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Editorial

Restrictive blood transfusion – is less really more?

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In this month's issue of *Anaesthesia*, Nordestgaard et al. provide data on the reduction in the rates of peri-operative red blood cell transfusion in the USA [1]. Following adjustment for several confounders, they observed a 45% reduction in peri-operative red blood cell transfusions over a 6-year period, which equated to 356,679 fewer red blood cell units. This reduction was not associated with an increase in peri-operative myocardial infarction, stroke or all-cause 30-day mortality and resulted in potential cost savings of just over £200 million.

These findings could have been due to many layers of practice improvements including better surgical techniques; more laparoscopic surgery; better pre-operative management and optimisation of patients at risk of bleeding; and immortal time bias. Immortal time, sometimes also referred to as survivorship bias, is a period of time in the follow-up period of a study during which an outcome of interest (e.g. death, stroke) cannot occur [2]. Bias is introduced when this time period is either excluded from the analysis or misclassified with regards to the treatment status [2]. The biggest change in the study was observed in patients undergoing orthopaedic surgery (64% decrease) and this might be related to factors such as tourniquet use, more arthroscopic surgery, routine administration of tranexamic acid and increasing cell salvage use [3].

Despite adjusting for some of these factors in the regression models, not all were accounted for and residual confounding may still persist due to other unidentified factors. An important omission was the data on cell salvage use that were not available to the authors. This was a significant development precisely during their study period. The Association of Anaesthetists guidelines recommend using cell salvage where blood loss greater than 500 ml is anticipated [3]. Cell salvage can reduce the rate of exposure of red blood cell transfusion by a relative 38% [3]. Data on the use of tranexamic acid and whether hospitals had established patient blood management programmes are also not shown. Tranexamic acid safely reduces blood loss and red blood cell transfusion requirements across multiple surgical specialties and it is now included in the World Health Organization list of 'essential medicines' [4]. However, the optimal dose, route and timing of administration of tranexamic acid is less clear. Network meta-analyses are currently underway to identify an optimal peri-operative dosing regimen to standardise clinical care [4]. Both tranexamic acid and cell salvage are now key components of a multimodal patient blood management strategy. Recent evidence suggests that comprehensive peri-operative patient

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blood management programmes can reduce red blood cell transfusion rates by up to 45%, reduce hospital length of stay and lower total number of postoperative complications [5].

Nordestgaard et al. also speculate that adherence to restrictive transfusion practices, which have become increasingly popular since 2010, may have contributed to a reduction in red blood cell transfusion rates and they point to a lower pre-transfusion haematocrit at the end of the study period in Fig. 4c of their paper. However, the pre-transfusion haematocrit was approximately 33% which equates to a haemoglobin concentration of 110 g.l⁻¹. This could be classed as a liberal transfusion threshold.

Although these findings may provide some temporary reassurance to blood transfusion services in terms of reducing demand, modelling studies have suggested that blood availability will need to increase again to meet the demands of an ageing population [6]. There is already a growing demand for universal blood groups (e.g. O negative) and for minor blood groups that may be needed to support patients requiring multiple transfusions (e.g. sickle cell disease) [6]. In addition, blood services continue to encounter problems in attracting and retaining young donors [7]. These issues were highlighted in a recent James Lind Alliance Blood Donation and Transfusion priority-setting partnership exercise where the top three research priorities were [7]:

- 1 What would encourage more people (especially Black and ethnic minority groups or people with a rare blood type) to donate blood?
- 2 How can health professionals be discouraged from using blood inappropriately?
- 3 How can the wastage of donor blood be minimised?

Peri-operative cardiovascular events and transfusion

Nordestgaard et al. report no increase in adverse clinical outcomes associated with restrictive transfusion strategies, such as myocardial ischaemia, stroke and all-cause 30-day mortality. The rates observed are comparable with other large administrative database studies [8]. However, it is important to note that the event rates in all these studies are likely to be an underestimate. Such databases are subject to administrative coding errors, reporting bias and immortal time bias. The authors do not provide data on the aetiology of myocardial infarction or on the use of cardiovascular medical therapies such as beta-blockers, statins and antiplatelets in the peri-operative period and therefore the effect, if any, of these interventions cannot be evaluated.

These interventions are likely to contribute to immortal time bias. Various approaches have been described to eliminate immortal time bias including using time-dependent Cox regression analyses, only studying 'survivors' of the immortal period by moving the start of the follow-up to the end of the immortal period or a time matched, nested case-control analysis of the study cohort [2].

It is now well recognised that the dominant pathology in peri-operative myocardial infarction is myocardial oxygen supply and demand mismatch, and not plaque rupture and thrombosis. As a result, the majority of ischaemic events in the peri-operative period are often silent and missed clinically. A recent prospective, observational study in critically ill patients found that more than 95% of myocardial infarctions were undetected by clinical teams [9].

Restrictive transfusion strategies may not always be indicated or appropriate. Evidence from systematic reviews suggests that liberal transfusion strategies may reduce myocardial infarction rates in patients with acute and chronic cardiovascular disease, and even in those without known cardiovascular disease [10]. Two recent pilot trials, conducted in patients with traumatic brain injury [11] and in those undergoing major vascular surgery [12], observed harm in patients randomly assigned to lower red blood cell transfusion thresholds and benefits at higher thresholds. Participants randomly assigned to the liberal threshold groups experienced lower mortality, less post-traumatic vasospasm, improved neurological status [11] and fewer major vascular complications [12]. Larger trials are warranted to confirm or refute these early results. The results of the ongoing Myocardial Ischemia and Transfusion randomised controlled trial (NCT02981407) are also eagerly awaited. Although the focus of research so far has been on cardiovascular events and mortality, the effect of a restrictive or liberal transfusion strategy on renal function is not yet known. Peri-operative acute kidney injury is common, with estimates ranging from 5% to 40%, and studies are beginning to investigate whether this is influenced by transfusion strategies [13].

These conflicting results highlight some of the limitations in major trials and large database studies undertaken to date such as: underpowered sub-group analyses and fixed interventions masking divergent effect in at-risk sub-groups; effect of immortal time bias and the absence of important confounders in routine datasets; and the lack of measurement of long-term patient-centred outcomes, although data are beginning to emerge on these [14].

Although restrictive transfusion thresholds lead to fewer red blood cell transfusions, is haemoglobin or

haematocrit the best indicator for a transfusion? A recent systematic review found that transfusion did not generally improve tissue oxygenation or microcirculation in critically ill patients, unless there was prior evidence of reduced tissue oxygenation or abnormal microcirculatory indices using assessment tools such as near infrared spectroscopy, spectral imaging and tissue microdialysis [15]. These findings remained constant regardless of which assessment method was used. Furthermore, recent evidence suggests that blood donor characteristics (e.g. age, sex), collection and processing methods and recipient characteristics, such as age and body mass index, significantly influence changes in haemoglobin concentrations after transfusion [16]. Further research into these areas may allow for a bespoke approach towards transfusion in the future, but this may also have an impact on blood donation strategies.

Another unintended consequence of widespread adoption of restrictive transfusion practices is that more patients are likely to be discharged from hospital with anaemia. A recent large retrospective study of over 445,000 patients showed that the prevalence of moderate anaemia (haemoglobin between 70 and 100 g.l⁻¹) increased from 20% to 25% over a 4-year period [17]. In addition, the proportion of patients whose anaemia had resolved within 6 months of hospital discharge decreased from 42% to 34%. Although this was not associated with increased rehospitalisation or mortality, the impact of anaemia on physical function and health-related quality of life was not investigated. The relationship between persisting, and often

untreated, anaemia and fatigue and poor quality of life has been described in survivors of critical illness and trials are currently underway to address this [18].

Guidelines, guidelines and even more guidelines

In their discussion, Nordestgaard et al. speculate that adherence to restrictive transfusion guidelines may have contributed to the observed reduction in red blood cell transfusion rates. However, some limitations need to be considered when addressing the role of guidelines. Guidelines are one of the approaches applied in clinical practice to bridge the gap between actual and recommended evidence-based practice. Other strategies include audit, feedback, quality improvement projects and, increasingly for transfusion practice, computerised decision support systems. Traditionally, guidelines may have been consensus statements driven by the opinions of experts, but increasingly guidelines are developed with higher methodological rigour. The emergence of the grading of recommendations, assessment, development and evaluation (GRADE) approach has also strengthened the quality but many still continue to suffer from methodological weaknesses [19].

There has been an exponential increase in the number of clinical guidelines over the past three decades. The current total in the International Guidelines Library (<https://g-i-n.net>) stands at 6859, and this is likely to be an underestimate of the actual number. Relevant to transfusion

Table 1 Examples of inconsistent recommendations in transfusion guidelines relevant to peri-operative medicine.

Guideline group	Recommendation	Strength of recommendation	Quality of evidence
Association of Anaesthetists 2016 [23]	Apply restrictive transfusion threshold (Hb 70–80 g.l ⁻¹) depending on patient characteristics and haemodynamics. Uncertainty remains for patients with ischaemic heart disease, including acute coronary syndrome and after cardiac surgery, and higher threshold (80 g.l ⁻¹) may be more appropriate in such circumstances	Not reported Not reported	Not reported Not reported
American Association of Blood Banks [24]	For patients undergoing orthopaedic surgery or cardiac surgery and those with pre-existing cardiovascular disease, the AABB recommends a restrictive RBC transfusion threshold (haemoglobin level of 80 g.l ⁻¹)	Strong	Moderate
Frankfurt Patient Blood Management Consensus 2019 [25]	The panel recommended a restrictive transfusion threshold (haemoglobin concentration < 80 g.l ⁻¹) in patients with hip fracture and cardiovascular disease or other risk factors Expert panel suggests further research in patients undergoing noncardiac or nonorthopaedic surgery The panel recommended a restrictive RBC transfusion threshold (haemoglobin concentration < 75 g.l ⁻¹) in patients undergoing cardiac surgery	Conditional Strong	Moderate Moderate

Hb, haemoglobin; RBC, red blood cell.

medicine, a recent systematic review identified 30 guidelines related to the transfusion of red blood cells that have been developed since 2006 [20]. At least ten of these are relevant to anaesthesia, peri-operative medicine or critical care, and the timeline of the publication of these guidelines is demonstrated in the Supporting Information (Fig. S1) of the paper by Nordestgaard et al. [1].

Despite guideline development often being carried out by reputable professional bodies, concerns regarding their usefulness, and even trustworthiness, remain [19]. The development of guidelines on the same topic by several different organisations can leave the reader confused particularly if there are different recommendations based on the same primary evidence, as highlighted in Table 1. It leads to unnecessary duplication of effort and is a waste of time and money, especially when the cost of developing a guideline is thought to be more than \$100,000, which approximately equates to £77,000 or €90,000 [20]. Furthermore, depending on how quickly the relevant field is evolving, guidelines can quickly become outdated.

The final recommendations of any guideline are, not infrequently, a reflection of the composition of individuals on the working party, including (sometimes heated) discussion about recommendations in the face of limited, if any, high-quality evidence. Panels may be unbalanced and include a disproportionate number of content experts, each with their own prejudices, bias and conflicts of interest. This is especially pertinent for guidelines involving pharmaceuticals. Patient representatives and healthcare economists are often not included and as a result patient preferences and cost-effectiveness analysis may not be addressed. Consensus may be achieved through voting (such as a Delphi) process but the precise wording of the question can influence interpretation of the evidence and subsequent decision making. These processes are often not clear enough to the clinician reading the final report. It is therefore not surprising that strong recommendations are made in the presence of weak evidence and there is disagreement with similar guidelines written by other groups (Table 1). The widespread adoption of recommendations based on weak evidence can accidentally lead to patient harm, reinforce traditional practices and reduce the drive for research. Many of the issues discussed above have been highlighted by the example of the Surviving Sepsis Campaign guidelines, which continue to divide the intensive care community. Some have called for them to be retired completely [21].

Collaborative models, where a single, diverse and multidisciplinary panel takes ownership to develop statements, have the potential to use standardised guideline development processes and promote

transparency. In order to quickly incorporate new evidence into pre-existing guidelines, *Intensive Care Medicine* and the *British Medical Journal* Rapid Recommendation Group have recently introduced the concept of rapid practice guidelines [22]. Here, researchers perform a timely systematic review and in parallel, a panel including methodologists, researchers, clinicians and patients will choose the most important outcomes. The systematic review and evidence will be assessed using the GRADE approach, and recommendations for practice will be generated. This would then be submitted to the relevant journal for rapid peer review and publication.

In conclusion, Nordestgaard et al. should be congratulated on analysing a large, complex national database and providing important data for blood transfusion services globally. The limitations of such retrospective studies are well understood but the authors have raised important questions on clinically diagnosed peri-operative cardiovascular events, while also providing us with an opportunity to discuss the strengths and limitations of clinical guidelines.

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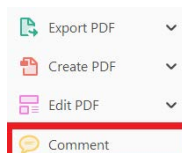
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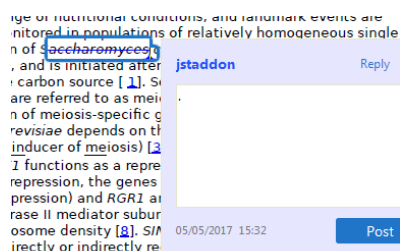
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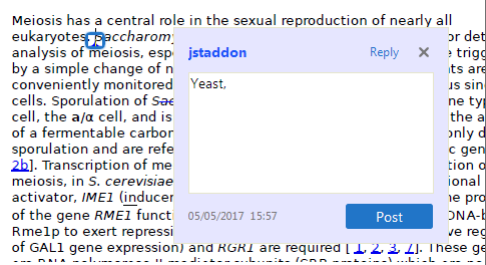
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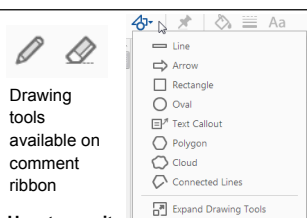
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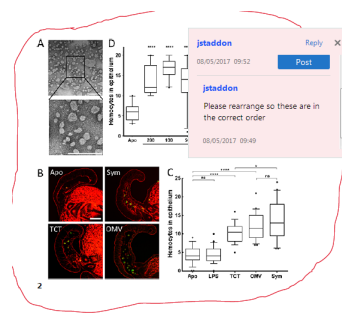


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