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REVIEW ARTICLE

Acute respiratory distress syndrome in acute pancreatitis

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Abstract

Development of organ failure is one of the major determinants of mortality in patients with acute pancreatitis (AP). Acute respiratory distress syndrome (ARDS) is an important cause of respiratory failure in AP and is associated with high mortality. Pathogenesis of ARDS in AP is incompletely understood. Release of various cytokines plays an important role in development of ARDS in AP. Increased gut permeability due to various toxins, inflammatory mediators, and pancreatic enzymes potentiates lung injury by gut-lymph-lung axis leading on to increased translocation of bacterial endotoxins. Various scoring systems, serum levels of various cytokines and lung ultrasound have been evaluated for prediction of development of ARDS in AP with varying results. Various drugs have shown encouraging results in prevention of ARDS in animal models but these encouraging results in animal models are yet to be confirmed in clinical studies. There is no specific effective treatment for ARDS. Treatment of sepsis and local complications of AP should be done according to the standard management strategies. Lung protective ventilatory strategies are of paramount importance to improve outcome of patients of AP with ARDS and therefore effective coordination between gastroenterologists and intensivists is needed for effective management of these patients.

Keywords Acute lung injury · Acute pancreatitis · Fluid collection · Mechanical ventilation · Pancreatic necrosis

Introduction

Acute pancreatitis (AP) is an inflammatory disease of pancreas that triggers release of various pro-inflammatory mediators like zymogens, cytokines, and various vasoactive substances causing systemic inflammation, endothelial dysfunction, increased vascular permeability, and development of organ failures. Though most patients develop mild episode of AP (80%), 10% to 20% develop moderately severe or severe AP with various life-threatening local and systemic complications [1]. Development of organ failure is one of the major determinants of mortality in patients with AP [2]. Incidence of AP is increasing worldwide without major change in mortality rates [3, 4]. In recent years, there has been a phenomenal increase in various minimally invasive endoscopic and laparoscopic techniques for management of various local complications due to AP that have led on to improved outcomes of patients with these local complications [5]. Though organ failure remains a major cause for mortality in patients with AP, management strategies of various organ failure have not witnessed any paradigm change over last years.

Acute respiratory distress syndrome (ARDS) is a life-threatening form of respiratory failure due to inflammatory pulmonary edema causing hypoxia [6]. Berlin definition of ARDS is the most accepted definition which has defined specific time frame from clinical insult to development of new onset respiratory symptoms, specific chest X-ray findings, and severity of ARDS according to Pao_2:Fio_2 ratio [7] (Table 1). ARDS is not a primary disease per say, but it is the end result of various direct and indirect respiratory insults. Pneumonia, inhalation injury, and aspiration remains the major direct causes while sepsis, major burn injury, and pancreatitis are major indirect causes of ARDS [6]. Despite development in prevention and management strategies of various diseases, incidence and mortality of ARDS remained the same over a period of time, which is a major challenge of current times. Absence of effective predictive and preventive strategies remains a major hurdle in improving outcomes in patients with ARDS [8, 9].

In this review, we will discuss the epidemiology of ARDS, its pathophysiology, strategies for its prediction, prevention, and management in patients with AP.

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Table 1 Definition of acute respiratory distress syndrome as proposed in Berlin's criteria [7]

Characteristic	Criteria used
Timing	Occuring within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities that are not fully explained by effusion, lobar/lung collapse or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload
Oxygenation	
Mild	200 mmHg < PaO_2/Fio_2 ≤ 300 mmHg with PEEP or CPAP ≥5 cm H_2O
Moderate	100 mmHg < PaO_2/Fio_2 ≤ 200 mmHg with PEEP ≥5 cm H_2O
Severe	PaO_2/Fio_2 ≤ 100 mmHg with PEEP ≥5 cm H_2O

Acute respiratory distress syndrome in AP

Modified Atlanta Classification has divided AP into mild, moderately severe, and severe categories based on the presence and persistence of organ failure, local, and systemic complications. Cardiovascular, renal, and respiratory failures are the important factors for stratifying severity of AP [1]. Modified Marshall scoring system is used to define and judge the severity of organ failure in AP [1, 10]. Definition of respiratory failure according to modified Marshall scoring requires Po_2:Fio_2 ratio less than 300 (score ≥ 2); they have defined severity score 2, 3, and 4 as Po_2:Fio_2 ratio between 201–300, 101–200, and ≤ 100, respectively. Though Modified Marshall scoring has defined criteria for respiratory failure, whether the failure is due to some treatable causes like pleural effusion, atelectasis, pulmonary edema, or ARDS is not specified. Similarly, though the severity of respiratory failure according to this criterion is similar to Berlin definition of ARDS, other Berlin's criteria are not clarified. According to Berlin definition, onset and worsening of respiratory symptoms should be within 7 days of clinical insult [7]. However, in AP with late-onset organ failure due to local complications, this criterion might not hold true. Though ARDS is one of the most common causes of respiratory failure in AP and is associated with high mortality, Berlin definition has not been validated specifically in AP [11]. So, ideal definition of ARDS in AP requires modification in both the modified Marshall Score and in Berlin definition. It requires large multicenter prospective trials for evolution of better definition and understanding of ARDS in AP. Moreover, future trials should have uniform reporting pattern whether respiratory failure is due to ARDS or due to other causes.

Several studies have shown that respiratory failure is the most common organ failure in AP. Schepers et al. reported that 240 of 639 patients with AP developed organ failure. Respiratory failure was the most common type of organ failure (92%) in that study with a 37% mortality. It was the most common type of organ failure in both early and late phase of AP. Moreover, it was first to appear and persist for longest duration in patients with multiple organ failure. In that study, respiratory failure lasted for a median of 19 days compared to 10 days for renal and 7 days for cardiovascular failure [2]. Similarly, a study by Johnson and Abu-Hilal showed that respiratory failure was the most common type of organ failure in patients with AP. In that study, 13.8% patients died and respiratory failure was present in 87% of them, either as single organ failure or associated with multiple other organs [12]. Karakattu et al. did retrospective analysis of 813,120 hospitalized patients with AP, out of whom 21,415 (2.63%) had acute respiratory failure with a mortality of 17%. In their study, age > 80 years, presence of septic shock, acute kidney injury, disseminated intravascular coagulation, and need for mechanical ventilation or vasopressors were independent predictor of mortality [13].

Pathogenesis

Pathogenesis of AP-induced ARDS is incompletely understood (Fig. 1). However, autopsy studies have shown that pathogenesis of AP-induced ARDS is not different from ARDS due to other causes [14]. Pancreatic injury in AP causes release of variety of cytokines and inflammatory mediators which are responsible for development of systemic inflammatory response syndrome and finally results in a variety of organ failures. Lung damage in ARDS occurs in three phases: an exudative phase (phase I) with diffuse alveolar damage, microvascular injury, damage to type I pneumocyte, increased permeability of pulmonary vasculature, and lung edema; proliferative phase (phase II) where type II pneumocyte hyperplasia and lung repair occurs, which ensues about 7–14 days after injury; and fibrotic phase (phase III) in which there is resolution of acute inflammatory cells and development of fibrosis [15].

Consequent to pancreatic injury, trypsin gets released and it causes damage to pulmonary vasculatures directly and increases their permeability. More importantly, trypsin causes activation of other mediators like phospholipase A2 and various complement factors, which also play important role in development of ARDS [11, 16]. Pulmonary surfactant is one of the major substrates for phospholipase A2. Studies have shown correlation between serum level of phospholipase A2

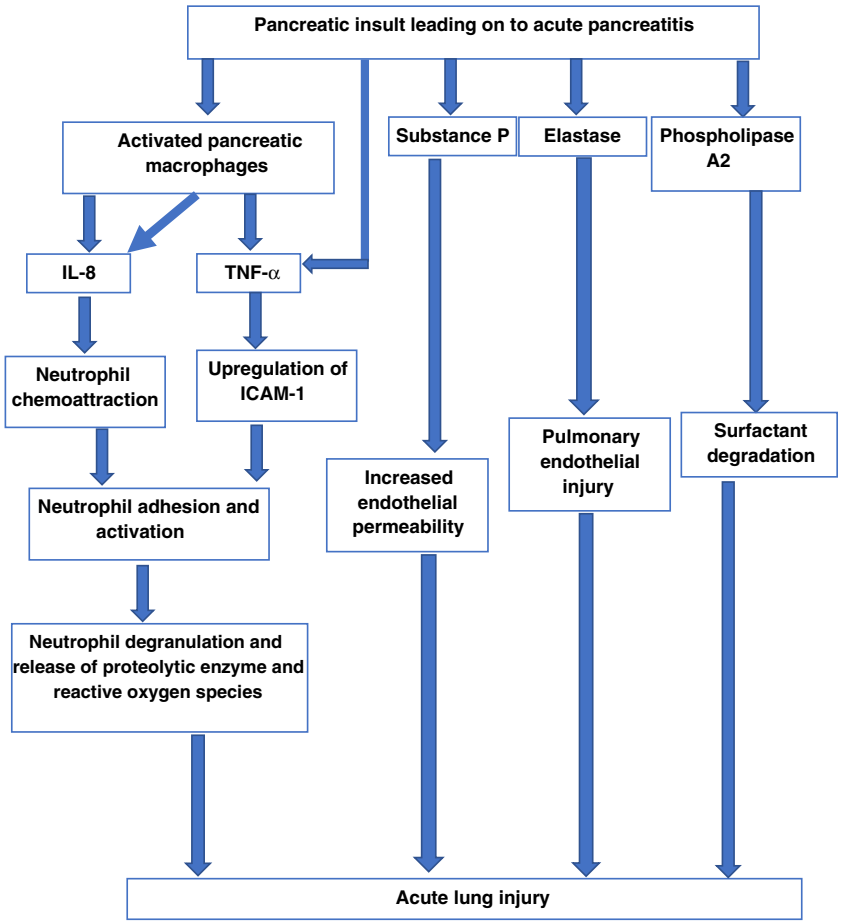

Fig. 1 Pathogenic mechanisms of lung injury in acute pancreatitis. *ICAM-1* intercellular adhesion molecule-1, *IL* interleukin, *TNF* tumor necrosis factor

and extent of lung injury. Moreover, serum levels of phospholipase A2 of pancreatic and extra-pancreatic origin have been found to be correlated with lung injury score [17–19]. Platelet activating factor (PAF) is a potent biological mediator, which stimulates white cells and facilitates their migration into tissue spaces. In experimental pancreatitis, PAF was found to be elevated in pancreas, ascitic fluid, and lung [20]. Lexipafant, a powerful PAF inhibitor, has also shown some beneficial effect in patients with pancreatitis without survival benefit [21, 22]. Tumor necrosis factor-α (TNF-α) is also an important mediator of inflammation in early stage of AP. It causes recruitment of inflammatory cells, their activation, and increase in lung damage [23]. Moreover, it favors acinar cell necrosis over apoptosis, which itself is associated with increase in inflammation [24]. A variety of chemokines like IL-8 is also elevated in AP. IL-8 is a strong attractant of neutrophils and studies have shown that bronchoalveolar lavage (BAL) IL-8 levels are higher in patients with AP and ARDS compared to those without ARDS [25, 26]. Moreover, IL-8 and anti-IL-8 antibody complex levels in BAL have been also been found to correlate with development of ARDS in patients with AP [27]. Other pro-inflammatory cytokines like IL-1β and IL 6 are also found to be elevated in patients with AP. These cytokines are important activators of macrophages, enhances B and T cell activation, and potentiates inflammation [28, 29]. Macrophage migration inhibitory factor (MIF) is derived mainly from T lymphocytes and inhibits random migration of macrophages. It is also a potent pro-inflammatory cytokine. Its levels in lungs have been found to be elevated in experimental severe pancreatitis and anti-MIF antibodies were found to significantly improve the survival in animal models [30]. Contrary to these cytokines, IL-10 is an anti-inflammatory cytokine, which prevents production of pro-inflammatory mediators like TNF-α, IL-6, and IL-1β from macrophages and T cells [31, 32]. In AP, studies have shown lower levels of IL-10 and administration of IL-10 have shown to decrease severity of AP in experimental animal models [32, 33]. Various adhesion molecules like E- or P-selectins, intracellular adhesion molecule (ICAM-1), and platelet endothelial adhesion molecule-1 (PECAM-1) have also been shown to be upregulated; these increase the risk of various organ failures including ARDS [34]. Neuropeptide substance-P is an inflammatory mediator found to be involved in pathogenesis of AP. Neurokinin receptor-1 (NK-1R) is a receptor for biological actions of substance-P. Blockade of NK-1R have been found to decrease the risk of

induced pancreatitis and associated lung injury in experimental animal models [35].

In recent years, gut-lymph-lung axis has been shown to play an important role in development ARDS in patients with AP [36]. Gut permeability has been found to be increased in patients with AP and various toxins, inflammatory mediators, and pancreatic enzymes have been shown to potentiate lung injury through the gut-lymph-lung axis. Studies have shown that in patients with AP, levels of cytokines and pancreatic enzymes in lymph correlate more closely to development of ARDS than plasma levels [37]. Moreover, blocking the abdominal lymphatic flow has been shown to attenuate AP-induced lung injury in rats [38]. Gram-negative infection causes release of various endotoxins, which can easily translocate due to increased gut permeability, and might potentiate development of ARDS [39]. Toll-like receptor 4 (TLR 4) initiates inflammatory signaling pathway after getting activated by these endotoxins [40]. Heparan sulphate is derived from extra-cellular matrix and is found to be elevated in AP. It is a potent activator of TLR-4 potentiating the inflammation and converting local inflammation into a systemic inflammatory state [41] (Table 2).

Differential diagnosis

As discussed earlier, respiratory failure in AP can be due to causes other than ARDS also. Hypoxemia without radiological abnormality, basal atelectasis, pulmonary edema, pleural effusion, pancreato-pleural fistula, or pulmonary embolism are amongst the important causes of respiratory failure in AP [42]. Careful history, clinical examination, and radiological imaging is necessary to diagnose these entities. As treatment of these diseases is completely different than ARDS and many of the conditions have an effective therapy, careful exclusion of these diseases should be done before diagnosis of ARDS is made.

Table 2 Cytokines and other inflammatory mediators suspected to play important role in pathogenesis of acute respiratory distress syndrome in acute pancreatitis

- Trypsin
- Phospholipase A2
- Platelet-activating factor
- IL-1β, IL-6, IL-8, IL-10, TNF-α
- Nitric oxide
- Macrophage migration inhibitory factor
- Free fatty acids
- Intracellular adhesion molecule (ICAM-1)
- E- or P-selectins
- Substance-P
- Gut-lymph-lung axis
- Toll like receptor 4
- Heparan sulphate
- Complement factors

IL interleukin, *TNF* tumor necrosis factor, *ICAM* intercellular adhesion molecule

Prediction of acute respiratory distress syndrome in AP

Prediction of ARDS still remains one of the most important challenges in at-risk, critically ill patients. Various scoring systems have been developed to predict the development of ARDS in such critically ill patients. Lung Injury Prediction Score (LIPS) is one of the most widely used scores for prediction of ARDS in at-risk patients. Gajic et al. evaluated 5584 at-risk patients and followed them prospectively to know the incidence and risk factors of ARDS. 6.8% of at-risk patients developed ARDS after a median of 2 days. The authors formed LIPS score comprising of predisposing condition, alcohol abuse, obesity, hypoalbuminemia, Fio_2 requirement, respiratory rate, diabetes mellitus, and acidosis. Score ≥ 4 had very high negative predictive value of 97% but limited positive predictive value of 18%. Score ≥ 4 had sensitivity, specificity, and area under curve (AUC) of 69%, 78%, and 0.8% respectively. In that study, however, only 5.8% of patients were having AP. Severity of AP was not provided, and only 3% patients of AP developed ARDS in that study. So, generalizability of results in patients with AP on a large scale remains doubtful [43]. The same score also got validated by subsequent studies showing similar sensitivity, specificity, and AUC [44, 45]. However, LIPS scoring system as described above had limited positive predictive value; so, subsequent studies have evaluated role of other markers like acute physiology and chronic health evaluation II (APACHE II) scoring system, IL-6, IL-8, angiopoietin 2, and sE-selectin, for their role of prediction of ARDS in critically ill patients. However, many of these studies were single-center study with small sample size; therefor, these did not become standard of care. Amongst these markers, angiopoietin 2 has shown promising results when it was added to LIPS. Studies have shown that addition of angiopoietin 2 to LIPS increased positive predictive value (PPV) form 18%, 45% to 60% with similar negative predictive value (NPV), sensitivity, and specificity [46, 47]. Similarly, Levitt et al. prospectively enrolled 100 patients with bilateral chest X-ray abnormality (not due to left atrial hypertension) and followed them for development of ARDS. Initial oxygen requirement > 2 L/min, air opacities beyond bases on chest X-ray, use of immunosuppressants, and presence of SIRS were predictor of development of ARDS [48]. In recent years, lung ultrasound has also shown its role in prediction of ARDS and treatment response in critically ill patients by estimation of extravascular lung volume (EVLW) [49–51].

Very few studies have evaluated risk factors for prediction of ARDS in patients with AP. Samanta et al. prospectively evaluated 107 patients with AP and role of various cytokines

levels (TNF α, IL-6, IL-8, IL-10, and IL-1β) in prediction of development of ALI. In their study, 51 patients developed ARDS and patients with ARDS had higher cytokine levels compared to patients without ARDS. Moreover, patients with persistent ARDS had increased TNF α, IL-6, IL-8, and IL-1β levels on day 3 compared to baseline suggesting the important role of cytokines in development of ARDS especially during early phase of AP. Authors concluded that presence of IL-6 ≥ 80 pg/mL or IL-8 ≥ 100 pg/mL along with SIRS on presentation had sensitivity and specificity of 73% and 95% for prediction of development of ARDS [52]. Skouras et al. have shown usefulness of lung ultrasound in prediction of ARDS in patients with AP. They prospectively enrolled 41 patients of AP and checked for presence of comet tail artifacts on lung ultrasound. In their study, more patients with ARDS had comet tail artifacts. They showed that ultrasonography of non-dependent area of the lung along with high CRP can predict ARDS development in patients with AP [53]. Similarly, Katageri et al. also evaluated the role of serial lung ultrasound in AP. They showed that patients with severe ARDS had higher number of B-lines compared to patients with moderate or mild ARDS. Moreover, increase in B-line score over 48 h was associated with increased need for intervention or increased risk of mortality [54]. These two studies show role of increased vascular permeability and EVLW in development of ARDS as shown by increased comet tail artifacts and B-lines. Recently, the role of artificial neural network (ANN) has also been explored for prediction of ARDS in patients with AP. ANN is a highly complex analytical technology which can analyze interactions amongst various disease-related risk factors more efficiently than routine statistical methods. Fei and colleagues recently explored the role of ANN in prediction and severity of AP-associated ARDS. ANN model was constructed on 152 randomly chosen severe AP patients and then validated on 32 patients. They selected 13 variables and formed ANN model with accuracy of 84.43%. Pancreatic necrosis rate, lactate dehydrogenase level, and oxyhemoglobin saturation were the most important independent variables in that ANN. ANN model also showed good accuracy (73.1%) in predicting severity of ARDS according to Berlin's definition [55]. Role of miroRNAs (miR) have been also explored recently for prediction of ARDS in AP. Initially, Shi et al. evaluated role of miR-127 for identification of ARDS in AP in rats as well as in patients with APs [56]. Lu et al. investigated 287 different miR in serum samples of 24 patients with severe AP. They found role of 12 circulating miR in prediction of lung injury in patients with AP [57]. These studies have explored various methods of prediction of ARDS in patients with AP. However, after prediction of ARDS in AP patients, whether change in treatment modality or intensification of treatment changes the final clinical outcome is not known. So, clinical usefulness of this prediction models in decreasing morbidity and mortality remains questionable in present time (Table 3). Multicenter large-scale studies exploring tailored treatment according to the severity of ARDS might give us better answer in future.

Can we prevent acute respiratory distress syndrome in AP?

Prevention of ARDS in critically ill and at-risk patients is a dream of intensivist that is yet to be achieved. Many drugs have been tried in critically ill patients as well as in patients with AP to prevent development of ARDS; however, none of them have yet achieved major success. As discussed in pathogenesis, various drugs have been explored to prevent or to reduce severity of ARDS in AP. However, all of these studies are on animal and human trials for prevention of ARDS in AP are limited. Initially, lexipafant (PAF antagonist) was shown to reduce the incidence of organ failure in phase II study [21]. However, double-blinded placebo control study did not show benefit of lexipafant in prevention of any type of organ failure [22]. Menadione (vitamin K3) has shown beneficial role in reducing severity of pancreatitis and associated ARDS by downregulating substance-P and H_2S signaling via NF-Kβ pathway in mice models [58]. Other molecules like surfactant protein D, lipoxin A4, methysulfonylmethane, scopoletin, IL-22, and emodin have been also found to be useful in alleviating AP-induced ARDS by reducing pulmonary edema, TNF-α production, IL-1β, IL-6, and MMP-9 expression in various animal studies [59–63]. However, these encouraging results in animal models are yet to be confirmed in clinical studies.

As roles of activated platelets have been postulated in endothelial injury and neutrophilic chemotaxis, aspirin has also been tried for prevention of development of ARDS. Initial retrospective studies have shown a beneficial role of prehospitalization aspirin in development of ARDS [64, 65]. However, recent multicentric prospective, double-blind study of aspirin on development of ARDS in at-risk patients presenting to emergency department has not shown benefit in either development of ARDS or ventilator free time or mortality [66]. Corticosteroids (anti-inflammatory) were thought to be effective for prevention of ARDS in at-risk patients. However, multicentric large trials have failed to show any benefit of steroids in prevention of ARDS [67–70]. Similarly, though initial retrospective study showed probable role of prehospital use of statin in prevention of ARDS, subsequent large multicentric trial has not shown any role of statin in development of ARDS [71–73]. Renin-angiotensin-aldosterone system (RAAS) has been shown to play an important role in pathogenesis of ARDS. Angiotensin-converting enzyme (ACE) activity has also been found to be increased in bronchoalveolar lavage fluid in patients with

Table 3 Studies explored role of various molecules for predicting acute respiratory distress syndrome in acute pancreatitis

Study	Study design	Module used	Comments
Samanta et al. [52]	107 patients of AP followed prospectively; 51 patients developed ARDS	Measured TNF α, IL-6, IL-8, IL-10, and IL-1β at baseline and at day 3	• On admission presence of SIRS plus IL-6 ≥ 80 pg/mL or IL-8 ≥ 100 pg/mL can predict development of ARDS with sensitivity and specificity of 73% and 95% • Shows important role of cytokines in early development of ARDS
Skouras et al. [53]	41 patients of AP prospectively followed	Used lung ultrasound to check comet tail artifacts	• Lung ultrasonography of non-dependent area of lung along with contemporaneous and maximum CRP can predict the ARDS development in patients with AP (AUC = 0.708)
Katageri et al. [54]	Enrolled 17 patients with severe acute pancreatitis and followed them prospectively	Evaluated role of serial lung ultrasound for severity of ARDS, need for intervention and mortality	• Patients with severe ARDS had higher number of B-lines • Patients requiring intervention or patients with mortality had increase in B-line score over 48 h
Fei et al. [55]	Derivations cohort of 152 patients of AP and validation cohort of 32 patients of AP	Evaluated role of artificial neural network (ANN)	• ANN formed with 13 variables with an accuracy of 84.43% for prediction of ARDS • Pancreatic necrosis rate, lactate dehydrogenase level and oxyhemoglobin saturation were the most important independent variables in that ANN • Can predict the severity of ARDS according to Berlin's definition with 73% accuracy
Lu et al. [57]	Checked serum samples of 24 patients of AP for micro-RNAs	Evaluated 287 different micro-RNAs	• Found role of 12 circulating micro-RNAs in predicting ARDS

AP acute pancreatitis. *ARDS* acute respiratory distress syndrome, *SIRS* systemic inflammatory response syndrome, *AUC* area under curve

ARDS compared to patients without ARDS [74]. RAAS blockade with ACE inhibitor or angiotensin receptor blocker (ARB) has shown beneficial effect in retrospective studies [75]. However, recent study did not find beneficial effect of prehospitalization ACE inhibitor or ARB on development of ARDS on at-risk patients [76]. N-acetyl cysteine has been evaluated in small studies for prevention of ARDS with some positive results [77, 78]. Inhaled steroids, β2-agonist, and hypertonic saline have also been tried for prevention of ARDS in at-risk patients without much efficacy [76, 79].

Management of acute respiratory distress syndrome in AP

Management protocol of ARDS in AP is the same as for ARDS due to other causes. Management of AP according to standard guidelines is of utmost importance [80–82]. Treatment of sepsis and local complications of AP should be done according to the laid-down management strategies. Management of ARDS is dependent on the severity. For patients with mild ARDS, oxygen supplementation with other conservative management can be provided. If patients deteriorate or develop more hypoxia, then non-invasive ventilation or mechanical ventilation should be provided [83]. As many of the patients with moderate or severe ARDS require mechanical ventilation, which sometime may cause baro-trauma, it is very necessary to understand and follow various lung protective strategies. Moreover, some general principles in management of ARDS like fluid restrictive strategy and early use of neuromuscular blockade in patients with mechanical ventilation have been associated with improved lung function, shortened duration of mechanical ventilation, and reduced mortality [84, 85]. The primary target of lung protective ventilation is low-tidal volume strategy (4–8 mL/kg of predicted body weight) with inspiratory plateau pressure < 30 cm H_2O. Trials have shown mortality benefit with low-tidal volume strategy [86, 87]. Prone positioning has also shown benefits in ARDS with better ventilation-perfusion matching, less ventilation-induced lung injury by more uniform distribution of tidal volume, and better oxygenation due to more lung recruitment. It has shown mortality benefit especially in patients with severe ARDS if done for at least 12 h per day [88, 89]. Similarly, in patients with moderate or severe ARDS on ventilatory support, high positive end-expiratory pressure (PEEP) is associated with better oxygenation and lower mortality

Table 4 General principles in management of acute respiratory distress syndrome [83, 85, 109]

Intervention	ARDS severity
Control of sepsis with source control and antibiotic	All ARDS severity
Fluid restrictive strategy	All ARDS severity
Early and short neuromuscular blockade	Moderate or severe ARDS
Mechanical ventilation	
Low tidal volumes (6–8 mL/kg)	All ARDS severity
Low inspiratory pressure (< 30 cmH_2O plateau pressure)	All ARDS severity
Higher PEEP	Moderate or severe ARDS
Recruitment maneuvers	Moderate or severe ARDS
High-frequency oscillatory ventilation	Moderate or severe ARDS
Prone positioning	Severe ARDS
Veno-venous extra-corporeal oxygenation	Severe ARDS

ARDS acute respiratory distress syndrome, *PEEP* positive end-expiratory pressure

compared to lower PEEP [90, 91]. Patients with ARDS develop dependent atelectasis due to increased lung weight from interstitial and alveolar edema which exacerbates lung injury during mechanical ventilation by limiting available lung volume. Lung recruitment maneuvers (RMs) can reduce atelectasis by transient elevation in applied airway pressure to open the collapsed lung and increasing the number of alveolar units participating in tidal ventilation. Various RMs like prolonged high continuous positive airway pressure (30–40 cm H_2O) or progressive incremental increase in PEEP have shown to be beneficial with improved oxygenation and reduced mortality [92, 93]. High-frequency oscillatory ventilation (HFVO) is a novel ventilatory setting which delivers very small tidal volumes at higher mean airway pressure causing recruitment of collapsed lung units and improved oxygenation [94, 95]. However, need for deep sedation to prevent spontaneous inspiratory efforts and expertize with this modality limits its routine use. Similarly, veno-venous extra-corporeal membrane oxygenation which drains blood from the large central vein and pumps it through gas exchange device which causes oxygenation of blood and removes excess carbon dioxide has been also tried in ARDS without much promising results [89, 96, 97].

Apart from the above-mentioned ventilatory strategies, several pharmacological therapies have also been tried in patients with ARDS. β2 agonist increases sodium transport by activating β2-receptors on type I and II alveolar cells and reduces pulmonary edema. However, trials using intravenous or inhaled salbutamol have not yielded promising results [79, 98]. Glucocorticoids, which have strong anti-inflammatory and anti-fibrotic action have been tried in treatment of ARDS. Low-dose steroids (methylprednisolone ≤ 2 mg/kg or equivalent) used early in the course of ARDS (within 14 days) were shown to reduce duration of ventilation, ICU stay, and mortality [99–102]. However, due to increased risk of complication (especially neuromyopathy and infection) and inadequate data, its general use cannot be recommended at present [99, 103]. Inhaled nitric oxide has also not been found to reduce mortality across any severity of ARDS [104, 105]. Statins have also been tried in ARDS. However, results of large multicentric trails have failed to show any benefit in either ventilatory free days or mortality [106, 107]. Keratinocyte growth factor (KGF) has been found to improve alveolar epithelial repair; however, result of studies using KGF has shown higher 28-day mortality [83, 108]. So, at present, there are no convincing pharmacological treatment available to reduce severity or mechanical ventilation days or mortality in patients with ARDS (Table 4).

Conclusion

Respiratory failure is the most common type of organ failure in AP and is associated with high mortality. ARDS, one of the most common causes of respiratory failure in AP, is still a poorly understood entity. Though a few studies have shown promising results for prediction of ARDS in AP, preventive strategies for development of ARDS is still in an infantile phase. Lung protective ventilatory strategies are of paramount importance to improve outcome of patients with AP with ARDS and therefore effective coordination between gastroenterologists and intensivists is needed for effective management of these patients.

Author contributions Jimil Shah: drafting of manuscript
Surinder Singh Rana: critical evaluation of manuscript

Compliance with ethical standards

Conflict of interest JS, and SSR declare that they have no conflict of interest.

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References

1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102–11.
2. Schepers NJ, Bakker OJ, Besselink MG, et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. Gut. 2019;68:1044–51.
3. Krishna SG, Kamboj AK, Hart PA, Hinton A, Conwell DL. The changing epidemiology of acute pancreatitis hospitalizations: a decade of trends and the impact of chronic pancreatitis. Pancreas. 2017;46:482–8.
4. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas. 2006;33:323–30.
5. Rana SS. An overview of walled-off pancreatic necrosis for clinicians. Expert Rev Gastroenterol Hepatol. 2019;13:331-43.
6. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med. 2017;377:562–72.
7. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307:2526–33.
8. Villar J, Sulemanji D, Kacmarek RM. The acute respiratory distress syndrome: incidence and mortality, has it changed? Curr Opin Crit Care. 2014;20:3–9.
9. Villar J, Blanco J, Kacmarek RM. Current incidence and outcome of the acute respiratory distress syndrome. Curr Opin Crit Care. 2016;22:1–6.
10. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med. 1995;23:1638–52.
11. Browne GW, Pitchumoni C. Pathophysiology of pulmonary complications of acute pancreatitis. World J Gastroenterol. 2006;12:7087–96.
12. Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. Gut. 2004;53:1340–4.
13. Karakattu S, Devani K, Reddy C, Hoskere G. Predictors and outcomes of acute respiratory failure amongst the patients hospitalized with acute pancreatitis. Chest. 2017;152:A217.
14. Lankisch PG, Rahlf G, Koop H. Pulmonary complications in fatal acute hemorrhagic pancreatitis. Dig Dis Sci. 1983;28:110–6.
15. Matthay MA, Zemans RL. The acute respiratory distress syndrome: pathogenesis and treatment. Annu Rev Pathol. 2011;6:147–63.
16. Berry AR, Taylor TV, Davies GC. Pulmonary function and fibrinogen metabolism in acute pancreatitis. Br J Surg. 1981;68:870–3.
17. Büchler M, Malfertheiner P, Schädlich H, Nevalainen TJ, Friess H, Beger HG. Role of phospholipase A2 in human acute pancreatitis. Gastroenterology. 1989;97:1521–6.
18. Kortesuo PT, Nevalainen TJ, Büchler M, Uhl W. Characterization of two phospholipases A2 in serum of patients with sepsis and acute pancreatitis. Eur J Clin Chem Clin Biochem. 1992;30:263–9.
19. Uhl W, Schrag HJ, Schmitter N, Aufenanger J, Nevalainen TJ, Büchler MW. Experimental study of a novel phospholipase A2 inhibitor in acute pancreatitis. Br J Surg. 1998;85:618–23.
20. Kingsnorth A. Role of cytokines and their inhibitors in acute pancreatitis. Gut. 1997;40:1–4.
21. Kingsnorth AN, Galloway SW, Formela LJ. Randomized, double-blind phase II trial of Lexipafant, a platelet-activating factor antagonist, in human acute pancreatitis. Br J Surg. 1995;82:1414–20.
22. Johnson CD, Kingsnorth AN, Imrie CW, et al. Double blind, randomised, placebo controlled study of a platelet activating factor antagonist, lexipafant, in the treatment and prevention of organ failure in predicted severe acute pancreatitis. Gut. 2001;48:62–9.
23. Norman JG, Fink GW, Denham W, et al. Tissue-specific cytokine production during experimental acute pancreatitis. A probable mechanism for distant organ dysfunction. Dig Dis Sci. 1997;42:1783–8.
24. Malka D, Vasseur S, Bödeker H, et al. Tumor necrosis factor alpha triggers antiapoptotic mechanisms in rat pancreatic cells through pancreatitis-associated protein I activation. Gastroenterology. 2000;119:816–28.
25. Donnelly SC, Strieter RM, Kunkel SL, et al. Interleukin-8 and development of adult respiratory distress syndrome in at-risk patient groups. Lancet. 1993;341:643–7.
26. Miller EJ, Cohen AB, Nagao S, et al. Elevated levels of NAP-1/interleukin-8 are present in the airspaces of patients with the adult respiratory distress syndrome and are associated with increased mortality. Am Rev Respir Dis. 1992;146:427–32.
27. Kurdowska A, Noble JM, Grant IS, Robertson CR, Haslett C, Donnelly SC. Anti-interleukin-8 autoantibodies in patients at risk for acute respiratory distress syndrome. Crit Care Med. 2002;30:2335–7.
28. Mayer J, Rau B, Gansauge F, Beger HG. Inflammatory mediators in human acute pancreatitis: clinical and pathophysiological implications. Gut. 2000;47:546–52.
29. Rotstein OD. Circulating cytokines in predicting development of severe acute pancreatitis. Crit Care. 2014;18:575.
30. Sakai Y, Masamune A, Satoh A, Nishihira J, Yamagiwa T, Shimosegawa T. Macrophage migration inhibitory factor is a critical mediator of severe acute pancreatitis. Gastroenterology. 2003;124:725–36.
31. Kasama T, Strieter RM, Lukacs NW, Burdick MD, Kunkel SL. Regulation of neutrophil-derived chemokine expression by IL-10. J Immunol. 1994;152:3559–69.
32. Van Laethem J-L, Eskinazi R, Louis H, Rickaert F, Robberecht P, Devière J. Multisystemic production of interleukin 10 limits the severity of acute pancreatitis in mice. Gut. 1998;43:408–13.
33. Rongione AJ, Kusske AM, Kwan K, Ashley SW, Reber HA, McFadden DW. Interleukin 10 reduces the severity of acute pancreatitis in rats. Gastroenterology. 1997;112:960–7.
34. Wang X, Sun Z, Börjesson A, Andersson R. Inhibition of platelet-activating factor, intercellular adhesion molecule 1 and platelet endothelial cell adhesion molecule 1 reduces experimental pancreatitis-associated gut endothelial barrier dysfunction. Br J Surg. 1999;86:411–6.
35. Sun J, Bhatia M. Blockade of neurokinin-1 receptor attenuates CC and CXC chemokine production in experimental acute pancreatitis and associated lung injury. Am J Physiol Gastrointest Liver Physiol. 2007;292:G143–53.
36. Flint RS, Windsor JA. The role of the intestine in the pathophysiology and management of severe acute pancreatitis. HPB (Oxford). 2003;5:69–85.
37. Montravers P, Chollet-Martin S, Marmuse JP, Gougerot-Pocidalo MA, Desmonts JM. Lymphatic release of cytokines during acute lung injury complicating severe pancreatitis. Am J Respir Crit Care Med. 1995;152:1527–33.
38. Peng H, Zhi-Fen W, Su-Mei J, Yun-Zhen G, Yan L, Li-Ping C. Blocking abdominal lymphatic flow attenuates acute hemorrhagic necrotizing pancreatitis -associated lung injury in rats. J Inflamm (Lond). 2013;10:9.

39. Gray KD, Simovic MO, Chapman WC, et al. Endotoxin potentiates lung injury in cerulein-induced pancreatitis. Am J Surg. 2003;186:526–30.
40. Sharif R, Dawra R, Wasiluk K, et al. Impact of toll-like receptor 4 on the severity of acute pancreatitis and pancreatitis-associated lung injury in mice. Gut. 2009;58:813–9.
41. Liu H, Li Y, Wang L, Chen H, Guan J, Zhou Z Aggravation of acute pancreatitis by heparan sulfate in mice. Scand J Gastroenterol. 2009;44:626–32.
42. Kumar P, Gupta P, Rana S. Thoracic complications of pancreatitis. JGH Open. 2018;3:71–9.
43. Gajic O, Dabbagh O, Park PK, 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.
44. Trillo-Alvarez C, Cartin-Ceba R, Kor DJ, et al. Acute lung injury prediction score: derivation and validation in a population-based sample. Eur Respir J. 2011;37:604–9.
45. Soto GJ, Kor DJ, Park PK, et al. Lung injury prediction score in hospitalized patients at risk of acute respiratory distress syndrome. Crit Care Med. 2016;44:2182–91.
46. Agrawal A, Matthay MA, Kangelaris KN, et al. Plasma Angiopoietin-2 predicts the onset of acute lung injury in critically ill patients. Am J Respir Crit Care Med. 2013;187:736–42.
47. Xu Z, Wu GM, Li Q, et al. Predictive value of combined LIPS and ANG-2 level in critically ill patients with ARDS risk factors. Mediat Inflamm. 2018;2018:1739615.
48. Levitt JE, Bedi H, Calfee CS, Gould MK, Matthay MA. Identification of early acute lung injury at initial evaluation in an acute care setting prior to the onset of respiratory failure. Chest. 2009;135:936–43.
49. Zhou Y, Fan Q, Cavus O, Zhang X. Lung ultrasound: predictor of acute respiratory distress syndrome in intensive care unit patients. Saudi J Anaesth. 2018;12:457–61.
50. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. Chest. 2008;134:117–25.
51. Lichtenstein DA. Lung ultrasound in the critically ill. Ann Intensive Care. 2014;4:1.
52. Samanta J, Singh S, Arora S, et al. Cytokine profile in prediction of acute lung injury in patients with acute pancreatitis. Pancreatology. 2018;18:878–84.
53. Skouras C, Davis ZA, Sharkey J, et al. Lung ultrasonography as a direct measure of evolving respiratory dysfunction and disease severity in patients with acute pancreatitis. HPB (Oxford). 2016;18:159–69.
54. Katageri B, Rana SS, Bhatia A, et al. 448 - serial lung ultrasound in the assessment of volume status and disease severity in acute pancreatitis. Gastroenterology. 2018;154:S–103.
55. Fei Y, Gao K, Li W-Q. Artificial neural network algorithm model as powerful tool to predict acute lung injury following to severe acute pancreatitis. Pancreatology. 2018;18:892–9.
56. Shi N, Deng L, Chen W, et al. Is MicroRNA-127 a novel biomarker for acute pancreatitis with lung injury? Dis Markers. 2017;2017:1204295.
57. Lu X-G, Kang X, Zhan L-B, Kang LM, Fan ZW, Bai LZ. Circulating miRNAs as biomarkers for severe acute pancreatitis associated with acute lung injury. World J Gastroenterol. 2017;23:7440–9.
58. Amiti, Tamizhselvi R, Manickam V. Menadione (vitamin K3) inhibits hydrogen sulfide and substance P via NF-κB pathway in caerulein-induced acute pancreatitis and associated lung injury in mice. Pancreatology. 2019;19:266–73.
59. Leema G, Tamizhselvi R. Protective effect of scopoletin against cerulein-induced acute pancreatitis and associated lung injury in mice. Pancreas. 2018;47:577–85.
60. Cui H, Li S, Xu C, Zhang J, Sun Z, Chen H. Emodin alleviates severe acute pancreatitis-associated acute lung injury by decreasing pre-B-cell colony-enhancing factor expression and promoting polymorphonuclear neutrophil apoptosis. Mol Med Rep. 2017;16:5121–8.
61. Shi Z, Ye W, Zhang J, et al. LipoxinA4 attenuates acute pancreatitis-associated acute lung injury by regulating AQP-5 and MMP-9 expression, anti-apoptosis and PKC/SSeCKS-mediated F-actin activation. Mol Immunol. 2018;103:78–88.
62. Yu J, Ni L, Zhang X, Zhang J, Abdel-Razek O, Wang G. Surfactant protein D dampens lung injury by suppressing NLRP3 inflammasome activation and NF-κB signaling in acute pancreatitis. Shock. 2019;51:557–68.
63. Qiao Y-Y, Liu X-Q, Xu C-Q, Zhang Z, Xu HW. Interleukin-22 ameliorates acute severe pancreatitis-associated lung injury in mice. World J Gastroenterol. 2016;22:5023–32.
64. Chen W, Janz DR, Bastarache JA, et al. Prehospital aspirin use is associated with reduced risk of acute respiratory distress syndrome in critically ill patients: a propensity-adjusted analysis. Crit Care Med. 2015;43:801–7.
65. Erlich JM, Talmor DS, Cartin-Ceba R, Gajic O, Kor DJ. Prehospitalization antiplatelet therapy is associated with a reduced incidence of acute lung injury: a population-based cohort study. Chest. 2011;139:289–95.
66. Kor DJ, Carter RE, Park PK, et al. Effect of aspirin on development of ARDS in at-risk patients presenting to the emergency department: the LIPS-A randomized clinical trial. JAMA. 2016;315:2406–14.
67. Weigelt JA, Norcross JF, Borman KR, Snyder WH. Early steroid therapy for respiratory failure. Arch Surg. 1985;120:536–40.
68. Bone RC, Fisher CJ, Clemmer TP, Slotman GJ, Metz CA. Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. Chest. 1987;92:1032–6.
69. Luce JM, Montgomery AB, Marks JD, Turner J, Metz CA, Murray JF. Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. Am Rev Respir Dis. 1988;138:62–8.
70. Khilnani GC, Hadda V. Corticosteroids and ARDS: a review of treatment and prevention evidence. Lung India. 2011;28:114–9.
71. Falagas ME, Makris GC, Matthaiou DK, Rafailidis PI. Statins for infection and sepsis: a systematic review of the clinical evidence. J Antimicrob Chemother. 2008;61:774–85.
72. O'Neal HR Jr, Koyama T, Koehler EAS, et al. Prehospital statin and aspirin use and the prevalence of severe sepsis and acute lung injury/acute respiratory distress syndrome. Crit Care Med. 2011;39:1343–50.
73. Bajwa EK, Malhotra CK, Thompson BT, Christiani DC, Gong MN. Statin therapy as prevention against development of acute respiratory distress syndrome: an observational study. Crit Care Med. 2012;40:1470–7.
74. Idell S, Kueppers F, Lippmann M, Rosen H, Niederman M, Fein A. Angiotensin converting enzyme in bronchoalveolar lavage in ARDS. Chest. 1987;91:52–6.
75. Honiden S, Gong MN. Diabetes, insulin, and development of acute lung injury. Crit Care Med. 2009;37:2455–64.
76. Ruthman CA, Festic E. Emerging therapies for the prevention of acute respiratory distress syndrome. Ther Adv Respir Dis. 2015;9:173–87.
77. Miller AC, Rivero A, Ziad S, Smith DJ, Elamin EM. Influence of nebulized unfractionated heparin and N-acetylcysteine in acute lung injury after smoke inhalation injury. J Burn Care Res. 2009;30:249–56.
78. Zingg U, Hofer CK, Seifert B, Metzger U, Zollinger A. High dose N-acetylcysteine to prevent pulmonary complications in partial or total transthoracic esophagectomy: results of a prospective observational study. Dis Esophagus. 2007;20:399–405.

79. Gao Smith F, Perkins GD, Gates S, et al. Effect of intravenous β-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. Lancet. 2012;379:229–35.
80. Arvanitakis M, Dumonceau J-M, Albert J, et al. Endoscopic management of acute necrotizing pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines. Endoscopy. 2018;50:524–46.
81. Crockett SD, Wani S, Gardner TB, et al. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. Gastroenterology. 2018;154: 1096–101.
82. Tenner S, Baillie J, DeWitt J, Vege SS; American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108:1400–15; 1416.
83. Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. JAMA. 2018;319:698–710.
84. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010;363:1107–16.
85. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354:2564–75.
86. Needham DM, Colantuoni E, Mendez-Tellez PA, et al. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. BMJ. 2012;344:e2124.
87. Needham DM, Yang T, Dinglas VD, et al. Timing of low tidal volume ventilation and intensive care unit mortality in acute respiratory distress syndrome. A prospective cohort study. Am J Respir Crit Care Med. 2015;191:177–85.
88. Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368:2159–68.
89. Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/ Society of Critical Care Medicine Clinical Practice Guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;195:1253–63.
90. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA. 2010;303:865–73.
91. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004;351:327–36.
92. Fan E, Wilcox ME, Brower RG, et al. Recruitment maneuvers for acute lung injury: a systematic review. Am J Respir Crit Care Med. 2008;178:1156–63.
93. Huh JW, Jung H, Choi HS, Hong SB, Lim CM, Koh Y. Efficacy of positive end-expiratory pressure titration after the alveolar recruitment manoeuvre in patients with acute respiratory distress syndrome. Crit Care. 2009;13:R22.
94. Young D, Lamb SE, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. N Engl J Med. 2013;368: 806–13.
95. Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med. 2013;368:795–805.
96. Del Sorbo L, Cypel M, Fan E. Extracorporeal life support for adults with severe acute respiratory failure. Lancet Respir Med. 2014;2:154–64.
97. Peek GJ, Mugford M, Tiruvoipati R, 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.
98. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Matthay MA, Brower RG, et al. Randomized, placebo-controlled clinical trial of an aerosolized β_2-agonist for treatment of acute lung injury. Am J Respir Crit Care Med. 2011;184:561–8.
99. Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA. 1998;280: 159–65.
100. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006;354:1671–84.
101. Tang BMP, Craig JC, Eslick GD, Seppelt I, McLean AS. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. Crit Care Med. 2009;37:1594–603.
102. Lamontagne F, Briel M, Guyatt GH, Cook DJ, Bhatnagar N, Meade M. Corticosteroid therapy for acute lung injury, acute respiratory distress syndrome, and severe pneumonia: a meta-analysis of randomized controlled trials. J Crit Care. 2010;25: 420–35.
103. Cho Y-J, Moon JY, Shin E-S, et al. Clinical practice guideline of acute respiratory distress syndrome. Tuberc Respir Dis (Seoul). 2016;79:214–33.
104. Adhikari NKJ, Dellinger RP, Lundin S, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. Crit Care Med. 2014;42:404–12.
105. Fan E, Mehta S. High-frequency oscillatory ventilation and adjunctive therapies: inhaled nitric oxide and prone positioning. Crit Care Med. 2005;33:S182–7.
106. National Heart, Lung, and Blood Institute ARDS Clinical Trials Network, Truwit JD, Bernard GR, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. N Engl J Med. 2014 ;370:2191–200.
107. Agus A, Hulme C, Verghis RM, et al. Simvastatin for patients with acute respiratory distress syndrome: long-term outcomes and cost-effectiveness from a randomised controlled trial. Crit Care. 2017 ;21:108.
108. Ware LB, Matthay MA. Keratinocyte and hepatocyte growth factors in the lung: roles in lung development, inflammation, and repair. Am J Phys Lung Cell Mol Phys. 2002;282:L924–40.
109. Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute respiratory distress syndrome. Ann Intensive Care. 2019;9:69.