Acute respiratory distress syndrome

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Acute respiratory distress syndrome presents as hypoxia and bilateral pulmonary infiltrates on chest imaging in the absence of heart failure sufficient to account for this clinical state. Management is largely supportive, and is focused 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 extracorporeal membrane oxygenation. The use of inhaled nitric oxide is rarely indicated and both β_2 agonists and late corticosteroids should be avoided. Mortality remains at approximately 30%.

Introduction

Acute respiratory distress syndrome is a form of non-cardiogenic pulmonary oedema, due to alveolar injury secondary to an inflammatory process, that can be either pulmonary or systemic in origin. This syndrome presents as acute hypoxaemia with bilateral pulmonary infiltrates on chest imaging, which are not wholly due to heart failure. As a syndrome, it is characterised by the presence of several criteria. Since the original description by Ashbaugh and colleagues in 1967,[1] four definitions have been used to determine the presence of acute respiratory distress syndrome (table).[2–5]

The American European Consensus Conference definition,[3] which was published in 1994, was the first agreed and widely used definition. However, it had numerous limitations across all four diagnostic criteria (panel), and, as a result, the European Society of Intensive Care Medicine engaged in a consensus process to generate an improved definition for acute respiratory distress syndrome. The Berlin definition,[5] which was published in 2012, was validated in over 4000 patients' data: on the basis of hypoxaemia, acute respiratory distress syndrome is classified as mild (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen [PaO_2/FiO_2] of 200–≤300 mm Hg), moderate (PaO_2/FiO_2 100–≤200 mm Hg), or severe (PaO_2/FiO_2 ≤100 mm Hg). The most important updates to the definition are the stipulation of a minimum positive end-expiratory pressure (PEEP) of 5 cm H_2O, (PEEP can increase oxygenation, which is a key criterion of the syndrome—this update was to establish a minimum standard for mechanical ventilation); the acknowledgment that acute respiratory distress syndrome can be diagnosed in the presence of cardiac failure; a requirement for new respiratory failure, or worsening of chronic respiratory disease, within 7 days; and the inclusion of chest CT as an alternative form of imaging for the demonstration of lung infiltrates.

Search strategy and selection criteria

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" for articles published in English between Jan 1, 1967, and July 31, 2015. We focused on papers published from 2012 onwards and on those describing treatment in human adults. We also searched the reference lists of articles identified by this search and selected those we deemed most relevant.

Epidemiology

The landmark ARMA study,[28] which was published in 2000, demonstrated the benefits of a low-tidal-volume, low-airway-pressure ventilatory strategy in acute respiratory distress syndrome and marked the establishment of lung protective ventilation as the standard of care. Despite this advance, the syndrome remains highly prevalent, with, in the lung-protective era, estimated incidences per 100 000 patients per year of 34 in the USA[29] and approximately five to seven in Europe.[30–32] Its epidemiology is probably under-reported in less developed health-care systems, in which, as a result of resource limitations, few patients meet the current definition for diagnosis, despite 4% of all hospital admissions having a clinical state similar to that of acute respiratory distress syndrome.[33] 7% of patients in the intensive-care unit (ICU), and 16% of those receiving mechanical ventilation, have acute respiratory distress syndrome.[34]

Based on control group survival in randomised controlled trials[35–38] published in the past 3 years, 28 day mortality is approximately 20–40%. A further 15–20% of patients will die by 12 months, largely because of comorbidities rather than residual effects of acute respiratory distress syndrome.[39] The LUNGSAFE study[40] showed that the syndrome remains common and has a mortality of approximately 40%, and emphasised the global burden. Although, in general, ICU survivors have no reduction in health-related quality of life, full recovery is often limited in those who had acute respiratory distress syndrome. Many have muscle wasting, limiting weakness, and neuropsychiatric illness, including cognitive impairment, anxiety, depression, and post-traumatic stress disorder.[41–43] 6 years after ICU discharge, just over 50% have returned to work.[44] Despite these extrapulmonary deficits, respiratory function returns close to normal.[42]

Risk factors

The development of acute respiratory distress syndrome has been described in the setting of numerous illnesses and injuries, which are broadly classed as being pulmonary or systemic in origin. Pneumonia is the most

	Murray, 1988[2]	AECC, 1994[3]	Ferguson, 2005[4]	Berlin, 2012[5]
Onset	Acute or chronic, not specified	Acute, not specified	Within 72 h	New or worsening within 1 week
Risk factor	Required	Not required	Required	Not required
Oxygenation (mm Hg)	PaO_2/FiO_2 >300 (0) PaO_2/FiO_2 225–299 (1) PaO_2/FiO_2 175–224 (2) PaO_2/FiO_2 100–174 (3) PaO_2/FiO_2 <100 (4)	Acute lung injury: PaO_2/FiO_2 <300 Acute respiratory distress syndrome: PaO_2/FiO_2 ≤200	PaO_2/FiO_2 <200	Mild: PaO_2/FiO_2 200–300 Moderate: PaO_2/FiO_2 100–199 Severe: PaO_2/FiO_2 <100
PEEP (cm H_2O)	≤5 (0) 6–8 (1) 9–11 (2) 12–14 (3) ≥15 (4)	Not specified	≥10	Minimum PEEP of 5 required
Infiltrates on chest radiograph	No quadrants (0) One quadrant (1) Two quadrants (2) Three quadrants (3) Four quadrants (4)	Bilateral infiltrates on a frontal chest radiograph	Bilateral airspace disease involving two or more quadrants on a frontal chest radiograph	Bilateral infiltrates involving two or more quadrants on a frontal chest radiograph or CT
Heart failure	..	Pulmonary artery wedge pressure ≤17 mm Hg Absence of left atrial hypertension	No clinical evidence of congestive heart failure (based on pulmonary artery catheter with or without echocardiogram)	Left ventricular failure insufficient to solely account for clinical state
Static compliance (mL/cm H_2O)	≥80 (0) 60–79 (1) 40–59 (2) 20–39 (3) ≤19 (4)	..	Static compliance <50 (with patient sedated, tidal volume 8 mL/kg ideal bodyweight, PEEP ≥10)	Removed
Severity	Mild Moderate Severe	Based on oxygenation criteria	..	Based on oxygenation criteria
Specificity for diffuse alveolar damage	Autopsy: 74%[6] (lung injury score ≥2·5)	Autopsy: 30%,[6] 50%,[7] 66%,[8] 70%[9] Biopsy: 29%,[10] 47%,[11] 40%[12]	Autopsy: 69%[6]	Autopsy: 45%[13] Biopsy: 58%[14]

Data in parentheses in the Murray column are scores; the total number of points scored is divided by the number of categories included, giving the Murray lung injury score. A score of 0 signifies no lung injury is present, a score of 0·1–2·5 signifies mild to moderate lung injury, and a score greater than 2·5 signifies severe lung injury. AECC=American European Consensus Conference. PaO_2=partial pressure of arterial oxygen. FiO_2=fraction of inspired oxygen. PEEP=positive end-expiratory pressure.

Table: **Definitions of acute respiratory distress syndrome**

common risk factor for the development of the syndrome, and, along with aspiration, has the highest associated mortality; trauma-related illness has the lowest.[29]

Inappropriately administered mechanical ventilation is an important contributor to both the development and worsening of acute respiratory distress syndrome.[28,45] This ventilator-induced lung injury can occur by several mechanisms, including excessive lung stretch (volutrauma)[46] or pressure (barotrauma), repetitive alveolar opening and closing, which causes a shearing injury (atelectrauma), and potential oxygen toxicity.[47] These processes also drive excessive systemic inflammation, with the ability to induce non-pulmonary organ failure (biotrauma). In a randomised controlled trial[45] of 150 critically ill mechanically ventilated patients, ventilation with 10 mL rather than 6 mL per kg of predicted bodyweight was associated with a five-times increase in the odds of developing acute respiratory distress syndrome. This finding has been substantiated in a further randomised controlled trial[48] in 400 patients at risk of pulmonary complications undergoing general anaesthesia for major abdominal surgery. A non-lung-protective ventilatory strategy of 10–12 mL/kg tidal volume ventilation with no PEEP was compared with lung-protective ventilation of 6–8 mL/kg tidal volume with PEEP of 6–8 cm H_2O plus a recruitment manoeuvre every 30 min. The lung-protective group had fewer major complications (10·5% *vs* 27·5%; relative risk [RR] 0·40, 95% CI 0·24 to 0·68; p=0·001), required less respiratory support by day 7 (5% *vs* 17%; 0·29, 0·14 to 0·61; p=0·001), and had a shorter hospital stay (11 *vs* 13 days; difference –2·45 days, –4·17 to –0·72; p=0·006).

Genetics

The search for potential genes conferring susceptibility to the development of, or that alter the outcome from, acute respiratory distress syndrome is methodologically complex. Genotype, phenotype, race, environment, injury, and therapy interact in variable and uncertain ways to contribute to clinical outcomes. More than 40 candidate genes associated with the development or outcome of acute respiratory distress syndrome have been identified, although these investigations have either largely not been sufficiently robust to provide clear answers, or have yet to be replicated.[49] Some of the more promising genes include

***Panel*: Problems with the AECC definition and subsequent Berlin definition of acute respiratory distress syndrome**

Acuity
- AECC: not specified
- Berlin: almost all patients meet criteria for acute respiratory distress syndrome within a week[15]

Oxygenation
- AECC: no minimum requirement for PEEP, which can strongly modify oxygenation;[16] differences in ratio of the PaO_2 to the FiO_2 across differing PEEP and FiO_2[16]
- Berlin: level of PEEP not considered in determining severity[17]

Radiography
- AECC: poor interobserver agreement on interpretation of chest radiographs, even between experts;[18,19] no standardised set of chest radiographs for comparison or education; difficult to differentiate hydrostatic from permeability pulmonary oedema on chest radiographs;[20] consolidation might be visible on CT, but not by chest radiography[21]

Heart failure
- AECC: unvalidated use of high pulmonary artery occlusion pressure to exclude alveolar injury as the cause of, or as a contributor to, pulmonary oedema in acute respiratory distress syndrome;[22] poor medical and nursing knowledge of the correct interpretation of pulmonary artery catheter data;[23,24] high interobserver variability in interpretation of pulmonary artery catheter tracings;[25] poor interobserver agreement on the clinical identification of left atrial hypertension

Autopsy or biopsy studies
- Both: around 50% of patients meeting the definitions of acute respiratory distress syndrome do not have diffuse alveolar damage;[8,12,14,26] prevalence of diffuse alveolar damage decreases with rising PaO_2/FiO_2 ratio;[13] only 75% of severely hypoxaemic patients with acute respiratory distress syndrome have diffuse alveolar damage[13]

Duration
- Both: patients with acute respiratory distress syndrome persisting <24 h have much better outcomes than do those with ARDS persisting >24 h[27]

Acute lung injury term
- AECC: inconsistency with the use of the term acute lung injury, which has been used to refer to either patients with mild hypoxaemia only (PaO_2 >200 mm Hg) or as an umbrella term for all those meeting the definition of acute respiratory distress syndrome,[5] including moderate and severe hypoxaemia

Recognition
- Both: many clinicians fail to recognise acute respiratory distress syndrome[6]

AECC=American European Consensus Conference. PEEP=positive end-expiratory pressure. PaO_2=partial pressure of arterial oxygen. FiO_2=fraction of inspired oxygen.

ACE, *SOD3*, interleukin 10, *MYLK*, *NFE2L2*, *NAMPT*, *SFTPB*, *TNF*, and *VEGF*.[50] The search for a genetic susceptibility to either the onset, or worsening, of the syndrome might prove difficult until issues with the specificity of the definition of acute respiratory distress syndrome and improved phenotyping of patients are addressed. However, a gene with a clearer association with acute respiratory distress syndrome is *ACE*. This association came to prominence during the severe acute respiratory syndrome (SARS) epidemic, when the ACE2 protein, which contributes to the regulation of pulmonary vascular permeability, was identified as the receptor for the novel coronavirus that caused SARS.[51]

Pathogenesis

After the onset of the primary illness, the inflammatory alveolar injury occurring has been described in terms of three sequential phases (figure 1), which overlap substantially.[26] The process begins with the exudative phase and immune-cell-mediated destruction of the barriers of the alveolar epithelial–interstitial–endothelial complex, allowing plasma, plasma proteins, and cellular content to successively flood the interstitium and airspace. Classically, acute respiratory distress syndrome is recognised to be a neutrophil-driven disease; however, experimental data have shown that alveolar neutrophilia can occur without increased alveolar permeability.[52] Additionally, the involvement of cells from the innate (including macrophages[53] and platelets[54]) and adaptive immune systems in the pathogenesis of acute respiratory distress syndrome is increasingly recognised.[55] 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, which impedes 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 coexisting with altered vasomotor tone (both vasoconstriction and vasodilation) and microthrombi. Pulmonary hypertension results, increasing right ventricular afterload. This right ventricular dysfunction can 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, which leads to refractory hypoxia.

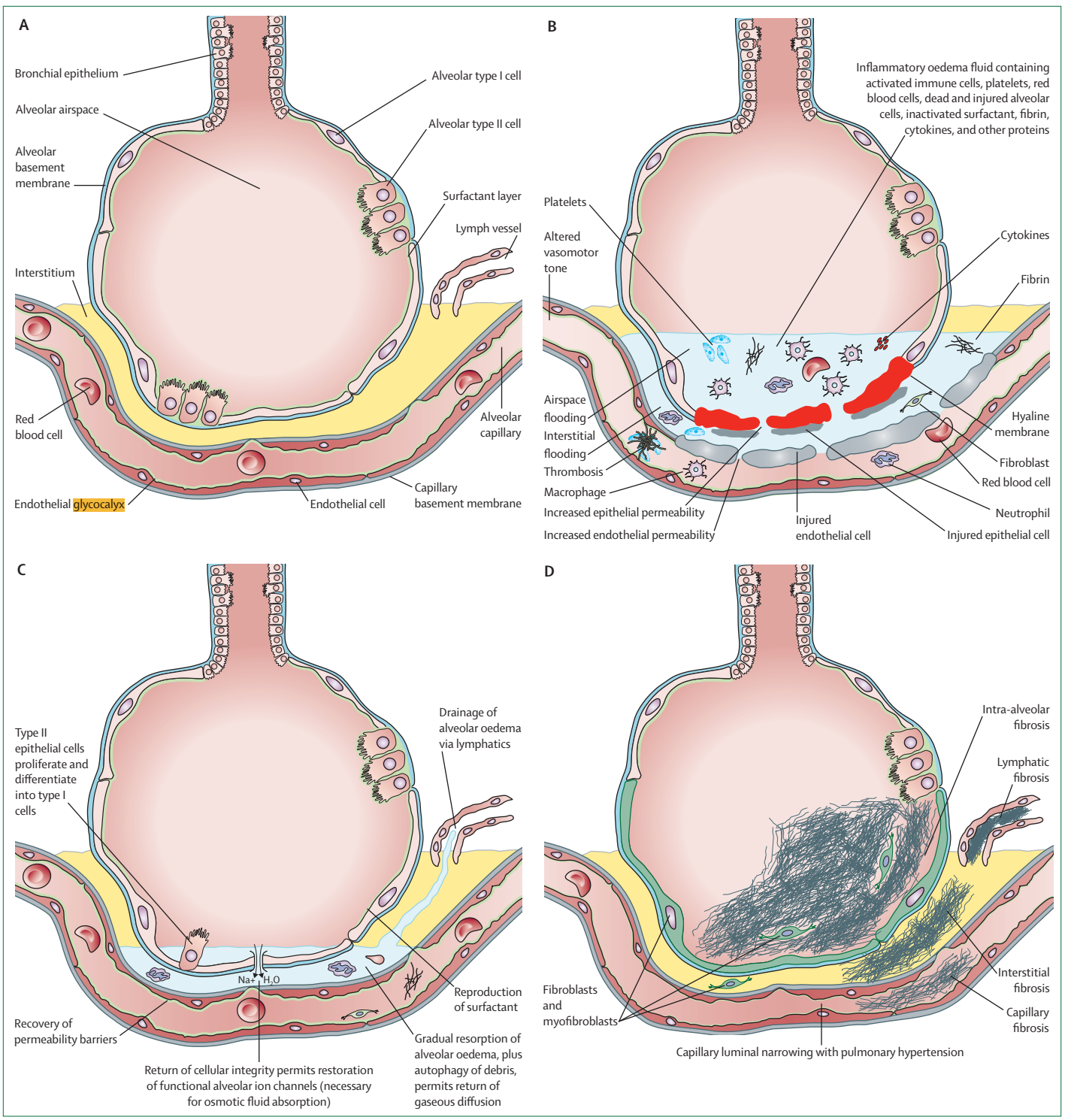

***Figure 1*: A normal alveolus (A), plus the sequential exudative (B), proliferative (C), and fibrotic (D) phases in the pathogenesis of acute respiratory distress syndrome**

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, and remaining debris is cleared by inflammatory cells. Vasomotor tone begins to return to normal, microthrombi are cleared, and pulmonary hypertension lessens. As

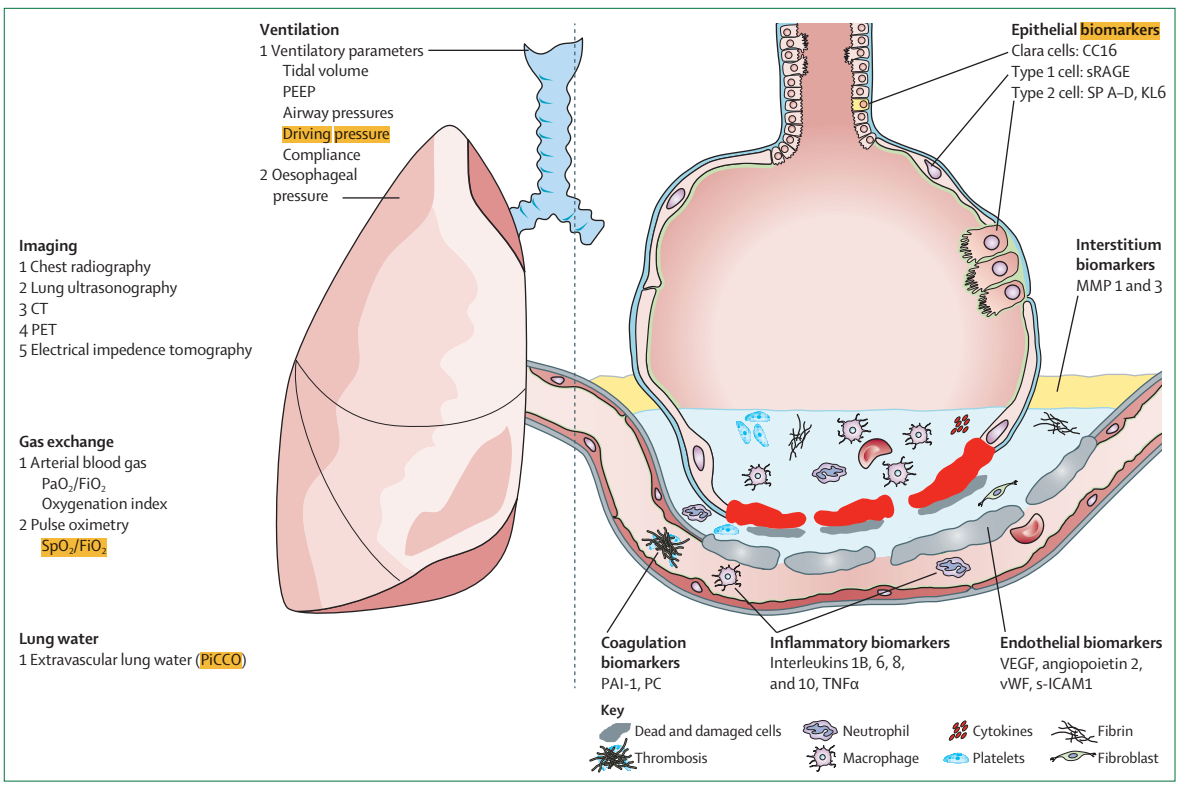

***Figure 2*: Clinical and research investigational modalities used in acute respiratory distress syndrome**
PEEP=positive end-expiratory pressure. PaO_2/FiO_2=ratio of partial pressure of arterial oxygen to fraction of inspired oxygen. SpO_2/FiO_2=ratio of peripheral arterial oxygen saturation to fraction of inspired oxygen. PiCCO=Pulse Contour Cardiac Output. TNF-α=tumour necrosis factor α. vWF= von Willebrand factor.

reparation continues, shunt reduces, leading to improved oxygenation that is followed, often more slowly, by recovering pulmonary compliance. The third fibrotic phase develops inconsistently, and comprises 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 is thought to be the pathognomonic pathological finding of acute respiratory distress syndrome,[5] is defined by the presence of hyaline membranes, and can be detected either by lung biopsy or at autopsy. However, it is not specific and can also occur in the absence of the criteria for acute respiratory distress syndrome.[14] Many patents who fulfil the diagnostic criteria for acute respiratory distress syndrome do not have diffuse alveolar damage.[13]

Clinical patterns have been recognised in patients with acute respiratory distress syndrome—eg, those with a pulmonary cause have more consolidation and less alveolar collapse and interstitial oedema than do those with non-pulmonary causes.[56] Subphenotypes have been described, and are classified by clinical and biological characteristics with differing clinical outcomes and response to treatment.[57,58] A hyperinflammatory phenotype is associated with worse metabolic acidosis, higher vasopressor requirements, increased mortality, and a better response to higher PEEP. Subphenotypes will provide further mechanistic insight to the pathophysiology of acute respiratory distress syndrome, which is likely to inform the development of personalised therapies.

Diagnosis and monitoring

The Berlin definition for acute respiratory distress syndrome is an evolution of the American European Consensus Conference definition (table), which was recognised to have numerous flaws. The revised definition, although improved, still has limitations. Several investigational modalities are potentially helpful in monitoring the clinical course (figure 2). Sequential imaging via both chest radiography and CT (figure 3) provides qualitative measures of disease evolution, and CT also provides specific quantitative measures of oedema, aeration, and recruitability. Extravascular lung water, which reflects the degree of pulmonary oedema, can be measured with a PiCCO [Pulse Contour Cardiac Output] monitor (Pulsion Medical Systems, Feldkirchen, Germany) and is associated with mortality in patients with acute respiratory distress syndrome.[60,61] Similarly, lung ultrasonography (figure 3) can be used to estimate extravascular lung water,[62,63] and to allow differentiation of the syndrome from cardiogenic pulmonary oedema.[64] Pulmonary wedge[65] and central venous pressures[65,66] have little correlation with volaemic status or fluid

responsiveness and are unlikely to offer benefit in routine management (neither offers any benefit over the other).[67]

The PaO_2/FiO_2 ratio is a measure of oxygenation that is used to classify acute respiratory distress syndrome as mild, moderate, or severe (table). Although easy to calculate, it is an imperfect measure, because of its variability with differing PEEP[16] and tidal volumes.[68] The oxygenation index—the product of mean airway pressure and FiO_2, divided by PaO_2—is an alternative to PaO_2/FiO_2 and might be superior, because it includes mean airway pressure, which reflects PEEP.[69] Respiratory system compliance helps with the monitoring of pulmonary mechanics, although it was not included in the Berlin definition because it lacked additional discriminatory value.[5] Pulmonary dead space fraction is associated with mortality in acute respiratory distress syndrome (odds ratio 1·45, 95 % CI 1·15–1·83; p=0·002), but is technically challenging to measure and not frequently used.[70] Bronchoalveolar lavage permits sampling of the alveolar space and helps with the identification of infectious causes of acute respiratory distress syndrome and with diagnosis of malignancy or haemorrhage.

The absence of a biomarker to define the diagnosis, responsiveness to therapy, and prognosis of acute respiratory distress syndrome is problematic and limits progress in the field.[71,72] Differing pathologies damage lung tissue in diverse ways, producing inconsistent signals from numerous injured cell types. These signals are further confounded by age, comorbidities, and iatrogenic effects such as excessive fluid administration and harmful ventilation. Many candidate biomarkers (figure 2) have been investigated, but a single, clear biomarker has proved difficult to find. Biomarkers have been measured in both blood and bronchoalveolar lavage fluid, but are too inaccurate for clinical use. Combinations of biomarkers could be used to identify specific phenotypes of patients with acute respiratory distress syndrome who might respond differentially to therapies, but further work is required to confirm these initial findings.[57]

Open lung biopsy remains the gold standard for diagnosis of diffuse alveolar damage. Small, single-centre observational studies of open lung biopsy in highly selected populations show low specificity of the clinical diagnosis of acute respiratory distress syndrome for the presence of diffuse alveolar damage.[10–12,14] Most patients with acute respiratory distress syndrome undergoing this procedure have resulting alterations in management,[10–12,73,74] improved outcomes,[73] and little noteworthy morbidity.[10–12,14,73,74] These studies are limited by their selective nature and their constrained ability to examine the entire lung. Open lung biopsy is usually reserved for exceptional cases in which there is a genuine diagnostic dilemma and poor response to therapy.

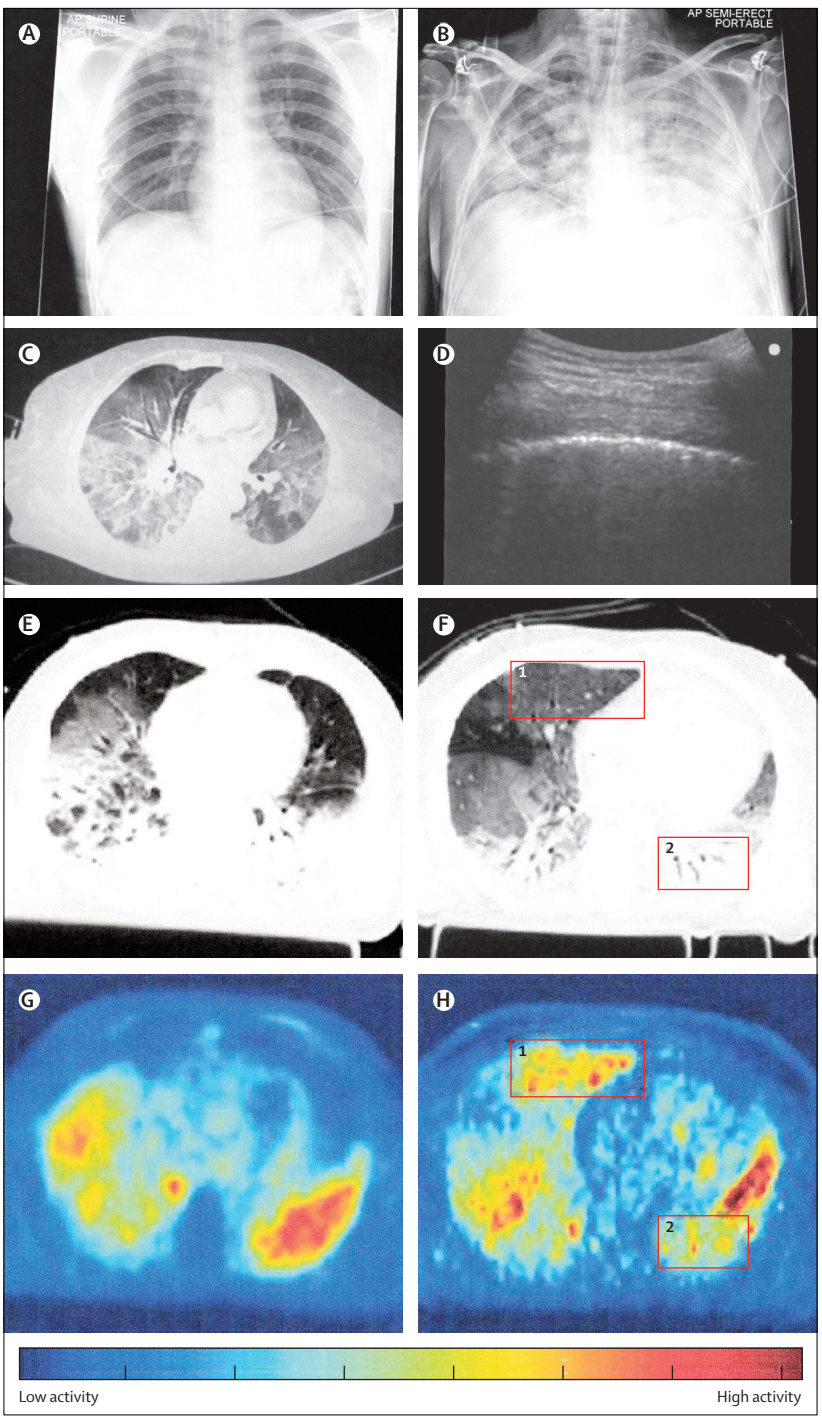

Figure 3: **A normal chest radiograph (A), and a chest radiograph demonstrating bilateral alveolar infiltrates consistent with acute respiratory distress syndrome (B); chest CT showing bilateral pneumonitis and consolidation with air bronchograms consistent with acute respiratory distress syndrome (C); lung ultrasonogram illustrating smooth pleural line, absence of horizontal A lines, and presence of vertical B lines suggestive of acute respiratory distress syndrome (D); and PET demonstrating increased areas of metabolic activity, reflective of underlying inflammation (E–H)**

Figures E and F are reproduced from Bellani and colleagues,[59] by permission of Wolters Kluwer Health.

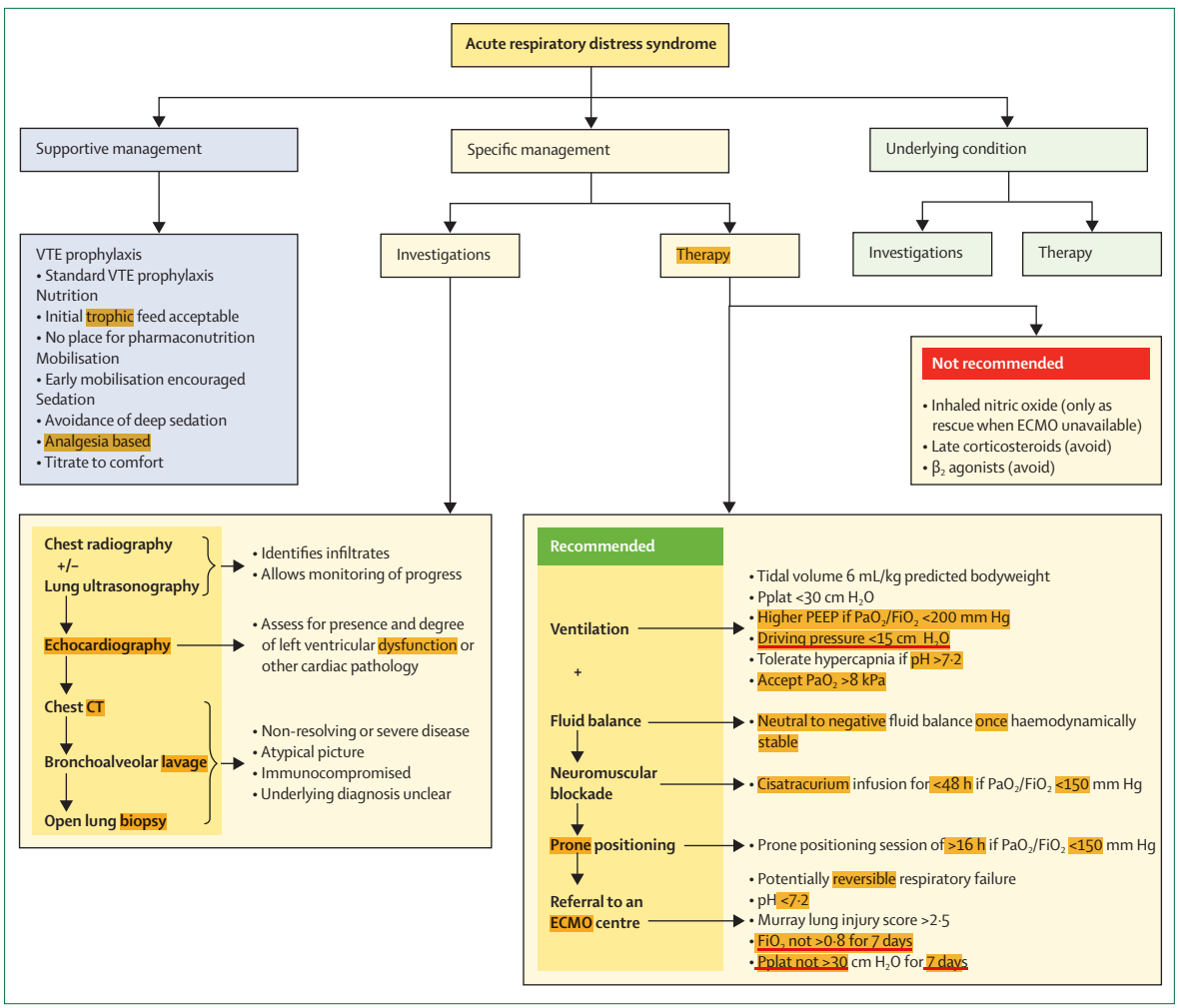

Figure 4: **Algorithm of a suggested evidence-based approach to the management of acute respiratory distress syndrome**
VTE=venous thromboembolism. PaO_2=partial pressure of arterial oxygen. FiO_2=fraction of inspired oxygen. ECMO=extracorporeal membrane oxygenation. Pplat=airway plateau pressure. PEEP=positive end-expiratory pressure.

Management: conventional mechanical ventilation

Management of acute respiratory distress syndrome can be classed as specific or supportive; addressing the underlying causative condition is also necessary (figure 4). Specific measures include both maintenance of gas exchange and manipulation of the underlying pathophysiology. Supportive therapies include sedation, mobilisation, nutrition, and prophylaxis for venous thromboembolism.

Four randomised controlled trials[75–78] published between 1998 and 1999 provided mixed results for the optimal tidal volume in acute respiratory distress syndrome. In the landmark ARMA study,[28] which was published in 2000 by the ARDSnet group, a traditional ventilatory strategy of 12 mL per kg of predicted bodyweight tidal volume in combination with a plateau airway pressure ≤ 50 cm H_2O was compared with a lower tidal volume of 6 mL per kg of predicted bodyweight in combination with a plateau airway pressure of 30 cm H_2O or less in 861 mechanically ventilated patients with acute respiratory distress syndrome. The study was stopped early, because, despite initially worse oxygenation, low-tidal-volume ventilation was associated with an 8·8% (95% CI 2·4–15·3) absolute reduction in mortality (39·8% *vs* 31·0%; p=0·007), and significantly more ventilator-free days (10 [SD 11] *vs* 12 [11]; p=0·007). Importantly, less injurious ventilation was associated with more days free of non-pulmonary organ failure (12 [11] *vs* 15 [11]; p=0·006). Tidal volume was estimated from predicted bodyweight, which is dependent on height and sex, and calculated as 50+0·91×(height in cm−152·4) for men and 45·5+0·91×(height in cm−152·4) for women. Lung-protective ventilation is associated with improved outcomes if used early in the course of acute respiratory distress syndrome,[79] and reduced mortality at 2 years.[80]

Despite the adoption of a volume-limited and pressure-limited protective ventilatory strategy, critically ill

mechanically ventilated patients with acute respiratory distress syndrome receiving a tidal volume of 6 mL/kg and a plateau pressure of 30 cm H_2O or less can still be exposed to tidal hyperinflation, whereby the smaller-than-usual aerated section of the lung (so-called baby lung)[81] receives a larger-than-usual volume of gas, resulting in greater biotrauma and fewer ventilator-free days than those in patients without tidal hyperinflation.[82] Similarly, a post-hoc review[83] of the ARDSnet database did not demonstrate a safe upper limit for plateau pressures in patients with acute respiratory distress syndrome. Volume-limited and pressure-limited ventilation can cause hypercapnic acidosis, and the overall clinical effect of protective ventilation and hypercapnia is uncertain.[84] Hypercapnic acidosis could provide protective effects in the setting of high-tidal-volume ventilation, but a beneficial effect is not noted in patients receiving lung-protective ventilation.[85]

PEEP prevents lung unit collapse at the end of the respiratory cycle. Beneficial effects include the maintenance of functional residual capacity, improved compliance, and higher mean airway pressure, which result in decreased shunt with enhanced oxygenation, and reduced atelectasis and biotrauma. These advantages should be weighed against the effects of raised intrathoracic pressure—namely, decreased venous return and increased right ventricular afterload.[86] Numerous methods of setting the PEEP level have been described, including most recently oesophageal balloon manometry.[87] In the lung-protective era, four randomised controlled trials[87–90] have been done to answer the question of whether higher or lower pressure is superior, with a suggestion that higher PEEP could be beneficial. A meta-analysis[91] of three of these trials also showed a possible benefit for a high PEEP setting in acute respiratory distress syndrome, which was associated with both lower in-hospital mortality (34·1% *vs* 39·1%; RR 0·90, 95% CI 0·81–1·00; p=0·049) and less requirement for mechanical ventilation by day 28 (hazard ratio [HR] 1·16, 95% CI 1·03–1·30; p=0·01).[91] The EPVent randomised controlled trial,[87] in which oesophageal-balloon manometry-guided PEEP was compared with use of the ARDSnet PEEP–FiO_2 table, showed that oesophageal-guided PEEP provided increased oxygenation and compliance, which translated into higher PEEP (18 cm *vs* 12 cm H_2O on day one) and associated improved adjusted 28 day mortality (RR 0·46, 95% CI 0·19–1·0; p=0·049).[87] A further meta-analysis that included this additional study showed non-significant improvements in 28 day mortality with higher PEEP (pooled RR 0·90, 95% CI 0·79–1·02), without a significantly higher risk of barotrauma (1·17, 0·90–1·52).[92]

The driving pressure, which is defined as the difference between plateau and end-expiratory pressures, has 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.[93] On the basis of derivation and validation cohorts from 3562 patients recruited into nine randomised controlled trials, Amato and colleagues[93] reported that an increase in driving pressure of 7 cm H_2O was associated with increased 60 day mortality (RR 1·41, 95% CI 1·31–1·51; p<0·001). According to the statistical method of multilevel mediation analysis, none of the three main components of lung-protective ventilation was individually associated with reduced mortality, but they acted via a reduced driving pressure to exert their beneficial effects.

Driving pressure could help to 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, it is the normal tidal volume of most mammalian species.[94] As the available functional lung volume falls in acute respiratory distress syndrome as a result of collapse and consolidation, perhaps the delivered tidal volume should also decrease. Although evidence suggests that targeting of driving pressure is prudent, whether driving pressure relates causally to outcome remains to be established in a prospective, randomised controlled trial. This concept is being investigated in the setting of studies of extracorporeal carbon dioxide removal to facilitate very-low-tidal-volume or ultra-protective ventilation.[95] Although these data for driving pressure are post hoc, observational in nature, and necessitate confirmation in a prospective study, an upper limit for driving pressure of 15 cm H_2O could be appropriate in the interim.

Atelectatic areas of lung can 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 reaerated region. Three commonly used such recruitment manoeuvres are sighs, sustained inflations, and extended sighs.[96] Brief periods of raised intrathoracic pressure also impede venous return to the right atrium, predisposing to hypotension. Preclinical data have shown divergent effects of recruitment manoeuvres on alveolar epithelial and endothelial function.[97] A systematic review,[98] based on 40 studies, showed that recruitment manoeuvres increased oxygenation, but little information about the long-term effects of these interventions and no clear guidance on the usefulness of this procedure was available.

There are few robust randomised controlled trials to guide the choice of mode of mechanical ventilation. The authors of a 2015 Cochrane review, summarising three randomised controlled trials consisting of 1089 patients in total, concluded that evidence was insufficient to promote the use of either volume-controlled or pressure-controlled ventilation over the other.[99] 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 suboptimum control groups in the studies done and concerns about possible high tidal volume and mean airway pressure.[100] Non-invasive ventilation can be tried

in mild acute respiratory distress syndrome. A small study[101] of 40 patients showed reduced requirement for invasive mechanical ventilation and a non-significant reduction in mortality with this approach. This result should be tempered by those of a much larger meta-analysis of 540 patients, documenting failure of non-invasive ventilation in almost 50% of patients.[102] The advent of high-flow nasal oxygen allows for simpler, more tolerable respiratory support. In an observational study, 18 (40%) of 45 patients with moderate acute respiratory distress syndrome (mean PaO_2/FiO_2 137 mm Hg) treated with high-flow nasal oxygen required invasive mechanical ventilation.[103] As with non-invasive ventilation, more severe illness was associated with an increasing likelihood of treatment failure.

Management: adjuncts to respiratory support

Prone positioning

Placing a patient prone while they receive 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.[104] Several studies[105–108] produced conflicting results about the efficacy of prone positioning ventilation in acute respiratory distress syndrome. Although prolonged prone positioning's association with physiological improvement was increasingly recognised,[109] in these studies prone ventilation was of short duration. Additionally, subsequent meta-analyses[110,111] suggested benefit specifically in the most hypoxaemic patients receiving lung-protective ventilation. The PROSEVA study[112] was designed to address these shortcomings. 466 patients with severe acute respiratory distress syndrome (which was defined as a PaO_2 of less than 150 mm Hg while being ventilated with an FiO_2 of 0·6 or greater) who were receiving lung-protective ventilation were randomly assigned to either the supine position or daily prone position sessions lasting at least 16 h. Prone position ventilation was associated with reduced 28 day mortality compared with supine ventilation (32·8% *vs* 16·0%, p<0·001; HR 0·44, 95% CI 0·29–0·67). There were no additional complications associated with prone positioning, although the centres involved were all experienced with this technique. This magnitude of effect, although large, was predicted by a previous meta-analysis.[111]

Neuromuscular blockade

The hypoxaemia of severe acute respiratory distress syndrome might necessitate excessive ventilatory support, risking the development of ventilator-induced lung injury. Paralysis removes endogenous effort, improving respiratory mechanics and lowering oxygen consumption. In the ACCURSY study,[113] cisatracurium-besylate-induced paralysis was compared with placebo in 340 patients with early severe acute respiratory distress syndrome. Neuromuscular blockade for 48 h resulted in—after adjustment for baseline PaO_2/FiO_2, plateau pressure, and Simplified Acute Physiology II scores—a reduced adjusted HR for death at 90 days (0·68, 95% CI 0·48–0·98; p=0·04). Importantly, the frequency of complications, including ICU-acquired weakness, did not differ between groups. Although promising, additional large clinical trials are required to confirm these findings.

Extracorporeal life support

Because 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 has failed. In addition to replacing endogenous alveolar gaseous exchange, extracorporeal gas exchange—either extracorporeal membrane oxygenation (ECMO) or extracorporeal carbon dioxide removal—allows reduction in ventilatory settings, reducing the risk of ventilator-induced lung injury. At present, the evidence base for these interventions is sparse, consisting of case series, observational cohort studies, and one randomised controlled trial. In the CESAR study,[114] rather than directly assessing ECMO in refractory hypoxaemia, investigators compared management at a referring centre with management at a tertiary centre capable of providing ECMO in 180 patients. The cohort managed at the ECMO centre had a higher rate of survival without disability at 6 months than did those managed at referring centres (63% *vs* 47%; RR 0·69, 95% CI 0·05–0·97; p=0·03), although only 75% of the group received ECMO. Two observational studies, one from Australia and New Zealand[115] and one from the UK,[116] also showed high rates of survival with ECMO in patients with influenza A (H1N1) with refractory hypoxaemia on maximum ventilatory support. However, ECMO is a scarce and expensive resource that is often available only at specialist centres (figure 4) and associated 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 few regional centres.

Non-conventional mechanical ventilation

High-frequency oscillatory ventilation is the provision of small tidal volumes (typically 2 mL per kg of predicted bodyweight) at high frequencies of up to 900 breaths per min, via several atypical mechanisms of gas transfer. This mode of ventilation also affords separation of oxygenation, which is dependent on FiO_2 and mean airway pressure, from carbon dioxide removal, which is an active process that depends on the pressure amplitude and frequency of oscillation. Two large randomised controlled trials, from Canada (OSCILLATE)[35] and the UK (OSCAR),[36] failed to

show benefit from this mode of ventilation. OSCILLATE showed harm associated with high-frequency oscillatory ventilation, 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

In the past 5 years, statins and β_2 agonists have been investigated in large placebo-controlled, phase 3 randomised studies. In addition to their cholesterol-lowering effects, statins have pleotropic properties, making them an attractive potential therapy. In the Irish Critical Care Trials Group's HARP-2 study,[37] simvastatin was assessed in 540 patients with early acute respiratory distress syndrome. Although 80 mg simvastatin was not associated with harm, there was no benefit in ventilator-free days (simvastatin 12·6 days [SD 9] *vs* control 11·5 days [10·4]; p=0·21), days free of non-pulmonary organ failure (19·4 [11·1] *vs* 17·8 [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,[38] exploring rosuvastatin in 745 patients with sepsis-associated acute respiratory distress syndrome. The study was stopped for futility and showed no significant difference between the rosuvastatin and placebo groups in 60 day in-hospital mortality (28·5% *vs* 24·9%; p=0·21) or ventilator-free days (15·1 [SD 10·8] *vs* 15·1 [11·0]; p=0·96). Rosuvastatin was, however, associated with a small decrease in the number of days free of renal and hepatic failure, indicating possible harm.

Preclinical data suggest that β_2 agonists could modify several pulmonary mechanisms. They increase alveolar-fluid clearance, are cytoprotective, and have anti-inflammatory properties, which prompted investigation of salbutamol as a potential therapy for acute respiratory distress syndrome.[117–119] In the UK BALTI-2 study,[120] intravenous salbutamol was given at a dose of 15 µg per kg of ideal bodyweight per h; the trial was terminated for safety reasons after recruiting 326 patients of a planned 1334. Salbutamol was associated with increased 28 day mortality compared with placebo (34% *vs* 23%, RR 1·47, 95% CI 1·03–2·08), and decreased ventilator-free and organ-failure-free days; its effects were possibly mediated through cardiac and metabolic toxicity, in the form of arrhythmias and lactic acidosis. The US ARDSnet ALTA study[121] of inhaled salbutamol (5 mg every 4 h for up to 10 days in 282 patients) was stopped for futility. There was no significant difference between the active and placebo groups in the primary outcome of ventilator-free days (14·4 *vs* 16·6, 95% CI for difference –4·7 to 0·3; p=0·087) or the secondary outcome of in-hospital mortality (23·0% *vs* 17·7%, –4·0 to 14·7; p=0·30), although patients with shock at baseline in the salbutamol group had fewer ICU-free days than did those in the placebo group.

Two other pharmacotherapies deserve mention—corticosteroids and nitric oxide. Acute respiratory distress syndrome is an inflammatory lung injury, and the use of corticosteroids would thus appear ideally suited to it, 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 of or against the use of corticosteroids,[122,123] although the US ARDSnet steroid study suggested harm if corticosteroid therapy was started more than 14 days after the onset of the syndrome.[124] Nitric oxide is an inhaled pulmonary vasodilator that improves ventilation–perfusion matching, resulting in increased oxygenation. However, this increase in oxygenation does not translate into improved patient-centred outcomes.[125] Nitric oxide is associated with numerous complications, including renal failure and rebound pulmonary hypertension.[125] Various other anti-inflammatory and pathophysiologically (figure 5) targeted drugs have been investigated, but have not demonstrated robust effectiveness.[126,127]

Fluid management

Acute respiratory distress syndrome is a form of pulmonary oedema, and thus fluid therapy is an essential aspect of management. Fluid excess is increasingly linked to detrimental outcomes across the spectrum of critical illnesses.[128] A general paradigm exists of early fluid loading for resuscitation and organ rescue during

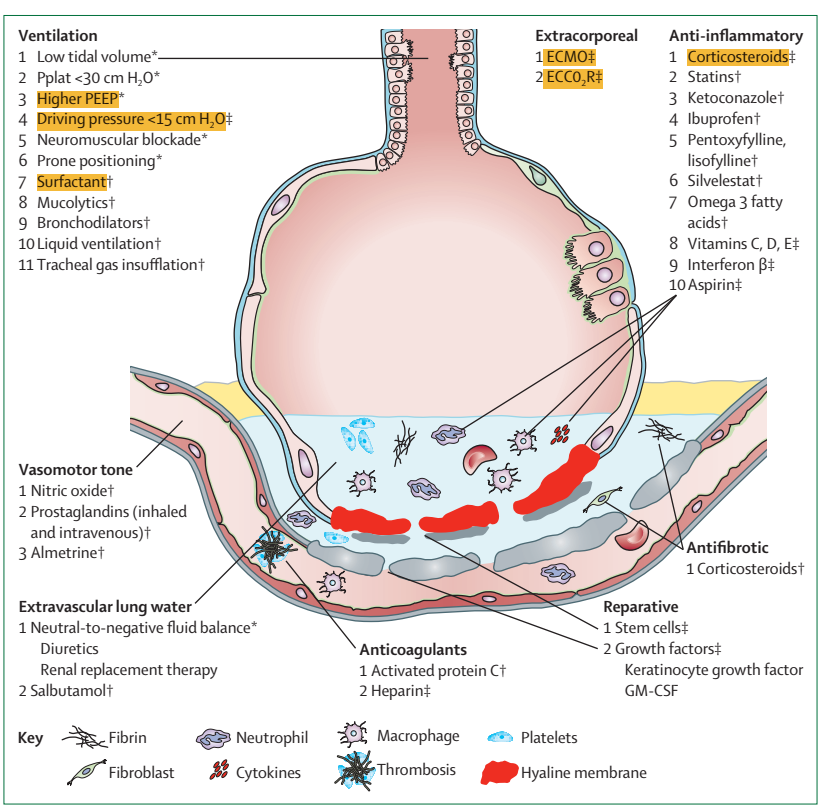

Figure 5: **Acute respiratory distress syndrome therapies in clinical use**
Pplat=airway plateau pressure. GM-CSF=granulocyte–macrophage colony-stimulating factor. PEEP=positive end-expiratory pressure. ECMO=extracorporeal membrane oxygenation. $ECCO_2R$=extracorporeal carbon dioxide removal. *Evidence supports use. †No supporting evidence base, or evidence of harm. ‡Undergoing active research.

the presentation stage of the illness, followed by fluid unloading (deresuscitation)—either spontaneous or induced—after haemodynamic stability has been achieved.[129] Fluid-induced lung injury describes the development of lung injury after intravenous fluid administration. The rapid administration of saline in healthy volunteers can cause pulmonary interstitial oedema;[130] patients with sepsis can experience decreased oxygenation and worsening lung injury scores as a result of fluid bolus administration after initial resuscitation.[131]

In a randomised controlled trial[132] in 1001 patients with acute respiratory distress syndrome managed with lung-protective ventilation (FACTT), a detailed algorithm targeting cardiac filling pressures in the setting of haemodynamic stability was used for a comparison of liberal and conservative fluid strategies. At 1 week, a conservative strategy was associated with a net neutral fluid balance compared with a 7 L positive balance in the control arm, resulting in significantly increased oxygenation, a better lung injury score, more ventilator-free and ICU-free days, and fewer blood transfusions in the conservatively managed group. There was no difference between the conservative and liberal strategies in the primary outcome of death at 60 days (25·5% [SD 1·9] *vs* 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, showed an increased incidence of cognitive impairment in the deresuscitated group (adjusted odds ratio 3·35 [95% CI 1·16–9·70] to 5·46 [1·92–15·53]).[133]

A small randomised controlled trial[134] of combined therapy with albumin and furosemide administration in 37 hypoproteinaemic patients with acute respiratory distress syndrome demonstrated improvements in oxygenation, fluid balance, and haemodynamics. A further small follow-up study by the same group, in which furosemide administration with or without albumin supplementation was compared, suggested that the combination was superior to furosemide administration alone. However, in the large randomised controlled ALBIOS trial,[135] in which investigators examined a strategy of albumin administration to maintain plasma albumin concentrations higher than 30 g/L in patients with sepsis and septic shock, beneficial effects on respiratory sequential organ failure assessment (SOFA) score were not associated with higher plasma albumin concentrations, although a specified subgroup analysis was not done for this outcome. Therefore whether albumin has a place in the management of acute respiratory distress syndrome remains unclear. On the basis of available evidence, synthetic colloids do not have any role in the management of the critically ill.[136]

Supportive therapy

Nutrition

Investigators in the EDEN study explored the effect of low-volume trophic feeding for up to 6 days in 1000 non-malnourished patients with early acute respiratory distress syndrome.[137] Despite separation of calorific delivery between groups (roughly 400 kcal per day *vs* full feeding of 1300 kcal per day), neither 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) nor the secondary outcomes of 60 day mortality (23·2% *vs* 22·2%; 1·0, –4·1 to 6·3; p=0·77) or infectious complications differed between groups. The full feed group, however, received more prokinetic agents, and spent more days with increased gastric residual volume, vomiting, and constipation. Additionally, there was no difference in physical or cognitive function in survivors at 1 year.[138]

The ability to modulate the inflammatory response via immunonutrition—ie, the delivery of immune-enhancing dietary agents such as fish oils, glutamine, selenium, vitamins, and other antioxidants—has long been a potential target. Early studies were suggestive of benefit, especially when used in acute respiratory distress syndrome.[139] But randomised controlled trials have not shown efficacy for a range of additives in either patients with acute respiratory distress syndrome[140] or those needing general critical care.[141–143] In the OMEGA study,[144] the twice daily use of the n-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid, γ-linolenic acid, and a mixture of antioxidants, was compared with use of an isocaloric control in 272 patients with early acute respiratory distress syndrome who were also receiving enteral nutrition. Despite an eight-times increase in plasma n-3 fatty acid concentrations in the intervention group, 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, and a non-significant increase in mortality. A subsequent small phase 2 study of fish oils in 90 patients again failed to demonstrate benefit in this population.[140] A meta-analysis[145] supported a lack of efficacy associated with fish oil supplementation in patients with acute respiratory distress syndrome, and a consensus paper summarising current nutritional evidence did not support the administration of pharmaconutrients.[146]

Sedation and mobilisation

There are no direct comparative studies of the optimum choice of sedative or depth of sedation to be obtained in patients with acute respiratory distress syndrome. In general, patients should be lightly sedated, with emphasis on analgesia, and benzodiazepines should be avoided when possible.[147] Early deep sedation in mechanically ventilated patients is associated with increased mortality;[148] by contrast, early mobilisation has been associated with improved outcomes in mechanically ventilated patients with acute respiratory failure.[149]

Controversies and uncertainties

Despite promising preclinical and early clinical data, most large phase 2 and 3 studies of therapeutic interventions in acute respiratory distress syndrome

have failed to demonstrate efficacy. There are many reasons for this failure, but arguably the most important is the limitation of the current definitions of acute respiratory distress syndrome in terms of the identification of patients expressing the biological target under investigation. In approximately half of patients who meet diagnostic criteria and subsequently undergo post-mortem examination, the pathognomonic finding of diffuse alveolar damage is not present.[6–9,13] These patients could have a mixture of coexisting conditions. In most positive trials so far, the improved outcome was a result of less injurious mechanical ventilation in the intervention group. All mechanically ventilated patients are at risk of ventilator-induced lung injury, and thus the limitation of recruiting a heterogeneous cohort based on the definition of acute respiratory distress syndrome is minimised. However, when a therapy aimed at a specific biological target is investigated, such heterogeneity assumes greater importance and reduces the ability to detect any possible effect.

This issue raises the question as to whether the unsuccessful therapeutic trials reported would have had the same results had it been possible to identify specific phenotypes responsive to the therapy under investigation. Constructing a trial in which 50% of the study population does not have the biological target under investigation is problematic and has clear implications for the evidence base for acute respiratory distress syndrome, which has been largely reliant on the American European Consensus Conference and Berlin definitions. In the era of personalised therapy, discovery of a biomarker or panel of biomarkers that can not only identify a specific population, but also, more importantly, define the responsiveness to therapy is essential.[71,72]

Guidelines for the ventilatory management of acute respiratory distress syndrome have been issued by the Scandinavian Society of Anaesthesiology and Intensive Care Medicine[150] and the Brazilian Association of Intensive Care Medicine and the Brazilian Thoracic Society.[151,152] Guidelines from the American Thoracic Society on mechanical ventilation in adults with acute respiratory distress syndrome and from the UK Intensive Care Society on management are in development.

Contributors

RMS and DFM contributed equally to the design, writing, and revision of this Seminar. RMS created the figures.

Declaration of interests

DM reports fees for consultancy from GlaxoSmithKline, Bayer, Peptinnovate, and SOBI. His institution has received funds for his undertaking of 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. RMS declares no competing interests.

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Prolonged glucocorticoid treatment in acute respiratory distress syndrome

We were disappointed that Rob Mac Sweeney and Daniel F McAuley's Seminar (Nov 12, p 2416)[1] on acute respiratory distress syndrome overlooked much of the evidence for prolonged glucocorticoid treatment. The authors reference two outdated meta-analyses[2,3] that have contradictory results. The basis for the inconsistency between these two meta-analyses can be explained and current evidence suggests a net benefit for glucocorticoids in acute respiratory distress syndrome.[4]

In the 1980s, on the basis of a faulty laboratory model, clinical investigations focused on 1 day administration of massive doses of methylprednisolone (120 mg/kg per day) for prevention or treatment of acute respiratory distress syndrome. Unfortunately, these obsolete trials are often combined with contemporary trials in meta-analyses despite serious inconsistencies,[3] producing misleading results. Over the past 20 years, randomised controlled trials have instead investigated low-to-moderate daily doses (methylprednisolone equivalent ≤1 mg/kg for early acute respiratory distress syndrome, or ≤2 mg/kg for late acute respiratory distress syndrome) for 1–4 weeks; meta-analyses should focus on these randomised trials, which are relevant today.

Our systematic review[4] included trial-level and patient-level meta-analyses of eight randomised trials (n=619) investigating prolonged glucocorticoid treatment in patients with acute respiratory distress syndrome. With high certainty, glucocorticoids improved time to extubation (10·1 fewer days, 95% CI −13·1 to −7·1) and mechanical ventilation-free days at day 28 (5·8 more days, 95% CI 3·8 to 11·5), and with moderate certainty reduced in-hospital mortality by 24% (95% CI 2 to 41) for patients randomised before day 14. Importantly, avoiding sudden discontinuation of glucocorticoids after extubation is essential to preserve improvement. These results are consistent with a meta-analysis[5] of 13 randomised trials (n=2005) investigating glucocorticoid treatment in community-acquired pneumonia, which is the leading cause of acute respiratory distress syndrome.

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Authors' reply

G Umberto Meduri and Reed A C Siemieniuk incorrectly suggest our Seminar[1] misinterprets the literature regarding corticosteroids in acute respiratory distress syndrome. Although more recent studies might have refined the research question, older studies still remain the best evidence to address the question such studies originally asked, and so are not outdated. These older studies are the reason high-dose steroids are not used today.

The meta-analysis[2] by Meduri and colleagues pooled individual participant data from four randomised controlled trials. Only 322 patients with acute respiratory distress syndrome were included in the individual participant data meta-analysis. The trials from which these data were obtained suffer heterogeneity in terms of steroid used, dosing, timing, and duration, as well as methodological flaws. A further four randomised trials of steroids in different conditions were included in Meduri and colleagues' meta-analysis, which are less relevant to our Seminar on acute respiratory distress syndrome. The methodological quality of Meduri and colleague's meta-analysis[2] is limited by the absence of an a-priori published protocol. An equally recent meta-analysis[3] of steroids in acute respiratory distress syndrome also found evidence for substantial publication bias. The most recent acute respiratory distress syndrome steroid trial[4]—of which Meduri is a co-author—that found low dose of hydrocortisone did not improve mortality was also not included in Meduri and colleagues' meta-analysis.[2] There is a risk of academic bias with Meduri being the primary author of the meta-analysis,[2] as well as being an author on almost half the randomised controlled trials referenced in the meta-analysis. Independent groups have interpreted the literature differently, with international guidelines[5,6] on acute respiratory distress syndrome published in the past 2 years uniformly recommending against the use of steroids.

Although we accept that existing evidence for steroids in acute respiratory distress syndrome includes the possibility of patient benefit, this remains unproven. A personalised approach to the use of steroids might be more appropriate. Long-term follow-up of survivors to define the potential for harm is also needed. Use of corticosteroids in acute respiratory

distress syndrome should be the subject of an adequately powered multicentre randomised controlled trial with long-term follow-up. Data from ongoing randomised controlled trials (NCT01731795, NCT01757899, and NCT02819453) will help to determine the role of steroids in acute respiratory distress syndrome. As such data become available, we will update the recommendation in our Seminar.[1] For now, the recommendation that steroids should be avoided is appropriate. Steroids might or might not be beneficial in acute respiratory distress syndrome, but the data are insufficient to support their use, regardless of how much one might wish for it to be so.

DFM reports fees for consultancy from GlaxoSmithKline, Bayer, Peptinnovate, Boehringer Ingelheim, and SOBI. His institution has received funds for his undertaking of 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. RMS declares no competing interests.

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Beyond ESPAC-4: better surgery and systemic therapy

We appreciate the commentary on our Article (March 11, p 1011)[1] by Gaël Deplanque and Nicolas Demartines (March 11, p 985)[2] concluding that the ESPAC-4 trial "…clearly establishes the combination of gemcitabine and capecitabine as a new standard of care in the adjuvant setting of pancreatic ductal adenocarcinoma".

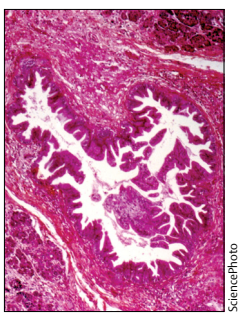
We would caution against the approach taken by Deplanque and Demartines that attempts to interpret the findings in terms of a cure. In our discussion we comment only on the grounds of extending overall survival, which should be the primary outcome worthy of discussion in a condition with such a poor prognosis. Furthermore, it is dangerous to extrapolate cure from measures of relapse-free survival and tumour recurrence from this analysis because it is not possible to predict what will happen to the patients still at risk. Further analyses with longer follow-up are required to get a better estimate of the number of patients who remain alive and disease free after an extended period.

The estimates of the number of patients needed to treat should follow Altman and Andersen's method[3] for time-to-event outcomes that gives an estimate of needing to treat 15 patients with the combination of gemcitabine and capecitabine rather than gemcitabine alone, and not 25 patients, to save one more life. We would also counter the claim that no patients had crossed the 5-year survival boundary. Between Nov 10, 2008, and March 9, 2011, 162 patients were randomised into the trial permitting a minimum follow-up of 5 years in these patients by the time of the data cutoff on March 9, 2016.

We would reiterate the need raised by Deplanque and Demartines to improve not only the number of patients who are suitable for surgery but also to improve the outcomes of patients following surgery. Adjuvant chemotherapy clearly has a place in a condition that was once considered chemoresistant and the data from our ESPAC-4 trial,[1] as from previous ESPAC trials, have shown that patients with better surgical outcomes (typically R0 and N0) are more likely to benefit from adjuvant chemotherapy than from no adjuvant chemotherapy or the more efficacious adjuvant chemotherapy—eg, hazard ratio for death favouring combination adjuvant chemotherapy in ESPAC-4 for R0 was 0·68 (95% CI 0·49–0·93) compared with 0·90 (0·72–1·13) for R1. Not only is more surgery required then, but surgery with better outcomes.[4] The role of neoadjuvant therapy also needs defining notably to increase the overall and R0 and N0 resections.[5]

The primary endpoint was overall survival, measured as the time from randomisation until death from any cause. The median time from surgery to randomisation was 64 days (range 21–111), so the actual estimated survival from the time of surgery is a median of 64 additional days to the estimated median 25·5 months in the gemcitabine group and 28·0 months in the gemcitabine plus capecitabine group.[1]

As Deplanque and Demartines note, fitter patients are more likely to tolerate six cycles of adjuvant chemotherapy, and it has been shown using data from the ESPAC-3 trial[6] that completing all six cycles is an important factor in ensuring that the effect of adjuvant therapy is realised and might mean waiting sometime after 8 weeks after surgery. In the ESPAC-3 trial[6] the estimated median time from surgery to randomisation was 45 days (IQR 29–57) and from randomisation to the start of chemotherapy was 10 days (5–18) for the fluorouracil plus folinic acid group and 8 days (5–14) for the gemcitabine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