

Should we reconsider triggers for red blood cell transfusion ?

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Summary : Very few randomized controlled trials on the benefits of red blood cell (RBC) transfusions in humans have been published. Consequently, most clinical practice guidelines remain based on expert opinion, animal studies and the limited human trials available. In the absence of definitive outcome studies, numerous theoretical arguments have been put forward either to support or to condone the classic transfusion threshold of 10 g/dL. However, the limited data available from randomized controlled trials suggest that a restrictive transfusion strategy (transfusion threshold between 7 and 8 g/dL) is associated with decreased transfusion requirements, that overall morbidity (including cardiac morbidity) and mortality, hemodynamic, pulmonary and oxygen transport variables are *not* different between restrictive and liberal transfusion strategies and, finally, that a restrictive transfusion strategy is not associated with increased adverse outcomes. In fact, a restrictive strategy may be associated with decreased adverse outcomes in younger and less sick critical care patients.

The majority of existing guidelines conclude that transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it falls below a threshold of 6 g/dL in healthy, stable patients or more in older, sicker patients. In anesthetized patients, this threshold should be modulated by factors related to the dynamic nature of surgery, such as uncontrolled hemorrhage, coagulopathy, etc.

Since transfusions are administered to correct inadequate oxygen delivery, whether global or regional, reliable monitors of tissue oxygenation will be required to study the benefits (or lack thereof) of RBC transfusions. The quest for a universal transfusion trigger, the holy grail of transfusion medicine, must be abandoned. All RBC transfusions must be tailored to the patient's needs, at the moment the need arises.

In conclusion most published recommendations are appropriate but their conclusions are limited, as they are commensurate with existing knowledge. Reliable monitors to guide transfusion therapy and well conducted trials to determine optimal transfusion strategies are required.

Transfusions have been in clinical use for over 50 years and are assumed to be an indispensable part of modern medical practice, especially to allow more and more aggressive therapy in older, sicker and debilitated patients. Yet, despite long-

standing utilization and well-entrenched beliefs on the benefits of erythrocyte transfusion, very few well-conducted studies are available to support existing clinical practice guidelines. A majority of clinicians would agree with the recommendation by the National Institutes of Health that the only justification for the transfusion of red blood (RBC) cells is the need to augment oxygen transport to the tissues (1). Unfortunately, at present, it is not possible to determine precisely, in every day clinical practice, when oxygen transport does not meet oxygen requirements. Global oxygenation may be measured but requires the insertion of a pulmonary artery catheter while regional tissue oxygenation is often impossible to measure and can only be evaluated clinically. Other indications for red cell transfusions, such as the preservation of hemostatic function, have been studied in animal experiments but are poorly documented in humans, specially in the surgical context (2).

Thus, the lack of well-conducted studies on the benefits of transfusions and our inability to adequately monitor tissue oxygenation have forced clinicians to rely on "expert opinion" for guidance. This article is an update of our previous reviews (3-5). We will attempt to determine if the existing recommendations for RBC transfusions should be re-examined, in light of the (few) studies published on the treatment of acute anemia.

BENEFITS/RISKS OF RBC TRANSFUSIONS

Overall, the benefits of RBC transfusions are related to the patient's capacity to compensate for anemia. Obviously, younger and healthier patients should be able to tolerate anemia more easily than

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older or sicker patients. The problem is to determine when patients fall into the "at-risk" category and become unable to tolerate anemia, especially when they cannot manifest symptoms of inadequate oxygen delivery, such as when they are in the intensive care unit or under anesthesia. Benefits are also related to the capacity of transfused RBC to correct the risks of anemia. While it is assumed that transfused RBC are immediately functional and correct the physiological deficit secondary to anemia, little objective evidence supports this assumption. As we are all well aware since the AIDS epidemic, transfusions are not without risks. The demonstrated complications of transfusions are numerous and range from acute incompatibility reactions to the transmission of infectious diseases. Evidence supporting the immunosuppressive effects of RBC transfusions is controversial, but a majority of transfusion specialists feel concerned by this issue. Thus, the benefits/risks analysis of RBC transfusions remains, even today, extremely complex. Unfortunately, definitive evidence to support many of the purported benefits and/or risks of RBC transfusions is lacking.

As mentioned previously, in the absence of definitive outcome studies, a number of arguments based on animal experiments and/or theoretical considerations have been put forward by experts to justify or to condone RBC transfusions. The arguments *in favor* of RBC transfusions to maintain a hemoglobin (Hb) concentration above 100 g/L (note : 10 g/L = 1 g/dL) include the minimal risks of transfusions secondary to donor screening and systematic testing of blood ; a decreased risk of morbidity/mortality in patients with cardiovascular disease ; the restoration of peripheral blood volume and, consequently, the improved perfusion of the gastrointestinal tract ; the contribution of RBC to coagulation and the improved hemostasis that ensues ; an improved functional status and well-being of patients, specially that of elderly patients undergoing major orthopedic procedures.

Yet, the arguments *against* RBC transfusions to maintain a Hb concentration above 100 g/L are not less compelling. The risks of transfusions are not restricted to transmission of existing pathogens. New diseases may emerge (e.g. transmission of West Nile virus recently) and the incidence of the "classic" complications of RBC transfusions remains high (much higher, in fact, than the transmission of viral diseases). Reducing transfusions should minimize the immunomodulating complications of transfusions. Several studies have shown that low hemoglobin concentrations are well toler-

ated, even in patients with cardiovascular disease, as will be discussed later. Finally, lower Hb concentrations may reduce the risks of thrombotic events.

ARGUMENTS ARE INTERESTING, BUT WHAT DATA DO WE HAVE ?

Randomized controlled trials of transfusion

Surprisingly, considering the massive number of RBC transfusions administered every year, very few randomized controlled trials on the benefits of RBC transfusions have been published. Twelve studies of allogeneic transfusion have compared a restrictive strategy to liberal erythrocyte transfusion (6-17). They are presented in the Table. Excluding the study on children with sickle cell anemia, a little over 1500 patients have been studied over a period of 47 years, a minuscule sample size considering 12 million units of RBC are transfused every year in the USA alone.

From these (limited) data, we can draw a number of conclusions. First, a restrictive transfusion strategy (transfusion threshold between 70 and 80 g/L) is associated with decreased transfusion requirements in all studies where transfusion requirements are reported. It should be noted, however, that the ranges of hemoglobin levels studied have evolved over time. For example, in the oldest study (1956), the liberal strategy aimed to restore a normal blood volume while the "restrictive" strategy aimed to maintain RBC volume at 70%-80% of normal. Second, overall morbidity (including cardiac morbidity) and mortality, hemodynamic, pulmonary and oxygen transport variables are *not* different between groups. Finally, with possibly one exception, a restrictive transfusion strategy is not associated with increased adverse outcomes. In the study by LOTKE *et al.*, one patient in the delayed retransfusion of autologous blood experienced an acute myocardial infarction, but the total number of patients was small (17). All other complications were transient (lethargy, confusion, orthostatic hypotension), occurred in older patients, and the responsibility of anemia remains unclear. In the largest of the studies, the TRICC trial (15), a restrictive strategy was associated with a statistically significant decrease of adverse outcomes in younger and less sick patients.

The above mentioned studies were, recently, submitted to a meta-analysis that supports our initial reading of the literature. CARSON *et al.* con-

Table

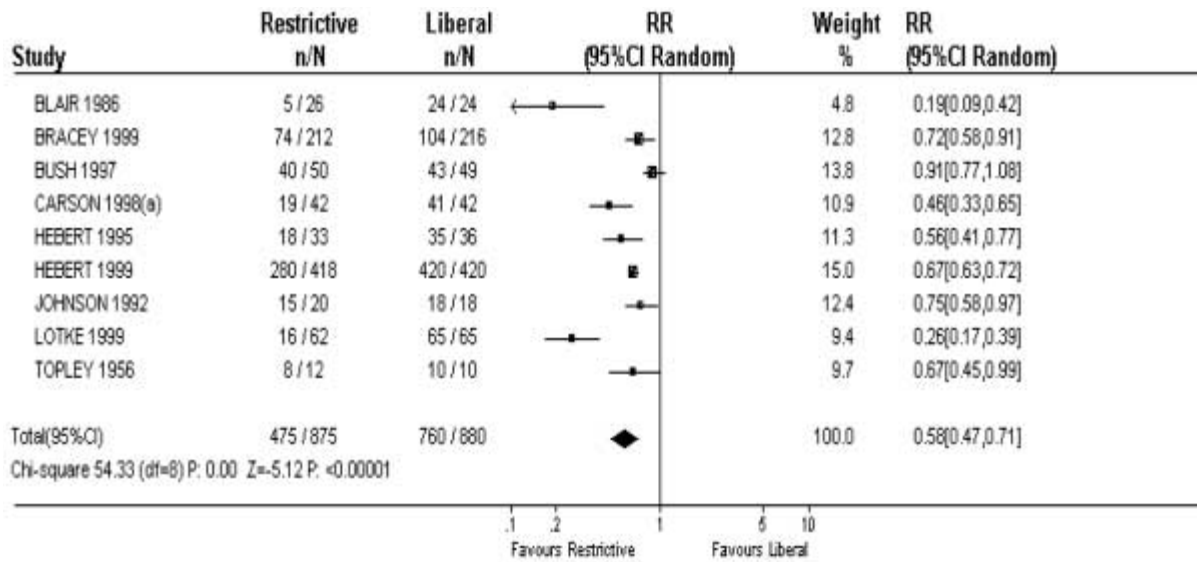
Randomized studies of allogeneic transfusion comparing a restrictive strategy to liberal erythrocyte transfusion

Author, year	Patient population	Number of pts	Outcomes for which <i>no</i> differences were observed between groups	Outcomes for which a restrictive transfusion strategy was <i>beneficial</i>
TOPLEY <i>et al.</i> , 1956 (6)	Trauma	22	Mortality (?) Outcomes difficult to assess because of the absence of formal criteria	Exposure to transfusion <i>Increased</i> complications (“serious illness”) in “under-transfused” group ? (see text for details)
WEISEL <i>et al.</i> , 1984 (7)	Myocardial revascularization	27	Mortality Myocardial infarction rate Pulmonary edema and hemodynamic variables	Exposure to transfusion
BLAIR <i>et al.</i> , 1986 (8)	Gastrointestinal hemorrhage	50		Exposure to transfusion Rebleeding rate
FORTUNE <i>et al.</i> , 1987 (9)	Critical care (adult trauma)	25	Hemodynamic and oxygen transport variables	Exposure to transfusion Intrapulmonary shunt
JOHNSON <i>et al.</i> , 1992 (10)	Myocardial revascularization	38	Hospital complications Length of stay Ischemic events	Exposure to transfusion
HÉBERT <i>et al.</i> , 1995 (11)	Critical care (pilot study)	69	Mortality Organ failure rate Length of stay in ICU and hospital	Exposure to transfusion
VICHINSKY <i>et al.</i> , 1995 (12)	Sickle cell anemia and surgery	604	Serious complications related to sickle cell disease	Transfusion-related complications (hemolytic reactions and alloantibodies)
BUSH <i>et al.</i> , 1997 (13)	Major vascular surgery	99	Mortality, Cardiac morbidity Length of hospital stay Hemodynamic variables and O ₂ consumption	Exposure to transfusion in the anemic subgroup
CARSON <i>et al.</i> , 1998 (14)	Hip fracture surgery (pilot study)	84	Mortality, Length of stay Complications, Capacity of mobilization	Exposure to transfusion
HÉBERT <i>et al.</i> , 1999 (15)	Critical care	838	Overall mortality at 30 days Mortality in patients with cardiac disease	Exposure to transfusion Mortality in patients age < 55 Mortality in patients Apache ≤ 20 Mortality during hospitalization
BRACEY <i>et al.</i> , 1999 (16)	Myocardial revascularization	428	Overall morbidity and mortality Fatigue and anemia	Exposure to transfusion
LOTKE <i>et al.</i> , 1999 (17)	Total knee arthroplasty	152	Pain assessment Well-being scores Progress at physical therapy	Exposure to transfusion <i>Increased</i> non surgical complications in delayed transfusion group ? (see text for details)

firmed that, as expected, restrictive transfusion triggers decrease hematocrit levels and reduce the proportion of patients transfused allogeneic RBC and the total number of RBC units transfused (Figs. 1-3) (18). Importantly, the use of a restrictive transfusion strategy does not adversely affect mortality, cardiac morbidity and length of hospital stay (Figs. 4-6). Nevertheless, the clinical application of this meta-analysis should be prudent given the preponderance of the TRICC trial on the overall results. Since a majority of patients came from the intensive care setting, it may be difficult to generalize conclusions to patient populations receiving transfusions in other settings such as surgery or obstetrics for example.

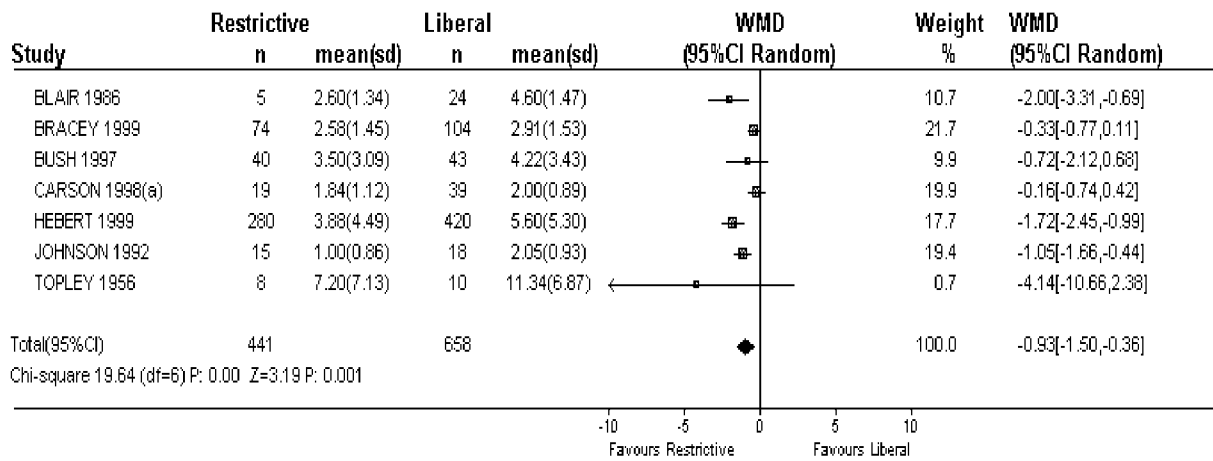
Respiratory and cardiovascular morbidity and mortality

HÉBERT and colleagues analyzed two subgroups of patients from their large multicenter TRICC trial to determine if transfusion strategy impacted outcomes related to mechanical ventilation (19) and to cardiovascular disease (20). A liberal transfusion strategy (destined to maintain Hb concentration between 10 and 12 g/dL) did not decrease the duration of mechanical ventilation in a heterogeneous population of 713 critically ill patients. 19 Similarly, based on their findings in 357 critically ill patients, a restrictive RBC transfusion strategy (destined to maintain Hb concentration



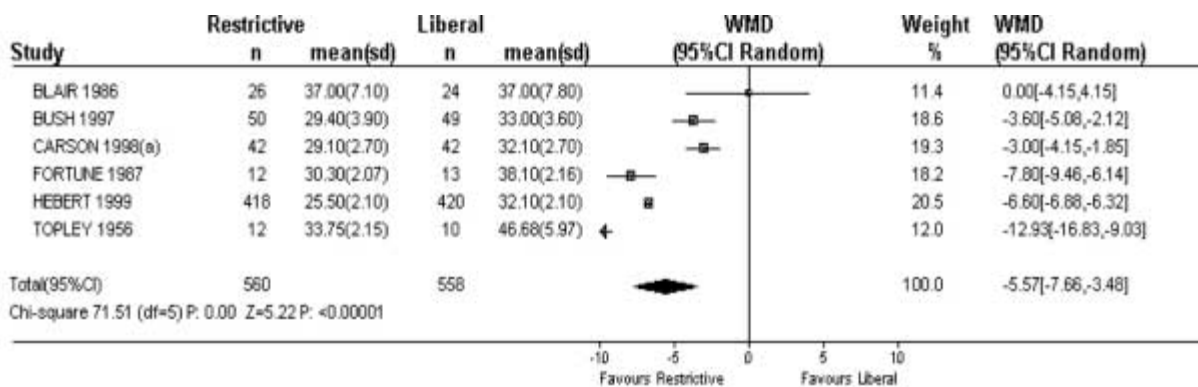
RR = relative risk, CI = confidence interval

Fig. 1. — Effect of ‘restrictive’ transfusion triggers on the use of allogeneic blood transfusion



WMD = weighted mean difference

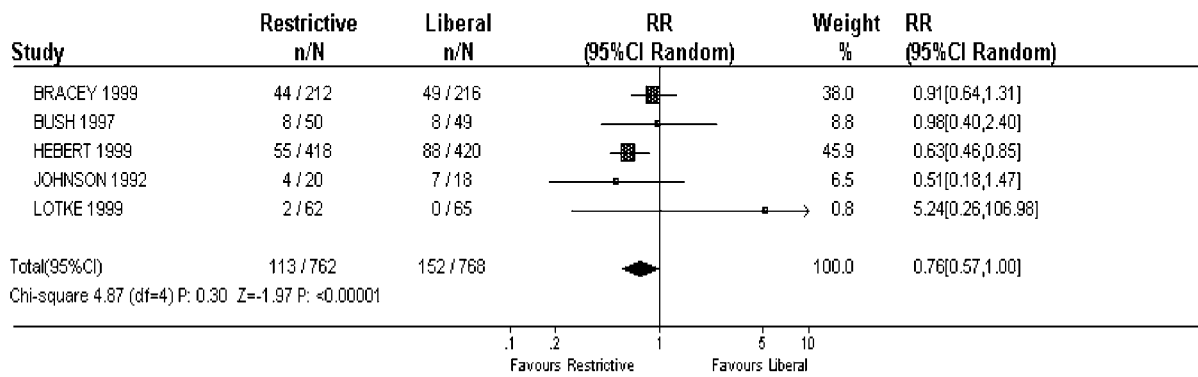
Fig. 2. — The effect of ‘restrictive’ transfusion triggers on the number of units of blood transfused



WMD = weighted mean difference

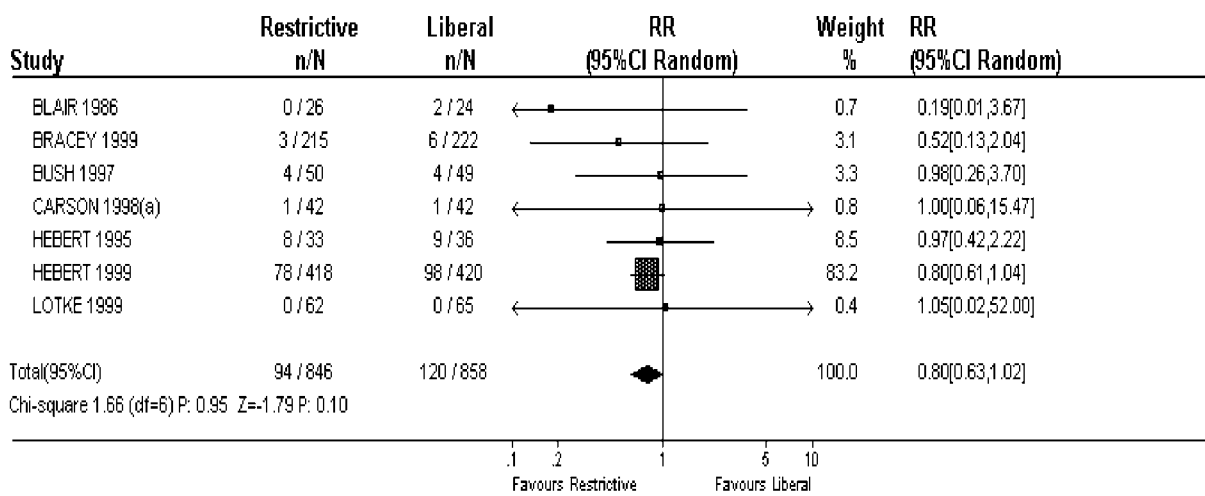
Fig. 3. — The effect of ‘restrictive’ transfusion triggers on hematocrit levels

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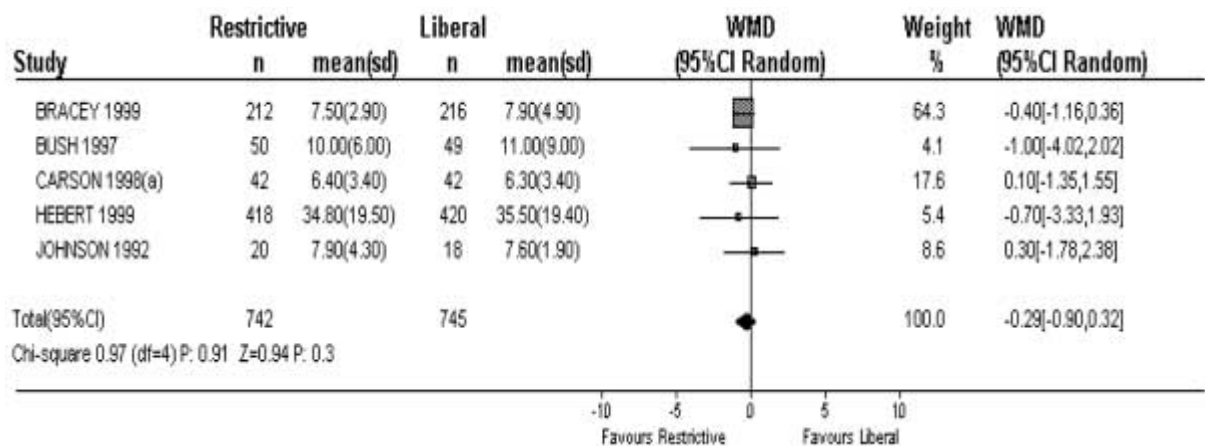
RR = relative risk, CI = confidence interval

Fig. 4. — Effect of 'restrictive' transfusion triggers on cardiac events



RR = relative risk, CI = confidence interval

Fig. 5. — Effect of 'restrictive' transfusion triggers on 30 day all cause mortality



WMD = weighted mean difference

Fig. 6. — Effect of 'restrictive transfusion triggers on hospital length of stay

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between 7 and 9 g/dL) appeared to be safe in most critically ill patients with cardiovascular disease, with the *possible* exception of patients with acute myocardial infarction and unstable angina (20). The evidence available at present does not support increased transfusion thresholds (9-10 g/dL and more) in patients with cardiovascular disease (14, 18, 21). To the contrary, hemoglobin concentrations as low as 7-8 g/dL appear to be well tolerated, at least in stable patients. So why continue to recommend high hemoglobin concentrations in patients with cardiovascular disease ?

In patients with cardiovascular disease, improved outcome with a liberal transfusion trigger is possibly supported by a retrospective review of patients who declined transfusions for religious reasons. That study showed an increasing mortality in patients with, compared to patients without, cardiovascular disease as *preoperative* hemoglobin concentration fell below 10 g/dL (22). A similar, observational study published in 2002 showed that mortality is not increased in patients with, compared to patients without, cardiovascular disease when the *postoperative* hemoglobin level is greater than 6 g/dL (23). Severe postoperative anemia increased mortality and morbidity, specially below 5-6 g/dL, but not more so in patients with cardiovascular disease than in patients without. The most common postoperative complications were congestive heart failure, arrhythmia and pneumonia while myocardial infarction was an uncommon outcome. Such observational studies are of interest as they describe the risks of perioperative anemia in patients who refuse transfusion but fail to demonstrate the beneficial effects (or lack thereof) of RBC at different transfusion triggers.

Recently, the retrospective study by WU *et al.* attempted to determine the benefits of RBC transfusions in elderly patients with acute myocardial infarction and various degrees of anemia (24). The study suffers from several, important limitations including its retrospective nature ; the lack of a temporal relationship between hematocrit, transfusions and mortality ; and the borderline statistical significance of the results despite the impressive number of subjects included. In fact, mortality was statistically (and convincingly) increased only when the initial hematocrit was below 24% in non-transfused patients or above 36.1% in *transfused* patients. The authors conclude that their data suggest that elderly patients with an acute MI will benefit from transfusions inasmuch as the hematocrit on admission is 30% or lower, possibly 33%. The accompanying editorial comment by GOODNOUGH

and BACH (25) concluded : "On the basis of the evidence presented by WU *et al.*, we recommend that hematocrit levels should be maintained above 33 percent in patients who present with acute myocardial infarction". While many clinicians may be tempted to share the editorialists' opinion, their conclusion is incorrect inasmuch as it extends WU *et al.*'s interesting, albeit debatable findings to patients under the age of 65, a population that was not included in their data review (26).

We know that clinical evidence to support transfusion guidelines is insufficient and that most recommendations are guided by consensus rather than by science. Now that we have a study (even if it remains open to discussion) on the benefits of transfusions in elderly patients with an acute MI, we must resist the temptation of improperly extending WU *et al.*'s conclusions. On the contrary, we now have to conduct similar (or better) studies for all the other patient populations likely to benefit from erythrocyte transfusions.

Thus, we agree with the recommendations formulated by WALSH and McCLELLAND in a 2003 editorial. "Patients with stable or mild coronary artery disease can probably be managed with transfusion triggers of 7-8 g/dL unless they have evidence of worsening ischaemia or infarction. Patients with severe, symptomatic disease should probably have a transfusion trigger nearer 9-10 g/L...clinicians should regularly reassess the likely myocardial oxygen supply/demand balance of their patients...and modify their transfusion decisions based on this information" (27).

Hemoglobin concentrations and hemostasis

An often-ignored effect of RBC transfusion is the improvement of hemostatic function. Transfusion of RBC shortens the bleeding time in anemic thrombocytopenic patients despite persistent thrombocytopenia (28). In non-thrombocytopenic rabbits, the microvascular bleeding time varied inversely with the hematocrit, animals with hematocrit levels above 35% having shorter bleeding times than animals with hematocrits lower than 35% (29). Erythrocytes have been shown to modulate biochemical and functional responsiveness of activated platelets, suggesting that erythrocytes contribute to thrombosis and hemostasis and supporting the concept that thrombus formation is a multicellular event (30-32). Another mechanism by which erythrocytes modulate hemostasis is the rheological effect of red cells on the margination of platelets (33). Under normal circumstances, red

cell flow is maximal at the center of a vessel, tending to push platelets towards the periphery of the vessel lumen, thereby optimizing their interaction with injured endothelium and promoting hemostasis (34, 35). At present the optimal hematocrit/hemoglobin concentration to avoid/treat a hemostatic disorder remains unknown. Limited experimental evidence suggests that hematocrits higher than those required to provide a normal oxygen delivery, and possibly as high as 35%, may be required to sustain hemostasis in bleeding patients. Further investigations into the role of the hemoglobin concentration or hematocrit on hemostasis appear warranted.

A FEW EXAMPLES OF EXISTING RECOMMENDATIONS

In 1996, the American Society of Anesthesiologists made the following recommendations in their Practice Guidelines for Blood Component Therapy, based on available category II-2 and II-3 evidence and expert opinion. "The task force concludes that (1) transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it is less than 6 g/dL, especially when the anemia is acute ; (2) the determination of whether intermediate hemoglobin concentrations (6-10 g/dL) justify or require RBC transfusion should be based on the patient's risk for complications of inadequate oxygenation ; (3) the use of a single hemoglobin "trigger" for all patients and other approaches that fail to consider all important physiologic and surgical factors affecting oxygenation are not recommended ; (4) when appropriate, preoperative autologous blood donation, intraoperative and postoperative blood recovery, acute normovolemic hemodilution, and measures to decrease blood loss (deliberate hypotension and pharmacologic agents) may be beneficial ; and (5) the indications for transfusion of autologous RBCs may be more liberal than for allogeneic RBCs because of the lower (but still significant) risks associated with the former" (36).

More recently, in 2002, the Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps) published the French recommendations on the transfusion of allogeneic red cells, plasma and platelets (the recommendations are available, in French, at <http://afssaps.sante.fr/htm/5/5000.htm>). These recommendations, based on a systematic review of the literature, were prepared by different expert working groups. The preliminary document was then submitted to external reviewers in

view of preparing the final version of the recommendations. While we must be wary of transfusion thresholds, the Afssaps recommends the following for red cell transfusions :

- 7 g/dl in healthy patients (no specific disease condition)
- 8-9 g/dl in patients with known cardiovascular disease
- 10 g/dl in patients who do not tolerate lower concentrations ; in the presence of an acute coronary syndrome or manifest heart failure.

Afssaps recognizes that the level of the recently published recommendations is only that of an expert consensus (lowest level of evidence) and, consequently, the recommendations are accompanied by detailed recommendations for the preoperative, intraoperative and postoperative periods, in obstetrics, for vital emergencies, etc. While these are some of the most recent and up to date recommendations for red cell transfusions, we have to admit that little has changed since the ASA published its recommendations more than seven years ago.

Other national organizations are in the process of preparing/revising their recommendations. We expect they will not be able to add much to the comprehensive practice guidelines already published by professional associations such as the American Society of Anesthesiologists or the Agence Française de Sécurité Sanitaire des Produits de Santé. We believe the lack of new evidence is responsible for this regrettable lack of progress in transfusion medicine.

SHOULD RECOMMENDATIONS FOR RBC TRANSFUSIONS BE RECONSIDERED ? CAN THEY BE IMPROVED ?

The majority of existing guidelines conclude that transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it falls below a threshold of 6 g/dL in healthy, stable patients or more in older, sicker patients. Nowadays, few clinicians would argue that higher hemoglobin concentrations are necessary, except under very unusual circumstances. In healthy adults, the threshold of 6 g/dL, possibly 5 g/dL, is slightly above critical oxygen delivery, the value of oxygen delivery at which oxygen consumption becomes dependent of oxygen delivery. These numbers, established both in humans (37) and in animals, are fairly consistent. In anesthetized patients, this threshold should

be modulated by factors related to the dynamic nature of surgery, such as uncontrolled hemorrhage, coagulopathy, etc.

On the other hand, the degree of anemia that can be tolerated in older and sicker patients remains a subject of considerable controversy. For example, common clinical paradigms dictate that older, anemic patients with decreased left ventricular function require RBC transfusions to increase oxygen delivery and consumption. The study by CASUTT *et al.* (38) showed that, in adult patients after cardiovascular surgery, the increase in cardiac output resulting from a blood transfusion was inversely related to cardiac index, oxygen delivery and oxygen consumption before transfusion. As might have been expected, increases in oxygen delivery and consumption were inversely related to oxygen consumption before transfusion. However, even in these high-risk patients (97% ASA class IV), changes in cardiac index, oxygen delivery, and oxygen consumption were not related to preoperative ejection fraction (range 25%-87%), age (range 32-81 yrs.), and pre-transfusion hemoglobin concentration (range 5.0-11.8 g/dL), an indication of the patients' excellent tolerance to anemia. CASUTT *et al.* concluded that including oxygen delivery and oxygen consumption variables into the transfusion decision might enable a more individual use of allogeneic blood in specific situations. The findings of this and previous studies on the benefits of erythrocyte transfusions lead us to believe that further discussions on the optimal hemoglobin concentration in a given clinical context can only remain sterile.

The quest for a universal transfusion trigger, the holy grail of transfusion medicine, must be abandoned. All RBC transfusions must be tailored to the patient's needs, at the moment the need arises. Let us consider the following analogy: the administration of penicillin to all patients with a given degree of fever (the "universal fever trigger") would, no doubt, cure a few patients, but would be useless in many and harmful in some. Clinicians realize that such a "universal fever trigger" doesn't make sense, because it fails to take into account the underlying pathophysiology of the disease responsible for the fever. Yet, this is the way RBC transfusions are still administered by many. While the situation may have improved somewhat with the publication of randomized controlled trials (14, 15) and meta-analyses (18, 39), it has been shown that significant variation exists in transfusion practices among anesthesiologists practicing in the USA (40) and in Europe (41). However, it is comforting to

know that an educational outreach can substantially improve the appropriateness of blood product use in surgery (42).

Since transfusions are administered to correct inadequate oxygen delivery, whether global or regional, reliable monitors of tissue oxygenation will be required to study the benefits (or lack thereof) of RBC transfusions. Monitors will be invaluable in anesthetized patients who cannot express symptoms of inadequate tissue oxygenation (e.g. myocardial or cerebral ischemia). Also, more studies like that of HÉBERT *et al.* must be conducted to determine, in different patient populations, the appropriateness of different transfusion strategies.

CONCLUSION

Published recommendations are, for the most part, appropriate as they are commensurate with existing knowledge. Clinicians and their patients urgently need reliable monitors of oxygenation and hemostasis to guide transfusion therapy and well conducted trials to determine optimal transfusion strategies.

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