

Pharmacotherapy for Prevention and Treatment of Acute Respiratory Distress Syndrome

Current and Experimental Approaches

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Abstract

The acute respiratory distress syndrome (ARDS) arises from direct and indirect injury to the lungs and results in a life-threatening form of respiratory failure in a heterogeneous, critically ill patient population. Critical care technologies used to support patients with ARDS, including strategies for mechanical ventilation, have resulted in improved outcomes in the last decade. However, there is still a need for effective pharmacotherapies to treat ARDS, as mortality rates remain high. To date, no single pharmacotherapy has proven effective in decreasing mortality in adult patients with ARDS, although exogenous surfactant replacement has been shown to reduce mortality in the paediatric population with ARDS from direct causes. Several promising therapies are currently being investigated in preclinical and clinical trials for treatment of ARDS in its acute and subacute, exudative phases. These include exogenous surfactant therapy, β_2 -adrenergic receptor agonists, antioxidants, immunomodulating agents and HMG-CoA reductase inhibitors (statins). Recent research has also focused on prevention of acute lung injury and acute respiratory distress in patients at risk. Drugs such as captopril, rosiglitazone and incyclinide (COL-3), a tetracycline derivative, have shown promising results in animal models, but have not yet been tested clinically. Further research is needed to discover therapies to treat ARDS in its late, fibroproliferative phase. Given the vast number of negative clinical trials to date, it is unlikely that a single pharmacotherapy will effectively treat all patients with ARDS from differing causes. Future randomized controlled trials should target specific, more homogeneous subgroups of patients for single or combination therapy.

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) arise from direct or indirect injury to the lungs, and results in a life-threatening form of respiratory failure. ALI/ARDS is both common and serious: 6.5–8.5% of patients admitted to an intensive care unit (ICU) will be diagnosed with ALI or ARDS,^[1–3] and approximately one-quarter to one-half of these patients will succumb to this disease process.^[1,4–6] Over the past 40 years, ARDS has been the focus of extensive basic science and clinical research, although no single pharmacotherapy has been shown to reduce mortality in a large, randomized, controlled, multicentre trial of adult patients. The reasons for this are manifold, and include issues of dosing, route of administration and timing of the various interventions tested. More importantly, however, may be the nature of the disorder itself: the diagnosis of ARDS envelops a heterogeneous group of patients with varying causes and pathophysiological mechanisms at work. The notion that a therapeutic agent that can successfully alter a single biological target in an animal model of

ALI will reduce mortality in *all* patients with ARDS may be unrealistic. Nonetheless, there is reason for hope on the scientific horizon.

Recent advances have been made in our understanding of the pathophysiological mechanisms underlying ALI/ARDS, leading to the identification of potential novel targets for pharmacological intervention. Some therapies are best aimed at preventing the development of ARDS, while others treat the syndrome as it unfolds or aid in its resolution. The challenge lays in identifying the subgroup of patients most likely to benefit from such focused therapy. This paper reviews the current experimental and existing approaches to managing ARDS, highlighting the pathophysiological basis for their use and potential for future clinical development.

1. Pathophysiology and Clinical Course

ALI may occur following a direct insult to the pulmonary system such as aspiration of gastric contents, bacterial pneumonia or viral pneumonitis (e.g. H1N1 influenza virus), or an indirect

insult such as the systemic inflammatory response associated with pancreatitis, sepsis or multiple trauma. Table I shows common direct and indirect causes of ALI/ARDS. Whether this ‘first hit’ to the lung is direct or indirect, a pulmonary inflammatory response may occur, which often is adaptive and self-limited. However, when coupled with repeated ‘hits’ to the lung from insults such as injurious mechanical ventilation or other secondary processes such as hypotension, a cycle of intense inflammation and worsening pulmonary injury ensues. The ‘multiple hit’ theory of ARDS progression also provides a framework for studying the disease process (figure 1).

Clinically, ALI manifests as bilateral airspace disease observed on chest radiograph and hypoxaemia, such that the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) is greatly reduced. According to the 1994 American European Consensus Conference (AECC) definition, a chest radiograph consistent with pulmonary oedema and a $\text{PaO}_2/\text{FiO}_2$ ratio <300 is sufficient to diagnose ALI in the setting of an inciting pulmonary insult and the absence of congestive heart failure. The aforementioned criteria but with a $\text{PaO}_2/\text{FiO}_2$ ratio <200 is classified as ARDS.^[8] Although differentiated by the AECC definition, ALI and ARDS are often grouped together for the purpose of clinical trial enrolment and are treated as a single entity throughout this review.

Although not all patients follow the same clinical course, progression of ALI/ARDS may

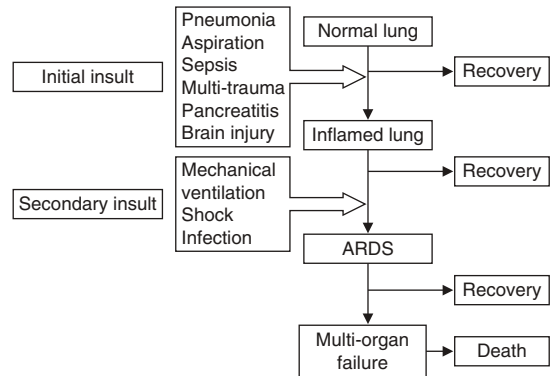


Fig. 1. ‘Multiple hit’ theory of acute respiratory distress syndrome (ARDS) progression. The ‘first hit’ to the lung incites a pulmonary inflammatory response, which, when coupled with repeated ‘hits’ to the lung from injurious mechanical ventilation or other secondary insults, may lead to the pathological manifestations of ARDS. The most common cause of death in ARDS is multiple organ dysfunction syndrome (reproduced from Bosma et al.^[7] [2007], with permission).

be considered along a pathophysiological timeline of early, mid and late phases, with considerable overlap between these phases. Table II summarizes the pathogenetic mechanisms at work during each phase, linking each biological pathway to a potential drug therapy. A general overview of the pathophysiology of ARDS is provided here, with more detailed descriptions of the specific biologic pathways discussed in sections 3.1–3.3 as they pertain to each potential pharmacological therapy.

The early phase, within the first 72 hours of the inciting lung injury, is characterized by inflammatory damage to the alveolar-capillary barrier. This results in increased vascular permeability, leading to interstitial and alveolar oedema as proteinaceous fluid fills the alveolar space. This inflammation-induced pulmonary oedema disrupts normal gas exchange and increases the work of breathing, leading to respiratory failure and the need for mechanical ventilation. Mechanical ventilation itself may cause secondary insult to the already inflamed oedematous alveoli. During each tidal breath induced by mechanical ventilation, unstable alveoli undergo cyclical collapse and shearing open, termed ‘atelectrauma’. Furthermore, the non-collapsed alveolar units may receive a

Table I. Direct and indirect causes of acute lung injury/acute respiratory distress syndrome

Direct causes	Indirect (systemic) causes
Bacterial pneumonia	Sepsis
Viral pneumonitis	Pancreatitis
High-risk viruses:	Surface burns
SARS coronavirus	Drug overdose
H1N1 influenza A virus	Transfusion-related acute lung injury
Gastric aspiration	Severe trauma (without contusion)
Blunt thoracic trauma with lung contusion	Cardiopulmonary bypass
Near drowning	
Smoke inhalation	
Meconium aspiration (infants)	

SARS = severe acute respiratory syndrome.

Table II. Pathophysiology of acute respiratory distress syndrome (ARDS)^a

Mechanism	Pathophysiological process	Potential therapeutic approach ^b
Early (0–72 hours)^a		
Damage to alveolar-capillary barrier	Capillary endothelial cell damage Alveolar epithelial cell damage	ACE inhibitors, ARBs, GM-CSF GM-CSF
Alveolar oedema formation	Protein leak into alveoli Fluid accumulation in alveoli	β_2 -Agonists, GM-CSF, diuretics
Neutrophil recruitment	Mediated by increased NF- κ B activity Mediated by increased ICAM-1 expression	PPAR- γ agonists
Neutrophil activation	Release proteases: MMPs HNE defensins Release AA metabolites: thromboxanes leukotrienes prostaglandins Modulation of neutrophil activation	Incyclinide Incyclinide, HNE inhibitors Ketoconazole Prostaglandin E1
Early-Mid (0–7 days)^a		
Delayed neutrophil apoptosis		
Intra-alveolar hyaline membrane formation		
Oxidant stress	Increased oxygen free radical production Decreased glutathione levels	N-acetylcysteine, α -tocopherol, ascorbic acid N-acetylcysteine
Increased inflammatory mediators	General Specific: PAF eicosanoids from omega-6 FA phosphatidic acid-1 α IL-8 TNF α	Corticosteroids, statins rhPAF acetylhydrolase Omega-3 FA supplementation Lisofylline Anti-IL-8 monoclonal antibody Anti-TNF α monoclonal antibody
Disruption of surfactant system	Surfactant impaired function/increased metabolism	Exogenous surfactant replacement
Activation of complement		
Activation of coagulation cascade	Decreased plasma protein-C levels	Drotrecogin alfa
Late (8–28 days)^a		
Organization and fibrosis	Proliferation of type II alveolar cells Organization of alveolar exudates Interstitial collagen-rich matrix formation Alveolar fibrosis/destruction	Corticosteroids

a Mechanisms causing pulmonary dysfunction may occur simultaneously and overlap in different stages of ARDS.

b See text for details.

AA=arachidonic acid; **ARB**=angiotensin receptor antagonist (blocker); **FA**=fatty acid; **GM-CSF**=granulocyte macrophage colony-stimulating factor; **HNE**=human neutrophil elastase; **ICAM-1**=intercellular adhesion molecule-1; **IL-8**=interleukin-8; **MMPs**=matrix metalloproteinases; **NF- κ B**=nuclear factor- κ B; **PAF**=platelet-activating factor; **PPAR- γ** =peroxisome proliferator activated receptor- γ ; **rhPAF**=recombinant human PAF; **TNF α** =tumour necrosis factor- α .

greater proportion of the delivered tidal volume, leading to damage due to overdistention or 'volutrauma'. Further breakdown of the endothelial-

epithelial barrier may occur with atelectrauma and volutrauma, along with the release of local proinflammatory mediators which further

propagate this cycle of ventilator-exacerbated lung injury.^[7]

As inflammation ensues, neutrophils are recruited to the lung. Damaged endothelial cells exhibit increased activity of the transcription factor nuclear factor- κ B (NF- κ B), which up-regulates the surface expression of intercellular adhesion molecule (ICAM)-1. ICAM-1 mediates leukocyte adhesion and migration across the endothelium to the alveolar epithelium. Activated neutrophils release proteases, such as matrix metalloproteinases (MMP) and neutrophil elastase (NE), which further damage the alveolar-capillary membrane.^[9] Activated neutrophils also contain high levels of arachidonic acid,^[10] which is metabolized into leukotrienes, prostaglandins and thromboxanes. Leukotrienes attract more neutrophils, prostaglandins are proinflammatory mediators, and thromboxanes play a role in vasoconstriction and platelet and leukocyte aggregation. Neutrophil recruitment and activation may be an adaptive physiological response to injury, or may incite a vicious cycle of inflammation and further damage.^[9]

At this stage, patients may recover from the initial insult, with clearance of the pulmonary oedema and restoration of the barrier between capillary endothelial and alveolar epithelial cells, or may progress to the exudative or mid phase of ARDS. It is not fully understood why two patients exposed to the same insult may have completely different clinical courses; however, genetic factors,^[11] co-morbid illnesses such as diabetes mellitus and alcohol addiction,^[12] nutritional status, medications and exposure to further insults are all likely to play a role. Understanding the host and environmental factors that place a patient at high risk of progressing to the exudative phase of ARDS will facilitate identification of targets for earlier intervention.

The exudative or subacute phase typically occurs over the 3–7 days following the initial insult. Pathologically, this mid phase is characterized by formation of intra-alveolar hyaline membranes rich in plasma proteins, fibrin and cellular debris.^[13] A biopsy of the lungs at this stage will show diffuse alveolar damage and, clinically, the lungs have poor compliance with ongoing gas exchange

problems including hypoxaemia and elevated dead space fraction. The inflammatory milieu within the alveoli, coupled with the cyclical opening, stretching and collapsing of alveoli via mechanical ventilation, initiates a number of pathogenic pathways in concert or in series. These include disruption of surfactant function and metabolism, ongoing neutrophil recruitment and activation, along with increased expression and release of inflammatory mediators, imbalance of oxidant and antioxidant activity, and activation of complement and coagulation cascades. Each of these pathways is further discussed to provide context for the drugs or therapies aimed at ameliorating these various mechanisms (see section 3).

Interestingly, only a minority of patients will succumb to severe hypoxaemia or hypercarbia, as the major source of mortality is not the pulmonary injury *per se*, but rather the occurrence of multiple organ failure. In this setting, the injured lung may represent a rich source of inflammatory mediators that could contribute to the development of multi-organ failure. For example, stress failure and necrosis of the endothelial-epithelial barrier may allow various inflammatory mediators, bacteria and endotoxins to quickly spread from the lungs into the systemic circulation. Indeed, it is this de-compartmentalization of inflammatory mediators from the lungs into the circulation that is felt to lead to cell apoptosis in distal organs,^[14] and ultimately multiple organ dysfunction syndrome (MODS) [figure 2].^[15] Once MODS develops, disease is often irreversible and mortality may increase significantly to 60–98%, the latter occurring when three or more organs are involved for a period of more than 7 days.^[15–17] Thus, a key to developing novel therapies that will reduce mortality in ARDS will be identification of the cellular and molecular mechanisms by which ARDS leads to MODS.

Survivors of the first week of ALI/ARDS may enter the late phase of the disorder, known as the fibroproliferative phase. During days 8–28, the exudates and hyaline membranes become organized, and fibrosis may become apparent. Type II alveolar cells proliferate and line the alveolar walls, fibroblasts migrate and differentiate into

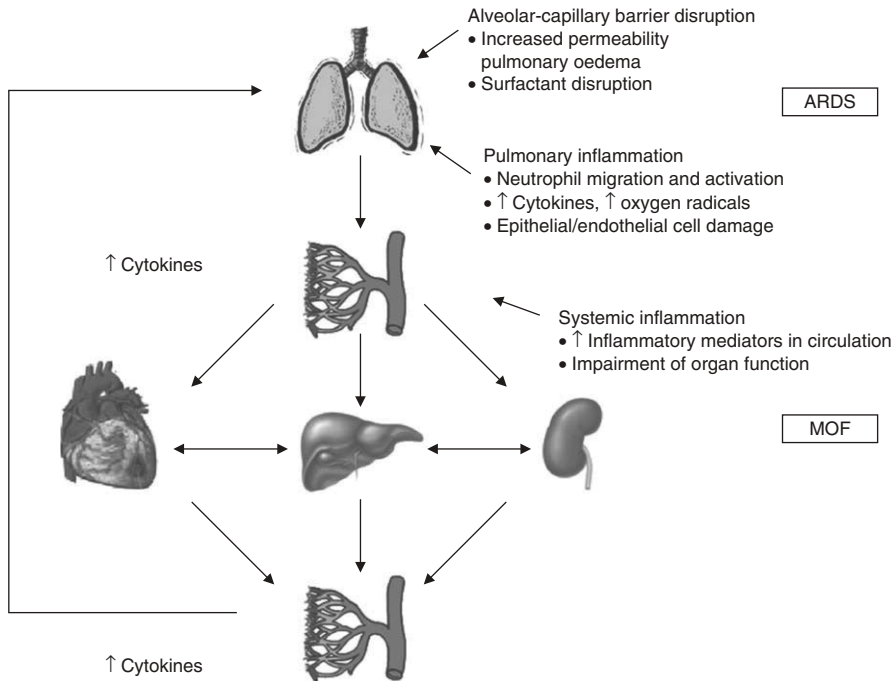


Fig. 2. Progression of acute respiratory distress syndrome (ARDS) to multi-organ failure (MOF). Initially, inflammatory damage to the alveolar-capillary barrier results in increased vascular permeability, leading to interstitial and alveolar oedema as proteinaceous fluid fills the alveolar space. There, the proteinaceous fluid interferes with the function and metabolism of the endogenous surfactant system. Coupled with this, neutrophils that infiltrate lungs are subsequently activated and represent an important source of inflammatory mediators and oxygen free radicals, inducing further epithelial and endothelial cell damage and an altered host immune response. Newly secreted mediators and/or spill-over of inflammatory mediators from the lung into the systemic circulation ultimately contribute to the development of MOF. Inflammatory mediators released from organs such as the liver, heart and kidney return to the lung via the systemic circulation and may contribute to further pulmonary inflammation. Thus, each new insult to the pulmonary system accelerates the acute lung injury cycle (reproduced from Bosma et al.^[7] [2007], with permission).

myofibroblasts in the interstitial and alveolar spaces, and a collagen-rich extracellular matrix is laid down in the interstitium.^[13] Alveoli may be destroyed, pulmonary vascular area may be reduced and chronic inflammation is generally present. Patients in the fibroproliferative phase of ARDS may slowly recover, or may fail to wean from mechanical ventilation and succumb to complications of a lengthy critical illness or pre-existing co-morbid illnesses. Pharmaceutical interventions for late ARDS must interrupt the fibrosing alveolitis and aid in resolution, remodelling and repair of injured lungs.^[13] Often, therapies that might be beneficial during the early phase of lung injury are started too late in the course of the disease, when fibrosis is already established, muting their potential efficacy. When

tested specifically for the late fibroproliferative phase of ARDS, anti-inflammatory therapies have yielded disappointing results. Basic science research examining mechanisms of idiopathic pulmonary fibrosis may illuminate therapeutic pathways for fibroproliferative ARDS, but further work is required in this area.

2. Supportive Care and Salvage Therapies

Although no pharmacological therapies have been proven to reduce mortality in large, randomized controlled trials (RCTs) involving adult patients, it appears that improvements in supportive care have reduced mortality to some extent. For example, mortality estimates ranged

from 55% to 65% as reported in the literature in the 1980s and early 1990s^[18-21] to more recent estimates of 32–46% in observational epidemiological studies^[1,2] and 25–31% in large clinical trials.^[5,6] Although this mortality reduction may in part reflect differences in diagnostic criteria used post publication of the 1994 AEC definition, undoubtedly the largest impact has been the move to more ‘protective’ strategies of mechanical ventilation.

In 2000, the National Institutes of Health-sponsored ARDS Network (ARDSnet) trial involving low tidal volume ventilation was published, and now constitutes the standard of care for patients with ALI and ARDS. This trial compared a traditional tidal volume of 12 mL/kg with a lower tidal volume of 6 mL/kg in 861 patients and reported a mortality reduction from 40% in the control arm to 31% in the treatment arm.^[5] These results definitively ended the debate fuelled by three previous inconclusive smaller trials regarding lower versus conventional tidal volumes. In terms of furthering ALI/ARDS research, several lessons have been learned from this landmark study. First, ARDSnet was set up to conduct well designed, large, phase III studies with a concerted effort to optimize patient enrolment through involvement of many centres in an organized and cohesive group.^[22] This enabled a study sufficiently powered to realize a mortality difference to be conducted within a reasonable timeframe, and pointed the way for other similarly structured ARDS research networks to become established. Second, the treatment arm was associated with lower oxygenation values than the conventional arm, highlighting the potential danger of relying on oxygenation or other physiological parameters as surrogates for mortality. Third, this study demonstrated that a non-pharmacological intervention could alter mortality, indicating that future RCTs need to be carefully standardized in all aspects of supportive care in both treatment and control arms.

One potential caveat ensuing from this study has been the assumption that any additional proven therapy would reduce mortality across a population as heterogeneous and diverse as that enrolled in the ARDSnet low tidal volume trial.

This approach may be misguided, as subsequent studies have demonstrated differences between patients with direct and indirect causes of ALI/ARDS in responsiveness to specific therapies.^[23,24] Research is ongoing to determine whether newer modes of mechanical ventilation, such as high-frequency oscillation (HFO), can further improve outcomes in ARDS relative to the ARDSnet low tidal volume strategy.^[25] In addition, other aspects of supportive care have been evaluated in large clinical trials, some conducted by ARDSnet, and have proven effective in reducing morbidity associated with critical illness. These include cautious fluid management,^[26,27] adequate nutrition,^[28] prevention of ventilator associated pneumonia,^[29-32] prophylaxis for deep venous thrombosis^[33] and gastric ulcers,^[34] weaning of sedation and mechanical ventilation as early as possible,^[35] and physiotherapy and rehabilitation.^[36] A recent review of all patients enrolled in ARDSnet studies between 1996 and 2005 showed that these advancements in critical care (aside from lower tidal volume ventilation) are likely responsible for the improved survival in ALI/ARDS patients in clinical trials noted over the last decade.^[37]

Additional modalities used as ‘rescue therapies’ for the ARDS patient at risk of succumbing to severe hypoxaemia or respiratory acidosis have also been tested, including nitric oxide, prone positioning, HFO and extracorporeal membrane oxygenation (ECMO). Nitric oxide^[38] and prone positioning^[39,40] have not been shown to reduce mortality or duration of mechanical ventilation in patients with ALI/ARDS, and are therefore not recommended for routine use. However, combined together, these therapies may provide a sustained improvement in oxygenation for patients with severe hypoxaemia and a mortality benefit for patients who are failing conventional mechanical ventilation strategies.^[39-41] A clinical trial of HFO for routine care of patients with ARDS is currently underway, but existing evidence supports its use as salvage therapy if instituted early for patients failing conventional ventilation,^[42] and may have additive benefits when combined with nitric oxide and prone positioning.^[43] Finally, ECMO has

Table III. Clinical trial acronyms

Acronym	Definition
ALTA	Albuterol ^a to Treat Acute Lung Injury
BALTI-1	Beta-Agonist Lung Injury Trial
CARDS	Calfactant for direct Acute Respiratory Distress Syndrome
CESAR	Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure
CORTIFLU	Low Doses Corticosteroids as Adjuvant Therapy for the Treatment of Severe H1N1 Flu
KARMA	Ketoconazole and Respiratory Management in ALI and ARDS
LARMA	Lisofylline and Respiratory Management in the treatment of ALI and ARDS
LaSRS	Late Steroid Rescue Study
SAILS	Statins for Acutely Injured Lungs From Sepsis
STIP	Statin Trial for Influenza Patients
STRIVE	Sivelestat Trial in ALI Patients Requiring Mechanical Ventilation

a Salbutamol.

recently been studied in the CESAR trial (see table III for a list of trial acronyms).^[44] This study showed that transferring adult patients with severe but potentially reversible respiratory failure, whose Murray score exceeds 3.0 or who have a pH of <7.20 on optimum conventional management, to a centre with an ECMO-based management protocol, significantly improved survival without severe disability. Recent evidence suggests ECMO is also useful for rescue therapy for adults with severe ARDS due to H1N1-influenza A virus infection.^[45]

3. Current and Experimental Pharmacological Treatments

Pharmacological treatments for ALI/ARDS may be employed prior to the onset of ARDS or in the early, mid or late phases of ARDS (table IV). Accordingly, their purpose may be to prevent ALI in those at risk, mitigate the pathogenic mechanisms responsible for the cycle of lung injury and systemic inflammation in established ARDS, or aid in lung healing and repair. Some therapies, such as corticosteroids, have been studied for prevention of ARDS, treatment of early

ARDS and treatment of late ARDS, and are discussed within each context.

3.1 Prevention of Acute Respiratory Distress Syndrome (ARDS) in Patients at Risk

The concept that ARDS may be prevented in those at high risk after an inciting insult is not new, but is one that is garnering greater attention in the scientific literature in recent years. Since no pharmacological agent has proven effective in treating established ARDS in adults, attention has turned to prophylactic treatment to prevent the development of ARDS in those at highest risk. Of course, any pharmacotherapy that is initiated prior to the diagnosis of disease must have a very high benefit to risk ratio and be cost effective. As such, it should have the following attributes: (i) be low risk, without serious adverse effects; (ii) be easily and widely applicable; and (iii) be relatively inexpensive. Drug classes studied for ARDS prevention include imidazoles (e.g. ketoconazole), ACE inhibitors, thiazolidinediones (e.g. rosiglitazone), chemically modified tetracycline derivatives, antioxidants, and corticosteroids and other immunomodulating agents.

3.1.1 Ketoconazole

Over 20 years ago, the first clinical trial examining prophylactic use of ketoconazole to prevent ARDS in patients at risk was published.^[46] The rationale for using ketoconazole, an antifungal drug with anti-inflammatory properties, was as follows. As mentioned in section 1, patients with ARDS have increased levels of arachidonic acid metabolites in their bronchoalveolar fluid.^[10,87] Metabolism of arachidonic acid leads to the production of leukotrienes, prostaglandins and thromboxanes. Thromboxane A₂ is a potent vasoconstrictor, and is involved with platelet and leukocyte aggregation, while leukotrienes act as powerful chemokines to attract neutrophils. Ketoconazole is an antifungal agent of the imidazole class which selectively blocks thromboxane synthetase. Ketoconazole also inhibits 5-lipoxygenase, the enzyme necessary to generate leukotrienes, and inhibits procoagulant activity.^[55] In addition to showing promise in preclinical

Table IV. Pharmacotherapy studied for prevention or treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)^a

Pharmacological agent	Class	Current evidence [SC/MC, phase (no. of patients/trial)]	Outcome	References
Prevention of ALI/ARDS				
Ketoconazole	Imidazole	3 SC clinical trials (n = 71, 54, 40)	Reduced incidence of ARDS	46-48
Captopril	ACE inhibitor	Animal model	Reduced severity of ARDS	49
Rosiglitazone	PPAR- γ agonist	Animal model	Reduced severity of ARDS	50
Incyclinide (COL-3)	Tetracycline derivative	Animal model	Reduced incidence of ARDS	51
α -Tocopherol, ascorbic acid	Antioxidants	1 SC clinical trial (n = 595)	No risk reduction for ARDS ^b	52
Methylprednisolone	Corticosteroid	4 SC clinical trials (n = 81, 75, 304, 42), MA	No risk reduction for ARDS ^c	53
rhPAF-acetylhydrolase	Indirect cytokine inhibitor	1 MC clinical trial, phase IIb (n = 127)	No risk reduction for ARDS	54
Treatment of established ARDS: acute and exudative phases				
Ketoconazole	Imidazole	1 MC clinical trial (n = 234)	No mortality reduction	55
Salbutamol (intravenous)	β_2 -Agonist	1 SC clinical trial (n = 40)	Reduced extravascular lung water	56
Salbutamol (aerosolized)	β_2 -Agonist	1 MC clinical trial (n = 279)	No reduction in ventilator-free days	57
Exosurf [®]	Surfactant (aerosolized)	1 MC clinical trial, phase III (n = 725)	No mortality reduction	58
Survanta [®]	Surfactant (instilled)	1 SC clinical trial, phase II (n = 59)	No safety concerns	59
Venticute [®]	rSP-C surfactant (instilled)	2 MC clinical trials, phase III (n = 448, 800)	No mortality reduction ^d	23,60
Calfactant (Infasurf [®])	Surfactant (instilled)	1 MC clinical trial [paediatric] (n = 153)	Mortality reduction	61
N-acetylcysteine, oxothiazolidine (Procyteine [®])	Antioxidants	2 MC, 1 SC clinical trials (n = 46, 61, 66)	No mortality reduction	62-65
Omega-3 fatty acids, α -tocopherol, ascorbic acid	Antioxidants	2 MC clinical trials, phase III, II (n = 272, 98)	No mortality reduction	66-68
Sivelestat	Neutrophil elastase inhibitor	2 MC clinical trials, phase III (n = 492, 230)	No mortality reduction	69,70
Depelestat	Neutrophil elastase inhibitor	Animal model, phase II ^e	Reduced lung inflammation	71
TLC-C-53 (Ventus [™])	Prostaglandin	2 MC clinical trials, phase III (n = 350, 102)	No mortality reduction	72,73
Molgramostim	Colony-stimulating factor	1 SC, 1 MC clinical trials, phase II (n = 10, 132 ^e)	Improved oxygenation; results not published	74,75
Lisofylline	Cytokine inhibitor	1 MC phase II/III clinical trial (n = 235)	No mortality reduction	76
Anti-IL-8 monoclonal antibody	Cytokine inhibitor	Animal model	Reduced pulmonary oedema	77,78
Methylprednisolone	Corticosteroid	2 MC clinical trials (n = 99, 91)	Conflicting results	79,80
Hydrocortisone	Corticosteroid	<i>Post hoc</i> analysis of 1 clinical trial (n = 177)	No mortality reduction ^f	81

Continued next page

Table IV. Contd

Pharmacological agent	Class	Current evidence [SC/MC, phase (no. of patients/trial)]	Outcome	References
Drotrecogin alfa	Anticoagulant	1 MC clinical trial, phase II (n = 75)	No mortality reduction	82
Rosuvastatin	Statins	2 cohort studies (n = 196, 178)	No mortality reduction	83,84
Treatment of established ARDS: fibroproliferative phase				
Methylprednisolone	Corticosteroid	2 MC clinical trials (n = 24, 180)	No mortality reduction ^g	85,86

a Excluding salvage therapies for severe hypoxaemia.

b Reduced risk of multiple organ dysfunction syndrome but not ARDS.

c Potentially increased risk of ARDS and death.

d Mortality reduction in subgroup of patients with direct cause of ARDS.

e Results not yet published.

f Mortality reduction in subgroup of patients with ARDS, septic shock and relative adrenal insufficiency.

g No mortality reduction in larger study, n = 180 (LaSRs).

IL-8=interleukin-8; **MA**=meta-analysis; **MC**=multicentre; **PPAR-γ**=peroxisome proliferator activated receptor-γ; **rhPAF**=recombinant human platelet-activating factor; **rSP-C**=recombinant surfactant protein-C; **SC**=single-centre.

animal studies, when given prophylactically to patients at risk of developing ARDS, ketoconazole has been shown to reduce the incidence of severe ARDS in three small trials.

A 1988 study of 71 patients admitted to a surgical ICU showed that in the group treated prophylactically with oral ketoconazole 200 mg/day, 2 of 35 patients (6%) ultimately developed ARDS, whereas 11 of 36 (31%) patients in the control group developed ARDS ($p < 0.01$).^[46] Similar results followed in a 1993 study of 54 patients with septic shock admitted to a surgical ICU, where the incidence of ARDS in the group treated with ketoconazole 400 mg/day was 15% (4 of 26 patients) compared with 64% (18 of 28 patients) in the control group ($p = 0.002$), and mortality was 15% versus 39%, respectively ($p = 0.05$).^[47] Although both of these studies were conducted prior to the 1994 AECC definition, ARDS was strictly defined in the aforementioned studies, including a $\text{PaO}_2/\text{FiO}_2$ ratio < 150 or intrapulmonary shunt $> 20\%$ in patients requiring mechanical ventilation and who had diffuse infiltrates on chest radiograph without clinical evidence of heart failure as pulmonary arterial occlusion pressures were < 18 mmHg. Building on the results of these two

studies, Sinuff and colleagues^[48] developed practice guidelines for prophylactic ketoconazole use, and tested the implementation and efficacy of these guidelines in two ICUs (one control and one active comparator). They reported a significantly decreased incidence of ARDS in the ICU population receiving ketoconazole prophylaxis, although mortality was equivalent within the two units.^[48]

In 2000, ARDSnet published the KARMA study evaluating oral ketoconazole versus placebo for patients within 36 hours of an established diagnosis of ALI or ARDS according to the 1994 AECC definition.^[55] The study was stopped early after enrolment of 234 patients for failing to show a difference in mortality or ventilator-free days. Of note, this study was designed to look at *early treatment* of ALI/ARDS rather than *prevention* of ARDS in patients at risk, and therefore did not necessarily negate the findings of the three previous smaller studies. Furthermore, a problem identified in the KARMA study was that even though blood ketoconazole concentrations were adequate, urinary metabolites of thromboxane were not affected, raising the possibility that the proper dose to achieve an anti-inflammatory effect was not given. However, since the KARMA

study showed no difference in mortality, widely considered the most important endpoint to achieve, further research on ketoconazole for ALI/ARDS ceased.^[55] Additionally, ketoconazole has numerous drug interactions and requires an acidic milieu to be absorbed via the enteral route, making routine use in the ICU complicated.

Further research should examine whether other drugs in the imidazole class given intravenously have similar anti-inflammatory properties, and also establish the inflammatory dose-response curve for ALI/ARDS. In addition, although the concept that prevention of ARDS will definitely lead to decreased mortality is intuitive, this still has to be proven in large multicentre clinical trials. The authors are unaware of any studies being conducted in this area presently.

3.1.2 ACE Inhibitors and Angiotensin II Receptor Antagonists

Angiotensin-converting enzyme (ACE) is produced in the lungs and is responsible for converting angiotensin I into angiotensin II, a peptide active in vasoconstriction and sodium-fluid balance to maintain blood pressure homeostasis. ACE inhibitors and angiotensin II receptor antagonists (blockers; ARBs) are classes of drugs commonly used to treat hypertension, and prevent progression of diabetic nephropathy in patients with diabetes. ACE inhibitors also help to preserve vascular structure and function, by exerting a protective effect on endothelial cells. Endothelial cell damage is the catalyst for the inflammatory and coagulation cascades activated in ALI/ARDS. Thus, the protection of endothelial cells offered by ACE inhibitors may have a beneficial role in ARDS.^[49]

Studies in transgenic mice have shown that ACE, angiotensin II and angiotensin II receptor type 1a may promote lung injury, whereas ACE2, a close homologue of ACE, and angiotensin II receptor type 2 may protect against severe lung dysfunction in models of ARDS.^[88] The ACE inhibitor captopril has been shown to prevent severe lung injury in an oleic acid-induced model in rats. In this model, captopril reduced expression of ICAM-1 in lung tissue, indicating a protective effect on endothelial cells, diminished

activity of tissue plasminogen activator, involved in coagulation, and blocked NF- κ B, the major signal transduction pathway that regulates the expression of multiple early-response genes related to inflammation.^[49] In humans, two small cohort studies have demonstrated that polymorphism of the ACE gene increases susceptibility to the development of ARDS and its outcome.^[89,90] Two additional studies, published only in abstract form to date, have examined the association between ACE inhibitor use and ARDS. A retrospective cohort study of 1423 adult critically ill patients found that 5.5% of patients developed ARDS after hospital admission, and that pre-existing, long-term use of an ACE inhibitor or ARB was associated with decreased risk of ARDS development, after adjusting for predisposing conditions (odds ratio [OR] 0.49; 95% CI 0.25, 0.94; $p=0.03$).^[91] The second abstract, a case-control study nested within a prospective cohort of 1553 critically ill patients at risk for ARDS, reported that patients on ACE inhibitors had a lower prevalence of respiratory failure on admission to ICU, but not lower incidence of ARDS after adjusting for confounders on multivariate analysis. However, among patients who developed ARDS, ACE inhibitor use was associated with lower mortality (adjusted hazard ratio 0.66; 95% CI 0.45, 0.99).^[92] The associations observed in these clinical studies is consistent with preclinical animal data, but requires further research prior to being applicable clinically.^[90]

3.1.3 Thiazolidinediones (Peroxisome Proliferator Activated Receptor- γ Agonists)

Peroxisome proliferator activated receptors (PPARs) are ligand-activated transcription factors related to thyroid hormone, steroid and retinoid receptors.^[50] There are three isoforms: PPAR- γ , PPAR- α and PPAR- β/δ . PPAR- γ plays a central role in glucose homeostasis. Thiazolidinediones, a class of oral antidiabetic drugs, are synthetic ligands for PPAR- γ . Synthetic PPAR- γ agonists also have anti-inflammatory properties, inhibiting proinflammatory cytokine production and macrophage activation *in vitro*.^[93,94] This action is mediated in part by antagonizing the activity of transcription factor NF- κ B. When activated,

NF- κ B induces overexpression of inflammatory cytokines such as tumour necrosis factor (TNF)- α , which in turn induces upregulation of ICAM-1 expression, as well as recruitment and activation of immune cells. ICAM-1, expressed on the surface of endothelial cells, mediates leukocyte adhesion and migration through endothelium into tissues. The anti-inflammatory properties of thiazolidinediones have been demonstrated *in vivo* in murine models of inflammatory bowel disease^[95] and rheumatoid arthritis.^[96] Rosiglitazone is the most potent selective PPAR- γ of the thiazolidinediones.

Prophylactic administration of rosiglitazone has been shown to attenuate ALI in an animal model of pancreatitis-associated ALI.^[50] In this study, rosiglitazone was dissolved and given intravenously to rats 30 minutes prior to induction of acute pancreatitis by sodium taurocholate. Compared with control group rats with acute pancreatitis and its associated lung injury, prophylactic administration of rosiglitazone resulted in a significantly lower histological pulmonary injury score, reduced pulmonary expression of TNF α and ICAM-1 messenger RNA, and decreased lung tissue myeloperoxidase activity, a measure of neutrophil infiltration in the lung.^[50] This suggests that prophylactic rosiglitazone mitigates the ALI associated with acute pancreatitis by its anti-inflammatory effect. Unfortunately, the safety of rosiglitazone has recently been questioned due to its augmentation of sodium and water retention, leading to increased incidence of congestive heart failure in diabetic patients placed on this drug long-term.^[97,98] Thus, further animal studies are needed to confirm the effects of rosiglitazone in acute pancreatitis and evaluate potential complications related to its use, prior to proceeding to human studies.

3.1.4 Tetracycline-Related Compounds

During the early phase of lung injury, neutrophils are recruited into the pulmonary vasculature and activated to release proteases, such as MMPs and NE, which damage the alveolar-capillary membrane,^[51] resulting in further release of inflammatory mediators. A single laboratory in the State University of New York (New York,

NY, USA) has demonstrated in various animal models that blocking the proteases NE, MMP-2 and MMP-9 with a unique modified tetracycline can prevent the increased pulmonary vascular permeability that ultimately leads to ARDS.

The same group has developed a 'two-hit' porcine model of sepsis plus gut ischaemia-reperfusion injury that parallels the insidious onset of sepsis-induced ARDS in humans. In this model, anaesthetized Yorkshire pigs undergo cross-clamping of the superior mesenteric artery for 30 minutes to induce intestinal ischaemia, followed by intraperitoneal placement of a faecal blood clot. Pigs are then awakened, extubated and taken to an animal ICU for 48 hours of continuous observation, where they receive intravenous fluids, broad-spectrum antibacterials and pain control medications. When the PaO₂/FiO₂ ratio falls below 250, pigs are anaesthetized and placed back on mechanical ventilation with tidal volumes of 10 mL/kg. In this model, they demonstrated that prophylactic administration of a synthetic, nonantimicrobial derivative of tetracycline called incyclinide (COL-3; CollaGenex Pharmaceuticals), prevented the development of both ARDS and septic shock.^[51] Incyclinide has not yet been tested in any human studies of ARDS prevention; however, the complex model developed by this group contains all the elements of a clinically relevant animal model and, therefore, these results show potential for phase II studies.

3.1.5 Antioxidants

Oxidative stress is associated with development of ARDS and MODS via direct tissue injury. Nathens and colleagues^[52] examined the effect of antioxidant supplementation using α -tocopherol and ascorbic acid in critically ill surgical patients. In a prospective RCT of 595 surgical ICU patients (mainly victims of trauma), they found antioxidants did not reduce the risk of developing ARDS, but did decrease the risk of developing MODS, and shortened duration of mechanical ventilation and length of ICU stay.^[52] Antioxidants supplementation and nutritional strategies are now being studied for critically ill patients with early signs of MODS,^[99] but not

specifically for ARDS prevention. Antioxidants and nutrition have also been studied for treatment of ARDS, and are further discussed in this context in section 3.2.3.

3.1.6 Corticosteroids

Given that excessive and protracted inflammation is the overriding principle responsible for the various pathophysiological mechanisms leading to ARDS, broad and potent anti-inflammatory drugs, such as corticosteroids, would seem to be a rational choice for prevention. Four RCTs, published between 1985 and 1988, have examined the use of corticosteroids to prevent the onset of ARDS in patients at risk. A recent meta-analysis of these studies demonstrated that preventive corticosteroids may actually increase the risk of developing ARDS in critically ill adults.^[53] Furthermore, the meta-analysis suggested a weakly increased risk of death associated with preventive corticosteroid therapy in those patients who ultimately developed ARDS. Thus, corticosteroid therapy is not recommended for preventing ARDS in those at risk. Corticosteroid therapy has also been extensively studied for the treatment of established disease in the early and late phases, and is discussed further in these contexts (see the Corticosteroids subsection of section 3.2.5 and section 3.3.1).

3.1.7 Recombinant Human Platelet-Activating Factor Acetylhydrolase

Platelet-activating factor (PAF) is a potent proinflammatory mediator that is degraded by the enzyme PAF acetylhydrolase. Recombinant human PAF acetylhydrolase (rhPAF-AH; epafipase) was studied in a phase IIb RCT to prevent ARDS in septic patients.^[54] 127 patients with severe sepsis were randomized to receive rhPAF-AH 1 mg/kg, rhPAF-AH 5 mg/kg or placebo. The incidence of ARDS was not different amongst the three groups, but 28-day all-cause mortality was significantly decreased in the 1 mg/kg treatment group compared with placebo (21% vs 44%; $p=0.03$). Therefore, although rhPAF-AH does not appear to be an effective prophylactic treatment for ARDS, it may hold promise for treatment of severe sepsis.

3.2 Treatment of Established ARDS: Acute and Exudative Phases

The majority of research to date has focused on treating ARDS once the diagnosis is established. Although many studies are designed to treat 'early ARDS', with randomization occurring within 48 hours of diagnosis, these studies also likely capture many patients in the exudative phase of ARDS with intra-alveolar hyaline membranes and histological diffuse alveolar damage at the time of enrolment. This problem arises in part because the diagnostic criteria for ARDS are subjective and lack sensitivity and specificity when compared with pathological diagnosis.^[100] Thus, timing an intervention at a certain point after 'diagnosis' could result in the patient receiving treatment in the early, mid or even late pathophysiological stage of ALI/ARDS. Some more recent studies are now targeting time after intubation rather than time after diagnosis to achieve more uniform timing of intervention. However, since the acute and exudative phases occur along a continuum and are not generally distinguished clinically, therapies targeting these phases will be considered concomitantly. Therapies currently under investigation for early and/or exudative ARDS include those targeting the disrupted surfactant system, oxidative stress and antioxidant activity, neutrophil recruitment and activation, expression and release of inflammatory mediators, activation of the coagulation cascade, and microvascular injury and leak. Treatment of the overall inflammatory response with agents such as corticosteroids has also been studied and is discussed. Finally, the only drugs specifically targeting resolution of the alveolar oedema of the acute phase are β_2 -adrenergic receptor agonists (β_2 -agonists).

3.2.1 β_2 -Adrenergic Receptor Agonists

Clearance of alveolar oedema depends on the balance between oedema formation and reabsorption. The rate of fluid reabsorption depends on the active transport of sodium and electrolytes; water follows in the direction of the transported electrolytes. The active transport of

salt and water occurs via epithelial sodium channels induced via Na^+/K^+ adenosine triphosphatase (ATPase).^[101] β_2 -Agonists are thought to increase alveolar fluid clearance via two possible mechanisms: (i) increasing the levels of intracellular cyclic adenosine monophosphate, which in turn upregulates Na^+/K^+ ATPase, causing increased sodium transport across alveolar type II cells; and (ii) reducing alveolar-capillary permeability, thereby decreasing oedema formation. Preliminary animal and *ex vivo* studies demonstrated the potential of β_2 -agonists to accelerate the rate of alveolar fluid clearance.^[102,103]

A small, single-centre RCT randomized 40 patients with ALI/ARDS to receive intravenous salbutamol (albuterol) 15 $\mu\text{g}/\text{kg}/\text{h}$ or placebo for 7 days.^[56] The primary endpoint of BALTI-1 was extravascular lung water measured by the single-indicator transpulmonary thermodilution system (PiCCO®; Pulsion Medical Systems) at day 7. Patients in the salbutamol group had lower extravascular lung water and plateau pressures, although oxygenation did not differ between the treatment and placebo groups. This latter finding was perhaps due to the vasodilatory effects of β_2 -agonists contributing to shunting of oxygen in the capillary bed. There was no difference in 28-day mortality or ventilator-free days, although the study was not sufficiently powered to detect a difference in these endpoints.^[56] Funded by the Medical Research Council, the same investigators in the UK are now conducting BALTI-2, using the same intravenous salbutamol protocol as in BALTI-1, but powered to detect clinically important outcomes.^[104] It will be interesting to determine if the physiological benefits observed in BALTI-1 confer a reduction in 28-day all-cause mortality in BALTI-2.

Aerosolized β_2 -agonists have fewer systemic adverse effects than intravenous preparations. The National Heart, Lung and Blood Institute (NHLBI), in conjunction with ARDSnet, conducted a study of an aerosolized β_2 -agonist, the ALTA study.^[105] The study was stopped for futility at the first interim analysis after enrolling 279 patients.^[57] There was no difference in the primary outcome of ventilator-free days to day 28. This study may have been negative for the

following reasons: (i) delivery of nebulized drug to lung injury sites may have been suboptimal, as was the case with aerosolized surfactant; and/or (ii) less severely ill patients with ALI (rather than ARDS with more severe hypoxaemia) may retain adequate alveolar fluid clearance without the need for upregulation with β_2 -agonists. Sixty-day mortality in the ALTA study was 19.7% compared with a 28-day mortality of 60% in the severely ill group of patients who received physiological benefit from intravenous salbutamol in BALTI-1.^[106]

3.2.2 Exogenous Surfactant Replacement

Exogenous surfactant administration has been very successful in treating and preventing neonatal respiratory distress syndrome (nRDS). Given the physiological and pathological similarities between nRDS and ARDS, exogenous surfactant therapy has been under investigation for treatment of ALI/ARDS for over a decade. Although clinical trial results have been largely disappointing, recent studies show promise. The strong scientific rationale for targeting the disrupted surfactant system, as well as lessons learnt from previous trials, therefore merit further attention.

Endogenous surfactant is composed of 90% lipids (mainly phosphatidylcholine and phosphatidylglycerol) and 10% proteins. The role of endogenous surfactant in the healthy lung is to decrease surface tension and thereby prevent alveolar collapse. In addition, surfactant plays a role in suppressing inflammation and scavenging free oxygen radicals. Four apoproteins have been identified, termed surfactant protein (SP)-A, -B, -C and -D. Whereas the presence of either or both of the hydrophobic surfactant proteins SP-B and -C are important for the biophysical function of surfactant, the hydrophilic proteins SP-A and -D perform the various host defence roles, including modulation of leukocytes, enhancement of the function of phagocytic cells^[107] and regulation of the host's immune system.^[108,109]

In ALI, disruption of the endogenous surfactant system occurs by a number of mechanisms: injury to alveolar type II cells results in abnormal synthesis and secretion of surfactant, serum proteins that leak into the airspace interfere with

surfactant function, serine endopeptidase and phospholipase A₂ cause degradation of surfactant, and, finally, mechanical ventilation, particularly with high tidal volumes, causes conversion of functional surfactant aggregate forms into dysfunctional forms. Without optimal surfactant function, there is high surface tension at the alveolar surface in a non-uniform pattern within the lung leading to alveolar instability and collapse. The presence of bacteria within the airspace may also release and activate endotoxins, a process that is augmented in the presence of an abnormal surfactant system. Based on the functional importance of the endogenous surfactant system in the normal lung and, more importantly, the consequences of an altered surfactant system in ALI/ARDS, there is good rationale to consider exogenous surfactant administration as a therapeutic intervention in these patients.^[109]

In 1996, a phase III, double-blind RCT tested an aerosolized, synthetic surfactant called Exosurf® (Glaxo Wellcome) in 725 patients with sepsis-induced ARDS.^[58] This study showed no significant difference in overall survival, duration of mechanical ventilation or oxygenation between the treatment groups and standard care. It was postulated that this lack of efficacy was due to a low level of alveolar deposition of the aerosolized preparation and/or due to the absence of surfactant proteins in the preparation.^[23] Currently, this surfactant preparation is not being evaluated for patients with ALI/ARDS and is no longer marketed in the US.

Shortly afterwards, a smaller, open-label phase II clinical trial evaluated tracheal instillation of a liquid bolus of the natural bovine extract surfactant, Survanta® (Ross Laboratories), in patients with severe ARDS.^[59] There was a trend toward decreased mortality in the group of patients receiving up to four doses of phospholipids 100 mg/kg surfactant compared with the patients in the control group (18.8% vs 43.8%; $p=0.075$), and no safety concerns were identified. However, Survanta® contains only very small amounts of SP-B. Coupled with concerns regarding resource limitations, no further clinical trials of this exogenous surfactant preparation for adults with ARDS have been performed.

Recognizing the importance of surfactant-specific proteins brought progress to clinical surfactant research. In 2004, results were published for two phase III clinical trials evaluating effect of a liquid, recombinant SP-C (rSP-C) surfactant, Venticute® (Nycomed), instilled intratracheally in patients with established ARDS.^[23] The two studies enrolled a total of 448 patients within 24 hours of diagnosis of ARDS and were powered to show a difference in ventilator-free days. Although oxygenation was significantly better during the 24-hour treatment period in the surfactant group, there were no significant differences noted in the number of ventilator-free days or in 28-day survival.^[23] A *post hoc* analysis demonstrated that patients with 'direct' causes of ARDS (i.e. pneumonia, witnessed aspiration of gastric contents or both) had a mortality benefit with surfactant treatment compared with standard care. A follow-up meta-analysis pooling results of five multicentre studies of rSP-C confirmed this finding: the subgroup of patients with severe ARDS due to pneumonia or aspiration had decreased mortality when treated with rSP-C (26.3% vs 39.3% in the usual care group; $p=0.018$).^[24] Subsequently, a prospective phase III RCT evaluating effect of Venticute® in 1200 patients with pneumonia or aspiration of gastric contents was conducted. The study was terminated at 800 patients due to futility. Neither these results nor the potential reasons for futility have been published to date.^[60]

Calfactant (Infasurf®, ONY Inc.) is a modified natural surfactant produced by extracting the phospholipids, neutral lipids and surfactant-specific proteins SP-B and SP-C from newborn calf lungs. In *in vivo* animal lung studies, calfactant has shown greater surface activity than Exosurf® and Survanta®,^[110-113] and the highest level of resistance to inactivation due to its high ratio of protein SP-B to phospholipids.^[114-116] From 2000 to 2003, calfactant was used in a multicentre study of ALI/ARDS in the paediatric population 1 week (full-term infants) to 21 years of age. Overall, calfactant significantly improved oxygenation and reduced mortality (19% vs 36%; $p=0.03$), although the greatest impact was observed in the subgroup of patients with direct ALI/ARDS while calfactant

had little effect in patients with indirect ALI or ARDS.^[61]

Indeed, calfactant is the first and only pharmacological agent to demonstrate a mortality benefit for treatment of ALI/ARDS. It is of note, however, that this study differs from other adult studies in that the majority of paediatric patients had direct causes of ARDS and the most common cause of death was respiratory failure, whereas adult studies have included a larger proportion of patients with indirect causes, such as sepsis, wherein the most common cause of death is multi-organ failure. Based on those encouraging results, Pneuma Pharmaceuticals began conducting a large phase III multicentre RCT of calfactant for direct ARDS (origin of ARDS must be infectious pneumonia, aspiration, near drowning, smoke inhalation without pulmonary burn or inhaled industrial gas) in adults and children. A total of 880 patients in two consecutive studies of patients under 12 and over 12 years of age was planned. However, after the first interim analysis in January 2010, the paediatric arm of the study was stopped for futility due to an unexpectedly low mortality rate. Recruitment in the adult arm (ages 12–85 years) is continuing as the interim analysis did not reveal futility or any safety concerns (Wilson D, University of Virginia Health Sciences Center, Charlottesville, VA, USA, personal communication).^[117]

3.2.3 Antioxidants and Nutrition

Since reactive oxygen species also contribute to the tissue damage incurred in ALI, antioxidant therapies have also been investigated as therapeutic options for established disease. N-acetylcysteine (NAC) is a commercially available antioxidant approved for the treatment of paracetamol (acetaminophen) toxicity. NAC is a precursor for glutathione, an antioxidant present in normal lungs and deficient in bronchoalveolar lavage fluid from ALI/ARDS patients. Additionally, because of its thiol group, NAC can scavenge reactive oxygen species such as hydrogen peroxide and superoxide anion. In an RCT of 46 patients, NAC and oxothiazolidine carboxylate (Procysteine[®], Clintec Technologies Inc.), another glutathione precursor, were studied for

their combined effect in ALI/ARDS but failed to reduce mortality compared with placebo,^[62] negating promising results of three prior small studies.^[63–65]

Interestingly, recent evidence suggests that genetic diversity may explain variable responsiveness to NAC. Glutathione-S-transferases (GSTs) are enzymes from a complex, multigene family with important roles in oxidative stress pathways. A study by Moradi and co-workers^[118] demonstrated that deletion of specific GST gene polymorphisms correlated with mortality and that treatment with NAC significantly lowered mortality in these subgroups of patients. These results suggest that patients with GST gene deletions are more vulnerable to oxidative stress contributing to ARDS and may be in greater need of antioxidant therapy.^[118]

Antioxidant supplementation to enteral nutrition rich in omega-3 fatty acids has also been investigated for patients with ALI/ARDS. While the rationale for nutritional antioxidants such as vitamins E and C is to reduce the oxidative stress present in ALI, the purpose of the omega-3 fatty acids is to reduce production of proinflammatory mediators. Eicosanoids, such as prostaglandins, thromboxanes and leukotrienes, derived from omega-3 fatty acids are generally much less proinflammatory than those derived from omega-6 fatty acids. Since omega-6 fatty acids compete with omega-3 fatty acids for the same rate-limiting enzymes in the production of eicosanoids, diets with a high proportion of omega-6 fats are thought to be proinflammatory and prothrombotic. Examples of polyunsaturated omega-3 fatty acids are α -linolenic acid, eicosapentaenoic acid and docosahexaenoic acid.^[119]

A phase II study enrolling 98 patients with ALI compared an antioxidant enteral feeding formula containing eicosapentaenoic acid, γ -linolenic acid and antioxidant vitamins with placebo, and observed improved oxygenation, reduced pulmonary inflammation, fewer days of mechanical ventilation and fewer non-pulmonary organ failures in the treatment arm, although there was no difference in mortality between this approach and the control group.^[66] ARDSnet proceeded to conduct the OMEGA study, a

phase III study examining efficacy of omega-3 and antioxidant supplementation to enteral nutrition. The study was stopped for futility, but results have not yet been published.^[67,68]

3.2.4 Modulation of Neutrophil Activity

Several therapies aimed at modulating neutrophil activity have been studied. To understand why previous clinical trials have been negative and highlight potential targets for novel therapies, it is important to understand the role of neutrophils in propagating lung injury and MODS.

Polymorphonuclear neutrophils (PMNs) form the first line of defence against invading pathogens, and neutropenia or defective neutrophil function predisposes the host to increased morbidity. Extensive clinical and experimental data support the role of the activated neutrophil in the pathogenesis of organ injury in sepsis. The lung is particularly vulnerable. Postmortem studies of patients with ARDS show massive pulmonary accumulation of neutrophils, with the highest counts in non-survivors.^[120] The pathological impact of neutrophils may be due to their activation, transmigration or delayed apoptosis. However, neutrophil-independent mechanisms of ALI must also exist, since ARDS has been described in neutropenic patients.

Neutrophil Activation

Neutrophil kinetics in the pulmonary circulation differ substantially from that of microvascular beds in the systemic circulation. The pulmonary circulation harbours a large intravascular reservoir of leukocytes, mainly neutrophils, referred to as the 'marginated pool'.^[121] This marginated pool may equal or even exceed the pool of circulating neutrophils and exchanges with the latter as an ongoing phenomenon. Thus, it is important to appreciate that circulating neutrophils, when isolated for experimental analysis, may not represent the characteristics of the entire population of neutrophils in the bloodstream. Intravital microscopic studies have revealed that, in contrast to the systemic circulation where neutrophil sequestration is almost exclusively confined to the venular compartment, the major site of neutrophil retention in the lung

is the alveolar capillary bed.^[122] Neutrophil activation can also lead to cytoskeletal changes that reduce cell deformability and slow their transit time through the alveolar capillaries. Since one of the earliest manifestations of ARDS is accumulation of large numbers of neutrophils in the alveolar capillaries, it is possible that the accumulation of neutrophils may initiate selective capillary blockade and arteriovenous shunting leading to hypoxia seen in ARDS.

NE inhibitors

Activated neutrophils also produce human NE (HNE), a protease capable of producing tissue damage by means of its degradation of elastin, fibronectin, laminin, collagen and proteoglycans. Normally, protease inhibitors impede NE, but in the setting of an overwhelming inflammatory response, neutrophils generate reactive oxidants that inactivate endogenous protease inhibitors, leaving the activity of HNE unchecked. This may lead to increased pulmonary inflammation and endothelial cell permeability.^[9] Sivelestat (Elaspol[®], ONO Pharmaceuticals) is a competitive inhibitor of NE. It was launched in Japan after a phase III study demonstrated reduced ICU stay and improved pulmonary function in patients with ALI associated with the systemic inflammatory response syndrome (SIRS).^[70] However, the STRIVE study^[69] was terminated early after randomizing 492 patients from 105 sites in six countries, when the Data and Safety Monitoring Board found a trend to increased mortality at 180 days. Final analysis revealed no difference in 28-day all-cause mortality (26% in both groups) or number of ventilator-free days between the treatment group and controls.

EPI-HNE-4 or depelestat (Debiopharm S.A.) is another HNE inhibitor currently under development for treatment of inflammatory pulmonary diseases, including ALI. In a repeated lung injury rat model depelestat administration afforded a significant protective effect on lung compliance and alveolar inflammation at day 14 compared with the control group.^[71] A phase II study examining safety and efficacy of intravenous depelestat for patients with ARDS has been completed, but results have not yet been published.^[123]

Neutrophil Transmigration

Neutrophil margination allows for a molecular interaction between the cell surfaces of the neutrophil and endothelial cell to occur. Subsequently, as a consequence of cell surface integrins and their ligands, neutrophils undergo adhesion with endothelial cells. Following adherence, neutrophils must pass through the endothelial monolayer, interstitial tissue and alveolar epithelium to reach the alveolar space. Passage of large numbers of activated neutrophils can cause epithelial damage, sloughing and increased permeability both due to mechanical force exerted by neutrophil pseudopodia as well as due to release of toxic substances such as proteinases (e.g. elastases, cationic peptides, defensins, oxidants and MMPs).^[9] While there are conflicting reports on the effects of elastase on increased epithelial permeability, cationic peptides such as defensins can cause both epithelial and endothelial cell injury. Defensin levels have been found to be greatly elevated in patients with ARDS and their levels correlate with the severity of lung injury.^[124] Neutralizing its effects could be important in the management of ARDS. Ongoing research is examining if defensins can be used to identify patients with ALI at an early stage.^[125]

Delayed Apoptosis of Neutrophils

Once egressed into the extravascular space, neutrophils cannot return to the circulation and their elimination is dependant upon their clearance by apoptosis and subsequent recognition and elimination by macrophages and other phagocytic cells. Normally, neutrophils are terminally differentiated cells with a terminal half-life of 5–6 hours *in vivo*. Upon completion of their lifespan, neutrophils institute a programme of cell death known as ‘apoptosis’ and are then removed from the circulation by the liver and spleen. Apoptosis, as opposed to necrosis, is believed to be crucial for resolution of inflammation as it does not result in loss of cell membrane integrity and bystander tissue damage by release of intracellular enzymes, proteases and reactive oxygen species.^[126]

Expression of neutrophil apoptosis is delayed in ARDS.^[127] This is not an unexpected finding, especially since PMN apoptosis is delayed in

other critically ill patients with sepsis, trauma and burns.^[128,129] Apoptosis of neutrophils may be an important consequence in determining the extent of lung injury. For example, it has been shown that the induction of neutrophil apoptosis by the administration of dead *Escherichia coli* prior to reperfusion resulted in significant improvement in lung injury.^[130] Induction of neutrophil apoptosis in the alveolar space has the potential for resolution of inflammation in ARDS, and can be carried out in a number of ways that could include multiple strategies such as ligation of Fas, activation of proapoptotic caspases and modulation of mitogen-activated protein kinases or transcription factors such as NF- κ B. Hastening neutrophil apoptosis in the alveolar space may also decrease the probability of secondary necrosis and further tissue damage in ARDS. It is intriguing that no significant differences were found between the expression of neutrophil apoptosis in patients at risk and those with established ARDS, nor did the extent of apoptotic inhibition correlate with overall outcome in ARDS.^[131] Therefore, while it is well established that ARDS is associated with accumulation of large numbers of neutrophils in alveolar spaces, their contribution to the severity of ARDS in humans remains uncertain.

In summary, targeting neutrophil responses in ARDS may have therapeutic potential. However, as has been learnt from various ALI and sepsis trials in the past, simple strategies to control dysregulated neutrophil behaviour may not be effective. Rather, key stages of neutrophil function and kinetics may need to be identified in different clinical phases of ARDS, and selective immunomodulation strategies may need to be identified for individual patients.

3.2.5 Other Immunomodulating Agents

In addition to modulation of neutrophil function, there are other facets of the immune and inflammatory response currently under investigation as potential therapeutic targets for treatment of ARDS. These include modulation of macrophage activity with granulocyte macrophage colony-stimulating factor (GM-CSF), inhibition of inflammatory mediators and broad

suppression of the inflammatory response with corticosteroids.

Prostaglandin Administration

Although most prostaglandins are proinflammatory mediators, prostaglandin E₁ (PGE₁) has potential beneficial effects in ALI, specifically due to its ability to modulate neutrophil activation. However, exogenous PGE₁ is associated with several adverse effects and patient intolerance due to haemodynamic instability has been observed. TLC-C-53 (Ventus™; The Liposome Company) is a liposomal dispersion of PGE₁. The development of PGE₁ in liposomal form may potentiate its role in neutrophil downregulation, improve peripheral delivery of the drug to the lung and decrease systemic adverse effects, thus providing a good rationale for testing in humans.^[73]

A phase III trial of 350 patients with ARDS randomized to intravenous TLC-C-53 at escalating doses for 7 days versus placebo found no difference in duration of mechanical ventilation or 28-day mortality between the treatment and control groups, although treatment was associated with accelerated improvement in oxygenation.^[72] However, more than 50% of patients required a dose reduction due to hypotension or hypoxaemia. Interestingly, those patients who tolerated and received at least 85% of the full dose had a shorter duration of mechanical ventilation. A subsequent multicentre phase III trial of TLC-C-53 in 102 ARDS patients^[73] demonstrated no differences in time to liberation from the ventilator or 28-day mortality; the trend to shorter duration of hypoxaemia in the treatment group failed to reach statistical significance.

Granulocyte Macrophage Colony-Stimulating Factor

GM-CSF has been shown to stimulate phagocytosis and oxidative functions of host defence neutrophils, monocytes and macrophages.^[74] In addition to its systemic actions, GM-CSF may also influence pulmonary host defence by modulating alveolar macrophage function and surfactant metabolism. As noted, apoptosis of neutrophils is an important mechanism by which these cells are cleared from inflamed lung regions, thereby facilitating resolution of inflammation.

Although both granulocyte colony-stimulating factor and GM-CSF are thought to inhibit neutrophil apoptosis, in animal models of lung injury, GM-CSF has been shown to help restore capillary barrier integrity,^[132] preserve alveolar epithelial function and improve alveolar fluid clearance.^[133] A pilot study of 45 patients with ARDS undergoing serial bronchoalveolar lavage found that patients who survived ARDS had higher concentrations of GM-CSF in the bronchoalveolar lavage fluid on day 1 than patients who died.^[134] The authors speculated that GM-CSF might improve survival by prolonging the neutrophil lifespan in the alveoli and/or inducing proliferation of alveolar macrophages, thereby improving host defence and reducing infectious complications in this setting.

In a phase II trial, molgramostim (Schering-Plough), a recombinant human GM-CSF, was given intravenously at a low dose (3 µg/kg) for 5 days to ten patients with severe sepsis and sepsis-related pulmonary dysfunction (defined as a PaO₂/FiO₂ ratio of <287 with a pulmonary infiltrate on chest radiograph).^[74] The primary outcome was 30-day survival, and secondary outcomes included oxygenation, occurrence of ARDS and degree of organ dysfunction at day 5. There was no difference in 30-day survival between the treatment and placebo groups, but oxygenation improved in the GM-CSF group. ARDS was present in four of ten patients in the GM-CSF group on study entry, but resolved in two of these patients by day 5, whereas in the placebo group ARDS was present in three patients on study entry and five patients on day 5. Organ dysfunction was similar between the two groups, with no change between study entry and day 5.

From July 2004 to July 2009, the NHLBI enrolled patients who had been diagnosed with ALI/ARDS for at least 3 days into a phase II RCT of recombinant GM-CSF (sargramostim [Leukine®], Genzyme Corporation) versus placebo.^[75] The primary outcome was the number of ventilator-free days during days 1–28. Secondary outcomes included measures of lung epithelial cell integrity, alveolar macrophage function, changes in severity of respiratory gas exchange, non-respiratory organ failure and incidence of

ventilator-associated pneumonia. This study has been completed, but results have not yet been published.^[75]

Cytokine Inhibitors

Cytokines are glycoproteins that act as messengers to cell surface receptors to promote or diminish the inflammatory cascade. Specific cytokines are observed in high amounts in the bronchoalveolar lavage fluid of patients with ARDS, and are thought to play an important role in propagating lung injury. Unsaturated phosphatidic acid plays an important role in intracellular signalling leading to neutrophil accumulation within the lungs, as well as pro-inflammatory cytokine expression and cell membrane oxidation, all of which leads to lung tissue damage.^[135] Lisofylline (Cell Therapeutics) is a cytokine inhibitor that impedes synthesis of phosphatidic acid-1 α and, therefore, was thought to hold potential for treatment of ARDS. However, ARDSnet stopped a phase II/III trial, the LARMA study, for futility after the first interim analysis failed to demonstrate any difference in 28-day mortality, ventilator-free days, organ failures or levels of circulating free fatty acids.^[76] Interleukin (IL)-8 is another potent chemoattractant for neutrophils, observed in high levels in patients with early ARDS^[136] and associated with increased mortality.^[137] Anti-IL-8 monoclonal antibody has been shown to reduce pulmonary oedema and neutrophil accumulation in animal models of ARDS^[77,78] but has not yet been tested in humans. Finally, TNF α has long been recognized as an important proinflammatory cytokine in ARDS, but more recent evidence suggests that it actually plays a dichotomous role in both contributing to permeability oedema but also increasing alveolar fluid clearance capacity. Monoclonal anti-TNF α antibodies have been tested in patients with sepsis with disappointing results.^[138] Given its dual role in alveolar oedema formation and resorption, a more sophisticated approach than simply blocking all TNF α activity is likely to be required in ARDS.

Corticosteroids

Studies examining the efficacy of corticosteroids for acute exudative ARDS have shown

conflicting results. In 1987, Bernard et al.^[80] published results of a study of 99 patients with ARDS randomized to high-dose pulse methylprednisolone (30 mg/kg every 6 hours for 24 hours) or placebo. There was no difference in 45-day mortality (60% vs 63%; p =nonsignificant) but the confidence intervals were wide, suggesting that the study may have been underpowered to detect a small difference in a population with heterogeneous outcomes. In 2007, Meduri and colleagues^[79] published their results of 91 patients with severe early ARDS (<72 hours) from five hospitals randomized to methylprednisolone 1 mg/kg/day for 28 days versus placebo. They found corticosteroids significantly reduced ICU mortality (21% vs 43%; p =0.03), duration of mechanical ventilation and length of ICU stay.^[79] Annane et al.^[81] published a *post hoc* analysis of 177 ARDS patients enrolled in an RCT of low-dose corticosteroids in septic shock. Patients in the treatment group received hydrocortisone 50 mg every 6 hours plus fludrocortisone 50 μ g/day for 7 days. Although there was no mortality difference for ARDS patients overall, ARDS patients with relative adrenal insufficiency and septic shock had significantly reduced mortality when treated with low-dose hydrocortisone (53% vs 75% in the placebo group; p =0.01).^[81] The use of corticosteroids for acute exudative ARDS remains controversial, although the evidence is more definitive for corticosteroid treatment initiated late for fibroproliferative ARDS (see section 3.3.1). A study examining low doses of corticosteroids as adjuvant therapy for lung injury associated with H1N1 influenza virus (CORTIFLU) is planned.^[139]

3.2.6 Activated Protein C

Microvascular injury and coagulation play critical roles in the pathogenesis of ALI. Plasma protein C levels are decreased in patients with ALI, and are associated with higher mortality and fewer ventilator-free days.^[82] Recombinant human activated protein C (rhAPC; drotrecogin alfa; Eli Lilly) was tested in a phase III clinical trial of patients and demonstrated a significant mortality reduction from 30% to 24% in patients with severe sepsis.^[140] A phase II study was sponsored by the NHLBI to determine if drotrecogin alfa

increased ventilator-free days in patients with ALI (patients with severe sepsis were excluded). The study was terminated by the Data Safety Monitoring Board. Although drotrecogin alfa significantly increased plasma protein C levels and decreased pulmonary dead space fraction, there was no significant difference in the number of ventilator-free days or in 60-day mortality (5 of 38 vs 5 of 37 patients, respectively; $p = 1.0$).^[82]

3.2.7 HMG-CoA Reductase Inhibitors (Statins)

HMG-CoA reductase inhibitors, commonly known as statins, have recently been proposed as a treatment for ALI/ARDS. The rationale for this is based on animal models suggesting that statins can attenuate organ dysfunction by reducing vascular leak and inflammation.^[84] A prospective cohort study in Ireland showed a nonsignificant trend towards lower odds of death in ARDS patients receiving a statin during their ICU admission (OR 0.27, 95% CI 0.06, 1.21; $p = 0.09$).^[83] However, a recently published retrospective cohort study from the Mayo Clinic (Rochester, MN, USA) showed no difference in mortality or organ dysfunction in ARDS patients treated with statins.^[84] STIP is currently enrolling patients admitted to an ICU with respiratory distress and a $\text{PaO}_2/\text{FiO}_2$ ratio < 300 due to the H1N1 pandemic strain of influenza.^[141] Patients in this trial will be randomized to receive rosuvastatin 20 mg/day or placebo for 21 days. Since this is a specific subpopulation of patients with ALI, findings from this study may not be generalizable to other ALI subgroups. The SAILS trial (also rosuvastatin 20 mg/day vs placebo) is also planned but not yet open for recruitment.^[142]

3.3 Treatment of Established ARDS: Fibroproliferative Phase

Patients who survive the early and exudative phases of ARDS generally enter a period from week 1 to 3 consisting of fibroproliferation and organization of exudative debris within the airspace. This fibroproliferative relatively 'late' phase either slowly resolves or progresses to fibrosis. During this phase, patients are at risk

of dying from other complications such as MODS, or may fail to wean from mechanical ventilation due to severely impaired respiratory muscle and lung function. Those who successfully wean off mechanical ventilation may have residual pulmonary fibrosis and reduced exercise capacity.

For resolution to occur, removal of inflammatory cells, cellular debris, and soluble and insoluble proteins needs to take place. As noted in section 3.2.4, apoptosis of neutrophils facilitates resolution of inflammation. Monocyte and macrophage phagocytic clearance of apoptotic cells appears to be an important mechanism by which neutrophils are cleared from inflamed lung regions. Soluble proteins are likely to be primarily removed via paracellular diffusion, but removal of insoluble proteins appears to depend on the function of alveolar macrophages. Mechanisms involved in remodelling of hyaline membranes and restoration of a functional alveolar-capillary barrier are incompletely understood at present, but therapeutic interventions aimed at modulation of phagocytosis/apoptosis are being evaluated. To date, far less research has targeted this later phase of the disease, as most trials have focused on earlier preventative processes.

3.3.1 Corticosteroids

Fibroproliferative ARDS is characterized by ongoing inflammation. In addition to being tested for prevention of ARDS, and treatment of the early and mid exudative phases, corticosteroids have also been tested for efficacy in reversing the fibrosing alveolitis of the late phase of ARDS. A study by Meduri and colleagues^[86] examined the effect of prolonged methylprednisolone therapy (2 mg/kg/day for 32 days) on 24 patients with severe ARDS that was unresolved after 7 days of respiratory failure. Although this study demonstrated a significant hospital mortality benefit (2 of 16 patients [12%] in the corticosteroid group died vs 5 of 8 [62%] in the placebo group), the significance of these findings was controversial for two reasons: the calculated sample size to demonstrate a 30% absolute difference in mortality was 99 patients but the study was terminated early after enrolment of 24 patients, and the mortality

in the placebo group was slightly higher than anticipated.^[86]

To shed further light on this issue, ARDSnet specifically designed a study to focus on the late fibrotic stage of the disease, called LaSRS.^[85] This study examined the role of corticosteroids in 180 patients in the late phase (>7 days from onset) of persistent ARDS. Methylprednisolone, dosed at 2 mg/kg/day for 14 days followed by tapering doses until day 25, was compared with placebo. There was no difference in 60- or 180-day mortality rates. Methylprednisolone improved oxygenation, respiratory system compliance and blood pressure, resulting in an increased number of ventilator-free and shock-free days; however, a higher rate of neuromuscular weakness and, if initiated more than 14 days after the onset of ARDS, a significant increased mortality was observed in the methylprednisolone group. Therefore, despite the improvement in cardiopulmonary physiology, methylprednisolone does not improve overall mortality in ARDS and is not recommended for treatment of late ARDS.

Given these results, the convincing lack of efficacy for prevention of ALI prior to diagnosis and the lack of evidence of benefit in the early phase, corticosteroids cannot be recommended for routine treatment of ALI/ARDS at any stage, at this time. Furthermore, it may prove to be exceedingly difficult to determine which individual patient might benefit from corticosteroids and at what specific point to intervene.

4. Potential for Future Clinical Development

Clearly, the current status of treatment options for patients with ALI/ARDS is suboptimal. At this time, the clinical management of patients with ALI/ARDS involves supportive therapy only. This primarily includes low stretch or 'lung protective' mechanical ventilation, conservative fluid management and adequate nutritional support. Although the term 'supportive' may sound somewhat discouraging, these are important observations, not only because they impact on the outcome of patients with ALI/ARDS but also because they should be embraced and implemented as 'standard

care' for this patient population. Furthermore, any new therapy being tested should be compared with optimal 'standard care'. Other methods proposed to offer greater protection to the lungs while providing mechanical support to respiration include HFO and ECMO. Studies into these modes are ongoing.

Although supportive therapies have reduced mortality, there is still significant need for improvements. Previous studies have provided important insight into the pathophysiology of ALI/ARDS. Research is ongoing into therapies to prevent ALI/ARDS in those at risk, treat it early in its course or aid in its resolution. Each of these goals is associated with specific challenges.

Demonstrating that a prophylactic intervention reduces mortality, morbidity and is cost effective is challenging at best. This is most likely to occur when the risk of acquiring the disease is high, the outcome of the disease is uniformly devastating and treatment for the disease is nonexistent. For some critically ill patients at risk for ARDS, this may be the case. However, the diagnosis of ALI/ARDS encompasses a very heterogeneous population, with incompletely understood risk factors and non-uniform, diverse outcomes. The greatest likelihood of success for prophylactic therapy will come when we have further delineated the subgroups at highest risk of dying from ALI/ARDS and have accurate diagnostic tests to identify these patients. For ALI/ARDS, specifically targeting the pathogenic mechanisms responsible for the increased risk of death in these patient subgroups would theoretically be high yield. Basic science research identifying genetic polymorphisms of patients with highest mortality or greatest need for specific therapies shows great promise in this regard, but is not yet clinically applicable. Until then, validating biomarkers and clinical indicators for poor prognosis in ALI/ARDS should remain a primary research goal.

Finding therapies to treat ARDS in its late fibroproliferative phase is also in great need. Too often patients survive the early and mid phase of ARDS only to succumb to complications in the late phase or undergo withdrawal of life support as they are unable to be weaned from mechanical

ventilation. Research into mechanisms of idiopathic pulmonary fibrosis may help identify common pathways to target for therapy. To date, the majority of research has focused on treating ALI/ARDS in its earlier stages, in the hope that the disease process may be reversed prior to the patient entering the fibroproliferative phase.

4.1 Lessons Learned from Research

Progress in finding therapies to treat established ARDS has been slow and hampered by a long series of negative clinical trials. However, there are several lessons to be learned from these RCTs. First, a 'one-size-fits-all' approach has not worked for pharmacotherapy for ARDS. In this sense, the syndrome of ALI/ARDS may be likened to cancer. Cancer as a broad term signifies the uncontrolled replication of abnormal cells, but there are specific chemotherapeutic treatments for specific types of cancer, depending on its origin. Some treatments may be effective for more than one type of cancer, but not for other types, and the magnitude of the benefit might vary according to the type and stage of disease. Oncologists would not design a trial enrolling all patients with differing types of cancer and expect to find a single drug that shows a survival benefit. Yet, that is what has been attempted with several large ARDS trials. Recent studies have demonstrated that direct ARDS is likely to respond differently than indirect ARDS, and in fact within these broad categories, pathogenesis may differ. Therefore, different therapies may need to be developed for specific aetiologies such as sepsis-related ARDS, SIRS-related ARDS and various direct causes of ARDS.

Second, a well designed negative RCT does not necessarily mean that the therapy tested should be abandoned. It means that the therapy is likely to not be appropriate for widespread application. However, just because a drug does not work for every ARDS patient does not necessarily mean it should not be used for anyone with ARDS. For example, there is no evidence for treating all patients with acute ARDS with corticosteroids, but there is evidence that treating ARDS patients with relative adrenal insufficiency and septic shock

with low doses of hydrocortisone is likely to be beneficial. Similarly, nitric oxide should not routinely be applied to all patients with ALI/ARDS, but may be useful in refractory hypoxaemia, particularly in conjunction with other ventilation rescue strategies.

Third, a negative RCT should potentially lead to further research so that we can gain further insight as to why the therapy failed to yield a clinical benefit. Thomas Edison, when asked why he pursued his quest to invent a functional and practical light bulb after innumerable failed attempts, is reported to have replied, "I have not failed. I've just found 10 000 ways that won't work". ARDS research should take us from bench to bedside and back to the bench again. Basic science can help us understand basic mechanisms of disease, discover why a therapy failed, then provide new ideas to apply to the clinical realm. RCTs are necessary to prove benefit and quantify risk prior to changing clinical practice. Since we are in urgent need of therapies to treat ALI/ARDS, it is necessary that RCTs continue to advance our clinical care. However, these RCTs need to be well founded in basic biology and physiology research, and focused on specific hypotheses regarding mechanisms of disease. Continuing to conduct large clinical trials on heterogeneous patients with ALI/ARDS from multiple aetiologies will not only prove ineffective but also add enormous cost to the healthcare system.

The most significant and promising finding from an RCT to date is that calfactant, the natural bovine surfactant rich in Sp-B and -C, reduces mortality in ALI from 36% in the control arm to 19% in the paediatric population. Indeed, calfactant is the first and only pharmacological agent to demonstrate a mortality benefit for treatment of ALI/ARDS. The ongoing CARDS study will attempt to reproduce that finding in adults with direct causes of ARDS.^[117] This trial is continuing enrolment after the first interim analysis, with a target completion date of March 2011.

5. Conclusion

Great gains have been made in providing supportive management to patients with ALI/ARDS.

Ongoing and future research efforts will provide important insights into the complex pathophysiology involved and may provide further rationale for patient-specific therapies and/or combination therapies targeting the various mechanisms contributing to this disorder. Understanding who is at greatest risk of succumbing to ALI/ARDS and establishing the optimal time to intervene will be essential to improving mortality for this syndrome.

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References

- Brun-Buisson C, Minelli C, Bertolini G, et al. Epidemiology and outcome of acute lung injury in European intensive care units: results from the ALIVE study. *Intensive Care Med* 2004 Jan; 30 (1): 51-61
- Bersten AD, Edibam C, Hunt T, et al. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian states. *Am J Respir Crit Care Med* 2002 Feb 15; 165 (4): 443-8
- Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002 Jan 16; 287 (3): 345-55
- Cooke CR, Shah CV, Gallop R, et al. A simple clinical predictive index for objective estimates of mortality in acute lung injury. *Crit Care Med* 2009; 37 (6): 1913-20
- The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342 (18): 1301-8
- 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 Jul 22; 351 (4): 327-36
- Bosma KJ, Lewis JF. Emerging therapies for treatment of acute lung injury and acute respiratory distress syndrome. *Expert Opin Emerg Drugs* 2007; 12 (3): 461-77
- Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149: 818-24
- Zemans R, Colgan SP, Downey GP. Transepithelial migration of neutrophils: mechanisms and implications for acute lung injury. *Am J Respir Cell Mol Biol* 2009; 40 (5): 519-35
- Triggiani M, De Marino V, de Crescenzo G, et al. Arachidonic acid remodeling in human inflammatory cells migrating to the lung in vivo. *Int Arch Allergy Immunol* 1997 May-Jul; 113 (1-3): 190-2
- Gao L, Barnes KC. Recent advances in genetic predisposition to clinical acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2009; 296: L713-25
- Moss M, Parsons PE, Steinberg KP, et al. Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock. *Crit Care Med* 2003; 31 (3): 869-77
- Raghavendran K, Pryhuber GS, Chess PR, et al. Pharmacotherapy of acute lung injury and acute respiratory distress syndrome. *Curr Med Chem* 2008; 15 (19): 1911-24
- Imai Y, Parodo J, Kajikawa O, et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. *JAMA* 2003 Apr 23; 289 (16): 2104-12
- Papathanassoglou ED, Moynihan JA, Ackerman MH. Does programmed cell death (apoptosis) play a role in the development of multiple organ dysfunction in critically ill patients? A review and a theoretical framework. *Crit Care Med* 2000; 28 (2): 537-49
- Barriere SL, Lowry SF. An overview of mortality risk prediction in sepsis. *Crit Care Med* 1995 Feb; 23 (2): 376-93
- Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995 Oct; 23 (10): 1638-52
- Sloane PJ, Gee MH, Gottlieb JE, et al. A multicenter registry of patients with acute respiratory distress syndrome: physiology and outcome. *Am Rev Respir Dis* 1992 Aug; 146 (2): 419-26
- Fowler AA, Hamman RF, Good JT, et al. Adult respiratory distress syndrome: risk with common predispositions. *Ann Intern Med* 1983 May; 98 (5 Pt 1): 593-7
- Montgomery AB, Stager MA, Carrico CJ, et al. Causes of mortality in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1985 Sep; 132 (3): 485-9
- Milberg JA, Davis DR, Steinberg KP, et al. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983-1993. *JAMA* 1995 Jan 25; 273 (4): 306-9
- NHLBI ARDS Network. About the ARDS Network [online]. Available from URL: <http://www.ardsnet.org/about> [Accessed 2010 May 6]
- Spragg RG, Lewis JF, Walrath HD, et al. Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. *N Engl J Med* 2004; 351 (9): 884-92
- Taut FJH, Rippin G, Schenk P, et al. A search for subgroups of patients with ARDS who may benefit from surfactant replacement therapy. *Chest* 2008; 134: 724-32
- The Oscillation for ARDS treated early (OSCILLATE) trial pilot study [ClinicalTrials.gov identifier NCT00474656]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2010 May 23]
- Rosenberg AL, Dechert RE, Park PK, et al. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury. A retrospective

- review of the ARDSnet tidal volume study cohort. *J Intensive Care Med* 2009; 24 (1): 35-46
27. Wheeler AP, Bernard GR, Thompson BT, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006; 354 (21): 2213-24
 28. Pontes-Arruda A, DeMichele S, Seth A, et al. The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data. *JPEN J Parenter Enteral Nutr* 2008 Nov; 32 (6): 596-605
 29. Blamoun J, Alfakir M, Rella ME, et al. Efficacy of an expanded ventilator bundle for the reduction of ventilator-associated pneumonia in the medical intensive care unit. *Am J Infect Control* 2009 Mar; 37 (2): 172-5
 30. Bouza E, Perez MJ, Munoz P, et al. Continuous aspiration of subglottic secretions in the prevention of ventilator-associated pneumonia in the postoperative period of major heart surgery. *Chest* 2008 Nov; 134 (5): 938-46
 31. Chan EY, Ruest A, Meade MO, et al. Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis. *BMJ* 2007 Apr 28; 334 (7599): 889
 32. Drakulovic MB, Torres A, Bauer TT, et al. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet* 1999 Nov 27; 354 (9193): 1851-8
 33. Crowther MA, Cook DJ. Thromboprophylaxis in medical-surgical critically ill patients. *Curr Opin Crit Care* 2008 Oct; 14 (5): 520-3
 34. Cook DJ, Reeve BK, Guyatt GH, et al. Stress ulcer prophylaxis in critically ill patients: resolving discordant meta-analyses. *JAMA* 1996 Jan 24; 275 (4): 308-14
 35. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008 Jan 12; 371 (9607): 126-34
 36. Chiang LL, Wang LY, Wu CP, et al. Effects of physical training on functional status in patients with prolonged mechanical ventilation. *Phys Ther* 2006 Sep; 86 (9): 1271-81
 37. Erickson SE, Martin GS, Davis JL, et al. Recent trends in acute lung injury mortality: 1996-2005. *Crit Care Med* 2009 May; 37 (5): 1574-9
 38. Adhikari NKJ, Burns KEA, Friedrich JO, et al. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *BMJ* 2007 Apr 14; 334 (7597): 779
 39. Alsaghir AH, Martin CM. Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. *Crit Care Med* 2008 Feb; 36 (2): 603-9
 40. Sud S, Sud M, Friedrich JO, et al. Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *CMAJ* 2008; 178 (9): 1153-61
 41. Borelli M, Lampati L, Vascotto E, et al. Hemodynamic and gas exchange response to inhaled nitric oxide and prone positioning in acute respiratory distress syndrome patients. *Crit Care Med* 2000 Aug; 28 (8): 2707-12
 42. Mehta S, Granton J, MacDonald RJ, et al. High-frequency oscillatory ventilation in adults: the Toronto experience. *Chest* 2004 Aug; 126 (2): 518-27
 43. Chan KP, Stewart TE, Mehta S. High-frequency oscillatory ventilation for adult patients with ARDS. *Chest* 2007 Jun; 131 (6): 1907-16
 44. 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 (9698): 1351-63
 45. Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. *JAMA* 2009 Nov 4; 302 (17): 1888-95
 46. Slotman GJ, Burchard KW, D'Arezzo A, et al. Ketoconazole prevents acute respiratory failure in critically ill surgical patients. *J Trauma* 1988; 28 (5): 648-54
 47. Yu M, Tomasa G. A double-blind, prospective, randomized trial of ketoconazole, a thromboxane synthetase inhibitor, in the prophylaxis of the adult respiratory distress syndrome. *Crit Care Med* 1993; 21 (11): 1635-42
 48. Sinuff T, Cook DJ, Peterson JC, et al. Development, implementation, and evaluation of a ketoconazole practice guideline for ARDS prophylaxis. *J Crit Care* 1999; 14 (1): 1-6
 49. He X, Han B, Muram M, et al. Angiotensin-converting enzyme inhibitor captopril prevents oleic acid-induced severe acute lung injury in rats. *Shock* 2007; 28 (1): 106-11
 50. Chen C, Xu S, Wang W-X, et al. Rosiglitazone attenuates the severity of sodium taurocholate-induced acute pancreatitis and pancreatitis-associated lung injury. *Arch Med Res* 2009; 40: 79-88
 51. Steinberg J, Halter J, Schiller H, et al. Chemically modified tetracycline prevents the development of septic shock and acute respiratory distress syndrome in a clinically applicable porcine model. *Shock* 2005; 24 (4): 348-56
 52. Nathens AB, Neff MJ, Jurkovich GJ, et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. *Ann Surg* 2002; 236 (6): 814-22
 53. Peter JV, John P, Graham PL, et al. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. *BMJ* 2008; 336: 1006-9
 54. Schuster DPM, Metzler M, Opal S, et al. Recombinant platelet-activating factor acetylhydrolase to prevent acute respiratory distress syndrome and mortality in severe sepsis: phase IIB, multicenter, randomized, placebo-controlled, clinical trial. *Crit Care Med* 2003; 31 (6): 1612-9
 55. The ARDS Network Authors for the ARDS Network. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2000; 283 (15): 1995-2002
 56. Perkins GD, McAuley DF, Thickett DR, et al. The Beta-Agonist Lung Injury Trial (BALTI): a randomized placebo-controlled clinical trial. *Am J Respir Crit Care Med* 2006 Feb 1; 173 (3): 281-7
 57. Matthay MA, Brower R, Thompson BT, et al. Randomized, placebo-controlled trial of an aerosolized beta-2 adrenergic agonist (albuterol) for the treatment of acute lung injury [abstract]. *Am J Respir Crit Care Med* 2009; 179 (Meeting Abstracts): A2166

58. Anzueto A, Baughman RP, Guntupalli KK, et al. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome: Exosurf Acute Respiratory Distress Syndrome Sepsis Study Group. *N Engl J Med* 1996 May 30; 334 (22): 1417-21
59. Gregory TJ, Steinberg KP, Spragg R, et al. Bovine surfactant therapy for patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1997 Apr; 155 (4): 1309-15
60. Venticute in patients with pneumonia or aspiration of gastric contents and intubation/ventilation/oxygenation impairment (BY2001/M1-007) [ClinicalTrials.gov identifier NCT00074906]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2010 May 20]
61. Willson DF, Thomas NJ, Markovitz BP, et al. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. *JAMA* 2005; 293 (4): 470-6
62. Bernard GR, Wheeler AP, Arons MM, et al. A trial of antioxidants N-acetylcysteine and procysteine in ARDS: the Antioxidant in ARDS Study Group. *Chest* 1997 Jul; 112 (1): 164-72
63. Suter PM, Domenighetti G, Schaller MD, et al. N-acetylcysteine enhances recovery from acute lung injury in man: a randomized, double-blind, placebo-controlled clinical study. *Chest* 1994; 105 (1): 190-4
64. Bernard GR, Swindell BB, Meredith MJ, et al. Glutathione (GSH) repletion by n-acetylcysteine (NAC) in patients with the adult respiratory distress syndrome (ARDS) [abstract]. *Am Rev Respir Dis* 1989; 139: A221
65. Jepsen S, Herlevsen P, Knudsen P, et al. Antioxidant treatment with N-acetylcysteine during adult respiratory distress syndrome: a prospective, randomized, placebo-controlled study. *Crit Care Med* 1992 Jul; 20 (7): 918-23
66. Gadek JE, DeMichele SJ, Karlstad MD, et al. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome: Enteral Nutrition in ARDS Study Group. *Crit Care Med* 1999 Aug; 27 (8): 1409-20
67. NHLBI ARDS Network. Omega study: information update. 2009 Aug 13 [online]. Available from URL: <http://www.ardsnet.org/node/78857> [Accessed 2010 May 20]
68. Early versus delayed enteral feeding and Omega-3 fatty acid/antioxidant supplementation for treating people with acute lung injury or acute respiratory distress syndrome (the EDEN-Omega study) [ClinicalTrials.gov identifier NCT00609180]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2010 May 20]
69. Zeiher BG, Artigas A, Vincent JL, et al. Neutrophil elastase inhibition in acute lung injury: results of the STRIVE study. *Crit Care Med* 2004; 32 (8): 1695-702
70. Tamakuma G, Shiba T, Hirasawa H. A phase III clinical study of neutrophil elastase inhibitor ONO-5046 Na in SIRS patients. *J Clin Ther Med (Japan)* 1998; 14: 289-318
71. Honore S, Attalah HL, Azoulay E, et al. Beneficial effect of an inhibitor of leukocyte elastase (EPI-hNE-4) in presence of repeated lung injuries. *Shock* 2004; 22 (2): 131-6
72. Abraham E, Baughman R, Fletcher E, et al. Liposomal prostaglandin E1 (TLC C-53) in acute respiratory distress syndrome: a controlled, randomized, double-blind, multicenter clinical trial. TLC C-53 ARDS Study Group. *Crit Care Med* 1999 Aug; 27 (8): 1478-85
73. Vincent JL, Brase R, Santman F, et al. A multi-centre, double-blind, placebo-controlled study of liposomal prostaglandin E1 (TLC C-53) in patients with acute respiratory distress syndrome. *Intensive Care Med* 2001; 27 (10): 1578-83
74. Presneill JJ, Harris T, Stewart AG, et al. A randomized phase II trial of granulocyte-macrophage colony-stimulating factor therapy in severe sepsis with respiratory dysfunction. *Am J Respir Crit Care Med* 2002; 166 (2): 138-43
75. A randomized trial of GM-CSF in patients with ALI/ARDS [ClinicalTrials.gov identifier NCT00201409]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2010 May 20]
76. The ARDS Clinical Trials Network, National Heart Blood and Lung Institute, National Institutes of Health. Randomized, placebo-controlled trial of lisofylline for early treatment of acute lung injury and acute respiratory distress syndrome. *Crit Care Med* 2002; 30 (1): 1-6
77. Folkesson HG, Matthay MA, Hebert CA, et al. Acid aspiration-induced lung injury in rabbits is mediated by interleukin-8-dependent mechanisms. *J Clin Invest* 1995 Jul; 96 (1): 107-16
78. Bao Z, Ye Q, Gong W, et al. Humanized monoclonal antibody against the chemokine CXCL-8 (IL-8) effectively prevents acute lung injury. *Int Immunopharmacol* 2010; 10 (2): 259-63
79. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest* 2007; 131: 954-63
80. Bernard GR, Luce JM, Sprung CL, et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. *N Engl J Med* 1987 Dec 17; 317 (25): 1565-70
81. Annane D, Sèbille V, Bellissant E, Ger-Inf 05 Study Group. Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. *Crit Care Med* 2006; 34 (1): 22-30
82. Liu KD, Levitt J, Zhuo H, et al. Randomized clinical trial of activated protein C for the treatment of acute lung injury. *Am J Respir Crit Care Med* 2008 Sep 15; 178 (6): 618-23
83. Irish Critical Care Trials Group. Acute lung injury and the acute respiratory distress syndrome in Ireland: a prospective audit of epidemiology and management. *Crit Care* 2008; 12 (1): R30
84. Kor DJ, Iscimen R, Yilmaz M, et al. Statin administration did not influence the progression of lung injury or associated organ failures in a cohort of patients with acute lung injury. *Intensive Care Med* 2009; 35 (6): 1039-46
85. 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 (16): 1671-84
86. 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 (2): 159-65
87. Bernard GR, Reines HD, Halushka PV, et al. Prostacyclin and thromboxane A2 formation is increased in human sepsis syndrome: effects of cyclooxygenase inhibition. *Am Rev Resp Dis* 1991; 144 (5): 1095-101

88. Imai Y, Lachmann B, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung injury. *Nature* 2005; 436: 112-6
89. Marshall RP, Webb S, Bellingan GJ, et al. Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002; 166: 646-50
90. Jerng JS, Yu CJ, Wang HC, et al. Polymorphism of the angiotensin-converting enzyme gene affects the outcome of acute respiratory distress syndrome. *Crit Care Med* 2006; 34 (4): 1001-6
91. Trillo-Alvarez CA, Kashyap R, Kojicic M, et al. Chronic use of angiotensin pathway inhibitors is associated with a decreased risk of acute respiratory distress syndrome [abstract]. *Am J Respir Crit Care Med* 2009; 179: A4638
92. Gong MN, Bajwa EK, Thompson BT, et al. Use of ACE inhibitors and development and outcome in ARDS [abstract]. *Am J Respir Crit Care Med* 2009; 179: A5095
93. Ricote M, Li AC, Willson TM, et al. The peroxisome proliferator-activated receptor- γ is a negative regulator of macrophage activation. *Nature* 1998; 391: 79-82
94. Jiang C, Ting AT, Seed B. PPAR- γ agonists inhibit production of monocyte inflammatory cytokines. *Nature* 1998; 391: 82-6
95. Su CG, Wen X, Bailey ST, et al. A novel therapy for colitis utilizing PPAR- γ ligands to inhibit the epithelial inflammatory response. *J Clin Invest* 1999; 104 (4): 383-9
96. Shiojiri T, Wada K, Nakajima A, et al. PPAR γ ligands inhibit nitrotyrosine formation and inflammatory mediator expressions in adjuvant-induced rheumatoid arthritis mice. *Eur J Clin Pharm* 2009; 448: 231-8
97. Khanderia U, Pop-Busui R, Eagle KA. Thiazolidinediones in type 2 diabetes: a cardiology perspective. *Ann Pharmacother* 2008 Oct; 42 (10): 1466-74
98. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007; 298 (10): 1189-95
99. Trial of glutamine and antioxidant supplementation in critically ill patients (REDOXS) [ClinicalTrials.gov identifier NCT00133978]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2010 May 20]
100. Esteban A, Fernandez-Segoviano P, Frutos-Vivar F, et al. Comparison of clinical criteria for the acute respiratory distress syndrome with autopsy findings. *Ann Intern Med* 2004 Sep 21; 141 (6): 440-5
101. Matthay MA, Folkesson HG, Clerici C. Lung epithelial fluid transport and the resolution of pulmonary edema. *Physiol Rev* 2002 Jul; 82 (3): 569-600
102. Sakuma T, Okaniwa G, Nakada T, et al. Alveolar fluid clearance in the resected human lung. *Am J Respir Crit Care Med* 1994; 150 (2): 305-10
103. Mutlu GM, Dumasius V, Burhop J, et al. Upregulation of alveolar epithelial active Na⁺ transport is dependent on beta2-adrenergic receptor signaling. *Circ Res* 2004; 94 (8): 1091-100
104. Balti-2 (Beta Agonist Lung Injury Trial-2). 2009 [online]. Available from URL: <http://www2.warwick.ac.uk/fac/med/research/ctu/trials/ecr/balti2> [Accessed 2010 May 20]
105. Drug study of albuterol to treat acute lung injury (ALTA) [ClinicalTrials.gov identifier NCT00434993]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2010 May 20]
106. McAuley DF, Matthay MA. A role for β_2 agonists in ARDS: the question remains unanswered. *JICS* 2009; 10 (3): 172-3
107. Crouch E, Wright JR. Surfactant proteins a and d and pulmonary host defense. *Annu Rev Physiol* 2001; 63: 521-54
108. Lewis JF, Veldhuizen RA. The future of surfactant therapy during ALI/ARDS. *Semin Respir Crit Care Med* 2006; 27 (4): 377-88
109. Lewis JF, Veldhuizen RA. The role of exogenous surfactant in the treatment of acute lung injury. *Ann Rev Physiol* 2003; 65: 613-42
110. Noguee L, Garnier G, Dietz H. A mutation in the surfactant protein B gene responsible for fatal neonatal respiratory disease in multiple kindreds. *J Clin Invest* 1994; 93 (4): 1860-3
111. Clark JC, Wert SB, Bachurski CJ. Target disruption of the surfactant protein B gene disrupts surfactant homeostasis, causing respiratory failure in newborn mice. *Proc Natl Acad Sci U S A* 1995; 92: 7794-8
112. Wang Z, Gurel O, Baatz J. Differential activity and lack of synergy of lung surfactant proteins SP B and SP C in interactions with phospholipids. *J Lipid Res* 1996; 37: 1749-60
113. Seeger W, Grube C, Gunther A, et al. Surfactant inhibition by plasma proteins: differential sensitivity of various surfactant preparations. *Eur Respir J* 1993; 6 (7): 971-7
114. Willson D. Calfactant. *Expert Opin Pharmacother* 2001; 2 (9): 1479-93
115. Hall SB, Venkitataman AR, Whitsett JA, et al. Importance of hydrophobic apoproteins as constituents of clinical exogenous surfactants. *Am Rev Respir Dis* 1992; 145: 24-30
116. Ferring M, Vincent JL. Is outcome from ARDS related to the severity of respiratory failure? *Eur Respir J* 1997; 10: 1297-300
117. Calfactant for direct acute respiratory distress syndrome (CARDS) [ClinicalTrials.gov identifier NCT00682500]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2010 May 20]
118. Moradi M, Mojtahedzadeh M, Mandegari A, et al. The role of glutathione-S-transferase polymorphisms on clinical outcome of ALI/ARDS patient treated with N-acetylcysteine. *Resp Med* 2009; 103 (3): 434-41
119. Singer P, Shapiro H. Enteral omega-3 and acute respiratory distress syndrome. *Curr Opin Clin Nutr Metab Care* 2009; 12: 123-8
120. Steinberg KP, Milberg JA, Martin TR, et al. Evolution of bronchoalveolar cell populations in the adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994; 150: 113-22
121. Kuebler WM, Goetz AE. The marginated pool. *Eur Surg Res* 2002; 34: 92-100
122. Lien DC, Wiltz W, Wagner JR, et al. Physiological neutrophil sequestration in the lung: visual evidence for localization in capillaries. *J Appl Physiol* 1987; 62: 1236-43
123. Safety and efficacy study of depelestat in acute respiratory distress syndrome (ARDS) patients [ClinicalTrials.gov

- identifier NCT00455767]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2010 May 20]
124. Ashitani J, Mukae H, Arimura Y, et al. High concentrations of alpha-defensins in plasma and bronchoalveolar lavage fluid of patients with acute respiratory distress syndrome. *Life Sci* 2004 Jul 16; 75 (9): 1123-34
 125. Biological markers to identify early sepsis and acute lung injury [ClinicalTrials.gov identifier NCT00825357]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2010 May 20]
 126. Marshall JC, Watts FL. Programmed cell death (apoptosis) and the resolution of systemic inflammation. *Can J Surg* 1997; 40 (3): 169-74
 127. Martin TR, Nakamura M, Matute-Bello G. The role of apoptosis in acute lung injury. *Crit Care Med* 2003; 31 (4 Suppl.): S184-8
 128. Taneja R, Parodo J, Jia SH, et al. Delayed neutrophil apoptosis in sepsis is associated with maintenance of mitochondrial transmembrane potential and reduced caspase-9 activity. *Crit Care Med* 2004; 32 (7): 1460-9
 129. Chitnis D, Dickerson C, Munster AM, et al. Inhibition of apoptosis in polymorphonuclear neutrophils from burn patients. *J Leukoc Biol* 1996; 59: 835-9
 130. Sookhai S, Wang JJ, McCourt M, et al. A novel therapeutic strategy for attenuating neutrophil-mediated lung injury *in vivo*. *Ann Surg* 2002; 235 (2): 285-91
 131. Matute-Bello G, Liles WC, Radella FI, et al. Neutrophil apoptosis in the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1997; 156: 1969-77
 132. Pelaez A, Bechara RI, Joshi PC, et al. Granulocyte/macrophage colony-stimulating factor treatment improves alveolar epithelial barrier function in alcoholic rat lung. *Am J Physiol Lung Cell Mol Physiol* 2004 Jan; 286 (1): L106-11
 133. Paine III R, Wilcoxon SE, Morris SB, et al. Transgenic overexpression of granulocyte macrophage-colony stimulating factor in the lung prevents hyperoxic lung injury. *Am J Pathol* 2003; 163 (6): 2397-406
 134. Matute-Bello G, Liles WC, Radella F, et al. Modulation of neutrophil apoptosis by granulocyte colony-stimulating factor and granulocyte/macrophage colony-stimulating factor during the course of acute respiratory distress syndrome. *Crit Care Med* 2000 Jan; 28 (1): 1-7
 135. Abraham E, Bursten S, Shenkar R, et al. Phosphatidic acid signaling mediates lung cytokine expression and lung inflammatory injury after hemorrhage in mice. *J Exp Med* 1995; 181: 569-75
 136. Goodman ER, Kleinstein E, Fusco AM, et al. Role of interleukin 8 in the genesis of acute respiratory distress syndrome through an effect on neutrophil apoptosis. *Arch Surg* 1998 Nov; 133 (11): 1234-9
 137. Miller EJ, Cohen AB, Matthay MA. Increased interleukin-8 concentrations in the pulmonary edema fluid of patients with acute respiratory distress syndrome from sepsis. *Crit Care Med* 1996; 24 (9): 1448-54
 138. Lucas R, Verin AD, Black SM, et al. Regulators of endothelial and epithelial barrier integrity and function in acute lung injury. *Biochem Pharmacol* 2009 Jun 15; 77 (12): 1763-72
 139. Low doses corticosteroids as adjuvant therapy for the treatment of severe H1N1 flu (CORTIFLU) [ClinicalTrials.gov identifier NCT01014364]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2010 May 20]
 140. Bernard GR, Ely EW, Wright TJ, et al. Safety and dose relationship of recombinant human activated protein C for coagulopathy in severe sepsis. *Crit Care Med* 2001 Nov; 29 (11): 2051-9
 141. STIP: Statin Trial for Influenza Patients [ClinicalTrials.gov identifier NCT00970606]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2010 May 20]
 142. Statins for Acutely Injured Lungs from Sepsis (SAILS) [ClinicalTrials.gov identifier NCT00979121]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://www.clinicaltrials.gov> [Accessed 2010 May 20]

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