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12 Do Nonventilatory Strategies for Acute Lung Injury and ARDS Work?

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The inflammatory injury suffered by the alveolar epithelium-endothelium complex provides multiple potential therapeutic targets. The inflammatory process could be inhibited at any stage from the genome to inflammatory signaling to leukocyte activation. Similarly, the various pathophysiologic consequences of alveolar injury could be amenable to pharmacologic intervention. The injurious process affects local alveolar ventilation, gas diffusion, and perfusion leading to reduced compliance, ventilation-perfusion mismatch, and respiratory failure. This chapter reviews the evidence for past, present, and potential future pharmacologic therapies for acute lung injury and acute respiratory distress syndrome (ALI/ARDS). Therapies can be classified as aiming to improve the pathophysiologic consequences of ALI/ARDS or as anti-inflammatory, although a large degree of overlap exists.

THERAPIES TO TREAT PATHOPHYSIOLOGIC CONSEQUENCES OF ALI/ARDS

Surfactant Deficiency

Surfactant is an endogenous mixture of phospholipids and proteins A to D produced by type 2 alveolar cells. It reduces alveolar surface tension, preventing alveolar collapse, and has anti-inflammatory and antimicrobial properties. Exogenous surfactant administration has been successfully used in neonatal respiratory distress syndrome, a condition of reduced surfactant production. Early trials in ARDS demonstrated physiologic improvements[1–7]; however, later phase 3 trials failed to show an improvement in mortality.[8,9] A meta-analysis of surfactant trials in ALI/ARDS reported an increase in oxygenation without an improvement in duration of ventilation or mortality.[10]

Various reasons have been proposed for these results. Although the neonatal syndrome is due to reduced production, the situation is more complex in ALI/ARDS. Surfactant is affected by increased removal, altered composition, reduced efficacy, and reduced production. Potential limitations of these phase 3 studies include the use of suboptimal surfactant formulation, dose and duration of therapy, inadequate alveolar delivery, and late initiation of therapy. The effect of calfactant (a calf protein B and C–based surfactant) in ALI/ARDS is currently being studied (NCT00682500), whereas trials of Surfaxin (a synthetic protein B–based surfactant) (NCT00215553) and HL-10 (a pig protein B and C–based surfactant) (NCT00742482) have recently been terminated, and results are awaited. Pending new research, surfactant therapy is not recommended (Table 12-1).

Limitation of Generation of Alveolar Edema

Alveolar flooding is primarily dependent on three factors: capillary hydrostatic pressure, oncotic pressure, and alveolar-capillary permeability. Capillary permeability is increased in ALI/ARDS. Reducing hydrostatic pressure and increasing oncotic pressure may ameliorate the development of pulmonary edema.

Reducing capillary hydrostatic pressure targeted to pulmonary artery occlusion pressure (PAOP)[11] and central venous pressure (CVP)[12] may be associated with improved outcome in ALI/ARDS, although fluid management guided by a pulmonary artery catheter (PAC) compared with a central venous catheter offers no advantage in ALI/ARDS.[13] Both a positive fluid balance[14–17] and increased extravascular lung water (EVLW)[18] are associated with poor outcomes in ARDS. Guiding fluid therapy with EVLW measurement rather than PAOP may be better.[19]

Hydrostatic pressure may be reduced by restricting fluid intake, increasing fluid output with either diuretics or renal replacement therapy (RRT), or decreasing vasomotor tone with vasodilators. The phase 3 Fluid and Catheter Treatment Trial (FACTT) study demonstrated improvements in secondary outcomes such as duration of ventilation and intensive care unit (ICU) stay with a restrictive fluid strategy. Fluid balance was dictated by a protocol of diuretic administration based on filling pressures.[12] Total 7-day fluid balance was about 0 mL, compared with about 7000 mL in the liberal fluid strategy. Although there was no difference in mortality, importantly there was no increase in renal failure or organ hypoperfusion with fluid restriction.

Animal models have demonstrated reduced pulmonary edema through reductions in pulmonary vascular pressures and permeability with RRT. Two small observational studies

Table 12-1 **Summary of Nonventilatory Strategies for ALI/ARDS***

Recommended	Not Recommended as Routine Therapy	Investigational
Restrictive fluid strategy	Surfactant	Extravascular lung water–guided fluid strategy
Diuretics	Intravenous vasodilators	Renal replacement therapy
Low central venous pressure	Pulmonary artery catheter	Albumin
		β-Agonists
		Insulin
		Gene therapy
		Growth factors
		Stem cells
	Inhaled NO	Inhaled prostacyclin
	Activated protein C	Endothelin antagonists
	Antithrombin III	Almitrine
		Tissue factor pathway inhibitor
		Factor VIIai
		Heparin
		Thrombomodulin
	Steroids (for established ALI/ARDS)	Steroids (for early ALI/ARDS)
	Ketoconazole	Complement antagonism
	Ibuprofen	Interferon-β
	N-acetylcysteine	Anti-CD14 antibody
	Procysteine	Anti-CD18 antibody
	Lisofylline	Pentoxifylline
	Sivelestat	Granulocyte-macrophage colony-stimulating factor
		Depelestat
		Vitamins C and E
		Statins
		Renin-angiotensin system modulation
		Omega-3 fatty acids
		Induced hypothermia

*Therapies with mixed results in clinical studies (e.g., steroids) require further evaluation before a specific recommendation can be made.

in humans have provided mixed results. Ten children with ALI/ARDS after bone marrow transplantation or chemotherapy treated with RRT had an 80% survival rate, in contrast to a historical survival rate of 15%.[20] Thirty-seven adults with renal failure and ALI/ARDS treated with RRT and a zero fluid balance had no pulmonary improvements within the first 24 hours of treatment.[21] The role of RRT in the management of ALI/ARDS remains uncertain.

The choice of fluid for resuscitation in ALI/ARDS remains unclear. Theoretically, a colloid with higher oncotic pressure would be more suitable than a crystalloid, but this has not been borne out in a large trial of albumin versus saline in critical illness.[22]

Hypoproteinemia is associated with the development of lung injury and is a marker of weight gain and death. Two small studies have investigated the use of furosemide with albumin infusions in hypoproteinemic patients with ALI. Both showed increases in total serum protein and more negative fluid balances with furosemide and albumin administration. This was associated with improved oxygenation, but there was no mortality benefit.[23,24]

Albumin also exerts antioxidant effects through its thiol group. Nonsurvivors of ALI/ARDS have reduced thiol values.[25] The infusion of albumin is associated with increased plasma thiol levels in sepsis[26] and ALI/ARDS[27] and decreased markers of oxidant injury.

A study is presently ongoing to investigate whether minimizing EVLW, measured by transpulmonary thermal indicator dilution using the Pulse Contour Cardiac Output (PiCCO) and directed by the FACTT diuretic algorithm, is superior to CVP-guided therapy (NCT00624650). A phase 2 study investigating the role of recombinant human atrial natriuretic peptide (Carperitide) in minimizing pulmonary edema in ARDS has recently been completed, and results are awaited (NCT00030121).

Lung injury is often heralded by a rise in pulmonary vascular resistance, with an imbalance between pulmonary vasoconstrictors and vasodilators being seen in animal endotoxin shock models. Intravenous adenosine reduces EVLW, whereas intravenous nitroprusside and nitroglycerin also reduce pulmonary edema generation, but at the expense of increasing ventilation-perfusion mismatch. To date, there is no clear evidence to support the role of vasodilator treatment in ALI/ARDS.

Maximizing Alveolar Fluid Clearance

Alveolar fluid clearance (AFC) is impaired in more than 50% of patients with ALI/ARDS, with this group having higher mortality rates.[28] β-Agonists upregulate AFC by increasing sodium ion transport from the alveolar space. A clinical trial of intravenous salbutamol in ALI/ARDS demonstrated reduced EVLW and a trend toward increased survival.[29] A retrospective study of salbutamol exposure in ALI suggested an association between higher exposure and improved outcome.[30] β_2-Agonists may exert several

other beneficial effects in ALI/ARDS, including increased surfactant secretion, decreased lung endothelial permeability, decreased airway resistance, and decreased airway pressures. A large United Kingdom multicenter study is in progress examining the effects of intravenous salbutamol on outcome in ALI/ARDS (ISRCTN38366450), whereas an Acute Respiratory Distress Syndrome Network (ARDSNet) inhaled β-agonist study has recently been terminated, and results are awaited (NCT00434993). β-Agonists are not currently recommended for treatment of ALI/ARDS.

Another potential future treatment is gene therapy to increase the expression of the ion channels and pumps needed for AFC. An animal study investigating overexpression of the β_1-subunit of the sodium-potassium adenosine triphosphatase (ATPase) pump demonstrated increased rates of AFC and improved survival.[31] If the alveolar epithelium is severely injured, cellular regeneration may be required before a functioning epithelial layer can be manipulated.

Epithelial and Endothelial Repair

Stem cells have the capacity for limitless self-renewal and differentiation. Embryonic stem cells are pluripotent and have the ability to differentiate into any cell type in the body, whereas adult stem cells are multipotent and have the ability to differentiate into several cell types, including cell types of other organ systems.

Stem cells provide three therapeutic opportunities.[32] First, endogenous stem cells may be stimulated by exogenously administered growth factors. Keratinocyte growth factor (KGF), hepatocyte growth factor, and transforming growth factor-α (TGF-α) have all been shown to reduce the effects of ALI in animal models. Epidermal growth factor, TGF-α, and KGF can all upregulate AFC. KGF has other potentially useful effects, including cytoprotection, augmented surfactant secretion, and an antioxidant effect. The administration of exogenous growth factors has not yet been directly studied in human trials of ALI/ARDS. Vascular endothelial growth factor (VEGF) promotes angiogenesis and regulates vascular permeability. Genetic polymorphisms of the VEGF gene are associated with lower levels of VEGF and increased mortality in ALI/ARDS.[33] Although VEGF increases alveolar permeability in ALI/ARDS,[34] its administration enhances alveola repair in vitro and in animal models. The role of VEGF in ALI/ARDS is being studied (NCT00319631).

Secondly, administration of exogenous stem cells, either embryonic or adult, can provide repair to an injured alveolus. Animal studies have been promising. In a lipopolysaccharide (LPS)-induced ALI/ARDS model, bone marrow progenitor cells localized to the site of injury and differentiated into endothelial and epithelial cells. Autologous transplantation of endothelial progenitor cells preserves endothelial function and maintains the integrity of the pulmonary alveolar-capillary barrier, whereas administration of mesenchymal stem cells reduces the severity of ALI/ARDS in mice.[35] Patients with pneumonia[36] and ALI/ARDS[37] have higher levels of endothelial progenitor cells, and these higher levels correlate with improved outcome. Mesenchymal stem cells were originally thought to act as a source of regenerative cells by differentiating into, and locally replacing, lethally injured cells. However, their primary mechanism of action may be through the secretion of growth factors, cytokines, and other signaling molecules to cause the trophic modulation of inflammation, cell death, fibrosis, and tissue repair.[38]

The third role of stem cells is their ability to deliver gene therapy to the injured lung. Endothelial progenitor cells have been used to deliver vasodilatory genes to the pulmonary vasculature with resultant decreases in PAOPs in experimental pulmonary hypertension. In one study, nontransfected mesenchymal stem cells reduced the severity of ALI/ARDS in a mouse LPS model, whereas administration of mesenchymal stem cells transfected with the human angiopoietin-1 gene only demonstrated a small additional improvement.[35] Human studies are awaited.

Vasodilators

Nitric oxide (NO) is an endogenous vasodilator produced by the endothelium. When administered by inhalation, it vasodilates the circulation of ventilated alveoli, thus potentially reducing shunt and pulmonary hypertension. Early studies demonstrated physiologic improvements with NO in ARDS[39–43]; however, mortality remained unchanged. Two meta-analyses showed no mortality benefit[44,45] and reported possible harm due to methemoglobinemia, toxic nitrogen compounds, increased pulmonary edema, rebound pulmonary hypertension, and renal failure. Because NO is expensive, possibly harmful, and without a mortality benefit, its routine use is not recommended, although it may have a place as salvage therapy for severe hypoxemia given its ability to increase oxygenation.[46]

Prostacylins are derivatives of arachidonic acid and have potentially beneficial effects, including vasodilation, inhibition of platelet aggregation, reduction of neutrophil adhesion, and inhibition of both macrophage and neutrophil activation. Inhaled prostaglandin I2 (PGI2; prostacyclin) has been compared with inhaled NO in ARDS.[47–49] PGI2 has similar efficacy and some advantages, including minimal systemic effects, absence of platelet dysfunction, easy administration, harmless metabolites, and no requirement for monitoring. No placebo-controlled randomized trial has yet studied PGI2 in ARDS, but an ongoing study aims to show that nebulized PGI2 (iloprost) decreases pulmonary hypertension selectively and improves oxygenation in ARDS (NCT00314548).

Intravenous prostacyclin in the form of PGE1 has also been investigated in ARDS. Although vasodilatory effects can cause hypotension and increase pulmonary shunting, prostacyclin is anti-inflammatory and can increase both cardiac output and oxygen delivery and improve oxygen extraction during reduced oxygen delivery. Early studies[50–52] in ARDS showed no significant benefit, although the dose delivered was questioned.[53] PGE1 was reformulated as liposomal PGE1 to increase pulmonary drug delivery and minimize side effects. Again, despite a promising preclinical study,[54] subsequent studies were negative.[55,56]

Endothelin-1 is a potent vasoconstrictor that has been implicated in the pathophysiology of lung injury. Tezosentan, an endothelin receptor antagonist, has been investigated in animal models of lung injury and with mixed results thus far.

Vasoconstrictors

Almitrine is a pulmonary vasoconstrictor that may increase hypoxic pulmonary vasoconstriction and reduce shunt. In a small ARDS study, oxygenation was improved, with minimal increase in pulmonary vascular pressures.[57] The combination of intravenous almitrine to decrease blood flow to hypoxic lung units and inhaled NO, to increase blood flow to ventilated lung units, has been investigated in both experimental lung injury and a small clinical study.[58] Both found the combination superior than either therapy alone at increasing Pa_{O_2}, with a minimal rise in pulmonary artery pressure. Further research is required.

Coagulation

An imbalance between fibrinogenesis and fibrinolysis in ARDS results in widespread fibrin deposition in the alveolar airspace, interstitium, and blood vessels. Pulmonary intravascular thrombosis and vasoconstriction can lead to the development of increased pulmonary vascular dead space, a known independent predictor of mortality in ALI/ARDS. Several anticoagulants have been proposed as potential therapies in ALI/ARDS and have undergone investigation in animal models. Tissue factor pathway inhibitor (TFPI), factor VIIai, heparin, antithrombin III, activated protein C (APC), and thrombomodulin have all been shown to have beneficial effects at this level of investigation.[59]

Protein C levels are lower in patients with ALI/ARDS than normal controls, and the level of protein C correlates with clinical outcome.[60] However, a small randomized controlled trial of APC in ALI/ARDS did not reduce either duration of ventilation or mortality, although pulmonary vascular dead space was decreased.[61] A further study investigating APC in inflammatory and infectious ALI/ARDS is in progress (ISRCTN52566874). A phase 2 trial of recombinant TFPI demonstrated improvements in lung dysfunction score and survival.[62] Therapeutic modulation of the coagulation system is not recommended in ALI/ARDS.

ANTI-INFLAMMATORY THERAPY

Glucocorticoids

Steroids possess a myriad of anti-inflammatory properties stretching from the genome to the macrophage. In the 1980s, several trials unsuccessfully examined the role of short-course, high-dose methylprednisolone in preventing the development of ARDS in high-risk patients.[63–66] A trial of high-dose steroids early in the course of ARDS was negative,[67] but a recent study in 91 patients with prolonged low-dose methylprednisolone showed reduced inflammation and organ dysfunction, plus reduced duration of mechanical ventilation and ICU stay.[68]

Excessive alveolar fibrosis is a feature of established ARDS, and the antifibrotic properties of steroids have been investigated in this setting. Observational studies[69–72] showed promising results and were followed by a small randomized controlled trial that suggested a beneficial effect on outcome.[73] However, the ARDSNet Late Steroid Rescue Study demonstrated no overall effect on mortality, with increased mortality when steroids were commenced 7 days after the onset of ALI/ARDS.[74] A recent meta-analysis[75] and systematic review[76] concluded that steroids have no role in preventing ARDS but may have a role in treating ARDS. Further studies are required to definitively answer this question, and studies of low-dose steroids in early ARDS are planned (NCT00562835 and NCT00773058). Corticosteroid therapy is covered in detail in Chapter 22.

Proinflammatory Mediator Inhibition

Eicosanoids are derivatives of arachidonic acid and act as proinflammatory mediators. They are produced through the activity of either 5-lipoxygenase to produce the leukotrienes or cyclooxygenase to produce prostanoids.

Ketoconazole is an imidazole antifungal agent with anti-inflammatory properties, specifically an ability to block leukotriene and thromboxane A_2 synthesis, and an antimacrophage effect whereby proinflammatory cytokine secretion is reduced. Small studies reported positive results for the prevention of ARDS in high-risk patients.[77–79] A large subsequent study by the ARDSNet group of ketoconazole in 234 patients with ARDS demonstrated no beneficial effects.[80]

Ibuprofen is a nonsteroidal anti-inflammatory agent that inhibits cyclooxygenase. In a large sepsis study of 448 patients, ibuprofen diminished prostanoid production and was associated with a trend toward decreased duration of pulmonary dysfunction and ARDS, but this did not reach statistical significance.[81] Modulation of other inflammatory mediators has also been investigated, but to date, no treatment has been shown to effectively reduce mortality.

Complement can contribute to ALI/ARDS by the generation of C3a and C5a, which attract neutrophils to the lungs and activate them. Complement can also cause cellular injury through the production of the membrane attack complex, C5b-9. Complement receptor-1 is a cell surface receptor on erythrocytes and leukocytes that can inhibit both classic and alternative complement pathways. Animal studies have provided a basis for further investigation, and a human phase 1 study in 24 patients with ARDS has demonstrated the safety of recombinant soluble cytokine receptor-1 and its ability to inhibit the complement cascade.[82] Further studies are awaited.

Insulin has anti-inflammatory effects through inhibition of the proinflammatory transcription factor NFkB. In a rat model of endotoxin-induced ALI/ARDS, tight glycemic control to 90 to 110 mg/dL reduced the severity of lung injury.[83] The role of intensive insulin therapy in preventing ALI/ARDS by maintaining tight glycemic control (80 to 110 mg/dL) is being studied in a phase 2 trial (NCT00605696).

Other current studies of potential anti-inflammatory treatments include a trial investigating the safety, tolerability, and efficacy of recombinant human interferon-β in ALI/ARDS (NCT00789685) and a phase 2 trial of IC14, a recombinant chimeric monoclonal antibody to CD14, to block CD14-medicated cellular activation in patients with sepsis-induced ALI (NCT00233207). This trial has recently been terminated, and results are awaited. Anti-inflammatory therapy for ALI/ARDS is not recommended.

Table 12-2 **Summary of Omega-3 Polyunsaturated Fatty Acid (PUFA) Supplementation Studies in ALI/ARDS**

Study	Omega-3 PUFA	Other Antioxidants	Number in Trial	Setting	Nonmortality Benefits	Absolute Mortality Reduction
Singer et al, 1986[86]	EPA and GLA	Yes	100	ALI	Yes	No
Pontes-Arruda et al, 2006[87]	EPA and GLA	Yes	156	Sepsis and ARDS	Yes	19%
Pacht et al, 2003[88]	EPA and GLA	Yes	43	ALI/ARDS	Yes	Not reported
Gadek et al, 1999[89]	EPA and GLA	Yes	146	ARDS	Yes	No
Elamin et al, 2005[90]	EPA and GLA	Yes	16	ARDS	Yes	Not reported

EPA, eicosapentaenoic acid; GLA, γ-linolenic acid.

Immunonutrition

Nutrition plays various roles in the management of ALI/ARDS. The use of a feed high in fat and low in carbohydrate can reduce carbon dioxide production and thus ventilatory requirements.[84] Enteral nutrition can stimulate gut and lung immunoglobulin A (IgA) defense mechanisms.[85] The omega-3 polyunsaturated fatty acids found in fish oil, eicosapentaenoic acid (EPA), γ-linolenic acid (GLA), and docosahexaenoic acid (DHA) can reduce the production of arachidonic acid from membrane phospholipids.

Clinical studies in ALI/ARDS have demonstrated the benefit of fish oil supplementation with reductions in pulmonary neutrophil infiltration, microvascular permeability, pulmonary vascular resistance, duration of ventilation and ICU stay, and improved mortality.[86–90] This benefit from fish oil supplementation in ARDS has been supported in a recent systematic review on immunonutrition.[91] Further studies of fish oils in ALI/ARDS are in progress in Spain (ISRCTN63673813) and the United States (NCT00351533) (NCT00609180). This latter ARDSNet study will also investigate early versus late feeding as well as antioxidants in ARDS. These studies will inform the use of immunonutrition in ALI/ARDS. Omega-3 fatty acid–based nutrition may have a role to play in the management of ALI/ARDS (Table 12-2).

Anti–Adhesion Molecule Therapy

The adhesion of immune cells to the endothelium to facilitate diapedesis is a vital step in the accumulation of neutrophils in the alveolus. The blockage of adhesion molecules is a potential therapeutic target in ALI/ARDS. Blockage of CD18, a neutrophil adhesion molecule, has been shown to attenuate the development of experimental lung injury. To date, there are no human studies.

Effector Cell Inhibition

Pentoxifylline is a phosphodiesterase inhibitor with anti-inflammatory effects, acting against both neutrophils and macrophages. A small phase 1 study of pentoxifylline in six ARDS patients did not show any advantage in either gas exchange or hemodynamic parameters.[92]

Lisofylline is a pentoxifylline derivative with slightly differing anti-inflammatory mechanisms. Although it also inhibits neutrophil accumulation and downregulates pro-inflammatory cytokines, it additionally has an effect on reducing levels of oxidized free fatty acids. Animal studies of lisofylline in the treatment of ARDS were promising, but again, a large multicenter study by the ARDSNet group in 235 patients with ALI/ARDS was negative.[93]

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is involved in the development and homeostasis of alveolar macrophages. It also plays a role in the prevention of alveolar epithelial apoptosis. A small study of 10 patients with ALI demonstrated an improvement in oxygenation with GM-CSF over a 5-day period.[94] A further study of GM-CSF in ARDS is under way in the United States (NCT00201409)

Activated neutrophils release neutrophil elastase, which plays a key role in alveolar injury, leading to increased vascular permeability and alveolar flooding. EPI-hNE-4 is a neutrophil elastase inhibitor that improved pulmonary compliance without affecting immune function during *Pseudomonas aeruginosa*–induced pneumonia in rats. A phase 3 multicenter trial of Depelestat (EPI-hNE-4) in ARDS has completed and is awaiting publication (NCT00455767). Sivelestat is a reversible, competitive inhibitor of neutrophil elastase. After promising animal studies, sivelestat underwent a phase 3 study, in which it improved pulmonary function and reduced duration of ICU stay, with trends toward a reduction in duration of mechanical ventilation and mortality.[95] However, the international Sivelestat Trial in ALI Patients Requiring Mechanical Ventilation (STRIVE) study in 492 ALI patients was stopped prematurely after an increase in the 180-day all-cause mortality rate was noted. No pulmonary improvements occurred, and the 28-day mortality rate was not reduced.[96]

Antioxidant Therapy

Activated neutrophils and macrophages partly exert their injurious effects through the generation of reactive oxygen species. Pulmonary glutathione, an antioxidant, is reduced in ARDS. *N*-acetylcysteine and procysteine are precursors for glutathione, and their administration can replete pulmonary glutathione levels in ARDS. Small

studies of *N*-acetylcysteine in ALI/ARDS reported mixed results,[97–100] whereas a study of procysteine in ARDS was halted in 1998 owing to increased mortality (unpublished data). *N*-acetylcysteine can also downregulate NFkB, with resultant reduction in neutrophil chemoattractant messenger RNA (mRNA) and alveolitis in a rat model of lung injury.

Vitamin C and E administration in the critically ill reduced duration of mechanical ventilation and ICU stay without decreasing the incidence of ARDS.[101]

Statins

Statins were introduced into clinical practice as cholesterol-lowering agents through inhibition of HMG-CoA reductase and have since been shown to possess pleiotropic actions both dependent and independent of HMG-CoA reductase inhibition. Statins exert beneficial effects on inflammation and coagulation as well as epithelial, endothelial, and immune cells function.[102] Several retrospective studies have demonstrated that prior statin therapy is associated with improved survival in sepsis, including pneumonia.[103–107] Patients with ALI/ARDS receiving treatment with a statin during admission had a 73% lower odds of death, although this failed to reach statistical significance (odds ratio, 0.27; 95% confidence interval, 0.06 to 1.21; $P = .09$).[108] In contrast, another study suggested no benefit.[109] A recent study has shown pretreatment with a statin[110] reduces pulmonary markers of inflammation in an inhaled LPS-induced model of lung injury in healthy volunteers. The ongoing phase 2 HARP-prevention (ISRCTN56543987) and Hydroxymethylglutaryl-CoA reductase inhibition in Acute lung injury to Reduce Pulmonary oedema and inflammation (HARP) (ISRCTN70127774) studies are investigating the effect of simvastatin in the prevention and treatment of ALI/ARDS and will further inform this area. Several groups, including the ARDSNet and the Irish Critical Care Trials group are currently considering undertaking multicenter studies to address the role of statins in ALI/ARDS.

Angiotensin-Converting Enzyme Inhibitors

The SARS epidemic led to the discovery of a novel coronavirus, the receptor for which is a variant of the angiotensin-converting enzyme (ACE) implicating the renin-angiotensin system (RAS) in ALI/ARDS. ACE converts angiotensin I into angiotensin II, and angiotensin II acting through the angiotensin I receptor mediates vasoconstriction, alveolar permeability, and lung injury. ACE2 degrades angiotensin II, and therefore excessive ACE activity or ACE2 deletion is associated with worse lung injury.

Genetic observational studies in humans have supported the concept that the RAS system is important in the development and outcome of ALI/ARDS. ACE DD genotype is associated with increased ACE activity and worse outcome in ALI/ARDS.[111–113] A retrospective study has shown that prior treatment with an ACE inhibitor was associated with decreased mortality in patients requiring hospitalization for community-acquired pneumonia.[107] Therapeutic modulation of the RAS with recombinant ACE2, ACE inhibition, and angiotensin I receptor blockade with losartan attenuate pulmonary inflammation in rodent models of LPS-induced ALI/ARDS and ventilator-induced lung injury. Human studies are awaited.

Induced Hypothermia

Hypothermia decreases metabolism by 25% at 33°C, reducing oxygen consumption and carbon dioxide production and thus ventilatory demand. It also decreases proinflammatory gene transcription and exerts an anti-inflammatory effect. In animal models, induced hypothermia reduces the expression of intracellular adhesion molecule-1, interleukin-1β levels, the pulmonary accumulation of neutrophils, and histologic lung damage. Several case reports have documented the successful use of hypothermia (33° to 34°C) for severe ALI/ARDS.[114–116] To date, there has been only one small study of 19 patients with sepsis-associated severe ALI/ARDS treated with induced hypothermia. The mortality rate was reduced by 33% at a mean temperature of 33.7 °C. The reduction in body temperature was associated with a reduction in alveolar-arterial oxygen gradient, heart rate, and cardiac index and an increase in oxygen extraction, although interestingly, oxygen consumption remained unchanged.[117] Further research is required.

REASONS THAT PHARMACOLOGIC THERAPY IS INEFFECTIVE IN ALI/ARDS

Despite repeated promising preclinical and clinical phase 1 and 2 studies of therapies for ALI/ARDS, no nonventilatory strategy has yet convincingly been shown to improve outcome. The many reasons for the scientific failure of translation from bench to bedside include limitations of animal models, poorly understood human factors, study methodologic flaws, and the use of oxygenation as an outcome measure in a condition in which only a small minority die from refractory hypoxemia.[118,119] The use of pharmacologic agents as adjuncts to increase oxygenation allowing the limitation of injurious ventilation may be associated with improved outcomes, but this remains to be tested.

AUTHORS' RECOMMENDATIONS

- Despite promising scientific advances, nonventilatory strategies for ALI/ARDS remain elusive.
- The best evidence we have is for minimizing pulmonary edema through fluid restriction when appropriate.
- Other therapies may occasionally be justified as salvage therapy in severe ALI/ARDS, but with the knowledge that their risk-to-benefit ratio remains unclear.

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