A new perspective on best transfusion practices

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Introduction

More than a decade has passed since the publication of the results of the Transfusion Requirements in Critical Care (TRICC) trial, supporting the restriction of red blood cell (RBC) transfusions in the gravest patients[1]. Since then, some reports are indicative of improvements in transfusion practices (mostly as regards reduced haemoglobin [Hb] thresholds at which patients are transfused[2-4]). Nonetheless, the overall use of allogeneic RBC transfusions in clinical practice remains relatively high and still varies widely among many centres and practitioners[5-7]. The latest data from the U.S. Department of Health and Human Services indicate that over 14.6 million units of RBC or whole blood were transfused in the USA in 2006, which is a 3.3% increase from the previous report[8]. Similarly, the Agency for Healthcare Research and Quality (AHRQ) reported that in 2007, blood transfusions were given in one in every ten hospital admissions in which a procedure was performed; this is a 140% increase from 1997, making transfusion the fastest growing common procedure in hospitals in the USA[9].

Allogeneic blood transfusions have historically been linked with a myriad of risks and complications. Some risks (e.g. transfusion reactions and transmission of pathogens) have been largely mitigated through advancements in blood banking (e.g. screening for antibodies and markers of infective agents), although these risks are not likely to ever be completely eliminated[10,11]. Some other risks and complications (e.g. immunomodulation and transfusion-related acute lung injury [TRALI]) appear to have more subtle and elusive aetiologies and are more difficult to tackle[11]. The presence of leukocytes, residual plasma, and the effects of blood storage have been investigated as possible causes of harmful consequences of banked allogeneic blood[12-15]. Notably, a number of clinical trials on the effects of storage age of blood on patients' outcomes are underway: the results of these trials could substantially change the transfusion practice landscape, if they demonstrate that the currently accepted shelf-life of banked blood is too long and should be revised[16-19]. The other potential threat to safe, readily available transfusions is the aging population which could result in more recipients and fewer donors, putting more pressure on the less than 10% margin that currently exists between the number of collected and transfused blood units[8]. Finally, direct and indirect costs associated with transfusion have been rising steadily[20], providing another motivation for improving transfusion practices.

Blood as a therapeutic

Despite widespread use, transfusion decisions are often taken in the absence of adequate training and based on limited and frequently low quality evidence alongside an often exaggerated anxiety towards any level of anaemia. Before being approved for clinical use, new therapeutics are expected to undergo rigorous randomised controlled trials to establish their safety and efficacy in the target population for the intended indication. In contrast, allogeneic blood transfusion has largely enjoyed a privileged status as a therapeutic, "grandfathered" to our era from the early twentieth century. There has been no pivotal randomised controlled trial to demonstrate its safety and efficacy, and none is expected to be done anytime soon. Hence, the benefits of transfused blood are largely assumed and possibly skewed by the early success stories of blood in resuscitating bleeding obstetric and trauma patients who previously bled to death before transfusion was practical.

As discussed above, the safety of allogeneic blood has been a major cause of concern, and

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exposing patients to risks that are not outweighed by tangible benefits should be avoided. The potential efficacy of transfused RBC can be attributed to three main aspects: a circulatory (volume) effect, a rheological effect (blood flow/viscosity), and oxygen transportation. Although the effect of transfused blood on circulatory volume may be much more immediate than its effect on oxygen transportation, RBC transfusions are not usually recommended today just as a volume-expander (possibly except for some cases of trauma and massive blood loss). In some circumstances, this effect is likely to be considered more a foe than a friend (i.e. transfusion-associated circulatory overload [TACO][21]). Secondly, blood viscosity has been suggested to be an important factor for maintaining microvascular circulation, but the positive effect of blood transfusion in this regard is most pronounced in severe haemodilution which is not routinely the case in the vast majority of patients transfused in the clinic today. Furthermore, the positive rheological effect of transfusion in these cases is uncertain[22,23]. Conversely, blood viscosity that is too high may hinder optimal perfusion, and as a result, treatment strategies such as triple-H (hypervolaemia, haemodilution, hypertension) therapy in subarachnoid haemorrhage have arisen[24]. Finally, the rise in Hb following RBC transfusion (1 g/dL per unit of RBC on average[25]) is viewed as the main reason for giving blood, but evidence suggests that transfused blood may not necessarily result in improved oxygen delivery or oxygen consumption at the tissue level in the majority of RBC-transfused patients[26-29].

Notwithstanding local circulatory interruptions (e.g. myocardial infarction due to an occluded coronary artery), the key issue in determining ischaemia is the balance between the global oxygen delivery (DO_2) and the global oxygen consumption (VO_2). The ratio of the two (VO_2/DO_2) is called the oxygen extraction ratio and is normally around 20-30%, allowing a significant safety margin. As the DO_2 decreases and approaches VO_2, a point (the so-called critical DO_2 or $DO_{2\,CRIT}$) is reached when the DO_2 is no longer sufficient to keep up with the VO_2, resulting in a drop in VO_2 and development of tissue ischaemia. Nonetheless, it should be remembered that in the majority of patients, the wide margin between the VO_2 and DO_2 means that despite a decrease in DO_2 in varying degrees of anaemia, VO_2 is unaffected and remains stable (so-called DO_2-independency[27]).

DO_2 is a function of cardiac output (CO) and the arterial oxygen content (CaO_2), as follows:

$$DO_2 = CO \times CaO_2$$

Oxygen is carried in blood from the lungs to the other organs in two forms: bound to the haem group of Hb within the RBC, and dissolved in plasma. The sum of these two components in the arterial blood coming out of the heart makes up the CaO_2:

$$CaO_2 = \underset{\text{Hb-bound } O_2}{(SaO_2 \times [Hb] \times \text{constant})} + \underset{\text{Plasma-dissolved } O_2}{(PaO_2 \times \text{constant})}$$

where SaO_2 is the Hb oxygen saturation, [Hb] is the blood Hb concentration, and PaO_2 is the partial pressure of oxygen in arterial blood. The "constant" values depend on the units used for other parameters, but under physiological conditions and for patients breathing in air at normal atmospheric pressure, the amount of plasma-dissolved oxygen is negligible compared with the bulk of oxygen that is bound to Hb[27]. Nonetheless, this can change in conditions such as severe anaemia or treatment with hyperbaric oxygen[30].

Based on these equations, it can be seen that in an anaemic patient, increasing [Hb] (e.g. through transfusion) can result in increased CaO_2 which itself would result in increased DO_2. Increased DO_2 in turn should ensure that the balance between the DO_2 and VO_2 is maintained and VO_2 is not decreased (or if already decreased, ensure its recovery), resulting in prevention or reversal of ischaemia. This chain of events is the ultimate reason why RBC units are transfused to millions of patients every year, but what happens in reality can be much more complicated. Reviews of studies indicate that on average, while RBC transfusion is almost always associated with an increase in [Hb], and often associated with increased DO_2, VO_2 is usually not increased, and ischaemia (e.g. as indicated by blood lactate level) is rarely improved[28,31,32]. Reasons for this may include (transient) inability of transfused RBC to effectively deliver oxygen to the end organs (due to depleted 2,3-diphosphoglycerate), decreased functional capillary density, other known and unknown effects of blood storage, or to the fact that most of the transfused

patients are effectively in the DO_2-independent phase and are not likely to be experiencing (or at risk of) ischaemia[33,34]. Hence, many patients who are transfused may not be having any benefits from blood.

The ultimate clinically relevant verdict on safety and efficacy of transfusion should be based on effect on a patient's outcome, and whether transfusion improves it. A glance at several cohort studies published in the recent decade indicate that blood transfusions have been linked with increased short- and long-term mortality, longer stays in hospital/intensive care units, and a higher incidence of various complications and morbidities (systemic inflammatory response syndrome, atrial fibrillation, renal failure, prolonged ventilator support, serious infections, cardiac ischaemia, etc.) in different populations of surgical and non-surgical patients[35-54]. The fact that these observations are based on retrospective uncontrolled studies raise the possibility of a bias toward transfused patients being sicker at baseline, although the associations often persist after adjustment for the potential confounders[55]. Moreover, data from RCT (although there are many fewer of these and many are linked to the TRICC trial) often either confirm these observations, or indicate that restricting blood transfusions to patients has no negative effect (with the possible exception of patients with severe ischaemic heart disease[1,55-61]). A meta-analysis of 17 trials involving a total of 3,746 patients (heavily dominated by data from the TRICC trial) concluded that restrictive transfusion strategies reduced the rate of infectious complications while not negatively affecting the occurrence of other complications including mortality, cardiac events, stroke or thromboembolic events, compared with liberal transfusion strategies in patients without serious cardiac comorbidites[62]. Recently, Carson and colleagues specifically looked at elderly patients with a history (or risk factors) of cardiovascular disease who were undergoing hip surgery in the Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) trial. They randomised 2,016 such patients to restrictive *vs* liberal transfusion strategies and concluded that liberal transfusion was not associated with improved outcomes (mortality, ability to walk independently, acute coronary syndrome and other complications) compared with a restrictive transfusion strategy in this high-risk population[63]. Interestingly, in a recent pilot randomised clinical trial in patients with acute myocardial infarction, liberal transfusion was actually associated with increased mortality (38% *vs* 13%) although the data are from very limited number of patients (n=45) and further studies are needed[64]. Another randomised trial in 55 pre-term infants found that long-term neurocognitive outcomes of the children who were randomised to the liberal transfusion arm were worse than those randomised to the restrictive transfusion strategy[65]. Taken together, the evidence supports the notion that restrictive transfusion strategies are at least as good as (and likely better than) liberal transfusion approaches with regards to clinical outcomes of the patients, including those with cardiac conditions.

It should be noted that the results of the studies cited here are based on the average of the studied population (or subgroups of the study patients) and they do not necessarily reflect what may be happening at the level of individual patients. While it seems that RBC transfusions (or liberal use of them) are more likely to cause harm than benefits in the majority of patients, there appears to be a (relatively small) group of patients in whom the benefits of transfusion are likely to outweigh the harm; i.e. transfusion is likely to prevent/reduce ischaemia, and improve patients' outcomes. The challenge lies in identifying these patients and transfusing them on a timely basis, without unnecessarily exposing other patients to the risks of blood.

Recommendations for red blood cell transfusion

Clinicians have long been trying to formulate indications for blood transfusion to guide transfusion practices. Perhaps the oldest and most famous of these indications is the "10/30" rule which stipulates that the Hb of surgical patients should be maintained at or above 10 g/dL (or the haematocrit at or above 30%). Although the application of this rule has been extended to non-surgical settings as well (particularly in the intensive care unit), it is not based on any direct clinical evidence, and its merit has been repeatedly challenged[66,67]. A summary of more recent transfusion guidelines is provided here with the reminder that indications for RBC transfusion are subject of ongoing debate, and likely to change as our understanding of

the physiology of oxygen transport, tolerance of anaemia and ischaemia improves, and methods to accurately quantify relevant physiological parameters and detect ischaemia become available for routine use in clinical practice. The guidelines discussed here (in chronological order of publication) are those of the College of American Pathologists (CAP[68]), the American Society of Anesthesiologists (ASA[69]), the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists (STS/SCA[70]), the Society of Critical Care Medicine (SCCM[32]), the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI[71-73]) and the American Association of Blood Banks (AABB[74]). Another set of guidelines developed by the British Committee for Standards in Haematology, Blood Transfusion Task Force were reviewed but not discussed here for brevity as the recommendations were largely reiterated in the guidelines published later[75].

Transfusion guidelines from the College of American Pathologists

The most dated of all the guidelines discussed here, the CAP guidelines focus on conditions of acute (surgical and non-surgical) as well as chronic anaemia. In patients with acute anaemia, the main factors to consider in making transfusion decisions are the Hb before the blood loss, the extent of the blood loss, and presence of other medical conditions that may adversely affect the tolerance of anaemia. Based on these considerations, RBC transfusions are almost always indicated if Hb <6 g/dL, and rarely indicated if Hb >10 g/dL. For patients with Hb 6-10 g/dL, the decision depends on the extent of the blood loss, underlying cardiac disease, and overall clinical status. Based on the extent of the blood loss, previously healthy patients do not usually need transfusion when losing up to 30-40% of their total blood volume, and their volume loss should be replaced using crystalloids and colloids. In contrast, patients with underlying disease may be more susceptible and need RBC transfusion at smaller volumes of blood loss, depending on the Hb level and the nature of their underlying comorbidities. Acute loss of more than 40% of the total blood volume usually indicates need for RBC transfusion in almost all patients. The CAP guidelines state that, ideally, the final transfusion decision should be made and the response to therapy should be monitored based on indicators of peripheral tissue oxygenation. However, in routine practice and in the absence of these parameters, attention must be directed toward clinical signs and symptoms including heart rate and blood pressure, Hb level, comorbidities, prior medical history, and whether bleeding is active or controlled. Transfusion based on arbitrary Hb triggers alone is discouraged. Finally, it should be noted that reliance on vital signs may be inadequate in anaesthetised patients because of the effects of anaesthetic agents and the possibility of "silent" ischaemia[68].

The CAP guidelines recommend beginning the management of an acutely anaemic patient first by correcting hypovolemia through infusion of crystalloids and colloids. However, in cases of massive bleeding, it may be preferred not to restore euvolaemia completely until bleeding is controlled, as a measure to help to minimise blood loss through so-called permissive hypotension. When RBC transfusion is indicated in acute haemorrhage, it should be given quickly to correct the oxygen deficit, while the patient is monitored for the negative side effects of massive transfusion (hypothermia, hyperkalaemia, acidosis, and hypocalcaemia due to excessive citrate of banked blood)[68].

As opposed to those with acute anaemia, patients with chronic anaemia are almost always euvolaemic. Depending on the aetiology of anaemia (e.g. hypoproliferation, nutritional deficiencies, chronic blood loss, renal failure), specific treatment including pharmacological agents should be given as appropriate. Transfusion therapy should be guided for each patient based on individually determined target Hb/haematocrit levels to avoid anaemia symptoms and functional impairment. When transfusion is indicated, the smallest number of RBC units needed to correct the signs and symptoms of anaemia should be given slowly (normally over 2-4 hours for each unit). Under normal conditions and on average, the equivalent of one unit of RBC is replaced by newly produced RBC each week, and this can provide a baseline to determine RBC replacement needs of patients with varying degrees of marrow function. Hence, the frequency and dose of RBC transfusions should be determined based on the level of bone marrow compensation, comorbidities, cardiovascular tolerance of the volume transfused, alloimmunisation, as well as scheduling and availability of compatible blood[68].

Transfusion guidelines from the American Society of Anesthesiologists

The ASA transfusion guidelines are focused on the perioperative setting. Preoperative evaluation of the patients should include a complete medical history, family history and relevant laboratory work-ups to identify risk factors for ischaemia and bleeding (e.g. coagulopathy). Patients can be prepared for surgery through optimisation of RBC mass using pharmacological interventions and adjustment of anticoagulant medications. During and immediately after the surgery, patients should be monitored for blood loss, Hb/haematocrit level, perfusion status, and indicators of ischaemia using parameters such as blood pressure, heart rate, oxygen saturation, urine output, and electrocardiographic changes among others[69].

In the perioperative setting, RBC transfusion is usually indicated in otherwise healthy patients if Hb <6 g/dL, and rarely indicated if Hb >10 g/dL. In patients with Hb 6-10 g/dL, evidence of organ ischaemia, rate and amount of bleeding, intravascular volume status, and risk factors for complications of inadequate oxygenation (e.g. low cardiopulmonary reserve) should be considered to guide transfusion decisions[69].

Transfusion guidelines from the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists

The STS/SCA transfusion guidelines specifically address the cardiac surgery patient, with emphasis on measures to reduce transfusion in this setting. In general cardiac surgery patients, RBC transfusions are considered to be reasonable if Hb <6 g/dL, and reasonable in most postoperative patients if Hb <7 g/dL (albeit in the absence of substantial evidence to support this recommendation). Additionally, RBC transfusion may not be unreasonable in certain patients with Hb ≤ 10 g/dL in the presence of critical ischaemia in other organs (e.g. central nervous system or gastrointestinal tract). On the other hand, RBC transfusions are unlikely to improve oxygen transport if Hb >10 g/dL and are not recommended for patients with Hb levels in this range[70].

For patients undergoing cardiopulmonary bypass, RBC transfusion is considered reasonable if Hb ≤6 g/dL, and possibly at higher Hb levels in patients at risk of decreased cerebral oxygen delivery (i.e. patients with diabetes, carotid stenosis, or a history of cerebrovascular accidents). It is not unreasonable to maintain Hb ≥7 g/dL in patients with a risk of critical end-organ ischaemia. In patients undergoing cardiopulmonary bypass with a Hb >6 g/dL, patient-related factors (e.g. age, severity of illness, cardiac function, and risk of end-organ ischaemia), extent of blood loss, oxygen saturation, electrocardiographic or echocardiographic evidence of myocardial ischaemia, and other relevant parameters should be considered when deciding whether to give a transfusion[70].

Transfusion guidelines from the Society of Critical Care Medicine

These guidelines specifically address transfusion in the intensive care setting. In general critically ill patients, RBC transfusion is indicated in patients with evidence of haemorrhagic shock, and may be indicated for acutely bleeding patients with evidence of haemodynamic instability or inadequate oxygen delivery. A "restrictive" strategy (transfusion when Hb <7 g/dL) is as effective as a "liberal" transfusion strategy (transfusion when Hb <10 g/dL) in haemodynamically stable patients, with the possible exception of patients with acute myocardial ischaemia. The use of Hb level alone as a "trigger" for transfusion should be avoided and transfusion decisions should be based on patient's intravascular volume status, evidence of shock, duration/extent of anaemia, and cardiopulmonary physiological parameters. Nonetheless, in patients requiring mechanical ventilation, resuscitated critically ill trauma patients, and patients with stable cardiac disease, RBC transfusion should be considered if Hb <7 g/dL. RBC transfusion may be beneficial in patients with acute coronary syndrome with Hb ≤8 g/dL on hospital admission. RBC transfusion should not be considered as an absolute method to improve VO_2 alone. In the absence of acute bleeding, transfusions should be given as single units[32].

Each patient with sepsis must be assessed individually with regards to RBC transfusion needs since optimal transfusion triggers in such patients are not known. In patients with (or at risk of) acute lung injury or acute respiratory distress syndrome, every effort should be made to avoid transfusion; RBC transfusion should not be considered as a method to facilitate weaning from mechanical ventilation.

Finally, in patients with moderate/severe traumatic brain injury, no benefit for a "liberal" transfusion strategy (Hb >10 g/dL) has been demonstrated, and patients with subarachnoid haemorrhage must be assessed individually since optimal transfusion triggers are not known in this population[32].

Transfusion guidelines from the Italian Society of Transfusion Medicine and Immunohaematology

These guidelines specifically address the perioperative period[71-73]. The main factors to consider for transfusion decisions include Hb, amount and rate of blood loss, and clinical condition of the patient, particularly, presence of signs of reduced oxygen delivery[72]. The guidelines recommend use of point-of-care automated Hb/haematocrit analysers as a means of monitoring patients better and optimising transfusion practice[72]. In acute haemorrhage, there may be a delay before the systemic Hb/haematocrit levels adjust to blood loss (although it has been suggested that initial haematocrit in trauma patients may be predictive of shock and bleeding[76]), and the amount of acute blood loss in addition to the clinical condition of the patients should be the main determinants of transfusion decisions. In cases of acute loss of <15% of total blood volume (750 mL) RBC transfusion is not necessary, particularly if there was no pre-existing anaemia. Acute loss of 15-30% of total blood volume (~750-1,500 mL) is also not an indication for RBC transfusion, unless in the context of pre-existing anaemia or cardiopulmonary disease. However, in cases of acute loss of 30-40% of total blood volume (~1,500-2,000 mL) RBC transfusion will probably be necessary, and it will become a "life-saving" therapy if >40% of the total blood volume (>2,000 mL) is lost acutely[72].

Based on the Hb levels in acute anaemia, SIMTI guidelines consider RBC transfusions to be almost always necessary when Hb ≤6 g/dL. When the Hb level is 6-8 g/dL, RBC transfusion is not necessary in the absence of risk factors (e.g. coronary heart disease, heart failure, cerebrovascular disease) or when anaemia is adequately compensated, but it may be necessary in the presence of risk factors or signs of tissue hypoxia (e.g. tachycardia, hypotension, electrocardiographic signs of ischaemia, lactic acidosis). When the Hb level is 8-10 g/dL, transfusion is only indicated when signs of tissue hypoxia are present. RBC transfusion is not indicated when Hb>10 g/dL or merely to increase circulatory volume[72]. The same criteria are recommended for the post-operative period[71].

Transfusion guidelines from the American Association of Blood Banks

The AABB guidelines focus on Hb transfusion thresholds in hospitalised, haemodynamically stable adults and children[74]. The guidelines recommend restrictive RBC transfusion strategies in hospitalised patients in general. In the critical care unit, transfusion can be considered at Hb levels of 7 g/dL or less. In patients undergoing surgery, transfusion can be considered for patients with a Hb level at below the threshold of 8 g/dL, or for patients with symptoms of inadequate oxygen delivery (e.g. chest pain, orthostatic hypotension or tachycardia despite adequate fluid therapy)[74].

In hospitalised, haemodynamically stable patients with pre-existing cardiovascular comorbidity, restrictive transfusion strategies are suggested, and transfusions should only be considered at Hb levels of 8 g/dL or less, or in presence of symptoms of inadequate oxygen delivery[74]. However, the AABB guidelines did not make recommendations with regard to restrictive *vs* liberal transfusion strategies in cases of acute coronary syndrome, given the limited evidence available[74]. Finally, the guidelines suggest that transfusion decisions in all hospitalised stable patients should be made based on symptoms as well as the Hb levels, although the available evidence was found to be of low quality. The guidelines highlight the need for further research, particularly clinical trials in specific populations of patients (e.g. patients with cardiovascular disease and the elderly) as well as trials evaluating Hb thresholds lower than 7-8 g/dL[74].

Other considerations

Comparison of the guidelines discussed here and other guidelines[75] reveals substantial similarities (Table I). It is commonly emphasised the Hb alone is not a very informative parameter to use as a basis for transfusion decisions. Nonetheless, RBC transfusion is usually indicated if Hb <6 g/dL, and rarely indicated if Hb >10 g/dL. For patients with Hb 6-10 g/dL, other factors should be considered when making decisions. These include patient-related factors (e.g.

Table I - Transfusion guidelines at a glance. A side-by-side comparison of key provisions of transfusion guidelines.

	CAP (1998)[68]	ASA (2006)[69]	STS (2007)[70]	SCCM (2009)[32]	SIMTI (2011)[71-73]	AABB (2012)[74]
Target population	General	Perioperative (general)	Cardiac surgery	Critically ill	Perioperative (general)	Hospitalised, haemodynamically stable
RBC usually indicated	Hb <6 g/dL	Hb <6 g/dL	Hb <6 g/dL (Hb <7 g/dL in postoperative patients and higher if risk of end-organ ischaemia)	Hb <7 g/dL if ventilated, trauma, or stable cardiac disease (Hb <8 g/dL in acute coronary syndrome)	Hb <6 g/dL (Hb 6-8 g/dL if risk factors present; Hb 6-10 g/dL if symptoms of hypoxia present)	Hb ≤7 g/dL in critically-ill patients; Hb ≤8 g/dL in surgical patients, or patients with pre-existing cardiovascular disease; When symptoms are present
RBC rarely indicated	Hb >10 g/dL	Hb >10 g/dL	Hb >10 g/dL	Hb >10 g/dL	Hb >10 g/dL	
Equivocal	Hb 6-10 g/dL	Hb 6-10 g/dL				Patients with acute coronary syndrome
Factors to consider in making the decision	Peripheral tissue oxygenation, clinical signs and symptoms, Hb, extent/rate of bleeding	Ischaemia, extent/ rate of bleeding, volume status, risk factors for hypoxia complications	Age, severity of illness, cardiac function, ischaemia, extent/ rate of blood loss, Hb, SVO_2	Volume status, shock, duration/ extent of anaemia, cardiopulmonary parameters	Rate of blood loss, Hb level, risk factors, symptoms of hypoxia/ ischaemia	Hb levels as well as symptoms (chest pain, orthostatic hypotension, unresponsive tachycardia, heart failure)

Legend AABB: American Association of Blood Banks; ASA: American Society of Anesthesiologists; CAP: College of American Pathologists; Hb: haemoglobin; SCCM: Society of Critical Care Medicine; SIMTI: Italian Society of Transfusion Medicine and Immunohaematology; STS: Society of Thoracic Surgeons; SVO_2: mixed venous oxygen saturation.

age, comorbidities, risk of ischaemia), amount and rate of blood loss, and evidence of ischaemia.

It should be emphasised that while most of these recommendations are "steps in the right direction" (at least from the antiquated 10/30 rule or haphazard transfusion practices), not all these recommendations are based on strong evidence. For instance, the evidence supporting the CAP recommendation that loss of 40% or more of total blood volume would necessitate transfusion in almost all patients is unclear and questionable. Similarly, the data underlying the statement in the SCCM guidelines that RBC transfusion may be beneficial in acute coronary syndrome patients with Hb ≤8 g/dL is less than clear. Moreover, while the presence of comorbidities are commonly considered as evidence of greater susceptibility to the negative effects of anaemia and more need for RBC transfusion, comorbidities may also make patients more susceptible to risks of transfusion, and hence extra caution is warranted.

The ultimate goal of transfusion should not be to achieve or maintain an arbitrary Hb level, but should be to avoid ischaemia and improve outcomes. Before giving RBC, attempts should be made to optimise the haemodynamic status of the patient, and ensure that adequate oxygen therapy is supplied. Finally, when RBC transfusion is indicated, informed consent, following adequate discussion of the indication for blood and the potential risks and benefits, should be obtained from the patients. As mentioned earlier, single unit transfusions are preferred, particularly in the absence of active massive blood loss.

While most guidelines include some transfusion indications based on Hb levels, the baseline Hb level could affect the lowest Hb level that patients can tolerate. It has been suggested that the percentage drop in Hb level from the baseline may be more important than the absolute drop, with less tolerance and higher risks associated with a >50% drop in Hb from baseline in cardiac surgery patients[77]. Nonetheless, more studies are needed to validate this finding further in other populations of patients.

A shift from Hb-based transfusion triggers towards so-called "physiological" triggers indicative of tissue oxygenation status and ischaemia is the key to establishing better transfusion practices. Some suggested physiological RBC transfusion triggers for anaemic patients in surgical, non-surgical and critical care settings include mean arterial pressure <60 mmHg (or <70-80% of baseline), heart rate >110-130 pulse/min (or >120-130% of baseline), new ST-segment depression or elevation of at least 0.1 mV in an electrocardiogram, new wall motion abnormality in trans-oesophageal or trans-thoracic

echocardiography, mixed venous oxygen partial pressure <32 mmHg, oxygen extraction ratio >40%, mixed venous oxygen saturation <60%, or >10% decrease in VO_2. Normovolaemia is assumed for all triggers and anaemia should be the only probable cause for these triggers to be valid for transfusion decisions[78,79]. Wider application of these and other physiological indicators of transfusion requires further investigation to validate them, as well as more research and development efforts to make them available at the bedside and in routine clinical practice. Another emerging technology is non-invasive monitoring of Hb levels, which can provide the patient's Hb and its trend in real-time. However, more clinical data are needed to establish the value of this approach.

Another aspect of transfusion practice that is receiving ever more attention is the quality of the transfused RBC units. The removal of white blood cells from banked blood appears to provide some advantages in terms of reducing the risk of some complications and the use of leucoreduced RBC units is a reasonable approach[80]. The more debated issue is the age of blood and negative effects of storage on banked blood which have been linked to unfavourable outcomes. It is to be hoped that the ongoing trials addressing this issue will demonstrate whether the currently accepted blood storage duration should be revised and preference be given to transfusion of fresher RBC units[16]. Finally, a host of strategies collectively dubbed "Patient Blood Management" have been developed to simultaneously reduce transfusion use and improve patients' outcomes[81]. While better transfusion practices are an important tenet, discussion of other effective approaches employed in Patient Blood Management is beyond the scope of this article.

Implementing better transfusion practices

An effective way of promoting better transfusion practices in clinical practice is through the implementation of the key points of the guidelines and indications as part of RBC order forms. As an example, the order set currently in used at Englewood Hospital and Medical Center (EHMC; Englewood, NJ, USA) asks ordering physicians to specify the indication for transfusion, and provides advice on recommended approaches to manage patients better. An excerpt of the order set is given in the Table II. Implementation of better transfusion practice in the context of wider Patient Blood Management approaches has resulted in substantial reduction of transfusion rates and volumes at EHMC without any negative effect on the quality of patients' care and outcomes[82].

Table II - Streamlining RBC ordering. Summary of the criteria used in the RBC order set at Englewood Hospital and Medical Center (NJ, USA).

Check one box:
1. Acute Anaemia *(Before considering transfusion, all efforts should be made to control active bleeding)* □ Acute blood loss and symptomatic (Loss of >30% of estimated blood volume with Hb <7 mg/dL; tachycardia or hypotension not corrected by fluids alone, or mixed venous O_2 saturation <55%) □ Evidence of ACTIVE ischaemia (New ECG changes AND symptomatic)
2. Chronic Anaemia *(Treatable cause of anaemia should be ruled out first: iron/folate/ B_{12} deficiencies; consider using erythropoiesis-stimulating agents)* □ Patient symptomatic (Tachycardia or hypotension not corrected by fluids alone, or mixed venous O_2 saturation <55%) □ Patient is undergoing active treatment anticipated to cause significant anaemia

Conclusion

Considered for decades as a gift of life, blood transfusion is emerging as a treatment with limited efficacy and substantial risks, further under pressure from staggering associated costs and limited supplies. Evidence indicates that a great number of the patients who are being transfused today may not be having many tangible benefits from the transfusion, as the transfused blood fails to achieve its primary goals – prevention of ischaemia and improving clinical outcomes. The challenge lies in identifying those patients who are at risk of complications of severe anaemia (ischaemia) and transfusing them, without exposing other patients to unwarranted risks of inappropriate transfusions. Better transfusion practice should not be viewed as an option, but a necessity to ensure clinicians are giving benefit and not doing harm to their patients.

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Irwin Gross has been a consultant for Strategic Healthcare Group, LLC.

Steven Hill has been a consultant for Bayer and Masimo; has received research and grant support from Medtronic; and has been a speaker with honorarium for Bayer and OrthoBiotech. He is currently Treasurer of SABM and serves on the SABM Board of Directors.

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