New UK guidelines for the management of adult patients with ARDS

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Acute respiratory distress syndrome (ARDS) was first reported in a case series from Denver in 1967,[1] and remains a major problem in the severely ill. This was highlighted by data from the recently published Large observational **study** to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) trial, which recorded admissions over 4 weeks to 459 intensive care units (ICUs) in 50 countries and included 29 144 patients. In total, 3022 (10.4%) cases fulfilled ARDS criteria, including almost a quarter of those supported with invasive mechanical ventilation.[2] ARDS was associated both with high mortality and prolonged length of stay. In addition, long-term follow-up studies of patients with ARDS indicate high long-term morbidity and decreased quality of life.[3] There is therefore a real need to improve outcomes in ARDS.

With this aim in mind, the Intensive Care Society (ICS)/Faculty of Intensive Care Medicine (FICM) guideline for the management of the ARDS in adults was published towards the end of 2018.[4] The multidisciplinary Guideline Development Group used Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[5] The group allocated selected outcomes as being either of critical (mortality up to 1 year, quality of life at 3 months) or high importance (quality of life at 6–12 months, length of ICU and hospital stay and treatment-associated harms). Ten interventions used in patients with ARDS were examined, based on existing recommendations and the experience of committee members, and informed by a survey of ICS members. The evidence-based findings are summarised in table 1. Two strong recommendations (using GRADE terminology) in favour of interventions and one strong recommendation against an intervention were made. Where mechanical ventilation is required, the use of low tidal volumes (<6 mL/kg ideal body weight) and airway pressures (plateau pressure <30 cmH_2O) was recommended. For patients with moderate-to-severe ARDS, determined by the ratio of arterial oxygen partial pressure to fractional inspired oxygen (P:F ratio ≤20 kPa), prone positioning was recommended for at least 12 hours/day. By contrast, high frequency oscillation was not recommended. Four interventions received a 'weak recommendation'. This indicates that some patients may benefit in some circumstances from the intervention. These included the use of a conservative fluid management strategy, mechanical ventilation with high positive end-expiratory pressure (PEEP) and the use of the neuromuscular blocking agent cisatracurium for 48 hours. Extracorporeal membrane oxygenation (ECMO) was suggested as an adjunct to protective mechanical ventilation for patients with very severe ARDS. Inhaled nitric oxide received a weak recommendation against its use.

Guideline groups can also identify interventions which may be beneficial but where existing data produce very imprecise estimates of possible effect size. On this basis, the group made two research recommendations for the use of corticosteroids and extracorporeal carbon dioxide removal.

COMPARISON WITH ATS GUIDELINE

Replication is essential in research. Do the UK guidelines mirror other international recommendations? The American Thoracic Society, European Society of Intensive Care Medicine, Society of Critical Care Medicine (ATS/ESICM/SCCM) clinical practice guidelines for the mechanical ventilation of patients with ARDS[6] considered 6 interventions, which were included in the 10 interventions considered by the ICS/FICM group. Importantly, the recommendations from both sets of guidelines are consistent, with only minor differences. Recommendations for the use of low tidal volumes, prone positioning (in severe ARDS) and against the use of high frequency oscillation were concordant between guidelines. Moreover, suggestions for the use of higher PEEP in patients with moderate-to-severe ARDS were also concordant. In contrast, the ATS/ESICM/SCCM guideline panel could not reach consensus on a recommendation for the use of prone positioning in patients with moderate ARDS. Similarly, the UK group decided that the loose definition of recruitment manoeuvres and a paucity of evidence mitigated against assessing this intervention that was 'suggested' by the ATS/ESICM/SCCM group. Finally, given the inclusion of only a single randomised controlled trial for veno-venous ECMO, no recommendation was provided for or against its use in patients with severe ARDS.

UPDATE WITH RESPECT TO RECENT TRIAL RESULTS

One problem with rigorous guidelines is that they may be out of date, even before publication. Since the release of both sets of guidelines, a number of important clinical trials have been published which could affect the status of the recommendations. The Alveolar Recruitment Trial (ART) evaluated the effect of a recruitment manoeuvre and PEEP titration according to best respiratory system compliance as compared with a conventional low PEEP strategy on 28-day mortality in patients with moderate-to-severe ARDS.[7] The lung recruitment and titrated PEEP strategy was associated with increased 28-day and 6-month mortality, decreased ventilator-free days and increased risk of air leaks like pneumothorax. These important results would need to be included in a future revision of the guidelines. The experimental intervention bundled the use of a recruitment manoeuvre and PEEP titration, resulting in higher PEEP levels in this group. This might suggest a need to reconsider the weak recommendation made for high PEEP in the guidelines. However, it is difficult to separate the contribution of each component on the worse outcomes observed in this trial. Furthermore, the ART trial used very aggressive recruitment manoeuvres with inspiratory pressures as high as 60 cm of water and titrated PEEP from a high level (20 cm of water). The negative results of this trial compared with the positive results in previous trials using lower airway pressure to 'open' the injured lung may be attributable to haemodynamic effects or associated ventilator-associated lung injury. Alternatively, a trial recruiting exclusively severe ARDS cases or only patients who 'respond' to recruitment by increasing the amount of lung accessible for ventilation may increase the chances of a positive response to an open

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Table 1 Summary of the FICM/ICS guideline recommendations for the management of ARDS in adult patients

Topic	GRADE recommendation	Conditions
Tidal volume	Strongly in favour	Tidal volume ≤6 mL/kg ideal body weight; plateau pressure <30 cmH_2O.
Prone positioning	Strongly in favour	Proning for ≥12 hours/day. Patients with moderate-to-severe ARDS (P:F ratio ≤20 kPa).
High frequency oscillatory ventilation	Strongly against	
Conservative fluid management	Weakly in favour	
Higher peek end-expiratory pressure	Weakly in favour	Patients with moderate or severe ARDS (P:F ratio ≤27 kPa).
Neuromuscular blocking agents	Weakly in favour	Evidence only for cisatracurium besylate. Continuous 48 hours infusion. Patients with moderate-to-severe ARDS (≤20 kPa).
Extracorporeal membrane oxygenation	Weakly in favour	With lung-protective mechanical ventilation. Patients with severe ARDS, lung injury score ≥3 or pH <7.20 due to uncompensated hypercapnoea.
Inhaled vasodilators	Weakly against	Evidence only for inhaled nitric oxide
Corticosteroids	Research recommendation	
Extracorporeal carbon dioxide removal	Research recommendation	

The colours (green, red and blue) correspond to the GRADE recommendation
ARDS, acute respiratory distress syndrome; FICM, Faculty of Intensive Care Medicine; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICS, Intensive Care Society.

lung approach,[8] but would be difficult to recruit to and to deliver.

The Esophageal Pressure-Guided Ventilation 2 (EPVent2) trial evaluated the effect of an oesophageal pressure-guided PEEP strategy as compared with an empirical high PEEP-FiO_2 strategy on a composite outcome of death and days free from mechanical ventilation at day 28 in patients with moderate-to-severe ARDS.[9] There was no significant difference in the primary outcome between groups. Importantly, early end-expiratory transpulmonary pressure was not significantly different between groups. Given the lack of separation between groups in airway and transpulmonary pressures, as well as the lack of a significant difference in the primary outcome, it is unlikely that the addition of these data would alter the evidence synthesis supporting the conditional recommendation for higher PEEP.

Finally, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial evaluated the effect of veno-venous ECMO as compared with conventional lung protective mechanical ventilation on mortality in patients with severe ARDS.[10] However, because 25% of the control group crossed over to receive ECMO, to an extent the trial evaluated the effects of early veno-venous ECMO to conventional lung protective mechanical ventilation with the option of transitioning to ECMO. The primary outcome of 60-day mortality was not significantly lower with veno-venous ECMO, although most secondary outcomes favoured the ECMO group. A post hoc Bayesian re-analysis and conventional meta-analysis including EOLIA both suggested a benefit for veno-venous ECMO in patients with severe ARDS.[11] These data augment the evidence synthesis supporting the conditional recommendation for veno-venous ECMO in patients with severe ARDS. However, only a formal re-evaluation using GRADE methodology could determine whether the strength of the recommendation would change.

CONCLUSIONS

One of the purposes of guidelines is to collate and analyse available evidence associated with a specified area of clinical management. For adult patients with ARDS, the UK guideline development group found strong evidence in favour of two interventions (low tidal volume ventilation and prone positioning) and against high frequency oscillation. For the remaining seven commonly used interventions, there was a lack of high-quality evidence to support a strong recommendation. Without a doubt, the quality of clinical trials has improved progressively from a low baseline, for example, with a couple of exceptions none of the studies we examined included an economic assessment or quality of life data that would now be expected. The quality of published critical care studies has improved progressively within subject areas, and the results of initial studies inform the design of subsequent trials, which may devalue standard meta-analysis in favour of 'the ultimate' phase III clinical trial. For example, when assessing prone positioning in successive clinical trials the intervention was modified to extend the duration of proning and the population was changed from all adult patients to those with moderate and severe hypoxaemia. Based on the most recent study,[12] the ICS/FICM/BTS group made a strong recommendation for prone positioning for at least 12 hours/day in patients with a P:F ratio of <20 kPa.

If the publications of guidelines alone improved clinical practice, then patient outcomes would have been transformed in the last 20 years. Unfortunately, there is a large body of work demonstrating that the translation of clinical guidelines into improvement in practice is often disappointing. For example, the critical care community has been very aware of the adverse effects of high tidal volume ventilation for many years. Despite this knowledge, and other factors including a failure to calculate the ideal body weight, higher tidal volume ventilation is still widespread. A secondary analysis of individual patient data from three large ARDS studies showed that only approximately one-third of participants were initially ventilated with recommended low tidal volumes.[13] Failure to adhere to best practice with respect to protective mechanical ventilation compounds the effect of missing the diagnosis of ARDS and certainly contributes to poor outcomes.

There are many possible explanations for this gap between best practice and reality including lack of knowledge and organisational problems. We have been impressed by the various national audits, conducted by both the British Thoracic Society and the National Confidential Enquiry into Patient Outcome and Death, in driving up standards. We therefore suggest that the ARDS guidelines provide a timely benchmark to conduct a National ARDS audit, which we believe would identify suboptimal practice, but more importantly would improve outcomes for patients with ARDS.

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