related ARDS through NLRP3 inflammasomes in alveolar macrophages and pulmonary VE cells, thereby preventing the release of proinflammatory mediators (ICAM-1 and HMG-B1) and preventing damage to the tight and adhesive junctions caused by decreased lung claudin-1 and VE cadherin levels (95,96).

Intrinsic lymphocytes

Type 2 intrinsic lymphocytes are the most common lymphocytes in mouse and human lungs (accounting for 30% of all intrinsic lymphocytes) (97,98). Research has shown that the increased activation of type 2 intrinsic lymphocytes in sepsis induced by cecum ligation and puncture (CLP) may be one of the causes of sepsis-related ARDS (99). Another study suggests that type 2 intrinsic lymphocytes protect against sepsis-related ARDS by inhibiting the release of IL-33 and damage to endothelial cells. IL-33 mediates the expansion of type 2 intrinsic lymphocytes by binding to ST2 receptors (100). The IL-9 produced by type 2 intrinsic lymphocytes can prevent caspase-1 activation and pulmonary endothelial cell death, reducing the severity of sepsis-related ARDS (100). Research also indicates that before sepsis caused by lethal *Staphylococcus aureus* (*S. aureus*) occurs, type 2 innate lymphocytes can be preactivated by intratracheal injection of IL-33, inducing an increase in lung eosinophils to protect the host from the effects of ARDS and prevent death (101). Therefore, type 2 intrinsic lymphocytes can be beneficial or deleterious in sepsis-associated ALI-related mortality depending on their activation stage.

Endothelial cell damage in sepsis-related ARDS

A healthy pulmonary vascular system can prevent pulmonary edema caused by increased hydrostatic pressure, including low permeability of the alveolar epithelium, a protein permeability gradient between blood vessels and interstitium, a hydrostatic pressure gradient from surrounding vessels to central blood vessels, lymphatic vessel flow, and pleural and mediastinal subsidence when hydrostatic pressure is too high, allowing for the fluid filtered from the pulmonary microvessels to the interstitium to be largely reabsorbed into the circulation. However, when the VE barrier has high permeability to proteins and other solutes, the protein permeation gradient between blood vessels and stroma disappears, and the stroma is easily submerged. Healthy pulmonary endothelial cells largely inhibit inflammation and coagulation, while activated endothelial cells do the opposite. Various stimuli, such as hypoxia, cytokines, chemokines, thrombin, LPS, and DAMPs, can shift endothelial cells into a dysregulated and leaking state, thereby attracting inflammatory cells (102,103). The interruption of connections between adjacent endothelial cells and changes in the cytoskeleton lead to the separation of cells and allows for the formation of endothelial gaps. Due to the activation of endothelial cells, typical deposits of platelets and neutrophils occur, usually neutrophil platelet aggregates. Research has shown that cell apoptosis can also lead to vascular barrier dysfunction (104-106).

Treatment

Sepsis remains a major medical problem, affecting millions of people worldwide every year and causing one sixth to one third of patients to die (107-109). Therefore, for the treatment of sepsis-related ARDS, it is necessary to actively respond to lung injury and implement a series of treatment and protection measures while not ignoring the relevant treatment of needle sepsis.

Early and effective antibacterial treatment

The early administration of appropriate antibiotics is one of the most effective interventions for reducing the mortality

rate of patients with sepsis (110-112). In a retrospective study of 2,700 Canadian patients with septic shock over a 15-year period, it was found that only 50% of patients received effective antibiotic treatment within 6 hours after the onset of hypotension (113). When septic shock occurs, for every hour of delayed administration, the survival rate decreases by 12% (113). In another study of patients receiving treatment in New York hospitals, for every additional hour from the emergency room to reaching antibiotic use, the in-hospital mortality rate increased by 1.04% (112). In addition to this, two studies found that for every additional hour of antibiotic administration, the hospital mortality rate increases accordingly (114,115). However, in other studies, a correlation between antibiotic timing and mortality was supported (116-121). It should be pointed out that all studies in the above were observational analyses, and there is a risk of bias due to factors such as insufficient sample size, insufficient risk adjustment, and variability in the duration of antibiotic extension (122). Limited data from resource-limited context suggest that timely administration of antibiotics is beneficial and potentially feasible in patients with sepsis and septic shock (123-128). However, the necessity of the early use of antibiotics must be balanced with the potential harm associated with providing unnecessary antibiotics to uninfected patients (129,130). These adverse reactions include allergies, kidney damage, thrombocytopenia, *Clostridium difficile* (*C. difficile*) infection, and antibiotic resistance (131-136). According to the latest guidelines of SSC, antibiotics should be administered within 1 hour when there is a clear presence of sepsis or septic shock caused by infection, and pathogen testing should be conducted before antibiotics are administered; if there is only suspicion of sepsis but no shock, the presence of infectious or noninfectious diseases should be determined; if persistent infection is a possibility, antibiotics should be administered within 3 hours after this assessment (18).

For the selection of antibiotics, according to the 2021 guidelines, the following is recommended for patients with high-risk sepsis and septic shock with methicillin-resistant *S. aureus* (MRSA), initial antibiotics should be applied for MRSA; however, if there is no MRSA risk for the patient, antibiotics should not be administered (18). In regard to MRSA infection, a study has shown that an antibiotic delay >24–48 hours is associated with increased mortality, while other studies have reported contrasting findings (137). Still other research suggests that the use of drugs to treat MRSA in patients with sepsis is associated with higher mortality rates, especially in patients without MRSA (138-141). For high-risk patients with multidrug-resistant (MDR) bacteria, the use of empirical treatment with two drugs that can be applied for Gram-negative bacteria is recommended to increase the likelihood of sufficient coverage; in patients with lower MDR risk, the use of a single drug for empirical treatment is recommended, as using two drugs does not have significant benefits and heightens the risk of antibiotic-related adverse reactions, including direct toxicity, *C. difficile* infection, and the development of drug resistance (142). Only when there is suspicion of a high risk of fungal infection should broad-spectrum antifungal treatment should be initially administered (18). Fungal-induced sepsis and septic shock are the most common condition in the ICU and are associated with poor prognosis (143-147). Some observational studies suggest that timely initiation of appropriate empirical antifungal therapy may be associated with reduced mortality (147,148). It is not recommended that patients undergo antiviral treatment, and specific treatment should be informed by the relevant guidelines (18). Except for certain clinical situations such as pandemics, viral infections are rarely the cause of sepsis. A recent study showed that viruses are recorded in less than 4% of infections (149), but the expected effects of empirical antiviral therapy are still unclear (142).

Recovery

Sepsis inflammation leads to endothelial dysfunction, resulting in the loss of venous motor tension and barrier function, accompanied by a decrease in systemic vascular resistance, which results in a relatively low blood volume state that clinically manifests as hypotension (50). Therefore, timely and effective fluid resuscitation is crucial for the stabilizing tissue hypoperfusion caused by sepsis and septic shock (150-152). The 2021 SSC guidelines recommend the administration of at least 30 mL/kg of crystal infusion within 3 hours of initial liquid resuscitation (18). A retrospective analysis of adult patients with sepsis or septic shock who visited the emergency department showed that failure to receive 30 mL/kg of crystalline fluid resuscitation within 3 hours of sepsis onset was associated with greater in-hospital mortality, delayed remission of hypotension, and prolonged ICU hospitalization, but not with the complications of ARDS (153). Most patients require continued infusion after initial resuscitation, which indicates that this medication needs to be balanced with the risk of fluid accumulation (especially in patients with ARDS that requires long-term mechanical ventilation). Therefore, after the initial liquid

resuscitation, a dynamic evaluation of liquid reactivity should be performed to determine whether additional liquid or vasoactive drugs are needed (18).

Selection of resuscitation fluid

Early rapid large capacity expansion, also known as the concept of "sufficient expansion", combined with vasoactive drugs on the basis of sufficient expansion. Liquid therapy is a crucial link in the recovery of sepsis and septic shock. Although, theoretically, albumin is more likely to maintain filling pressure than are crystals (154), its cost is higher and its conventional use does not have significant benefits. A randomized controlled trial comparing albumin and crystal solution was conducted on 12,492 patients, and the results showed no difference in 30- or 90-day mortality rates between the two groups of patients (155). Another meta-analysis also reported that compared to the albumin group, the crystal group had lower static filling pressure and mean arterial pressure, but there was no difference in mortality at 28 or 90 days (156). This also supports the recommendation in the 2021 SSC guidelines to use crystalline solutions in the resuscitation of patients with sepsis and septic shock (18). In the selection of crystal solutions, physiological saline has been used (157), but its potential side effects include high chloride metabolic acidosis, renal vasoconstriction, increased cytokine secretion, etc., which has led to an increasing interest in balanced salt solubility. In subsequent studies, it was shown that compared to physiological saline, balanced salt solution is associated with reduced mortality (158-160). In addition, the use of albumin in patients undergoing extensive crystal therapy is recommended when appropriate, as the use of albumin can lead to higher blood pressure, higher static filling pressure, and lower fluid balance in the early and late stages (154,156). Artificial colloidal hydroxyethyl starch has been shown to lead to a higher risk of death and is thus not recommended (161,162). After the first rapid fluid replacement, it is necessary to evaluate fluid reactivity because expansion does not equate to an increase in cardiac output. Therefore, fluid reactivity needs to be evaluated after the initial resuscitation is completed or when fluid loss is not significant.

Selection of vasoactive drugs

In patients in a state of shock, in addition to active fluid resuscitation, vasopressors are also typically necessary. There has been extensive research on traditional drugs such as norepinephrine, epinephrine, vasopressin, and dopamine, as well as newer drugs such as angiotensin II and levosimendan. Among these, norepinephrine is considered as a first-line drug for septic shock (18). According to many clinical trials, norepinephrine has better efficacy and fewer adverse events compared to other vasoactive drugs (163). In a randomized controlled trial, there was no significant difference in 28-day mortality between the vasopressin group and the norepinephrine group, but the use of vasopressin reduces the risks involved with renal replacement therapy (164). A study on combination therapy showed that there was no difference in 28-day mortality between a norepinephrine group and a norepinephrine-plus-vasopressin group, while in a subgroup analysis, it was found that adding vasopressin for patients with milder shock receiving norepinephrine at less than <15 μg/min increased survival (165). In a systematic review of ten randomized controlled trials, it was found that vasopressin combined with norepinephrine reduced mortality compared to the use of norepinephrine alone (18). However, the threshold for adding vasopressin varies across different studies and remains undefined. However, initiating use of vasopressin when the dose of norepinephrine is between 0.25 and 0.5 μg/kg/min has been recommended (164).

Mechanical ventilation

Ventilator parameters

For adults with sepsis-related ARDS, a low-tidal-volume (6 mL/kg) mechanical ventilation strategy is commonly used (18). Some meta-analyses have shown that patients with ARDS who use pressure and volume limiting strategies have a lower mortality rate (164). For those with ARDS, it has also been reported that compared to a tidal volume of 12 mL/kg, a tidal volume of 6 mL/kg is associated with a 9% decrease in mortality rate (166). However, the tidal volume for individual patients needs to be adjusted based on factors such as platform pressure, PEEP, chest and abdominal compliance, and the patient's respiratory work. Some clinicians believe that as long as the platform pressure can be maintained at ≤30 cmH_2O and the tidal volume at >6 mL/kg, it is also safe (167). A retrospective study found that even in the presence of platform pressure ≤30 cmH_2O, tidal volume should be reduced, as lower platform pressure is associated with reduced in-hospital mortality (167). A recent analysis suggests that tidal volume leading to a driving pressure (platform pressure minus set PEEP) below 12–15 cmH_2O may be beneficial for patients who do not engage in spontaneous breathing (168). A systematic evaluation involving five randomized controlled trials found a relationship between platform pressure and mortality (169). The LUNG SAFE study reported a correlation between platform pressure and mortality rate, but when the platform pressure was below

20 cmH_2O, the relationship between the two was not significant (170). A secondary analysis of five observational studies found that the risk of death increases with an increase in platform pressure above 29 cmH_2O (171). Therefore, in patients with ARDS, a tidal volume greater than 6 mL/kg and a plateau pressure greater than 30 cmH_2O should be avoided. If the tidal volume drops to 6 mL/kg and the platform pressure is still greater than 30 cmH_2O, the tidal volume can be further reduced to 4 mL/kg. Due to the serious patient ventilator asynchrony and patient discomfort caused by a very low tidal volume, the respiratory rate should be increased up to 35 times/min during the period of tidal volume reduction (18).

For patients with moderate-to-severe ARDS, a high PEEP should be adopted (18). The application of a higher PEEP in those with ARDS can open up lung units to participate in gas exchange and increase PaO_2 (18). A patient level meta-analysis reported that among all patients with ARDS examined, higher PEEP was not beneficial; however, using higher a PEEP in those with moderate-to-severe ARDS (PaO_2/FiO_2 ≤200 mmHg) can reduce mortality but not in those with mild ARDS (172). Another study suggested that patients with ARDS with increased PEEP and improved oxygenation have a lower risk of death and that this correlation is stronger in patients with more severe ARDS (PaO_2/FiO_2 <150 mmHg) as compared to those with less severe ARDS (173-175). However, the optimal method for applying higher-level PEEP is currently unclear. One option is to increase PEEP based on bedside measurements of chest lung compliance, with the aim of achieving the best compliance and achieving a good balance between lung recruitment and excessive expansion; the second method is to increase the PEEP when the patient receives a tidal volume of 6 mL/kg until the platform pressure reaches 28 cmH_2O (174); the third method involves using the FiO_2 PEEP table to adjust PEEP; however, a PEEP >5 cmH_2O is typically required to avoid lung collapse (176).

Pulmonary atelectasis

Temporarily increasing transpulmonary pressure can help open atelectasis alveoli to facilitate gas exchange, but it may also lead to excessive expansion of lung units, resulting in ventilator-induced lung injury and transient hypotension. A study and analysis were conducted on the traditional lung recruitment strategy using continuous positive airway pressure (such as 30–40 cmH_2O for 30–40 seconds) followed by a decrease in PEEP based on optimal respiratory static compliance or blood oxygen saturation, as well as the lung recruitment method using PEEP incremental method. The results showed that the lung recruitment method using incremental PEEP method can increase the 28-day mortality rate, while the traditional recruitment strategy can improve the 28-day mortality rate. This demonstrates that the incremental PEEP method is highly unsuitable for lung recruitment (177,178). Although the effect of lung recruitment can initially improve oxygenation, the effect may be temporary (179). Although some patients with severe hypoxemia can benefit from it, there is almost no evidence to support routine use in all patients with ARDS. Therefore, the 2021 SSC guidelines recommend lung recruitment only for patients with moderate-to-severe ARDS (18,179). During the process of lung recruitment, the patient's condition should be closely monitored, and if the condition worsens, it should be stopped immediately (18).

Prone position ventilation

A meta-analysis was published in 2017, which was an update of a meta-analysis conducted in 2010. This repeated meta-analysis confirmed previous research findings indicating that in patients with ARDS and $PaO_2/PaCO_2$ ratio <200, ventilation in a prone position for more than 12 hours per day yielded better survival rates (180-182). Another meta-analysis including this study showed that compared to ventilation in the supine position, ventilation in the prone position provides a lower mortality rate in patients with severe ARDS, as indicated by improvement in oxygenation function measured by changes in the PaO_2/FiO_2 ratio (181,183). Most patients respond to treatment in the prone position with improved oxygenation and may also demonstrate improved lung compliance. Although the prone position may be associated with potential life-threatening complications, including tracheal intubation detachment, this was not found to be significant in the co-analysis. However, prone position ventilation is associated with an increase in pressure ulcers, and it is important to note that some patients may have contraindications to it.

The application of neuromuscular blocking agents (NMBAs)

The most common indication for using NMBAs in the ICU is to promote mechanical ventilation, which can improve chest wall compliance, prevent patient ventilator asynchrony, and reduce peak airway pressure. In addition, the use of NMBA can reduce oxygen consumption by reducing respiratory work. Compared with mild sedation strategies, continuous infusion of NMBA does not increase mortality rate. On the contrary, it can reduce mortality rate and lower the risk of barotrauma. However, the impact on ventilator-free days and mechanical ventilation duration is still unclear (36,184-187), and the benefits and potential

Table 2 The main key point summary

Key points	Details
Epidemiology	Research has shown that the mortality rate of ARDS caused by sepsis is higher than that caused by other factors
Risk factors	identifying the risk factors for ARDS is a key therapeutic goal in improving the prognosis of those with ARDS. Smoking not only increases the risk of invasive pneumococcal pneumonia but also increases the incidence of septic shock and 30-day mortality
Early screening and diagnosis of sepsis	PCT, CRP, vital signs, infection signs, qSOFA or SOFA standards, the NEWS and the MEWS contribute to prognosis and treatment
Pathology and physiology	The release of IL-6 disrupts the integrity of the alveolar capillary barrier, increasing permeability and leading to sepsis-related ARDS
Inflammatory imbalance caused by sepsis	in the case of endogenous sepsis, liver cells release a large amount of HMGB-1, which binds with bacterial endotoxins
Recovery	Most patients require continued infusion after initial resuscitation, which indicates that this medication needs to be balanced with the risk of fluid accumulation (especially in patients with ARDS that requires long-term mechanical ventilation). Therefore, after the initial liquid resuscitation, a dynamic evaluation of liquid reactivity should be performed to determine whether additional liquid or vasoactive drugs are needed
Selection of resuscitation fluid	After the first rapid fluid replacement, it is necessary to evaluate fluid reactivity because expansion does not equate to an increase in cardiac output. Therefore, fluid reactivity needs to be evaluated after the initial resuscitation is completed or when fluid loss is not significant
ECMO	The evidence for the use of VV ECMO in sepsis-induced ARDS is limited. VV ECMO provided by expert centers reduced the mortality rate of patients with severe ARDS

ARDS, acute respiratory distress syndrome; PCT, procalcitonin; CRP, C-reactive protein; SOFA, sequential organ failure assessment; qSOFA, positive quick SOFA; NEWS, National Early Warning Score; MEWS, Modified Early Warning Score; IL-6, interleukin 6; HMGB-1, high mobility group box-1 protein; ECMO, extracorporeal membrane oxygenation; VV, venovenous.

hazards of NMBA application are still uncertain (18).

Oxygenation target

Patients receiving mechanical ventilation in the ICU usually inhale higher concentrations of oxygen and have a higher arterial oxygen partial pressure. Conservative use of oxygen can reduce oxygen exposure and alleviate lung and systemic oxidative damage. There is limited evidence regarding the use of conservative oxygenation targets (PaO_2: 55–70 mmHg; SPO_2: 88–92%) in patients with sepsis-related ARDS (188-190). One study reported that the mortality rate of patients receiving conservative oxygen therapy in the ICU was significantly lower than that of patients receiving conventional oxygen therapy (187). In recent systematic reviews and meta-analyses of various clinical syndromes, it has been found that conservative oxygen therapy is associated with lower mortality rates in adults with acute diseases compared to free oxygen therapy (191). However, there is a report showing that there is no difference in the 28-day survival rate regardless of whether patients with ARDS are treated with conservative oxygen therapy (192).

Extracorporeal membrane oxygenation (ECMO)

Venovenous (VV) ECMO is used in patients with severe acute respiratory failure to promote gas exchange in environments with refractory hypoxemia or hypercapnic respiratory acidosis (193). However, the evidence for the use of VV ECMO in sepsis-induced ARDS is limited, with only two randomized controlled trials in the past 10 years evaluating the potential efficacy of VV ECMO in treating severe ARDS (194,195). A recent systematic review found that VV ECMO provided by expert centers reduced the mortality rate of patients with severe ARDS (193).

Conclusions

After in-depth exploration of the risk factors, early identification and diagnosis, pathophysiology, and treatment of sepsis-related ARDS, we have achieved a certain degree of understanding in its pathophysiology. However, sepsis remains a common and difficult-to-cure critical illness. In response to the high mortality rate of sepsis-related ARDS, some progress has been made, such as rapid identification of sepsis and effective antibiotic treatment, early fluid resuscitation, lung-protective ventilation, etc. (*Table 2*). However, further research is needed regarding the long-term effects of related aspects such as lung recruitment, prone

ventilation, and the application of NMBAs and ECMO.

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Footnote

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