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# **Acute Respiratory Distress Syndrome**

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## **Summary**

The acute respiratory distress syndrome presents as hypoxia, bilateral pulmonary infiltrates on chest imaging, and the absence of heart failure sufficient to account for this clinical state.

Management is largely supportive, focusing on protective mechanical ventilation, and the avoidance of fluid overload. Patients with severe hypoxaemia can be managed with early short-term use of neuromuscular blockade, prone position ventilation or extra-corporeal membrane oxygenation. The use of inhaled nitric oxide is rarely indicated and both  $\beta_2$  agonists and late steroids should be avoided. Mortality currently remains at approximately 30%.

## **Introduction**

The acute respiratory distress syndrome (ARDS) is a form of non-cardiogenic pulmonary oedema, due to alveolar injury secondary to an inflammatory process, either pulmonary or systemic in origin. This syndrome presents as acute hypoxaemia with bilateral pulmonary infiltrates on chest imaging, not wholly due to heart failure.

## **Definitions**

As a syndrome, ARDS is characterised by the presence of several criteria. Since the original description by Ashbaugh and colleagues in 1967,<sup>1</sup> four definitions have been used to determine the presence of this condition (Table 1).<sup>2-5</sup> The American European Consensus Conference definition<sup>3</sup> (AECC), published in 1994, provided the first agreed and widely used definition. However, this definition had numerous limitations across all four diagnostic criteria (Table 2). Due to the limitations in the AECC definition, the European Society of Intensive Care Medicine began a consensus process to generate an improved definition for ARDS. The Berlin definition,<sup>5</sup> published in 2012, was validated on over four thousand patient's data and, based on hypoxaemia, categorises ARDS as mild ( $200 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mm Hg}$ ), moderate ( $100 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mm Hg}$ ), or severe ( $\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mm Hg}$ ). The most important updates to the ARDS definition are the stipulation of a minimum positive end-expiratory pressure (PEEP) of 5 cmH<sub>2</sub>O, (as PEEP can increase oxygenation, which is a key criterion of the syndrome, this was to establish a minimum standard for mechanical ventilation), the acknowledgement that ARDS can be diagnosed in the presence of cardiac failure, a requirement for new respiratory failure, or worsening of chronic respiratory disease, within a seven day period, and the inclusion of chest computed tomography (CT) as an alternative form of imaging for the demonstration of lung infiltrates.

## **Epidemiology**

The landmark ARMA study, published in 2000, demonstrated the benefits of a low tidal volume, low airway pressure ventilatory strategy in ARDS and marked the establishment of lung protective ventilation as the standard of care for patients with ARDS.<sup>6</sup> Despite this advance, ARDS remains a highly prevalent condition, with, in the lung-protective era, estimated incidences per 100,000 patients per year of 34 in the USA<sup>7</sup> and approximately 5 to 7 in Europe.<sup>8-10</sup> Its epidemiology is likely under reported in less developed systems, where, due to resource limitations, few patients meet the current definition for its diagnosis, despite 4% of all hospital admissions having a clinical state comparable to ARDS.<sup>11</sup> Seven percent of ICU patients, and 16% of those receiving mechanically ventilation, suffer from this condition.<sup>12</sup> Based on control group survival in recent randomized controlled trials, 28-day mortality is currently approximately 20 to 40%. A further 15

to 20% of these patients with ARDS will die by 12 months, largely due to co-morbidities rather than a residual ARDS effect.<sup>13</sup> The recent LUNGSAFE study found that ARDS remains common and has a mortality of approximately 40%, confirming the global burden of ARDS.<sup>14</sup> Although general ICU survivors show no reduction in health-related quality of life, for survivors of ARDS, full recovery is often limited. Many suffer muscle wasting and limiting weakness as well as neuropsychiatric illness, including cognitive impairment, anxiety, depression and post-traumatic stress disorder.<sup>15-17</sup> Six years after ICU discharge, just over 50% have returned to work.<sup>18</sup> Despite these extra-pulmonary deficits, respiratory function returns close to normal.<sup>16</sup>

### **Risk Factors**

The development of ARDS has been described in the setting of numerous illnesses and injuries, broadly categorised as being pulmonary or systemic in origin. Pneumonia is the most common risk factor for the development of ARDS, and along with aspiration has the highest associated mortality, while trauma-related ARDS has the lowest.<sup>7</sup> Inappropriately administered mechanical ventilation is an important contributor to both the development and worsening of ARDS.<sup>6,19</sup>

This ventilator-induced lung injury (VILI) may occur from several mechanisms, including excessive lung stretch (volutrauma)<sup>20</sup> or pressure (barotrauma), repetitive alveolar open and closing, causing a shearing injury (atelectrauma), as well as potential oxygen toxicity. These processes also drive excessive systemic inflammation, with the ability to induce non-pulmonary organ failure (biotrauma).<sup>21</sup> In a randomized controlled trial in 150 critically ill mechanically ventilated patients without ARDS, ventilation with 10 ml/kg predicted body weight (PBW), in comparison with 6 ml/kg PBW, was associated with a five-fold increase in the odds of developing ARDS.<sup>19</sup> This finding has been substantiated in a further randomized controlled trial in 400 patients at risk of pulmonary complications undergoing general anaesthesia for major abdominal surgery. A non-lung protective ventilatory strategy of 10 to 12 ml/kg tidal volume ventilation with zero PEEP was compared with lung-protective ventilation of 6 to 8 ml/kg tidal volume with PEEP of 6 to 8 cmH<sub>2</sub>O plus a recruitment manoeuvre every 30 minutes. The lung-protective group had less major complications (10.5% vs 27.5%; RR 0.40, 95% CI 0.24 to 0.68; P=0.001), required less respiratory support by day 7 (5% vs 17%; RR 0.29, 95% CI, 0.14 to 0.61; P=0.001) and had a shorter hospital stay (11 vs 13 days, difference -2.45 days; 95% CI -4.17 to -0.72; P=0.006).

### **Genetics**

The search for potential genes conferring susceptibility to the development of ARDS or altering outcome from ARDS is methodologically complex. Genotype, phenotype, race, environment,

injury, and therapy interact in variable and uncertain ways to contribute to clinical outcomes. To date over 40 candidate genes associated with the development or outcome from ARDS have been identified, although these investigations have either largely lacked the methodological robustness to provide clear answers, or have yet to be replicated.<sup>22</sup> Some of the more promising genes include angiotensin converting enzyme, extracellular superoxide dismutase 3, interleukin-10, myosin light chain kinase, nuclear factor erythroid 2-related factor, pre-B cell colony-enhancing factor, surfactant protein B, tumour necrosis factor and vascular endothelial growth factor.<sup>23</sup> The search for a genetic susceptibility to either the onset, or worsening, of ARDS may prove difficult until issues with the specificity of the ARDS definition (see the section “Controversies & Uncertainties”) and improved phenotyping of patients with ARDS are addressed. However, a gene with a clearer association with ARDS is the angiotensin-converting enzyme gene. This came to prominence during the SARS epidemic, where the ACE-2 protein, which contributes to the regulation of pulmonary vascular permeability, was identified as the receptor for the novel coronavirus responsible for SARS.<sup>24</sup> This suggests ACE inhibition could be a potential therapeutic target worth investigating.

### **Pathogenesis**

Following the onset of the primary illness, the inflammatory alveolar injury occurring has been described in terms of three sequential phases (Figure 1), although there is considerable overlap.<sup>25</sup> The process begins with the exudative phase and immune-cell mediated destruction of the permeability barriers of the alveolar epithelial-interstitial-endothelial complex, allowing plasma, plasma proteins and cellular content to successively flood the interstitium and airspace. Classically ARDS is recognised to be a neutrophil driven disease, however, experimental data have shown that alveolar neutrophilia can occur without increased alveolar permeability.<sup>26</sup> In addition, it is increasingly recognised that cells from the innate (including macrophages<sup>27</sup> and platelets<sup>28</sup>) and adaptive immune systems are involved in the pathogenesis of ARDS.<sup>29</sup> Further neutrophils and macrophages are recruited to this inflammatory focus, propagating the initial insult. The inflammatory exudate produced physically interacts with surfactant, initially causing dysfunction, followed by, as the epithelial injury progresses, loss of surfactant production, impeding alveolar patency. The loss of epithelial ion channels impairs the generation of osmotic forces required to return oedema fluid to the interstitium. These injuries, plus the development of hyaline membranes and decreased pulmonary compliance, result in disrupted gaseous diffusion. Alveolar vascular damage also occurs, with increased permeability co-existing with altered vasomotor tone, both vasoconstriction and vasodilation, as well microthrombi. Pulmonary hypertension results, increasing right ventricular afterload. This right ventricular dysfunction may be further exacerbated

by mechanical ventilation and fluid overload. This combination of epithelial and endothelial damage results in worsening ventilation-perfusion mismatch and loss of hypoxic pulmonary vasoconstriction, leading to refractory hypoxia.

The proliferative phase marks attempts at recovery, with restoration of the type II alveolar cell population, and subsequent differentiation into type I alveolar cells. Regeneration of a functioning epithelial layer permits the clearance of exudative fluid into the interstitium, whilst remaining debris is cleared by inflammatory cells. Vasomotor tone begins to return to normal, microthrombi are cleared and pulmonary hypertension lessens. As reparation continues, shunt reduces leading to improved oxygenation, matched by better lung mechanics and recovering pulmonary compliance. The third fibrotic phase develops inconsistently, consisting of the failure of removal of alveolar collagen, which is laid down early in the injury process, combined with the development of cystic changes, limiting functional recovery. Diffuse alveolar damage (DAD) is considered to be the pathognomic pathological finding of ARDS,<sup>5</sup> is defined by the presence of hyaline membranes, and can be found either at lung biopsy or autopsy. However, DAD is not specific for ARDS, as DAD can also occur in the absence of the criteria for ARDS,<sup>30</sup> and many patients who fulfil the diagnostic criteria for ARDS do not have DAD.<sup>31</sup> Clinical patterns have been recognised in patients with ARDS; for example, those with a pulmonary cause suffer more consolidation and less alveolar collapse and interstitial oedema than those of non-pulmonary causes.<sup>32</sup> More recently, ARDS subphenotypes have been described, categorised by clinical and biological characteristics with differing clinical outcomes and response to treatment,<sup>33,34</sup> with a hyper-inflammatory phenotype being associated with worse metabolic acidosis, higher vasopressor requirements and increased mortality, as well as a better response to higher PEEP. These subphenotypes will provide further mechanistic insight to the pathophysiology of ARDS, which is likely to inform the development of personalised therapies.

### **Diagnosis and Monitoring**

The BERLIN definition for ARDS is an evolution of the AECC definition (Table 1), which was recognised to have numerous flaws. The revised definition, while improved, is recognised to still have limitations. Several investigational modalities are potentially helpful in monitoring the clinical course (Figure 2).

Sequential imaging via both chest radiography and CT (Figure 3) provide qualitative measures of disease evolution, in addition to specific quantitative measures of oedema, aeration and recruitability with CT. Extra-vascular lung water, reflective of the degree of pulmonary oedema,



may be measured with a PiCCO monitor and is associated with mortality in patients with ARDS.<sup>35,36</sup> Similarly, lung ultrasound (Figure 3) may be used to estimate extravascular lung water,<sup>30,38</sup> as well as allow the differentiation of ARDS from cardiogenic pulmonary oedema.<sup>39</sup> Pulmonary wedge<sup>40</sup> and central venous pressures<sup>40,41</sup> have little correlation with volaemic status or fluid responsiveness and are unlikely to offer benefit in routine management. Unsurprisingly, neither offer benefit over the other in the management of ARDS.<sup>42</sup>

The ratio of the partial pressure of arterial oxygen to the fractional inspiratory concentration of oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) is a measure of oxygenation, and used to categorise ARDS as mild, moderate or severe (Table 1). Although easy to calculate, it is an imperfect measure, due to its variability with differing levels of PEEP<sup>43</sup> and tidal volume.<sup>44</sup> The oxygenation index, the product of mean airway pressure and fractional inspiratory concentration of oxygen, divided by the arterial partial pressure of oxygen is an alternative to  $\text{PaO}_2/\text{FiO}_2$  and may be superior, due to its inclusion of mean airway pressure, which is reflective of PEEP.<sup>45</sup> Respiratory system compliance aids in the monitoring of pulmonary mechanics, although it was not included in the Berlin Definition as it lacked additional discriminatory value.<sup>5</sup> Pulmonary dead space fraction is associated with mortality in ARDS, having an odds ratio of 1.45 (95 % CI 1.15 to 1.83;  $P=0.002$ ), although is technically challenging to measure and not frequently used.<sup>46</sup> Bronchoalveolar lavage permits sampling of the alveolar space and aids in the identification of infectious causes of ARDS, as well as diagnosing malignancy or haemorrhage.

The absence of a biomarker to define the diagnosis, responsiveness to therapy and prognosis of ARDS is problematic and limits progress in the field.<sup>47,48</sup> Differing pathologies damage lung tissue in diverse ways, producing inconsistent signals from numerous injured cell types. These signals are further confounded by age, co-morbidities and iatrogenic effects such as excessive fluid balance and harmful ventilation. Numerous candidate biomarkers (Figure 2) have been investigated, however, at present a single, clear biomarker has proved difficult to find. Biomarkers have been measured in both blood and bronchoalveolar lavage fluid, but at present are too inaccurate for clinical use. Combinations of biomarkers may identify specific phenotypes of patients with ARDS who may respond differentially to therapies, but further work is required to confirm these initial findings.<sup>33</sup>

Open lung biopsy remains the gold standard for diagnosing DAD. Small, single centre observational studies in highly selected patient populations using open lung biopsy report low specificity of the clinical diagnosis of ARDS for the presence of DAD.<sup>30,49–51</sup> The majority of patients with ARDS undergoing this procedure have resulting alterations in management,<sup>49–53</sup>

improved outcomes,<sup>52</sup> with a relatively low level of significant morbidity.<sup>30,49–53</sup> These studies are limited by their selective nature, where open lung biopsy is usually reserved for nonresolving ARDS, plus their constrained ability to examine the entire lung. Open lung biopsy is usually reserved for exceptional cases where there is a genuine diagnostic dilemma and a lack of response to therapy.

## **Management**

Management of ARDS can be categorized as specific, supportive and that of the underlying causative condition (Figure 4). Specific measures include both maintenance of gas exchange and manipulation of the underlying pathophysiology. Supportive therapies include sedation, mobilisation, nutrition, and venous thromboembolism prophylaxis.

### **Conventional Mechanical Ventilation**

Four randomized controlled trials published between 1998 and 1999 provided mixed results regarding the optimal tidal volume in ARDS.<sup>54–57</sup> The landmark ARMA study,<sup>6</sup> published in 2000 by the ARDSnet group, compared a traditional ventilatory strategy of 12 ml/kg PBW tidal volume in combination with a plateau airway pressure  $\leq 50$  cm H<sub>2</sub>O, with a lower tidal volume of 6 ml/kg PBW in combination with a plateau airway pressure  $\leq 30$  cm H<sub>2</sub>O in 861 mechanically ventilated patients with ARDS. The study was stopped early, as, despite initially worse oxygenation, lower tidal volume ventilation was associated with a 9% absolute mortality reduction (39.8% vs 31.0%,  $P=0.007$ ; 95 % CI, 2.4% to 15.3%), with increased ventilator-free days ( $10\pm 11$  vs  $12\pm 11$ ;  $p=0.007$ ). Importantly, less injurious ventilation was associated with more non-pulmonary organ failure-free days ( $12\pm 11$  vs  $15\pm 11$ ;  $p=0.006$ ). Tidal volume was estimated from PBW, which is dependent on height and gender, and calculated as  $50 + 0.91 \times (\text{height in cm} - 152.4)$  for males and  $45.5 + 0.91 \times (\text{height in cm} - 152.4)$  for females. Lung protective ventilation is associated with improved outcomes if used early in the course of ARDS,<sup>58</sup> and reduced mortality at 2 years.<sup>59</sup>

Despite the adoption of a volume and pressure limited protective ventilatory strategy, critically ill mechanically ventilated patients with ARDS receiving a tidal volume of 6 ml/kg and a plateau pressure  $\leq 30$  cmH<sub>2</sub>O may still be exposed to tidal hyperinflation, where the smaller than usual aerated section of the lung (“baby lung”)<sup>60</sup> receives a larger than usual volume of gas, resulting in greater biotrauma and less ventilator-free days than those without tidal hyperinflation.<sup>61</sup> Similarly, a post hoc review of the ARDSnet database failed to demonstrate a safe upper limit for plateau pressures in patient with ARDS.<sup>62</sup> Volume and pressure limited ventilation may cause hypercapnoeic acidosis, with the overall clinical effect of protective ventilation and hypercapnoea

being uncertain.<sup>63</sup> Hypercapnoeic acidosis may provide protective effects in the setting of high tidal volume ventilation, but a beneficial effect is not seen in patients receiving lung protective ventilation.<sup>64</sup>

PEEP prevents lung unit collapse at the end of the respiratory cycle. Beneficial effects include the maintenance of functional residual capacity, improving compliance and higher mean airway pressure, resulting in decreased shunt with enhanced oxygenation, as well as reduced atelectasis and bio-trauma. These advantages must be weighed against the effects of raised intra-thoracic pressure, namely decreased venous return and increased right ventricular afterload.<sup>65</sup> Numerous methods of setting the PEEP level have been described, including most recently oesophageal balloon manometry<sup>66</sup>. In the lung protective era, four randomized controlled trials<sup>66-69</sup> have addressed the question of whether a higher or lower level is superior, with a suggestion higher PEEP may be beneficial. A meta analysis of three of these studies also reported a possible benefit for a higher PEEP setting in ARDS, with both a lower in-hospital mortality (34.1% vs 39.1%; relative risk 0.90; 95% CI, 0.81 to 1.00; P = 0.049) and less requirement for mechanical ventilation by day 28 (hazard ratio, 1.16; 95% CI, 1.03 to 1.30; P=0.01).<sup>70</sup> The EPVent randomized controlled trial, comparing oesophageal balloon manometry guided PEEP with the ARDSnet PEEP-FiO<sub>2</sub> table,<sup>6</sup> found oesophageal guided PEEP to provide increased oxygenation and compliance. This translated into a higher PEEP (18 vs 12 cm H<sub>2</sub>O on day one) with associated improved adjusted 28 day mortality, with a relative risk of 0.46 (95% CI, 0.19 to 1.0; P = 0.049).<sup>66</sup> A further meta analysis, including this additional study, found a non-statistically significant improvement with higher PEEP values, with a pooled relative risk for 28 day mortality of 0.90 (95% CI 0.79 to 1.02), without a significantly higher risk of barotrauma (pooled relative risk 1.17, 95% CI 0.90 to 1.52).<sup>71</sup>

The driving pressure, defined as the difference between plateau and end-expiratory pressures, has very recently been suggested as the mediator for the beneficial effects of the three main components of lung protective ventilation, namely low tidal volume, low plateau pressure and high PEEP.<sup>72</sup> Using derivation and validation cohorts from 3,562 patients recruited into nine randomized controlled trials, Amato reported an increase in driving pressure of 7 cmH<sub>2</sub>O was associated with increased 60 day mortality, with a relative risk of 1.41 (95% CI 1.31 to 1.51; P<0.001). Using the statistical method of multilevel mediation analysis, none of the three main components of lung protective ventilation were individually associated with reduced mortality, but acted via a reduced driving pressure to exert their beneficial effects. Driving pressure may help calibrate the mechanical stress delivered by the ventilator to the functional aerated lung volume. Although 6 ml/kg tidal volume is recognised as “low tidal volume ventilation”, in reality this is the normal tidal volume for

most mammalian species.<sup>73</sup> As the available functional lung volume falls in ARDS, due to collapse and consolidation, perhaps the delivered tidal volume should also decrease. It is also worth noting that while current evidence suggests it is prudent to target driving pressure, whether driving pressure relates causally to outcome remains to be established in a prospective, randomized controlled trial. This concept is currently being investigated in the setting of studies using extracorporeal carbon dioxide removal, to facilitate very low tidal volume or ultra-protective ventilation.<sup>74</sup> Although this data for driving pressure is post hoc, observational in nature, and requires confirmation in a prospective study, an upper limit for driving pressure of 15 cm H<sub>2</sub>O may be appropriate in the interim.

Atelectatic areas of lung may be re-expanded by the application of brief periods of sustained high transpulmonary pressure, usually followed by the application of higher levels of PEEP to maintain and stabilise this newly re-aerated region. Three commonly used such recruitment manoeuvres are sighs, sustained inflations and extended sighs.<sup>75</sup> Brief periods of raised intrathoracic pressure also impede venous return to the right atrium, predisposing to hypotension. Pre-clinical data have reported divergent effects of recruitment manoeuvres on alveolar epithelial and endothelial function.<sup>76</sup> A systematic review, based on 40 studies, found recruitment manoeuvres increased oxygenation, with little information regarding the long term effects of these interventions and no clear guidance on the usefulness of this procedure.<sup>77</sup>

There are few robust randomised controlled trials to guide the choice of mode of mechanical ventilation. A recent Cochrane Review summarising three randomized controlled trials consisting of 1,089 patients concluded there was insufficient evidence to promote the use of either volume- or pressure-controlled ventilation over the other.<sup>78</sup> Airway pressure release ventilation is used for its ability to maintain a high mean airway pressure, and thus maintain alveolar recruitment, while permitting spontaneous ventilation. Unfortunately the evidence base is limited by suboptimal control groups in the studies to date and concerns regarding possible high tidal volume and mean airway pressure.<sup>79</sup> Non-invasive ventilation may be tried in mild ARDS. A small study of 40 patients reporting reduced requirement for invasive mechanical ventilation and a non-significant reduction in mortality with this approach.<sup>80</sup> This result should be tempered by a much larger meta analysis of 540 patients documenting failure of NIV in almost 50%.<sup>81</sup> The advent of high flow nasal oxygen (HFNO) allows a simpler, more tolerable form of respiratory support. An observational study reported a 40% requirement for invasive mechanical ventilation in a cohort of 45 patients with severe ARDS (mean PaO<sub>2</sub>/FiO<sub>2</sub> 137 mm Hg) treated with high flow nasal oxygen.<sup>82</sup> As with noninvasive ventilation, higher illness severity was associated with an increasing likelihood of

HFNO failure.

## Adjuncts to Respiratory Support

### Prone Positioning

Placing a patient prone whilst receiving invasive mechanical ventilation provides many physiological advantages for the management of refractory hypoxaemia, including redistribution of consolidation from dorsal to ventral areas of the lung, removal of the weight of the heart and mediastinum from the lung, improved alveolar ventilation, shunt reduction with increased oxygenation and reduced pulmonary inflammatory cytokine production.<sup>83</sup> Several studies<sup>84-87</sup> produced conflicting results regarding the efficacy of prone positioning ventilation in ARDS. Although it was increasingly recognised that prolonged prone positioning was associated with physiological improvement,<sup>88</sup> these studies used short duration of prone ventilation. In addition, subsequent meta analyses<sup>89,90</sup> suggested benefit specifically in the most hypoxaemic patients receiving lung protective ventilation. The PROSEVA study,<sup>91</sup> sought to address these shortcomings. It randomized 466 patients with severe ARDS, defined as having a  $\text{PaO}_2 < 150$  mm Hg whilst being ventilated with an  $\text{FiO}_2 \geq 0.6$ , and receiving lung protective ventilation, to either the supine position or daily prone position sessions lasting at least 16 hours. Prone position ventilation was associated with reduced 28 day mortality [32.8 % vs 16 %,  $p < 0.001$ ; hazard ratio of 0.44 (95% CI, 0.29 to 0.67)]. There were no additional complications associated with prone positioning, although the centres involved were all experienced with this technique. This magnitude of effect, whilst large, was predicted by a prior meta analysis.<sup>90</sup>

### Neuromuscular Blockade

The hypoxaemia of severe ARDS may require excessive ventilatory support risking the development of VILI. Paralysis removes endogenous effort, improving respiratory mechanics and lowering oxygen consumption. The ACCURSY study compared cisatracurium besylate induced-paralysis with placebo in 340 patients with early severe ARDS, and showed neuromuscular blockade for 48 hours, after adjustment for baseline  $\text{PaO}_2/\text{FiO}_2$ , plateau pressure and Simplified Acute Physiology II scores, resulted in a reduced adjusted hazard ratio for death at 90 days (HR 0.68, 95% CI 0.48 to 0.98;  $P=0.04$ ). Importantly, there was no difference in the rate of complications, including ICU-acquired weakness. Although promising, additional large clinical trials are required to confirm these findings.

### Extra-corporeal Life Support

As mechanical ventilation is reliant on a functional alveolus for gaseous diffusion, it is unable to provide life saving respiratory support when a critical volume of alveolar units have failed. In addition to replacing endogenous alveolar gaseous exchange, extra-corporeal gas exchange, either extra-corporeal membrane oxygenation (ECMO), or extra-corporeal carbon dioxide removal (ECCO<sub>2</sub>R), allows reduction in ventilatory settings, reducing the risk of VILI. At present the evidence base for these interventions is limited, consisting of case series, observational cohort studies and one randomized controlled trial. The CESAR study, rather than directly evaluating ECMO in refractory hypoxaemia, compared ongoing management at a referring centre with management at a tertiary centre capable of providing ECMO in 180 patients.<sup>92</sup> The cohort managed at the ECMO centre had a higher rate of survival without disability at six months (63% versus 47%; RR 0.69; 95% CI 0.05 to 0.97, P=0.03), although just 75% of this group received ECMO. Two observational studies, from Australia/New Zealand<sup>93</sup> and the UK<sup>94</sup> also reported high rates of survival with ECMO in H1N1 influenza A patients with refractory hypoxaemia on maximal ventilatory support. However, ECMO is a scarce and expensive resource, limited to specialist centres (Figure 4), with well recognised complications including bleeding, vascular damage, and risks from interhospital transfer. Despite widespread and growing use worldwide, at present there is an absence of level one evidence for its efficacy. In the UK, ECMO is a nationally commissioned service provided at a limited number of regional centres.

### Nonconventional Mechanical Ventilation

High frequency oscillatory ventilation (HFOV) is the provision of small tidal volumes (typically 2 ml/kg PBW) at high frequencies of up to 900 breaths per minute, using a number of atypical mechanisms of gas transfer. This mode of ventilation also affords separation of oxygenation, dependent on FiO<sub>2</sub> and mean airway pressure, from carbon dioxide removal, which is an active process, dependent on the pressure amplitude and frequency of oscillation. Two recent large randomized controlled trials, from Canada (OSCILLATE)<sup>95</sup> and the UK (OSCAR),<sup>96</sup> failed to show benefit from this mode of ventilation. OSCILLATE reported harm with HFOV, possibly due to the high mean airway pressure generated, causing haemodynamic compromise and requiring higher doses and duration of vasopressor, in addition to more sedation and paralysis.

### Pharmacotherapy

Recent drugs to be investigated in large phase three placebo controlled, randomised studies include statins and β<sub>2</sub> agonists. In addition to their cholesterol lower effects, statins have pleiotropic properties making them an attractive potential therapy. The Irish Critical Care Trials Group's HARP-2 study<sup>97</sup> examined simvastatin in 540 patients with early ARDS. This study failed to



demonstrate improvements in short term clinical outcomes. Although the administration of simvastatin 80 mg was not associated with harm, there was no benefit in ventilator-free days (simvastatin  $12.6 \pm 9$  days vs control  $11.5 \pm 10.4$ ;  $P=0.21$ ), nonpulmonary organ failure-free days ( $19.4 \pm 11.1$  vs  $17.8 \pm 11.7$ ;  $P = 0.11$ ) or 28-day mortality (22.0% vs 26.8%;  $P = 0.23$ ). The US ARDSnet group ran a similar study, SAILS,<sup>98</sup> exploring rosuvastatin in 745 patients with sepsis-associated ARDS. The study was stopped for futility and found no significant difference in 60-day in-hospital mortality (rosuvastatin 28.5% vs placebo 24.9%;  $P=0.21$ ) or ventilator-free days ( $15.1 \pm 10.8$  vs  $15.1 \pm 11.0$ ;  $P = 0.96$ ). Rosuvastatin was, however, associated with a small decrease in the number of renal and hepatic failure-free days indicating possible harm.

Preclinical data indicated  $\beta_2$  agonists could modify a variety of mechanisms, including increasing alveolar fluid clearance, being cytoprotective and having anti-inflammatory properties, which prompted investigation of salbutamol as a potential therapy for ARDS.<sup>99,100,101</sup> The UK BALTI-2 study<sup>102</sup> used intravenous salbutamol at 15  $\mu\text{g}/\text{kg}$  ideal bodyweight per hour, but was terminated for safety reasons after recruiting just 326 patients out of a planned 1,334. Salbutamol increased 28-day mortality (34% vs 23%, RR 1.47; 95% CI 1.03–2.08), whilst decreasing ventilator-free days and organfailure-free days, possibly mediated through cardiac and metabolic toxicity, in the form of arrhythmias and lactic acidosis. The US ARDSnet ALTA study<sup>103</sup> examined inhaled salbutamol (albuterol) 5mg four hourly for up to 10 days in 282 patients, before being stopped for futility. There was no statistical difference in the primary outcome of ventilator-free days (albuterol 14.4 vs placebo 16.6; 95% CI for difference,  $-4.7$  to  $0.3$ ;  $P=0.087$ ), or secondary outcome of in-hospital mortality (23.0% vs 17.7%; 95% CI for difference,  $-4.0$  to  $14.7$ %;  $P=0.30$ ), although patients with shock at baseline in the salbutamol group had fewer ICU-free days.

Two other pharmacotherapies deserve mention – steroids and nitric oxide. As an inflammatory lung injury, the use of steroids would appear ideally suited to this condition, with their ability to dampen both inflammation and fibrosis. Unfortunately, despite a plethora of trials, there is inadequate evidence to make a definitive recommendation in favour or against the use of steroids in ARDS,<sup>104, 105</sup> although the US ARDSnet steroid study suggested harm if steroid therapy was started after more than 14 days following the onset of ARDS.<sup>106</sup> Nitric oxide (NO) is an inhaled pulmonary vasodilator, which improves ventilation/perfusion matching, resulting in increased oxygenation. However, this increase in oxygenation does not translate into improved patient-centred outcomes.<sup>107</sup> NO is associated with numerous complications including renal failure and rebound pulmonary hypertension.<sup>107</sup> Various other anti-inflammatory and pathophysiologically (Figure 5) targeted drugs have been investigated, but fail to demonstrate robust effectiveness.<sup>108,109</sup>

## Supportive Therapy

### Fluid Management

As ARDS is a form of pulmonary oedema, fluid therapy is vital to the management of this condition. Fluid excess is increasingly linked to detrimental outcomes across the spectrum of critical illnesses.<sup>110</sup> A general paradigm exists of early fluid loading for resuscitation and organ rescue during the presentation stage of the illness, followed by fluid unloading (deresuscitation), either spontaneous or induced, after haemodynamic stability has been achieved.<sup>111</sup> Fluid-induced lung injury (FILI) is a concept describing the development of lung injury following intravenous fluid administration. The rapid administration of saline in healthy volunteers can cause pulmonary interstitial oedema,<sup>112</sup> while septic patients can suffer decreased oxygenation and worsening lung injury score with fluid bolus administration after initial resuscitation.<sup>113</sup>

In a randomized controlled trial in 1,001 patient with ARDS managed with lung protective ventilation (FACTT),<sup>114</sup> a detailed algorithm targeting cardiac filling pressures in the setting of haemodynamic stability was used to compare liberal and conservative fluid strategies. At one week, a conservative strategy was associated with a net neutral fluid balance, compared with a seven litre positive balance in the control arm, resulting in increased oxygenation, a better lung injury score, more ventilator-free and ICU-free days, and less blood transfusions. There was no difference in the primary outcome of death at 60 days (conservative strategy 25.5±1.9% vs liberal strategy 28.4±2.0%; 95% CI for difference -2.6 to 8.4%, P=0.30) or incidence of organ failures. A follow-up study at 2 years, however, reported an increased incidence of cognitive impairment in the deresuscitated group {adjusted odds ratio 3.35 (95% CI 1.16–9.70) to 5.46 (95% CI 1.92 to 15.53)}.<sup>115</sup>

A small randomized controlled trial, evaluating combined therapy of albumin and furosemide administration in 37 hypoproteinaemic patients with ARDS, demonstrated improvements in oxygenation, fluid balance and haemodynamics.<sup>116</sup> A further small follow-up study by the same group, comparing furosemide administration with or without albumin supplementation, suggested the combination was superior to furosemide administration alone. The recent large randomized controlled trial ALBIOS, examining a strategy of albumin administration to maintain plasma albumin levels above 30 g/L in patients with sepsis and septic shock, did not report beneficial effects on respiratory SOFA score with a higher plasma albumin level, although this was not a specified subgroup analysis.<sup>117</sup> Therefore it remains unclear whether albumin has a place in the



management of ARDS. On the basis of current evidence, synthetic colloids do not have any role in the management of the critically ill.<sup>118</sup>

### Nutrition

The EDEN study explored the effect of lower volume trophic feeding for up to six days in 1,000 non-malnourished patients with early ARDS.<sup>119</sup> Despite separation of calorific delivery between groups (approximately 400 kcal/day versus full feeding of 1,300 kcal/day), there was no difference in the primary outcome of ventilator-free days (14.9 vs 15.0; difference, -0.1 [95% CI, -1.4 to 1.2]; P=0.89), or secondary outcomes of 60-day mortality (23.2% vs 22.2%; difference, 1.0% (95% CI, -4.1% to 6.3%); P=0.77) or infectious complications. The full feed group, however, received more prokinetic agents, suffered more days with increased gastric residual volume, vomiting, and constipation. Additionally, there was no difference in physical or cognitive function in survivors at year.<sup>120</sup>

The ability to modulate the inflammatory response via immunonutrition, the delivery of immune enhancing dietary agents such as fish oils, glutamine, selenium, vitamins and other anti-oxidants, has long been a potential target. Early studies were suggestive of benefit, especially when used in ARDS.<sup>121</sup> More recent randomised controlled trials failed to demonstrate efficacy from a range of additives, both in ARDS populations<sup>122,123</sup> and general critical care.<sup>124-126</sup> The OMEGA study<sup>122</sup> compared the twice daily use of the n-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid,  $\gamma$ -linolenic acid and a mixture of antioxidants, with an isocaloric control in 272 patients with early ARDS also receiving enteral nutrition. Despite increasing the plasma n-3 fatty acid levels eight-fold, there were clear signals of harm necessitating the termination of the study, including decreased ventilator-free, non-pulmonary organ failure-free and ICU-free days, as well as a non-significant increase in mortality. A subsequent small phase II study of fish oils in 90 patients with ARDS again failed to demonstrate benefit in this population.<sup>123</sup> A recent meta analysis supported a lack of efficacy from fish oil supplementation in ARDS patients,<sup>127</sup> while a consensus paper summarising current nutritional evidence does not support the administration of pharmaconutrients.<sup>128</sup>

### Sedation & Mobilisation

There are no direct comparative studies in ARDS patients examining the optimal choice of sedative or depth of sedation to be obtained. In general, patients should be lightly sedated, with emphasis on analgesia, and a focus on avoiding benzodiazepines where possible.<sup>129</sup> Early deep sedation in mechanically ventilated patients is associated with increased mortality<sup>130</sup> while, in contrast, early

mobilisation has been associated with improved outcomes in mechanically ventilated patients with acute respiratory failure.<sup>131</sup>

### **Controversies & Uncertainties**

Despite promising preclinical and early clinical data, the overwhelming majority of large phase 2 and 3 studies of therapeutic interventions in ARDS have failed to demonstrate efficacy. There are numerous reasons for this, but arguably the most important is the limited performance of the current definitions of ARDS in identifying patients expressing the biological target under investigation. Approximately half of patients who meet ARDS criteria, subsequently die and undergo post mortem examination, fail to demonstrate the pathognomic finding of DAD.<sup>31,132–135</sup> These patients can suffer from a mixture of co-existing conditions. The studies to date demonstrating efficacy have largely reduced harm from VILI, a condition for which all mechanically ventilated patients are at risk, thus minimising the limitation of heterogeneous cohort recruitment based on the ARDS definitions. However, when a therapy aimed at a specific biological target is investigated, such heterogeneity assumes greater importance, reducing any possible effect size.

This raises the question as to whether the therapeutic trials which have found no difference to date would have returned the same results had it been possible to identify specific phenotypes responsive to the therapy under investigation. Constructing a trial where 50% of the study population does not have the biological target under investigation is problematic. This has clear implications for the current evidence-base for ARDS, which has been largely reliant on the AECC definition, and more recently the Berlin definition. In the current era of personalised therapy, it is vital a biomarker or panel of biomarkers is identified which can not only identify a specific population, but more importantly, define the responsiveness to therapy.<sup>47,48</sup>

### **Guidelines**

Guidelines on the ventilatory management of ARDS have been issued by the Scandinavian Society of Anaesthesiology and Intensive Care Medicine<sup>136</sup> and the Brazilian Association of Intensive Care Medicine and the Brazilian Thoracic Society.<sup>137,138</sup> Guidelines from the American Thoracic Society on mechanical ventilation in adults with ARDS and the UK Intensive Care Society on the management of ARDS are in development.

### **Summary**

ARDS is the clinical manifestation of an underlying acute inflammatory alveolar disorder, presenting as the syndrome of hypoxia, bilateral pulmonary infiltrates on chest imaging, and the

absence of heart failure sufficient to account for this clinical state. ARDS is typically seen in critically ill mechanically ventilated patients, and is precipitated by a range of disorders, either pulmonary or systemic in origin. Management is largely supportive, focusing on protective ventilation, with tidal volume of 6 ml / kg predicted body weight, higher PEEP and the avoidance of plateau airway pressures greater than 30 cm H<sub>2</sub>O. Fluid overload should be prevented by limiting excessive fluid resuscitation, combined with early diuresis once haemodynamic stability has been restored. Patients with severe hypoxaemia should be managed with early short-term use of neuromuscular blockade and prone positioning ventilation, with ECMO currently reserved for those with the most severe disease.  $\beta$ 2 agonists and late steroids should be avoided, and inhaled nitric oxide limited to rescue therapy in those not suitable for ECMO. Mortality currently remains at approximately 30%.

### **Competing Interest Statement**

Dr Mac Sweeney reports no conflicts of interest.

Prof McAuley reports receiving fees for consultancy from GlaxoSmithKline, Bayer, Peptinnovate and SOBI. His institution has received funds for him undertaking bronchoscopy as part of a clinical trial funded by GlaxoSmithKline. He is also a named inventor on a patent for a pharmacotherapy for the treatment of acute respiratory distress syndrome held by his institution.

### **Contributor Statement**

Dr Mac Sweeney and Prof McAuley contributed equally to the design, writing and revision of this article. Dr Mac Sweeney created the diagrams.

### **Search Strategy**

We searched the Cochrane Library and PubMed with the terms: “acute respiratory distress syndrome”, “acute lung injury”, “adult respiratory distress syndrome”, “acute respiratory failure”, and “hypoxic respiratory failure”. We limited the search to papers from January 1967 to July 2015, focusing on papers from 2012 onwards, and to papers describing treatment in human adults published in English. We also searched the reference lists of identified articles and selected those we deemed most relevant.

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### **Fast Facts**

The acute respiratory distress syndrome (ARDS) is a form of non-cardiogenic pulmonary oedema, due to alveolar injury secondary to an inflammatory process This syndrome presents as acute

hypoxaemia with bilateral pulmonary infiltrates on chest imaging, not solely due to heart failure.

### **Definition**

ARDS is defined by the Berlin Definition, consisting of four components in the presence of a risk factor:

- an acute onset, or worsening of a pre-existing lung condition, within seven days.
- hypoxaemia, with a  $\text{PaO}_2 / \text{FiO}_2 < 300$  mmHg in the presence of a minimum positive end-expiratory pressure (PEEP) of at least 5 cmH<sub>2</sub>O.
- either the absence of heart failure or heart failure insufficient to solely account for the clinical state.
- bilateral pulmonary infiltrates on chest imaging.

### **Epidemiology**

- ARDS has an estimated incidence per 100,000 patients per year of 34 in the USA and approximately 5 to 7 in Europe.
- It is stratified by the  $\text{PaO}_2 / \text{FiO}_2$  into mild ( $< 300$  mmHg), moderate (200 – 300 mm Hg) and severe forms ( $< 100$  mm Hg).
- Mortality at day 28 is approximately 20 to 40%.

### **Risk Factors**

- Risk factors for ARDS are either pulmonary (pneumonia, aspiration, contusion, inhalational injury etc) or non-pulmonary (non-pulmonary sepsis, pancreatitis, burns, trauma etc).
- Pneumonia and aspiration have the highest associated mortality, with trauma having the lowest.
- Inappropriately delivered mechanical ventilation can both cause and worsen pre-existing lung injury.

### **Pathogenesis**

- ARDS has been described in three sequential, although overlapping, stages– an initial inflammatory exudative phase, where the alveolar lining is damaged; a proliferative phase, where alveolar repair occurs; and a fibrotic phase, with the deposition of fibrin.
- Diffuse alveolar damage, characterised by the presence of hyaline membranes, is considered the pathognomic pathological finding, but is not specific for this syndrome.
- Ventilation-perfusion mismatch is the primary reason for the presence of hypoxaemia.

### **Diagnosis**

- As ARDS is a syndrome, its presence or absence is a binary phenomenon – either the defining criteria are met or not.
- Chest radiography or computed tomography can identify bilateral infiltrates reflective of



alveolar oedema, as well as track the evolution of the condition, clarify patterns of disease, and possibly recruitability.

- Echocardiography is useful to exclude significant cardiac failure.
- Open lung biopsy may have a role in non-resolving ARDS, possibly allowing a treatable cause to be identified.
  - At present, no biomarker has been identified.

### **Management**

- Mechanical ventilation focuses on the delivery of a tidal volume of 6 ml/kg predicted body weight, a plateau pressure less than 30 cm H<sub>2</sub>O, a higher rather than lower PEEP, and possibly a driving pressure less than 15 cm H<sub>2</sub>O,
- Prone positioning and neuromuscular blockade may be of use in severe hypoxaemia, while the avoidance of fluid overload is also recommended.
- Extra-corporeal life support is used as rescue therapy for severe hypoxaemia and has superseded nitric oxide, which should be restricted to those unsuitable for extra-corporeal support.
- No drug therapy has yet demonstrated efficacy for ARDS, with some, including  $\beta$ 2 agonists, being harmful.

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