Acute respiratory distress syndrome

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Abstract

Acute respiratory distress syndrome (ARDS) is a devastating clinical condition characterized by poor gas exchange and bilateral interstitial opacification demonstrated on chest imaging. Despite years of research, the mortality associated with ARDS remains high. Early recognition and treatment of the underlying cause, combined with strategies to reduce ventilator-induced lung injury are key to optimising the likelihood of survival. This article will provide an update on the most recent evidence base on clinical practice, including the use of acute severe respiratory failure bundles and extracorporeal techniques to support lung protective ventilation.

Keywords Acute respiratory distress syndrome; ARDS; ECMO; extracorporeal life support; hypoxia; intensive care; lung protection; ventilation

Royal College of Anaesthetists CPD Matrix: 2C02, 2C04

Learning objectives

After reading this article, you should be able to:

- define acute respiratory distress syndrome (ARDS) using the Berlin Criteria
- list the aetiological factors associated with the development of ARDS
- list the investigations that should be considered when a diagnosis of ARDS is suspected
- outline the supportive management strategies that are utilised to treat ARDS

Introduction

Acute respiratory distress syndrome (ARDS) is represented by an acute deterioration in gas exchange associated with alveolar inflammation, increased pulmonary vascular permeability and oedema, in the context of normal cardiac function.[1] A wide variety of disease processes can cause ARDS. Since ARDS often presents in partnership with multi-organ failure it is one of the most common disease processes that is presented to the Intensivist.

Recognizing the underlying cause of ARDS and multi-organ failure is paramount. Despite early recognition and treatment, the inflammatory state driving ARDS and impairing oxygenation can persist, leading to difficulty in providing mechanical ventilation. In this situation it is important to minimize further lung injury by ensuring lung protective ventilation is delivered. As Intensivists, we now accept that the role of mechanical ventilation in ARDS is not to provide 'normal' gas exchange but to ensure gas exchange is 'safe'.

Following the influenza A H1N1 pandemic in 2009/10 a UK expert working group developed national recommendations on the standardized management of severe refractory hypoxic respiratory failure. The adoption of an acute severe respiratory failure bundle by critical care units ensures that patients with ARDS receive standardised, high quality care that is aligned to the most recent evidence base.

Definition

Epidemiological quantification of ARDS is challenging owing to the heterogeneous nature of this multi-faceted condition. In an attempt to address this, the American European Consensus Conference definition was introduced in 1994. This was the first international consensus that allowed diagnostic standardisation and improved quantification of ARDS. This was revised in 2012 and formalised as the Berlin Definition. At the time of writing, the Berlin Definition is the current consensus definition which takes into consideration oxygenation, timing, chest imaging and origin of pulmonary oedema. The Berlin Definition also describes a spectrum of severity according to the PaO_2/FiO_2 ratio (Table 1). In order to satisfy a diagnosis of ARDS the following criteria must be met:

- PaO_2/FiO_2 ratio <39 kPa (despite the application of a positive end expiratory pressure greater than 5 cmH_2O)
- pulmonary oedema not explained by cardiac failure
- bilateral opacification on chest imaging and
- occurring within 1 week of clinical insult.

Aetiology

ARDS is thought to occur as a result of an initial physiological insult which can either be pulmonary or non-pulmonary. The most common cause of ARDS is pneumonia. Trauma, sepsis, aspiration, inhalational injury, pancreatitis and burns are other common causes of ARDS frequently seen in our critical care cohort (Table 2).

Following the initial respiratory insult, the progression of ARDS is thought to be commonly exacerbated by inappropriate ventilation resulting in volutrauma, barotrauma and atelectrauma (Table 3).

Pathogenesis

Essentially ARDS occurs as a result of an inflammatory response affecting the alveoli. This inflammation leads to a reduction in the surface area available for effective gas exchange resulting in

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The Berlin Definition of acute respiratory distress syndrome

Criteria	Description
Timing	Acute hypoxaemia within 1 week of clinical insult
Chest imaging	Bilateral opacification on chest imaging (CT or CXR)
Origin	Respiratory failure not fully explained by cardiac failure or fluid overload
Oxygenation: mild ARDS	$PaO_2/FiO_2 < 300$ mmHg (<39 kPa) with the application of at least 5 cmH_20 of positive end expiratory pressure
Oxygenation: moderate ARDS	$PaO_2/FiO_2 < 200$ mmHg (<26.7 kPa) with the application of at least 5 cmH_20 of positive end expiratory pressure
Oxygenation: severe ARDS	$PaO_2/FiO_2 < 100$ mmHg (<13.3 kPa) with the application of at least 5 cmH_2O of positive end expiratory pressure

Table 1

Aetiology of acute respiratory distress syndrome

Pulmonary	Pneumonia
	Aspiration
	Inhalational injury
	Pulmonary contusions/direct chest trauma
	Near-drowning
	Pulmonary vasculitis
Non-Pulmonary	Trauma
	Sepsis
	Burns
	Pancreatitis
	Fat embolism
	Cardiopulmonary bypass
	Transfusion-related lung injury (TRALI)

Table 2

Mechanisms of ventilator-induced lung injury

Volutrauma	Excessive lung stretch as a result of inappropriately high tidal volumes.
Barotrauma	Excessive alveolar pressure as a result of inappropriate ventilator setting or poor respiratory compliance.
Atelectrauma	Repetitive opening/closure of alveoli, generally as a result of inadequate positive end-expiratory pressure leading to alveolar damage.
Biotrauma	Systemic inflammation leading to increased capillary leak and alveolar damage.

Table 3

hypoxaemia. This alveolar inflammation is described in three classical phases:

- exudative phase
- proliferative phase
- fibrotic phase.[1]

In the initial exudative phase there is immune mediated destruction of the alveolar-capillary unit. This allows the entry of plasma, plasma proteins and white cells (predominantly neutrophils) into the lung interstitial tissue and alveoli, much like any other inflammatory process. The alveoli become overwhelmed with inflammatory exudate leading to a dramatic reduction in ventilation/perfusion matching. This ventilation/perfusion mismatch can lead to acute pulmonary hypertension, which in severe cases can cause right heart failure. This can be devastating, especially given that the introduction of mechanical ventilation and anaesthesia in the context of pulmonary hypertension and right heart failure can cause cardiovascular collapse. The significance of right heart failure in ARDS is an evolving area of research.

Again, much like any other inflammatory process, following the exudative phase of inflammation there is an attempt at cellular recovery. This marks the start of the proliferative phase of ARDS. In this phase, type II alveolar cells differentiate into type I alveolar cells. There is a return of alveolar capillary integrity and function leading to the clearance of exudative fluid.

In the fibrotic stage there is deposition of collagen which leads to chronic changes in the alveolar composition. This leads to a chronic reduction in the ability for gas exchange. The development of this fibrotic stage is inconsistent, is difficult to predict and may have a genetic component to its development. Ultimately, affected patients may be left with chronic respiratory impairment.

Investigations

As with any patient admitted to critical care with respiratory failure, arterial blood gas (ABG) measurement and a chest X-ray (CXR) should be performed. ABG measurement will allow quantification of the severity of ARDS by calculation of the PaO_2/FiO_2 ratio and CXR is essential to facilitate the diagnosis of bilateral disease.

In addition to these an additional sequence of tests should be performed including:

- Blood borne virus screen including HIV testing. Any patient admitted with severe respiratory failure triggers a requirement to test for blood borne viruses. This is essential as a positive diagnosis of a blood borne virus will change the threshold for performing more invasive investigations such as broncho-alveolar lavage.
- Community-acquired pneumonia screen including endotracheal aspirates for culture and sensitivity, urine legionella antigen testing and serum pneumococcus.
- CT imaging of the chest is helpful to demonstrate the underlying lung architecture and quantify disease severity. Specifically, a CTPA scan can ensure that pulmonary embolism has been excluded as cause of hypoxia. Additionally a high resolution CT scan can provide more detailed

information particularly when auto-immune conditions and interstitial lung disease form part of the differential.
- Autoimmune screen including serum ANA, ANCA, ESR and complement levels. If there is the suspicion of an auto immune process then additional targeted auto-antibody measurement such as anti-GBM antibody should be considered.
- Echocardiogram to exclude a cardiogenic component and to determine the severity of pulmonary hypertension and right heart failure.
- Broncho-alveolar lavage can be considered to obtain deep respiratory sampling in cases where the underlying diagnosis is uncertain. This can be helpful if an atypical disease process such as *Pneumocystis jirovecii* pneumonia (PCP) is suspected.

Patients who progress to requiring extracorporeal life support (ECLS) will also need a CT scan of brain to exclude intra-cerebral haemorrhage as the provision of ECLS relies on the use of anti-coagulation. It is possible to provide ECLS without anti-coagulation however this is not routine.

A Murray Score should be calculated in all patients with severe ARDS as this will further quantify severity and determine whether ECLS is indicated (Table 4). The Murray score is calculated by adding together all four composite scores then dividing that by four. Suitable patients with a Murray score of two or more should be considered for referral to an ECLS centre.

Management

Although the mainstay of management is mechanical ventilation, ARDS can occur in non-ventilated patients. The use of nasal high-flow humidified oxygen therapy and non-invasive ventilation is possible to support oxygenation in patients with ARDS. However, as ARDS is commonly associated with severe illness and multi-organ failure, it is more common-place for patients with ARDS to require invasive mechanical ventilation.

The care of patients with ARDS might include[1]:
- identification and treatment of the underlying cause
- lung protective ventilation
- positive end-expiratory pressure and alveolar recruitment
- attention to fluid balance
- consideration of steroid therapy
- neuro-muscular blockade
- prone position ventilation
- additional supportive measures
- extracorporeal life support.

Treatment of underlying cause

The most common cause of ARDS is pneumonia therefore initial treatment of ARDS should include broad spectrum antibiotics as per hospital protocol for severe community acquired pneumonia. Anti-viral therapy such as oseltamivir should be considered if influenza is a suspected precipitant.

Lung protection ventilation

The goal of ARDS management is to avoid secondary ventilator-induced lung injury as described previously. In the landmark ARMA study by the Acute Respiratory Distress Syndrome Clinical Trials Network (ARDSnet) group, patients were matched to receive either high (12 ml/kg ideal body weight) tidal volumes with a maximum plateau pressure of 50 cmH_2O or low (6 ml/kg ideal body weight) tidal volumes with a maximum plateau pressure of 30 cmH_2O.[2] The ARDSnet trial demonstrated a sizable and statistically significant mortality reduction in the low tidal volume group. This has led to the development of 'lung protective ventilation' being the gold standard ventilation strategy when providing mandatory ventilation in patients with ARDS. It is standard practice to accept safe ventilation rather than normalize gas exchange. Therefore, titrating ventilation to achieve a $PaO_2 > 8$ kPa is recommended. In addition, permissive hypercapnia is tolerated except in patients where neuro-protection needs prioritised.

Positive end-expiratory pressure (PEEP) and alveolar recruitment

PEEP maintains alveolar recruitment and thus maximizes the surface area available for gas exchange. The application of PEEP also prevents atelectrauma, improves lung compliance, maintains functional residual capacity and improves ventilation-perfusion matching. The evidence base supporting the application in ARDS is evolving. A meta-analysis of three randomised controlled trials (RCTs) demonstrated a survival benefit for patients with moderate or severe ARDS when a PEEP of 13 cmH2O was compared to a PEEP of 8 cmH_2O.[3] In a recently published study assessing lung recruitment and titrated PEEP however, application of PEEP at 16 cmH_20 in conjunction with a recruitment manoeuvre led to a worse outcome than routine PEEP target of 12 cmH_2O.[4] It may thus be that moderate levels of PEEP should be the routine target but that individual patients require appropriate titration towards safe gas exchange.

Airway pressure release ventilation (APRV), is essentially ventilation with an inverse I:E ratio, providing high levels of PEEP throughout the ventilator cycle. This makes physiological sense; in the bilevel APRV study a benefit in oxygenation,

Murray score

Parameter/Score	0	1	2	3	4
PaO_2/FiO_2	>/ = 40 kPa	30–39.9 kPa	23–29.9 kPa	13–22.9	<13
CXR	Normal	1 point for each CXR quadrant affected by consolidation.			
PEEP	<5	6–8	9–11	12–14	>15
Compliance (ml/cmH_2O)	>80	60–79	40–59	20–39	<20

Table 4

pulmonary compliance and mortality was described with the application of early APRV compared to standard lung protection ventilation.[5] Routine use of APRV cannot at present be recommended, as this was a single centre study and APRV has numerous potential side effects which include haemodynamic collapse as a result of reduced venous return or acute cor pulmonale and alveolar rupture leading to subcutaneous emphysema, pneumomediastinum and pneumothorax. A multi-centre APRV study is required.

The use of oesophageal pressure monitoring as a surrogate for pleural pressure can be used to titrate PEEP. Using this targeted approach, PEEP is adjusted to minimised the transpulmonary pressure gradient which is thought to be a significant factor in the development of ARDS. However, a recent trial demonstrated no clear benefit over standard management.[6]

High-frequency oscillatory ventilation (HFOV) historically provided the ultimate open lung strategy. Following the OSCAR and OSCILLATE studies, the use of HFOV can no longer be recommended. These were both large multi-centre randomised control trials which revealed no survival advantage. Furthermore, the OSCILLATE trial demonstrated an increase in mortality associated with HFOV.

Fluid balance

Fluid management in patients with ARDS is problematic. Patients with multi-organ failure invariably end up with a positive fluid balance, particularly in the early phase of their ICU admission. However, strict fluid balance aiming towards a neutral to negative balance is a vital part of improving oxygenation in patients with ARDS. The pathophysiology of ARDS is non-cardiogenic pulmonary oedema as a result of capillary dysfunction. Therefore, ensuring a negative balance and thus reducing capillary hydrostatic pressure makes physiological sense. In the National Institute of Health (NIH) ARDSnet FACTT study (Fluid and Catheter Therapy Trial) a conservative fluid strategy was compared with a liberal fluid strategy. The FACTT study did not demonstrate a mortality benefit; however, it did describe improved lung function and reduced ICU stay. It is therefore recommended that patients with ARDS should be managed with a relatively conservative fluid balance aiming for an overall neutral balance by day seven.

Steroid therapy

Corticosteroid therapy was initially described in an attempt to minimised alveolar inflammation and thus improve gas exchange. It has also been hypothesized that the use of corticosteroids could minimize late fibro-proliferative disease and potentially fibrosis. The evidence base regarding early low dose steroids (1−2 mg/kg methylprednisolone) may demonstrate a survival benefit; however, late steroid use has consistently failed to demonstrate a survival benefit and in some studies has revealed harm. Thus, use of steroids in the management of ARDS cannot be universally recommended. Various respiratory conditions which may mimic ARDS are associated with improved outcomes when managed with corticosteroids. Conditions such as vasculitis, steroid-responsive interstitial lung diseases and *P. jirovecii* may benefit from primary or adjunctive use of steroids. In such circumstances liaison with specialists is recommended. Steroids should be avoided in cases of viral pneumonitis.

Prone position ventilation

Adopting prone position ventilation aims to improve ventilation-perfusion matching, recruitment of dorsal lung units, reduced mediastinal lung compression and facilitate improved sputum clearance. A recent randomised controlled trial − Prone Positioning in Severe Acute Respiratory Distress Syndrome (PROSEVA) − demonstrated improved oxygenation in patients who received early prone ventilation sessions[7] with an associated mortality benefit. Until this point existing literature demonstrated improved oxygenation without a mortality benefit. In this study all centres had significant experience in delivering prone ventilation. Prone ventilation was also found to be a low-risk intervention. It is worth noting that the study was conducted during an influenza H1N1 pandemic which may have supported the positive results of the trial. We would recommend early prone ventilation sessions in patients with severe ARDS as a low-risk strategy to improve ventilation. It is essential that critical care staff receive regular training in moving patients to a prone position and providing ongoing nursing support to minimised the risk of pressure injuries.

Neuromuscular blockade

Neuromuscular blocking drugs provide optimal ventilator synchrony, reduce peak airway pressures, reduce oxygen consumption and improve pulmonary compliance. The use of neuromuscular blocking drugs, particularly for long periods of time, is thought to increase the risk of awareness, haemodynamic instability and ICU-acquired weakness. In 2010, a large trial demonstrated improved oxygenation and a survival advantage for patients with severe ARDS managed with early neuromuscular blockade (NMB) via a cis-atracurium infusion.[8] This led to the acceptance of NMB as a standard of care in the management of patients with severe ARDS. Very recently however, the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) was discontinued early as a result of futility. This may lead to changes in practice in the future with a more nuanced approach to the use of such drugs.

Additional supportive measures

As with any other critically unwell patient, ARDS management should consist of high quality supportive management including sedation, delivery of appropriate nutrition, stress ulcer prevention and venous thromboembolism prophylaxis. Malnutrition should be avoided though it is worth noting that the EDEN (Early Versus Delayed Enteral Feeding to Treat People With Acute Lung Injury or Acute Respiratory Distress Syndrome) investigators found no difference in outcome as a result of early nutritional support. Physiotherapists should be involved in order to help prevent mucous plugging and atelectasis, and to provide active and passive limb movements which thus reduce muscle deconditioning and support early mobilisation and rehabilitation. Unless neuromuscular blocking drugs are being administered, sedation should be delivered at the lowest level to allow safe care using analgesic agents in preference to hypnotic agents.

Extracorporeal life support

Extracorporeal life support (ECLS) includes the use of extracorporeal membrane oxygenation (ECMO) or extracorporeal carbon dioxide removal (ECCOR). The use of ECLS is traditionally thought

of as a rescue therapy for refractory hypoxaemia despite mechanical ventilation. However, the use of ECLS to facilitate ultra-low tidal volumes, allow a reduction in mean airway pressures and provide further protection from ventilator-induced lung injury is currently under research. Despite the perceived benefits and potential of ECLS, the corresponding evidence base is inconsistent. In a landmark study, 180 patients with severe ARDS were randomised to receive either standard management or referral to a tertiary centre for consideration of ECMO.[9] In the tertiary referral group survival was 16% higher than the control group. There was unfortunately a lack of standardisation in the control group and in the intervention group not all patients received ECMO. This study most likely confirmed the benefit of applying a standardised package of care for patients with severe ARDS rather than demonstrate evidence to support ECMO per se. Two observational studies have demonstrated a survival advantage for the use of ECMO during the influenza H1N1 outbreak.[10] The application of ECLS shows promise in this population, since patients with severe influenza should be expected to have a good recovery providing they survive acute hypoxia.

On current evidence the use of ECLS should be considered early in patients with ARDS and on a case by case basis. ECMO as a rescue therapy for the dying patient with ARDS is unlikely to lead to a positive outcome.

Summary

ARDS is a multi-faceted condition and is a common reason for admission to critical care. Despite evolving clinical practice and significant research mortality remains high with no curative agent identified. The only measures that have consistently improved survival are steps to minimise further harm such as ventilator-induced lung injury. The use of an acute severe respiratory failure bundle of care is strongly recommended. ECLS demonstrates promise in a selected groups of patients. However, this is an expensive, labour-intensive resource with a significant side effect profile. With evolving research and improved technology this may become an increasingly more viable option. ◆

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