Acute respiratory distress syndrome on the intensive care unit

Acute respiratory distress syndrome is a life-threatening condition that is common in critically ill patients. Historically, diagnosis has been difficult and prognosis has been poor, but the Berlin definition and developments in medical therapies provide promise that we can improve outcomes for these patients in the future.

Acute respiratory distress syndrome describes widespread lung injury caused by overwhelming inflammation. The hallmarks of the syndrome include hypoxaemia, ventilation–perfusion (V/Q) mismatch, impaired lung compliance and bilateral infiltrates on chest X-ray (Dushianthan et al, 2011). A swift diagnosis is essential for survival of these patients but remains a clinical challenge. The Berlin definition has helped to clarify the criteria for making a diagnosis of acute respiratory distress syndrome and may serve as an invaluable tool. The management of acute respiratory distress syndrome is largely supportive, and treatment is focused on the initial condition that has led to it. This review appraises the Berlin definition and discusses diagnostic strategies, including the potential value of biomarkers. It also outlines the current management of the condition and future perspectives with regard to medical therapies.

Epidemiology, aetiology and pathogenesis

The reported incidence of acute respiratory distress syndrome varies from 4–58/100 000 per year (Dushianthan et al, 2011). Although it is a rare condition in the general population, it commonly affects critically ill patients and has been estimated to complicate up to 15% of intensive care unit admissions (Frutos-Vivar et al, 2004). Mortality rates may be as high as 44% and in those who do survive there remains a significant burden of physical, psychiatric and cognitive morbidities (Dushianthan et al, 2011).

Acute respiratory distress syndrome may arise from several pulmonary and non-pulmonary causes, summarized in *Table 1*, of which sepsis is undoubtedly the most common. Determining aetiology is important as the course and outcome of acute respiratory distress syndrome will vary accordingly. For example, mortality rates are lower among trauma patients compared to those with a diagnosis of sepsis (Frutos-Vivar et al, 2004). Risk factors for acute respiratory distress syndrome include genetic predisposition, age, Afro-Caribbean ethnicity, chronic alcohol abuse, liver disease, pregnancy, obesity and immunosuppression (Dushianthan et al, 2011).

The pathophysiology underlying acute respiratory distress syndrome is complex and not completely understood. A direct or indirect insult to the lungs is believed to trigger an inflammatory response involving the release of several pro-inflammatory cytokines and activation of neutrophils and alveolar macrophages. This leads to an increase in capillary permeability and necrosis of the alveolar epithelium, the result of which is extensive alveolar oedema and compromised surfactant production. Overall, there is poor lung compliance, alveolar collapse and V/Q mismatch, which manifest clinically as rapidly progressive dyspnoea, tachypnoea and hypoxaemia. The condition can be further exacerbated by fibrosis of the alveoli that occurs after the acute inflammatory phase.

Table 1. Causes of acute respiratory distress syndrome

Pulmonary causes	**Pneumonia**
	Gastric aspiration
	Pulmonary contusion
	Fat emboli
	Near drowning
	Inhalation injury
	Vasculitis
	Reperfusion pulmonary oedema after transplantation or pulmonary embolectomy
Non-pulmonary causes	**Sepsis**
	Severe trauma with shock
	Massive transfusion
	Cardiopulmonary bypass
	Drug overdose
	Acute pancreatitis
	Obstetric events

Most common causes are highlighted in bold. Adapted from Dushianthan et al (2011)

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Definitions

Until recently, both research and clinical assessment for acute respiratory distress syndrome have been hindered by the ambiguity surrounding its definition. Acute respiratory distress syndrome was first described by Ashbaugh et al (1967) as the rapid onset of tachypnoea and hypoxaemia combined with poor lung compliance and bilateral infiltrates on chest X-ray. However, the presentation described is similar to that seen in many other conditions causing 'flash' pulmonary oedema such as acute heart failure and renal artery stenosis. As a result, pulmonary artery catheters have been widely used in the past to aid diagnosis. The pulmonary artery catheter is used to measure pulmonary artery wedge pressure, which should not be raised in acute respiratory distress syndrome, and can thus help to exclude cardiogenic causes of respiratory failure. However, more recently assessment using a pulmonary artery catheter has become less popular since the procedure is highly invasive, results can be difficult to interpret and there is insufficient evidence to suggest that it improves outcomes (Wheeler et al, 2006).

In 1994 the American-European Consensus Conference definition described three diagnostic criteria for acute respiratory distress syndrome (Bernard et al, 1994). These consisted of hypoxaemia (partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2) ratio of <200 mmHg), bilateral infiltrates on chest X-ray and a pulmonary artery wedge pressure ≤18 mmHg. It also defined a milder syndrome with a less severe hypoxaemia called acute lung injury (PaO_2/FiO_2 ratio <300 mmHg). Although this was a significant step forward in developing a clinical definition of acute respiratory distress syndrome, it had several limitations. It did not specify a time frame for acute onset, did not account for the variations in PaO_2/FiO_2 that occur with different ventilator settings and it promoted perhaps unnecessary use of the pulmonary artery catheter. Moreover, although chest X-ray is a cheap and non-invasive investigation, the bilateral infiltrates found in acute respiratory distress syndrome are non-specific and interpretation of the radiograph is highly subjective between clinicians.

The Berlin definition

Given the limitations of previous definitions, it is unsurprising that acute respiratory distress syndrome is believed to remain undiagnosed in 50% of patients (Ferguson et al, 2005). In 2012 an expert panel convened with the objective of forming a feasible, reliable and valid definition of acute respiratory distress syndrome (Ranieri et al, 2012). The resultant Berlin definition is summarized in *Table 2*. Notably, this definition excludes the term acute lung injury and re-classifies the disease as mild, moderate or severe based on the degree of hypoxaemia. Furthermore, it standardizes the ventilator settings at which oxygenation should be measured. A minimum positive end-expiratory pressure of 5 cmH_2O was chosen since above this threshold the PaO_2/FiO_2 ratio correlates most reliably with survival (Ferguson et al, 2012).

Other important features include clarification of the acuity of onset and recognition of chest computed tomography as a more useful diagnostic tool than chest X-ray. Computed tomography images show heterogeneous infiltrates that predominate in gravity-dependent regions of the lung, a highly specific feature of acute respiratory distress syndrome (Dushianthan et al, 2011). The Berlin criteria also do not require the use of a pulmonary artery catheter, since many patients with severe acute respiratory distress syndrome can have elevated pulmonary artery wedge pressure as a result of increased pleural pressures and vigorous fluid resuscitation (Ferguson et al, 2012).

The Berlin definition predicts survival more reliably than the American-European Consensus Conference criteria (Ferguson et al, 2012). Its validity has been further demonstrated by studies correlating its criteria with other well-established surrogates of lung injury. Thille et al (2013) assessed the autopsy results of 712 patients who had been identified as having acute respiratory distress syndrome according to the Berlin definition. Diffuse alveolar damage was seen in 89% of patients and the proportion of patients with diffuse alveolar damage increased with the severity of acute respiratory distress syndrome. The Berlin definition undoubtedly signifies

Table 2. The Berlin definition of acute respiratory distress syndrome

Criteria	1. Onset within 1 week of an established precipitant of lung injury or development of new or worsening respiratory symptoms		
	2. Bilateral shadowing present on chest X-ray or chest computed tomography that is not caused by effusions, lung collapse or nodules		
	3. Respiratory failure secondary to pulmonary oedema that is not caused by congestive cardiac failure or fluid overload. Hydrostatic oedema should be objectively excluded using investigations such as echocardiography in cases where no risk factors for acute respiratory distress syndrome are present		
Severity	Mild	Moderate	Severe
	PaO_2/FiO_2 = 200–300 (and positive end-expiratory pressure or continuous positive airway pressure ≥5 cmH_2O)	PaO_2/FiO_2 = 100–200 (and positive end-expiratory pressure ≥5 cmH_2O)	PaO_2/FiO_2 ≤100 (and positive end-expiratory pressure ≥5 cmH_2O)

Adapted from Ranieri et al (2012)

huge progress in characterizing acute respiratory distress syndrome. However, it was not designed as a prognostication tool and does not include all the clinical features which strongly predict mortality, such as signs of fibrosis on high resolution computed tomography, seen in the early stages of acute respiratory distress syndrome (Barbas et al, 2014).

Future of the Berlin definition

The Berlin definition is still fairly new and further feedback is required from clinicians and researchers in order to fully understand its feasibility and identify practical challenges in its clinical uptake. It is likely that the Berlin definition will evolve over time as our understanding of acute respiratory distress syndrome improves through studies using more carefully selected patient cohorts.

Since the publication of the definition, an observational study found that acute respiratory distress syndrome patients with cor pulmonale had significantly worse outcomes (Boissier et al, 2013). It has therefore been suggested that the Berlin definition includes a new subcategory for these patients as their management may differ from that of typical patients with acute respiratory distress syndrome, requiring pulmonary artery vasodilator therapy and different ventilator strategies.

Additionally, current research into potential biomarkers and genes involved in the disease process may yield better diagnostic and prognostic markers that could be used to enhance the definition.

Additional investigative tools

Bronchoalveolar lavage

Bronchoalveolar lavage is mainly used to identify pathogens and target antibiotic therapy in septic patients. It may also help diagnosis since the lavage fluid typically contains a high proportion of neutrophils (Dushianthan et al, 2011). Bronchoalveolar lavage is generally well tolerated but may transiently worsen hypoxaemia and trigger haemodynamic compromise so is not appropriate in severely unwell patients (Steinberg et al, 1993).

Biomarkers

There has been growing interest in finding a biomarker for acute respiratory distress syndrome which could be used to overcome diagnostic uncertainties, predict outcomes and monitor disease progression. Several inflammatory cytokines, endothelial proteins, epithelial proteins and coagulation factors have been investigated as possible surrogates for the presence of acute respiratory distress syndrome. These include interleukin (IL)-6, IL-8, soluble intercellular adhesion molecule (sICAM)-1, surfactant proteins A, B, C and D, vascular endothelial growth factor, angiopoietin (Ang)-2, heparin-binding protein and von Willebrand factor. However, although many of these demonstrated potential in early studies, none have shown success as diagnostic or prognostication tools on further validation (Binnie et al, 2014).

The most promising evidence to date has been from studies on the endothelial protein Ang-2. Raised levels of Ang-2 are found in patients with acute respiratory distress syndrome and correlate with mortality (Gallagher et al, 2008). However, further study is still needed in order to fully establish the value of Ang-2 in clinical practice. A multicentre trial found that baseline Ang-2 levels were consistently higher in patients with non-infective causes of acute respiratory distress syndrome regardless of outcomes, suggesting that Ang-2 may not be a reliable prognostic tool in certain patients (Calfee et al, 2012).

Challenges in biomarker identification

The lack of success in finding a suitable biomarker of acute respiratory distress syndrome can be explained by a number of factors. The main reason for this is that rather than being a well-defined disease, acute respiratory distress syndrome reflects heterogeneous processes that result in a common injury. Multiple interactions between the pulmonary endothelium, epithelium, interstitium, blood vessels, and inflammatory and coagulation systems mean that there is a plethora of potential factors and signalling molecules to select biomarkers from. Moreover, it has been reported that only half of patients with acute respiratory distress syndrome have diffuse alveolar damage on lung pathology, indicating that the pathological process varies between patients, making the discovery of a single biomarker of the condition improbable (Binnie et al, 2014).

It is more likely that defining a biochemical profile using a combination of several biomarkers will provide a valuable approach to diagnosis. In doing this, there is also the potential to use our knowledge of certain serological patterns to identify subgroups of patients with differing pathophysiology who may benefit from specific treatments. This will be achieved through further work involving biomarker analysis in more specific subgroups of acute respiratory distress syndrome patients. Alternatively, a broader and less labour intensive approach to generate potential markers could be considered by screening for RNA or DNA markers with microarray analysis.

Effectively validating potential biomarkers has also proved to be a major difficulty. A valid biomarker should consistently show high sensitivity and specificity for acute respiratory distress syndrome. Additionally, an ideal biomarker would be able to predict the onset of acute respiratory distress syndrome before it is clinically apparent. Therefore, the biomarker must be validated in all patient populations that are at risk of acute respiratory distress syndrome (including intensive care unit, trauma and obstetric patients) and also in patients who do not have acute respiratory dis-

tress syndrome but are critically ill with hypoxaemia. This can be problematic, as it requires access to large patient cohorts that must be selected with consistent inclusion criteria. The Berlin definition will certainly help to standardize the selection of patients, and including biomarker analysis into large-scale acute respiratory distress syndrome trials may help to attain sufficient numbers (Binnie et al, 2014). Additionally, the validity of the biomarker must also be shown through correlation with a 'gold standard' surrogate for acute respiratory distress syndrome such as pathological findings. However, this is again complicated by the non-uniform pathophysiology of the syndrome.

Management

The management of acute respiratory distress syndrome involves supportive measures, such as ventilation, while the underlying cause of lung injury is treated. Nutritional support, conservative fluid management and prevention of infection, stress ulcers and venous thromboembolism are equally important but will not be discussed in this review.

Ventilation

Most patients with acute respiratory distress syndrome will need to be intubated and mechanically ventilated until the lungs recover from their injury. The aim is to improve oxygen saturations to 88–95% without causing ventilator-induced lung injury. This should be achieved by ventilation using low tidal volumes to avoid barotrauma and atelectasis. Current ventilator practices have been significantly influenced by findings from a large trial by the ARDS Network comparing 'conventional' tidal volume ventilation to low tidal volume ventilation (6 ml/kg) with permissive hypercapnia. The low tidal volume group had a 9% absolute reduction in mortality (Brower et al, 2000). This has been confirmed by subsequent studies that have also indicated that higher tidal volumes are associated with increased release of inflammatory cytokines creating a higher risk of further lung injury (Determann et al, 2010).

The level of positive end-expiratory pressure is also an important factor in ventilated acute respiratory distress syndrome patients. Higher positive end-expiratory pressure can help to correct V/Q mismatch by increasing alveolar recruitment and reducing alveolar collapse. However, high levels of positive end-expiratory pressure are also associated with worse pulmonary oedema and over-distension of the alveoli. Although studies have shown conflicting results, a meta-analysis by Briel et al (2010) concluded that there was a significant reduction in mortality when higher positive end-expiratory pressure was used. The inconsistencies can be explained by the volume of potentially recruitable lung, which varies considerably between patients. Higher positive end-expiratory pressure will benefit patients with large recruitable volumes but is more likely to be damaging in those with smaller volumes or no recruitable lung. Positive end-expiratory pressure levels should therefore be adjusted after assessment of the individual patient. To aid this decision, the ARDS Network has also produced a table on appropriate positive end-expiratory pressure according to patient oxygenation (Briel et al, 2010).

Several alternative ventilation techniques have been assessed in acute respiratory distress syndrome, for which high-frequency oscillatory ventilation has been the most widely practiced. High-frequency oscillatory ventilation uses oscillations in pressure to achieve oxygenation via rapid exchanges of small tidal volumes. It has been shown by previous studies to improve V/Q mismatch and lower the incidence of ventilator-induced lung injury since there is greater lung recruitment with smaller tidal volumes (Chan et al, 2007). However, the higher airway pressures achieved by this technique confer a greater risk of lung hyperinflation, pneumothorax and haemodynamic instability. Two large randomized controlled trials have recently demonstrated that high-frequency oscillatory ventilation does not reduce mortality compared to standard methods of ventilation and should only be used in carefully selected patients (Goffi and Ferguson, 2014).

Recruitment manoeuvres, such as rapid increases in positive end-expiratory pressure and inspiratory holds to improve oxygenation, remain controversial. Although one systematic review showed that oxygenation improved after a manoeuvre, the effect was transient and associated with several complications including cardiovascular compromise and ventilator-induced lung injury (Fan et al, 2008).

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation involves oxygenation of the patient's blood via an external membrane oxygenator, bypassing the need for ventilation and its associated complications. However, it is a complex procedure that is currently only performed in specialist centres as a rescue therapy for patients with unresponsive hypoxaemia. There has been heightened interest in extracorporeal membrane oxygenation, but there remains insufficient evidence to support its universal implementation.

The CESAR trial is the only randomized controlled trial that has been performed for extracorporeal membrane oxygenation in acute respiratory distress syndrome over the last two decades (Peek et al, 2009). It contradicted earlier studies by demonstrating higher survival rates in extracorporeal membrane oxygenation patients by 20% compared to controls that received other 'best practice'. However, the trial did not use a consistent management protocol for the control group and extracorporeal membrane oxygenation was not performed on all the patients in the treatment group, which may account for these findings.

Prone positioning

Prone positioning is believed to improve oxygenation in patients with respiratory failure by minimizing lung compression from the anterior mediastinum and redistributing blood flow to viable areas of lung. Although prone positioning was initially demonstrated to have no impact on mortality, more recent work has suggested that there is a survival benefit in patients diagnosed with severe acute respiratory distress syndrome (Gattinoni et al, 2010). However, given the increased risk of pressure ulcers and tube displacement, it has been suggested that prone positioning should only be considered in patients if there is access to a nursing team with the relevant expertise.

Pharmacological therapies

Despite a large body of work on the subject, pharmacological therapies have a limited role in the treatment of acute respiratory distress syndrome. Neuromuscular blocking agents have shown the most promise in adults so far. They are used to improve patient-ventilator synchrony, leading to reduced work of breathing and lower risk of muscle damage and hyperinflation. Furthermore, there is evidence that neuromuscular blocking agent infusion attenuates the inflammatory response in acute respiratory distress syndrome, protecting against further lung injury (Forel et al, 2006). Although neuromuscular blocking agents improve oxygenation and reduce mortality (Alhazzani et al, 2013), their side effects include longer ventilator weaning and neuromyopathy, which is associated with longer intensive care unit stays and higher mortality. Further studies are required to determine the significance of these risks and whether patients benefit sufficiently from neuromuscular blocking agents to justify them.

Nitric oxide is an endogenous vasodilator that can selectively increase blood flow to ventilated areas of lung when inhaled. Although this improves V/Q mismatch and oxygenation, the latest Cochrane review indicated that its effect in acute respiratory distress syndrome is transient with no overall survival benefit (Afshari et al, 2011). Inhaled nitric oxide may play a role in enhancing the benefit of other treatments such as high-frequency oscillatory ventilation and prone positioning, but further investigation into this is necessary.

Corticosteroids are likely therapeutic candidates for acute respiratory distress syndrome because of their extensive anti-inflammatory effects. However, systematic reviews have not indicated that they have any benefit in prevention or treatment of acute respiratory distress syndrome (Tang et al, 2009). In fact, one phase III trial found that corticosteroid therapy in the late stages of acute respiratory distress syndrome increased mortality (Steinberg et al, 2006).

Despite success in paediatric populations, clinical trials using exogenous surfactant therapy in adult patients have not shown survival benefits (Davidson et al, 2006). This is surprising since endogenous surfactant functions to improve lung compliance, which is significantly reduced in acute respiratory distress syndrome. It has been suggested that negative results from trials are the result of suboptimal dosing, delivery and timing of the treatment. Unlike paediatric respiratory distress syndrome, mortality in acute respiratory distress syndrome is normally related to multi-organ impairment and thus solely targeting lung compliance may be insufficient to impact survival. Evidence exists that patients with acute respiratory distress syndrome caused by pneumonia and aspiration may benefit from surfactant therapy (Taut et al, 2008).

Several other agents have also been evaluated including anticoagulants, ketoconazole, prostanoids and β2-agonists. However, none of these have been found to affect mortality in randomized controlled trials. More recently, statins and angiotensin-converting enzyme inhibitors have been investigated as potential therapies. Statins appear to reduce mortality in critically ill patients, including those with acute respiratory distress syndrome, but randomized controlled trials are needed to fully assess their benefit (De Loecker and Preiser, 2012).

Future perspectives

Stem cell and gene-based therapies are also under investigation. Mesenchymal stem cells have been shown to protect against lung injury in several animal models of acute respiratory distress syndrome but are yet to reach the stages of clinical trials (Wang et al, 2013). Their

KEY POINTS

- Acute respiratory distress syndrome is a serious condition that is common on the intensive care unit and has numerous causes.
- Complex and heterogenous pathological processes underlie the condition but result in a common, non-specific presentation of rapidly progressive respiratory failure.
- The Berlin definition has helped to clarify the clinical definition of acute respiratory distress syndrome and will serve as a useful diagnostic tool. It highlights chest computed tomography, measurement of partial pressure of arterial oxygen to fraction of inspired oxygen ratio and objective exclusion of hydrostatic pulmonary oedema with echocardiography as key diagnostic strategies.
- Biomarkers may, in the future, play a role in aiding the diagnosis and prognostication of acute respiratory distress syndrome. However, it is more likely that this will be in the form of a panel of combined biomarkers rather than a single protein.
- Management is largely supportive and medical treatment centres on addressing the underlying cause. Low tidal volume ventilation with positive end-expiratory pressure improves survival.
- Pharmacological therapies are not currently used for management. Future research focusing on well-characterized patient subsets may yield more promising results.

anti-inflammatory and regenerative properties suggest that they are promising candidates for management of acute respiratory distress syndrome. The potential of gene therapy remains more primitive but is likely to develop as our understanding of the molecular changes underlying the condition evolves. Potential targets currently under study include genes highly expressed by fibroblasts and leukocytes as well as genes involved in cell repair.

Conclusions

Acute respiratory distress syndrome is a serious medical condition that commonly affects critically ill patients. Mortality and morbidity remain high as a result of diagnostic challenges and lack of effective medical treatments. However, development of the Berlin definition provides hope that the outlook for these patients will improve. The definition shows significant promise in aiding diagnosis and improving the quality of therapeutic trials and biomarker studies by allowing more rigorous patient selection. **BJHM**

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