

# Acute lung injury and the acute respiratory distress syndrome: a clinical review



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Acute respiratory distress syndrome and acute lung injury are well defined and readily recognised clinical disorders caused by many clinical insults to the lung or because of predispositions to lung injury. That this process is common in intensive care is well established. The mainstay of treatment for this disorder is provision of excellent supportive care since these patients are critically ill and frequently have coexisting conditions including sepsis and multiple organ failure. Refinements in ventilator and fluid management supported by data from prospective randomised trials have increased the methods available to effectively manage this disorder.

## Definition and diagnosis

Acute respiratory distress syndrome and acute lung injury were first described in 1967, and are characterised by the abrupt onset of clinically significant hypoxaemia with presence of diffuse pulmonary infiltrates. These infiltrates show on radiograph (figure) as pulmonary oedema resulting from increased pulmonary vascular permeability.<sup>1</sup> These disorders affect patients of all ages and usually happen soon after an easily identified triggering event (panel 1). The likelihood of developing acute lung injury depends on the predisposing disorder; some events (eg, severe sepsis) are more likely to progress to lung injury than others. The risk of individuals developing acute lung injury also depends on patients' characteristics. For example, alcoholism is a predisposing factor<sup>2</sup> and data now suggest the possibility of a genetic predisposition.<sup>3,4</sup> Although the causes of acute lung injury have been segregated into direct and indirect injuries, outcomes are similar in both categories if age, underlying chronic illnesses, and severity of non-pulmonary illness and gas-exchange abnormalities are controlled for.<sup>5-8</sup>

When the hypoxaemia in acute lung injury is severe (partial arterial pressure of oxygen [ $\text{PaO}_2$ ]/fractional concentration of oxygen in inspired air [ $\text{F}_i\text{O}_2$ ] <200), the disorder is termed the acute respiratory distress syndrome. However, most epidemiological and interventional studies use the broader range of gas-exchange abnormality ( $\text{PaO}_2/\text{F}_i\text{O}_2$  <300) and refer to the overall disorder as acute lung injury. These definitions have limitations: for example, the physiological thresholds do not need standardised ventilatory support. The use of positive end-expiratory pressure (PEEP) can improve oxygenation indices sufficiently to convert patients meeting the definition of acute respiratory distress syndrome to have acute lung injury, and can change the physiology in the lung such that the patient does not meet the criteria for acute lung injury or acute respiratory distress syndrome. Another factor that affects the definition of acute respiratory distress syndrome is the substantial variability of physicians' interpretations of radiographs.<sup>9</sup> Nevertheless, this nomenclature developed by international consensus is nearly a decade old and is widely accepted<sup>10</sup> (panel 2).

For consistency and clarity we use the inclusive term acute lung injury for the remainder of this Review.

Because acute lung injury has no pathognomonic laboratory or radiographic feature, diagnostic confusion could occur with other diseases that cause hypoxaemia and show pulmonary oedema on radiographs (panel 3).<sup>11</sup> Although the term acute lung injury helps to identify a group of patients who can generally be treated in the same way, there are important exceptions. For example, several rare diseases (eg, acute eosinophilic pneumonia) do have a specific treatment and, if not carefully considered, could be overlooked under the general classification of acute lung injury. Clinicians should carefully think about all patients meeting the definition of acute lung injury to ensure that they do not miss an underlying disease with a specific treatment.

Left atrial hypertension from either intravascular volume overload or heart disease (eg, mitral stenosis, left ventricular failure) most often present the diagnostic dilemma. Historically, efforts have been made to distinguish acute lung injury from hydrostatic pulmonary oedema by measuring pulmonary vascular permeability in research settings and by measuring pulmonary-artery occlusion pressure in clinical settings. The distinction between these two disorders was thought to be especially important for patients entering clinical studies, but this measurement has mainly been abandoned with the realisation that exceeding an arbitrary pulmonary-artery occlusion pressure does not exclude a diagnosis of acute lung injury since a concurrent illness could raise this

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## Search strategy and selection criteria

We searched the Cochrane Library and MEDLINE (for entries up to October, 2005). We used the search terms "acute lung injury", "ALI", "acute respiratory distress syndrome", and "ARDS". Animal and human studies were reviewed. We mainly selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search and selected those we judged relevant. Generally, preference was given to large randomised human clinical trials, but several review articles, letters, and editorials were included because they provided a comprehensive overview of histopathology or a historical view of treatment. The reference list was subsequently modified during the peer-review process on the basis of comments from reviewers and updated with newer publications.

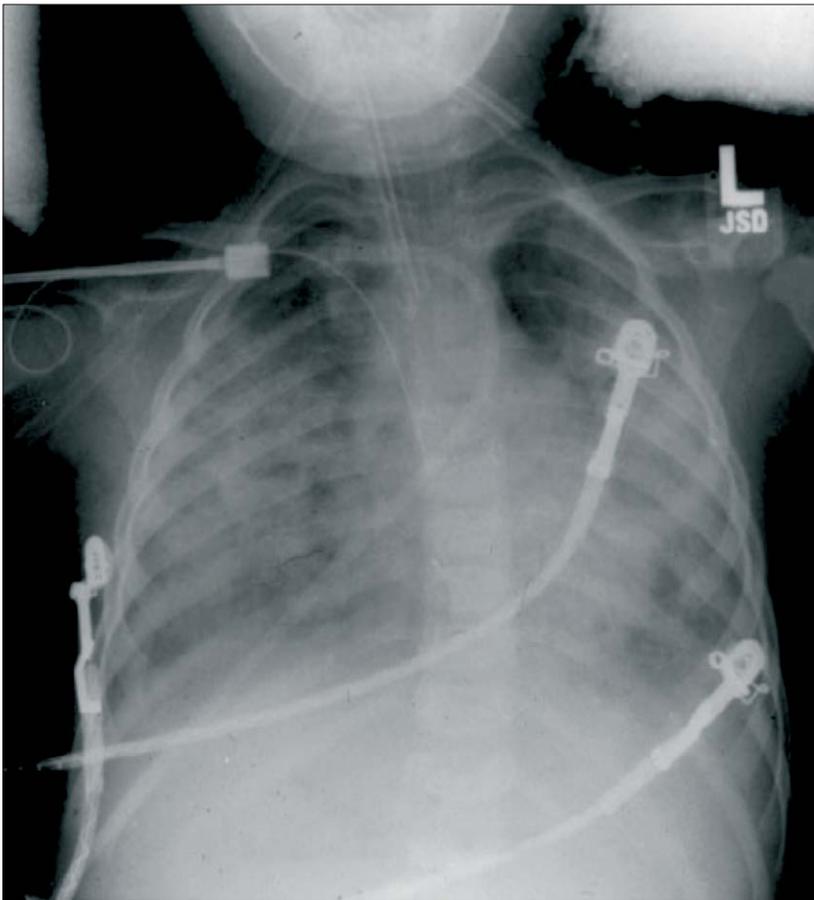


Figure: Frontal portal chest radiograph showing diffuse bilateral infiltrates consistent with acute lung injury

pressure. Such a situation could happen in a patient with pneumonia-induced septic shock, diffuse bilateral pulmonary infiltrates, and refractory hypoxaemia who has undergone large-volume fluid resuscitation. In this

#### Panel 1: Causes of acute lung injury

##### Direct injury

- Pneumonia
- Gastric aspiration
- Drowning
- Fat and amniotic-fluid embolism
- Pulmonary contusion
- Alveolar haemorrhage
- Smoke and toxic gas inhalation
- Reperfusion (pleural effusion drainage, embolectomy)
- Unilateral lung re-implantation

##### Indirect injury

- Severe sepsis
- Transfusions
- Shock
- Salicylate or narcotic overdose
- Pancreatitis

setting, pulmonary-artery occlusion pressure could well exceed 18 mm Hg, although the patient would still have acute lung injury. Additionally, without great diligence, measurements of bedside pulmonary-artery occlusion pressure do not have the precision needed to make this distinction, because they vary greatly.<sup>12,13</sup> Even when pulmonary-artery occlusion pressure is less than 18 mm Hg, one cannot confirm that oedema is the result of altered permeability because reduced colloid oncotic pressure promotes oedema in the absence of permeability changes.<sup>14,15</sup>

#### Prevalence and outcomes

Depending on how the syndromes are defined and where the survey is undertaken, the reported frequency of acute lung injury varies widely. The frequency seems to be increased in developed countries and if less stringent criteria for hypoxaemia are used. Estimates worldwide range from 1.5 to 75 cases per 100 000 population.<sup>16,17</sup> Irrespective of differences in estimates, hundreds of thousands of cases occur worldwide every year and are associated with substantial morbidity, cost, and mortality.<sup>18,19</sup>

Mortality rates of acute lung injury also vary greatly depending on the age of the patient and presence of non-pulmonary organ dysfunctions; advanced age, shock, and hepatic failure are most predictive of death whereas young trauma patients have the best outcomes.<sup>20</sup> Paradoxically, for a disease known predominantly to cause hypoxaemia, the initial degree of gas-exchange impairment is a poor predictor of outcome unless severe (eg,  $\text{PaO}_2/\text{F}_2\text{O}_2 < 50$ ).<sup>7,21</sup> Severe hypoxaemia that persists for days has a greater predictive value.<sup>22</sup> Two decades ago, mortality from acute lung injury was often reported as 50–70% but has since declined over time.<sup>23</sup> Reasons for this improvement are unknown; however, advances in supportive care are thought to have decreased extrapulmonary organ failures, which could account for most of the change.<sup>24</sup> In the most recent randomised trials,<sup>25</sup> overall 28-day mortality is reported as 25–30% whereas mortality in community-based surveys is 35–40%.

For most patients with acute lung injury, outcome is determined in 7–10 days, by which time about half of patients have died or have been weaned off treatment.<sup>26</sup> Nevertheless, a substantial proportion have a slow recovery, with up to 10% of patients needing more than 1 month of ventilation. Data suggest that the survival for patients with persistent, severe acute lung injury could be much better than previously thought, with survival rates near to 70%.<sup>27</sup> Lung function in survivors of acute lung injury returns to normal over 6–12 months<sup>28</sup> but recovery of lung function is probably not the most important problem. Neuropsychiatric problems and neuromuscular weakness are now known to happen frequently and often delay return to school or work by months and can occasionally be permanent.<sup>29–32</sup>

## Histopathology

Early acute lung injury is characterised histologically by a diffuse neutrophilic alveolar infiltrate, with haemorrhage, and the accumulation of a protein-rich pulmonary oedema. During this acute, so-called exudative phase, a panoply of cytokines (eg, tumour necrosis factor, interleukin 1, interleukin 8) incites and perpetuates inflammation. By increasing oxidant stress and protease activity, the inflammatory mixture in the alveoli and interstitium reduces surfactant production, and inactivates remaining surfactant, thereby promoting widespread atelectasis. Additionally, elastases damage the structural framework of the lung, and both alveolar-capillary and epithelial-cell injury can be seen. Damage of the epithelial barrier exacerbates the tendency for alveolar flooding, and delays recovery by impairing fluid clearance. A procoagulant tendency is seen in the lung as concentrations of anticoagulant proteins (protein C, protein S) fall and expression of procoagulant proteins (tissue factor) and anti-fibrinolytic proteins (plasminogen activator inhibitor 1) increases.<sup>33,34</sup> Together, these changes are probably responsible for capillary thrombosis.<sup>35</sup>

Afterwards, some patients with acute lung injury have a fibroproliferative phase, during which chronic inflammation, fibrosis, and neovascularisation take place.<sup>36</sup> Unfortunately, this phase has no specific features, apart from time that allows the clinician to distinguish the exudative period from the fibroproliferative period. We do not know why most survivors rapidly resolve the acute inflammation but some progress to the chronic phase. Another mystery is why the histological changes of fibroproliferation can be seen in some patients in days, but not occur in others for weeks.

## Pathophysiology

In the early phase of acute lung injury, leakage of oedema fluid into the lung and inflammatory cellular infiltrates cause diffusion abnormalities and ventilation-perfusion mismatch, which clinically manifest as hypoxaemia. Concurrently, cellular infiltration, diffuse atelectasis, and oedema fluid reduce thoracic compliance. The combination of regional alveolar over-distention and small-vessel thrombosis increases dead space. Hypoxaemic vasoconstriction and capillary obliteration raise pulmonary-artery pressures, and if raised pressures are sustained, cor pulmonale can occur. Increased dead-space ventilation, reduced lung compliance, and hypoxaemia combine to greatly increase the effort of breathing. Eventually, oxygen demands exceed ventilatory capability, and hypoxaemic, hypercarbic respiratory failure will take place if left untreated.

## Treatment

Acute lung injury has no specific treatment, although some doctors would argue that ventilation with a normal tidal volume, which results in reduced airway pressure, is a specific treatment. The mainstay of

### Panel 2: Simplified consensus definition of acute lung injury

- Acute onset (less than 7 days)
- Severe hypoxaemia ( $\text{PaO}_2/\text{F}_i\text{O}_2 < 300$  for acute lung injury, or 200 for acute respiratory distress syndrome)
- Diffuse bilateral pulmonary infiltrates on frontal radiograph consistent with pulmonary oedema (these can be patchy and asymmetric, and pleural effusions can be present)
- Absence of left atrial hypertension (pulmonary-artery wedge pressure  $< 18$  mm Hg if measured)

### Panel 3: Differential diagnosis of acute lung injury

- Left ventricular failure
- Intravascular volume overload
- Mitral stenosis
- Veno-occlusive disease
- Lymphangitic carcinoma
- Interstitial and airway diseases
  - Hypersensitivity pneumonitis
  - Acute eosinophilic pneumonia
  - Bronchiolitis obliterans with organising pneumonia

treatment is supportive care, mainly to avoid iatrogenic complications and treat the underlying cause, while maintaining adequate oxygenation. Almost all patients with acute lung injury need positive-pressure ventilation with supplemental oxygen and PEEP. Physical support is usually provided by use of a cuffed tracheal tube. Although some patients can be successfully supported with non-invasive mask ventilation, few large, well conducted randomised trials demonstrate the feasibility of non-invasive ventilation or indicate its benefits over tracheal-tube-delivered ventilation.<sup>37,38</sup>

### Supportive care

A treatment for the cause of acute lung injury is desirable. Measures for the prevention of deep vein thrombosis, gastrointestinal bleeding, and pressure ulcers should be provided for all patients.<sup>39</sup> The head of the bed should be raised to an angle of at least 30° to reduce the risk of hospital-acquired pneumonia, probably for all patients, but at least for those who are enterally fed.<sup>40</sup> Although enteral nutrition is widely advocated, few data are available to guide selection of the formula; optimum delivery location; timing of initiation, rate of administration, and clinical practice is highly heterogeneous.<sup>41</sup> All invasive catheters should be inserted with maximum barrier precautions and chlorhexidine skin preparation.<sup>42</sup> Standardised, goal-directed sedation practices are sensible because they decrease the length of mechanical ventilation and intensive care unit stay.<sup>43</sup> Glucose control that is more stringent than is traditionally maintained could be beneficial, although this strategy has not been tested exclusively in patients with acute lung injury.<sup>44</sup>

### Mechanical ventilation, oxygen, and PEEP

Few of the many combinations of ventilatory mode, rate, tidal volume, flow rate and pattern,  $F_iO_2$ , and PEEP, have undergone rigorous testing in human beings with durable, clinically important endpoints such as mortality. Therefore, how to best ventilate and oxygenate patients with acute lung injury is controversial. Historically, the primary goal was to achieve near normal arterial blood gases, even if high tidal volumes and minute ventilations had to be used.<sup>45,46</sup> Arterial blood gases were obtained frequently to monitor treatment in some patients after each ventilator change. In this traditional approach, the risks of airway pressure were perceived as small because the complications of high airway pressures (eg, pneumothorax), were believed to be uncommon, readily apparent, unavoidable, and easily treated.<sup>47</sup> Tidal volumes that were 50–100% larger (10–15 mL/kg of actual bodyweight) than those of spontaneously breathing healthy controls at rest (5–7 mL/kg predicted bodyweight) would normally have been provided.<sup>48,49</sup> Supplemental oxygen was supplied, usually with low PEEP, and when the required oxygen concentration reached a value that prompted physician concern, PEEP was increased to maintain an acceptable  $PaO_2$  at an acceptable  $F_iO_2$ . The definition of acceptable differed by physician but there was some consensus that  $PaO_2$  greater than 60 mm Hg with  $F_iO_2$  less than 0.6 mm Hg were desirable.<sup>50,51</sup> Heterogeneity in selection of tidal volume, and positive end expiratory pressure- $F_iO_2$  combinations existed because few data were available to guide choices.<sup>52</sup> Wide variations in reported practices continue today.<sup>53,54</sup>

In the past 5 years, advances have been made in the ventilation of patients with acute lung injury, which centre on three issues: the realisation that alveolar involvement is heterogeneous, awareness that the bodyweight of many patients is substantially larger than predicted, and recognition that the damage caused by a ventilator when adjusted to maintain normal blood gases could be substantial but not immediately apparent. Lung CT scans of patients with acute lung injury showed the heterogeneous nature of alveolar effects. Imaging revealed that portions (typically dependent regions) of the lung were densely infiltrated, while other areas appeared normal or near normal.<sup>55–57</sup> This finding suggests that the forcing of supra-normal, and perhaps normal, tidal volumes into the injured lung will result in over-distention and injury of the most compliant alveoli. Moreover, evidence has suggested that injury to normal alveoli could result from airway pressures traditionally thought to be safe. This notion was supported by animal studies indicating that alveolar overdistention can not only perpetuate, but can also cause lung injury, and gave rise to the idea that tidal volumes should be reduced to around the smaller volume of aerated lung in acute lung injury (ie,

the baby lung).<sup>58–60</sup> Furthermore, animal studies showed that the injury from the large tidal volume was not simply a mechanical event of tearing alveoli, but rather that high-volume ventilation led to local and systemic inflammation, sometimes referred to as biotrauma<sup>61</sup>

Lung capacity is predominantly affected by age, sex, and height, yet tidal volume was customarily indexed to actual bodyweight. With the recognition that patients from the intensive care unit were, on average, nearly 20% larger than their ideal bodyweight, traditional tidal volumes were probably too large and should be reduced to at least those appropriate for age, sex, and height.<sup>62</sup> This finding led to the decision by some investigators to index tidal volume to predicted bodyweight, a potentially important decision to prevent barotrauma.

Several animal studies confirmed that high airway pressures applied to healthy lungs caused rapid histopathological changes identical to those seen in human beings with acute lung injury and could lead to systemic inflammation and extrapulmonary organ damage. This finding has been confirmed in human studies and remains the leading theory to explain how lower tidal volume ventilation reduces extrapulmonary organ failures and improves survival rates. Additionally, data now suggest that mechanically ventilated patients without acute lung injury have an increased likelihood of developing lung injury with large tidal volumes.<sup>63</sup>

Animal studies of lung injury have also shown that smaller tidal volumes were associated with reduced oedema formation<sup>64</sup> After these studies, several case series suggested potential benefit of smaller tidal volumes in various lung diseases.<sup>65,66</sup> Four small randomised trials examined the practice of reduced tidal volume ventilation in patients with, or at risk of, acute lung injury. Three<sup>67–69</sup> of these studies failed to show benefit of lower tidal volume ventilation. The fourth study<sup>70</sup> used a more complex approach than the other three, by testing the lower inflection point of lung compliance (P<sub>flex</sub>) to set PEEP, undertaking recruitment manoeuvres (sustained increases in ventilator pressure), and using ventilation with smaller tidal volumes. This study<sup>70</sup> showed a striking survival benefit compared with a traditional approach, but was not conclusive because of: its small size; the technical difficulty of P<sub>flex</sub> measurement; the high mortality rate in the control group; and the fact that many patients studied had an uncommon cause of lung injury.

The US National Institutes of Health Network for Acute Respiratory Distress Syndrome (NIH ARDS Network) investigated whether lower tidal volume ventilation was beneficial by undertaking a large randomised multicentre study<sup>26</sup> of volume-assisted controlled ventilation, which compared a traditional tidal volume (12 mL/kg of predicted bodyweight) with a smaller tidal volume (6 mL/kg of predicted bodyweight). In both groups, breath size was indexed to predicted bodyweight, and plateau pressure limits mandated

additional tidal volume reductions if those pressure limits were exceeded. PEEP and  $F_{iO_2}$  were set by use of an arbitrary, but prospectively defined, scale to achieve an arterial saturation of 88–95% or  $PaO_2$  of 55–80 mm Hg. When this strategy was applied, rapid increases in respiratory rate, decreases in  $PaO_2/F_{iO_2}$ , and modest increases in  $PaCO_2$  were often seen. Although these physiological changes seem to be adverse and a cause for concern, and continue to hamper the use of lower tidal volumes by some clinicians, the changes seem to be unimportant for most patients. This trial<sup>26</sup> showed a significant reduction in 28-day mortality from 40% to 31%, with an increase in the number of days free of ventilation and extrapulmonary organ failure. This study also confirmed and built on previous findings that larger breaths were associated with a delayed resolution of the inflammatory response.<sup>71,72</sup> This study<sup>26</sup> has four notable differences from previous unsuccessful trials: it used the lowest tidal volume of all the trials; it linked tidal volume to predicted bodyweight; it had specific rules to treat respiratory acidosis, allowing the respiratory rate to increase to 35 breaths per min and buffering the acidosis with sodium bicarbonate if needed; and it was the largest study, allowing for detection of smaller survival differences.

This study has generated substantial debate,<sup>73–77</sup> with some experts asserting that it was irrelevant because usual practice had already adopted lower tidal volumes. A few postulated that smaller volumes were beneficial only because the higher tidal volume was excessively high.<sup>78</sup> Others theorised that reduction of tidal volume was not necessary if plateau pressures were below a safe threshold.<sup>79</sup> Tidal volumes for 6 and 12 mL/kg predicted bodyweight were even claimed to be suboptimum, with the best tidal volume being between the two.<sup>78</sup> The benefit seen in the smaller breath group has been speculated not to be directly related to the tidal volume reduction, but rather to the high respiratory rates induced by intrinsic PEEP.<sup>80–82</sup> Finally, there were concerns that smaller tidal volumes would require more sedation or paralysis.

These hypotheses are not supported by data. For example, physicians have reported using a tidal volume greater than 10 mL/kg for more than 60% of patients.<sup>50</sup> Other contemporary clinical trials also reported tidal volumes in the 10–15 mL/kg range,<sup>82</sup> and a substantial number of enrolled patients were ventilated with a tidal volume greater than 10 mL/kg before entering the study.<sup>26</sup> Surveys of practice continue to show that clinicians are ventilating patients with acute lung injury with tidal volumes greater than 6 mL/kg.<sup>83–86</sup> The theory that lower tidal volume resulted in an improved outcome solely because the group with traditional tidal volume was ventilated with artificially large and perhaps harmful tidal volume has also been refuted because the other unsuccessful trials of lower tidal volumes used

similar volumes in the groups that had conventional higher tidal volume were more likely to survive than patients assigned higher tidal volumes, when adjusted for bodyweight.<sup>67–69</sup> Further examination of the data suggests that for every baseline plateau-pressure quartile, patients randomly assigned lower tidal volumes had a lower mortality, with no detectable safe threshold.<sup>26,87</sup> This finding provides strong evidence that use of reduced tidal volume is sensible, even when the initial plateau pressure is less than 30–32 cm  $H_2O$ .

Results from published trials have not accorded with the hypothesis that both the tidal volume selections of 6 and 12 mL/kg of predicted bodyweight were suboptimum and that the best tidal volume lies either between these values or at less than 6 mL, but this theory is obviously the most difficult to test. If a consensus could be reached on mode and pulmonary end expiratory- $F_{iO_2}$  strategy, a study of tens of thousands of patients assigned to tidal volumes ranging from less than 6 mL/kg to almost 12 mL/kg would be needed to find the best tidal volume; such a study would not be feasible. The theory that the benefit of lower tidal volume resulted from tachypnoea-induced intrinsic PEEP is not supported by measurements of auto-PEEP in a large subset of enrolled patients,<sup>88</sup> nor by data from a subsequent study of higher PEEP using the reduced tidal volume approach.<sup>89</sup> Finally, no evidence supports the concern that patients ventilated with this lower tidal volume strategy needed more sedation, or paralysis.<sup>90</sup>

A pressure-limited mode of ventilation could be better than volume-cycled ventilation. A small randomised trial<sup>91</sup> supports this notion, in which decreased extrapulmonary organ failures and mortality were seen with pressure-controlled ventilation. Unfortunately, the size of the study, baseline imbalances, and the very high mortality rate seen in the volume-ventilated group, call into question the generalisability of the results. Confirmation awaits additional large randomised controlled trials.<sup>91,92</sup> No randomised controlled trials suggest that high-frequency ventilation improves survival of adult patients with acute lung injury,<sup>93–95</sup> despite improving oxygenation.

Thus, we can conclude that use of smaller tidal volumes (6 mL/kg of predicted bodyweight) that is indexed to predicted bodyweight results in reduced markers of inflammation, higher survival, and fewer organ failures than traditional tidal volumes (12 mL/kg of predicted bodyweight). A key caveat is that tidal volume must be reduced even further if plateau pressures exceed 30 mm Hg.<sup>26</sup> Although we need further investigation of mechanical ventilation strategies that improve outcomes, the ARDS Network study<sup>26</sup> (the largest positive-ventilation trial undertaken) serves as a rational starting point for current clinical practice, and a benchmark against which future ventilation strategies should be tested.

### Effects of PEEP

By recruiting atelectatic alveoli and increasing functional residual capacity of supine patients, PEEP reduces intrapulmonary shunting and improves oxygenation in many lung diseases.<sup>96</sup> PEEP might also have detrimental effects: because it could increase the amount of lung water and, in some cases, PEEP could over-distend compliant alveoli and worsen ventilation perfusion matching, or even create dead space.<sup>97</sup> Furthermore, by raising intrathoracic pressure, PEEP can decrease venous return and increase right-ventricular impedance, thereby causing hypotension.<sup>98</sup>

Animal studies<sup>58,61</sup> have shown that even low amounts of PEEP can reduce the development of ventilator-associated lung injury induced by high cyclic ventilator pressures. The known physiological benefits on oxygenation and the animal study results suggest that PEEP would improve the atelectasis of early lung injury and might even prevent development of acute lung injury in high-risk patients. Unfortunately, use of prophylactic PEEP has failed to show benefit in at least one large clinical trial.<sup>99</sup> Nevertheless, some doctors do not believe the question of prophylactic PEEP has been resolved because the trial enrolled patients with various diseases at very different risks of acute lung injury, and used modest amounts of (8 cm H<sub>2</sub>O) of PEEP. Although not protective against the development of acute lung injury, a low amount of PEEP is given to most ventilated patients to prevent atelectasis.<sup>50</sup>

In established acute lung injury, PEEP is routinely used to recruit the lung or prevent reversal of recruitment, thereby decreasing oxygen requirements, and improving other measures of lung function such as shunt fraction and compliance. PEEP titration to improve lung compliance or oxygen delivery has not shown any important clinical benefits. The range of clinical practice is wide and has included use of very high amounts of PEEP, which could be harmful.<sup>52,53</sup>

To test the hypothesis that high amounts of PEEP would further increase the survival benefit of the lower tidal volume ventilation strategy, a large clinical trial<sup>89</sup> was done in which all patients were ventilated with 6 mL/kg predicted bodyweight of tidal volume but were randomly assigned to receive treatment using the PEEP-F<sub>I</sub>O<sub>2</sub> scale from the original trial,<sup>26</sup> or using higher PEEP and lower F<sub>I</sub>O<sub>2</sub> combinations. The approach of higher amounts of PEEP with a lower tidal volume was also used by Amato and colleagues,<sup>70</sup> and incorporated recruitment manoeuvres in a subset of patients. In the first 4 days of the trial, although the higher PEEP group had higher pressure (14 mm Hg) than in the lower PEEP group (8 mm Hg), and oxygenation and lung compliance were better in the higher PEEP group, no benefit on survival, time on ventilator, or non-pulmonary organ function was shown. Furthermore, no benefit of higher PEEP was seen in patients with direct versus indirect injury, by severity of initial gas-exchange abnormality, or

after adjustment for a possible imbalance in age of study participants between groups.<sup>89</sup>

To explore the many reports of improved physiological variables after a recruitment manoeuvre<sup>100–105</sup> a subset of patients who had higher PEEP in this study<sup>106</sup> were randomly assigned to receive 35–40 cm H<sub>2</sub>O continuous positive airway pressure for 30 s or a so-called sham recruitment manoeuvre. Unfortunately, neither striking nor lasting improvement was recorded in respiratory system compliance or oxygenation, but transient reductions were seen in blood pressure.<sup>106</sup> The authors of this study did not exclude the possibility of benefit from other recruitment manoeuvre strategies and encouraged future studies.

However, the study of higher versus lower PEEP<sup>89</sup> confirmed that when ventilated with 6 mL/kg predicted body weight, both groups had mortality rates of about 25%, as in the original lower tidal volume study.<sup>26</sup> These results also suggest that in the range of values tested, higher concentrations of PEEP are probably not harmful. In view of these findings, we advocate use of 6 mL/kg predicted bodyweight tidal volume, and the lowest PEEP-F<sub>I</sub>O<sub>2</sub> combination that produces acceptable oxygenation as a starting point for treatment. We do not advocate routine use of recruitment manoeuvres; however, recruitment manoeuvres are not unreasonable in patients with refractory hypoxaemia in an attempt to improve oxygenation.

### Prone positioning and recruitment manoeuvres

Because most lung infiltrates are seen in dependent lung regions, it was postulated that prone positioning of patients redistributes blood flow and ventilation to the least affected areas of the lung, promotes secretion clearance; and shifts the weight of the mediastinal contents anteriorly, to assist in the recruitment of atelectatic regions.<sup>107</sup> Animal and human studies suggest that lung compliance and alveolar recruitment, seen as infiltration on radiographs are improved by prone positioning.<sup>108,109</sup> Additionally, animal studies suggest that prone positioning can restrict the degree of experimental lung injury.<sup>110</sup> The practice was inexpensive and seemed to be safe with the possible exception of an increased risk of regurgitation and inadvertent extubation.<sup>111</sup> Hence, many clinical studies of prone positioning in acute lung injury and other lung diseases were undertaken.<sup>112–116</sup> Their findings consistently show that about two-thirds of all treated patients have a measurable improvement in oxygenation (PaO<sub>2</sub>/F<sub>I</sub>O<sub>2</sub> ratio) shortly after prone positioning. Unfortunately, the improvement is often transient, and no study has shown that prone positioning improves important clinical outcomes such as survival, time on ventilation, or time in the intensive care unit.

Debate continues as to whether improved outcomes could be demonstrated by using larger studies, studying sicker patients, treating patients earlier, or by applying

prone positioning for a longer time each day, than has been done in previous studies. The failure to show a survival benefit from this practice could be because most patients with acute lung injury do not succumb to refractory hypoxaemia, but rather multiple organ failure.<sup>117</sup> Therefore, measures improving oxygenation will probably prove important to survival only in a few patients. With current data, we do not advocate routine prone positioning of all patients but acknowledge that it might be a useful practice to boost oxygenation in a patient who is refractory to conventional treatment. Unfortunately, no recommendations can be offered on the optimum timing or duration of prone positioning until large randomised trials provide more information.

### Corticosteroids

Many human trials suggest that treatment of patients at risk of acute lung injury with high doses of glucocorticoids does not decrease the frequency of the disease.<sup>118–121</sup> Likewise, despite the striking inflammatory reaction in the alveoli, rigorous human studies suggest that high-dose glucocorticoids do not modify the course of acute lung injury when given early in the course of the disease.<sup>122</sup> Despite failed studies of prevention or early treatment, great interest remains in the use of corticosteroids for the salvage of patients with persistent acute lung injury. Although this practice has often been regarded as treatment of the fibroproliferative phase, histological documentation of this is unusual.

Several small uncontrolled studies suggest some clinical benefits of extended therapy with moderate-dose to high-dose glucocorticoids,<sup>123–125</sup> including modification of the inflammatory response.<sup>126</sup> Eventually, a small, prospective randomised crossover trial was undertaken, in which patients with acute lung injury that had persisted for more than 7 days were randomly assigned to placebo and 16 patients with the disease randomly assigned to high-dose methylprednisolone.<sup>127</sup> Half of the patients assigned to placebo crossed over to methylprednisolone treatment because of failure to improve their lung injury score by one point or more, whereas no patient treated with corticosteroids crossed over to placebo. Analysis by intention to treat showed a significant reduction in mortality; per-protocol analysis showed no survival benefit.<sup>128</sup> To reconcile this issue, the largest randomised, blinded trial so far of methylprednisolone versus placebo has been completed. Preliminary results have shown no difference in 60-day or 180-day mortality, despite improvements in gas exchange, blood pressure, and time on ventilator in patients given methylprednisolone.<sup>27</sup> Conclusions from this study about the value of corticosteroids in late persistent acute lung injury will almost certainly be controversial. We do not recommend corticosteroids to prevent or treat early acute lung injury. Although data that show a survival benefit in the treatment of established acute lung injury

are scarce, corticosteroids could offer some benefit with respect to gas exchange and haemodynamic stability.

### Extracorporeal support

Extracorporeal membrane oxygenation and CO<sub>2</sub> removal have been attempted in patients with acute lung injury deemed refractory to conventional ventilatory support. Use of extracorporeal membrane oxygenation in children has been accepted as a useful support technology; however, it is rarely used in adults. Clearly, extracorporeal membrane oxygenation improves oxygenation, and extracorporeal CO<sub>2</sub> removal improves CO<sub>2</sub> clearance, but neither has been shown to improve survival or time on ventilation in controlled clinical trials.<sup>129–132</sup> However, extracorporeal support has not conclusively shown outcome benefits and has been associated with substantial risks (eg, infection, bleeding) and costs, therefore, it cannot be recommended.

### Fluid management

Animal and human data suggest that when lung-capillary permeability increases, lung water accumulates to a greater degree than usual at lower pressures of pulmonary-artery occlusion.<sup>133</sup> Additionally, animal studies suggest that reduction of lung water improves oxygenation, and lung compliance.<sup>134,135</sup> Human trials show improved physiological endpoints with various diuretic approaches to reduce lung water, including diuresis without vascular pressure measurement, intravascular pressure-targeted diuresis, and diuresis guided by direct measurements of lung water.<sup>135–139</sup> However, abundant data suggest that prompt resuscitation of haemodynamically unstable patients improves outcome, whereas the same resuscitative efforts given later might not be helpful and could be harmful.<sup>140–143</sup> These resuscitative protocols centre on fluid administration. In both the restrictive and liberal fluid-giving approaches, various endpoints have been used as therapeutic targets.

Therefore, does a conservative or liberal approach to fluid therapy alter outcomes, what are the optimum targets for resuscitation, and how should they be measured? A large randomised clinical trial has suggested no benefit of pulmonary-artery catheter insertion in patients with acute lung injury, but this trial has received criticism because they did not apply a specific protocol to guide use of catheter-derived data.<sup>144</sup>

### Vasodilators

Both non-selective (nitroprusside, hydralazine) and semi-selective (nitric oxide, prostaglandin E1, prostacyclin) vasodilators have been tested for the treatment of acute lung injury.<sup>145,146</sup> Of these compounds, nitric oxide has been most widely studied, and like prone positioning, results are relatively consistent among studies: oxygenation and pulmonary vascular resistance are

#### Panel 4: Unproven treatments for acute respiratory distress syndrome

- Ketoconazole<sup>160,161</sup>
- Pentoxifylline and lisofylline<sup>162,163</sup>
- Nutritional modification<sup>164,165</sup>
- Antioxidants<sup>166,167</sup>
- Neutrophil elastase inhibition<sup>168</sup>
- Surfactant<sup>169–176</sup>
- Liquid ventilation<sup>177,178</sup>
- $\beta$ -adrenergic agonists<sup>179,180</sup>
- Nitric oxide<sup>147–154</sup>

improved, but those changes do not translate into better clinical outcomes.<sup>147–152</sup> Based on existing data, routine use of nitric oxide or other vasodilators to treat acute respiratory distress syndrome cannot be recommended.<sup>153,154</sup>

#### Weaning from ventilation and other treatments

For haemodynamically stable patients taking spontaneous breaths, who need less than 50% supplemental oxygen and less than 8 cm H<sub>2</sub>O PEEP, no method of weaning has been shown to be better than spontaneous breathing that is either unassisted or with a minimum level of pressure support. If a period of closely observed spontaneous breathing is successful, patients can be extubated.<sup>155–159</sup>

Several other treatments have been used to either modify inflammation or change the mechanical properties of the lung with acute injury (panel 4). Unfortunately, none of these treatments has so far shown convincing improvements in outcomes in large controlled studies.

#### Conclusion

Acute lung injury and acute respiratory distress syndrome are common, costly, and potentially lethal diseases, for which treatment of the underlying cause is the first step to recovery. Prevention of nosocomial complications has an important role to achieve the optimum outcome. With respect to lung support, the only ventilatory practice proven to be beneficial in a large randomised trial is reduction of tidal volume to 6 mL/kg predicted bodyweight (or lower if needed), to achieve a plateau pressure of less than 30 cm H<sub>2</sub>O. This reduced tidal volume is coupled with use of the minimum F<sub>O<sub>2</sub></sub>-PEEP combination that is sufficient to achieve a saturation of 88–95% or a corresponding PaO<sub>2</sub>. Results from a large randomised study of fluid management suggest that conservative fluid use shortens time on ventilator and in the intensive care unit, but does not change survival.<sup>181</sup>

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