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Acute Respiratory Distress Syndrome in adults: diagnosis, outcomes, long-term sequelae, and management.

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Summary

Acute respiratory distress syndrome (ARDS) is characterised by acute hypoxaemic respiratory failure with bilateral infiltrates on chest imaging, which is not fully explained by cardiac failure or fluid overload. ARDS is presently defined by the Berlin criteria. In this *Series* paper the diagnosis, management, outcomes and long-term sequelae of ARDS are reviewed. Potential limitations of the ARDS definition and evidence that may inform future revisions is considered. Guideline recommendations, evidence, and uncertainties in relation to ARDS management are discussed. The future of ARDS strives towards a precision medicine approach, and the paradigm of treatable traits in ARDS diagnosis and management is explored.

Introduction

Acute respiratory distress syndrome (ARDS) is characterised by acute hypoxaemic respiratory failure with bilateral infiltrates on chest imaging, which is not fully explained by cardiac failure or fluid overload. [1] It is precipitated by a predisposing risk factor such as pneumonia, non-pulmonary sepsis, gastric aspiration, trauma, pancreatitis, burns, inhalation injury, drug overdose, multiple transfusions or shock. [2] The precipitating insult triggers a cascade of dysregulated inflammatory responses and cytokine activation. Injury to the alveolar epithelial-endothelial barrier may occur directly due to pulmonary insults, with primary damage to the lung epithelium, or indirectly due to a extrapulmonary insults, with primary damage to the vascular endothelium as a result of systemic inflammation. [3] However, it is important to recognise that the majority of patients with ARDS will likely have features of both direct and indirect lung injury. [3] The resultant disruption of the alveolar epithelial-endothelial barrier results in accumulation of a protein rich pulmonary oedema, surfactant dysfunction and impaired gas exchange. [4] It can be associated with physiological derangement, including decreased respiratory system compliance, increased physiological dead space, and increased shunting, along with histological features of lung oedema, inflammation, hyaline membranes and alveolar haemorrhage. [2] Classically, its histological hallmark was described as diffuse alveolar damage, however in autopsy data this has been reported to be present in less than half of patients with ARDS. [5]

In this *Series* we discuss the diagnosis, management, outcomes and long-term sequelae of ARDS. As the majority of critically ill patients with severe COVID-19 are likely to fulfil the criteria for ARDS[6], evidence related to COVID-19 ARDS is considered throughout this series. Panel 1 contextualises our current understanding of the similarities and differences between COVID-19 ARDS and ARDS due to other causes. [7-10]

Diagnosis

The utility of diagnostic tools in healthcare is their ability to inform clinical decision making and identify populations of patients with common sets of characteristics, outcomes and treatment responsiveness. [11] ARDS is a syndrome which as an entity has progressed through various iterations of diagnostic criteria since its first description by Ashbaugh *et al* in 1967. [12] There were no uniformly accepted criteria for ARDS until the development of the American-European Consensus Conference (AECC) definition for ARDS in 1994. [13] Addressing limitations of the AECC definition, the current Berlin definition (Panel 2) was developed in 2012 by consensus of an expert panel. [1] One benefit of a standardised definition for ARDS has been to facilitate recruitment into clinical trials which has led to the development of effective supportive therapies. A standardised definition also allows clinicians to readily understand the population recruited to a clinical trial and therefore apply the evidence generated from those trials to inform the treatment of the appropriate patients in clinical care. [14]

It is worth considering patients with ARDS represent a subset of a broader population of acute hypoxaemic respiratory failure (AHRF). The key difference between ARDS and acute hypoxaemic respiratory failure (AHRF) is the requirement for bilateral infiltrates on chest imaging. Evidence from the LUNGSAFE study indicates that outcomes are similar for patients with unilateral or bilateral infiltrates[15], suggesting the need for bilateral infiltrates as part of the syndromic definition of ARDS may not be needed. Further research is needed to understand the similarities and differences in the clinical and biological characteristics of patients with ARDS and AHRF.

With the evolution of clinical care and increasing recognition of the global burden of ARDS, it is timely to consider several aspects of the current syndromic definition of ARDS which might usefully be addressed in an updated ARDS definition. Figure 1 summarises how the ARDS criteria have evolved over time and how these criteria may evolve in the future.

Chest radiographic criterion for ARDS are recognised to have suboptimal inter-observer reliability and are underrecognized in clinical settings. [16] In research settings tools have been investigated to improve the reliability of ARDS diagnosis. The RALE score (Radiographic Assessment of Lung Oedema Score), using a visual assessment of four quadrant consolidation and infiltrate density, has been shown to have good intra-observer reliability and high diagnostic accuracy for ARDS. [17] A similar visual assessment score has been shown to correlate with important clinical outcomes including mortality and duration of ICU stay. [18] Artificial intelligence technology (utilising deep convolutional neural networks that can be trained to recognise findings on imaging) such as https://ardsdetect.com is another tool which has been shown to accurately identify bilateral airspace consolidation consistent with ARDS in research settings but requires further validation before clinical use. [19]
Ultrasound imaging is emerging as a safe, inexpensive, bedside tool for the evaluation of ARDS although the need for training is recognised to be essential before this can be implemented as a diagnostic imaging modality for pulmonary infiltrates.

SpO_2/FiO_2 ratio is an attractive alternative to PaO_2/FiO_2 ratio due to its availability and safety. These simple bedside tools may be useful in resource limited settings, and outside of the traditional ICU. [20-22] Evidence from retrospective analysis support the ability of the SpO_2/FiO_2 ratio to predict outcomes in patients with ARDS. [20] In resource limited settings, where mechanical ventilation, blood gas analysis and chest imaging may not be available, the Kigali modification utilising the SpO_2/FiO_2 ratio and lung ultrasound has been suggested and has been useful to evaluate ARDS in these settings. [23,24] Additionally the Kigali modification removes the requirement for positive-end-expiratory-pressure (PEEP) as ventilator resources may not be available. [23]

Lung ultrasound and SpO_2/FiO_2 ratio have limitations as diagnostic tools in ARDS. Lung ultrasound may overestimate ARDS, with a high false positive rate attributed to its high sensitivity for detecting interstitial infiltrates and consolidative changes. [25] Vercesi *et al* demonstrated this in a comparison of the Kigali modification with the Berlin criteria in a single centre observational study in the Netherlands. [25] In addition, pulse oximetry may cause disparities in the identification of occult hypoxaemia due to skin colour. [26] Further prospective studies are required to determine optimal SpO_2/FiO_2 thresholds for severity, which should account for differences in race and ethnic origin.

The requirement for positive pressure ventilation means many patients with non-cardiogenic AHRF and bilateral infiltrates cannot meet the current definition of ARDS. Given the increasing use of high flow nasal oxygen (HFNO), and that HFNO may deliver low levels of PEEP as one of its physiological benefits[27], there is interest in including HFNO at a rate of least 30L/minute in future definitions of ARDS. [28] This would allow those patients who would otherwise fulfil the definition of ARDS to be included in the population of ARDS. It is likely this population will have similar biological characteristics to patients with ARDS receiving positive pressure ventilation. This would also allow earlier identification of patients with ARDS, as well as facilitate recruitment to clinical trials at an earlier time point in their clinical course. There are potential limitations of this modification. For instance, in a single centre prospective study of 148 patients, PaO_2/FiO_2 was found to vary substantially after a change in respiratory support from HFNO to invasive ventilation. [29] Furthermore, Ranieri *et al* demonstrated patients fulfilling ARDS criteria on HFNO may have lower mortality rates. [30]

Currently no ARDS biomarker is recommended in clinical practice according to clinical guidelines. The Berlin Task Force considered biomarkers for inclusion in the previous ARDS revision but found they lacked sensitivity and specificity as a diagnostic tool. [2] Bos *et al* have recently reviewed potential biomarkers which could inform the diagnostic criteria of ARDS. [31] Markers of endothelial or epithelial injury, protein rich pulmonary oedema, and systemic or alveolar host response could be considered. A novel approach to assess for the presence of protein rich pulmonary oedema includes evaluation of fluid from heat moisture exchange (HME) filter, however this technique still requires validation with important outcomes in ARDS. [32,33]

There is increasing recognition of the limitations of a syndromic definition which ignores the significant biological and physiological heterogeneity within ARDS. This has driven a new paradigm focusing on the recognition of identifiable and treatable biological traits. [34] As a result in the future populations of patients may be identified by treatable traits rather than a syndromic definition of ARDS. Pioneering work by Calfee *et al* has identified biological phenotypes which may have differential treatment responsiveness. [35-37] The PHIND study (NCT04009330) aims to evaluate the ability of a point of care assay to prospectively identify these phenotypes at the bedside. ARDS phenotypes have also been identified by machine learning models using routinely available clinical data[38], which may prove a useful tool to incorporate into electronic health systems to phenotype patients in real time. Biological phenotypes, along with emerging data from multi-omic studies[39] and immunophenotyping[40] may inform treatable traits in ARDS that could be incorporated into future ARDS

criteria. The National Institute of Health has recently issued a call for funding applications to form a collaborative ARDS, Pneumonia, and Sepsis Phenotyping Consortium to seek to understand the heterogeneity and underlying mechanisms of critical illness. This is an important step towards precision medicine for ARDS. These biological phenotypes and treatable traits also may be present beyond ARDS and be common to other clinical syndromes seen in the critically ill. [41]

ARDS Management

Panel 3 summaries evidence based guidelines for the management of ARDS (published by the United Kingdom (UK) Faculty of Intensive Care Medicine (FICM) and Intensive Care Society (ICS) [42], French-speaking Intensive Care Society (SRLF) [43], jointly by the American Thoracic Society (ATS), European Society of Intensive Care Medicine (ESICM), and Society of Critical Care Medicine (SCCM) [44], and World Health Organisation (WHO) living guidelines for ARDS due to COVID-19. [45] A recent report by an expert panel in the UK suggested the supportive management of patients with ARDS due to COVID-19 should follow existing evidence based ARDS guidelines. [46] Here we consider the evidence regarding ventilation strategies, prone positioning, extracorporeal support, neuromuscular blockade and corticosteroids in the management of ARDS. Future directions for therapeutic interventions in ARDS are also discussed (Figure 2).

Ventilation strategies

Lung protective ventilation (tidal volumes <6 ml per kilogram predicted body weight (PBW) and plateau pressure ≤ 30 mmHg) is a key recommendation based on the findings of the landmark ARMA trial, with reduced mortality and increased days free of ventilation. [14] Randomised controlled trials (RCTs) of novel ventilatory strategies have continued to reinforce the benefit of lung protective ventilation. [47-49] Clinical trials investigating alternative ventilation strategies have not shown additional benefit compared to lung protective ventilation. [50-52] Airway pressure release ventilation (APRV) is an innovative pressure controlled mode of ventilation which delivers a prolonged high level of pressure (Phigh) with intermittent, time cycled pressure release to a low level of pressure (Plow). [53] Meta-analysis of APRV in AHRF (330 patients in five studies, three of which were in ARDS patients) suggests a benefit in hospital mortality, ventilation free days and ICU length of stay. [53] However, studies conducted to date have had methodological limitations[53], and a robust clinical trial is required to address the role of APRV in ARDS.

Guideline recommendations currently reserve high positive end expiratory pressure (PEEP) for patients with moderate to severe ARDS. A recent Bayesian network meta-analysis evaluated PEEP strategies and recruitment maneouvres in ARDS. [54] The key finding of this analysis was that in moderate to severe ARDS a strategy of higher PEEP without a lung recruitment manoeuvre was most likely to be beneficial (probability of mortality benefit 99%), while conversely it was found that a prolonged recruitment manoeuvre with higher PEEP probably caused harm (99% probability of increased mortality). [54] Heterogeneity of individual patient responses to PEEP strategies is recognised[55], and there is increasing interest in personalised PEEP strategies, although to date these have not demonstrated additional benefit over conventional PEEP strategies. [56,57]

Driving pressure (plateau pressure minus end expiratory pressure) may be an independent predictor of survival in patients with ARDS. [47] Amato *et al* demonstrated that driving pressure was the key mediator of the benefits of PEEP and tidal volume strategies. [47] An upper limit of 15 cmH_2O for driving pressure is currently recommended, above which there is significant lung stress[58] and mortality may increase. [47,59] Conversely, two clinical trials have now found increased mortality in the setting of lower driving pressure, suggesting driving pressure may not be as useful as originally expected to predict mortality. [57,60] Clinical trials that are underway to investigate PEEP strategies targeted to driving pressure (including the STAMINA trial NCT04972318) will provide important data to inform this debate.

Another novel concept which has been applied in the context of ARDS is mechanical power. Mechanical power is the amount of energy transferred from a mechanical ventilator to the respiratory system per unit of time, and is determined by the combined effects of applied tidal volume, driving pressure, respiratory rate, inspiratory flow and positive end expiratory pressure (PEEP), as well as determinants of mechanical properties of the lung (respiratory system elastance and airway resistance). [61] Mechanical power can be calculated as: power (J/min) = 0.098 x Tidal Volume x Respiratory Rate x [PEEP + (0.5 x Driving Pressure) + (Peak pressure - Plateau Pressure)]. [48] Mechanical power may be a better driver of lung protective ventilation, compared to individual ventilator parameters, as it considers the balance of these parameters as a whole. [62] Re-analyses of clinical trial and observational data have demonstrated mechanical power is associated with mortality outcomes. [48,63-66] In a retrospective analysis including 8207 patients a consistent increase in the risk of death was reported with

mechanical power greater than 17 J/min. [65] The complexity of interpretating mechanical power limit its clinical use, although recently Costa *et al* found the component variables of mechanical power most predictive of mortality were in fact the driving pressure and respiratory rate. [48] As these variables can be easily measured at the bedside, the additional benefit of mechanical power remains uncertain.

Heterogeneity of treatment effect is apparent in studies investigating ventilatory strategies in ARDS and suggest there may be phenotypes (or treatable traits) to direct personalised ventilatory strategies towards. Costa *et al* found patients with lower respiratory system compliance may be more likely to benefit from lower tidal volumes and lower driving pressures, while patients with higher compliance were predicted to benefit more from lower respiratory rates. [48] In a re-analysis of the EPVent-2 trial investigating oesophageal pressure guided PEEP in ARDS there was a differential effect on mortality dependent on disease severity as determined by the APACHE-II score. [67] Hyper- and hypo- inflammatory subphenotypes of ARDS have also been reported to respond differentially to PEEP strategies. [35] The findings from the LIVE trial, which investigated personalised mechanical ventilation tailored to lung morphology in patients with ARDS, highlights the need to align phenotypes with personalised ventilation strategies. [68] In this study in patients who received a ventilator strategy misaligned with lung morphology, mortality was substantially increased. [68]

Prone positioning

Prone positioning in patients with ARDS improves oxygenation, increases recruitability and reduces areas of alveolar overdistension, thus ensuring more homogenous aeration of the lung and potentially reducing ventilator induced lung injury. [69] Based on data from the PROSEVA multicentre RCT, mechanically ventilated patients with severe ARDS, defined as a PaO_2/FiO_2 ratio < 150mmHg with an FiO_2 of at least 0.6 and PEEP of at least 5 cmH_20 after an initial period of stabilisation of at least 12 hours should be ventilated in the prone position for at least 16 hours daily until clinical improvement. Prone ventilation should be instituted early and ideally within 36 hours of meeting these criteria. It is important to note that prone ventilation should be used alongside a lung protective ventilatory strategy and typically patients should be receiving a higher PEEP. [70] Prone position was associated with an improvement in mortality at day 28 (16% vs 33%, p<0.0001), which persisted at day 90 (24% vs 41%, p <0.0001). [70] Cumulative evidence from clinical trials performed prior to PROSEVA do not support the universal application of prone position for patients with less severe ARDS. [42,44] Despite evidence of benefit in the PROSEVA trial, the APRONET prospective international observational prevalence study found only one-third of patients with severe ARDS were treated in the prone position. [71] This may in part be explained by concerns regarding adverse events such as endotracheal tube obstruction, pressure sores and loss of venous access. [44] In the setting of COVID-19 ARDS, prone positioning has been safely implemented widely for ventilated patients. [8]

In the setting of COVID-19, the use of prone positioning has been extended to awake un-intubated patients, but there remains uncertainty with conflicting findings from recent trials. [72,73] The duration of prone position in these studies has been shorter than that found to be beneficial in sedated and paralysed patients receiving invasive mechanical ventilation, and was often limited by patient comfort. [72,73] There is no evidence to inform the use of prone positioning in awake un-intubated patients AHRF not due to COVID-19 and a clinical trial is required to answer this question.The role of prone position as an adjunct to ECMO therapy also remains uncertain, and is the subject of ongoing clinical trials (NCT04139733, NCT04607551).

Neuromuscular blockade

Previous guidelines made a weak recommendation for early neuromuscular blockade in patients with moderate to severe ARDS, although methodological limitations in the available evidence was noted. [42,43] More recently, the ROSE (Early Neuromuscular Blockade for ARDS) trial investigated the role of neuromuscular blockade with deep sedation compared to usual care with light sedation in patients with moderate to severe ARDS. [74] The trial was stopped for futility (after enrolling 1006 patients) and demonstrated no difference between groups in 90-day mortality. [74] On the basis of this evidence, the routine use of continuous neuromuscular blockade is not recommended in an unselected population of patients with ARDS. The ROSE trial did not specifically evaluate ventilator dyssynchrony, and 17% of patients in the control group received neuromuscular blockade during the first 48 hours, so there may be patients who still benefit from neuromuscular blockade to manage ventilator dyssynchrony. Furthermore, the number of patients receiving prone position and ECMO in the ROSE trial was low, and it is unknown if neuromuscular blockade interacts to facilitate the benefit associated with these interventions.

Extracorporeal support

In the era of lung protective ventilation, two RCTs have investigated the role of veno-venous extracorporeal membrane oxygenation (ECMO) for patients with severe ARDS. [75,76] The CESAR trial was a multicentre RCT which compared conventional management of ARDS with referral to an ECMO centre for consideration of ECMO. Of patients randomised to referral for ECMO, only 75% (68/90) received ECMO. [75] In the group randomised to ECMO referral, an improvement in the primary outcome of quality adjusted life years was seen at 6 months. [75] The CESAR trial had significant methodological limitations. However these limitations were addressed in the EOLIA trial which was an international RCT comparing ECMO to conventional treatment, with the option of ECMO as a rescue therapy if required. [76] While the primary outcome of mortality included a potentially beneficial treatment effect (relative risk 0.76, 95% CI 0.55 to 1.04, p=0.09), it did not achieve statistical significance. [76] A post-hoc Bayesian analysis reported a high probability that early ECMO was of benefit. [77] Furthermore, in a subsequent individual patient data meta-analysis including both of the CESAR and EOLIA RCTs, the precision of the treatment effect was improved (combined data for 429 patients) and a statistically significant benefit in mortality at day-90 was reported in the ECMO group (RR 0.75, 95% CI 0.6 to 0.94, p=0.013). [78,79] Together, on the basis of these data, it is recommended that patients with severe ARDS (as defined by a PaO_2/FiO_2 ratio of <50 mmHg for >3 hours, a PaO_2/FiO_2 ratio of <80 mmHg for >6 hours, or severe hypercapnic respiratory failure (pH of <7.25 with a PaCO2 ≥60 mm Hg for >6 hours)) should be treated with ECMO. It is important to emphasise that patients receiving ECMO should receive an overall management strategy similar to that used in the EOLIA trial. The provision of ECMO is complex and organisational characteristics of ECMO centres should be consistent with the organizations which delivered ECMO in the EOLIA trial or comply with the criteria for ECMO centres defined by expert groups. [80]

Evidence of benefit of ECMO has been extrapolated to a COVID-19 population, and ECMO has been delivered with reported mortality rates comparable to that of a general population of patients with non-COVID ARDS. [79] A recent large comparative effectiveness study reported ECMO use in a cohort of 7345 patients COVID-19 patients across five different countries. [81] ECMO therapy was delivered in 844 patients, and an analysis including patients with a PaO_2/FiO_2 ratio < 80 mmHg indicated ECMO was associated with a reduced mortality compared to conventional therapy (Risk Ratio 0.78, 95% CI 0.75 to 0.82). [81] While confirmation in a RCT would be desirable, these findings provide reassurance regarding the use of ECMO in a selected population of patients with severe COVID-19. Extracorporeal carbon dioxide removal ($ECCO_2R$) has been of interest in research settings to facilitate lower tidal volume ventilation. [60] The REST trial, which investigated $ECCO_2R$ in patients with AHRF found no difference in 90-day mortality, and there was an increased incidence of serious adverse events, including clinically important haemorrhage, in the $ECCO_2R$ group. [60] On this basis the use of $ECCO_2R$ for the treatment of ARDS is not recommended outside of randomised controlled.

Corticosteroids

The role of corticosteroids in ARDS management has been a longstanding controversy. [12] Steroids have potent anti-inflammatory effects that may be of benefit in ARDS. A significant development during the COVID-19 pandemic has been the benefits found with corticosteroid therapy for patients with severe COVID-19. [82-84] Corticosteroids are now suggested as standard of care for patients with COVID-19 ARDS, and there has been renewed interest in their role in non-COVID ARDS. Prior to the COVID-19 pandemic, numerous studies had investigated the role of corticosteroids in ARDS. [85] Unfortunately steroid regimes differed between studies (different types, doses and duration) and there were differences in the patient populations investigated (early versus late ARDS, some studies were prior to lung protective ventilation). Most recently, the DEXA-ARDS trial investigated high dose (20mg once daily for 5 days) followed by lower dose (10mg daily for 5 days) dexamethasone in patients with moderate to severe ARDS. [86] In the dexamethasone group there was an increase in ventilator free days (between group difference 4.8 days, 95% CI 2.57 to 7.03, p<0.0001) and a reduced 60-day mortality (21% versus 36%, between group difference -15.3%, 95% CI -25.9 to -4.9, p=0.0047). A subsequent meta-analysis (999 patients from 8 RCTs in non-COVID ARDS) found a mortality benefit in favour of corticosteroid use (risk ratio 0.71, 95% CI 0.54 to 0.92). [85] There was evidence of an association with hyperglycaemia, but no certain evidence supported concerns regarding other adverse events including neuromuscular weakness, GI bleeding or infection. Of note however, an early trial investigating methylprednisolone in persistent ARDS found an association with increased risk of late mortality (day-60 and day-180) when steroids were initiated beyond day-14 of ARDS onset. [87]

It is increasingly recognised that misestimation of predicted control event rates and treatment effects (used to inform sample size calculations) is common in ARDS RCTs, and this may have contributed to the uncertainty of evidence related to corticosteroids in ARDS. [88] Using Bayesian methods, Saha *et al* demonstrate the strength of

evidence for corticosteroids in ARDS favours benefit, and supports the prioritisation of future clinical trials investigating corticosteroids in patients with non-COVID ARDS. [88]

Future directions for therapeutic interventions in ARDS

Many clinical trials investigating pharmacological interventions in patients with ARDS have failed to show benefit. Specific pharmacological agents which have failed to show benefit have included inhaled prostaglandins[89], statins[90,91], aspirin[92], surfactant[93], activated protein-C[94,95], and Sivelestat[96]. Other agents including beta-2 agonists[97,98] and keratinocyte growth factor[99], which had promising pre-clinical data, had potential for harm.

One novel therapeutic of interest in ARDS are Mesenchymal Stromal Cells (MSCs). These multipotent, plastic adherent cells can be derived from multiple sources including bone marrow, umbilical cord or adipose tissue and have pleiotropic immunomodulatory, reparative and antimicrobial actions. [100] RCTs investigating MSCs in ARDS and COVID-19 have supported their safety, however efficacy has not yet been established. [101-105] While attractive in targeting multiple therapeutic pathways in ARDS, MSCs are known to respond to their biological microenvironment and may also be subject to heterogenic treatment effects in different patient phenotypes. [106]

The recent interest in biological phenotypes and treatable traits in patients with ARDS which may respond differently to therapeutic interventions has been supported by promising findings from re-analyses of previous clinical trial datasets. In a re-analysis of the HARP-2 (Simvastatin for ARDS) trial patients with a hyper-inflammatory phenotype treated with simvastatin were found to have significantly improved 28-day survival. [36] Figure 2 illustrates how therapeutic interventions may align with treatable traits in this future era of precision medicine for ARDS. There is also a need for continued translational research to identify novel treatable traits and therapeutic agents targeting these traits. [107-109] There may also be a role for a personalised approach to existing interventions in ARDS, and existing data sets may prove useful to identify populations that are most responsive.

Alongside the recent identification of biological phenotypes and treatable traits, the benefits of adaptive platform trials in establishing effective therapeutics for COVID-19 have been clearly demonstrated. Building on this background, the I-SPY COVID-19 trial established a phase 2 platform trial for investigation of novel therapeutics in COVID-19. [110] It is important to capitalise on these developments to develop an international precision medicine platform phase 2 trial to test new therapies for patients with ARDS, which can adapt to incorporate new treatable traits and treatment. Collaboration between the global scientific community (including experts in ARDS, precision medicine and adaptive trial design) will be needed to drive this research agenda for precision medicine in ARDS forward. [111]

Outcomes in ARDS patients

The LUNG SAFE study was the largest observational study of the epidemiology, patterns of care, and clinical outcomes of ARDS, conducted in a cohort of 29,144 patients admitted to 459 Intensive Care Units from 50 countries across five continents. [16] In the LUNG SAFE study 23% of patients requiring mechanical ventilation had ARDS. Patients with ARDS had a median duration of ventilation of eight days, and ICU and hospital length of stay of 10 and 17 days respectively. 28-day mortality was 35% and increased with severity of hypoxia, with rates greater than 40% in patients with severe ARDS. Considering geo-economical variation, PROVENT-iMiC (International Multicentre Prospective study of invasively ventilated patients in ICUs from 10 Asian Middle Income Countries) reported a lower proportion of patients with ARDS at the initiation of ventilation (7%) compared to the LUNGSAFE study. [112] Ventilation practices were similar, but there were differences in outcomes including a higher mortality rate (45%), shorter duration of ventilation (median four days) and shorter duration of ICU (median five days). [112] Disparities may relate to geo-economical variation in the case mix, or may relate to resource availability. Similarly, excess mortality in patients with ARDS has been reported in other LMIC countries. [113,114]

Outcomes of patients in clinical trials provide another perspective on ARDS outcomes. A systematic review of 28-day mortality in control arms of recent ARDS clinical trials reported a mortality rate of 29% (26 trials, 2766 patients, year 2016-2020). [115] Discrepancies between outcomes for ARDS patients in RCTs and observational studies are recognised; RCTs are more restrictive in their patient selection, and lung protective ventilation is usually more rigidly implemented. [116] Furthermore, heterogeneity of outcomes reported in clinical trials occurs (Juschten *et al* reported 28-day mortality ranging from 10% to 67% in a systematic review of 67 RCTs between 2000 and 2019), and this may limit the generalisability of trial findings to the clinical setting. [117]

While data from a pre-COVID era show few patients with ARDS die from irreversible respiratory failure (estimates vary depending on definition but are reported to be between <1% to 9%[118,119]), ARDS has a direct and measurable effect on patient mortality. [120] Compared to patients in ICU who do not have ARDS, ARDS increases the mortality rate by 15%.[120] In the setting of ARDS related to sepsis, the attributable mortality rate has been reported to be even higher (up to 37%).[121] In a retrospective cohort of 127 ARDS patients, pulmonary dysfunction was reported as a leading cause of death in 28% (other reported causes included sepsis in 29%, neurological dysfunction in 17% and cardiac dysfunction in 10%).[119]

Epidemiological trends and outcomes for ARDS patients are unlikely to remain static. [122] In the setting of COVID-19 ARDS, estimates of ARDS incidence have been considerably greater, and outcomes have varied over time, and between settings. [123-125] Ethnic and racial disparities in the epidemiology and outcomes of COVID-19 have been apparent. [126,127] It also remains unclear if there has been 'practice creep' with extrapolation of therapies proven to be of benefit in the setting of COVID-19 to non-COVID ARDS even where an evidence gap for these therapies exists in other causes of acute respiratory failure. Furthermore, COVID-19 has had an immeasurable impact on healthcare systems, particularly the delivery of respiratory and critical care services. [128] Such practice change may alter the epidemiology and outcomes of ARDS and future large population based observational studies of ARDS will be required to inform these uncertainties in the post-COVID era.

Sequelae of ARDS

New or worsening problems in physical, cognitive, or mental health status is common in ARDS survivors. Herein, we discuss evidence related to long-term sequelae for non-COVID ARDS, followed by emerging evidence in COVID-19 ARDS. Physical features commonly reported in non-COVID ARDS survivors include respiratory symptoms (dyspnoea, cough and sputum production) and reduced exercise capacity. [129] Respiratory symptoms do not usually correlate with the degree of impairment of pulmonary function or the extent of radiological abnormalities. [130] ARDS survivors continue to experience a spectrum of physical disorders related to sequelae of their critical illness (examples include tracheal stenosis, vocal cord dysfunction, dental damage and scarring related to interventions). [129] The prevalence of post-traumatic stress disorder is high in ICU survivors, with reported rates of up to 1 in 4 patients at 8 years. [131] Persistent psychiatric symptoms of depression and anxiety are reported in up to half of patients. [129,131] ARDS survivors have been shown to have impairments of cognitive function which include executive function, verbal reasoning, memory, and attention deficits. [132]

Given the burden of physical, mental and cognitive symptoms experienced by ARDS survivors, there is considerable decline in quality of life, employment, societal participation and residential status. [129,132-136] Kamdar *et al* have reported that 44% of previously employed ARDS survivors were jobless at 1 year, and at 5 years 30% had never returned to work. [135,136] Su *et al* found that one in five ARDS survivors who had returned to work were subsequently unable to sustain work. [137] In another study, Brown *et al* reported the percentage of ARDS survivors living independently at home at 6 months reduced from a pre-existing baseline of 91% to 45% at 6 months. [134] Use of healthcare resources is increased in ARDS survivors, with hospital re-admissions reported in up to 40% of survivors, up to a third of whom require re-admission to ICU. [132,138] ARDS survivors already have a high risk of mortality during their acute illness, but the risk of mortality persists in the long-term. At 1 year mortality rates of 11% have been reported, increasing to 20-34% at 5 years. [139,140] In a comparison of AHRF patients (many of whom are likely to have ARDS) to matched non-hospitalised adults, patients with AHRF experienced a 1.9 fold increase in late mortality. [141] The risk of late mortality was primarily attributable to the acute inciting event, while approximately 30% of the mortality risk was associated with hypoxaemic respiratory failure. [141]

Reports of longer-term outcomes of COVID-19 ARDS survivors are emerging and provide evidence of persistent physical, mental and cognitive deficits. [142-147] Evidence of persistent interstitial lung disease in mechanically ventilated patients with COVID-19 ARDS has been reported, but there remains uncertainty as to how this compares to a population of patients with non-COVID-19 ARDS. [148-150] Of note, some studies have reported better health related quality of life[145], and higher return to work rates in patients with COVID-19 ARDS compared to a non-COVID ARDS population. [145-147] However, patients with COVID-19 ARDS self-report lower disability and health-related quality of life before ICU hospitalisation and therefore may have a greater capacity for improvement following critical illness. [146] When adjusted for potential confounders at baseline, Hodgson *et al* report the incidence of new disability, health-related quality of life, psychological function and cognitive function was similar at 6 months between critically ill patients with and without COVID-

19. [146] The emerging impact of long COVID[151], and long term impacts of COVID-19 on organ function (including interstitial lung disease[148-150], and a variety of cardiac sequelae[152]) raises concerns regarding the full spectrum of morbidity in COVID-19 ARDS survivors.

Identification of interventions, both during critical care and after critical care, which improve recovery from critical illness has been identified as a priority by patients and their caregivers. [153] In a survey of UK hospital sites delivering intensive care services, 74% provided outpatient follow up services for ICU survivors and 18% provided physical rehabilitation programmes. [154] Internationally, reports of post ICU follow up vary considerably and there is no consensus approach on how these services should be configured. [155,156] ICU survivors have reported benefits of ICU recovery programmes and peer support[157,158], but to date there are no evidence-based interventions to improve long-term outcomes for patients with ARDS. [159,160] This remains an area of active research with ongoing clinical trials investigating potential post ICU interventions, as well as the mode of delivery in terms of face to face or virtual approaches to provide programmes to support recovery. It is critical that future clinical trials in ARDS also include multi-dimensional long-term outcomes.

Conclusion

ARDS is a clinical syndrome defined by acute hypoxaemic respiratory failure with bilateral opacities on chest imaging. As we enter the post-pandemic era there is uncertainty regarding the epidemiological landscape of ARDS, however it is clear patients with ARDS continue to have considerable morbidity and mortality in both the short and long term. ARDS criteria are under revision, and limitations which may be addressed have been considered. The evidence base for optimal supportive care and interventions in ARDS continues to evolve to address areas of uncertainty. As we enter an era of precision medicine in critical illness, the future of ARDS management strives towards identification of biological phenotypes and treatable traits and delivery of personalised therapeutic interventions.

Search strategy and selection criteria

References for this review were identified through searches of PubMed for articles published from the database inception to July 15, 2022 by use of the terms “ARDS”, “diagnosis”, “outcomes”, “ventilation”, “management” and “guidelines”. Relevant references cited in papers identified were also reviewed. We focused on clinical studies, and the final list of cited articles was selected on the basis of their relevance to the aims of this Series paper. Clinicaltrials.gov clinical trial registry was also searched using the term “ARDS” and a selection of trials were selected.

Author contributions

EG prepared the first draft of the manuscript and prepared the included figures. DMcA and COK reviewed and contributed to subsequent versions of the manuscript. All authors have reviewed and approved the final version.

Declarations of interest

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Panel 1: COVID-19 ARDS compared to non-COVID ARDS – summary of key features	
Feature	**Summary of key differences/similarities**
Timing	Onset may be > 7 days from SARS-COV-2 infection and symptom onset. [8,10]
Demographics	Disparities reported for non-white ethnic populations and health care workers. [7]
Thoracic imaging	Overlapping thoracic CT findings during acute phase, but predominance of diffuse pattern with ground glass opacities in COVID-19 ARDS. [10] Evidence of persistent interstitial lung disease but uncertainty regarding how this compares to non-COVID ARDS. [148]
Respiratory mechanics	Respiratory system mechanics (including compliance, plateau pressure and driving pressure) reported to be similar. [7-10]
Biomarkers	Reduced total white cell count (predominantly due to a reduced neutrophil count) in COVID-19. [9] Reduced IL-6 reported[7], but similarities in other markers of systemic inflammation and extrapulmonary organ dysfunction. [9] Hyperinflammatory phenotype less prevalent[161]
Coagulation	Higher platelet count and fibrinogen, lower prothrombin time and activated partial thromboplastin time in COVID-19 patients. [9] D-Dimer higher in non-COVID ARDS. [9] Higher incidence of deep venous thrombosis in COVID-19. [162]
Pharmacological agents	Pharmacological agents recommended for severe COVID-19 (including COVID-19 ARDS) include corticosteroids, IL-6 receptor blockers or Baricitinib (Janus Kinase JAK inhibitor). [45] Currently no specific pharmacological agents recommended for ARDS due to other causes.
Adjunctive therapy	Paucity of RCT evidence directly relevant to COVID-19 populations. Use of recruitment manoeuvres, prone position and neuromuscular blockade reported to be higher in COVID-19 ARDS populations. [8,9]
Critical care outcomes	Prolonged duration of ventilation in COVID-19 patients has been reported. [7] Mortality outcomes similar. [8-10]
Long term outcomes	No difference in incidence of new disability at 6 months. [146] Similar health-related quality of life, psychological and cognitive function at 6 months. [146] In COVID-19 survivors an increased return to work at 6 months[146] and 1 year has been reported. [145]

Panel 2: The Berlin Definition of Acute Respiratory Distress Syndrome[1]	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms.
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules.
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (eg, echocardiography) to exclude hydrostatic oedema if no risk factor present.
Oxygenation[b]	
Mild	200 mmHg > PaO_2/FIO_2 ≤ 300 mmHg with PEEP or CPAP ≥5 cmH_2O[c]
Moderate	100 mm Hg > PaO_2/FIO_2 ≤ 200 mmHg with PEEP ≥5 cmH_2O
Severe	PaO_2/FIO_2 ≤ 100 mm Hg with PEEP ≥5 cmH_2O
Abbreviations: CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure. a Chest radiograph or computed tomography scan. b If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2 x (barometric pressure/ 760)]. c This may be delivered noninvasively in the mild acute respiratory distress syndrome group.	

Panel 3: Current guideline recommendations for ARDS management				
	ICS/FICM[42]	SRLF[43]	ATS/ESICM/ SCCM[44]	WHO living guideline (COVID-19 ARDS) [45]
Non-invasive ventilation	-	-	-	Conditional recommendation in mild ARDS
Lung protective ventilation (LPV)	Recommended	Recommended	Recommended	Recommended
Prone positioning	Recommended in moderate to severe ARDS.	Recommended PaO_2/FIO_2 ratio <150mmHg.	Recommended in severe ARDS.	Recommended PaO_2/FIO_2 ratio <150 mmHg
High PEEP strategy	Recommended moderate/severe ARDS.	Recommended moderate/severe ARDS.	Recommended moderate/severe ARDS	Conditional recommendation for moderate/severe ARDS.
Driving Pressure	-	No recommendation due to insufficient evidence.	Research recommendation	Consider driving pressure as part of an individualised PEEP titration strategy.
Spontaneous ventilation	-	No recommendation due to insufficient evidence .	Research recommendation	-
Recruitment maneouvres	-	Not recommended	Not routinely recommended.	-
High frequency oscillatory ventilation	Not recommended	Not recommended	Not recommended	-
ECMO	Recommended in severe ARDS.	Recommended PaO_2/FIO_2 ratio <80 mmHg and/or LPV not possible.	Research recommendation	Conditional recommendation PaO_2/FIO_2 ratio < 80 mmHg despite LPV.
$ECCO_2R$	Research Recommendation	No recommendation due to insufficient evidence.	Research recommendation	-
Conservative fluid strategy	Recommended	-	-	Recommended
Neuromuscular blockade	Recommended in early moderate/severe ARDS.	Recommended in early ARDS with PaO_2/FIO_2 ratio < 150mmHg.	-	Not routinely recommended for all patients.
Inhaled vasodilators	Not recommended	May be used where hypoxaemia persists despite LPV and prone position, and before ECMO.	-	-
Corticosteroids	Research recommendation	-	-	Recommended
Other pharmacological agents	-	-	-	Interleukin-6 receptor blockers (Tocilizumab or sarilumab) or Baricitinib (Janus kinase inhibitor) -

				strong recommendation. Monoclonal antibodies (Casirivimab and imdevimab)– conditional recommendation for seronegative patients.
Abbreviations: LPV, Lung protective ventilation; PEEP, Positive end expiratory pressure; ECMO, Extracorporeal membrane oxygenation; $ECCO_2R$, Extracorporeal carbon dioxide removal.				

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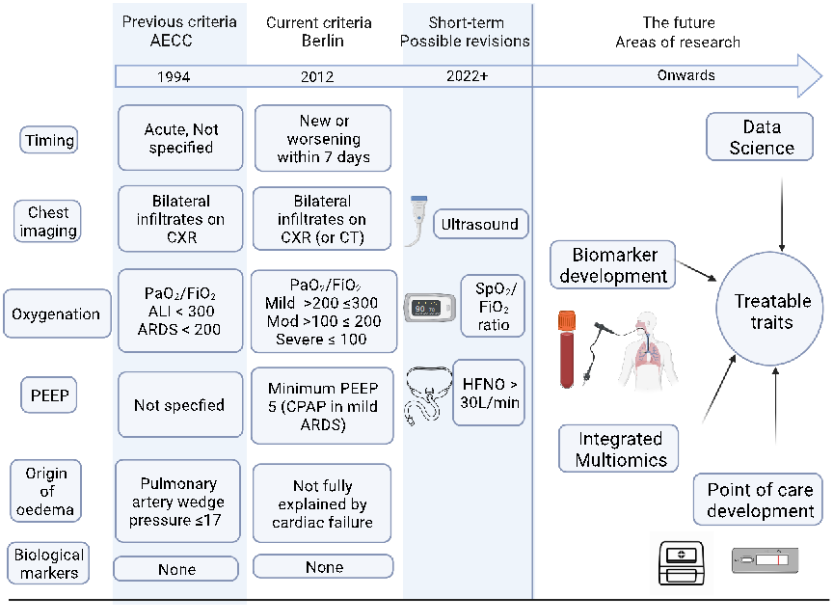

Figure 1 Timeline of ARDS criteria and future directions.

The first consensus ARDS criteria were the American-European Consensus Criteria (AECC) in 1994, followed by the Berlin Consensus Criteria in 2012. ARDS criteria are currently being revised and potential revisions are illustrated. The future of ARDS in the era of precision medicine strives towards identifying treatable traits.
CXR=Chest radiograph; CT=computerised tomography; ALI=Acute Lung Injury; ARDS=Acute Respiratory Distress Syndrome; PEEP=Positive End Expiratory Pressure; CPAP=Continuous Positive Airway Pressure; HFNO=High Flow Nasal Oxygen. Measurements (units) = PaO_2/FiO_2 ratio (mmHg), Pulmonary artery wedge pressure (mmHg), PEEP/CPAP (cmH_2O).

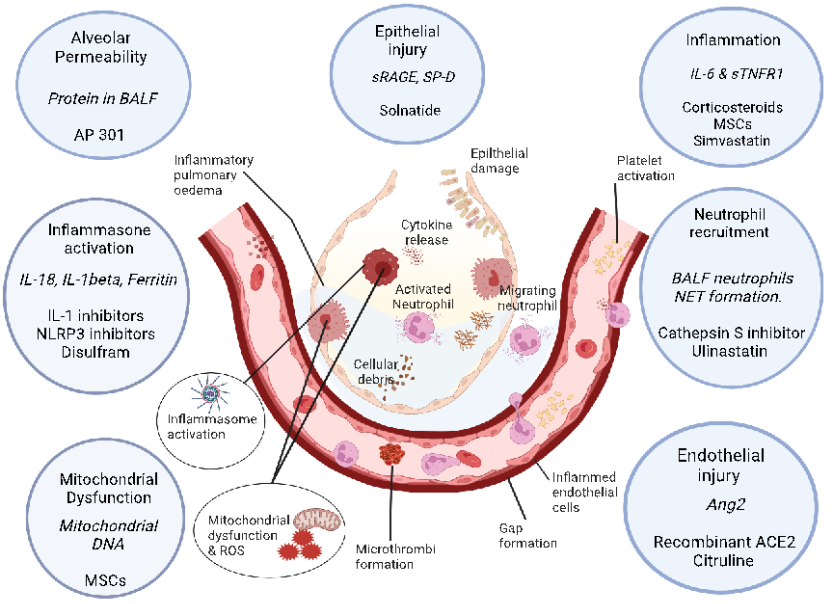

Figure 2: Potential treatable traits in ARDS: a pathophysiological model

Treatable traits may be identifed by biomarkers *(in italics)* which align with underlying pathophysiological mechanisms and may be targetted by specific therapeutics/interventions. Biomarkers illustrated are biological markers (obtained from biological samples). Alternative biomarkers may also include imaging, physiology, and clinical data, where they reflect an underlying pathophysiological process which may be responsiveness to therapy. The pathophysiological model illustrated here likely does not account for the complexities of interaction between pathophysiological mechanisms and individual patient responses. Integration of multiple modalities of information (clinical features, imaging, physiology, biological tests, and multi-omics data) may delinate further subphenotypes that may more reliably predict responsiveness to therapies/interventions.
BALF=Bronchoalveolar Lavage Fluid; MSCs=Mesenchymal Stromal Cells; ROS=Reactive Oxygen Species; NET=Neutrophil extracellular traps.