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Acute Respiratory Distress Syndrome

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Background

Acute respiratory distress syndrome (ARDS) is a significant cause of ICU-related morbidity and mortality. The recent LUNGSAFE global epidemiological study identified a prevalence of ARDS of 10.4% of ICU admissions and an estimated in-hospital mortality of 40% (Bellani et al., 2016). ARDS has been shown to be associated with enduring morbidity for survivors, including reduced exercise tolerance and physical quality of life, as well as psychological and emotional burden for survivors and their caregivers, and economic impact including increased disability and inability to return to employment (Herridge et al., 2011). It can therefore be argued that ARDS presents a significant global public health problem, and improvements in its recognition and management are a priority.

Definition

The definition of ARDS has changed over the decades. Ashbaugh and colleagues first described acute respiratory distress in adults in 1967 (Ashbaugh et al., 1967). The currently used Berlin definition bore out of a need for an improvement on the pre-existing American European Consensus Conference definition, published in 1994, due to inter-clinician variability in applying the definition criteria (Bernard et al., 1994). The Berlin definition, endorsed by the American Thoracic Society and the Society of Critical Care Medicine, was published in 2012 and is the result of a consensus reached by the European Society of Intensive Care Medicine (see **Table 1**) (Ranieri et al., 2012).

Table 1 Berlin definition of ARDS.

Criterion	*Berlin 2012 Definition*
Onset	New or worsening respiratory impairment within 7 days of clinical insult
Oxygenation	Mild: PaO2/FiO2 200–300 mmHg with PEEP $\geq$5 cmH_2O
	Moderate: PaO2/FiO2 100–199 mmHg with PEEP $\geq$5 cmH_2O
	Severe: PaO2/FiO2 $<$ 100 mmHg with PEEP$\geq$5 cmH2O
Imaging	Bilateral infiltrates over $\geq$2 quadrants on a frontal chest X-ray or CT
Origin of oedema	LVF or fluid overload insufficient to fully explain respiratory failure (need objective assessment, e.g., echocardiography)

PaO2, partial pressure of arterial oxygen; FiO2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; CT, computed tomography; LVF, left ventricular failure.

Etiology

The etiology of ARDS can be broadly divided in to pulmonary and extra-pulmonary causes (see **Table 2**). Pneumonia and non-pulmonary sepsis are the commonest causes of ARDS, accounting for 59.4% and 16% of cases globally in the LUNGSAFE study (Bellani et al., 2016).

Genetics

The study of genomics in ARDS is inherently challenging and complex. Due to the heterogeneity of the syndrome and associated host-pathogen interactions there is unlikely to be one gene critical to the pathogenesis of ARDS which could be studied further, for example in a mouse knockout model. There is currently no biomarker for ARDS, and it is under-recognized by clinicians, adding to the challenge of the use of genome-wide association studies. Since 2000 over 100 genes have been identified that are associated with risk of developing ARDS or outcome. Early genomic studies focussed on a candidate gene approach, where a gene and its genetic variant were selected based on pre-existing scientific knowledge and assumed implication in development of ARDS. Two genes identified in this way include a variant of the genes encoding angiotensin converting enzyme (*ACE*) and surfactant protein B (*SFTPB*) (Reilly et al., 2017). Ongoing genetics research could identify subgroups of patients likely to benefit from targeted therapies, thereby achieving the goal of precision medicine in ARDS.

Phenotypes in ARDS

Latent class analysis of study populations has identified subphenotypes of ARDS. The first of these studies used data from the National Heart, Lung, and Blood Institute—(NHLBI) sponsored ARDS Network in the US. The cohorts of the ARMA and ALVEOLI trials were studied, with two phenotypes of ARDS identified. Phenotype 1 was found to be associated with reduced 90-day mortality, and more days free from mechanical ventilation and multi-organ failure than phenotype 2. Further study of clinical and biological markers revealed that patients with phenotype 2 were more likely to be on vasopressors at baseline, more likely to have sepsis-associated ARDS, have a higher heart rate and minute ventilation, lower systolic blood pressure, have higher plasma concentrations of IL-6, IL-8, soluble TNF receptor-1, plasminogen activator inhibitor 1, and lower plasma concentrations of bicarbonate and protein C. The opposite was found for phenotype 1. Phenotype 1 is also referred to as a hypoinflammatory phenotype, and type 2 as hyperinflammatory ARDS.

The hyperinflammatory subphenotype had a significantly different response to PEEP in the ALVEOLI trial and to fluid management strategy in the FACTT trial as compared to the hypoinflammatory subphenotype (Calfee et al., 2014; Famous et al., 2017). Latent class analysis was applied to a UK and Ireland cohort of patients with ARDS in the HARP-2 trial. Two subphenotypes were identified with clinical and biological characteristics similar to those seen in the US cohorts and identified a significant survival benefit in patients with hyperinflammatory subphenotype of ARDS treated with simvastatin as compared to placebo (Calfee et al., 2018).

Table 2 Common causes of ARDS.

Pulmonary	*Extra-pulmonary*
Pneumonia—community-acquired; nosocomial (including VAP)	Non-pulmonary sepsis
Aspiration of gastric contents	Trauma
Pulmonary contusions	Burns
Fat embolism (e.g., after long bone fractures)	Pancreatitis
TRALI	Cardiopulmonary bypass
Inhalation injury	Drug overdose
	Near-drowning

VAP, ventilator-associated pneumonia; TRALI, transfusion-related acute lung injury.

Pathogenesis

The pathophysiology of ARDS can be thought of in three main overlapping phases: exudative, proliferative, and fibrotic (see Fig. 1). In the exudative phase there is accumulation of protein- and cell-rich fluid in the alveoli and interstitium. The integrity of the alveolar epithelial-interstitial-endothelial barrier is disrupted, resulting in flooding of the lungs with plasma, plasma proteins and innate immune cells, namely neutrophils, macrophages and platelets. The activated neutrophils and macrophages secrete chemokines, further driving inflammation. There is also loss of ion channels in the plasma membranes of alveolar epithelial cells, impairing maintenance of the usual osmotic forces. The exudate causes impairment, and subsequently loss, of surfactant production by type 2 alveolar cells, and ultimately a fall in pulmonary compliance. Alveolar endothelial cells upregulate the synthesis of tissue factor. This, in combination with a reduction in plasma concentrations of proteins C and S, causes thrombosis of pulmonary capillaries and deposition of fibrin in the extravascular compartment. This can progress to pulmonary hypertension, increasing right ventricular (RV) afterload and potentially causing RV failure. The protective effects of hypoxic pulmonary vasoconstriction are lost, leading to ventilation and perfusion mismatch and refractory hypoxia.

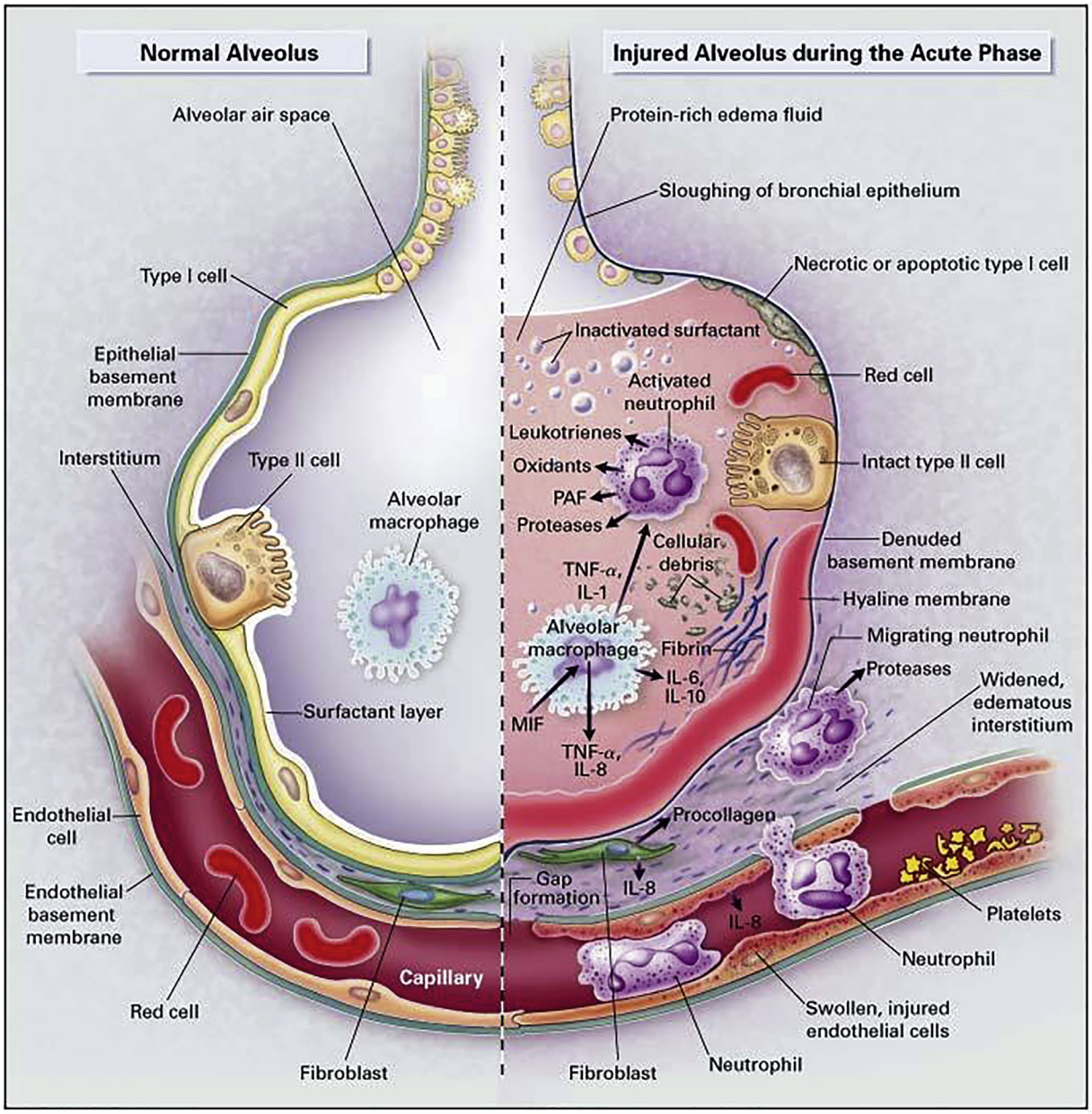

Fig. 1 Pathophysiology of ARDS in the alveolus. On the left, normal alveolus; on the right, the injured alveolus in the acute phase. From Ware LB and Matthay M (2000) The acute respiratory distress syndrome. *The New England Journal of Medicine 342*: 1334–49. With kind permission of the Massachusetts Medical Society.

The proliferative phase follows, which represents gradual recovery of the lungs. Epithelial growth factors, e.g., FGF-7 (a keratinocyte growth factor), stimulate proliferation of type 2 alveolar cells (Proudfoot et al., 2011). Type 2 cells are also progenitors for type 1 alveolar cells and some differentiate into these, leading to restoration of an intact epithelial barrier. Return of functioning ion channels aids reabsorption of exudate to be cleared by lymph vessels. Cellular debris is cleared by autophagocytosis. Microthrombi clear and vasomotor tone normalizes, lessening pulmonary hypertension. These changes result in a reduction in shunt, an increase in gaseous diffusion, and gradual recovery of pulmonary compliance.

The third phase, fibrotic, is inconsistent and affects a small proportion of patients. It is characterized by neovascularisation and fibroproliferation. Mesenchymal cells proliferate, and myofibroblasts and fibroblasts deposit collagen in the extracellular matrix. Some patients go on to develop widespread changes in keeping with pulmonary fibrosis, with subpleural and intrapulmonary cystic change.

Management of ARDS

There is no one proven pharmacotherapy, and management includes that of the underlying cause.

Non-Invasive Ventilation

High flow nasal cannulae oxygen is often used in acute hypoxaemic respiratory failure. Warmed, humidified oxygen is delivered at flow rates of up to 60 L per minute. Benefits of its use include the creation of an oxygen reservoir in the nasopharynx, reducing anatomical dead space, the generation of around 3 cmH_20 of PEEP, and improved patient compliance as it is generally more comfortable than a tight-fitting non-invasive ventilation (NIV) mask. As it generates lower pressures than NIV or invasive ventilation it may be associated with less iatrogenic lung injury. As per the Berlin definition, the diagnosis of ARDS includes the application of at least 5 cmH_20 of PEEP. Nonetheless there have been studies looking at the use of high flow nasal oxygen in ARDS where the application of 5cmH20 of PEEP has not been a prerequisite to inclusion. Three meta-analyzes of studies into intubation rates in patients with mild ARDS have shown that intubation rates for patients on high flow nasal oxygen are lower than those on conventional oxygen therapy but similar to patients on NIV (Frat et al., 2015; Ou et al., 2017; Monro-Somerville et al., 2017). Nonetheless some concerns remain as to whether the use of high flow nasal oxygen can be falsely reassuring, leading to delayed intubation.

Whilst NIV in the forms of BiPAP and CPAP have an evidence base for their use in hypercapnic exacerbations of COPD or acute cardiogenic pulmonary oedema respectively, the literature does not conclusively support its use in type 1 respiratory failure such as ARDS. Clinical practice varies from one institution to another. Data collected as part of the LUNG SAFE study showed patients across all severities of ARDS to be treated with NIV: 14.3% of mild ARDS, 17.3% moderate, and 13.2% of patients with severe ARDS at the time of study recruitment. Patients being treated with NIV had higher recorded minute volumes than those patients receiving invasive mechanical ventilation. A statistically significant increase in mortality was observed in patients with moderate-severe ARDS (P/F ratio <150 mmHg) being managed with NIV (36.2%) compared to invasive mechanical ventilation (24.7%) ($P = .033$) (Bellani et al., 2017). In a 2015 study by Frat and colleagues, whilst intubation rates were similar in patients on NIV and high flow nasal oxygen, mortality was significantly increased in patients who received NIV. This could be due to higher levels of PEEP being delivered via face mask NIV, leading to increased patient discomfort and intolerance, increased air leak around the mask impairing oxygenation, and the occurrence of lung injury due to higher pressure settings on NIV than that delivered by high flow nasal oxygen. This hypothesis was tested by Patel and colleagues who found the use of a CPAP hood to be associated with reduced rates of intubation and mortality as compared to CPAP delivered via face mask (Patel et al., 2016). However, this was a single center study and there is not enough evidence to recommend the use of CPAP in ARDS.

Conventional Invasive Mechanical Ventilation

The landmark ARDSNet ARMA paper published in 2000 brought about the advent of lung protective ventilation (LPV), now a standard of care in all mechanically ventilated patients with ARDS Network (2000). Prior to this publication, routine mechanical ventilation parameters included a tidal volume of 10–15 mL/kg (higher than physiological norms in health), and the use of high airway pressures in an attempt to normalize arterial partial pressure of carbon dioxide ($PaCO_2$) and pH. This study was performed to investigate potential benefits of prioritizing protecting the lung from ventilator-associated lung injury (VALI) based on promising results in experimental animal studies. The usual care group ventilation parameters were tidal volumes of 12 mL/kg with plateau pressure ≤ 50 cmH_2O, and the intervention group were treated with tidal volumes of 6 mL/kg and plateau pressure ≤ 30 cmH_2O. The trial was stopped early due to overwhelming benefits seen in the intervention arm. A reduction in mortality of 22% was observed, with more days free from mechanical ventilation, and lower plasma concentrations of IL-6 (used as a marker of lung and systemic inflammation) in the intervention arm compared to usual care.

LPV parameters commonly used today are:

- Tidal volume 6 mL/kg ideal body weight
- Target $SpO_2 \geq 88\%$

- Positive end-expiratory pressure (PEEP) 5–10 cmH_2O but higher PEEP (typically 10–15 cmH_2O) if PaO2/FiO2 ratio <20 kPa, ensuring plateau pressure is <30 cmH_2O
- Permissive hypercapnia with target pH >7.2

A 2015 Cochrane review concluded there was insufficient evidence to recommend either volume-controlled or pressure-controlled ventilation over the other when providing LPV to patients with ARDS (Chacko et al., 2015).

PEEP ensures airway pressure remains above atmospheric pressure at the end of expiration. It can be beneficial in recruitment of partially collapsed alveoli and minimizing atelectrauma, thereby improving pulmonary compliance, functional residual capacity and oxygenation of arterial blood. The associated rise in intrathoracic pressure can however lead to haemodynamic instability through a reduction in venous return and an increase in right ventricular afterload. Higher PEEP may also cause VALI through over-distension of alveoli and increasing plateau pressure. The ARDSNet protocol for the ARMA trial included a table of incremental FiO2/PEEP combinations to achieve target oxygenation, with the option of either lower FiO2/higher PEEP or higher FiO2/lower PEEP (see **Table 3**) (The Acute Respiratory Distress Syndrome Network, 2000). Studies have been conducted to investigate optimum PEEP strategy in ARDS, with the focus on a low-PEEP versus a high-PEEP strategy (Meade et al., 2008; Mercat et al., 2008; The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network, 2004). A recent systematic review and meta-analysis evaluated 8 clinical trials comparing higher and lower PEEP in a total of 2728 patients. Across all included trials, mean PEEP in higher PEEP cohort was 15.1 (± 3.6) cmH_2O, and 9.1 (± 2.7) cmH_2O in the lower PEEP cohort. In six of the trials, patients received low-tidal volume ventilation. Higher PEEP levels were associated with improved PaO2/FiO2 ratios, but no statistically significant difference was found for ventilator-free days or mortality. Higher PEEP/lower FiO2 strategies were associated with reduced mortality as compared to lower PEEP/higher FiO2 ventilation (Walkey et al., 2017).

Briel et al. (2010) previously performed a systematic review and meta-analysis of individual patient data from three RCTs (ALVEOLI, LOVS, EXPRESS), totaling 2299 patients. In-hospital mortality was lower in patients with moderate-severe ARDS (P/F ratio <200 mmHg) ventilated with higher PEEP, a relative mortality reduction of 10%, whereas there was the suggestion of harm in patients with mild ARDS being ventilated with higher PEEP. This may suggest patients with more severe ARDS demonstrate more recruitability, whereas patients with mild ARDS may not and therefore suffer the harmful effects of higher PEEP.

There is marked heterogeneity in the lung parenchyma in ARDS, with reduced respiratory system compliance, and the set tidal volumes and airway pressures are delivered to aerated, functional areas of the lungs. Driving pressure refers to the difference in airway pressures between plateau pressure and PEEP (see **Fig. 2**). Amato and colleagues hypothesized that driving pressure, where tidal volume is adjusted for functional lung size rather than predicted healthy lung size, would correlate more closely with survival than tidal volume or PEEP alone. They analyzed individual patient data from 3562 patients (from 9 RCTs) with ARDS receiving invasive mechanical ventilation with no spontaneous respiratory efforts. On testing of four ventilatory parameters (tidal volume,

Table 3 ARDS Network PEEP/FiO2 table.

Lower PEEP/Higher FiO2		*Higher PEEP/Lower FiO2*	
PEEP	*FiO2*	*PEEP*	*FiO2*
5	0.3	5	0.3
5	0.4	8	0.3
8	0.4	10	0.3
8	0.5	12	0.3
10	0.5	14	0.3
10	0.6	14	0.4
10	0.7	16	0.4
12	0.7	16	0.5
14	0.7	18	0.5
14	0.8	20	0.5–0.8
14	0.9	22	0.8
16	0.9	22	0.9
18	0.9	22	1.0
18–24	1.0	24	1.0

PEEP, positive end-expiratory pressure (cmH_20); FiO2, fractional inspired concentration of oxygen.

$$\Delta P = P_{PL} - PEEP$$

$$\Delta P = V_T/C_{RS}$$

Fig. 2 Equations for calculation of driving pressure. ΔP, driving pressure; P_{PL}, plateau pressure; V_T, tidal volume; C_{RS}, respiratory system compliance.

plateau pressure, PEEP, and driving pressure), driving pressure was found to correlate most strongly with mortality (RR of death 1.36; 95% CI 1.17–1.58; $P < .001$) even when all other parameters were as per lung-protective ventilation. It is suggested that each element of lung protective ventilation contributes to a reduction in mortality in ARDS if they also contribute to a reduction in driving pressure. (Amato et al., 2015) Notably, however, in the ART trial, 2017, the control arm had higher driving pressures than the intervention arm yet had better outcomes. A prospective RCT is needed to determine causality, if any, regarding the impact of driving pressure on mortality.

Recruitment maneuvers are brief periods of sustained high transpulmonary pressure delivered to the lungs. They are performed with the aim of opening up collapsed and consolidated areas of lung and are often followed by increasing the level of applied PEEP in an effort to keep them open. This is termed open-lung ventilation. Recruitment maneuvers expose the lung to very high pressures, can cause over-distension of already open alveolar units, and can cause cardiovascular instability and collapse due to the marked rise in intrathoracic pressure. A commonly performed recruitment maneuver is the application of CPAP of around 40 cmH_20 for up to 40 s. A staircase recruitment maneuver refers to progressive increases in PEEP over several minutes. The optimal way to perform a recruitment maneuver and its efficacy has been investigated in numerous studies. In 2011, Hodgson and colleagues published a pilot study for the Permissive Hypercapnia Alveolar Recruitment and Low Airway Pressure (PHARLAP) trial. This was a small 20-patient study comparing staircase recruitment maneuvers and high PEEP to standard ARDSNet ventilation using the published tables. Outcomes measured included PEEP, days free from mechanical ventilation, ICU and hospital length of stay, survival to hospital discharge, and plasma concentrations of IL-8 and TNF-α as surrogate markers of VALI. PEEP was higher in the intervention arm (PHARLAP 12.5 ± 0.5 cmH_20 vs. control 9.5 ± 0.5 cmH_20, $P = .004$), however no significant difference in days free from mechanical ventilation, length of stay in ICU or hospital, or hospital survival were found between the 2 groups. Patients in the intervention arm had lower plasma concentrations of IL-8 and TNF-α than those in the control arm, suggesting a possible reduction in VALI in patients receiving staircase recruitment maneuvers and high PEEP (Hodgson et al., 2011). This pilot study was not powered for these outcomes, but led on to the phase 2 PHARLAP RCT. This showed no difference in days free from mechanical ventilation, higher PEEP, plateau airway pressures, and PaO2/FiO2 ratios on days 1 and 3 in the intervention arm, but also higher rates of cardiovascular adverse events (Hodgson et al., 2019). Recruitment to this study was stopped early in October 2017 due to the findings of the ART trial.

The Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) was a multicentre open-label RCT conducted in 120 ICUs in 9 countries. The study population was adults with moderate-severe ARDS who had been receiving invasive mechanical ventilation for less than 72 h at the time of recruitment. Patients were randomized to receive either aggressive recruitment maneuvers (CPAP of up to 50 cmH_20 for 20–26 min) with high PEEP (up to 45 cmH_20) or low PEEP as per the ARDSNet tables. The primary outcome was 28-day mortality, and secondary outcomes included length of stay in ICU and hospital, incidence of air leaks, and days free from mechanical ventilation. A significant increase in mortality was observed in the intervention arm (55.3% vs. 49.3% in control arm; HR 1.2; 95% CI 1.01–1.42; $P = .041$), which persisted at 6 months. More air leaks were seen in the intervention arm, with more pneumothoraces and deaths by day 7 (7 patients in intervention arm vs. 0 patients in control arm), fewer days free from mechanical ventilation by day 28 (5.3 days in intervention arm vs. 6.4 days in control arm, 95% CI -2.1 to -0.1; $P = .03$), and more markers of cardiovascular instability, with more patients reported to have new severe hypotension, new requirements for vasopressors, or escalating doses of vasopressors in the intervention group (Writing Group for ART Investigators, 2017). The clear signal of harm shown in this trial illustrates that recruitment maneuvers and use of high PEEP in an open lung approach as in this study should be avoided in patients with moderate-severe ARDS.

Adjuncts to Conventional Invasive Mechanical Ventilation

Neuromuscular blockade

Intravenous infusions of non-depolarising neuromuscular blocking agents (NMBAs), mainly atracurium and cis-atracurium, are sometimes used in patients with moderate-severe ARDS. Although the mechanism of their benefit is uncertain, their use reduces the work of breathing for the patient and patient-ventilator dyssynchrony, and therefore may reduce plateau airway pressures and lung stress. Concerns associated with the use of NMBAs include the need for heavy sedation, the potential for awareness under paralysis, increased risks of thromboembolic events, and ICU-acquired weakness. Prior to the publication of the ROSE trial in 2019 (The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, 2019), the majority of the evidence base for the use of NMBAs came from three French multicentre RCTs, all from the same group of investigators (Forel et al., 2006; Gainnier et al., 2004; Papazian et al., 2010). These trials all supported the use of early intravenous infusions of cis-atracurium for 48 h in patients with moderate-severe ARDS, demonstrating a reduction in mortality at both 28 days and time of hospital discharge, as well as reducing the incidence of barotrauma and no apparent increase in the risk of ICU-acquired weakness. A US-based trial, Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome (ROSE trial), was published in 2019. This trial recruited 1006 patients with PaO2/FiO2 ratio <150 mmHg and PEEP ≥ 8 cmH_20 who were randomized to receive either a 48-h infusion of cis-atracurium with deep sedation or usual care with light sedation. No statistically significant difference in 90-day mortality was observed (42.5% in intervention arm vs. 42.8% in control arm; percentage point difference -0.3; 95% CI -6.4 to 5.9; $P = .93$). Of note, 17% of patients in the control arm received NMBA, which may have reduced any mortality benefit in the intervention group. There are some important differences between the ROSE and ACURASYS trials. In ROSE, patients in the usual care arm received light sedation, in keeping with current practices in critical care, whereas both arms in ACURASYS received deep sedation. Deep sedation is associated with increased risk of cardiovascular depression and instability, which may contribute to increased

morbidity and mortality. The ROSE trial had a high PEEP strategy using the table from the ALVEOLI trial, whereas previous RCTs used the published ARDSNet PEEP table.

A recent meta-analysis combined the results of 5 RCTs, including ROSE, totalling 1461 patients with a mean PaO2/FiO2 ratio of 104 ± 35 mmHg, and found no mortality difference at 28 or 90 days, or in duration of mechanical ventilation. Cis-atracurium infusions were found to lower the risk of barotrauma, but no difference in prevalence of ICU-acquired weakness was seen (Ho et al., 2020).

Current guidelines on the management of ARDS provide a weakly positive recommendation for the use of intravenous infusions of cis-atracurium for 48 h in patients with early moderate-severe ARDS (Griffiths et al., 2019).

Prone positioning

In ARDS, in the supine position there is collapse and consolidation of predominantly the dorsal lung. The anterior chest wall is free, and this can lead to overdistension of the aerated lung, contributing to V/Q mismatch and ventilator-associated lung injury. In the prone position, anterior chest wall compliance is reduced, and the dorsal aspects of the lungs (where there is a greater number of alveolar units) are recruited, leading to an improvement in oxygenation (see **Fig. 3**).

Early RCTs in ARDS did demonstrate an improvement in oxygenation in the prone position, however no mortality benefit was seen. These trials were performed before the advent of lung-protective ventilation, and proning was performed for short periods of time. The PROSEVA trial (Guérin et al., 2013) used different inclusion criteria and duration of proning. A total of 466 patients were recruited with severe ARDS, as defined as a PaO2/FiO2 ratio <150 mmHg, on a FiO2 ≥ 0.6, with PEEP ≥ 5 cmH_20 and being ventilated with tidal volumes of 6 mL/kg of predicted body weight. Patients in the intervention arm were proned for 16 consecutive hours per day until pre-specified improvement criteria were met. A statistically significant difference in mortality was seen at 28 days (16% in prone arm vs. 32.8% in supine arm; $P < .001$) and at 90 days (23.6% in prone arm vs. 41% supine arm; $P < .001$).

Following on from the publication of PROSEVA, a Cochrane systematic review in 2015 recommended the use of prone positioning for at least 16 consecutive hours per day in patients who are severely hypoxaemic within 48 h of commencing invasive mechanical ventilation (Bloomfield et al., 2015). Contraindications to the use of prone positioning include unstable spinal injuries, open chest or abdomen following surgery, the use of central cannulation for VA-ECMO, new tracheostomy, within 24 h of cardiac surgery and third-trimester pregnancy. Prone positioning can be used with caution in second-trimester pregnancy.

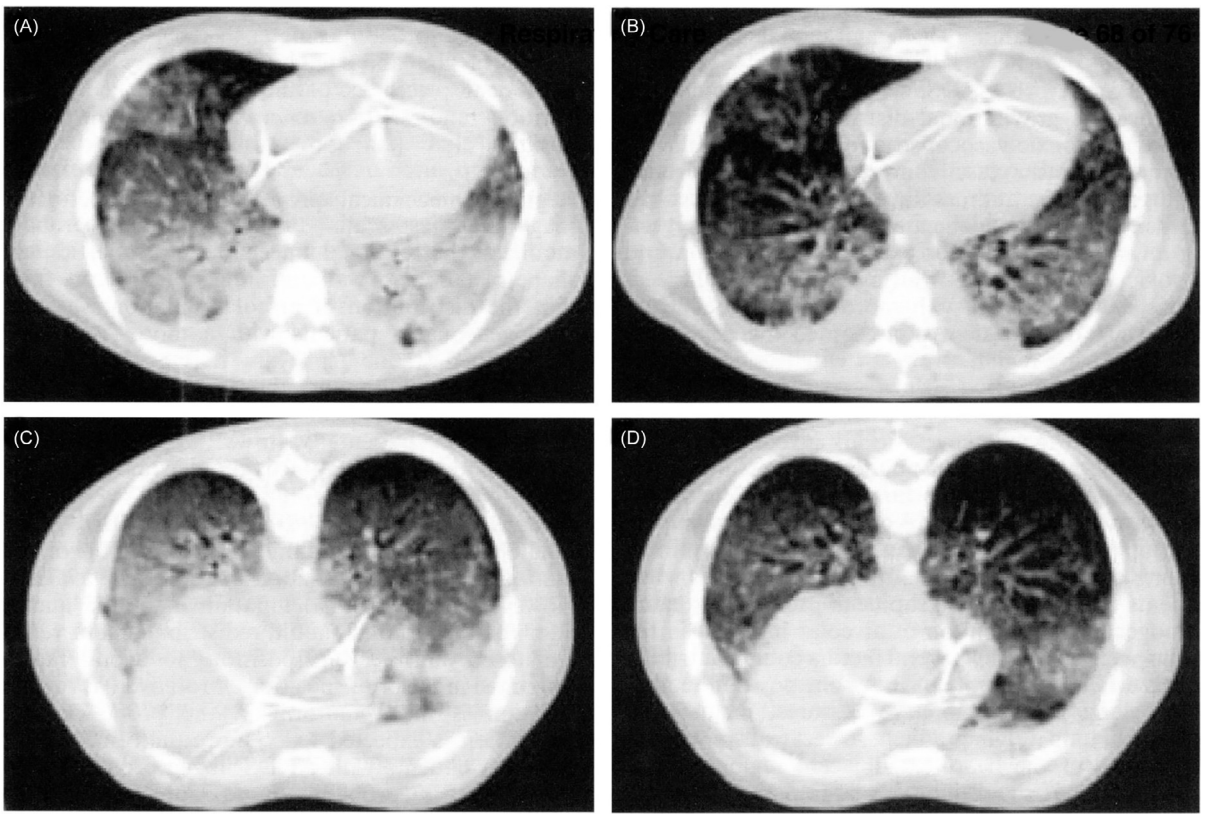

Fig. 3 Effects on lung densities of supine positioning at (A) end-expiration and at (B) end-inspiration, and prone positioning at (C) end-expiration and (D) end-inspiration. At end-expiration, densities moved from dorsal to ventral regions. At end-inspiration, ventilation improved in prone compared to supine position. Reproduced with permission of the © ERS 2021: European Respiratory Journal 20 (4) 1017–1028; https://doi.org/10.1183/09031936.02.00401702. Published 1 October 2002.

Prone positioning is not without complications, particularly in ICUs where it is not performed regularly and where staff are unfamiliar with it. Reported complications include pressure sores, facial oedema, injuries to the eyes, cardiovascular instability, kinking or displacement of the endotracheal tube or invasive lines, and injuries to staff. In the UK, the Faculty of Intensive Care Medicine has published guidelines for medical and nursing staff on the practicalities of proning a patient, monitoring and preventing complications.

Inhaled pulmonary vasodilator

Nitric oxide (NO) is a potent endogenous vasodilator through relaxation of vascular smooth muscle cells. It can be administered exogenously in an inhaled form and has been used as a rescue therapy in patients with severe acute respiratory failure. Inhaled NO (iNO) causes pulmonary vasodilatation in well-ventilated regions of the lungs, thereby reducing V/Q mismatch. It also reduces pulmonary vascular resistance, improving right ventricular ejection fraction, and can be used to manage acute cor pulmonale. It is known to inhibit platelet aggregation, so concerns exist regarding increased bleeding risk for patients being treated with it. A recent Cochrane systematic review examined 14 RCTs in both adults and children who were randomized to receive iNO for severe respiratory failure (Karam et al., 2017). Whilst PaO2/FiO2 ratios significantly improved at 24 h in patients receiving iNO (mean difference 15.91 (95% CI 8.25–23.56)), this did not persist at 48 or 72 h, and no mortality benefit was conferred. There was also no difference in duration of mechanical ventilation, or length of stay in ICU or hospital. No statistically significant difference in risk of bleeding was found (RR 0.88 (95% CI 0.43–1.79)), however there was an increased risk of renal impairment in adults (RR 1.59 (95% CI 1.17–2.16)).

On the basis of this Cochrane review there is no evidence to support the use of iNO in patients with ARDS as no mortality benefit was observed, and there is an increased risk of renal impairment.

Non-Conventional Invasive Mechanical Ventilation

Airway pressure release ventilation

Airway pressure release ventilation (APRV) can be thought of as long periods (T_{HIGH}) of CPAP at a high pressure (P_{HIGH}), with brief periods (T_{LOW}) of pressure release to a lower pressure (P_{LOW}). It is a form of open lung ventilation and spontaneous ventilation can be performed on it. In theory, prolonged periods of time at a higher pressure maximize recruitment, and short periods of time at a low pressure minimize or prevent derecruitment, thereby minimizing dynamic strain. A greater proportion of the ventilatory cycle is spent at a higher mean airway pressure than in conventional invasive mechanical ventilation, providing a longer period of time for homogenous ventilation to be achieved across alveolar units with varied compliances. A drawback of APRV is the inability to accurately measure or target low tidal volumes.

APRV was first described in 1987 by Stock and colleagues (Stock et al., 1987). This was an animal study involving 10 dogs where they demonstrated improvements in arterial oxygenation and clearance of carbon dioxide. Several animal studies have since been performed, predominantly porcine models. One such study (Roy et al., 2013) used an induced-sepsis porcine model, comparing LPV to APRV in the prevention of ARDS. They demonstrated improved gas exchange and preservation of lung architecture in the group ventilated with APRV compared to LPV. At the time of writing, two prospective RCTs comparing APRV to LPV in human adults have been performed (Maxwell et al., 2010; Zhou et al., 2017). Maxwell and colleagues randomized 63 patients needing invasive mechanical ventilation after severe trauma to either APRV or LPV. This trial was not specific to patients with pre-existing ARDS at the time of recruitment, and no statistically significant difference in days free from mechanical ventilation or mortality were seen. Zhou and colleagues randomized 138 patients with ARDS who had been mechanically ventilated for less than 48 h to either APRV or LPV as per ARDSNet. Pneumonia and extra-pulmonary sepsis were the commonest causes of ARDS in both patient groups. Around 60% of patients in each group had a PaO2/FiO2 ratio of <150 mmHg. This was a single center study in China, and the primary outcome was days free from invasive mechanical ventilation in the first 28 days since recruitment. The APRV group had more days liberated from a ventilator (median 19 days, IQR 8–22) than the LPV group (median 2 days, IQR 0–15) ($P < .001$), and a shorter length of stay in ICU ($P = .003$). There was no observed significant difference in ICU mortality. Further research into the use of APRV in ARDS is needed.

APRV should only be used in the setting of a clinical trial.

High frequency oscillatory ventilation

High frequency oscillatory ventilation (HFOV) is a form of invasive mechanical ventilation where gas is delivered to the airway in small volumes, usually 1–2 mL per kilogram, less than dead space, at a frequency of 3–15 Hz, in an effort to prevent VALI. Gas exchange occurs via alternative methods of Taylor-type dispersion, cardiac oscillatory mixing, and Pendelluft. Whilst this mode of ventilation is still used in pediatric critical care, there is evidence of harm in its use in adults with ARDS. The OSCAR trial was a UK-based multicentre RCT comparing use of HFOV and conventional mechanical ventilation in moderate-severe ARDS. Seven hundred and 95 patients were recruited, 397 randomized to conventional ventilation and 398 to HFOV. No statistically significant difference in 30-day mortality was seen (Young et al., 2013). OSCILLATE was an international multicentre RCT comparing HFOV to conventional ventilation in patients with moderate-severe ARDS. The trial was stopped early after 548 patients were randomized due to the signal of harm observed in the HFOV arm. A statistically significant difference in mortality was observed (HFOV arm 47% mortality, conventional ventilation arm 35% mortality; RR of death in HFOV arm 1.33 (95% CI 1.09–1.64; $P = .005$).

HFOV was also associated with higher mean airway pressures, and increased use of sedatives, NMBAs, and vasopressors (Ferguson et al., 2013).

Extracorporeal Life Support

Venovenous extracorporeal membrane oxygenation

Venovenous extracorporeal membrane oxygenation (VV-ECMO) is a rescue therapy for patients with severe, potentially reversible acute respiratory failure. Percutaneous cannulae are sited, draining blood from the right atrium via a cannula in the right internal jugular vein or a femoral vein, and returning oxygenated blood via a cannula sited in the contralateral femoral vein. Mechanical ventilation settings are reduced to allow the lungs to "rest." Its use has been increasing since the H1N1 pandemic in 2009. Indications for consideration for VV-ECMO include failure of conventional ARDS management, including NMBAs and prone positioning, severe hypoxaemia (PaO2/FiO2 <80 mmHg), Murray score >3, and hypercapnia with associated uncompensated acidaemia (pH <7.2). Contraindications to its use include chronic underlying respiratory disease, not a candidate for lung transplantation, advanced cancer, and intracerebral hemorrhage. Relative contraindications include invasive mechanical ventilation for more than 7 days, particularly if FiO2 >0.8 or prolonged high airway pressures. Complications associated with VV-ECMO can be severe or fatal, including hemorrhage associated with anticoagulation use, cerebrovascular accidents, bacteraemia, fungaemia, and complications related to malfunction or mismanagement of the ECMO circuit, such as oxygenator failure.

Despite the documented use of VV-ECMO to manage severe ARDS since the 1970s, there is a paucity of evidence for its use. The CESAR trial (Peek et al., 2009) was a UK study investigating the safety, efficacy, and cost-effectiveness of ECMO in severe, potentially reversible respiratory failure. Patients were randomized in a 1:1 fashion to either continue with conventional ventilation or to be transferred to Glenfield Hospital in Leicester for consideration for ECMO. The primary outcome was death or severe disability (defined as being bedbound or unable to wash or dress independently) at 6-month follow-up. The results showed a signal of benefit for those patients being transferred for the consideration of ECMO (63% in ECMO group survived to 6 months without severe disability vs. 47% in conventional ventilation group; $P = 0.03$; NNT = 7), however notably 24% of patients transferred to the ECMO center remained on conventional ventilation as they improved within 12 h of their arrival to the specialist ICU. The EOLIA trial (Combes et al., 2018) is the largest multicentre ECMO RCT to date, and investigated if early ECMO in severe ARDS decreased mortality at 60 days. The trial was stopped early when 75% of the planned number of patients was reached due to predetermined rules regarding futility being met. Patients in the conventional ventilation arm could crossover to receive ECMO, of which 28% did, however seven of these patients were crossed over to receive venoarterial ECMO due to cardiac arrest. No statistically significant difference in 60-day mortality was seen (ECMO group 35%, conventional ventilation 46%; RR 0.79; 95% CI 0.55–1.04; $P = .09$). One strength of EOLIA over the CESAR trial was that all patients who were randomized to receive ECMO got it, however the study is underpowered and the significant proportion of patients in the control arm crossing over to receive ECMO brings about the question of clinician equipoise.

VV-ECMO continues to be used as a rescue therapy in severe ARDS with a potentially reversible cause, though it is not without risks and is not suitable for every patient. The CESAR trial highlighted the benefits of the involvement of specialist ECMO centers in the management of these patients.

Extracorporeal carbon dioxide removal

Ultra-low tidal volume ventilation (tidal volumes 3–4 mL/kg of ideal body weight) applies the principles of LPV to a stricter degree in an effort to further reduce the risk of VALI. Ultra-low tidal volume ventilation can cause potentially injurious hypercapnia. Extracorporeal carbon dioxide (CO_2) removal (ECCO2R) describes the use of ultra-low tidal volume ventilation, permitting lower plateau airway pressures, while CO_2 is removed from patient's circulating blood in an extracorporeal circuit similar to that used for ECMO. At the time of writing, ECCO2R is only used in a trial setting. SUPERNOVA was a phase 2, multicentre, single arm safety and feasibility study to determine if ECCO2R safely permitted the use of ultra-low tidal volume ventilation in 95 patients with moderate ARDS (Combes et al., 2019). The primary outcome, tidal volume 4 mL/kg predicted body weight with PaCO2 not exceeding 20% of baseline value and pH >7.3, was reached by 78% of patients within 8 h and 82% of patients within 24 h. Six serious adverse events occurred, 2 of which were attributable to ECCO2R: 1 intracerebral hemorrhage, and 1 pneumothorax occurring during cannulation. The REST trial is a phase 3 multicentre RCT investigating if VV-ECCO2R improves outcomes in severe ARDS (REST, 2021). At the time of writing recruitment has ceased and results are awaited.

Fluid Management

Fluid resuscitation is often indicated in the initial phase of many critical illnesses associated with ARDS, for example septic shock, burns, and pancreatitis, with the goal of optimizing cardiac output and oxygen delivery. As per the Berlin definition, noncardiogenic pulmonary oedema is a feature of ARDS. This occurs due to disruption of the epithelial-interstitial-endothelial alveolar barrier. An increase in hydrostatic pressure due to an increase in intravascular volume exacerbates pre-existing alveolar oedema, worsening oxygenation further. Following the initial resuscitation phase, many clinicians practice deresuscitation through either a conservative fluid management strategy or the use of diuretics.

The FACTT trial was a US-based multicentre RCT comparing a liberal fluid management strategy to a conservative one in patients with ARDS who were receiving LPV as per the ARDS Network. A complex protocol was followed, detailing target CVP or PAOP

values, and the use of vasoactive agents and furosemide as guided by urine output (ARDS Network, 2006). Overall, patients in the conservative arm had a mean 7-day fluid balance of −136 mL as compared to +6992 mL in the liberal arm. Although no significant difference in 60-day mortality was seen, there were statistically significant differences in many clinically important outcomes. Patients in the conservative fluid management arm had better oxygenation indices, lower plateau airway pressures, more days free from mechanical ventilation in the first 28 days ($P < .001$), and shorter duration of stay in ICU ($P < .001$). There was no significant between-group difference in PaO2/FiO2 ratios ($P = .07$), but also no increase in non-pulmonary organ failure in the conservative fluid arm. These results were confirmed in a recent systematic review and meta-analysis (Silversides et al., 2016), with shorter ICU stays, less time spent on a mechanical ventilator, and no increase in the incidence of acute kidney injury or the use of renal replacement therapy in patients who had been deresuscitated after initial resuscitation, either through a conservative fluid management strategy or the use of diuretics.

Trialed Pharmacotherapies

Statins

In recent years there has been increasing evidence to show statins have anti-inflammatory actions (Jain and Ridker, 2005). These actions have been demonstrated to reduce lung inflammation in murine and preclinical experimental human models of ARDS. Two prospective placebo-controlled RCTs have been carried out to determine if enteral administration of statins in patients with ARDS confers clinical benefit: the SAILS and HARP-2 studies (ARDS Network, 2014; McAuley et al., 2014).

SAILS was a US-based multicentre RCT comparing daily enteral rosuvastatin 40 mg (a hydrophilic statin) to placebo in patients with sepsis-related ARDS who had been mechanically ventilated for less than 48 h. A total of 745 patients were randomized, but no significant difference was observed in days free from mechanical ventilation or mortality. Patients who had been randomized to receive rosuvastatin did have fewer days free from hepatic or renal impairment. Patients in the intervention arm had higher plasma concentrations of alanine aminotransferase and creatine kinase, however the study authors argue that the between-group differences were small and clinical relevance is uncertain. HARP-2 was a UK-based multicentre RCT comparing daily enteral simvastatin 80 mg (a lipophilic statin) to placebo in 540 patients with ARDS of any cause. Again, no significant difference was observed in the number of days free from mechanical ventilation, non-pulmonary organ failure, length of stay in ICU or hospital, or mortality. With growing interest in precision medicine and the identification of hypoinflammatory and hyperinflammatory phenotypes of ARDS, data from the HARP-2 study was re-examined (Calfee et al., 2018). Notably, survival at days 28 and 90 was better in the patients with hyperinflammatory ARDS phenotype who had received simvastatin than those who received placebo ($P = .008$ and $P = .03$ respectively). No such difference was observed in the hypoinflammatory ARDS subset. This illustrates the need for predictive enrichment when trialing potential pharmacotherapies in ARDS.

Corticosteroids

As ARDS is associated with an unchecked inflammatory response which can lead to fibrosis it is plausible that corticosteroids would be of benefit in its management. Numerous studies have been performed examining the role of corticosteroids in the prevention and management of ARDS. Systematic reviews of these studies have failed to show a statistically significant mortality benefit, however many of these trials were conducted prior to the publication of the ARMA trial, so LPV was not used. The LASARUS trial, the largest ARDS Network steroid trial, changed its ventilatory strategy during the study following on from the results of the ARMA trial (Steinberg et al., 2006). The DEXA-ARDS trial was published in February 2020 (Villar et al., 2020). This was a prospective RCT comparing dexamethasone to placebo in patients with moderate-severe ARDS. Patients in the intervention arm received intravenous dexamethasone 20 mg once daily for 5 days, followed by 10 mg once daily for 5 days, or until extubation when the trial drug was stopped. The primary endpoint was days free from mechanical ventilation. The trial was stopped early at 88% of planned participants due to slow recruitment. Statistical significance was reached for both days free from mechanical ventilation ($P < .0001$) and mortality at day 60 ($P = .0047$) in the treatment arm. No significant increase in the risk of hyperglycaemia or new infections were found in the dexamethasone group.

Corticosteroids investigated in previous ARDS trials have been largely hydrocortisone or methylprednisolone. Dexamethasone differs to these steroids as it is a pure glucocorticoid. A lack of mineralocorticoid activity means there is no sodium, and therefore water, retention which could cause volume overload and worsen pulmonary oedema. Concerns remain about the use of steroids in ARDS due to associated adverse effects including immunosuppression, gastrointestinal bleeding, psychosis, and ICU-acquired weakness. It is also not clear if they would be of benefit in ARDS of any cause. Further good quality RCTs are needed before their use can be mandated in all patients with ARDS.

COVID-19-Associated ARDS

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was the name given to the novel coronavirus by the International Committee on Taxonomy of Viruses on 11th February 2020. On the same day the World Health Organization declared the name of the associated disease as COVID-19. COVID-19 caused a global pandemic in 2020, which continues at the time of writing in January 2021. The commonest reason for hospitalization for patients with COVID-19 is hypoxaemic respiratory failure, which can progress to ARDS. There is debate as to whether COVID-19 ARDS differs from ARDS due to other aetiologies. One distinguishing feature is an

increased prevalence of thromboembolism in COVID-19, for example pulmonary emboli leading to pulmonary hypertension and acute cor pulmonale.

Early in the pandemic, faced with a novel disease and vast numbers of patients requiring hospitalization and oxygen therapy, there was uncertainty across the global medical community as to how best to manage COVID-19-associated ARDS. Fears of a lack of adequate oxygen supplies in hospitals and exposing healthcare staff to aerosols generated debate and variation in clinical practice, sometimes contrary to pre-existing ARDS guidelines for non-COVID-19 ARDS. Patients with ARDS received treatment with NIV ± self-proning, invasive ventilation, and ECMO. Internationally, numerous trials are underway to investigate efficacy of ventilation strategies and various pharmacotherapies. In June 2020 the RECOVERY trial reported a statistically significant reduction in mortality for hospital patients with COVID-19 on oxygen and those receiving invasive mechanical ventilation who were administered a 10-day course of low-dose dexamethasone (Horby et al., 2020). Subsequently, the use of dexamethasone to these cohorts of patients is approved by many health organizations.

Until the results of other clinical trials are available, it is recommended patients with COVID-19-associated ARDS are managed using the existing evidence base for ARDS due to other aetiologies, namely lung-protective ventilation, prone positioning, conservative fluid management, and referral for ECMO where appropriate.

Summary

ARDS is a syndrome resulting from a pulmonary or extra-pulmonary insult, and its management includes that of the underlying cause. As well as ARDS-specific management, general supportive ICU care is important. There is an established evidence base for the management of ARDS, with lung protective ventilation at its core in the initial treatment.

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