Intensive Care Med (2018) 44:2257–2259
https://doi.org/10.1007/s00134-018-5468-2

EDITORIAL

Focus on randomised clinical trials

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Introduction

Randomised clinical trials (RCT) are the core of evidence-based medicine (EBM) because their results may inform clinical practice, either directly or after the uptake in systematic reviews and clinical practice guidelines. While the interpretation and translation of RCT results into clinical practice is complex [1, 2], the continued development, conduct and publication of RCTs advances our knowledge and care, even though the majority of trials produce neutral results. Importantly, the trials should have the highest possible internal and external validity to have full impact on clinical practice. In this article, we highlight recent RCTs published in *Intensive Care Medicine* (ICM). Their results add to what appears to be a constant theme in critical care, 'less is more' based on RCT results (Table 1) [3].

Less is more is a constant theme also in ICM

Several systematic reviews and RCTs published in ICM add to the 'less in more' theme in critical care. The use of conservative vs. more liberal fluid strategies, after the initial management of patients with sepsis or ARDS, showed no significant effect on mortality, but reduced time on mechanical ventilation with conservative fluid strategies in meta-analysis of RCTs [4]. Stricter glycaemic control in critically ill patients did not result in improved outcomes as compared to less strict control in two network meta-analyses of RCTs, and the rates of hypoglycaemia were increased with stricter control [5, 6], as was 90-day mortality in the largest trial [7]. Along these lines, an RCT of early goal-directed nutrition vs. standard nutritional care in mechanically ventilated ICU patients resulted in more episodes of severe hyperglycaemia and higher use of insulin, and not in improvements in shorter- or longer-term patient-important outcomes [8]. Statins did not reduce the mortality in patients with ARDS, but increased markers of muscle and liver injury in an individual patient data meta-analysis of six placebo-controlled RCTs [9]. The use of intravenous polyspecific immunoglobulin G did not improve any outcomes in patients with necrotising soft tissue infections in a small single-centre, placebo-controlled RCT [10]. In a small single-centre RCT, the use of biomarkers of candida infection facilitated early discontinuation of empiric antifungal treatment in mixed ICU patients [11]. Meanwhile, the use of molecular detection of pathogens in patients with suspected severe infections resulted in more frequent microbiological diagnosis and appropriate antimicrobial cover [12]. Clearly, the safety of any reductions in antibiotic use based on these two interventions should be tested in large multicentre RCTs with lowest possible risk of bias. On the other hand, delays in the administration of antibiotic and in source control may be associated with worse outcome in patients with septic shock, but a multifaceted educational intervention did not reduce such delays as compared with standard education in a cluster RCT of 40 German hospitals [13].

We also care for patients' relatives, but RCTs testing interventions aimed at them are rare. This should change because we cannot predict the benefits and harms of interventions given with the best of intentions to improve the well-being of the relatives. In an RCT of relatives to patients who had died in ICU, a condolence letter failed to alleviate grief symptoms and may have worsened depression and PTSD-related symptoms [14].

Do clinical practice guidelines based on RCT results improve care?

Intuitively, the answer to this question would be yes. However, there are data indicating harm from guideline implementation driven by recommendations based on low-quality evidence [15]. The same may have occurred

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Table 1 Randomised clinical trials done in the ICU setting where the results indicated that doing less is as good or better than doing more

Intervention vs. control in the pivotal trial	Interventions that can be used less in the ICU
Lower vs. higher tidal volume in patients with ARDS: the ARMA trial	Less use of higher tidal volumes
Restrictive vs. liberal blood transfusion in general ICU patients with anaemia: the TRICC trial	Less use of blood transfusion
Low dose dopamine vs placebo in ICU patients with SIRS and early renal dysfunction	Less use of dopamine
Albumin vs. saline in general ICU patients: the SAFE trial	Less use of albumin
Strict vs. moderate glycaemic control in general ICU patients: the NICE-SUGAR trial	Less use of strict glycaemic control
HES vs. crystalloid in patients with sepsis: the 6S trial	No more use of HES
Higher- vs. lower-intensity CRRT in ICU patients with AKI: the RENAL trial	Less intensive CRRT
APC vs. placebo in ICU patients with persistent septic shock: the PROWESS shock trial	No more use of APC
Restrictive vs. liberal blood transfusion in ICU patients with septic shock and anaemia: the TRISS trial	Less use of blood transfusion
Targeted temperature management at 33 °C vs 36 °C in unconscious adult survivors of out-of-hospital cardiac arrest: the TTM trial	Less use of cooling to 33 °C
HFOV vs. standard ventilation in patients with moderate-to-severe ARDS: the OSCILLATE trial	Less use of HFOV
Early vs. late parenteral nutrition in ICU patients to supplement insufficient enteral nutrition: the EPANIC trial	Less use of early parenteral nutrition
Permissive underfeeding vs. standard enteral feeding in adult ICU patients: the PERMIT trial	Less use of early enteral nutrition
Pantoprazole vs. placebo in ICU patients at risk of gastrointestinal bleeding: the SUP-ICU trial	Less use of prophylactic pantoprazole

AKI acute kidney injury, *APC* activated protein C, *ARDS* acute respiratory distress syndrome, *CRRT* continuous renal replacement therapy, *HES* hydroxyethyl starch, *HFOV* high-frequency oscillatory ventilation, *SIRS* systemic inflammatory response syndrome

with the initial Surviving Sepsis Campaign (SSC) guideline promoting strict glycaemic control, which was later shown to harm patients [7]. However, guideline groups continue to issue recommendations despite low or very low levels of evidence, as has been the case for the latest iterations of the SSC guideline and those for the management of critical illness-related corticosteroid insufficiency [16, 17]. In both these guidelines, most statements were based on low- or very low-quality evidence, meaning that further research is likely to change the estimates informing these statements. Highlighting the uncertainty in guidelines including the call for more trials on questions with low evidence base may promote the conduct of RCTs in the critical care community and among funders.

Ideally, the implementation of guidelines basing most statements on lower-quality evidence should be tested in trials. This was done in a single-centre RCT in cardiac surgical patients at risk of acute kidney injury (AKI) [18]. The implementation of a care bundle, based on the KDIGO guideline [19], reduced the frequency and severity of AKI after surgery as compared with standard care. These promising results call for more RCTs of guideline implementation. And many more RCTs should be done in the critical care setting in general, given the high degree of uncertainty as shown by the large numbers of recommendations based on low-quality evidence in the clinical practice guideline [16, 17]. If done to the highest standards, RCTs may inform patient care regardless of the results showing benefit, harm or neutral effect of the intervention (Table 1). In any case, it is crucial that the critical care community understands that recommendations based on low-quality evidence may change direction with the evolution of better evidence.

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Compliance with ethical standards

Conflicts of interest
The Dept. of Intensive Care, Rigshospitalet has received support for research from Fresenius Kabi, CSL Behring and Ferring Pharmaceuticals.

Received: 3 October 2018 Accepted: 13 November 2018
Published online: 15 November 2018

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