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Acute respiratory distress syndrome

Nuala J Meyer, Luciano Gattinoni, Carolyn S Calfee

Acute respiratory distress syndrome (ARDS) is an acute respiratory illness characterised by bilateral chest radiographical opacities with severe hypoxaemia due to non-cardiogenic pulmonary oedema. The COVID-19 pandemic has caused an increase in ARDS and highlighted challenges associated with this syndrome, including its unacceptably high mortality and the lack of effective pharmacotherapy. In this Seminar, we summarise current knowledge regarding ARDS epidemiology and risk factors, differential diagnosis, and evidence-based clinical management of both mechanical ventilation and supportive care, and discuss areas of controversy and ongoing research. Although the Seminar focuses on ARDS due to any cause, we also consider commonalities and distinctions of COVID-19-associated ARDS compared with ARDS from other causes.

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Introduction

Acute respiratory distress syndrome (ARDS) is the acute onset of hypoxaemia and bilateral pulmonary oedema due to excessive alveolocapillary permeability. Although ARDS has a codified clinical definition, known as the Berlin definition (panel 1) with stages that estimate mortality risk,[1] there is no single test to identify or exclude the diagnosis. The heterogeneity of ARDS, evident in its causes, manifestations, and response to therapy,[2,3] challenges clinicians and scientists to provide impeccable supportive care and discover new therapies. This Seminar summarises current knowledge regarding ARDS epidemiology and risk factors, differential diagnosis, and clinical management, and highlights controversial topics and ongoing research. This Seminar also includes a section on the COVID-19 pandemic and ARDS.

Epidemiology and outcomes

ARDS is more common than initially believed. In 2016, a study of patients in 459 intensive care units (ICUs) from 50 countries reported that 10% of ICU patients and 23% of mechanically ventilated patients fulfilled criteria for ARDS.[4] Although the survey was done during the winter viral season and included ARDS that resolved rapidly,[5] the hospital mortality of 35–45% closely resembled that described by the large datasets used to validate the Berlin definition.[1,4] Even patients whose ARDS resolved rapidly had a mortality rate of 31%.[6]

Search strategy and selection criteria

We searched PubMed from database inception to Dec 14, 2020, using the search terms "Acute Respiratory Distress Syndrome", "ARDS", "acute lung injury", "positive end expiratory pressure", "COVID-19", "SARS-CoV-2", "prone position", and "neuromuscular blockade". The search was limited to studies of humans. Returned lists of articles were then screened manually by reading abstracts to exclude neonatal lung injury and neonatal respiratory distress syndrome. Comprehensive reviews that have been published within the past 3 years were also read in full, and their reference lists were reviewed. Remaining manuscripts were read in full and their references reviewed when appropriate.

Given that many patients with diffuse lung injury supported with high-flow nasal cannula (HFNC) do not meet the ARDS Berlin definition, which requires positive pressure ventilation,[1] the incidence of ARDS is probably even higher. The COVID-19 pandemic has highlighted this limitation, as many patients are treated without mechanical ventilation.[7,8] Men might be slightly more likely to develop ARDS, although outcome is largely similar between sexes.[9] Women—and patients of shorter stature—are less likely to receive lung protective ventilator tidal volumes.[10] For patients with severe persistent ARDS, women had higher mortality than men.[11] Black patients might have a reduced risk of developing ARDS,[9] and Black and Hispanic patients with ARDS had a higher mortality in at least one study, which seemed to be mediated by increased severity of illness.[12] Tobacco use, alcohol use, hypoalbuminaemia, chemotherapy within the previous 6 months, and ambient air pollutant exposure[4,13–16] can increase ARDS risk, whereas, in some studies, patients with diabetes were less likely to develop ARDS.[17,18]

Panel 1: The Berlin definition of ARDS and observed mortality[1]

- Acute onset (within 7 days of new or worsening respiratory symptoms)
- Bilateral radiographical opacities that are not fully explained by effusion, atelectasis, or masses
- Arterial hypoxaemia defined by thresholds:
  - Mild: 200 < PaO_2/FiO_2 ratio ≤300 mm Hg, on CPAP* or PEEP† ≥5 cm H_2O (observed mortality 27%)
  - Moderate: 100 < PaO_2/FiO_2 ratio ≤200 mm Hg, on PEEP ≥5 cm H_2O (observed mortality 32%)
  - Severe: PaO_2/FiO_2 ratio ≤100 mm Hg, on PEEP ≥5 cm H_2O (observed mortality 45%)
- Identified risk factor for ARDS (if no clear risk factor, exclude heart failure as a cause)
- Not exclusively due to cardiac causes

ARDS=acute respiratory distress syndrome. CPAP=continuous positive pressure ventilation. FiO_2=fraction of inspired oxygen. PaO_2=partial pressure of oxygen. PEEP=positive end-expiratory pressure. *CPAP delivered by non-invasive or invasive ventilation. †PEEP delivered by invasive mechanical ventilation.

Panel 2: **Classic precipitants of ARDS**

Common precipitants

- Pneumonia (bacterial and viral are the most common, whereas fungal, mycobacterial, and parasitic pneumonia are less common)
- Non-pulmonary sepsis
- Aspiration of gastric contents
- Non-cardiogenic shock
- Pancreatitis
- Severe trauma or high-risk surgery (eg, esophagectomy)
- Drug overdose
- Ischaemia-reperfusion injury

Less common precipitants

- Smoke inhalation
- Drowning
- Vape or e-cigarette use
- Multiple transfusion of blood products

Diagnoses not typically classified as ARDS

- Vasculitis
- Diffuse alveolar haemorrhage
- Drug-induced pneumonitis
- Organising pneumonia
- Hypersensitivity pneumonitis
- Acute eosinophilic pneumonia
- Acute exacerbation of interstitial lung disease
- Acute chest syndrome (ie, sickle cell disease)
- Alveolar proteinosis
- Malignancy

ARDS=acute respiratory distress syndrome.

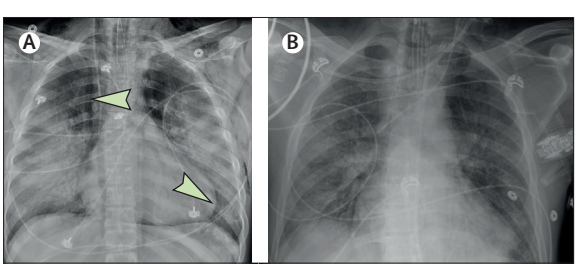

Figure 1: **Chest radiographs**
(A) Vaping-associated lung injury with pneumomediastinum (arrows). (B) SARS-CoV-2 infection.

Mortality for ARDS remains sobering; observational studies consistently report greater than 30% hospital mortality,[4] with one large trial of moderate to severe ARDS reporting 43% in-hospital mortality at 90 days.[19] The proportion of ARDS mortality that is attributable to the syndrome itself (as opposed to risk factors and comorbidities) has been challenging to determine, but was estimated for sepsis-associated ARDS at 27–37%.[20] The cause of death is more commonly sepsis and multiple organ failure than respiratory failure.[21] Although most ARDS survivors recover normal or near-normal pulmonary function, many remain burdened by functional limitations related to muscle weakness, deconditioning, or psychological sequelae of severe illness.[22,23] Cognitive impairment is also distressingly common, affecting almost half of survivors at 2 years.[24,25]

Causes and risk factors

Since its initial description,[26] ARDS has been recognised as a clinical condition that develops in the setting of various causes or risk factors (panel 2). The most common risk factors are pneumonia and non-pulmonary sepsis, followed by aspiration of gastric contents.[4,27] Trauma and blood product transfusion are less common ARDS risk factors in the modern era as ventilator, fluid, and transfusion management has evolved,[4,28] whereas new causes such as e-cigarette or vaping product use-associated lung injury (EVALI) have emerged.[29,30] Bacterial and viral pneumonias frequently cause ARDS, with sporadic spikes in global ARDS incidence due to pandemic influenza[31] and emerging viruses including SARS-CoV-2[32,33] and the coronaviruses responsible for SARS[34] and MERS.[35,36] Identification of a specific cause for ARDS remains a crucial therapeutic goal to improve outcomes associated with ARDS.[37] Although genetic susceptibility to ARDS is suggested by the variability with which clinical risk factors predict ARDS development and by the replicated association of numerous genetic variants with ARDS risk,[38,39] the attributable risk of any singular genetic polymorphism to ARDS risk or outcome seems small.

Diagnostic considerations

No single diagnostic test confirms or refutes a diagnosis of ARDS. Furthermore, it must be emphasised that ARDS is a syndrome rather than a specific pathologic entity and is currently identified by purely clinical criteria. As elaborated by the Berlin definition,[1] ARDS diagnosis requires that new or worsening respiratory distress and bilateral chest radiographical abnormalities be present for 7 days or fewer, that heart failure cannot fully explain the hypoxaemia and radiographical infiltrates, and that the impaired oxygenation be clinically significant. By comparison with previous definitions,[40] the Berlin definition provided more specific guidance on chest radiograph patterns consistent with ARDS—bilateral opacities consistent with pulmonary oedema (figure 1) that can be patchy or asymmetric[1]—and those that are inconsistent with ARDS, including isolated pleural effusions, atelectasis, or tumours.[1]

Imaging

CT can fulfil the radiographical ARDS criterion, replacing or adding to chest radiograph,[1] and can quantify lung oedema and potential recruitability of lung parenchyma.[41] Chest CT can identify abnormalities that mimic ARDS on a radiograph, including pleural effusions, severe obesity with atelectasis, or nodules and masses, and can suggest interstitial lung disease.[42,43] CT

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can be challenging to obtain for severely hypoxaemic patients and those receiving high dose vasoactive medications, continuous renal replacement therapy, or other ICU interventions. CT exposes patients to ionising radiation, which restricts its repeatability, and is expensive. Lung ultrasonography can identify alveolar flooding using bilateral B line patterns, defined as three or more discrete vertical lines arising from the pleura in an intercostal space, representing hyperechoic reverberation artifacts[44] (figure 2). Ultrasonography is portable, inexpensive, free from radiation, can be repeated as needed, and monitors lung recruitment[45] and resolution of alveolar processes. Lung ultrasound has been proposed as an alternative to chest radiography for resource-limited settings in the Kigali modification to the Berlin definition of ARDS.[46] However, sonographic B lines from hydrostatic pulmonary oedema are indistinguishable from those in ARDS. Combining cardiac and lung ultrasonography can suggest a cardiogenic process,[47] although heart failure and ARDS can coexist.[48] Ultrasound visualises primarily subpleural lung zones and can yield poor-quality images in the presence of extensive overlying soft tissue (as seen with obesity) or subcutaneous oedema.

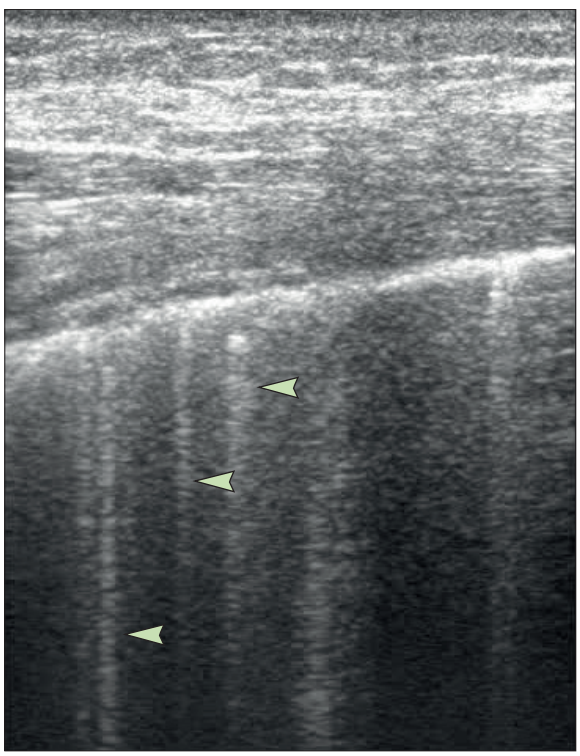

Figure 2: **Lung ultrasound image showing B lines**
B lines (arrows) are the vertical lines in the lower half of the image. Diffuse B lines (≥3 per region in multiple fields) are consistent with pulmonary oedema or acute respiratory distress syndrome.

Determining the inciting cause

Although some ARDS precipitants can be self-limited and others do not have specific treatment, prompt recognition, and treatment of reversible insults such as infection, hypersensitivity, or autoinflammation is essential. Clinical history provides crucial information about the duration of symptoms, an infectious prodrome or travel history, exposures, behaviours, or localising symptoms that might guide imaging or serological testing. Understanding the patient's comorbidities is essential to consider risks for infectious and sterile (eg, blunt trauma, pancreatitis, postoperative) processes.

The initial diagnostic approach for a patient with suspected ARDS focuses upon determining whether the patient has pneumonia or another infection because pneumonia and sepsis are the most common underlying diagnoses. Blood cultures should be drawn for all patients without an obvious sterile insult, and consideration should be given to obtaining sputum, tracheal aspirate, or bronchoalveolar lavage samples if safe to do so. The value of bronchoscopy, with sensitivity only 58% in one prospective study,[49] is likely to be superior to sputum, especially for fungal causes (eg, *Pneumocystis jirovecii*), *Legionella*, or atypical pathogens (eg, *Nocardia* or *Actinomyces* bacteria). Bronchoalveolar lavage can also prompt consideration of alternative diagnoses to ARDS (panel 2) using a differential cell count and fluid cytology to identify eosinophilic pneumonia, alveolar proteinosis, or diffuse alveolar haemorrhage, or suggest hypersensitivity pneumonitis.[43] In EVALI, bronchoalveolar lavage analysis detected vitamin E acetate in the majority of cases and never among healthy controls, implicating this chemical in the syndrome.[50] With the advent of molecular testing, bronchoalveolar lavage or nasopharyngeal swab with PCR can detect numerous viral pathogens, which might prompt pathogen-specific treatment or isolation precautions[51,52] and reduce exposure to potentially unnecessary antibiotics.

Open lung biopsy is not commonly done during ARDS because there are risks and a lack of useful information in most cases.[53] Transbronchial biopsy through a flexible bronchoscope is possible but still poses risks of bleeding and pneumothorax, and diagnostic yield might be only 35%.[54,55] Consideration for biopsy increases as physicians question whether the patient has an alternative to ARDS, particularly a disease that might be treatable.[55]

Underlying biology

Many different mechanisms contribute to the syndrome clinicians recognise as ARDS and, in different individuals, the role played by any one process can vary considerably. Pulmonary oedema occurs when fluid is filtered from the circulation into the lung extravascular spaces faster than it can be removed. In ARDS, pulmonary oedema arises primarily from a defect in alveolocapillary permeability, rather than primarily due to hydrostatic pressure. In this section, we discuss the key principles of ARDS pathogenesis; two detailed reviews[56,57] should be used for greater detail.

Endothelial permeability

Healthy lung vasculature has several safety features to prevent lung flooding across a range of vascular hydrostatic pressures. Fluid filtered from the pulmonary microvasculature into the interstitium is largely reabsorbed into the circulation due to low alveolar epithelial permeability, a protein osmotic gradient between vessel and interstitium, a hydrostatic pressure gradient from peripheral to central vessels, lymphatic flow, and pleural and mediastinal sinks when hydrostatic pressure is excessive.[58–61] However, when the vascular barrier becomes highly permeable to protein and solutes, the protein osmotic gradient is lost and the interstitium is easily flooded.

Healthy pulmonary endothelium largely inhibits inflammation and coagulation, whereas activated endothelium does the opposite.[62] Stimuli as varied as hypoxia, cytokines, chemokines, thrombin, primed leukocytes, lipopolysaccharide, and damage-associated molecular patterns (DAMPs) can shift the endothelium towards a dysregulated, leaky state that attracts inflammatory cells.[63,64] Disruption of bonds between adjacent endothelial cells[65] and cytoskeletal changes[66] cause cells to pull away from one another and allows endothelial gap formation. Apoptosis also contributes to a dysfunctional vascular barrier.[67–69] The activated endothelium recruits activated neutrophils that release their nuclear contents to form, with activated platelets, neutrophil extracellular traps.[70] As pulmonary endothelium is disrupted, typically vascular-sequestered coagulation factors interact with tissue factor expressed by alveolar epithelial cells and alveolar macrophages, triggering activation of the extrinsic coagulation cascade.[71]

Alveolar epithelial injury, permeability, and dysfunction

An intact alveolar epithelium is a robust defence against alveolar flooding; not only is it relatively impermeable, but its active sodium and chloride transport helps drive oedema resolution.[64,72] In ARDS, both epithelial barrier function and fluid clearance are weakened or inactive.[73] Epithelial injury can be incited directly by microbial pathogens, acid injury (eg, aspiration of gastric contents), hyperoxia, or mechanical stretch (eg, by the ventilator).[74–76] Some of these insults cause epithelial apoptosis or necrosis, whereas others disrupt intercellular junctions, which increase epithelial permeability.[75,77,78] Circulating factors (eg, DAMPs or cell-free haemoglobin) and microbial products, toxins, and circulating immune cells and inflammatory mediators can damage the epithelium.[56,57,79]

Dysregulated lung inflammation

Accumulation of white blood cells, particularly neutrophils, in the lung and alveolar space is clinically and pathologically significant in ARDS.[26,80] Neutrophils from people with ARDS are activated and functionally distinct: they have enhanced chemotaxis, enhanced metabolic activity, delayed apoptosis, and a novel transcriptional signature.[81–83] Activated neutrophils and platelets interact in the injured lung to form neutrophil extracellular traps, complexes of filamentous chromatin fibres and neutrophil-derived proteins,[70] which could help sequester pathogens but also confer lung injury.[84] Alveolar macrophages exert both proinflammatory and anti-inflammatory responses and contribute to epithelial permeability.[85,86] In addition to dysregulated innate immunity, adaptive immunity also seems to play a major role in lung host defence and in the resolution of injury. Regulatory T cells were shown to have a crucial role in lung injury resolution in research done in animals and are detectable in bronchoalveolar fluid from humans with ARDS.[87]

Mechanical stress

Biomechanical forces also contribute to lung injury and ARDS. Rescue of patients with severe hypoxaemia has always relied upon mechanical ventilation; therefore, the concept that the ventilator could both rescue and harm patients is not new. Recognition that positive-end expiratory pressure (PEEP) could be lifesaving was emphasised in the original description of ARDS by Ashbaugh and colleagues[26] in 1967, and subsequent research showed that the combination of large tidal volumes and zero PEEP induced haemorrhagic pulmonary oedema.[88–90] Lung injury due to excessive mechanical strain or stress is sometimes termed ventilator-induced lung injury (VILI), and ventilation strategies that reduce VILI have been a major advancement in the care for patients with ARDS. A clinical trial of a tidal volume and pressure-limited ventilation strategy reduced mortality compared with ventilation with larger tidal volumes and more permissive airway pressures.[91] A so-called low-stretch ventilation strategy with specific limits on ventilator set tidal volume and lung end-inspiratory (plateau) pressure was associated with reductions in plasma and bronchoalveolar lavage concentrations of inflammatory markers such as interleukin (IL-)1, IL-6, IL-8, and tumour necrosis factor α.[92,93] Research done in experimental models suggests that lung-derived circulating mediators can amplify lung injury and epithelial permeability, and some have proposed VILI as a mechanism by which lung injury propagates injury in distant organs (eg, the kidney or brain), leading to multiorgan system failure via biotrauma.[94,95] Although debate remains as to how to identify the optimal ventilation strategy for each individual patient, a general practice of avoiding overdistension and minimising cyclic atelectasis by appropriate use of PEEP form our current recommendations.[96,97]

Initial management

Standard ventilator management

Mechanical ventilation does not cure ARDS; however, it does allow time for the body to recover from the disease

that led to respiratory failure, providing adequate oxygenation and removing carbon dioxide without inducing VILI or other side-effects. In this section, we will discuss the standard approach to mechanical ventilation of ARDS (panel 3), and also discuss the associated challenges and controversies.

Tidal volume and plateau pressure: lung-protective ventilation

The recommended size of the ventilated breath, or tidal volume, has changed as we have learned more about ARDS and shifted from targeting a normal partial pressure of carbon dioxide (PCO_2) to controlling lung distension.[98,99] Following the hypothesis that lung rest could be beneficial,[100] and that permissive hypercapnia[101] could be more appropriate than high-volume, high-pressure ventilation to treat an inflamed lung with its reduced volume of aeration, the value of low-stretch lung ventilation was established in 2000 in the ARMA trial,[91] which reported a survival advantage with tidal volumes of 6 cc/kg predicted bodyweight compared with 12 cc/kg predicted bodyweight. This trial also set a plateau pressure limit of 30 cm H_2O, with further tidal volume reductions as needed to keep plateau pressure below this goal. This concept is now widely accepted, and a lung-protective strategy targeting a tidal volume of less than 6 ml/kg predicted bodyweight and plateau pressure of less than 30 cm H_2O has become standard practice in ARDS management.[97,102]

In the original ARMA trial,[91] target pH was in the range of 7·30–7·45, with target partial pressure of oxygen (PaO_2) of 55–80 mm Hg or oxygen saturation (SpO_2) of 88–95%. A randomised controlled trial, published in 2020, compared targeting a conservative oxygenation goal (SpO_2 88–92%) to a liberal oxygenation goal (SpO2 ≥96%) in patients with ARDS,[103] with the hypothesis suggested by previous studies[104] that the conservative goal might prevent hyperoxic lung injury. However, 90-day mortality was higher in the conservative oxygenation group than the liberal oxygen goal group, and the trial was stopped early by the data safety monitoring committee. In the absence of subsequent data, we recommend that SpO_2 goals should be 93% or higher.

Positive end-expiratory pressure

PEEP is the pressure that maintains some degree of inflation during the end-expiratory pause. Higher PEEP increases mean airway pressure, which usually improves oxygenation. Maintaining inflation during exhalation also decreases the stress of alveoli collapsing and reinflating during the respiratory cycle, termed atelectrauma.[105] The most commonly used method for PEEP selection is to apply an algorithm matching PEEP to the fraction of inspired oxygen (FiO_2) that the patient requires.[91] This approach was tested in clinical trials by the ARDS network (ARDSNet) in the USA and is relatively simple to apply:[91] the higher the fraction of oxygen required, the more PEEP is applied. Three large trials[106–108] tested the hypothesis that a higher PEEP protocol would improve survival compared with the traditional ARDSNet PEEP protocol. For all three trials, no substantial differences in clinical outcomes were observed, suggesting that a high PEEP strategy was not superior for all patients with ARDS. Another trial applying an aggressive high PEEP strategy plus high-pressure recruitment manoeuvres found a statistically significant increase in mortality in the intervention arm; this approach is not recommended.[109] Increasing PEEP can decrease venous return and lower preload, decrease left ventricular afterload, and potentially decrease myocardial oxygen demand.[110] The effect on pulmonary vascular resistance (PVR) is unpredictable, as vascular compression by higher PEEP might increase PVR, yet PEEP-induced changes in aeration and oxygenation might decrease hypoxic vasoconstriction, lowering PVR. Similarly, the effect of PEEP on cardiac output depends on ventricular function, preload, and afterload.[110]

Prone position

Starting from the observation that oxygenation improved in patients in the prone position,[111] physiological studies

For **ARDSNet** see http://www.ardsnet.org

***Panel 3:* Key ventilator parameters for acute respiratory distress syndrome ventilation in a volume assist control mode**

Ventilator settings

- Tidal volume: size of a breath (mL) scaled to predicted bodyweight, as normal lung volume is generally determined by height
- Respiratory rate: breaths per minute
- Minute ventilation: total volume of gas breathed in 1 min; tidal volume multiplied by respiratory rate
- PEEP: a ventilator setting to maintain positive pressure in the lungs even when expiration has ended, resulting in an increased mean airway pressure and possibly recruited (ie, more aerated) lung parenchyma, measured in cm H_2O
- FiO_2: the proportion of oxygen in inspired air (1·0=100% FiO_2)

Ventilator measurements

- Airway peak inspiratory pressure: peak pressure generated by delivering a ventilator breath, composed of resistive and elastic elements
- Airway plateau pressure: pressure during an end-inspiratory hold (volume cycled mode) while the patient is passive; patient respiratory effort can cause inaccurate measurements
- Airway driving pressure: difference between plateau pressure and set PEEP

FiO_2=fraction of inspired oxygen. PEEP=positive end-expiratory pressure.

identified several mechanisms underlying this improvement, including decreasing the differential distribution of ventilation between ventral and caudal lung regions and shifting the density distribution of oedematous lung.[112,113] A series of randomised trials[114–116] paralleled the evolution of pathophysiological understanding;[117] although none of these trials individually showed a survival benefit to prone positioning, post-hoc analysis suggested potential benefit for the most severely hypoxaemic patients when prone position was combined with low stretch ventilation and applied for longer periods (16 h).[118] Based on these findings, a prospective study examined prone ventilation for 17 h per day for patients with moderate or severe ARDS and showed a statistically significant survival benefit.[119] Prone position should be strongly considered for patients meeting criteria (PaO_2/FiO_2 ratio persistently <150) and without contraindications. Careful attention must be applied during the proning procedure to avoid disruption of vascular access catheters and endotracheal tubes and, while the patient is proned, to avoid pressure-related complications. During the COVID-19 pandemic, prone positioning has also been used successfully in awake, non-intubated patients with acute hypoxaemic respiratory failure.[120,121]

Neuromuscular blockade

When oxygen consumption and associated carbon dioxide production increase, total ventilation must increase to maintain constant arterial $PaCO_2$ and pH. Hence, controlling oxygen consumption might have a possible benefit, especially in the early phase of ARDS.[122] Several approaches are possible such as reducing body temperature,[123] sedation,[124] and neuromuscular blockade.[125] Neuromuscular blockade also has the potential benefit of reducing ventilator dyssynchrony, which could lead to inadvertently high tidal volumes and transpulmonary pressures. In 2010, a large randomised study identified an adjusted mortality advantage with neuromuscular blockade (cisatracurium) compared with placebo in patients with moderate or severe ARDS (PaO_2/FiO_2 ratio <150 mm Hg), all of whom were deeply sedated.[126] However, concern about neuromuscular blockade and deep sedation worsening critical illness polyneuromyopathy or longer term functional outcomes led to variable use of cisatracurium.[102,127,128] A subsequent trial failed to show survival benefits in patients with moderate or severe ARDS who were randomly assigned to receive cisatracurium with deep sedation for 48 h compared with light sedation if tolerated, and goal-oriented sedation if not tolerated.[129,130] The control group showed that some cases of ARDS were difficult to manage even with deep sedation, prompting providers to use neuromuscular blockade in roughly 15% of patients in this group during the first 2 days.[129] Importantly, in both of these trials, protocolised duration of neuromuscular blockade was intentionally short (≤48 h), and there was no difference in the incidence of ICU-acquired weakness observed with neuromuscular blockade. Although neuromuscular blockade is thus not mandated for all patients with moderate or severe ARDS, short duration neuromuscular blockade use is safe and could enable improved gas exchange and ventilator synchrony. Our recommendation is to use neuromuscular blockade for patients in whom providers are otherwise unable to reach ventilation synchrony within lung protective targets, for patients with severe hypoxaemia despite deep sedation, and in individualised cases when plateau pressures are high or difficult to accurately measure. Once initiated, we recommend that clinicians consider daily whether neuromuscular blockade remains helpful and consider discontinuation at the earliest opportunity.

Supportive care

Although appropriate ventilator management is of paramount importance in ARDS, adherence to evidence-based supportive care is also crucial. In the setting of increased alveolar-capillary permeability, elevated hydrostatic pressure in the pulmonary vasculature leads to more rapid alveolar flooding than in patients with an intact alveolar-capillary barrier;[131] at the same time, adequate tissue perfusion is crucial for patients with multisystem organ failure, which describes many patients with ARDS. Optimal fluid management in patients with ARDS and concomitant vasopressor-dependent shock remains controversial, with ongoing studies (eg, NCT03434028 and NCT04569942) addressing this issue. However, for patients with ARDS who either never or no longer require vasopressors, the Fluid and Catheter Treatment Trial[48] (FACTT) showed that a fluid-conservative management strategy increased the number of ventilator-free days as compared with a fluid-liberal strategy, without increasing acute kidney injury or need for dialysis. Although the treatment algorithm used in FACTT was relatively complex, in practice, a strategy of diuresis targeted at a net even to negative daily fluid balance is feasible and likely to recapitulate the benefits of the FACTT protocol.[132] No specific caloric goal or supplementation has been proven superior for ARDS in large trials.[133,134] Management of pain, agitation or sedation, and delirium, along with immobility and sleep (PADIS), is important, and sedation practices can strongly affect patient outcomes.[128,135] International critical care guidelines support a goal-directed approach to PADIS that seeks light sedation,[136] and daily spontaneous breathing trials to test patients' readiness to liberate from mechanical ventilation.[137] For patients with ARDS, spontaneous breathing trials should not begin until patients have reached an appropriately low threshold of support on the ARDSNet ventilator grid, typically with a FiO_2 of 0·5 or less and PEEP less than or equal to 8 cm H_2O.

Pharmacotherapy

By stark contrast with ventilator and fluid management of ARDS, where clearly beneficial interventions have been

	Potential mechanisms	Key studies	Comments
Activated protein C	Anticoagulant, anti-inflammatory	Liu et al[138]	..
Anti-endotoxin antibodies	Bind endotoxin and thereby reduce inflammatory response	Bigatello et al[139]	..
Aspirin	Anti-inflammatory via antiplatelet effects	Kor et al[140]	Did not reduce ARDS development in patients at high risk
β-agonists	Improved alveolar fluid clearance	Matthay et al,[141] Gao Smith et al[142]	..
Ibuprofen	Anti-inflammatory, via inhibition of cyclooxygenase	Bernard et al[143]	Did not reduce ARDS development in sepsis
Interferon β-1a	Improve pulmonary endothelial barrier function	Ranieri et al[144]	..
Keratinocyte growth factor	Promote epithelial repair	McAuley et al[145]	..
Ketoconazole	Anti-inflammatory	The ARDS Network[146]	..
Lisofylline	Anti-inflammatory	The ARDS Network[147]	..
Neutrophil elastase inhibitor (eg, sivelestat)	Anti-inflammatory	Zeiher et al,[148] Iwata et al[149]	..
Nitric oxide (inhaled)	Pulmonary vasodilatation, improve V/Q mismatch	Gebistorf et al[150]	Improved oxygenation; increased acute kidney injury
Omega-3 fatty acids	Anti-inflammatory	Rice et al[134]	..
Procysteine and N-acetylcysteine	Reduction in oxidant injury via restoring glutathione	Bernard et al[151]	..
Prostaglandin E1	Pulmonary vasodilatation, improve V/Q mismatch	Fuller et al,[152] Vincent et al[153]	..
Statins (eg, simvastatin, rosuvastatin)	Anti-inflammatory; endothelial stabilisation	McAuley et al,[154] Truwit et al[155]	..
Surfactant	Promote epithelial repair, reduce atelectrauma	Spragg et al[156]	Effective in neonatal respiratory distress syndrome

ARDS=acute respiratory distress syndrome. V/Q=ventilation–perfusion.

Table 1: **Selected pharmacotherapies found to be ineffective for ARDS in human clinical trials**

identified through rigorous randomised trials, decades of clinical trials of pharmacotherapies for ARDS have failed to identify any consistently effective drugs. Most of the biological pathways thought to be dysregulated in ARDS have been targeted in clinical trials (table 1), including inflammation, epithelial injury, endothelial injury, and disordered coagulation, but no drugs targeting these pathways have proven consistently effective.[157] In 2020, vitamin D was proposed to have potentially beneficial immunomodulatory effects; however, in a randomised controlled trial of 1360 critically ill patients at high risk for ARDS or death, high dose vitamin D had no benefit on mortality or other outcomes.[158] Similarly, a clinical trial published in 2020 randomly allocated 301 patients with moderate to severe ARDS to receive either placebo or intravenous interferon-β-1a, thought to improve pulmonary endothelial barrier function, but found no benefit.[144]

Despite this discouraging track record, some phase 2 studies have identified potentially promising drugs. The CITRIS-ALI trial[159] investigated high dose vitamin C versus placebo in 167 patients with early sepsis and ARDS; although no difference was observed in the primary outcome of modified sequential organ failure assessment score at 96 h, patients treated with vitamin C had a significant reduction in 28-day all-cause mortality, compared with placebo (30% *vs* 46%, p=0·03). Vitamin C is also being studied in sepsis and might have beneficial effects on systemic inflammation, coagulopathy, alveolar fluid clearance, and formation of neutrophil extracellular traps.[160–162] Other potentially promising drugs in early phase clinical trials for ARDS include allogeneic mesenchymal stromal cells, carbon monoxide, sevoflurane, DNAse, and granulocyte-macrophage colony-stimulating factor.[163,164] The increasing interest in the use of enrichment strategies, either prognostic (enrolling patients at high risk for ARDS-related poor clinical outcomes) or predictive (enrolling patients with a biological phenotype well matched to the drug's mechanism) approaches, might improve the success rate of future studies.[165,166]

Rescue therapies

Despite maximal supportive therapy with optimal ventilator and fluid management, some patients with ARDS will continue to worsen, with development of severe and refractory hypoxaemia, hypercapnia or acidosis, elevated plateau pressures, or a combination. In these patients, clinicians can consider so-called rescue therapies—ie, adjunctive therapies for ARDS whose benefits have not been conclusively shown for all patients but could show benefit in individualised circumstances (table 2).[174] These therapies can include extracorporeal life support, alternative ventilator modalities or settings, or

	Proposed mechanism	Clinical settings for use	Potential risks	Key studies
ECMO	Allow ultraprotective ventilation; rescue oxygenation	Severe and persistent hypoxaemia ; severe and persistent acidosis; refractory elevated inspiratory plateau pressure; first 7 days of mechanical ventilation with reversible cause	Bleeding, vascular access complications, thrombocytopenia, stroke; only available at referral centres	Peek et al,[167] Combes et al[168]
Higher PEEP strategies	Recruit collapsed alveolar units, thereby improving compliance and oxygenation	Refractory hypoxaemia	Decreased preload leading to hypotension; barotrauma	Mercat et al,[106] Meade et al,[107] Brower et al[108]
Recruitment manoeuvre	Recruit collapsed alveolar units, thereby improving compliance and oxygenation	Refractory hypoxaemia , particularly in patients who seem PEEP responsive	Decreased preload leading to hypotension; barotrauma	Brower et al,[108] Cavalcanti et al[109]
Inhaled pulmonary vasodilators	Improve V/Q matching, reduce pulmonary vascular pressures	Refractory hypoxaemia	Associated with acute kidney injury; development of tachyphylaxis	Gebistorf et al[150]
Corticosteroids	Decrease inflammation	Refractory hypoxaemia	Immunosuppression, critical illness myopathy or neuropathy; increased duration of viral shedding in influenza or SARS-CoV-1; conflicting data on benefits; late administration associated with harm	Lewis et al,[157] Villar et al,[169] Steinberg et al,[170] Bernard et al[171]
CRRT	Additional fluid removal and acid clearance; theoretical cytokine clearance	Refractory acidosis in setting of plateau pressure limitation	Risks of vascular access, bleeding	..

Not recommended: high-frequency oscillatory ventilation.[172,173] ARDS=acute respiratory distress syndrome. CRRT=continuous renal replacement therapy. ECMO=extracorporeal membrane oxygenation. PEEP=positive-end expiratory pressure. V/Q=ventilation–perfusion.

Table 2: **Rescue therapies for ARDS**

select pharmacotherapies. It is important to emphasise that these therapies should be considered primarily for patients with severe and refractory ARDS and should not be considered for routine management of typical ARDS patients (table 2).

Several developments in rescue therapies merit additional discussion. Extracorporeal life support (one form of which is extracorporeal membrane oxygenation [ECMO]) uses cardiopulmonary bypass technology to pass the patient's blood through an oxygenator, which increases blood oxygen content without injurious ventilator pressures or volumes. The CESAR trial,[167] published in 2009, reported that a higher proportion of patients with severe ARDS were alive and disability-free when randomly allocated to being transferred to centres that provided extracorporeal life support, as compared with staying at the referring hospital. Most but not all transferred patients received extracorporeal life support.[167] In 2018, Combes and colleagues[168] reported the results of the EOLIA trial, which randomly assigned 249 patients with early and very severe ARDS to immediate venovenous ECMO or continued supportive care; notably, 28% of patients in the control arm crossed over to ECMO because they had refractory hypoxaemia.[168] Although patients randomly assigned to ECMO had an 11% absolute risk reduction for 60-day mortality compared with the control group (35% *vs* 46%, p=0·09), this outcome did not meet the predetermined criteria for statistical significance, and the trial was stopped early because of futility. Importantly, although conclusive benefit was not shown, ECMO appeared to be safe by comparison with conventional treatment, although with higher incidences of thrombocytopenia and bleeding requiring transfusion. The benefit of ECMO could partly be attributed to the reduced plateau pressures required by the ECMO protocol, the resulting lower tidal volumes, or both.[168] These data suggest that ECMO should be strongly considered in patients with very severe ARDS who are early in the course of disease (mechanical ventilation ≤7 days) and with potentially reversible respiratory failure. There is substantial global and local variation in decision making about in whom to initiate ECMO, how long to maintain ECMO, and when to withdraw care in patients on ECMO.[175,176] These decisions are highly personalised to local resources, the patient's condition and comorbidities, and patient and surrogate wishes, and a multidisciplinary process for such complex decisions is recommended.[176]

Corticosteroids have been considered as a potentially effective therapy for ARDS since the syndrome's original description[26] in 1967 and have persisted in the discussion of rescue therapies. Despite the intuitive appeal of an anti-inflammatory therapy for ARDS and numerous clinical trials of corticosteroids over the past several decades, results have been conflicting, and the topic remains controversial (figure 3). A 2019 Cochrane systematic review on corticosteroids in ARDS concluded, albeit with low-certainty evidence, that corticosteroids might improve the number of ventilator-free days up to day 28 in ARDS; however, the review was unable to draw firm conclusions about mortality or

other outcomes.[177] Villar and colleagues[169] reported results of a randomised (but not placebo-controlled or masked) clinical trial comparing dexamethasone to standard care for patients with moderate to severe ARDS; patients in the dexamethasone group had 4·8 more ventilator-free days compared with untreated patients, and a 15% absolute risk reduction in 60-day mortality (21% *vs* 36%).[169] However, there were several methodological issues with this trial, including lack of complete masking, high use of corticosteroids before enrolment, slow accrual and premature termination, and greater reintubation rate in the dexamethasone group. Importantly, corticosteroids might be harmful in influenza pneumonia, in which steroids have been reported to delay viral clearance, and when administered late in persistent ARDS (>14 days after diagnosis).[170,178,179] In the 2019 EVALI outbreak, corticosteroids were reported to be beneficial, although the natural history of EVALI remains unclear, and many patients improved in the absence of corticosteroid treatment.[180] In patients with acute respiratory failure requiring mechanical ventilation due to SARS-CoV-2 (most of whom presumably had ARDS), the RECOVERY trial[181] reported that dexamethasone increased survival. These data emphasise the importance of identifying the specific cause of ARDS, since the underlying cause can dictate treatment response. Further research is needed to identify which patients with ARDS are most likely to benefit from corticosteroids and which patients could be harmed.

Controversies and new research in ARDS

Personalising mechanical ventilation

The best method to select a patient's PEEP remains controversial. Randomised controlled trials to adjust PEEP based on the patient's oxygenation[182] or radiographical focality[183] have not shown a consistent benefit. One suggestion has been to use driving pressure (ie, plateau pressure minus PEEP) as an alternative target to optimise ventilatory parameters. In re-analysis of multiple randomised trials of ventilator strategies, driving pressure retained the strongest association with mortality compared with either tidal volume or plateau pressure,[184] suggesting that driving pressure minimisation might be beneficial. However, although randomised trials have shown benefit to a tidal volume pressure and plateau pressure-limited approach, no such evidence base exists for driving pressure. An approach to maintain a consistent, low driving pressure (12 cm H_2O) while doing recruitment manoeuvres and stepwise PEEP de-escalation to select the optimal PEEP resulted in excess mortality compared with traditional PEEP–FiO2 selection.[109] Despite a favourable pilot study,[185] use of oesophageal manometry to estimate pleural pressure and personalise PEEP to maintain a positive transpulmonary pressure did not reduce mortality or time on the ventilator.[186]

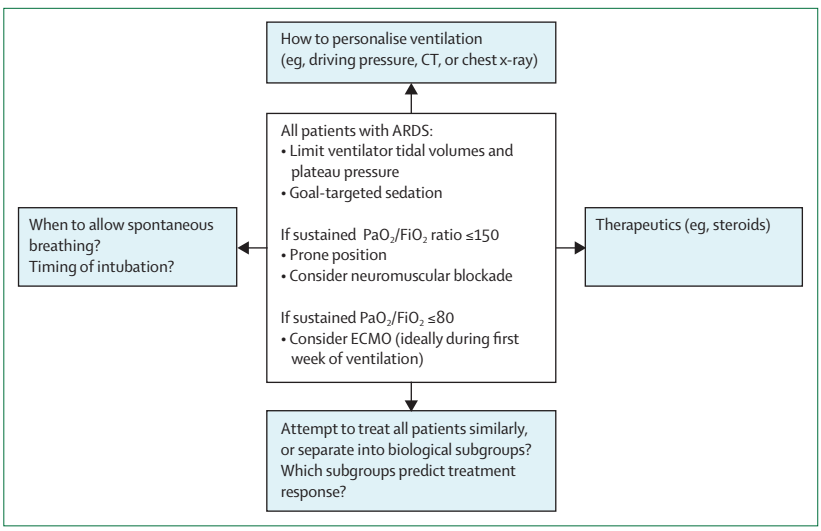

Figure 3: **Areas of consensus and controversy in ARDS management**
Central box shows the areas of consensus. Blue boxes show areas of controversy and new directions. ARDS=acute respiratory distress syndrome. ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. PaO_2=partial pressure of oxygen.

Spontaneous breathing during ARDS

Another topic of controversy in ARDS is deciding when patients should be permitted to set their own breathing pattern, tidal volumes, and respiratory flows. The putative advantages of spontaneous breathing in ARDS—either through ventilator modes that give the patient control of breath size and frequency or through non-invasive ventilatory support—include potentially improved distribution of ventilation matched to perfusion in dorsal-dependent lung regions,[187] reduced need for sedation, avoidance of complications of endotracheal intubation, and prevention of diaphragm atrophy.[188] Countering these possible benefits are potential disadvantages including dyspnoea and anxiety, increased oxygen consumption and carbon dioxide generation, ventilator asynchrony, and pendelluft,[189] a term describing movement of air from one region of the lung to another, which is not effective gas exchange.[189] Furthermore, there is concern that negative intrathoracic pressure generates large swings in transpulmonary pressure, which can incite pulmonary oedema, sometimes termed patient self-inflicted lung injury.[188,190]

Non-invasive ventilation[191] and HFNC[192] have been proposed as alternatives even in well established ARDS. Some studies have reported that patients with ARDS who were unsuccessfully treated with non-invasive ventilation, and subsequently required intubation, had worse outcomes.[193,194] It is possible that some of these patients developed negative transpulmonary pressures during non-invasive ventilation causing patient self-inflicted lung injury. The same reasoning might apply to HFNC.[195] However, HFNC reduced mortality when applied early in patients with acute hypoxaemic respiratory failure, many of whom probably had early ARDS.[196] No large-scale trial

has specifically addressed the optimal timing of intubation in ARDS.

Heterogeneity in ARDS

ARDS is by definition a syndromic diagnosis rather than a distinct pathological entity; therefore, patients with ARDS have great heterogeneity in their clinical, physiological, radiological, and biological phenotypes. Since the earliest consensus definition of ARDS,[40] this heterogeneity has been recognised as a potential barrier to effective therapy, but ARDS researchers and clinicians have lacked consensus on the usefulness of and optimal approach to further subdividing the syndrome.[40]

Clinically apparent subphenotypes of ARDS have been shown to differ physiologically and biologically.[197] In theory, extrapulmonary ARDS (eg, non-pulmonary sepsis) should first affect endothelial permeability, leading to prevalent diffuse oedema, whereas pulmonary ARDS should first affect the alveolar epithelium. Experimental data fit this model,[198] and patients with direct (ie, pulmonary) lung injury have lower severity of illness, fewer organ failures, more evidence of lung epithelial injury and lower concentrations of plasma biomarkers of endothelial injury, compared with patients with indirect (ie, extrapulmonary) lung injury.[199,200] However, after the first few days of ARDS, and indeed often in clinical practice, it is difficult to differentiate between pulmonary and extrapulmonary ARDS, and evidence that these phenotypes should alter treatment is insufficient.

***Panel 4*: Fundamental elements of initial intensive care unit care for patients with ARDS**

- Lung protective ventilation strategy: goal tidal volume ≤6 mL/kg, plateau pressure ≤30 cm H_2O, PEEP relative to FiO_2 set according to ARDS Network grids or local practice,[91] generally PEEP ≥5 cm H_2O
- Assiduous search for and treatment of underlying cause of ARDS
- Sedation and analgesia only as needed to promote comfort, ventilator synchrony
- Fluid conservative strategy including aggressive diuresis if needed to reach net negative fluid status, once shock has resolved (off vasopressors)
- Stress ulcer prophylaxis, deep venous thrombosis prophylaxis with subcutaneous heparin or low-molecular weight heparin, unless otherwise contraindicated
- Daily spontaneous breathing trials to assess for ventilator liberation beginning when the patient can tolerate FiO_2 ≤0·5 and PEEP ≤8 cm H_2O
- For patients with moderate to severe ARDS (PaO_2/FiO_2 ratio <150 mm Hg), consider:
  - Neuromuscular blockade, with goal duration <48 h
  - Prone positioning for at least 17 h per day

ARDS=acute respiratory distress syndrome. FiO_2=fraction of inspired oxygen. PaO_2=partial pressure of oxygen. PEEP=positive end-expiratory pressure.

In another example of clinically apparent heterogeneity, the LIVE trial[183] tested the value of personalising therapy according to radiological assessment of diffuse versus focal lung injury as compared with a conventional generalised approach.[183] The overall trial showed no difference in outcomes between the personalised and standard care groups; however, when the 20% of patients in the personalised group whose radiological phenotype was misclassified were excluded, the personalised strategy seemed beneficial. These results highlight the potential value, and challenges, of a targeted approach to ARDS trials and management.[201]

Investigators have applied unsupervised data-driven analytical approaches to ask whether there are unobserved subphenotypes within ARDS. Latent class analysis of clinical and protein biomarker data from five randomised trial cohorts of patients with ARDS identified two distinct and consistent subphenotypes in all five cohorts.[2,202–204] One subphenotype, representing about 30% of patients with ARDS, has higher plasma concentrations of inflammatory cytokines, lower plasma concentrations of the coagulation factor protein C and bicarbonate, a higher prevalence of shock, and consistently worse clinical outcomes than patients with the subphenotype characterised by lower inflammatory markers.[205] In secondary analyses of completed clinical trials, these two subphenotypes seemed to respond differently to PEEP, fluid management strategy, and simvastatin, although prospective confirmation of these findings is needed. Similarly, cluster analysis of plasma protein biomarker data identified two distinct ARDS subphenotypes, termed reactive and uninflamed.[206] The reactive subphenotype had worse clinical outcomes and different expression of 29% of genes measured in whole blood using an array-based analysis.[207] How ARDS subphenotypes identified with these two different approaches correspond to each other, or to transcriptomic-based subphenotypes of sepsis,[208] remains unknown. Prospective validation of subphenotype identification and differential treatment responses will be required before clinical care should be affected.

ARDS due to COVID-19

By May, 2021, there were over 160 million cases of confirmed COVID-19 worldwide, with over 3·3 million reported deaths.[209] This global pandemic has increased interest in ARDS due to SARS-CoV-2, as many clinical centres have become overwhelmed with patients with severe ARDS. Early reports highlighted unique features of COVID-19-associated ARDS,[210] although subsequent data suggested that it shares many physiological aspects with classic ARDS, including heterogeneity.[211] Similarly, early reports suggested a high prevalence of venous thrombosis and coagulopathy in COVID-19-associated ARDS,[212] and it will be important to compare these data with other causes of ARDS in which endothelial dysfunction and disordered coagulation are important factors.[213]

Remdesivir, a novel antiviral therapy that has shown in-vitro efficacy against coronaviruses, can shorten time to clinical improvement for patients hospitalised with severe COVID-19 disease and has received Emergency Use Authorisation by the US Food and Drug Administration for use in this setting; however, data on its efficacy are conflicting and WHO has recommended against its use.[52] The RECOVERY trial,[181] a large pragmatic randomised open-label study in the UK, reported that dexamethasone 6 mg daily for 10 days was associated with a lower 28-day mortality for hospitalised patients with COVID-19, with the largest effect seen in patients receiving mechanical ventilation.[181] Meta-analysis of seven randomised trials testing different steroid regimens that included over 1700 patients detected a summary odds ratio for death of 0·66 (95% CI 0·53–0·82, p<0·001) with similar estimates of effect for dexamethasone or hydrocortisone.[214] Hydroxychloroquine is not effective.[215] Numerous potential therapies are being urgently explored, including anticoagulation, immune modulatory approaches (eg, IL-6 receptor blockade), repurposed drugs (eg, azithromycin), convalescent plasma, and monoclonal antibodies. Although some of these therapies might ultimately prove beneficial, they all have potential to cause serious adverse events (eg, bleeding complications and immunosuppression). While awaiting more data, a prudent strategy for treatment of patients with COVID-19-associated ARDS is to adhere to the fundamental principles of initial care for ARDS (panel 4), including lung-protective ventilation, to treat with dexamethasone and consider remdesivir on the basis of published clinical trials, and to attempt to enrol patients in randomised controlled trials of novel therapies whenever feasible rather than applying untested therapies that could equally harm or benefit patients.

Conclusions

More than 50 years after its original definition, ARDS remains common and clinical outcomes remain sobering. Nowadays, ARDS is particularly relevant because of the global ARDS pandemic due to SARS-CoV-2 affecting millions worldwide. Substantial progress has been made over the past five decades in understanding the epidemiology and biology of this heterogeneous syndrome, and in developing an evidence-based approach to supportive care, premised on a low tidal volume and plateau pressure-limited ventilation strategy and an assiduous search for and treatment of the underlying cause of ARDS. Key future directions for ARDS include identification of which elements of treatment apply broadly to any patient meeting the syndrome's diagnostic criteria and which elements should be personalised to specific aspects of physiology and biology that could identify a more treatment-responsive subgroup.

Contributors

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