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EDITORIAL

Innovation and safety in critical care: should we collaborate with the industry? Con

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Introduction

Critical care has evolved tremendously over the last half-century and made it possible for thousands of critically ill patients to survive and recover from life-threatening, complex medical and surgical diseases. Despite this success, most interventions delivered to critically ill patients and most technologies used in critical care have been implemented without proper validation. While this development and implementation strategy may not differ from other areas of medicine or society as whole, its consequences appear clearly in the critical care setting. In critical care, interventions and technologies implemented without proper validation have harmed many patients and resulted in an enormous waste of resources. We know this because research programs led by academic networks with limited or no industry involvement have shown neutral or even harmful effects of standard care monitoring or interventions [1, 2]. The risk of us harming our patients is not trivial. In a systematic review of interventions that was shown to affect mortality in critical care trials [2], half of the interventions increased mortality and several of these interventions were in use in clinical practice at the time of testing.

The current state of critical care

The current state of critical care medicine in the developed part of the world is very complex; most of what we do is based on low-quality evidence [3–5]; many interventions are given off-label [6]; many decisions are taken with limited involvement of the patients; patients and their families have limited abilities to choose between clinicians and hospitals; and overall critical care is very costly [7]. The low quality of evidence is underlined by a systematic overview and critical appraisal of systematic reviews of ICU interventions [5]. It showed that < 1% of the available meta-analyses were adjudicated as having low risk of bias, that is, had been designed and reported according to standards for trustworthy systematic reviews [5]. One of the risk of bias domains is the role of funders.

Industry ties and investigator's and clinician's behaviour

Financial ties of the primary investigator of randomised trials have been associated with positive trial results [8]. Along this line, sponsorship of drug and device studies by a manufacturing company leads to more favourable efficacy results and conclusions than sponsorship by other sources [9]. Also, the drug approval process may be affected. Speakers at meetings of the FDA's Anesthetic and Analgesic Drug Products Advisory Committee, who disclosed a conflict of interest, were more likely to support drug approval than those who did not [10]. Closer to clinical practice, a majority of guidelines appear to have authors with industry affiliations including consultancies; research support and equity/stock ownership [11], but very few authors involved in guidelines give accurate disclosure of their conflicts of interest [12]. And recent data confirm that the pharmaceutical industry continues its marketing strategies towards doctors, with payments and meals, and that this is associated with greater prescribing [13]. Data also show an association between positive attitudes toward industry-physician interactions and less knowledge about evidence-based prescribing, as well as greater inclination to recommend brand-name drugs [14]. Taken together, there is a persistent association between doctors' economic ties to the industry and their attitudes, research outputs, recommendations and

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Table 1 Randomised clinical trials done by academic networks in the critical care setting where the results have resulted in improved care and outcome of patients

Trial	Results	Number needed to treat to prevent one death
CRASH [15]	In patients with head injury, the avoidance of corticosteroids resulted in reduced 14-day mortality	31
CRASH II [16]	In trauma patients at risk of significant bleeding, the use of tranexamic acid resulted in reduced mortality	67
ARMA [17]	ICU patients with acute lung injury, the use of mechanical ventilation with lower tidal volumes and pressures rather than higher volumes and pressures resulted in reduced 28-day mortality and increased number of days without ventilator use	11
NICE SUGAR [18]	In general ICU patients, a protocol aiming at blood glucose levels < 10 mmol/L (180 mg/dL) rather than normal blood glucose levels reduced the rates of hypoglycaemia and 90-day mortality	38
The 6S trial [19]	In ICU patients with sepsis, the use of crystalloid for resuscitation rather than hydroxyethyl starch reduced the use of dialysis and blood and 90-day mortality	13
WOMAN [20]	In women with post-partum haemorrhage, the use of tranexamic acid resulted in reduced mortality from bleeding	250

prescription patterns. This may stem from an implicit bias, which may be very difficult to control for.

The recent advances in critical care

Recent advances in critical care have come from the results of randomized trials done by publicly funded, academic research networks with limited or no industry involvement. The results of these trials have saved the lives of hundreds of thousands of patients (Table 1). Or the trials have identified interventions or technologies that offered no overall benefit to our patients. As a consequence we have simplified critical care and reduced the waste by the appropriate omission of several interventions and monitoring devices.

How can we further improve the care and safety of critically ill patients?

Most of what we do to patients in the complex setting of critical care is based on low-quality evidence. We could probably stop using some of these interventions and monitoring techniques—critical care may be simplified further. To facilitate this we need to do as many randomized trials as possible, in particular, trials of interventions and techniques used in many patients and those that are risky, costly or labour intensive. It is unlikely that the industry will sponsor such programs as the results will likely be that we shall reduce our use even further. Inherently, the industry's role, as for-profit organisations, is to sell more not less.

Our focus should, therefore, be on the engagement with the stakeholders that want improved care independent of commercial interests i.e. patients, relatives, the leadership of the departments and hospitals, the hospital owners and philanthropic organisations. We need to lobby among politicians, those governing the conduct of research and the public research funds and research leaders to promote the conduct of clinical trials. Again, it is unlikely that industry will be supportive at all these levels. Most importantly, we shall engage our clinical colleagues in clinical research programs with the specific goal of improving the care of our patients directly. Finally, we should summarize the data from low risk of bias trials, and therewith without industry ties, into low risk of bias systematic reviews and clinical practice guidelines, the panel members of which should have no ties to industry. Trustworthy clinical practice guidelines will reduce the waste even further by helping individual doctors and nurses to offer best care at the lowest possible cost.

Summary

Our short history in critical care has built a care model that promotes intensive monitoring and a combination of many complex interventions based on mainly physiological rationale. With more and more of these concepts failing at the testing stage in pragmatic trials, simplification of care is rational and will allow us to focus on what is important for patients. In this process, it is unlikely that the industry will play a major role, and we should instead focus on improving care independent of commercial interests.

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Compliance with ethical standards

Conflicts of interest

AP is member of the steering committee and Danish national investigator of the Sepsis-Act vasopressin trial in septic shock sponsored by Ferring Pharmaceuticals; his department is reimbursed for his time. The department has also received research funds from Fresenius Kabi for the EAT-ICU nutrition trial and CSL Behring for the INSTINCT trial on immunoglobulins for NSTI. JHL reports no conflicts of interests. IVDH reports no conflicts of interest.

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