Intensive Care Med (2010) 36:1107–1109
DOI 10.1007/s00134-010-1871-z

EDITORIAL

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The "sticky" business of "adherence" to transfusion guidelines

Received: 5 March 2010
Accepted: 8 March 2010
Published online: 4 May 2010

This editorial refers to the article available at:
doi:10.1007/s00134-010-1867-8.

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Red blood cell, frozen plasma, and platelet transfusions are potentially life-saving therapies for critically ill patients. In fact, transfusion therapy has aided the development and permitted the use of many more aggressive therapies introduced in the past 50 years (i.e., chemotherapy, bone marrow and organ transplantation, heart surgery). However, the adverse effects of transfusion, including increased mortality, have also been recognized in the last 30 years. Thus, either "undertransfusion" or "overtransfusion" could result in adverse clinical outcomes. Therefore, clinicians continue to provide "appropriate" transfusion therapy by avoiding these extremes and balancing the risk–benefit ratio in favor of optimal transfusion practice for each patient. While undertransfusion has not been frequently reported in the literature, global application of transfusion thresholds derived from previous randomized trials in critical care (TRICC) has contributed to lowering transfusion thresholds in critical care patients [1, 2]. Conversely, overtransfusion has received considerable attention. This attention was largely associated with transmission of human immune-deficiency virus (HIV) and hepatitis through blood transfusions. A multifactorial and effective response to this event has led to a marked reduction in transfusion-transmitted viral infections over the last three decades. However, there remain significant "noninfectious" adverse effects associated with transfusions, including transmission of bacterial contaminants, transfusion-associated acute lung injury (TRALI), mistransfusion (transfusion of the wrong blood to the wrong patient), and transfusion-associated circulatory overload (TACO). In addition, there is increasing concern that transfusion, which had once been viewed as a life-saving therapy, may result in increased mortality [3]. Transfusion should thus not be undertaken unless the risks of not receiving the transfusion exceed the risks of its administration.

To support the effort to optimize transfusion therapy and decrease variations in practice, numerous guidelines from national and international organizations have been promulgated. Additionally, numerous studies have examined the effectiveness of guidelines, either alone or in association with other interventions, to reduce transfusion utilization [4] and inappropriate transfusions [5]. In this issue, Westbrook et al. examined how current transfusion practice reflects transfusion guidelines in 47 critical care units in Australia and New Zealand. The authors showed that there were significant discrepancies in transfusion practice when compared with the guidelines

and that these differences appear to be greater for non-red-cell transfusions. While the results of this study could simply be viewed as failure to achieve optimal transfusion practice, the results can equally be viewed as highlighting limitations within current guidelines for transfusion practice.

Numerous guidelines for transfusion practice which have been published over the last three decades continue to have limitations. One of the primary limitations of transfusion guidelines has been the paucity of outcome data to indicate when blood product transfusions are appropriate. For red cell transfusions, there is good evidence from two randomized trials to guide the decision to transfuse in critically ill adult [6] and pediatric [7] patients. However, even this evidence suggesting that a red cell transfusion trigger of 70 g/L is appropriate (compared with 100 g/L) in stable nonbleeding patients may not be generalizable to other patient groups, especially those with cardiac disease or suffering from neurotrauma [8, 9]. This is of particular importance as 46% of patients who received red blood cell (RBC) transfusions in the current review were bleeding [10]. By contrast, the evidence for platelet and fresh frozen plasma (FFP) transfusion is much weaker. The only good evidence for platelet transfusions is for prophylactic transfusion in hematology/oncology, and there is no satisfactory evidence to guide the use of plasma transfusions.

Given the lack of evidence, it is not surprising that Westbrook et al. [10] found a continued high rate of transfusions in Australian and New Zealand intensive care units (ICUs) which were not adherent to guidelines. These high rates of nonadherent transfusions are consistent with previous studies of critical care patients in Europe [11] and the USA [12]. While this could simply be seen as a failure to follow best practice as defined by transfusion guidelines, the high rate of nonadherent transfusions could also be due to the inadequacy of current guidelines. A recent study evaluated five major transfusion guidelines, including the National Health and Medical Research Council (NHMRC)/Australian Society of Blood Transfusion (ASBT) guideline used in the study by Westbrook, with the AGREE tool and demonstrated low scores for all guidelines [13]. Most relevant, all guidelines received a score of <50% for applicability, which includes review criteria for monitoring or auditing.

The limitations of the transfusion guidelines for auditing transfusion practice are clearly demonstrated in the assessment of red cell transfusions. Westbrook et al. [10] are not able to clearly define the rate of inappropriate transfusions. If they use pretransfusion hemoglobin of <100 g/L (the upper limit of the acceptable range for a red cell transfusion trigger) then only 3% of all red cell transfusions would be considered inappropriate. Alternatively, if results from the TRICC trial [6] are used to determine an appropriate red cell transfusion (hemoglobin <70 g/L with no active bleeding or cardiac issues), then the inappropriate transfusion rate increases to 32.9%. This is confounded by the high proportion of bleeding patients in the current review, who would not have been included in the TRICC trial. Likely, the true rate of inappropriate transfusion lies somewhere between these two values, but current guidelines, which frequently report a wide range for appropriate red cell transfusion, do not allow for quantification of inappropriate red cell transfusions.

The evaluation of non-red-cell transfusion is even more problematic. The only randomized clinical trials (RCTs) of frozen plasma in adults evaluated the use of prophylactic transfusions after cardiac surgery and pancreatitis [14]. RCTs of platelet transfusions are limited to prophylactic transfusions in hematology/oncology patients, and there are no RCTs with cryoprecipitate. As a result, guidelines are based solely on expert opinion. These guidelines are often simplistic, using a single threshold [e.g., international normalized ratio (INR) of 1.5 or platelet count of 50×10^9/L]. Even with pretransfusion INR of <1.5, frozen plasma transfusion may still be appropriate in a massively bleeding patient. Alternatively, frozen plasma transfusion prior to a minor invasive procedure in a patient with INR of 1.8 or even higher may not be appropriate. The classification of all frozen plasma and platelet transfusions in bleeding patients as "clinically appropriate" recognizes the limitation that some transfusions which would be deemed inappropriate by guidelines may indeed be appropriate, particularly in an ICU setting. However, evaluation of the appropriateness of non-red-cell transfusion still needs to consider the type of bleeding and coagulation test results. In a single-center study, this did result in 20% of all frozen plasma transfusion being reclassified as "appropriate but not meeting clinical guidelines" [15].

There are at least two different components to transfusion adherence: transfusions given without having met a specific trigger, and transfusions not given when a specific trigger was met. By design, this study only focused on the former, but the latter may also represent inappropriate transfusion practice. In the case of RBC transfusion, the complexity of assessing both adherence to transfusion guidelines and the quality of those guidelines is further complicated by the inability to isolate the known risk of anemia and that of transfusion [16]. Since both anemia and transfusion have been assessed as independently increasing the risk of mortality, it continues to be important to define the crossover point at which the risk of anemia becomes greater than the risk of transfusion in acutely ill patients.

There have been two systematic reviews examining the use of interventions to change transfusion practice [4, 5]. While occasional studies demonstrated reductions in transfusions with the introduction of guidelines in isolation, others demonstrated that, to be most effective, guidelines should be combined with other interventions such as audit and feedback reminders, educational

outreach, and use of local opinion leaders or champions. Finally, at least two other studies have shown that, while interventions may have a short-term positive effect, their durability may be limited, with effects waning several years later.

Two words that merit careful use in the vocabulary of transfusion practice are "need" and "appropriate." While it is often said that a "patient *needed* a transfusion," it is always the clinician prescribing the transfusion who has determined the magnitude of the need based on individual patient factors. Unfortunately, published studies have still not provided the clinician with clear biological or clinical endpoints upon which "true" transfusion guidelines can be based for any given patient population. Whether or not a transfusion is "appropriate" must still be determined by a combination of the patient's unique clinical circumstances and the best evidence of the benefits and risks of transfusion, which is often articulated in guideline documents. The efforts of Westbrook et al. highlight the importance of having guidelines that are clinically relevant and useful. Guidelines alone may not be sufficient to change or improve transfusion practice, but they form a critical basis on which to monitor and improve clinical care.

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