

Scandinavian clinical practice guideline on fluid and drug therapy in adults with acute respiratory distress syndrome

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Conflict of interest

All authors declare no conflict of interest, according to Appendix B (completed for financial and intellectual conflicts of interest on a recommendation per recommendation basis).

Funding

Funding was provided solely from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI) and institutional and/or departmental sources.

Submitted 9 November 2015; accepted 13 February 2016; Submission 6 January 2016

Citation

Claesson J., Freundlich M., Gunnarsson I., Laake J. H., Møller M. H., Vandvik P. O., Varpula T., Aasmundstad T. A..Scandinavian clinical practice guideline on fluid and drug therapy in adults with acute respiratory distress syndrome. *Acta Anaesthesiologica Scandinavica* 2016.

doi: 10.1111/aas.12713

Background: The objective of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI) task force on fluid and drug therapy in adults with acute respiratory distress syndrome (ARDS) was to provide clinically relevant, evidence-based treatment recommendations according to standards for trustworthy guidelines.

Methods: The guideline was developed according to standards for trustworthy guidelines, including a systematic review of the literature and use of the GRADE methodology for assessment of the quality of evidence and for moving from evidence to recommendations.

Results: A total of seven ARDS interventions were assessed. We suggest fluid restriction in patients with ARDS (weak recommendation, moderate quality evidence). Also, we suggest early use of neuromuscular blocking agents (NMBAs) in patients with severe ARDS (weak recommendation, moderate quality evidence). We recommend against the routine use of other drugs, including corticosteroids, beta2 agonists, statins, and inhaled nitric oxide (iNO) or prostaglandins in adults with ARDS (strong recommendations: low- to high-quality evidence). These recommendations do not preclude the use of any drug or combination of drugs targeting underlying or co-existing disorders.

Conclusion: This guideline emphasizes the paucity of evidence of benefit – and potential for harm – of common interventions in adults with ARDS and highlights the need for prudence when considering use of non-licensed interventions in this patient population.

Editorial comment: what this article tells us

Current fluid and drug therapy recommendations for patients with ARDS are presented, together with a critical review of the evidence. These guidelines are sponsored by the Clinical Practice Committee of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI). The SSAI also owns this journal.

An electronic version of this guideline can be accessed at www.ssai.info/guidelines/

Following its identification by Ashbaugh in 1967,¹ the acute respiratory distress syndrome (ARDS) was first defined by an American-European Consensus Conference (AECC) in 1994.² The original definition was recently revised and is now known as the Berlin definition.³ Briefly, ARDS is defined as hypoxic respiratory failure, classified as mild ($26.6 \text{ kPa} < \text{PaO}_2/\text{FiO}_2 \leq 40 \text{ kPa}$), moderate ($13.3 \text{ kPa} < \text{PaO}_2/\text{FiO}_2 \leq 26.6 \text{ kPa}$), and severe ($\text{PaO}_2/\text{FiO}_2 \leq 13.3 \text{ kPa}$) (Table 1).

The underlying pathophysiology of ARDS is an evolving concept that involves the inflammatory cascade, fluid dynamics, lung mechanics and the pulmonary circulation.⁴ Recently both phenotypic and genotypic categorization have added to our understanding of ARDS.^{5,6} However, apart from lung mechanics, the manner in which our pathophysiological insight will ultimately influence therapy in ARDS remains unclear.

Numerous clinical trials have addressed whether different fluid and drug regimens may improve the clinical outcome of ARDS in general.⁷ In the present guideline, we systematically and transparently review the available

evidence for fluid and drug interventions in patients fulfilling the ARDS criteria regardless of the underlying disease.

The Clinical Practice Committee of the Scandinavian Society of Anaesthesia and Intensive Care Medicine (SSAI) initiated this work. The aim was to summarize the available evidence and provide recommendations according to new standards for trustworthy guidelines, as outlined by the Institute of Medicine (IOM), the Guideline International Network (GIN), and according to the GRADE methodology.^{8–10} Other authoritative sources such as UpToDate and the Surviving Sepsis Campaign have also applied GRADE in their guidelines for the adjuvant use of fluids and drugs in adults in ARDS.^{11,12}

Methods

Process

Members of the guideline task force were selected by the national societies of anaesthesiology in Denmark, Finland, Iceland, Norway, and Sweden, following invitation from the Clinical Practice Committee of the SSAI. We followed the standards for trustworthy guidelines, including the use of the GRADE system, management of intellectual and financial conflicts of interest on a recommendation per recommendation basis (see Appendix B), a peer review process, and a plan for updating of recommendations. We did not include patient representatives in the guideline process.

GRADE

As recently recommended for intensive care medicine,¹³ we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for formulating clinical

Table 1 The Berlin definition of the acute respiratory distress syndrome (ARDS)³:

- ARDS is characterized by the following four criteria:
- 1 Lung injury of acute onset, within 1 week of an apparent clinical insult and with progression of respiratory symptoms
 - 2 Bilateral opacities on chest imaging not explained by other pulmonary pathology (e.g. pleural effusions, lung collapse, or nodules)
 - 3 Respiratory failure not explained by heart failure or volume overload
 - 4 Decreased arterial PO_2/FiO_2 ratio:
 - mild ARDS: ratio is 201–300 mmHg ($\leq 39.9 \text{ kPa}$)
 - moderate ARDS: 101–200 mmHg ($\leq 26.6 \text{ kPa}$)
 - severe ARDS: $\leq 100 \text{ mmHg} (\leq 13.3 \text{ kPa})$

A minimum PEEP of 5 cmH₂O is required; it may be delivered non-invasively with CPAP to diagnose mild ARDS.

questions, assessing the quality of evidence, generating anticipated absolute effects, and moving from evidence to recommendations. Briefly, clinical questions were formulated in the so-called PICO format,¹⁴ which identify the relevant patient population and/or clinical problem (P), the intervention (I) under scrutiny as well as the comparator (C), and patient-important outcomes (O) (Table 2).

For literature review, we first searched the McMaster PLUS database to identify high-quality systematic reviews of randomized trials. If more than one relevant systematic review was identified, we chose the most recent one(s) with highest methodological quality (lowest risk of bias). We excluded studies with observational design and physiological studies based on our assumption that these would not provide us with higher quality evidence than what we would identify from available randomized

trials. If no recent high-quality systematic reviews were found, we searched the following databases: PubMed, Embase, Google Scholar, and the Cochrane Library (Appendix A). When available, published systematic reviews were used to identify relative effect estimates and assess the quality of evidence for the predefined patient-important outcomes. If we identified additional relevant trials not included in existing systematic reviews, we updated the meta-analyses with data from the identified RCTs. We generally used Mantel-Haenszel statistics and random effects models in the meta-analyses (Review Manager Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). In addition, we used trial sequential analysis to assess the potential for random errors (sparse data with spurious findings).^{15,16} Our review was completed in June 2015.

Table 2 Clinical problems and PICO questions used to assess evidence relevant to this guideline statement.

Informal clinical question	PICO Question			
	Population (P)	Intervention (I)	Comparator (C)	Outcomes (O)
1. Should liberal or restrictive fluid therapy be used in patients with ARDS?	Mechanically ventilated adults with acute respiratory distress syndrome (ARDS)	Liberal fluid therapy	Restrictive fluid therapy	Mortality 28/30 days 60–180 days -ICU -Hospital -Hospital
2. Should corticosteroids be used in patients with ARDS?		Corticosteroids at any dose or duration and route of administration	Placebo or none	Oxygenation efficiency
3. Should beta2 agonists be used in patients with ARDS?		Beta2 agonists at any dose or duration and route of administration	Placebo or none	Ventilator-free days
4. Should neuromuscular blocking agents (NMBAs) be used in patients with ARDS?		NMBAs at any dose or duration	Placebo or none	Days of mechanical ventilation
5. Should inhaled nitric oxide be used in patients with ARDS?		Inhaled nitric oxide at any dose or duration	Placebo or none	LOS in ICU
6. Should prostanoids be used in patients with ARDS?		Prostanoids at any dose or duration and route of administration	Placebo or none	Use of rescue therapies
7. Should statins be used in patients with ARDS?		Statins at any dose or duration	Placebo or none	Other organ failure
8. Should any other drugs be used in patients with ARDS?		Any other drug at any dose or duration and route of administration	Placebo or none	Barotrauma

We provide GRADE evidence profiles and Forest plots of meta-analyses in Appendix A. In keeping with the GRADE methodology, the quality of evidence for an intervention (i.e. our confidence in the effect estimates) was rated down for identified risks of bias (e.g. due to lack of blinding or early termination of studies), inconsistency (i.e. unexplained heterogeneity), indirectness (e.g. different patient populations or use of surrogate outcomes), and imprecision (wide confidence interval around the effect estimate).¹⁷ Importantly, however, when the outcome in question was death at any stage, we did not downgrade evidence due to lack of blinded outcome assessment. Accordingly, the quality of evidence was rated from 'high' to 'very low'.

We generated absolute effect estimates by applying baseline risk estimates to the relative effect estimates from the meta-analyses. Baseline risk estimates were taken from the control arms of randomized trials in the systematic reviews – in the absence of available high-quality observational data. Recommendations were based on the predefined PICO questions.

When moving from evidence to recommendations, four factors were considered and integrated: Benefits and harms, quality of evidence, values and preferences (of patients or their proxies), and cost considerations. GRADE classifies recommendations as strong when virtually all informed patients would choose the recommended management strategy. Weak recommendations, which reflect a close call between benefits and harms, uncertainty regarding treatment effects, questionable cost-effectiveness, or variability in values and preferences, apply when fully informed patients would choose different management strategies.^{10,18}

The group agreed upon the recommendations in this document. Strong recommendations were given the wording 'we recommend' and weak recommendations 'we suggest'.

Results

A general note on recommendations for unlicensed drug use

No drug or fluid regimen has been licensed for use in ARDS, a condition that is relatively rare

and highly lethal, and clearly outside the primary sphere of interest for pharmaceutical companies. Our task has been to investigate if there is evidence from empirical research that nevertheless supports the use of specific fluid regimens or drugs in adults with ARDS. We believe that any recommendation for the use of an intervention must be based on evidence from clinical trials that demonstrate clear net benefit with respect to patient-important clinically relevant outcomes in the population of interest. In the absence of such evidence, we must consider the risks: all interventions must be expected to carry a risk of side effects that may or may not be related to the condition that we seek to cure. Absence of proof of benefit should caution the clinician to consider the – often unknown and sometimes severe – risks that patients are subject to when interventions are used outside of their license and without any documentary support. We reason that we must recommend against the use of interventions in such cases.

Table 3 gives recommendations and key information, including briefly outlining benefits and harms, quality of evidence, values preferences, and cost considerations. Recommendations are mainly based on the absolute risk of death, being the most critical patient-important outcome. Death at some pre-specified time point following inclusion is also the primary outcome measure of the included studies. Follow-up time is variable, however, ranging from 28–30 days to 180 days (or ICU and hospital mortality). Interpretation and use of other patient-important outcomes were difficult as they were inconsistently and diversely reported across trials and in the systematic reviews.

Recommendation 1: Fluid therapy (Appendix S1; Table S1, Fig S1)

We suggest fluid restriction over a liberal fluid strategy in adults with ARDS (weak recommendation, moderate quality evidence). The physiological rationale for limiting fluid volume in ARDS has been detailed in numerous reviews and is supported by clinical evidence.^{19–21} Our recommendation is based on the results from the ARDS network trial (FACTT study)¹⁹ that compared a fluid-restrictive vs. fluid-liberal approach in adults with mild to severe ARDS

Table 3 Key recommendations and quality of evidence

Recommendation	Strength of recommendation	Benefits and harms	Quality of evidence Reason(s) for downgrading	Preferences and values	Resources
1. Fluid therapy We suggest use of a restrictive fluid therapy in adults with ARDS	Weak	In patients treated with restrictive fluid therapy in preference to a liberal fluid therapy, significantly more patients are likely to be weaned off mechanical ventilation by day 28. But enrolment in a conservative fluid-management strategy was associated with cognitive impairment in a follow-up study	Moderate Due to indirectness	Less time on ventilator may come at the cost of impaired cognitive function	No issues
2. Corticosteroids We recommend not using corticosteroids in routine therapy of adults with ARDS*	Strong	Corticosteroids confer no documented benefit in a general population of adults with ARDS and may increase risk of death in subgroups of patients (e.g. patients with influenza)	Low Due to inconsistency, imprecision	In patients with specific underlying disorders, e.g. chronic inflammatory disease, corticosteroids may be relevant	No issues
3. Beta2 agonists We recommend not using beta2 agonists as routine therapy of adults with ARDS*	Strong	Beta2 agonists confer no documented benefit in a general population of adults with ARDS and may increase the risk of arrhythmias, duration of mechanical ventilation, and death	Low Due to inconsistency, imprecision	In patients with specific underlying disorders, e.g. asthma, beta2 agonists may be relevant	No issues
4. Neuromuscular blocking agents (NMBAs) We suggest that NMBAs may be used in adults during the early stages of severe ARDS*†	Weak	In a general population of adult patients with ARDS, NMBAs compared with placebo result in significantly more patients to be discharged alive from hospital NMBAs will prevent spontaneous ventilatory efforts and may increase the need for sedation	Moderate Due to imprecision	Patients who can tolerate low levels of sedation may prefer not to be paralyzed during mechanical ventilation	The authors deem the extra cost associated with the intervention negligible compared with the total cost
5. iNO a) We recommend not using iNO as routine therapy in adults with ARDS	Strong	Nitric oxide improves oxygenation, but has no demonstrable effect on the risk of death and significantly increases the risk of kidney injury	Moderate Due to imprecision	Where hypoxemia by itself is immediately life-threatening, most patients and caregivers would accept any available	The authors deem the extra cost associated with the intervention very high compared with conventional therapy

Table 3 (Continued)

Recommendation	Strength of recommendation	Benefits and harms	Quality of evidence Reason(s) for downgrading	Preferences and values	Resources
b) We suggest that INO may be attempted in adults with ARDS and immediately life-threatening hypoxemia unresponsive to conventional therapy	Weak			measure that relieves hypoxemia if not known to increase the risk of death	
6. Prostanoids We recommend not using prostanoids as routine therapy of adults with ARDS*	Strong		There are no data to support the use of prostanoids in adults with ARDS. Data from children are sparse and inconclusive	Very low Due to indirectness and imprecision	The risk of potential harm has not been assessed
7. Statins We recommend not using statins as routine therapy of adults with ARDS*	Strong		Statins confer no documented benefit in a general population of adults with ARDS	Low Due to inconsistency and imprecision	In patients with specific underlying disorders, e.g. coronary heart disease, statins may be relevant
8. Any other drug We recommend not using any other drug as routine therapy of adults with ARDS*	Strong		There is no evidence to suggest that any other drug or combination of drugs confer benefit in a general population of adults with ARDS	No relevant data	The authors deem the extra cost associated with the intervention negligible compared with the total cost

*This recommendation does not preclude the use of drugs that may be indicated for any specific underlying cause or co-existing condition and †severe ARDS ($\text{PaO}_2/\text{FiO}_2 \leq 13.3 \text{ kPa}$ or 100 mmHg); moderate ARDS ($\text{PaO}_2/\text{FiO}_2 \leq 26.6 \text{ kPa}$ or $200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 40 \text{ kPa}$ or 300 mmHg).

(i.e. targeting either a neutral fluid balance or central venous pressure and pulmonary–artery–occlusion pressure at 10–14 mmHg and 14–18 mmHg, respectively). The quality of evidence was downgraded for indirectness because the only major effect on outcomes was a reduction in time on mechanical ventilation with no significant effect on mortality or other organ failure. Of note, in a post hoc analysis it was found that enrolment in the conservative fluid-management strategy was associated with cognitive impairment.²² Additional evaluation of this outcome in future research projects seem appropriate and may impact on recommendations if confirmed by higher quality evidence.

Recommendation 2: Corticosteroids (Appendix A; Table S2, Fig S2)

We recommend against the routine use of corticosteroids in any dose or duration in adults with ARDS (strong recommendation, low-quality of evidence). This does not preclude the use of corticosteroids targeting any underlying condition or co-existing disease in which steroids are indicated (e.g. auto-immune disease). Our recommendation is based on the systematic review by Ruan and et al.²³ that aggregated data from eight randomized trials and a total of 725 patients^{24–31} and found no difference between patients receiving steroids vs. patients not receiving steroids. The quality of evidence was downgraded due to significant unexplained heterogeneity between trials and imprecision around the effect estimate (risk ratio for death, 0.91; 95% CI 0.71–1.18). (See Footnote*)

Recommendation 3: Beta2 agonists (Appendix A; Table S3, Fig S3)

We recommend against the routine use of beta2 agonists in adults with ARDS (strong recommendation, low-quality of evidence). This does not preclude the use of beta2 agonists in patients with an underlying condition or co-existing dis-

ease in which beta2 agonists are indicated [e.g. asthma or chronic obstructive pulmonary disease (COPD)]. Our recommendation is based on a recent systematic review of three randomized trials with either inhaled³² or intravenous administration^{33,34} of beta2 agonists.³⁵ The results show either no effect (inhaled) or increased (intravenous route) risk of death (aggregate risk ratio, 1.14; 95% CI, 0.91–1.42) and a significant increase in the risk of cardiac arrhythmias (risk ratio, 1.8; 95% CI, 1.24–2.62) and time on mechanical ventilation (both routes of administration; mean difference, 2.2 days; 95% CI, 0.71–3.68). The quality of evidence was downgraded due to imprecision and inconsistency.

Recommendation 4: Neuromuscular blocking agents (NMBAs) (Appendix A; Table S4, Fig S4)

We suggest that neuromuscular blocking agents (NMBAs) may be used in the early stages of severe ARDS (weak recommendation, moderate quality of evidence). This recommendation is based on findings from three randomized trials^{36–38} and a systematic review and meta-analysis by Alhazzani et al.³⁹ No individual trial demonstrated significant benefit from the use of NMBAs, but aggregate data from all trials demonstrated a significant effect on the risk of death (risk ratio, 0.70; 95% CI, 0.55–0.89). However, trial sequential analysis indicates that the findings in the systematic review may be subject to random errors (a spurious finding due to repetitive testing), as the total number of included patients of all trials was small compared to what would have been necessary in a randomized trial with sufficient power (Appendix A; Fig S4i I-II). Thus, the quality of evidence was downgraded due to imprecision.

Recommendation 5: Inhaled nitric oxide (iNO) (Appendix A; Table S5, Fig S5)

A. We recommend against the routine use of iNO in adults with ARDS (strong recommendation, moderate quality of evidence). This does not preclude the use of iNO in patients with an underlying condition or co-existing disease in which iNO is indicated (e.g. severe pulmonary hypertension). Our recommendation is based on two

*Following completion of our review, Norita et al. published a systematic review on the use of corticosteroids in ARDS (Norita H et al. Intern Med 2015; 54: 1473–9). The findings of this review do not alter our recommendation. Data will be included in a later iteration of our guideline.

recent systematic reviews^{40,41} that found no effect of iNO on the risk of death in adults with ARDS – regardless of their oxygenation status – and importantly, an increased risk of kidney injury, a very severe complication in ARDS patients (risk ratio, 1.8; 95% CI, 1.17–2.79). The quality of evidence was downgraded due to imprecision.

B. The above results notwithstanding, we suggest that iNO may be used as a rescue measure to temporarily increase oxygenation in patients with catastrophic hypoxemia and imminent risk of death (weak recommendation, moderate quality of evidence).

Recommendation 6: Prostanoids (Appendix A; Table S6, Fig S6)

We recommend against routine use of Epoprostenol inhalation in adults with ARDS (strong recommendation, very low quality of evidence). This does not preclude the use of Epoprostenol in patients with an underlying condition or co-existing disease in which it is indicated (e.g. severe pulmonary hypertension). Our recommendation is based on a recent Cochrane systematic review comprising one low risk of bias RCT ($n = 14$ children) that found no statistically significant effect of Epoprostenol on 28-day mortality.⁴² None of the other outcomes of interest were reported. The quality of evidence was downgraded for imprecision and indirectness.

Recommendation 7: Statins (Appendix A; Table S7, Fig S7)

We recommend against the routine use of statins in adults with ARDS (strong recommendation, low quality of evidence). This does not preclude the use of statins in patients with an underlying condition or co-existing disease in which statins are indicated (e.g. coronary heart disease). Our recommendation is based on two recently published randomized trials that showed heterogeneous and largely imprecise effects of either simvastatin or rosuvastatin on mortality and other patient-important outcomes.^{43,44}

Recommendation 8: Other drugs

In adults with ARDS, we issue a strong recommendation against the routine use of any drug

regimen that has not already been covered in the above paragraphs. Our strong recommendation is based on an a priori very low quality of evidence, i.e. the absence of relevant and well-performed randomized trials. Enthusiasm for the apparent logic of some therapeutic options should be tempered by the absence of supportive data from empirical evidence and unknown potential for harm.

Discussion

In adopting the GRADE system for guideline development, the SSAI has emphasized that guidelines should inform readers about clinically relevant issues based on current best evidence and avoid advice based solely on expert opinion.

We were able to use existing high-quality systematic reviews of randomized trials to answer most clinical questions. However, in assessing the evidence base for fluid therapy and statins, no relevant meta-analyses or systematic reviews were found. We, therefore, conducted meta-analyses ourselves, based on systematic literature searches (see Appendix A). Also, we amended the dataset from an existing meta-analysis of iNO to include data published by Adhikari et al.⁴¹

Several interventions included in our analysis highlight the importance of weighing benefits vs. harms by the clinician: Fluid restriction may shorten time on mechanical ventilation, but may also increase the risk of cognitive dysfunction following critical illness. Also, in the FACTT trial, allowance was made for less restrictive fluid management in patients with shock, making the overall results difficult to interpret¹⁹ (we have avoided developing guidance based on subgroup analyses only). Similarly, corticosteroids may possibly improve weaning from mechanical ventilation at the price of a higher death rate in the follow-up period.²⁹ On the other hand, data generally do not indicate a higher risk of infection in ARDS patients managed with steroids.

Beta-2-agonists have been widely used to manage mechanically ventilated patients with airway secretions and loosely defined airway ‘obstruction’ in mechanically ventilation. Trial data lend no support to such therapy. The

increased risk of arrhythmias, time on mechanical ventilation, and death seen in trials should remind us to reserve the use of these drugs for patients with true obstructive airways disease.

NMBAs are widely used by anaesthesiologists to facilitate endotracheal intubation and surgery. Recent interest for their use in patients with severe respiratory failure results from trials performed by the French intensive care network.^{36,38,45} These trials and the meta-analysis used in this guideline highlight several important methodological issues that we carefully considered before issuing a weak recommendation for use of NMBA in ARDS. The imprecise effect estimates and the fact that all trials have been performed in one intensive care network results in what we consider to be moderate quality of evidence for a reduction in death and no apparent increased risk of adverse events.³⁹ The results also receive some support from a large observational study in US hospitals.⁴⁶ In mechanically ventilated adults, receipt of a NMBA was associated with a reduced risk of in-hospital mortality (risk ratio, 0.88; 95% CI, 0.80–0.96).

Inhaled nitric oxide improves oxygenation, but it has no demonstrable effect on risk of death, and it significantly increases the risk of kidney injury. The finding that nitric oxide significantly improved oxygenation (p/f ratio; mean difference, 20.67 mmHg; 95% CI, 11.39–29.95)[†] exemplifies how misleading surrogate findings may be in the light of demonstrable harm to patients. However, in patients with life-threatening hypoxemia, the use of NMBAs and nitric oxide may provide transitory relief. We believe that most individuals would prefer risk of kidney injury if iNO could raise oxygen to a level that, for example, facilitated transportation to an ECMO centre. Rescue therapies for the most severe cases of ARDS will be the subject of a separate future SSAI clinical practice guideline. In general, existing data indicate that nitric oxide no longer has a role in routine management of adults with ARDS and should be curtailed.

Prostanoids has no proven beneficial effect and has only been assessed in 14 children. Consequently, prostanoids should not be used out-

side the context of randomized clinical trials. Similarly, statins and other drugs directed at the inflammatory cascade have yet to be proven beneficial.

Why develop Nordic guidelines for intensive care medicine? Across the Nordic societies, there is considerable professional, cultural, and economic homogeneity. This is important because there are many shared values, preferences, and resource considerations throughout our societies. These are important elements in the GRADE system. Intensive care medicine, and particularly mechanical ventilation, has a longstanding tradition in Nordic anaesthesiology, and much of the early pioneering work was done by anaesthetists in the Nordic countries.^{47–49} It is, therefore, only natural that SSAI develops guidelines and standards that emphasize the role of anaesthesiology in intensive care medicine.

The guideline process serves to inform us that, despite advances, many areas of our practice remain characterized by a paucity of high-quality evidence. Ideally, guideline developers work in concert with trialists to make informed choices when allocating resources for costly investigations. Close collaboration with research groups, including the Scandinavian Critical Care Trials Group (SCCTG), is therefore essential for further progress.

Limitations

A limitation of this work is that we have relied heavily on the use of the McMaster Plus database in selecting reviews for our work. We cannot exclude the possibility that an independent approach might have revealed additional data that were not included in our work. We do, however, find it highly unlikely that we could have improved on the quality of the algorithms used by McMaster.

Also, we restricted our recommendations to those that can be deduced from randomized trials only. The re-definition of hypoxic respiratory failure into mild, moderate, and severe ARDS³ simplifies trial selection. Our analyses still suffer from significant trial heterogeneity (i.e. variability in published studies with respect to the severity of illness in patients included in each trial, and also by the heterogeneous nature of any underlying disease and the

[†]Corresponds to 2.76 kPa (1.52–3.99).

timing of inclusion of patients following development of ARDS). Examples include corticosteroid trials that utilize a variety of dose regimens and duration of therapy (Appendix A; Table S2; Fig S2). This leaves the clinician who cares for ARDS patients and who applies our guideline, with the choice between a conservative approach based on available evidence from randomized trials, and careful use of new treatment options and physiological targets. We cannot exclude that available observational studies may provide valuable evidence to inform some of our recommendations. Indeed observational studies may result in moderate- to high-quality evidence according to the GRADE system although such cases are few and far between.⁵⁰

Further limitations of this guideline result from lack of stakeholder involvement, that is, patient groups and relatives, as well as regulatory bodies and hospital owners (i.e. public representatives). Also, we did not include intensive care nurses who care for patients with ARDS.

Although the rationale for many treatment options have been that the intervention has been shown to improve physiological parameters (e.g. oxygenation), the history of critical care research has often shown that such a strategy may be faulty. In a recently published analysis of multicentre critical care interventions, eight critical care interventions actually increased mortality.⁵¹ Also, we have learned that it is not obvious which part of our pathophysiological insight will provide therapeutic strategies that benefit patients; the practice of gentle ventilation derives from the 'baby lung' concept that was developed from experimental and clinical studies of lung mechanics in ARDS.⁵² In clinical practice, gentle ventilation will often challenge us to accept blood gases that are far from 'normal', yet the benefit to patients has been clearly demonstrated.⁵³ Conversely, inhaled nitric oxide may significantly improve oxygenation, particularly in the acute stage of ARDS,⁴⁰ but no clinical benefit has yet been demonstrated in randomized trials and there are severe side effects. Whether due to study design or harms that outweigh benefit, the available literature does not allow strong recommendations for any of the assessed ARDS interventions. We believe that it is correct to avoid giving recommendations based on physio-

logical data only and hope that gaps in our list of recommendations may stimulate future high-quality Scandinavian multicentre trials.

Conclusion

This clinical practice guideline, as well as the recently published guideline on mechanical ventilation in adults with ARDS,⁵⁴ represent a body of recommendations developed in accordance with the principles for trustworthy guidelines developed by the international guideline community and the GRADE working group. We invite readers of this guideline to carefully review the evidence base for our recommendations, adapt recommendations when necessary, and use the recommendations in a balanced manner also informed by their own judgment to guide clinical practice to the benefit of their patients.

Acknowledgement

The task force has received methodological and practical support from the Norwegian Knowledge Centre for the Health Services and the GRADE working group.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix A: GRADE evidence profiles, Forest plots, details of literature review.

Appendix B: Declaration of Conflicts of Interest.