RAND appropriateness panel to determine the applicability of UK guidelines on the management of acute respiratory distress syndrome (ARDS) and other strategies in the context of the COVID-19 pandemic

Original research

RAND appropriateness panel to determine the applicability of UK guidelines on the management of acute respiratory distress syndrome (ARDS) and other strategies in the context of the COVID-19 pandemic

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ABSTRACT

Background COVID-19 has become the most common cause of acute respiratory distress syndrome (ARDS) worldwide. Features of the pathophysiology and clinical presentation partially distinguish it from 'classical' ARDS. A Research and Development (RAND) analysis gauged the opinion of an expert panel about the management of ARDS with and without COVID-19 as the precipitating cause, using recent UK guidelines as a template.

Methods An 11-person panel comprising intensive care practitioners rated the appropriateness of ARDS management options at different times during hospital admission, in the presence or absence of, or varying severity of SARS-CoV-2 infection on a scale of 1–9 (where 1–3 is inappropriate, 4–6 is uncertain and 7–9 is appropriate). A summary of the anonymised results was discussed at an online meeting moderated by an expert in RAND methodology. The modified online survey comprising 76 questions, subdivided into investigations (16), non-invasive respiratory support (18), basic intensive care unit management of ARDS (20), management of refractory hypoxaemia (8), pharmacotherapy (7) and anticoagulation (7), was completed again.

Results Disagreement between experts was significant only when addressing the appropriateness of diagnostic bronchoscopy in patients with confirmed or suspected COVID-19. Adherence to existing published guidelines for the management of ARDS for relevant evidence-based interventions was recommended. Responses of the experts to the final survey suggested that the supportive management of ARDS should be the same, regardless of a COVID-19 diagnosis. For patients with ARDS with COVID-19, the panel recommended routine treatment with corticosteroids and a lower threshold for full anticoagulation based on a high index of suspicion for venous thromboembolic disease.

Conclusion The expert panel found no reason to deviate from the evidence-based supportive strategies for managing ARDS outlined in recent guidelines.

Key messages

What is the key question?

► Acute respiratory distress syndrome (ARDS) guidelines are based on trials that predate the COVID-19 pandemic, raising the question that alternative management strategies may be appropriate for COVID-19-associated ARDS which manifests some distinct pathophysiology and clinical features.

What is the bottom line?

► While specific disease-modifying treatments for COVID-19 are rapidly emerging, the basic supportive management of respiratory failure should follow existing ARDS guidelines.

Why read on?

► A Research and Development/ University of California Los Angeles (RAND/UCLA) panel judged the appropriateness in the management of ARDS associated with COVID-19 and ARDS that was not COVID-19-related of interventions recommended in guidelines and other commonly used management strategies where the evidence base is lacking.

INTRODUCTION

To date, SARS-CoV-2 has infected over 66 million people, causing more than 1.5 million deaths worldwide.[1] The associated COVID-19 pandemic precipitated a wave of critically ill patients that overwhelmed mature as well as developing health-care systems in multiple hot spots across the world. For example, the Office for National Statistics reports that since the start of the pandemic, there have been 63 852 COVID-19 deaths registered in England and Wales, up to 20 November 2020 (35 358 men and 28 494 women), which almost certainly underestimates the actual death toll.[2]

The most common cause of hospitalisation for patients with COVID-19 was acute respiratory

failure associated with viral pneumonia and sepsis syndrome, ultimately leading to acute respiratory distress syndrome (ARDS). A high proportion of these patients required respiratory support ranging from non-invasive and invasive mechanical ventilation to extracorporeal membrane oxygenation (ECMO). COVID-19-associated strain on health resource capacity highlighted the need to optimise the management of patients with ARDS, including those with mild ARDS, a category where the diagnosis is frequently missed.[3] Similarly, COVID-19-related ARDS is associated with a high mortality and prolonged length of intensive care unit (ICU) and hospital stay.[4] In addition, long-term follow-up studies of patients with ARDS have indicated high long-term loss of quality of life and employment.[5]

Although related to other coronaviruses that cause ARDS, SARS-CoV-2 infection was associated with a novel constellation of clinical features and distinct pathophysiology, for example, a high incidence of intravascular thrombosis.[6] Hence, the question of whether this is 'normal' ARDS or a distinct syndrome with correspondingly different management has been debated.[7] At the same time, a plethora of pronouncements on social media, multiple case series and some data from large platform studies and clinical trials have emerged. For example, non-invasive respiratory support strategies, including continuous positive airway pressure (CPAP) or high-flow nasal oxygen (HFNO), might provide sufficient support in some patients, obviating the need for invasive mechanical ventilation. However, these interventions may also cause harm, such as ventilator-associated lung injury (VALI), delay to invasive mechanical ventilation and exposure of a healthcare worker to COVID-19-laden aerosols. Uncertainty about the optimal approach to non-invasive respiratory support in COVID-19 has been reflected in variation in the recommendations of international guidelines and clinical practice.[8–12] Accordingly, in the context of the COVID-19 pandemic, the applicability of current international guidelines for the management of ARDS has been questioned.[7]

In 2018–2019, the UK Faculty of Intensive Care Medicine (FICM) and Intensive Care Society (ICS) produced a guideline using Grading of Recommendations Assessment, Development and Evaluation methodology[13] for the management of ARDS in adult patients that was adopted by the British Thoracic Society, henceforth referred to as the 'UK guideline'.[14] The recommendations of the UK guideline were broadly consistent with the American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guidelines 2017 for patients with ARDS,[15] which considered 6 of the 10 interventions considered by the UK group. Here, Research and Development/University of California Los Angeles (RAND/UCLA) Appropriateness Methodology was used to determine whether a multidisciplinary panel of experts from the UK were in favour of adhering to recommendations in the UK guideline for patients with COVID-19-associated ARDS. Assessment was also made of the appropriateness of other interventions that were either outside the scope of the ARDS guidelines or had been suggested during the COVID-19 pandemic.

METHODS

The RAND/UCLA appropriateness method uses a modified Delphi panel approach, thereby combining expert opinion with the best available evidence to determine the appropriateness of specific practices in defined clinical situations.[16] Using this method to score appropriateness is validated as a means of determining the benefit versus harm of a given intervention irrespective of the cost or resources. It is particularly useful in areas of uncertainty in which evidence is insufficient to guide clinical practice, such as in the COVID-19 pandemic.[17]

The aim of this RAND panel was to provide expert opinion on the appropriateness of various interventions used in the management of ARDS, as defined using the Berlin criteria,[3] in the context of the COVID-19 pandemic. The questionnaire sought to identify areas where it was appropriate to deviate from current guidelines for the management of ARDS in adult patients in the context of the COVID-19 pandemic, as well as addressing interventions that for various reasons are not part of existing guidelines. Where there was an acceptably low level of disparity, a corresponding recommendation was made about the routine use of the intervention in question.

The expert panel comprised intensive care practitioners from various professional groups and centres across the UK. Of the 16 experts who were originally invited, 2 declined because they felt that they had inadequate knowledge and 3 were unexpectedly unable to dial into the discussion panel meeting. The 11 remaining experts are listed in online supplemental table 1. A bibliography of references (online supplemental file 1) on the management of ARDS and COVID-19 published after the ICS UK guideline on the management of ARDS in adults[14] was sent to the expert panel with an invitation to a web-based questionnaire. The questionnaire was completed prior to an online meeting moderated by an expert in RAND methodology (PMI). Panellists rated the appropriateness of management options at different times during hospital admission for ARDS in the presence or absence of, or varying severity of SARS-CoV-2 infection. They were asked to grade the appropriateness of specific interventions on a scale of 1–9 (where 1–3 is inappropriate, 4–6 is uncertain and 7–9 is appropriate). The responses were summarised and anonymised before being presented at a virtual meeting in November 2020, which ensured a common understanding of the questions and focused on areas of disagreement, without trying to force consensus. The moderators provided expertise in RAND methodology, but neither expressed opinions on management nor voted.

After the meeting, a second online survey comprising 76 questions was completed. The second and final survey had been modified from the initial questionnaire following discussion at the meeting. Questions in the final survey were subdivided as follows: investigations (16), non-invasive respiratory support (18), basic ICU management of ARDS (20), management of refractory hypoxaemia (8), pharmacotherapy (7) and anticoagulation (7).

Several assumptions were made. First, the diagnoses of ARDS and COVID-19 were assigned arbitrarily and absolutely. Second, other than those areas addressed in the survey, the management of ARDS was assumed to be in line with the UK guideline.[14] Finally, care levels 2 and 3 (high dependency and critical care units) were defined by the Department of Health report 'Comprehensive Critical Care'.[18]

For each scenario, median scores were calculated with a score of <3.5 being considered inappropriate, ≥ 3.5 and <6.5 uncertain and ≥ 6.5 appropriate. We used the validated RAND disagreement index (DI) to define disagreement (DI ≥ 1) among panellists using the equation below.[16] Any scenario in which disagreement was found was scored as uncertain, regardless of the median score.

Equation 1: Calculation of DI for RAND analysis

$$\text{Disagreement Index (DI)} = \frac{70\text{th} - 30\text{th centile}}{2.35 + (1.5 \times \text{abs}(5 - 70\text{th} - 30\text{th centile}/2))}$$

where Abs is the absolute difference between the appropriateness score given and the panel median expressed as a positive number.

Table 1 Investigations on admission to level 2 or 3 care

	Investigations on admission to level 2 or 3 care (HDU or ITU)			
Time point	**Confirmed or suspected COVID-19***		**Non-COVID-19 ARDS†**	
Routinely on admission	CAP screen	Bronchoscopy‡	CAP screen	Bronchoscopy§
	Echocardiogram	CT thorax±CTPA	Echocardiogram	CT thorax±CTPA
	Autoimmune screen		Autoimmune screen	
Routinely on admission, repeated if clinically indicated	Procalcitonin	Troponin	Procalcitonin	Troponin
	Circulating biomarkers of HLH-like syndrome		Circulating biomarkers of HLH-like syndrome	

For each survey question, median scores were calculated with a score of <3.5 being considered inappropriate (red background), ≥3.5 and <6.5 uncertain (amber background) and ≥6.5 appropriate (green background).
*In the context of the pandemic.
†Outside the context of the pandemic.
‡Denotes disagreement (disagreement index >1).
§Bronchoscopy *if intubated*.
ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia (microbiology screen); CTPA, CT pulmonary angiogram; HDU, high dependency unit; HLH, haemophagocytic lymphohistiocytosis markers (ie, lactate dehydrogenase, ferritin); ITU, intensive therapy unit.

RESULTS

The final survey comprised 76 statements concerning the management of ARDS in adult patients with confirmed or suspected COVID-19 or patients with non-COVID-19-related ARDS: 35 were rated as appropriate, 33 as uncertain and 8 as inappropriate. Disagreement (DI>1) occurred in one scenario only. Online supplemental table 2 shows the RAND statements included in the final survey with associated median scores, DI and final appropriateness outcome category.

Investigations on admission to critical care of patients with confirmed or clinically suspected COVID-19 in the context of the pandemic versus those with respiratory failure or ARDS not associated with COVID-19 presenting outside the pandemic

It was deemed appropriate that all patients admitted to level 2 or 3 care should have a full community-acquired pneumonia (CAP) microbiology screen and echocardiogram irrespective of the aetiology of the ARDS. Routine bronchoscopy in intubated patients was rated uncertain, irrespective of the ARDS aetiology. This was driven by significant levels of disagreement between panellists denoted by a DI of 1.04 in patients with COVID-19, despite a median score of 3, whereas in non-COVID-19 patients, it was due to a median score of 6. (table 1)

Routine CT of the thorax was deemed uncertain, irrespective of the ARDS aetiology, as was performing a routine autoimmune screen in COVID-19-related ARDS. By contrast, autoimmune screening was deemed appropriate in non-COVID-19 ARDS. The use of circulating biomarkers of syndromes resembling haemophagocytic lymphohistocytosis (such as lactate dehydrogenase and ferritin), procalcitonin and troponin was deemed uncertain irrespective of the ARDS aetiology.

Use of non-invasive ventilatory strategies in patients with confirmed or clinically suspected COVID-19 in the context of the pandemic versus those with respiratory failure or ARDS not associated with COVID-19 presenting outside the pandemic

Irrespective of the aetiology and context of ARDS, the use of CPAP, nasal high-flow oxygen (NHFO) and awake proning was deemed to be of uncertain value. Non-invasive ventilation (NIV) was considered to be an inappropriate modality of respiratory support for all patients with ARDS regardless of the cause. Assessment of failure of non-invasive ventilatory strategies 1–4 hours after initiation by the presence of unacceptable arterial blood gas, unacceptable work of breathing and the failure to improve were all deemed appropriate. Where first-line non-invasive strategies had failed, it was deemed inappropriate to trial an alternative non-invasive ventilatory strategy, but appropriate to proceed to tracheal intubation and invasive mechanical ventilation. Results were consistent irrespective of the patient's COVID-19 status or pandemic context. (table 2)

Table 2 Non-invasive ventilatory strategies

	Standard care: non-invasive ventilatory strategies			
Intervention	**Confirmed or suspected COVID-19***		**Non-COVID-19 ARDS†**	
Trial of therapy if immediate invasive mechanical ventilation not required	NHFO	NIV	NHFO	NIV
	CPAP	Awake proning	CPAP	Awake proning
Indicators of failure of trial of non-invasive respiratory support	'Unacceptable' ABG	'Unacceptable' work of breathing Failure to improve	'Unacceptable' ABG	'Unacceptable' work of breathing Failure to improve
Trial of therapy after failure of first-line strategy	An alternative non-invasive strategy	Invasive mechanical ventilation	An alternative non-invasive strategy	Invasive mechanical ventilation

For each survey question, median scores were calculated with a score of <3.5 being considered inappropriate (red background), ≥3.5 and<6.5 uncertain (amber background) and ≥6.5 appropriate (green background).
*In the context of the pandemic.
†Outside the context of the pandemic.
ABG, arterial blood gas; ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; NHFO, nasal high-flow oxygen; NIV, non-invasive ventilation.

Table 4 Pharmacotherapy and anticoagulation

Intervention	Pharmacotherapy			
	Confirmed or suspected COVID-19* and established or incipient organ failure(s)			
Medical therapy	Standard-course CAP antibiotics	Low-dose corticosteroids on admission for 10 days	Late corticosteroids for failed weaning†	Antifibrotic therapy‡
	Remdesevir	Cytokine storm agents*	Pulmonary vasodilators§	
All patients without contraindication to anticoagulation	Standard thromboprophylaxis	Enhanced thromboprophylaxis	Full anticoagulation	Antiplatelet therapy
Indications for full anticoagulation	Standard indications	Clinical suspicion of VTE	Moderately raised D-dimer (≥4× ULN)	

For each survey question, median scores were calculated with a score of <3.5 being considered inappropriate (red background), ≥3.5 andb<6.5 uncertain (amber background) and ≥6.5 appropriate (green background).
*For example, tociluzimab.
†For example, intravenous methylprednisolone 2 mg/kg/day for 2–4 weeks.
‡For example, nintedanib for persistent respiratory failure with radiological evidence of lung fibrosis.
§For example, sildenafil for pulmonary hypertension or right ventricular failure; for example, nintedanib for persistent respiratory failure with radiological evidence of lung fibrosis.
ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; ULN, upper limit of normal; VTE, venous thromboembolism.

Basic management strategies in mechanically ventilated patients and adjuncts for refractory hypoxia with confirmed or clinically suspected COVID-19 in the context of the pandemic versus those with respiratory failure or ARDS not associated with COVID-19 presenting outside the pandemic

Lung-protective ventilation (defined as tidal volume <6 mL/kg ideal body weight and plateau pressure <30 cmH_20), prone positioning, use of higher end-expiratory pressure (PEEP) and conservative fluid management were all deemed appropriate irrespective of the context and aetiology of ARDS or time interval after intubation (defined as <48 hours or >48 hours). Continuous infusion of neuromuscular blocking agents was deemed uncertain irrespective of the time period considered or the aetiology of the ARDS. (table 3)

In patients with severe ARDS and refractory hypoxia, inhaled pulmonary vasodilators were deemed uncertain in COVID-19-related ARDS but inappropriate in non-COVID-19-related ARDS. Regardless of the ARDS aetiology, recruitment manoeuvres were deemed inappropriate, airway pressure release ventilation (APRV) was uncertain, while referral to an ECMO centre was rated appropriate.

Pharmacotherapy and anticoagulation in patients with confirmed or suspected COVID-19 and established or incipient organ failure

A 10-day course of low-dose corticosteroids on admission was the only appropriate pharmacotherapy in this patient group. Most other treatments (standard course of antibiotics, remdesevir, inhibitors of the cytokine storm, late-phase steroids for failed weaning and pulmonary vasodilators) were deemed uncertain, whereas antifibrotic therapy was deemed inappropriate. (table 4)

It was considered appropriate to prescribe standard thromboprophylaxis in all patients without contraindications, whereas the use of routine enhanced thromboprophylaxis, full anticoagulation and antiplatelet therapy were all considered uncertain. It was deemed appropriate to initiate full anticoagulation for standard indications, including confirmed or suspected venous thromboembolic disease, whereas initiation of full anticoagulation based solely on a moderately raised D-dimer (≥4 times upper limit of normal) was considered uncertain.

Table 3 Basic management strategies in mechanically ventilated patients

Time point	Basic management strategies in mechanically ventilated patients			
	Confirmed or suspected COVID-19*		Non-COVID-19 ARDS†	
First 48 hours after intubation	Lung-protective ventilation	Prone positioning	Lung-protective ventilation	Prone positioning
	Neuromuscular blocking agents	Higher PEEP	Neuromuscular blocking agents	Higher Peep
	Conservative fluid management		Conservative fluid management	
After the first 48 hours after intubation	Lung-protective ventilation	Prone positioning	Lung-protective ventilation	Prone positioning
	Neuromuscular blocking agents	Higher PEEP	Neuromuscular blocking agents	Higher PEEP
	Conservative fluid management		Conservative fluid management	
Severe ARDS and refractory hypoxia	Inhaled pulmonary vasodilators	Recruitment manoeuvres	Inhaled pulmonary vasodilators	Recruitment manoeuvres
	APRV	ECMO	APRV	ECMO

For each survey question, median scores were calculated with a score of <3.5 being considered inappropriate (red background), ≥3.5 and <6.5 uncertain (amber background) and ≥6.5 appropriate (green background).
*In the context of the pandemic.
†Outside the context of the pandemic.
APRV, airway pressure release ventilation; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation/referral to an ECMO centre; lung-protective ventilation, tidal volume <6 mL/kg ideal body weight and plateau pressure <30 cmH_2O; PEEP, positive end-expiratory pressure.

DISCUSSION

Responses of the experts to the final survey suggested that the management of adult patients with ARDS should be the same, regardless of the aetiology, specifically in the presence or absence of a COVID-19 diagnosis. Furthermore, it was recommended that clinicians should broadly adhere to existing published guidelines for the management of ARDS for relevant evidence-based interventions.[14] There was very little disagreement between experts; the DI was significant (DI >1) only when addressing the appropriateness of diagnostic bronchoscopy in patients with confirmed or suspected COVID-19. The appropriateness of routine bronchoscopy in the general ARDS population was uncertain. Fibre-optic bronchoscopy with bronchoalveolar lavage was relatively safe historically, having been associated with infrequent complications in hypoxaemic patients with acute respiratory failure[19] and a low risk of transmission of infection to healthcare workers.[20] In a case series of intubated patients with COVID-19-related ARDS, the results of bronchoscopy performed as clinically indicated, as opposed to routinely on admission (the survey question), were well tolerated and influenced decision-making around antimicrobial use in 50% of cases.[21]

Standard evidence-based management of ARDS according to guidelines centres around supportive strategies that aim to minimise VALI, which is a crucial determinant of outcome.[22] The impetus for treating COVID-19-related ARDS differently from 'general' ARDS arose partly from controversial observations suggesting that ARDS resulting from COVID-19 was a distinct entity.[23] In a case series of 32 patients with COVID-19, a phenotype was described with relatively preserved lung compliance and poor recruitability in response to an increase in PEEP.[24] The expert panel judged that five organ support strategies were appropriate for routine use in ARDS regardless of the aetiology. For all cases, protective mechanical ventilation using low tidal volumes and airway pressures, and a conservative fluid balance strategy were approved. For moderate and severe cases, prone positioning and the use of higher PEEP were deemed appropriate. These findings correlate with strong recommendations for protective ventilation and proning in the UK guidelines, whilst the other three strategies were suggested a weaker recommendation reflecting the evidence base.

Despite a relatively weak evidence base in ARDS generally, but in accordance with clinical practice in several countries, for patients with severe ARDS meeting criteria from the CESAR study that have become standard,[25] referral to an ECMO centre was deemed to be appropriate. Satisfactory outcomes of patients with COVID-19 who were supported with ECMO have been reported,[26] in accordance with data from the H1N1 influenza A pandemic of 2009–2010.[27] By contrast, there are fewer large studies demonstrating the safety and efficacy of APRV, and the experts were uncertain about the appropriateness of its use in all patients with ARDS.

Guidelines recommend the use of neuromuscular blockade (cisatracurium infusion) for the first 48 hours of invasive mechanical ventilation in patients with moderate-severe ARDS.[14] The expert panel thought the routine use of neuromuscular blockade to be of uncertain value both before and after the first 48 hours. This decision reflected the results of the recent Prevention and Early Treatment of Acute Lung Injury network's ROSE study of early cisatracurium infusion plus heavy sedation versus a usual-care approach without routine neuromuscular blockade and with lighter sedation targets.[28] The study was stopped at the second interim analysis for futility with 90-day mortality rates in the intervention and control groups of 42.5% and 42.8%, respectively. Recruitment manoeuvres were not addressed by the UK guideline development group, owing to difficulty in defining the intervention and a paucity of robust evidence, but their use was supported by the international guideline.[15] Recent studies in moderate-severe ARDS have suggested potential harm associated with high airway pressure (up to 60 cmH_2O) recruitment manoeuvres, which may have influenced experts' opinion that their use was inappropriate.[29]

Despite a plethora of conflicting guidance on the use of non-invasive ventilatory support in patients with COVID-19-related respiratory failure from the WHO, National Health Service England, British Thoracic Society, FICM/ICS/Royal College of Anaesthetists/Association of Anaesthetists and the Surviving Sepsis Campaign, the expert panel was unanimous in recommending no difference in the management regardless of the aetiology.[8–12] The use of NIV was deemed inappropriate, which may reflect reported survival of patients supported with NIV compared with NHFO and conventional oxygen therapy: NIV was associated with a higher 90-day mortality in patients with acute hypoxic respiratory failure, possibly by exacerbating VALI.[30 31] Similarly, the use of NIV compared with invasive mechanical ventilation was associated with a higher mortality in patients with moderately severe ARDS,[32] consistent with the feeling that the use of non-invasive strategies should not delay tracheal intubation. Hence, the relevant survey questions stipulated a limited trial of a non-invasive strategy lasting between 1 and 4 hours, and the experts deemed that a failure to improve would indicate invasive mechanical ventilation and not an alternative non-invasive strategy. The experts were not invited to choose between non-invasive strategies and for lack of discriminating evidence showed equipoise for the use of NHFO and CPAP, and the practise of awake proning.

One of the distinguishing clinical features of COVID-19 is the high prevalence of thromboembolic disease, frequently manifesting as pulmonary hypertension and increased dead space ventilation.[33] Using a random-effects model, meta-analysis of 20 studies that enrolled 1988 patients with COVID-19 rendered a weighted mean prevalence of venous thromboembolism of 31.3% (95% CI: 24.3% to 39.2%).[34] While standard prophylaxis was accepted as being appropriate for all seriously ill patients with COVID-19, there was equipoise from the panel for enhanced thromboprophylaxis (eg, double the recommended dose of low-molecular-weight heparin), full anticoagulation and the addition of antiplatelet agents. The panel judged that it was appropriate to anticoagulate fully a patient based on clinical suspicion of venous thromboembolism, but was uncertain about relying on a single laboratory-derived test like D-dimer, which is in accordance with international guidelines.[35] Similarly, for non-COVID-19 ARDS, the use of inhaled vasodilators (eg, nitric oxide) to manage refractory hypoxaemia was judged to be inappropriate, whereas there was uncertainty about their use in COVID-19 probably because the burden of pulmonary vascular disease outweighed potential adverse effects (an increased risk of renal failure), logistic challenges and the expense.[36] While an evidence base is lacking, numerous case series have reported on the use of inhaled nitric oxide for COVID-19, and the Surviving Sepsis Campaign suggested a brief trial as a rescue therapy for severe hypoxia.[12] National and international guidelines are increasingly suggesting enhanced thromboprophylaxis for critically ill patients with COVID-19. While full anticoagulation and antiplatelet dose aspirin are proposed treatment options for the REMAP-CAP and RECOVERY adaptive design platform trials,[37 38] our results suggest that trials of alternative

anticoagulation regimens may be complicated by a lack of equipoise.

It is axiomatic that despite active research dating back to the 1960s, there are no effective disease- modifying therapies for the management of ARDS. The UK guidelines recommended that owing to a paucity of adequate clinical trials further research be carried out into the role of corticosteroids in the management of ARDS, but no other drug treatments were considered.[14] Hence, the survey questions in this section addressed patients with COVID-19-related ARDS exclusively.

Following the recent H1N1 influenza A pandemic, the research community has been primed to take advantage of the unique potential for clinical trials presented by a global pandemic.[39] Numerous studies have tested several interventions in thousands of hospitalised patients with COVID-19. A meta-analysis of seven studies using corticosteroids in 1703 patients with COVID-19 requiring varying degrees of respiratory support from a minimum of supplemental oxygen showed a lower 28-day all-cause mortality in the group that had been given steroids.[40] In this respect, severe COVID-19 may differ from similar viral pneumonias causing ARDS. For example, a meta-analysis of observational studies in influenza suggested increased mortality with corticosteroid treatment.[41] The optimum drug, dose and timing of corticosteroid administration are not defined by existing studies. The experts were uncertain about the use of 'late' high-dose corticosteroids as well as other potential drug therapies that are still in clinical trials or for which the evidence is deemed to be equivocal. In the future, trials will probably select patient populations using laboratory tests for selected biomarkers that are paired with specific interventions to provide a personalised approach. For example, the procalcitonin assay may be used to curtail or initiate antibiotic therapy, circulating markers of inflammatory clotting cascade to modify anticoagulation regimens, and analysis of circulation cytokines and physiological parameters to select patients who are likely to respond to anti-inflammatory therapies that may be targeted monoclonal antibodies or pluripotent agents like statins.

One of the strengths of our study was the diversity of ARDS experts drawn from various UK centres and backgrounds with experience in managing patients with COVID-19 and ARDS. Conversely, the experts were exclusively UK-based and their opinions predominantly compared with the practice recommended by the most comprehensive and recent guideline for the management of ARDS which is also from the UK. RAND methodology is validated as a guide to decision-making in the absence of a robust evidence base. While the expert panel was provided with up-to-date literature, it was not possible to determine the extent to which these findings influenced responses. Similarly, it was impossible for our scenarios to encompass all cases encountered in clinical practice, and some of the interventions (high vs low PEEP, recruitment manoeuvres, conservative fluid balance and autoimmune screen) were poorly defined, reflecting inconsistency in clinical trials and routine practice. The fact that three of the expert panel helped to design the original survey is likely to have introduced an element of bias; conversely, in accordance with RAND methodology, the nature of the final questionnaire was changed from the original by the entire panel and moderator after the online meeting. We focused on selected management strategies, including those covered in recent guidelines, to aid decision-making in ARDS in the context of COVID-19. Inevitably, some important areas of care were not covered, and combinations of strategies were not addressed. The outcomes should be considered an adjunct to multidisciplinary decision-making rather than a replacement. The RAND methodology asks experts to decide about the appropriateness of a given intervention regardless of the resource utilisation and without considering anything other than patient benefit. Pandemics highlight utilitarian considerations, for example, resources in a pandemic may be critically limited and it is imperative to protect health workers from contagion. This was perfectly exemplified by the use of non-invasive respiratory support during the COVID-19 crisis when there was a real risk of oxygen delivery failure in hospitals, infection of staff and other patients by aerosols, and the saturation of the capacity to care for patients requiring invasive mechanical ventilation. Finally, knowledge is evolving at an unprecedented rate such that it will be important and challenging to keep up with new developments.

In conclusion, we have provided guidance concerning the management of COVID-19-related ARDS during the pandemic. The expert panel recommended adhering to evidence-based supportive strategies for managing ARDS as they have been described in recent guidelines. Similarly, for supportive strategies outside of existing guidelines, the recommendations were the same for ARDS regardless of whether it was associated with COVID-19 pneumonia. However, techniques for treating the distinct pathological features of COVID-19 have emerged thanks to powerful, methodologically innovative studies.

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Contributors The data have been verified by SM, PMI and MG. KD, AP, CS, SM, PMI and MG designed the original survey. The RAND methodology experts were MAS, SM and PMI. The literature searches were performed by MBM, LS and HY. The expert panel comprised PD, SJF, LGF, MG, DFM, IN, BP, AGP, CS, NTT and MPW. The first draft of the manuscript was written by MG, SM, PMI, DFM and AGP. All authors contributed to revising and final approval of the manuscript.

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