EDITORIAL

Getting down to the real question: effects of transfusion triggers on long-term survival and quality of life following septic shock

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From an intensivist's perspective, the main focus in the management of critically ill patients is survival to intensive care unit discharge. However, from a patient's perspective, the most relevant outcome is to return home in an acceptable functional state. For many years, this discrepancy has largely been ignored. Only through the last decade have we begun to understand the detrimental effects of critical illness on long-term survival and health-related quality of life (HQoL) [1, 2]. Accordingly, only a small number of multicenter randomized controlled trials have evaluated the effects of therapeutic interventions on long-term outcomes of critical illness (Table 1).

Long-term outcome is particularly poor for patients surviving sepsis or septic shock, with 5-year mortality rates reported as high as 60 % [3, 4]. Short-term organ dysfunction and the need for artificial life support have been identified as crucial risk factors for unfavorable long-term outcomes in septic shock survivors [5]. Re-admissions due to infectious, cardiovascular or pulmonary complications after an episode of sepsis are frequent and occur early following hospital discharge [6]. One possible cause of adverse long-term outcomes of septic shock is prolonged immunomodulation. Sub-clinical inflammation is a well-known risk factor for cardiovascular and all-cause mortality in non-critically ill patients. It has been hypothesized that critical illness induces a state of prolonged sub-clinical inflammation, thus contributing to impaired long-term survival and functional state [7].

Accordingly, abdominal sepsis has been found to induce and aggravate atherosclerosis in a murine model [8]. This observation aligns nicely with reports that sepsis survivors continued to exhibit elevated levels of inflammatory markers at hospital discharge [9] and have an increased subsequent risk of cardiovascular events. In addition, proteomics and metabolomics are profoundly altered by sepsis and may contribute to chronic organ dysfunction and impaired outcome.

The Transfusion-Requirements In Septic Shock (TRISS) trial [10] was a well-performed multicenter randomized controlled trial comparing a liberal (>9 g/dL) versus a restrictive (>7 g/dL) transfusion trigger in 998 septic shock patients. In this issue of the journal, Ryegard and colleagues present the results of a sub-study of the TRISS trial focusing on survival status and HRQoL at 1 year after randomization [11]. Once again, the authors found no between-group differences in any of these variables. In doing so, they could reject a ≥ 3 % increased risk of death associated with a restrictive transfusion threshold. The study has several strengths including its focus on long-term outcome and the high methodological quality of the underlying trial. On the other hand, the fact that the power analysis for the original trial was based on 90-day and not 1-year mortality [12] must be seen as a limitation of the present sub-study. As suggested by fairly wide confidence intervals, the patient population may have been too small to detect a significant difference in 1-year survival between study groups. As hemoglobin levels were not documented during the follow-up period, it is furthermore unclear whether different transfusion thresholds also translated into variable recovery patterns from anemia [13]. Chronic anemia could, for example, increase the risk of certain causes of death. Indeed, the authors argue in their discussion that "[...] restrictive

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Table 1 Examples of major randomized controlled multicenter trials that reported long-term (>90 days) survival and/or quality of life

First author (reference)	Condition studied	Interventions	Long-term survival measured	HQoL outcome	Findings
Lilja [16], Cronberg [17]	Cardiac arrest	Therapeutic temperature management at 33 versus 36 °C	180 days	Tests for memory, executive functions, attention/mental speed and cognitive function, SF-36 score	No differences between groups
Perner [18]	Severe sepsis	6 % HES 130/0.42 versus Ringer's acetate	1 year		No differences between groups
Wittbrodt [19]	Severe sepsis	6 % HES 130/0.42 versus Ringer's acetate	14 months	SF-36 score, assessment of pruritus	Worse HQoL in patients resuscitated with 6 % HES 130/0.42, no difference in pruritus between groups
Needham [20, 21]	ARDS	Trophic versus full enteral feeding	1 year	6-min-walk distance, cognitive function, SF-36 score, employment status	No differences between groups
Clermont [22]	ARDS	PAC versus central venous catheter	1 year	Health utilities index mark 2 (HQoL), costs	No differences in one-year survival or HQoL; PAC 75 % probability more expensive and less effective
Jackson [23]	Medical ICU patients	Wake up and breath protocol versus standard care plus spontaneous breathing trial	1 year	Cognitive, psychological and functional/quality-of-life outcomes	No differences between groups
Laterre [24]	Severe sepsis	Drotrecogin alfa versus placebo	1 year		No differences between groups
Steinberg [25]	ARDS	Methyl-prednisolone versus placebo	180 days		Methylprednisolone associated with increased 180-day mortality
Angus [26]	ARDS	Inhaled nitric oxide versus placebo	1 year	Quality of well-being score, functional state, costs	No difference between groups

HQoL health-related quality of life, ARDS acute respiratory distress syndrome, PAC pulmonary artery catheter, ICU intensive care unit

transfusion decreased rates of severe infectious complications in hospitalized patients and increased risk of myocardial infarction in patients with cardiovascular disease" [11]. Unfortunately, the causes of death during the 1-year follow-up period were not evaluated. Finally, while almost full datasets were available to determine 1-year survival status in the whole population, around 25–30 % of data were missing for the nested Danish cohort in which HqoL was determined.

The results of the TRISS trial and its latest sub-study clearly suggest that adoption of a restrictive transfusion policy in patients with septic shock is safe, does not result in relevantly worse short- and long-term outcomes, and spares valuable and short-supplied blood products. Although these results may not be extrapolated to non-septic critically ill patients, the landmark Transfusion Requirements in Critical Care (TRICC) trial showed equivalence of liberal versus restrictive transfusion triggers in a general intensive care population [14].

What are the implications of these results for future research? Both the TRICC and TRISS trials either excluded or enrolled too few patients particularly vulnerable to anemia, such as those after cardiac surgery, or with acute myocardial ischemia or brain injury [15]. Therefore, future studies still need to elucidate whether application of a restrictive transfusion trigger in critically ill patients with any of these conditions is equally safe. While Ryegard and colleagues could impressively display that the use of a restrictive transfusion threshold does not alter long-term survival and functional outcome of septic shock as compared to a liberal transfusion threshold, this must still be shown for a non-septic critically ill patient population. Given that 'one size fits all' approaches have repeatedly failed to improve the outcome of critically ill patients, future studies should also evaluate whether individual instead of fixed transfusion triggers could improve survival. For general critical care research, we desperately need more observational cohort studies which carefully assess quantitative and qualitative long-term outcomes that allow clinicians and researchers to identify subgroups with increased risks. We further suggest the systematic introduction of long-term survival and HqoL as secondary endpoints in future multicenter trials.

What are optimal long-term outcomes to assess? Is it 1-year survival or HqoL? Evaluation of survival status alone carries the delicate disadvantage that it is a binary variable but does not give any information on HqoL. On the other hand, when using HqoL scores as outcome variables, it is unclear which differences in score results are truly relevant. Other endpoints such as the rate of patients returning home or to their previous place of residency could meaningfully complement long-term

outcomes such as those assessed by the TRISS study group. Finally, and most importantly, the ultimate goal of studies in critical care should be to harmonize the intensivists' questions and hypotheses with patient-centered outcomes!

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Compliance with ethical standards

Conflicts of interest

None of the authors has a conflict of interest in regards of drugs, techniques or methods discussed in this manuscript. Not related to the manuscript, Dr. Russell reports patents owned by the University of British Columbia (UBC) that are related to PCSK9 inhibitor(s) and sepsis and related to the use of vasopressin in septic shock. Dr. Russell is an inventor on these patents. Dr. Russell is a founder, Director and shareholder in Cyon Therapeutics Inc. (developing a sepsis therapy). Dr. Russell has share options in Leading Biosciences Inc. Dr. Russell is a shareholder in Molecular You Corp. Dr. Russell reports receiving consulting fees from Cubist Pharmaceuticals (now owned by Merck; was formerly Trius Pharmaceuticals; developing antibiotics), Leading Biosciences (developing a sepsis therapeutic), Ferring Pharmaceuticals (manufactures vasopressin and is developing selepressin), Grifols (sells albumin), La Jolla Pharmaceuticals (developing angiotensin II; Dr. Russell chairs the DSMB of a trial of angiotensin II), CytoVale Inc. (developing a sepsis diagnostic), and Asahi Kasei Pharmaceuticals of America (AKPA) (developing recombinant thrombomodulin). Dr. Russell reports having received an investigator-initiated grant from Grifols that is provided to and administered by UBC.

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