

Guidelines seek unbiased recommendations

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Dear Editor,

We read with interest the editorial by Vincent which highlights the challenges in defining the optimal transfusion strategies in critically ill patient [1]. Although critical appraisal of guidelines is essential to ensure trustworthiness, we disagree with several points raised in the editorial.

First, we disagree with the claim that guidelines based upon RCTs are dangerous; for most clinical questions (including transfusion), high-quality RCTs remain the most trustworthy source of evidence. Although observational studies can provide invaluable insights and in some instances provide sufficiently high-quality evidence for guideline recommendations, they are invariably subject to confounding by indication. Indeed, there are many examples of clinical treatments supported by observational data that were subsequently refuted by high-quality RCTs [2–6]. The true danger to patients and society is clinical practice informed by low-quality evidence resulting in patient harm and wasted resources.

Figure 1, and the associated text, is interesting [1]. If clinicians could clearly classify patients to those who need transfusion and those who don't, such patients should not be entered in clinical trials. Unfortunately, in most instances, they cannot. No doubt groups are heterogeneous with respect to benefit, but until clinical criteria or biological enrichment strategies for identifying the populations for whom different thresholds are appropriate are well established, RCTs remain the ideal study methodology.

Second, we agree that RCTs that exclude numerous patients can lack generalizability. For this reason, the panel chose to make separate recommendations, where possible, for specific populations of critically ill patients. While the original TRICC trial [7] did exclude a high proportion of screened patients (87%), the more recent trials included in the guideline had higher enrollment rates and well-documented exclusion criteria [8–10]. An overview of inclusion/exclusion decisions for the RCTs included in the guidelines is presented in Table 1. While high rates of exclusion also raise the possibility of selection bias, virtually all trials were at low risk of bias with respect to randomization, allocation concealment, and use of intention-to-treat alongside per-protocol analyses, all of which minimize the risk of systematic differences between the baseline characteristics and prognoses between the allocation arms [11].

We do not have evidence in non-bleeding critically ill patients that individualized transfusion targets are better than crude hemoglobin (Hb). This specific question was assessed by the guideline panel, which identified ScvO₂, arteriovenous oxygen difference, cerebral tissue oxygenation, plasma lactate, and veno-arterial CO₂ gradient as potential alternative triggers. Only one (cerebral oxygenation during cardiac surgery) has been evaluated in an RCT [12]. This trial of 204 patients found similar transfusion rates, biomarkers of brain, kidney and myocardial injury, and costs in both arms. The panel concluded that insufficient evidence exists to justify the use of any of these “alternative” transfusion triggers. We do not know if they would result in improved patient outcomes or reduce the use of unnecessary blood products in non-bleeding critically ill patients [13]. The panel agrees that before widespread clinical adoption, alternative transfusion triggers should be rigorously evaluated in RCTs. We welcome such trials and hope that such techniques may supplement Hb-based thresholds in the future.

Table 1 Overview of patient exclusion reasons and percentage of RBC transfusion trials included in the ESICM transfusion guideline part I

Year	Lead author	Study centers (n)	Eligible patients screened (n)	Patients include (n, %)	Patients excluded (n, %)	Exclusion reasons (n)
2019	Gobatto	2	106	47 (44.3%)	59 (55.7%)	Refused consent (24), enrolled in other trial (12), unable to provide consent (9), moribund (6), withdrawn by physician (5), unable to follow-up (2), not accepting blood products (1)
2018	Laine	1	84	80 (95%)	4 (5%)	Declined participation (4)
2017	Bergamin	1	1223	300 (24.5%)	923 (75.5%)	Hematologic malignancy (407), enrolled in other trial (145), life expectancy under 24 h (132), Karnofsky score under 50 (83), coagulopathy (54), DNR (32), life-threatening bleeding (32), end-stage renal disease (22), prior transfusion reaction (16)
2017	Mazer	73	14,702	5243 (35.7%)	9459 (64.3%)	Patient refusal (2466), unable to provide consent (889), enrolled in other study (1108), unable to receive blood products (106), not approached for consent (1619), change in surgery schedule (375), other (2896)
2017	Koch	2	7104	722 (10.2%)	6382 (89.8%)	Off-pump procedure or surgeon decision (6036), not consented (300), administrative reasons (13), surgery canceled (11), declined participation (9), enrolled in other study (7), staff refusal (6)
2015	Mazza	3	63	63 (100%)	Not applicable	Not applicable
2015	Murphy	17	4582	2007 (43.8%)	2575 (56.2%)	Not approached for consent (1863), did not consent (2719), surgery not performed (26), clinician withdrawal pre-surgery (17), withdraw post-surgery pre-randomization (16), found to be ineligible post-op (9), trial ended prior to OR (9), patient withdrawal pre-surgery (7), missed on admission due to staff error (5), patient died in OR (4), patient withdrawal post-surgery pre-randomization (1)
2015	Almedia	1	234	198 (84.6%)	36 (15.4%)	DNR (21), enrolled in other trial (8), unable to consent (2), active bleed (1), coagulopathy (1), chronic anemia (1)
2014	Holst	32	1224	1005 (82%)	219 (18%)	Received transfusion in ICU (137), could not obtain consent (34), acute coronary syndrome (20), withdrew active therapy (17), life-threatening bleeding (16), previous transfusion reaction (4), declined transfusion (3), acute burns (3)

Table 1 (continued)

Year	Lead author	Study centers (n)	Eligible patients screened (n)	Patients include (n, %)	Patients excluded (n, %)	Exclusion reasons (n)
2014	Robertson	2	598	200 (33.4%)	398 (66.6%)	Fixed, dilated pupils (91), unable to locate next of kin (86), severe preexisting disease (67), penetrating injury (53), life-threatening systemic injury (53), refused consent (37), other (95)
2013	Walsh	6	287	100 (34.8%)	187 (65%)	Intracranial hemorrhage (25), expected survival less than 48 h (18), clinician refusal (18), enrolled in other trial (17), no next of kin (17), follow-up not feasible (12), brain injury (11), communication difficulties (3), no research staff available (2) erythropoietin therapy (2), bleeding (1), transfusion objection (1)
2013	Carson	8	452	110 (24.3%)	342 (75.7%)	Patient refused (198), physician refused (93), patient discharged before consent (31)
2012	Shehata	1	1854	219 (11.8%)	1635 (88.2%)	Coordinator unavailable (624), other (393), enrolled in another study (260), non-participating surgeon (188), unable to give consent (141), autologous premonition (29)
2011	Cooper	2	Not reported	34	Not reported	Not reported
2010	Hajjar	1	1765	512 (29%)	1084 (71%)	Chronic anemia (205), did not provide consent (169), enrolled in other study (124), emergency procedure (123), surgery without bypass (105), coagulopathy (93), aortic procedure (90), congenital heart defect (85), endocarditis (82), thrombocytopenia (78), ESRD (73), unable to receive blood (26)
2010	Naidech	1	230 screened, eligible not reported	44 (19%)	86 (81%)	No consent (31), inclusion exclusion reasons not given (155)
1999	Hébert	25	3206	838 (26%)	2368 (74%)	Physician refusal (598), patient/family refusal (603), previous transfusion (297), time limitation (256), no next of kin (174), language barrier (36), other reasons (404)
1999	Bracey	1	428	Not reported	Not reported	Not reported
1995	Hébert	5	Not reported	69	Not reported	Not reported

Third, the potential harms of restrictive transfusion in the studies highlighted in the editorial [8] are based upon a very selective review of the evidence. Unfortunately, there are even factually incorrect references in the editorial, including in a reference to the TRICC trial: “A reanalysis of the initial study by Hébert et al. revealed a harmful

effect of restrictive transfusion strategy in patients with ischemic heart disease and in those with high APACHE scores [6].” This is incorrect as the original TRICC trial studied APACHE II scores. The trial suggested benefit from restrictive transfusion in lower APACHE II scores. There was no difference in harm with higher APACHE II

scores. The reanalysis did not include APACHE II at all. The trials referenced in the editorial [7, 8] were included in a recent meta-analysis, which focused on patients with cardiovascular disease, and found no compelling evidence of harm [14]. Most trials included in the guideline showed no harm for the populations in which the editorial proposed possible harm. The misleading conclusions drawn from a selective reading of the evidence are one of the reasons why rigorous and transparent guidelines are necessary. The guideline utilized systematic reviews of the literature, which included all potentially relevant studies to develop non-biased recommendations.

Fourth, we emphasize that guidelines are not “rules” and that clinical judgement is always required when applying any evidence at the bedside. As clinicians, we must consider numerous factors when deciding to transfuse (e.g., rate of Hb decline, co-morbidities, patient willingness to accept transfusion). However, clinical judgement is also imperfect. In this regard, RCTs and guidelines assist clinicians and institutions to set general transfusion thresholds where benefits appear marginal for most patients—without them we would likely still be applying transfusion thresholds of 10 g/dL, with unnecessary use of blood products. Another approach is to consider liberal transfusion to be a novel intervention. We would argue that there is insufficient evidence to justify changing from a restrictive to a liberal transfusion practice based upon the existing data (even the highly selected evidence chosen for the editorial). Recognizing the need for clinical judgement, alongside the limitations of the existing evidence, most of the panel’s guideline statements are conditional/weak recommendations rather than strong recommendations.

Lastly, while we acknowledge the general enthusiasm toward big data and artificial intelligence, a recent systematic review found no performance benefit of machine learning over “traditional” logistic regression and clinical prediction models [15]. In addition, Collins and Moons recently have highlighted several issues regarding artificial intelligence, including over prediction, poor validation, lack of transparency, and poor reproducibility [16]. Clearly, there is still a need for methodologically rigorous RCTs, which remain the best design to evaluate the effectiveness and harm of clinical interventions and should form the basis of trustworthy clinical practice guidelines.

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Conflicts of interest

The authors declare that they have no competing interests.

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