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Anders Perner
John Myburgh

Ten 'short-lived' beliefs in intensive care medicine

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A. Perner (✉)
Department of Intensive Care, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
e-mail: anders.perner@rh.regionh.dk
Tel.: 45 35458333

J. Myburgh
The George Institute for Global Health, Sydney, Australia
e-mail: jmyburgh@georgeinstitute.org.au
Tel.: 61291131111

J. Myburgh
St George Clinical School, University of New South Wales, Sydney, Australia

Intensive care medicine is complex. Clinical practice guidelines based on data from clinical trials, systematic reviews and expert opinion aim to provide clinicians with recommendations about the safety and efficacy of interventions [1]. However, several recommendations in intensive care medicine have been changed or challenged following the publication of high-quality randomised clinical trials (RCTs) and systematic reviews (Table 1). These changes may be described in the following 'short-lived beliefs', perhaps highlighting important lessons based on trajectories of evidence-based medicine.

1. *Albumin increases mortality in critically ill* In 1998, a Cochrane review concluded that the administration of albumin was associated with a 6 % increased mortality compared to other types of fluids in a heterogeneous patient population [2]. Given the potential public health implications of this study, a prospective, blinded, pragmatic RCT was conducted to compare the effects of resuscitation with albumin to saline on 28-day mortality in 6,997 intensive care patients (the SAFE study) [3]. There was no difference in the efficacy of resuscitation or any patient-centred outcomes between the two groups, providing compelling evidence about the equivalence between albumin and saline in these patients. These results have had a substantive impacted on subsequent systematic reviews comparing colloids vs. crystalloids [4].
2. *Early goal-directed therapy (EGDT) improves outcome in septic shock* The concept of resuscitation bundles by the Surviving Sepsis Campaign (SSC) guidelines was heavily based on the concept of EGDT produced by the results of a single-centre, unblinded, underpowered RCT indicating a 16 % absolute reduction in mortality [1]. Concerns about the internal and external validity of this study prompted the conduct of three high-quality RCTs, two of which have been published demonstrating no effect of EGDT on mortality in septic shock [5, 6]. These results mandate revision of the SSC guidelines and resuscitation bundles.
3. *Activated protein C (APC) improves outcome in patients with septic shock and high risk of death* The use of APC was recommended in the first iteration of the SSC guidelines following the publication of an RCT reporting reduced mortality in patients with sepsis with the use of APC [1]. A subsequent confirmatory RCT requested by the authorities reported no reduction in mortality in patients with septic shock, resulting in the withdrawal of APC from the market [7].
4. *Low dose steroids improve outcome in septic shock* The 2004 iteration of the SSC guidelines recommended the use of hydrocortisone for patients with vasopressor-dependent septic shock on the basis of an

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Table 1 Recommendations which were subsequently challenged

Intervention	Early evidence base	Data that changed or challenged the recommendations
Albumin for critically ill	Meta-analysis of small, higher risk of bias RCTs	Large, high-quality RCT
EGDT for septic shock	Small, single-centre RCT	Two high-quality RCTs
APC for sepsis	Single, industry-driven RCT	Larger industry-sponsored RCT overseen by an academic steering committee
Steroids for septic shock	Single RCT of very sick patients	Larger RCT with inclusion of a broader cohort of patients
Tight glucose control	Single-centre RCTs	Larger, multicentre RCT
Tetrastarch for critically ill	Small RCTs with short follow-up time, some of which were retracted because of fraud	Two high-quality RCTs and several updated meta-analyses
Decompressive craniectomy for severe TBI	Case series and expert opinion	International RCT
Mild hypothermia for OHCA	Small trials with higher risk of bias	Larger, high-quality RCT
High-intensity RRT for kidney failure	Small, single-centre RCT	Large, high-quality RCT

APC activated protein C, *EGDT* early goal-directed therapy, *OHCA* out of hospital cardiac arrest, *RCT* randomised clinical trial, *RRT* renal replacement therapy, *TBI* traumatic brain injury

adjusted, subgroup analysis of a single RCT that demonstrated a reduction in 28-day mortality [1]. A larger, confirmatory trial with broader inclusion criteria showed no effect on mortality of hydrocortisone, and the direction of the recommendation was changed in the updated SSC guidelines [8]. A definitive large-scale, high-quality RCT is currently being conducted to address this fundamental question (ADRENAL: NCT01448109).

5. *Intensive blood glucose control (IBGC) improves outcome in ICU patients* Two single-centre, unblinded RCTs in ICU patients reported favourable outcomes associated with IBGC compared to conventional therapy [9]. These studies had substantive impact on the original SSC guidelines that recommended IBGC [1]. A subsequent high-quality, international RCT of 6,100 ICU patients reported a significant increase in 90-day mortality with IBGC, thereby refuting these recommendations and resulting in substantive amendments to the guidelines [8].
6. *Tetrastarches are safe in critically ill* After 40 years of hydroxyethyl starch (HES) use, the tetrastarches were introduced and rapidly adopted into clinical practice with little independent, high-quality evidence in spite of long-standing concerns about HES-induced kidney impairment. Two high-quality, investigator-initiated, blinded RCTs confirmed that the use of tetrastarches increased the use of renal replacement therapy in ICU patients requiring fluid resuscitation [10, 11] and increased mortality in patients with severe sepsis [11]. These observations have been consistently reported in high-quality systematic reviews questioning the role of HES in any patient population [4]. These studies have resulted in substantive changes to medical regulatory authorisations and guidelines that either prohibit or restrict the use of HES [8].
7. *Decompressive craniectomy improves outcome in severe traumatic brain injury (TBI)* Decompressive craniectomy for severe TBI has been recommended as an optional treatment in guidelines for refractory intracranial hypertension based on case series and expert opinion [12]. An international RCT reported that early decompressive craniectomy in severe diffuse TBI resulted in a significant increase in unfavourable neurological functional outcomes compared to standard practice, despite significant reductions in intracranial pressure and ICU length of stay [13]. This pivotal trial has resulted in amendments to clinical practice guidelines.
8. *Mild induced hypothermia improves outcome after out-of-hospital cardiac arrest* Hypothermia was recommended in the European Resuscitation Council (ERC) guidelines from 2010 based on data from a smaller RCT and a pseudo-randomised, single-centre trial [14]. A subsequent, high-quality, confirmatory RCT reported that mild hypothermia was not associated with improved patient-centred outcomes compared to controlled normothermia [15]. The ERC guidelines are scheduled to be updated this year.
9. *A complex, time- and biomarker-dependent blood transfusion strategy is beneficial in septic shock* The SSC guidelines recommend a complex protocol for blood transfusion based on the results of the initial EGDT trial and a multicentre RCT (TRICC) in ICU patients [8, 16]. A large, high-quality, confirmatory RCT showed no differences by time- and biomarker-independent blood transfusion at haemoglobin values of 7 vs. 9 g/dl on patient-centred outcomes in patients with septic shock [17].
10. *High-intensity renal replacement therapy (RRT) improves survival in ICU patients with kidney failure* In 2000, the results of a single-centre, unblinded, underpowered RCT indicated a 16 % absolute

reduction in mortality by higher- vs. lower-intensity RRT [18]. Concerns about the internal and external validity of this study prompted the conduct of a large, high-quality, multicentre RCT (RENAL), which showed no effect on mortality of higher- vs. lower-intensity RRT in ICU patients with kidney failure [19].

These examples support the perspective that data from RCTs with higher risk of bias may markedly overestimate the intervention effect [20]. Similarly non-randomised studies with case-mix adjustment and selection bias are likely to be amplified in the critical care setting, where multiple, time-dependent exposures, competing risks and co-interventions hamper the interpretation further.

These short-lived beliefs should prompt caution and circumspection among clinicians, guideline committee members and policymakers when results of non-randomised studies or RCTs with low internal or external validity indicate benefit or no harm from an intervention. If we as a community demand high-quality evidence before using or recommending an intervention, a biomarker or a monitoring device, industry, academia and funding agencies may more likely produce high-quality trials we can trust.

> "Good tests kill flawed theories; we remain alive to guess again" (Karl Popper).

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