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Acute lung injury

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Introduction

The clinical description that defines acute lung injury (ALI) has been around for more than 50 years. The clinical picture has carried many different definitions, but what was known as ALI is most recently reclassified as moderate or mild acute respiratory distress syndrome (ARDS). Whatever title it goes by, it remains a significant source of morbidity and mortality in the critically ill patient population. Most patients who fall under the ALI umbrella can have disease that ranges from short-term dyspnea all the way to refractory respiratory failure. Refining the diagnosis of ALI remains important because patients who are diagnosed with ALI enter important clinical pathways that have been associated with improved outcomes. ALI refers to a constellation of clinical criteria that manifests as progressive hypoxemia, dyspnea, and increased work of breathing. Although changes in fluid management and dedication to earlier source control have seen the incidence fall, ALI still has a high incidence (200,000 per year in the United States) and high overall mortality rate. ALI and/or ARDS accounts for more than 10% of all intensive care unit (ICU) admissions and accounts for 4% of all hospital admissions.[1] The recent advances in the understanding of pathophysiology have identified several biologic markers that are associated with worse clinical outcomes. Research into more sophisticated and protective means of ventilation have led to improvements in survival and a reduction in the duration of mechanical ventilation.

Despite a declining mortality rate, ALI remains a significant source of morbidity and mortality in the critically ill patient population. The mortality rate is reported as high as 60% in some patient populations and overall still remains approximately 40%.[1] It is estimated that ALI accounts for approximately 79,000 deaths per year in the United States which would make it 1 of the top 8 causes of death in 2018. For patients who survive the acute phase of ALI, there is evidence that the long-term quality of life is adversely affected.[1,2] The history of ALI dates back more than 50 years; however, progress in its treatment really only goes back 20 years due

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to a better understanding of the epidemiology and pathogenesis. With the high prevalence and still unacceptably high mortality rate ALI and/or ARDS would still qualify as medical crisis. As cytokine and cell signal pathways are explored, there is optimism that further improvements in medical outcomes can be reached. This monograph provides an overview of the evolution of the definition, pathogenesis, and treatment options available for ALI.

Definition

In 1967 Ashbaugh and colleagues described a clinical syndrome of "severe dyspnea, tachypnea, cyanosis that is refractory to oxygen therapy, loss of lung compliance, and diffuse alveolar infiltration seen on chest x-ray." They described this syndrome in 12 patients (7 of which died) who required positive pressure mechanical ventilation.[2] The onset of the syndrome was acute, typically within hours of the underlying clinical disorder. The majority of patients did not have a history of pulmonary disease. Adequate oxygenation required the use of continuous positive pressure with end expiratory pressures (PEEP). The earliest radiographic findings were patchy infiltrates indistinguishable from cardiogenic pulmonary edema that usually became confluent with progressive clinical deterioration. Lung compliance was substantially decreased. Gross pathology specimens had significant consolidation and were reported to resembled hepatic tissue but with large airways free from obstruction. Histological examination revealed hyaline membranes in the alveoli with microscopic atelectasis and intra-alveolar hemorrhage similar to infant respiratory distress syndrome.

In a subsequent paper, Petty and Ashbaugh refined and elaborated on what they termed the "adult respiratory distress syndrome."[3] In a review of 40 cases, the mechanism of lung injury was either direct (chest trauma, aspiration) or indirect (pancreatitis, sepsis) and, in some cases, was attributed to mechanical ventilation. Despite numerous etiologies, the physiologic and pathologic response of the lung was uniform. Although the onset was predictable, the resolution could cover a wide range of outcomes. In some patients the recovery was rapid and complete and in others it could result in permanent disability secondary to interstitial fibrosis. Overall, fatalities were primarily due to septic complications and not refractory hypoxia.[3]

Although a definition describing the manifestations of the disease was often used early in its history, a more precise definition was needed to allow focused study because there are so many inciting factors. In 1994, after almost 30 years of varying definitions, the American-European Consensus Conference Committee pushed for the adoption of a consensus definition for ALI and/or ARDS. This definition had 3 criteria: the acute onset of diffuse bilateral pulmonary infiltrates by chest radiograph; a PaO_2/FiO_2 $\leq$300 for ALI and $\leq$200 for ARDS; and a pulmonary artery wedge pressure (PAWP) $\leq$18 or no clinical evidence of left atrial hypertension.[4] This definition could be made with readily available clinical tools, a chest radiograph and an arterial blood gas, and included an objective numeric number. Although the subjective interpretation of the chest radiograph introduces some variability into the definition[5–8] it has been widely adopted for both clinical and research purposes. The emphasis on obtaining a PAWP is often omitted. One study found that up to 29% of patients with ALI had wedge pressures greater than 18 mm Hg. The researchers also found that most of the patients had normal cardiac output, suggesting that volume overload secondary to an aggressive resuscitation was to blame for the edema rather than cardiac dysfunction.[9] For this reason, modern updates to the definition of ALI and/or ARDS have been suggested that would rule out cardiac causes of pulmonary edema using an echocardiogram. Others have proposed removing the term ALI from the definition altogether. In an attempt to make the definition purely objective, the Berlin Definition was suggested in 2012.[10] This definition replaced ALI with mild, moderate, and severe ARDS as defined by the P_aO_2/F_iO_2 ratio (mild $\leq$ 300 mm Hg, moderate $\leq$ 200 mm Hg, and severe $\leq$ 100 mm Hg). This definition speaks to the point that ARDS and ALI are the same disease on a progressive scale. Other means of quantifying ALI and/or ARDS have been suggested such as the Murray Lung Injury Score,[11] Delphi Consensus Panel Definition,[12] and the Oxygentation Index[13]; however, despite a potentially more accurate correlation with the degree of lung injury, these tools have

not achieved widespread usage. The creation of a common definition has allowed researchers to work from a common starting point which ushered in an era of significant clinical research leading to improved patient outcomes.

Epidemiology

With the adoption of a common definition we have been able to get a clear idea of the epidemiology of ALI which was difficult to do in the first 30 years of studying the disease. After establishment of the consensus definition, Goss and colleagues[14] used the ARDS network database to identify ALI patients over a 3-year period, from 1996 to 1999. They reported an adjusted incidence of 64.2 cases per 100,000 person-years. In 2005, Rubenfeld and colleagues[15] conducted a large prospective, population-based validated cohort study of ALI incidence in a single county in Washington state containing multiple ICUs in 21 hospitals. They found the age-adjusted incidence was 86.2 per 100,000 person-years. When these data were extrapolated to the United States as a whole, the investigators estimated that the incidence of ALI was just less than 200,000 patients per year, with a mortality rate of 40%.[15] More recently, Li and colleagues [16] examined the incidence of ALI in the Mayo Clinic. They found a rate comparable to the reported data; however, interestingly, they found the incidence of the disease falling over the study period of 2001-2008. Further analysis revealed that the rate of community acquired ALI was static but the incidence of hospital acquired ALI was improving due to the improved critical care.

The distribution of ALI is not uniform across demographic classes. In the Rubenfeld cohort, similar to other studies,[17,18] the incidence of ALI increased with age from 16 per 100,000 person-years for those 15-19 years of age to 306 per 100,000 person-years for those 75-84 years of age.[15] These data would suggest that a spike in the incidence would be expected with the aging population. Although the most recent epidemiology data for ALI is 10 years old, we do know the number of elderly patients in the ICU continues to rise with the aging population.[19] The original description of ALI made an association between the pulmonary dysfunction and predisposing etiologies such as trauma, pneumonia, and pancreatitis.[2] More recent large epidemiology studies describe the most common antecedent pathologies as sepsis, pneumonia, aspiration, trauma, pancreatitis, large volume blood transfusions, and smoke or toxic gas inhalation.[20] Severe sepsis and multiple transfusions have been associated with the highest incidence of ALI; the lowest rates occur in patients with trauma or drug overdoses.[15,21] For patients with multiple comorbidities, chronic alcohol abuse, or chronic lung disease, the risk for lung injury is higher.[22] The causes can essentially be placed into 2 large groups. They can be grouped into direct pulmonary causes (pneumonia, pulmonary contusion, or inhalation injury) or indirect causes (trauma, burns, sepsis, and multiple blood transfusions). Although the groups may have different incidences of ALI development,[23] there is an unclear association with mortality rate.

Due to a vast collection of research and evolving therapeutic interventions, the ALI mortality rate has declined over the last 2 decades. In the 1980s, prior to the adoption of a uniform definition, mortality rates were approximately 64%-70%.[24–26] More recent studies now indicate a mortality risk of 29%-42%.[1,15,27–29] The precipitating pathology that caused ALI is an important determinant of the mortality rate. Numerous clinical disorders have been associated with the development of ALI, with various associated outcomes. Sepsis is associated with the highest mortality rate (43%), while noninfectious diagnoses such as major trauma carry a significantly lower risk of death (11%).[30] Two other demographic variables, age and race, have a reproducible relationship with outcomes in ALI. Not surprisingly, Rubenfeld and colleagues [15] found that mortality rate was significantly lower in patients 15-19 years of age (24%) compared to patients 85 years of age or older (60%). The pediatric population is not immune to ALI, but their low mortality rate (22%) emphasizes that age is an important factor in prognosis.[31] More recent studies have confirmed the association with age and also cited active neoplasm and chronic liver failure as nonmodifiable risk factors for poor outcomes.[32] Racial inequalities in outcome have also been observed in African-Americans and Hispanics since these 2 groups have a higher 60-day

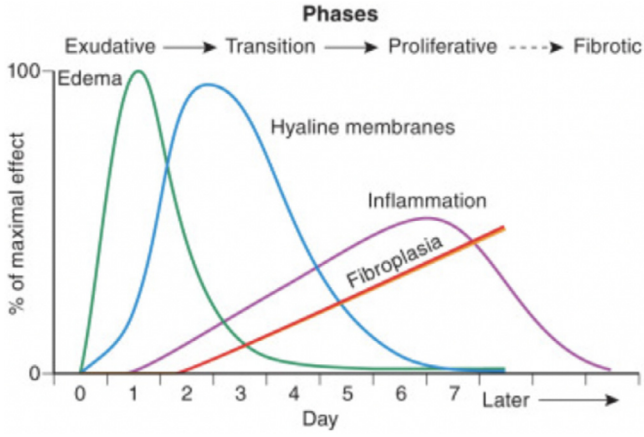

Fig. 1. Acute respiratory distress syndrome (ARDS) timeline. The 4 phases of ALI/ARDS follow a predictable pattern that produces related clinical effects. Therapeutic interventions are aimed at minimizing the alveolar changes in each phase and aborting progression to fibrogenesis which leads to permanent dysfunction.[168]

mortality rate (33%) compared to Caucasians (27%.)[33] This increased risk of death is independent of age, gender, ventilation strategy, lung injury etiology, comorbidities, or degree of hypoxemia.

It is important to remember that ALI develops in the setting of nonpulmonary organ failure. These patients often have cardiovascular collapse requiring vasopressors, hepatic dysfunction, and renal insufficiency. The multisystem organ failure causing ALI has a profound effect on the outcome of the ALI. One example would be a study by Kiu and colleagues that found that ALI in patients with concurrent acute kidney injury (defined as a serum creatinine >50% of baseline) more than doubled the mortality rate from ALI (26% to 56%, $P < 0.001$).[34]

Histology

The histologic changes that occur in ARDS in the lung were first described in 1977 by Bachofen and Weibel.[35] The histologic counterpart of ALI and/or ARDS is called diffuse alveolar damage (DAD) and the histologic evolution occurs in a reproducible pattern. From studies of ARDS, the pathologic changes appear to proceed consistently through discrete but overlapping phases: an early exudative (acute) phase, a subacute proliferative (organizing) phase, and a late fibrotic phase (Fig. 1). The acute phase (the first 1-6 days), is characterized by an influx of neutrophils, macrophages, and red blood cells in the alveoli. There is the initial development of distinctive hyaline membranes lining alveolar spaces. Interstitial and alveolar edema is frequently identified and acute alveolar hemorrhage may be present. Endothelial cells and pneumocytes undergo necrosis. The hyaline membranes mature as DAD continues into the organizing or subacute phase (days 7-14), and granulation tissue develops in the alveolar spaces. In an effort to heal the alveoli type II pneumocytes demonstrate marked reactivity and become hyperplastic. During the late fibrotic phase (after 14 days) squamous metaplasia, often times abundant enough to mimic carcinoma, may arise. Granulation tissue can lead to organizing fibrosis as collagen is deposited and fibroblasts move in. In the late-resolving or fibrotic phase there is dense collagen fibrosis and hyalinization of the alveolar walls.[36] Many patients do not move into the fibrotic stage but rather have a slow resolution of edema and inflammation. The stages occur in a continuum rather than in a strict chronologic fashion (Fig. 2). Biopsy specimens of ALI patients will show multiple phases simultaneously. For patients who survive ARDS, many cases resolve with minimal lung damage; however, patients may develop varying degrees of permanent damage that mimic changes found in end-stage lung disease.

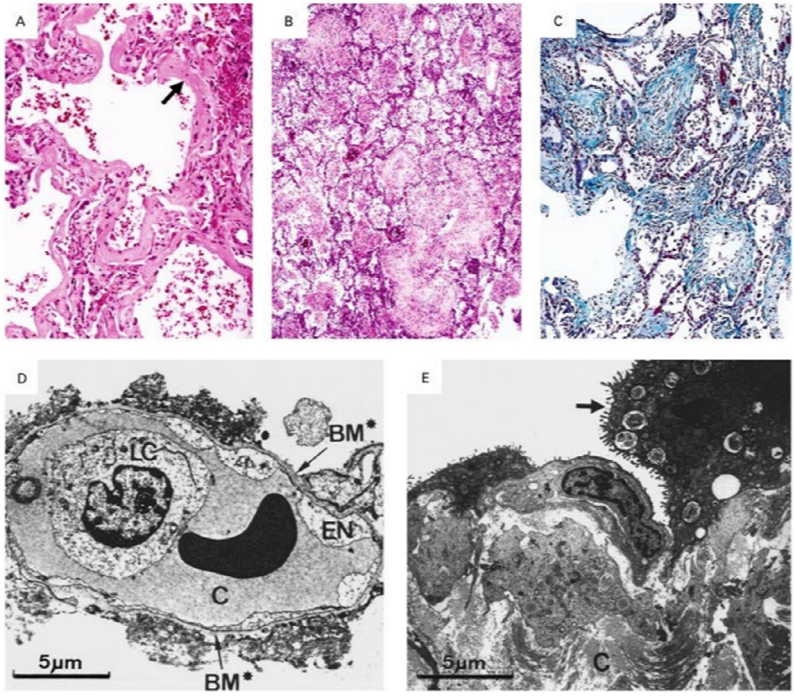

Fig. 2. Panel A shows a lung-biopsy specimen early histologic changes of ALI, two days after the onset of ALI caused by aspiration pneumonitis. Hyaline membranes have formed (arrow), with associated inflammation demonstrated by intraalveolar red cells and neutrophils. These findings are consistent with the pathological diagnosis of diffuse alveolar damage (hematoxylin and eosin, ×90). Panels B and C show late phase changes seen on a lung-biopsy specimens obtained 14 days after the onset of sepsis-associated acute lung injury. Panel B shows granulation tissue in the alveoli with a chronic inflammatory-cell infiltrate (hematoxylin and eosin, ×60). Trichrome staining in Panel C reveals collagen deposition (dark blue areas) in the granulation tissue, a finding that is consistent with the development of fibrosis (×60). Panel D shows a sample of lung tissue from a patient who had acute decompensation leading to death four days after the onset of acute lung injury; it shows breakdown of both the capillary endothelium and the alveolar epithelium, the central pathogenic feature that leads to pulmonary edema. There is an intravascular neutrophil (LC) in the capillary (C).The endothelium (EN) shows inflammation and vacuolization which is a sign of impending cell death. Loss of alveolar epithelial cells is seen with the formation of hyaline membranes on the epithelial side of the basement membrane (BM*). Panel E shows a specimen of lung tissue obtained from a patient during the fibrosing phase. The arrow indicates a typical type II alveolar epithelial cell with microvilli and lamellar bodies containing surfactant. The interstitium is thickened, with deposition of collagen (C).

Pathogenesis

Understanding the pathogenesis of ALI is important as current and future treatments are aimed at aborting this process and augmenting the repair mechanisms of the lung. ALI is a disorder of acute inflammation that causes disruption of the lung endothelial and epithelial barriers. Understanding the pathogenesis of ALI centers around determining how the edema gets into the lung airspace and the barriers to its removal. The alveolar–capillary membrane is comprised of the microvascular endothelium, interstitium, and alveolar epithelium. Cellular characteristics of ALI include loss of alveolar–capillary membrane integrity, excessive transepithelial neutrophil migration, and release of proinflammatory, cytotoxic mediators (Fig. 3).[22,37] The most important aspect is this early loss of lung vascular integrity. This allows the influx of the protein-rich fluid into the interstitial space and then the alveoli. The neutrophil is the common pathway for this loss of vascular integrity independent of the insult.[38–40] When an insult occurs, neutrophils accumulate in the pulmonary microvasculature and they become activated leading to the release

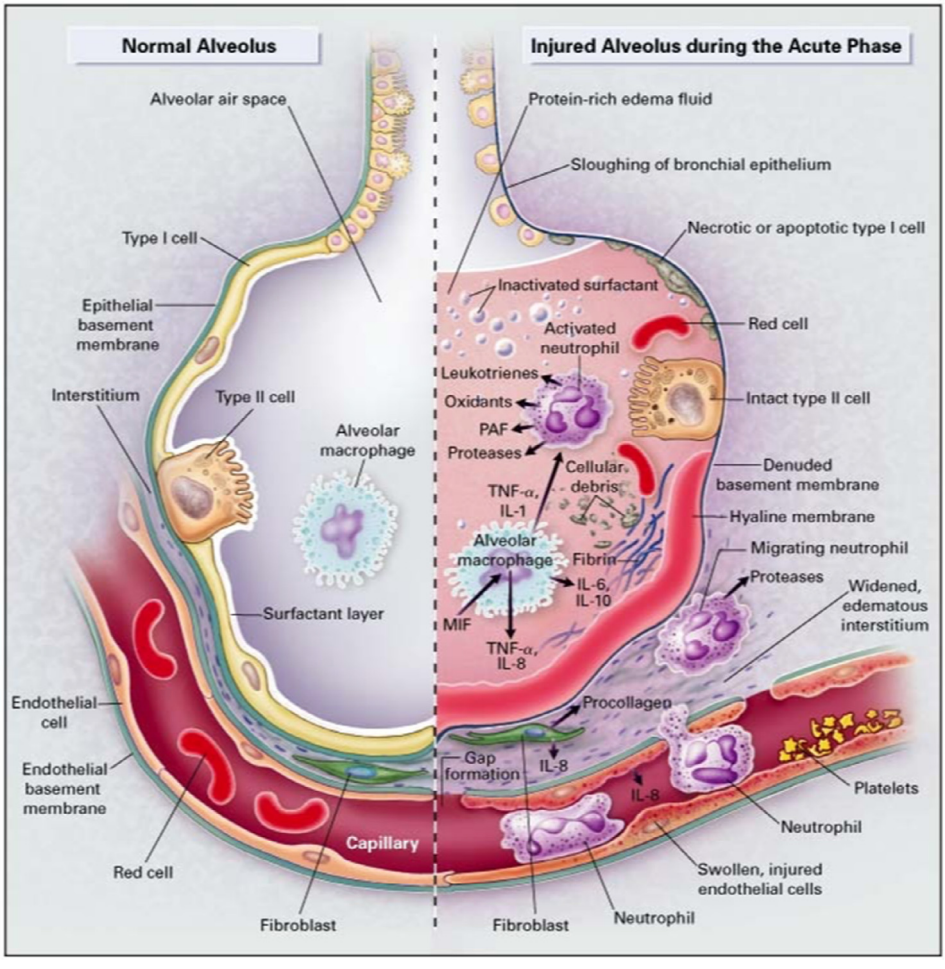

Fig. 3. The normal alveolus (left-hand side) and the injured alveolus (right-hand side) in the acute phase of ALI and the acute respiratory distress syndrome. There is loss of the integrity of the capillary endothelium and alveolar epithelium leading to increased pulmonary edema. with Hyalinization is occurring with hyaline membranes forming on the denuded basement membrane. Neutrophil migration is occurring with neutrophils marginating through injured endothelium and the interstitium into the air space. We can see the alveoli filling with protein-rich edema characteristic of ALI. In the air space, an alveolar macrophage is secreting cytokines, interleukin (IL)-1, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF)-α, which stimulates inflammation and eventually fibrosis (IL-1). Activated neutrophils release markers of inflammation such as leukotrienes, oxidants, platelet-activating factor (PAF) and proteases. This inflammatory process has lead to the inactivation of a surfactant and death of type I and II alveolar epithelial cells.

of several toxic meditators, including proteases, reactive oxygen species, proinflammatory cytokines, and procoagulant molecules. This results in increased vascular permeability. One such neutrophil mediator, Elastase, appears to degrade epithelial junctional proteins, possess proapoptotic properties, and perhaps have direct cytotoxic effects on the epithelium.[41–45] In some animal models, neutrophil depletion can be protective against the development of ALI.[46–48] While this may cause enthusiasm as a possible therapy in humans, it is important to recognize the important role that neutrophils play in innate immunity. Depletion of neutrophils may stop ALI from developing but would expose the patient to unchecked bacterial infections. In addition to Elastase other markers of pathologic vascular permeability have been identified. Several studies have

documented increased release of von Willebrand factor[49–51] and upregulation of intracellular adhesion molecule-1[52–54] following endothelial injury. Both of these biomarkers are independent predictors of mortality.

As important as understanding how injury to the lung microvascular endothelium results in initiating ALI, this mechanism alone does not explain how the disease progresses. Animal models suggest that the host can experience severe endothelial injury without experiencing alveolar epithelium damage. In these animal models, the edema that is the hallmark of ALI does not develop; in fact, edema does not develop until a corresponding injury to the alveolar epithelium occurs.[55] Once again, evidence would suggest that neutrophils play an important role in the development of epithelial injury. The number of neutrophils that migrate and degree of activation by inflammatory chemokines seem to correlate well with the injury to the epithelium and the degree of subsequent severity of ALI. Under normal conditions, the neutrophils cross into the alveolar space and essentially "close the door behind them" by resealing epithelial intercellular junctions. In pathologic conditions the increased number of neutrophils migrating across the epithelial barrier results in injury. Normally, type I and type II alveolar epithelial cells form tight junctions with each other, selectively regulating flow of fluid across the epithelial barrier. Secondary to this mass migration of neutrophils the injured epithelium results in increased permeability during the acute phase of lung injury and allows the deposition of protein-rich edema fluid into alveolar space. Injury to the epithelial cells also leads to disruption of normal means of evacuating this edema via epithelial Na channels and Na+/K+ATPase pumps.[22,56] Alveolar epithelial type II cell injury also leads to a loss of surfactant production,[57] decreasing overall pulmonary compliance. Finally, type II epithelial cells play a central role in the epithelial repair process; loss of their function can lead to disorganized, fibrosing repair.[58] All these factors result in the histologic changes seen in DAD that is the hallmark of ALI and/or ARDS.

In addition to the cytokines described, there are alveolar epithelial biomarkers including surfactant D (SP-D) and the receptor for advanced glycation end-products (RAGE) that have been shown to closely associate with outcomes in ALI. Due to the fact that alveolar epithelial injury is central to the development of ALI, it stands to reason that plasma surfactant protein (a byproduct of surfactant breakdown) levels would have prognostic value in ALI. Animals studies have shown that SP-D levels increase in ALI and/or ARDS and reflect epithelial permeability.[57,59] Using the ARDSNet low tidal volume data authors reported that increased baseline plasma SP-D levels were independently associated with mortality and fewer ventilator- and organ-failure free days. They also reported that lung protective strategies attenuated this rise signifying less alveolar damage.[60] RAGE, a transmembrane immunoglobulin primarily expressed on type I epithelial cells, can help differentiate ALI edema from hydrostatic edema as it is elevated in the former and normal in the later.[61] Calfee and colleagues[62] utilized the same ARDSNet samples and showed that increased RAGE levels were associated with increased morbidity and mortality and fewer ventilator-free and organ-failure-free days. These findings were independent of demographic variables and underlying pathology. Like the SP-D levels, it was shown that RAGE levels fell more rapidly in the lung protective strategy group when compared to high tidal volume cohort.

Biomarkers involved in the inflammatory and coagulation cascades found on the epithelium and endothelium predict morbidity and mortality in ALI. After stress, proinflammatory cytokines increase and can be used as a marker of the degree of physiologic insult and a marker of ongoing cellular injury. The proinflammatory cytokines tumor necrosis factor α, interleukin (IL)–1β, IL-6, IL-8, and IL-18 are the most studied with the closest correlation with morbidity and mortality. Meduri and colleagues[63] looked at bronchoalveolar lavage specimens collected in 27 ARDS patients. They found that initial and persistently elevated levels of IL-6, IL-8, and tumor necrosis factor-α were strongly predicative of mortality. These data also showed that plasma inflammatory cytokines mirrored the concentrations found in the bronchoalveolar lavage specimens. In yet another study using the ARDSNet low tidal volume ventilator data, Parsons and colleagues showed that even after adjustments for ventilator strategy, severity of illness, and organ dysfunction, higher plasma levels of IL-6 and IL-8 were independently associated with fewer organ failure- and ventilator-free days, and elevated IL-6 and IL-8 independently predicted higher

mortality. Moving past predicting outcomes, these data also showed that the low tidal volume ventilation is associated with a more rapid attenuation of the inflammatory response.[64] Other studies have demonstrated that lower tidal volume ventilation can attenuate the cytokine responses, suggesting that clinicians can decrease the inflammatory response with proper ventilator settings or potentially exacerbate the inflammatory response with improper ventilator settings.[64–67] Markers that play a role in the often-altered coagulation and fibrinolysis in the lung during injury, specifically protein C and plasminogen activator inhibitor-1, can be associated with outcomes. Ware and colleagues[68] compared ALI blood samples against patients with acute cardiogenic pulmonary edema and found that they could differentiate the source of the interstitial edema based on the low levels of protein C and higher plasma levels of plasminogen activator inhibitor-1 in the ALI samples. Furthermore, they discovered that low levels of protein C and higher levels of plasminogen activator inhibitor-1 were strong independent predictors of mortality, as well as ventilator-free and organ failure-free days.

The role of platelets in the pathogenesis of ALI and the inflammatory reaction in general has been greatly underappreciated. There is evidence that platelets may play an important role in neutrophil-mediated lung injury. Several recent studies point to a synergistic effect between platelets and neutrophils in causing lung endothelial injury. Platelets directly interact with neutrophils and monocytes and are themselves a source of proinflammatory cytokines. In recent experimental studies of ALI secondary to multiple etiologies,[69] platelet depletion markedly reduced lung injury in mouse models.

Resolution of ALI/ARDS is primarily dependent on restoring the function of the alveolar gas exchange mechanism. First the damaged pulmonary epithelium and endothelium must have their integrity restored. After that you can clear the interstitial fluid that is responsible for the V/Q mismatch in the lung. This is done by restoring the electrolyte balance and upregulating the alveolar transport mechanism to help clear the interstitial space of protein-rich edema fluid. Finally the alveoli must restore the normal secretion of surface active material from alveolar type-II cells.[37,70]

Treatment

The significant mortality decrease over the past 2 decades is secondary to improved ventilator strategies and a variety of critical care improvements. Improvement in ventilator management has been the most influential effect on mortality, but rethinking fluid management and a heightened sense of timely source control have been instrumental in both the treatment of ALI as well as its prevention. The same success cannot be attributed to many of the pharmacologic interventions that have been tried over the last 20 years, despite a deeper understanding of the pathophysiology that has not led to improved outcomes by using medications targeting at aborting that pathophysiology.

Ventilator strategies

The concept that positive pressure ventilation, especially high pressure, was injurious to the lung is not a recent finding. In the 1970s researchers showed that high tidal volumes (12-15 mL/kg) and high peak airway pressures 35-40 mm Hg) exacerbated ALI.[71,72] The most basic goal of lung protective ventilation is to deliver the least amount of required oxygen (preferably less than 60% FiO^2)[73] and avoid pressures greater than 35 cm H_2O.[74] Due to altered alveolar dynamics, the injured lung is prone to repetitive alveolar collapse and expansion while undergoing cycles of mechanical ventilation. Increased capillary permeability, surfactant deactivation and alveolar edema all lead to increased surface tension which promotes abnormal alveolar collapse during the expiratory phase. Once an alveolar unit is collapsed or fluid filled, the adjacent patent alveolar units undergo elevated distension stresses due to loss of the normal pressure balancing interconnections between neighboring alveoli. Repetitive alveolar collapse and expansion

and increased alveolar stress are the mechanisms driving ventilator-induced lung injury (VILI) which can occur when the acutely injured lung is exposed to mechanical ventilation.[75]

Open lung ventilation strategies strive to keep alveolar units open throughout the ventilator cycle, thus reducing the repetitive collapse which leads to VILI. Conventionally, positive expiratory-end pressure (PEEP) is combined with low tidal volume ventilation (4-8 cc/kg) to provide alveolar recruitment while avoiding overdistension. However, a hallmark of ARDS is the heterogeneity of lung injury. Thus, the optimal amount of PEEP required to avoid alveolar collapse remains unknown and likely varies throughout the lung.[76] Furthermore, the pressures delivered with conventional open lung ventilation may not be enough to adequately recruit injured lung or prevent cyclic collapse.[77]

Although many reports laid the ground work for lung protective strategies, the mortality benefit was described in 2 prospective randomized trials. In 2000, the ARDSNet trial is often credited with establishing lower tidal volumes lung protective strategies, but it was actually 2 years earlier in Brazil when Amato and colleagues[78] published a randomized trial showing the benefits of such a strategy. The lung protective strategy was built around lower tidal volumes (6 mL/kg), driving pressures $<$20 cm H_2O of water above the PEEP and higher levels of PEEP to maintain oxygenation. Those data did not establish a mortality benefit but did show a decrease in the complication rate and more ventilator-free days. This work paved the way for one of the most important critical care articles published. Not only have these data changed current ventilator management, the samples taken from this patient population have been used to carry out a substantial number of the studies cited in this review. To date, there remains 1 prospective randomized trial that has shown a clear mortality benefit to a ventilator management strategy. The value of a lung protective strategy in patients with ALI was shown in a study by the National Heart, Lung, and Blood Institute ARDS network's multicenter, randomized controlled trial of 861 patients with ALI and/or ARDS.[79] In this study, patients were randomized to 6 mL/kg tidal volume vs 12 mL/kg tidal volume with plateau pressure restrictions ($<$30 vs $<$50 cm H_2O). There was a significant mortality benefit seen in the low tidal volume group when compared to the high tidal volume group (31% vs 40%, $P = 0.007$). Patients in the low tidal volume group also had more ventilator-free and nonpulmonary organ failure-free days. This outcome benefit held even when controlling for the different etiologies of ALI including sepsis, aspiration, pneumonia, and trauma.[30] This strategy even tempered the inflammatory response (IL-6 and IL-8) associated with ALI.[64] One criticism of the study was that using 12 mL/kg tidal volumes was outdated as a means of determining tidal volumes, even at the time of the study. One could argue that it was low tidal volumes compared to volumes associated with overdistention, barotrauma, and increased deadspace V/Q mismatch. There are even data that show that minor increases in tidal volume can increase ICU mortality. Needham and collegueas showed that increasing tidal volumes as little as 1 mL/kg per body weight, from 6 mL/kg to 7 mL/kg, can lead to a 23% increase in mortality rate.[80] Also of interest is that despite the conclusive nature of the evidence for lung protective strategies that widespread adoption is not uniform. A 2016 report, 16 years after the publication of the ARDS lung protective ventilation report, showed that only two-thirds of the ARDS patients received ventilator management consistent with the published parameters.[1]

Within the context of lung protective ventilator strategies investigators have attempted to further tailor ventilator settings to the noncompliant ALI lung. There have been a multitude of studies looking at the effect of high PEEP vs low PEEP based algorithms. The 3 most cited studies are randomized control trials[81–83] that use a variation of a table that predetermines an escalating PEEP setting for escalating FiO_2 requirements. There is variation in the permissible plateau pressures allowed but otherwise study designs are similar. None of these trials showed a mortality benefit to higher PEEP levels and 2 of them were stopped early for futility. Higher PEEP levels may improve oxygenation and reduce VILI but may also cause circulatory depression and lung injury from overdistention. Amato and colleagues further examined the data and found that driving pressure (ΔP) as a measure of the patients' lung compliance was the best index for survival and that ventilator settings aimed at decreasing ΔP were strongly associated with increased survival.[84]

An alternative ventilator strategy for ARDS is airway pressure release ventilation (APRV) as a variation on the open lung concept. APRV generates a high continuous positive airway pressure (CPAP) with brief, intermittent expiratory releases. Generally, APRV uses a higher pressure (CPAP $\sim$ 30 cm H_2O) compared to low tidal volume ventilation strategies. Alveolar strain is viscoelastic in nature[85] meaning there is both a fast and slow component of deformation in response to pressure. Therefore, the prolonged, elevated CPAP provided by APRV may be more conducive to maintaining alveolar recruitment. Additionally, the expiratory release phase may allow ventilation without permitting derecruitment.

Use of early APRV in the setting of ARDS was recently studied in a randomized controlled trial of 138 patients who received either APRV or low tidal volume ventilation.[76] This study showed that the APRV group had fewer ventilator days and shorter ICU stays. There was no statistically significant difference in mortality. A meta-analysis of mechanically ventilated trauma patients[86] showed significantly lower mortality in the APRV groups and concluded that early use of APRV may prevent progression to ARDS. Several studies have shown equivocal or worse outcomes with APRV compared to conventional open lung ventilation, however none of these studies looked at early implementation which may be a key factor.[87–89] (therefore, APRV may be useful as an initial mode of ventilation rather than for rescue).

One proponent of APRV compares the acutely injured lung to a broken bone which must be cast in the correct position (ie, recruited) in order to facilitate healing.[75,90] This group has adopted a dynamic version of APRV called time controlled adaptive ventilation (TCAV). Here, the expiratory release parameter (T_{low}) is adjusted to terminate the expiratory phase at 75% of peak expiratory flow, thus allowing ventilator settings to adapt to changing lung compliance. The TCAV protocol has largely been used pre-emptively, prior to the onset of ARDS. However, the authors state it is well-suited to recruit and stabilize the lungs of those with ARDS as well. There is currently no randomized controlled trial comparing TCAV to low tidal volume strategies. Its use is supported by expert opinion and translational animal data.

Although the data supporting APRV in the setting of ALI and/or ARDS are currently limited, a compelling argument based on pathophysiology can certainly be made. Additionally, existing data suggest that APRV may be preventative when applied prior to the onset of ARDS,[91] which, if true, would be advantageous compared to conventional open lung ventilation. More studies are needed in order to effectively compare these 2 strategies.

High-frequency oscillatory ventilation (HFOV) has been used in the management of ALI and/or ARDS, with a mixed effect on outcomes. The rationale behind HFOV is to deliver oxygen at a constant mean airway pressure and use a diaphragm that oscillates at a high frequency (180-600 breaths per minute). The tidal volumes used often are less than the deadspace of the lung so that gas exchange occurs by gas mixing in the lung rather than typical exhalation and inhalation. This prevents cyclic overdistention of the alveoli and then snapping shut which is associated with alveolar damage. The largest and longest trials looking at this strategy have been in neonates.[92] This review showed that there was no clear benefit to HFOV but that patient selection, with too many less severe cases included, may have diminished the results. The effect that HFOV has in the adult population is even less clear. Often times HFOV is used as a rescue intervention which would naturally make it have an association with worse outcomes. There is evidence that HFOV can improve oxygenation in this setting and potentially mortality.[93–97] Further hindering the widespread adoption of HFOV were the results of the OSCILLATE trial which was a randomized multi-institutional trail showed that HFOV may actually increase the mortality rate in patients with severe-moderate ARDS.[98]

The ultimate means to control a patient's gas exchange is to take the dysfunctional injured lung out of the equation all together. Extracorporeal membrane oxygenation (ECMO) makes use of an artificial membrane lung and modified cardiopulmonary bypass to do the work of the failing lung and possibly the heart. The use of ECMO is resource intensive and carried out in a growing number of specialized centers around the country. Early referral to these centers has been shown to be a must if ECMO is to have a significant impact on patient outcomes.[99] There have been historical randomized trials looking at the use of ECMO that in general have been unable to show a clear association with decreased mortality of ECMO over conventional lung

protective strategies.[99–101] The most recent randomized trial looked at the use of ECMO as a rescue therapy in severe ARDS. In an international study ECMO was unable to improve the 60-day mortality rate (35% ECMO vs 46% conventional, $P = 0.09$) when compared to continued conventional ventilation. While centers continue to use ECMO as a salvage therapy in certain refractory patients research continues to strive to find definitive evidence of the value.

Prone positioning

Despite renewed enthusiasm for its application, prone positioning has been around since the 1970s.[102] Prone positioning makes use of the graded areas of ventilation and perfusion in the lung and the concept that flipping a patient now allows the areas of maximal perfusion to also be the areas of maximal ventilation, thereby temporarily correcting a patients ventilation and/or perfusion mismatch. There is little doubt that severe changes in the patient positioning will lead to improved oxygenation.[103,104] The issue with the data examining this positioning is whether this improved oxygenation leads to improved mortality. In contrast to earlier studies, the duration patients are left prone has been increased in recent studies with improved results. In a prospective randomized trial of 466 ARDS patients were placed prone for at least 16 hours within the first 48 hours of the onset of ARDS. The 28-day mortality rate was 16.0% in the prone group and 32.8% in the supine group ($P < 0.001$). The conclusion of the study was that in patients with severe ARDS, early application of prolonged prone-positioning sessions significantly decreased 28-day and 90-day mortality rates.[105] Similar results have been found in other studies[106,107] suggesting that in the most severe cases there is likely a survival benefit to extended periods of prone positioning if initialed early and for prolonged periods.

Fluid management

One other development in the management of ALI has been a refinement in fluid management. In earlier years of critical care there was a consensus that the patient had to "swell to get well." Liberal use of crystalloids likely contributed to the development of ALI and exacerbated the severity of the disease. The pulmonary edema that is the hallmark of ALI is worse with increased hydrostatic pressure and low oncotic pressure as seen in a crystalloid based resuscitation.[108] In 2006, the results of a prospective, randomized controlled trial comparing conservative vs liberal fluid management strategies were reported.[9] Authors titrated intravascular volume based off central venous pressures to keep patients on the liberal or conservative algorithm. The study did not show a significant difference in mortality rate, but the fluid conservative strategy improved oxygenation and severity of lung injury as well as reduced the duration of mechanical ventilation. Despite less fluid being given there was no increase in the occurrence of renal failure or shock. These data, as well as others,[9,109–112] paint a picture that patients need an appropriate early resuscitation but then often benefit from a more conservative resuscitation. Emerging from this literature is a simplified concept of keeping the patient "wet" early and "dry" late. In a parallel study, the authors looked at the effect of titrating intravascular fluid status using a pulmonary artery catheter vs a central venous catheter and found no difference in survival or organ function. The pulmonary artery catheter group did have nearly twice as many catheter related complications.[113]

Nutrition

Nutrition has been shown to be a powerful adjunct to the treatment of ALI. The importance cannot be overstated. ALI is a proinflammatory condition and leads to hypercatabolism which in turn can lead to malnutrition and loss of respiratory muscle strength. Providers must strive to avoid both underfeeding and the weakness that would result as well as overfeeding which

Table 1
Studies of pharmacologic interventions on acute lung injury.[169]

Treatment	Year	n	Findings	Author
Glucocorticoids (acute phase)	1987	99	No benefit	Bernard and colleagues[127]
Glucocorticoids (acute phase)	1988	75	No benefit	Luce and colleagues[170]
Surfactant	1996	725	No benefit	Anzueto and colleagues[151]
N-acetylcysteine	1997	42	No benefit	Domenighetti and colleagues[171]
Glucocorticoids (late phase)	1998	24	Decreased mortality	Meduri and colleagues[135]
Inhaled nitric oxide	1998	177	No benefit	Dellinger and colleagues[172]
Liposomal PGE 1 (high dose)	1999	350	No benefit	Abraham and colleagues[46]
Ketoconazole	2000	234	No benefit	NIH ARDS Network[125]
Liposomal PGE 1 (low dose)	2001	102	Reduced EVLW, improved survival trend	Vincent and colleagues[173]
Lisofylline	2002	235	Stopped for futility	NIH ARDS Network[126]
Glucocorticoids (late phase)	2005	180	No benefit	Steinberg and colleagues[132]
Salbutamol IV	2006	40	Improved survival trend	Perkins and colleagues[174]
Procysteine	2008	215	Stopped for futility	Morris and colleagues[175]
Activated protein C	2008	75	Stopped for futility	Liu and colleagues[176]

is associated with increased carbon dioxide production. Enteral nutrition has been shown to be superior to parenteral nutrition in a variety of populations but the effect that the timing and composition of the enteral feeds has on outcome has not previously been elucidated. There has been some evidence that ALI patients that received nutrition in the first 48 hours after intubation fared better than those without.[114–116] The ARDS Network showed that even if initial trophic enteral feedings could be started that there was a benefit reached in terms of ventilator-free and ICU-free days.[117] The mechanism of how enteral nutrition improves outcomes has been studied by comparing intestinal samples of patients treated with varying nutritional protocols and found that even low volume enteral feedings maintain the health of the intestinal mucosa and reduce inflammation by stimulating secretion of various immunologically active agents.[118–120]

There is also evidence that the type of nutrition can have an impact on outcomes in ALI. The use of feeds containing omega-3 fatty acids have been associated with decreased 28-day mortality, increased ventilator-free days and ICU-free days, and a reduction in the development of new organ failure.[121–123] Although there exist data to the contrary from an early terminated ARDSNet trail looking at omega-3 supplementation, those studies found no improvement in the same outcomes with supplementation and potentially harm.[124]

Pharmacologic interventions

As the understanding of the pathophysiology of ALI has improved we have identified numerous candidates for pharmacologic intervention. Although animal models and smaller human studies have shown promise there have not been any large clinical trials that have shown enough promise to recommend the use of a variety of pharmacologic interventions for the treatment of ALI (Table 1). Some of the early ARDSNet trials are indicative of much of the pharmacologic research aimed at ALI. Drugs aimed at specific components of the progression of ALI such as ketoconazole[125] and lisofylline[126] were unsuccessful in improving outcomes.

Systemic steroids have long been hypothesized to be a potential treatment for ALI given ALI's association with proinflammatory cytokines, however a consensus has never been reached. In the past, it has been demonstrated that high-dose steroids have no effect on ARDS when they are administered at the initial onset of disease.[127] More recently, it was demonstrated that when steroids are given during the subacute proliferative or late fibrotic stages of ARDS (7-14 days after initial presentation), there is improved survival.[128] It has also been discovered that patients who are given prolonged methylprednisolone compared to those who are given placebo are able to achieve unassisted breathing sooner, their in-hospital mortality is decreased, and they experience increased mechanical ventilation-free and ICU-free days.[129] The improved outcomes associ-

ated with steroid therapy in the late phases of ARDS are theorized to be related to the ability of steroids to counter the alveolar wall collagen fibrosis and hyalinization that occurs during these phases.[130]

One factor that has made standardizing steroid recommendations in ALI challenging is that not all studies investigating steroids and ALI have consistently used or documented low tidal volume modes of ventilation. In fact, one study that did use low tidal volume ventilation was unable to demonstrate a significant mortality benefit with glucocorticoid administration despite demonstrating improved pulmonary physiology.[131] Another study demonstrated that starting methylprednisolone more than 2 weeks after the initial onset of disease may actually increase mortality.[132] For these reasons, the routine use of systemic glucocorticoids in patients with ALI is not universally considered standard of care.

It is important to note that steroid treatment in the setting of ALI is not associated with an increased risk of infection[129] because there are some situations in which steroid use may be advised. For example, if the cause of ALI is due to an underlying pathological process that is treatable by steroids, steroids should not be withheld. If a patient's condition is untreatable with conventional ARDS therapy (such as ongoing hypoxemia despite low tidal volume ventilation), then such a patient may need an adjunct therapy such as steroids. In this setting, the benefits of most adjuncts would likely be outweighed by their risks.[133]

In 2017, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine released joint guidelines which included favoring the use of glucocorticoids in cases of early moderate to severe ARDS (defined as P_aO_2/F_iO_2 ratio <200 within 14 days of the initial onset of disease).[134] If glucocorticoids are to be administered, meta-analyses have demonstrated that in most cases the benefit is more likely to be achieved when steroid administration is prolonged (25-32 days) and initiated early (within 14 days of onset).[135] Studies are ongoing to assess whether there is a role for inhaled steroids in ALI, and to elucidate the ideal steroid dosing and timing of its administration.

In experimental and clinical studies there are data supporting earlier resolution of pulmonary edema with β-2 agonist therapy and this may be a potential treatment of ALI.[136–141] The reported mechanism of this expedited resolution of the pulmonary edema is decreasing inflammation and upregulating alveolar salt and water transport, which is one of the main mechanisms of clearing alveolar edema. There have been 2 prospective randomized trials looking at the use of β-2 agonists. A North American multicenter randomized was attempted but was stopped early after showing no benefit to β-2 agonist therapy when predefined futility markers were reached. The authors had some concerns about the fluid management in the groups and the inability to deliver the drug to the alveoli but made no recommendations about the use of the drug in ALI.[142] Another randomized clinical from the United Kingdom using intravenous salbutamol, a β-2 agonist, showed the treatment increased the 30-day mortality rate and caused the investigators to stop the trial early due to safety concerns. The results of these 2 studies showing no effect and potentially a harmful effect made further trials utilizing β-2 agonist unlikely.[143]

Due to the fact that research has shown a survival benefit in septic patients who were taking statins before the development of sepsis there has been some interest in the role of statins in ALI. Statins possess significant anti-inflammatory, immunomodulatory, and antioxidant effects which, it modulated, could abort the pathophysiology of the development of ALI. Data from small studies showed an inconsistent effect of morbidity and mortality when using statins after ALI had developed.[144,145] A meta-analysis[146] of 5 randomized controlled studies[144,147–150] including 650 patients was performed with no difference in mortality rate between patients receiving statins vs control (44/322 [14%] in the statins group vs 50/328 [15%] in the control arm, RR = 0.90 [95% confidence interval 0.65-1.26], $P = 0.6$). No differences in hospital stay ($P = 0.7$) were found.

Given the important role that surfactant and its loss at the alveolar epithelium plays in the development of ALI, there has been enthusiasm for the administration of exogenous surfactant. Research has led to the availability of both animal derived and synthetic preparations of exogenous surfactant. There are numerous small trials that have shown improved oxygenation with the administration of these drugs, but none have been powered to show a mortality benefit.

Randomized trials on the topic have also shown disappointing results with no long-term effect on survival.[151,152]

There is an association between increased pulmonary vascular resistance and increased mortality in ALI and/or ARDS.[153] Acute hypoxic vasoconstriction is the lung's attempt to shunt unoxygenated blood away from under ventilated alveoli. Vasoconstriction leads to a shunt and the greater the dysfunction, the greater the shunt and therefore ventilation/perfusion mismatch.[154] Inhaled vasodilators can reverse the vasoconstriction and reverse the ventilation and/or perfusion mismatch. The 2 most commonly used agents are inhaled nitric oxide (iNO) and inhaled prostacyclin. The inhaled route is preferred due to avoidance of systemic vasodilation and lowering of the mean airway pressure. The more studied is inhaled nitric oxide (iNO). There have been several randomized trials on the use of iNo that were summarized into a Cochrane analysis.[155] The meta-analysis summarizes what each of the individual trials showed which is that iNO improved oxygenation in the short term, but over an extended period of time did not affect mortality or length of mechanical ventilation. Inhaled prostacyclin was thought to be an ideal agent due to the fact it had not only vasodilatory effects but also its potent antiplatelet effect which prevents micro-thrombi. Like iNO, there are data that temporary improvements in oxygenation occur but long-term outcomes are unaffected.[156]

One exception to the ineffective pharmacologic interventions in ALI is the use of neuromuscular blockade. In a multicenter, double-blind trial, 340 patients presenting to the ICU with a P/F ratio of $<$150 within the previous 48 hours were randomly assigned to receive, for 48 hours, either cisatracurium besylate (178 patients) or placebo (162 patients). The hazard ratio for death at 90 days in the cisatracurium group, as compared with the placebo group, was 0.68 (95% confidence interval, 0.48-0.98; $P = 0.04$), after adjustment for both the baseline P/F ratio, plateau pressure and the Simplified Acute Physiology II score. In patients with severe ARDS, administration of a neuromuscular blocking agent in the first 48 after the onset of ARDS improved the adjusted 90-day survival rate and increased the time off the ventilator without increasing muscle weakness.[157]

As we look toward the future of pharmacologic intervention there has been promise in the use of bone marrow-derived mesenchymal stem cells (MSCs) in the treatment of ALI. The utility of these cells lies in the ability to graft themselves to the injured lung and differentiate to repair the main cells injured in the development of ALI, vascular endothelium and alveolar epithelium. In addition to acting as a patch to seal the barriers to the interstitium, the MSC decrease the proinflammatory cytokines and increase the anti-inflammatory cytokines, in particular IL-10.[158] MSCs also secrete locally active proteins (paracrine factors) that reduce the severity of ALI,[159–161] including growth factors, factors that regulate barrier permeability, and anti-inflammatory cytokines. These effects are independent of the cells' ability to graft themselves to the host lung, suggesting that these paracrine factors may play an important role. Gupta and colleagues in an ex vivo perfused lung preparation also showed that MSCs given 1 hour after endotoxin was effective in normalizing lung vascular and epithelial permeability to protein as well as reducing pulmonary edema and increasing the rate of alveolar fluid clearance.[162] Ongoing research focuses on translating these experimental studies to human clinical trials of patients with severe ALI.

Even more specific agents aimed at the development of pulmonary edema and inflammation have been studied. The nanopeptide AP301 which activates the pulmonary epithelium and endothelium sodium channels to help clear the alveolar fluid has been shown to be successful in animal models.[163] Human trials of inhaled AP301 showed equipoise, but subset analysis of severe cases leaves room for optimism.[164] Interferon β-1a plays a role in preventing endothelial leakage and preventing insterstitial edema and has been shown in an open label study of 37 patients to decrease the 28-day mortality rate by 81%.[165] MicroRNA are a recently discovered class of noncoding RNA that help to control gene expression. In an in vivo lung injury model it was shown that increased expression of these microRNA (specifically miR-127) leads to decreased pulmonary endothelial permeability, inflammatory migaration, and cytokine expression.[166] Also, via the stimulation of granulocyte-macrophage colony-stimulating factor, it is proposed that these microRNA can play a role in preventing and stimulating the resolution of ARDS.[167]

Conclusion

Although the incidence of ALI remains high, insight into its pathophysiology and early recognition has led to a decrease in mortality over the past 2 decades. Treatment has been focused on limiting its progression with ventilator strategies and pharmaceutical interventions that decrease the inflammation seen at the lung endothelial and epithelial barriers. Increased use of these treatment modalities in a protocolized fashion continues to lead to lower mortality and, even more importantly, stop ALI from developing.

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