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Acute respiratory distress syndrome

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Key points

- Acute respiratory distress syndrome (ARDS) is commonly encountered in the critical care population and is associated with a high mortality of between 27% and 45%.
- ARDS is diagnosed according to the Berlin definition and is characterized as mild, moderate, or severe depending on the Pa_{O_2}/FI_{O_2} ratio.
- Accepted management strategies include lung protective ventilation with tidal volumes limited to 6 ml kg^{-1}, positive end expiratory pressure increasing in line with oxygen requirement, and prone positioning in severe cases.
- Steroids, statins, inhaled nitric oxide, and high-frequency oscillation ventilation do not have a role in the routine management of adults with ARDS.
- Adverse functional and neuropsychological outcomes are increasingly recognized in long-term ARDS survivors.

Recognition of acute severe hypoxia of non-cardiogenic cause in critically ill patients has been long-standing. In 1967, Ashbaugh *et al.*[1] described a group of patients with 'acute onset of tachypnoea, hypoxaemia and loss of compliance after a variety of stimuli'. Since then further attempts to define, diagnose, and understand the aetiology of this condition have led to considerable advances in management.

With this review, we seek to provide an updated overview of acute respiratory distress syndrome (ARDS), including a revised definition and current evidence-based management.

Definitions and diagnosis

Although a common condition, there have been difficulties agreeing a standardized definition of ARDS. This has resulted in wide variation in the prevalence of ARDS in the literature. The year 1994 saw the acceptance of the American–European Consensus Conference (AECC) definition. This definition was particularly vulnerable to inter-clinician variability in interpretation of radiography, onset, and cardiac status.

To address this, the European Society of Intensive Care Medicine, endorsed by the American Thoracic Society and the Society of Critical Care Medicine, devised the currently used 'Berlin definition' in 2011 (Table 1).[2] This was a consensus definition evaluated using meta-analyses from four multi-centre clinical data sets and three single-centre data sets. It adds the identification of a known risk factor and a positive end-expiratory pressure (PEEP) >5 cm H_2O.

The resulting definition renders obsolete the previously used term acute lung injury (ALI) and instead categorizes ARDS as mild, moderate, or severe based on Pa_{O_2}/FI_{O_2} ratio. It defines acute onset as within 7 days of a known risk factor. Previously, cardiogenic causes were excluded using bedside assessment of left atrial pressures or using pulmonary artery pressures. Echocardiography is now recommended and takes account of those patients with congestive heart failure or left atrial hypertension who develop ARDS. The definition only requires that respiratory failure not be 'fully explained by cardiac failure or fluid overload'.

This definition has been found to have slightly better prediction validity for mortality with an area under the receiver-operating curve of 0.577 [95% confidence interval (CI), 0.561–0.593) *vs* 0.536 (95% CI, 0.520–0.553; $P < 0.001$) for the AECC definition. Cohort observation places mortality rates at 27% for mild ARDS, 32% for moderate, and 45% for severe.

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Of interest, factors widely perceived as clinically useful in the assessment of patients with ARDS such as high PEEP (>10 cm H_2O), static compliance of lungs, radiographic severity, and corrected expired volume >10 l min^{-1} were not predictive of mortality or other clinical outcomes. They were subsequently removed from the first draft of the Berlin definition.

Epidemiology

The reported incidence of ARDS has been affected by the subjectivity within the AECC definition. It has been estimated at 64 cases per 100 000 people.[3] Despite the expected improvements offered by the Berlin definition, it has been acknowledged that ARDS may be overdiagnosed. No gold standard is clinically available to identify true positive ARDS patients. Evidence of diffuse alveolar damage at post-mortem confirms the diagnosis in non-survivors, but biopsy for histology in the critically ill is rarely undertaken. Whilst clinically treating 'false-positive' patients seems unlikely to cause harm, recruitment of inappropriate patients to research trials may confound results.

Aetiology

The potential causes of ARDS are numerous and can be classified as pulmonary (such as pneumonia, pulmonary contusions, etc.) and extra-pulmonary (including burns, trauma, etc.). Pneumonia and non-pulmonary sepsis are the leading causes of ARDS.

It is accepted that there is a wide degree of variability in genetic predisposition to ARDS, but the precise genetic basis for this remains poorly understood.

Pathophysiology

ARDS is the end result of a complex interplay between various inflammatory mediators resulting in diffuse alveolar damage, non-cardiogenic pulmonary oedema, surfactant dysfunction, and atelectasis. The role of angiotensin II has been recognized as being of particular interest because of its ability to induce alveolar apoptosis and fibrosis, highlighting its future research potential.

Three overlapping phases are recognized in the course of the condition. Initially, the exudative (or acute) phase results in hypoxaemia and a reduction in pulmonary compliance owing largely to alveolar flooding with protein-rich fluid. Radiological evidence of infiltrates appears during this phase, which can last for up to a week. The proliferative (or subacute) phase may occur from day 5 onwards with further reduction in lung compliance and continued hypoxaemia owing to fibroproliferation and microvascular thrombus formation. Some patients show rapid clinical improvement at this stage others progress to the fibrotic or chronic phase, characterized by widespread fibrosis and lung remodelling which may be irreversible.

Computed tomography (CT) scans demonstrate the heterogeneity of the disease process, with small areas of relatively unaffected lung with potential for recruitment amongst segments of severely affected lung.

Investigations

ARDS is predominantly a clinical diagnosis, but adequate clinician experience is required to recognize the mimics of the disorder.

Bilateral lung infiltrates on chest radiographs are an early finding. Echocardiography may be used to quantify cardiac function as outlined above.

CT may be particularly useful in patients with an underlying pulmonary cause. However, transferring a patient with ARDS to scan is not without risk and may lead to subsequent increases in ventilatory support (Figs 1 and 2).

Management

Good supportive care and management of the underlying causes of illness is at the heart of the management of all critically unwell patients. We describe those areas where evidence has emerged to guide clinicians more specifically when dealing with ARDS subsequently.

Ventilation strategies

The severity of the condition usually mandates intubation of the trachea via a tracheal tube and mechanical ventilation. Previously, intensive care practitioners attempted to ventilate with high positive pressures until normal gas exchange was achieved. Repetitive, cyclical lung overstretching and collapse generate local and systematic inflammation and contribute to multi-organ failure and death.

Aggressive ventilator goals had a high cost as demonstrated by the ARDSnet group (National Heart, Lung and Blood Institute, National Institutes for Health). The landmark ARMA study[4] compared 'traditional' tidal volumes of 12 ml kg^{-1} of predicted body weight with a plateau pressure of 50 cm H_2O or less with lower tidal volumes of 6 ml kg^{-1} and a plateau pressure of 30 cm H_2O or less. Survival (31% *vs* 39.8%) and ventilator-free days were higher in the lower tidal volume group. Notably, minute ventilation was higher than previous low tidal volume studies and the treatment of acidosis may have contributed to the improved outcomes.

ARDSnet have also investigated the role of PEEP. PEEP is key in preventing the collapse of alveoli, thereby reducing shunt and ventilation/perfusion mismatch. Neither this nor any

Table 1 Berlin definition of acute respiratory distress syndrome (adapted from table 3 of original article 3)[3]

Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms.
Chest imaging*	Bilateral opacities not fully explained by effusions. Lobar/lung collapse or nodules.
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload. Needs objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factor present.
Oxygenation	Mild—26.6 kPa < Pa_{O_2}/FI_{O_2} ≤ 39.9 kPa with PEEP or CPAP ≥ 5 cm H_20 Moderate—13.3 kPa < Pa_{O_2}/FI_{O_2} ≤ 26.6 kPa with PEEP or CPAP ≥ 5 cm H_20. Severe—Pa_{O_2}/FI_{O_2} ≤ 13.3 kPa with PEEP ≥ 5 cm H_2O

*Chest radiograph or computed tomography scan.

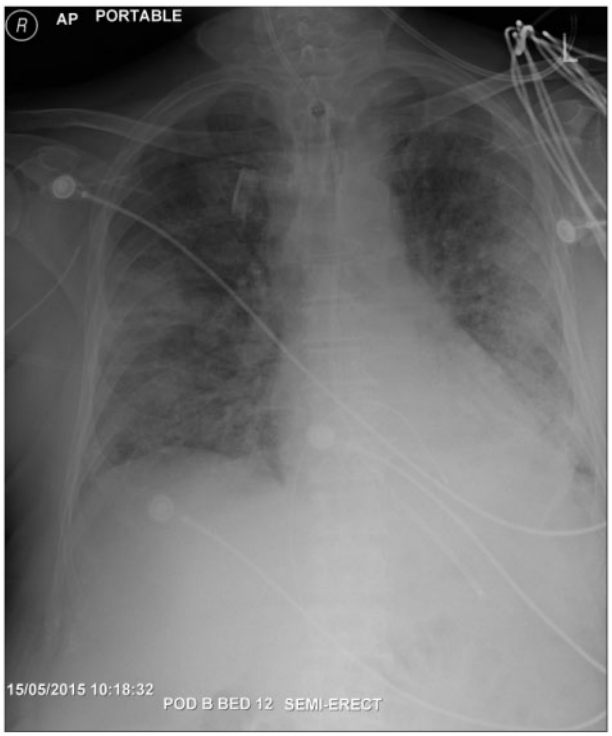

Fig 1 Chest radiograph demonstrating ARDS.

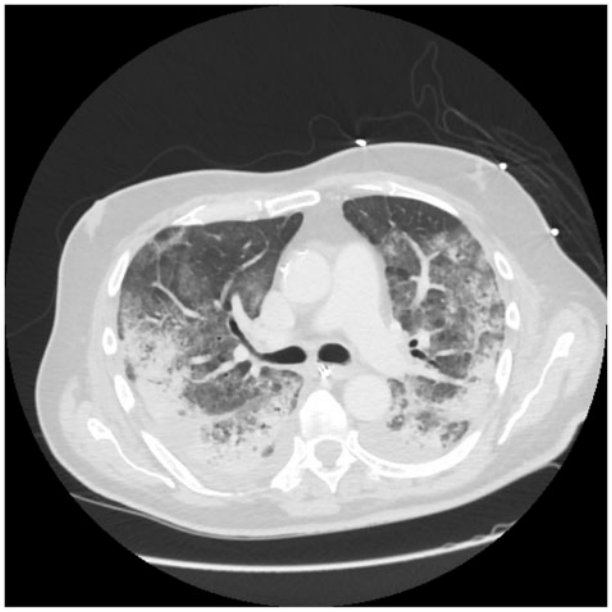

Fig 2 CT scan section demonstrating typical ARDS appearances of heterogenous lungs with relatively small areas of unaffected lung anteriorly in comparison with extensive posterior changes.

subsequent study has identified an optimal level of PEEP. However, ARDSnet recommend increasing PEEP in tandem with increasing FIO_2.

ARDS affects alveoli heterogeneously. Some areas may become stiffer and less easy to expand than more normal, compliant alveoli, which may become over-distended and damaged. Patients with ARDS have a smaller proportion of the lung available for ventilation and lower respiratory system compliance (C_{RS})—the so-called 'baby lung' concept. Delta P is an index that reflects this reduction in functional size of lung by taking into account lung compliance. Also known as the driving pressure, it is defined as tidal volume/respiratory system compliance (V_T/C_{RS}). It can also be defined as inspiratory plateau pressure minus PEEP. A *post hoc* analysis of data from 3562 patients with ARDS in nine previous randomized controlled trials (RCTs) evaluated this as a predictor of outcome.[5] In trials in which tidal volume and PEEP were included as independent variables, decreased delta P was the variable most strongly associated with survival. This suggests that reducing tidal volume in relation to lung compliance rather than in relation to ideal body weight alone could be the key to improving survival in ARDS. Further trials need to investigate whether PEEP increments are actually only protective when the increased PEEP allows the same V_T to be delivered at a lower delta P.

An individualized, stepwise approach to lung recruitment and PEEP selection has been described. This may redistribute the tidal volume and transpulmonary pressures more homogenously, improve overall compliance with an increased functional lung and allow further decrease in delta P without decreasing ventilation.[6] With evidence lacking for optimal PEEP levels, individual assessment of lung mechanics may be appropriate.

In addition to various ventilator strategies, it is sensible for the clinician to consider the basic mechanics of respiration. Every effort should be made to position the patient optimally to avoid extra-pulmonary causes of high ventilator pressures. Assessment for decompression of the distended, high-pressure abdomen with nasogastric drainage or by surgical means should also be considered.

High-frequency oscillation ventilation

Now infrequently used in the adult population, high-frequency oscillation ventilation (HFOV) delivers extremely low V_T (1–2 ml kg^{-1}) at very high rates (3–15 breaths per second). This strategy is based on the theory that low V_Ts and higher PEEP limit ventilator-associated lung injury.

Two major trials have evaluated HFOV. OSCILLATE[7] was a multi-centre, non-blinded RCT. The study was halted early after 548 ARDS patients were randomized to either HFOV or low V_T high PEEP strategies. Unfortunately, the HFOV group displayed an in-hospital mortality of 47% *vs* 35% for the low V_T high PEEP group. Possible confounders were more midazolam, neuromuscular block, vasopressors and higher mean airway pressures in the HFOV group. Higher levels of sedatives and neuromuscular-blocking drugs were also found in HFOV-treated patients in the OSCAR[8] trial. This study used lower airway pressures than OSCILLATE and demonstrated no mortality difference at 1 month. Whether airway pressures are the key to the difference in findings is unclear.

There is therefore no clear indication for the routine use of HFOV in ARDS, but it may be considered in refractory cases where access to extracorporeal membrane oxygenation (ECMO) is limited.

Prone positioning

The underlying principles of reducing ventilation/perfusion mismatching, increasing functional residual capacity, and recruitment of atelectatic lung underpin prone positioning strategy. Despite widespread use, for a considerable period, trials failed to show an impact on patient survival despite

improvement in oxygenation. However, in 2010, Gattinoni *et al.*[9] showed via meta-analysis of four major clinical trials that the absolute mortality of severely hypoxaemic ARDS patients may be reduced by around 10% with prone positioning.

Subsequently, the PROSEVA[10] trial showed an impressive mortality reduction at 28 days with prone ventilation in severe ARDS (16% prone *vs* 32% supine), with a number needed to treat of 6. The practical implications for prone ventilation and complications should be borne in mind. Prone positioning is best attempted in selected severe ARDS patients in a fully equipped, trained unit.

Extracorporal membrane oxygenation

ECMO has a role in both gas exchange and circulatory support. It is a modified cardiopulmonary bypass device used at the bedside for a number of days or weeks.[11] A full discussion of ECMO in practice is beyond the scope of this article. ECMO recently gained a particular role in the management of patients during the H1N1 2009 pandemic. This population largely comprised young patients with respiratory failure due to a non-necrotizing viral pneumonia with little co-morbid disease. CESAR[12] aimed to study conventional ventilation compared with randomization to ECMO for treatment of ARDS but was flawed in a number of ways, including lack of safety analysis of ECMO, lack of standardized ARDSnet recommended care, and the confounding factor of transferral to a tertiary centre for those randomized to ECMO. As such, their finding of improved survival with ECMO is difficult to interpret.

Other strategies

Fluid management

Given the increased pulmonary capillary permeability found in ARDS, excessive administration of fluid has been found to be deleterious to gas exchange. A conservative fluid management approach was compared with a liberal strategy in the Fluids and Catheters Treatment Trial (FACTT).[13] Reassuringly, no increased risk of renal failure was identified in the conservative fluid management arm. Although no mortality benefit was found, duration of ventilation and length of stay were reduced.

There is increasing interest in human albumin in the critical illness population and in particular in those with ARDS. A systematic review of RCTs studying ARDS patients and albumin use was conducted by Uhlig *et al.*[14] work, which involved a relatively small sample size, showed that albumin treatment improved oxygenation in the first 2 days and after 7 days compared with crystalloid therapy; however, this did not translate into a mortality difference. Postulations around changes in lung structure and function may explain the findings, but extensive research is required here to increase our understanding of the interplay between fluids and lung pathology. Previously, some research has indicated favourable physiological changes when albumin is given in combination with furosemide to ARDS patients with low serum albumin levels.[15] No significant adverse events occurred with treatment but improved oxygenation, weight loss, and normalization of serum protein levels were achieved. No direct impact of ventilator time or survival was identified. Without strong evidence dictating how this is achieved, there is increasingly a move to a negative fluid balance approach, which also aims to address low colloid oncotic pressure.

Nutrition

In critical illness, nutrition is a key part of treatment. Optimal feeding in ARDS has not been delineated. The EDEN[16] trial failed to establish a difference between standard full enteral feed and trophic feed in terms of the number of ventilator-free days or in survivor outcomes at 6 and 12 months.

Pharmacotherapy

Steroids

Pharmacological means of reducing the inflammatory processes known to occur in ARDS have been examined. Interesting results emerged from the Meduri[17] trial of low-dose methylprednisolone in early ARDS. Numbers were small (91 patients) and the placebo group had more patients with catecholamine-dependent shock, rendering the reduction in ventilator days less significant. The LaSRS[18] trial examined late rescue steroids for ARDS. This study reported an increase in ventilator- and ICU-free days but no improvement in mortality. In fact, those with persistent ARDS had higher mortality rates with a number needed to harm of 4. Therefore, steroids have not reliably shown improvement in hospital mortality and are not recommended for routine use.

Nitric oxide

Whilst inhaled nitric oxide (iNO) has been used historically, evidence of its efficacy is lacking. A meta-analysis of 12 RCTs totalling 1237 patients showed that despite improved oxygenation at 24 h, no mortality benefit was gained and found a possible link to other sequelae such as increased renal dysfunction. A new understanding that iNO may have complex systemic effects means that without clear mortality benefit in ARDS it has no role in current treatment.[19]

Other drug therapies

Statins have been considered for use in the treatment of ARDS because of their anti-inflammatory and immune-modulating effects, but unfortunately trial data for both rosuvastatin and simvastatin have been disappointing. Similarly ketoconazole has been investigated because of its anti-inflammatory properties, but no improvement in mortality or other end points could be demonstrated. Consequently the existing evidence does not support the use of these drugs.

Prognosis

Studies on the long-term outcomes of ARDS survivors are limited, but reductions in functional outcomes are increasingly recognized. In one study, examining 109 ARDS survivors, the 6-minute walking distances at 1, 3, and 5 years were 66, 67, and 76% of predicted values, respectively. None of the patients in this relatively young cohort had returned to normal function within the 5-year follow-up.[20]

Significant cognitive and psychiatric sequelae are also recognized in survivors as is persistent cognitive impairment in the longer term.

Conclusion

There has been a relatively recent change in the definition of ARDS, categorizing it as mild, moderate, or severe and based on Pa_{O_2}/FI_{O_2} ratio. There is a 45% mortality for severe ARDS and treatment is focused on preventing further lung damage with

attention paid to lower V_Ts, lower plateau ventilator pressures, and the use of PEEP. Prone positioning and ECMO may have a role in treating some patients along with attention to fluid management, but there is no role for routine use of steroids, statins, iNO, and HFOV.

Declaration of interest

None declared.

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MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at https://academic.oup.com/bjaed/pages/Podcasts.

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