Blood product transfusion in the critical care setting
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Current Opinion in Critical Care 2010, 16:309–316

Purpose of review
The past two decades have witnessed an extensive re-evaluation of transfusion therapy in the intensive care unit (ICU). The purpose of this review is to present the current state of knowledge regarding blood transfusion in the critically ill and to identify gaps in our current understanding for future research.

Recent findings
Accumulating evidence suggests a lack of efficacy with red blood cell (RBC), plasma, and platelet transfusion in the majority of critically ill patients. Evidence has also increasingly exposed previously under-recognized transfusion risks. The result is a growing number of recommendations for more restrictive RBC, plasma, and platelet transfusion strategies. An important exception to a more conservative transfusion practice occurs in patients with major trauma and life-threatening bleeding. Delaying RBCs, plasma and platelet component therapies in this population can promote the lethal triad of coagulopathy, acidosis, and hypothermia with a resultant increase in bleeding, greater transfusion requirements, and higher mortality.

Summary
Although we have made substantial progress in understanding the role of blood transfusion in the ICU, multiple important knowledge gaps persist. Future studies are needed to better define and characterize the impact of RBC storage, male-only plasma and platelet donor procurement procedures, and transfusion strategies in those requiring massive transfusion and with acute local or global tissue ischemia.

Keywords
leukocyte reduction, massive transfusion, red blood cell storage lesion, transfusion-related acute lung injury, transfusion-related immune modulation

Introduction
In the past two decades, we have witnessed increased scrutiny regarding efficacy and risk of the once unquestioned therapy of blood transfusion. Whereas primarily targeted at red blood cell (RBC) administration [1], similar concerns have been raised for other component therapies as well [2,3]. In perhaps no other environment has this re-evaluation been more extensive than the intensive care unit (ICU). With the notable exception of acute blood loss, enhanced understanding of the efficacy (or lack thereof) and risk of blood product administration has led to a pervasive trend to more conservative RBC, plasma, and platelet strategies. Nonetheless, numerous controversies and knowledge gaps persist. This review will address the current evidence-based indications for RBC, platelet, and plasma transfusions. We will address recent changes in transfusion strategies for patients with major trauma/massive transfusion as well as the major risks associated with transfusion therapy. We will specifically focus on the leading cause of transfusion-related mortality and transfusion-related acute lung injury (TRALI). This review will not address the use of blood product substitutes, transfusion practices in the critically ill pediatric population or the specific component therapies of cryoprecipitate, factor concentrates, or granulocyte infusions.

Red blood cell transfusion
The section of the review will focus on RBC transfusion in the ICU. Emphasis will be placed on indications, efficacy, risks, and implementation of evidence-based practice.

Red blood cell transfusion: indications
Clinical practice guidelines for RBC administration were recently developed by a joint planning group with multi-specialty collaboration [1]. After thorough review of the literature, the only well established recommendation for RBC transfusion remains acute hemorrhage with hemodynamic instability or inadequate oxygen delivery. In the absence of major bleeding, conservative transfusion practices (maintain hemoglobin > 7 g/dl) are recommended.
for nearly all other critically ill populations, including trauma, those requiring mechanical ventilation, and those with stable cardiac disease [1].

A possible exception to conservative RBC transfusion practice is in the early phases of local or global tissue ischemia as seen in patients with acute coronary syndrome (ACS) and severe sepsis/septic shock. Regarding the former, evidence suggesting an appropriate transfusion threshold remains conflicting and inconclusive [1]. Nonetheless, available data support RBC transfusion at a slightly higher hemoglobin concentration (≤8 g/dl) [4]. Similarly, the RBC transfusion threshold in patients with severe sepsis or septic shock is poorly defined. Although current guidelines suggest a liberal transfusion practice in the acute phase of sepsis resuscitation (hematocrit ≥30 as needed to achieve an ScvO₂ ≥70%) [5]; these recommendations are based on a single-center study [6] which was not specifically designed to address transfusion practice.

Red blood cell transfusion: efficacy

Few studies outside the setting of acute hemorrhage have shown meaningful benefit with RBC transfusion [1,7]. Despite the intention to increase end-organ oxygen utilization, multiple evaluations have failed to identify an increase in this endpoint with the administration of allogeneic RBCs [8]. Whereas the timing of intervention (early vs. late after shock onset) may explain some of the conflicting results [6,9], the adverse microcirculatory effects of stored RBCs provide additional explanation. Rapid decline in S-nitrosohemoglobin concentrations and reduced red cell deformability have been proposed as potential mechanisms of microcirculatory occlusion and resultant tissue ischemia [8].

Red blood cell transfusion: risks

Concern over the potential transmission of blood-borne pathogens such as human immunodeficiency virus (HIV) has led to a heightened awareness of the risks associated with allogeneic RBC transfusion. Chief among these concerns are the association of RBC transfusion with infection [7], pulmonary complications such as TRALI [10,11] and transfusion-associated circulatory overload (TACO) [12], multiorgan failure [13], and risk-adjusted mortality [14,15]. Whereas the causative factors associating transfusion with adverse outcomes remain poorly defined, much interest has been placed on the issues of a RBC storage lesion and transfusion-related immune modulation (TRIM).

The various changes that occur within both the RBC and storage media during ex-vivo preservation have been collectively termed the RBC 'storage lesion' (Fig. 1). These alterations can be extensive and are primarily classified into three broad categories: biochemical, biomechanical, and immunologic [16]. Reduced accumulation of inflammatory cytokines achieved by prestorage leukoreduction has decreased the incidence of febrile reactions associated with transfusion of stored RBCs. However, other changes related to the storage lesion have not been impacted by prestorage leukoreduction, and the overall clinical significance of this procedure remains unclear. Recently, Koch and colleagues [14]...
performed a large, single-center, retrospective review of RBC transfusion in patients undergoing cardiac surgery. When compared to those who received fresh blood (\(<14\) days old), patients who received older blood (\(>14\) days old) had a higher rate of in-hospital mortality (1.7 vs. 2.8\%, \(P = 0.004\)). However, concerns over the unequal distribution of patients who received massive transfusion tempered the results of this study. Although several additional studies have suggested the presence of higher mortality with increasing RBC storage age, findings to the contrary exist as well [17]. Prospective clinical trials comparing conventional vs. fresh (\(<7\) days old) RBC transfusion are currently under way.

Allogeneic RBC administration has also been noted to have profound affects on recipient immune function, a condition known as TRIM. Substantial epidemiologic evidence associates TRIM with an increased risk for nosocomial infections [7]. This association has been noted in multiple surgical populations in addition to those who are critically ill. Interestingly, recent evidence suggests a diminution of the association between RBC transfusion and adverse outcome [18]. This shift has been postulated to be the result of a move to leukoreduced blood [19] and is supported by a randomized controlled trial comparing cardiac surgery patients who received nonleukocyte-reduced RBC transfusions to patients who received leukocyte-reduced RBC product [20]. In this investigation, transfusion with leukoreduced RBCs was associated with fewer postoperative infections and reduced hospital mortality. Although substantial evidence supports the use of leukoreduced blood in cardiac surgery, these findings have not been consistently reproduced in other populations [21].

**Implementation of evidence-based transfusion in the intensive care unit**

Despite the growing body of literature suggesting a lack of efficacy with RBC administration in most clinical situations, approximately 40–50\% of patients admitted to the ICU will receive at least 1 allogeneic RBC unit [1]. The mean number of RBC transfusions per ICU patient is estimated to be 5 units with the average pretransfusion hemoglobin being 8.5 g/dl [1]. Interestingly, it has been shown that fewer than one in five patients are transfused for active bleeding [1] with most transfusions simply being for a low hemoglobin level [22]. Education, feedback and the use of simple decision support tools have had remarkable success in reducing inappropriate transfusion in the ICU [23].

**Fresh frozen plasma**

This section of the review will address plasma administration in the ICU. Though multiple plasma products exist, we will focus on the most commonly administered plasma product, fresh frozen plasma (FFP). We will specifically address indications, efficacy, and risk.

**Fresh frozen plasma: indications**

Each year, more than 3 million units of FFP are transfused in the US alone [24]. Despite efforts to educate care providers and limit the number of inappropriate plasma transfusions, FFP utilization continues to increase. In light of the limited number of indications for FFP administration (given below), much of this use appears to lack evidence-based support.

Evidence-based indications for FFP administration:

1. Replacement of inherited single coagulation factor deficiencies for which no virus-safe fractionated product exists [25].
2. Replacement of specific protein deficiencies such as C-1 esterase inhibitor [26].
3. Replacement of multiple coagulation factor deficiencies with associated severe bleeding and/or disseminated intravascular coagulation [25].
4. As a component of plasma exchange in patients with thrombotic thrombocytopenic purpura [25].
5. Reversal of warfarin anticoagulation when severe bleeding is present and prothrombin complex concentrates are not available [25].
6. Prevention of dilutional coagulopathy in patients with major trauma and/or massive hemorrhage [27].
7. Prevention of bleeding in patients with advanced liver disease and prolonged coagulation tests who are planned to undergo an invasive procedure [25].

Indeed, recent estimates indicate that at some institutions, up to 83\% of FFP transfusions do not follow published guidelines [28]. In the US, the most common reason for FFP administration is an attempt to normalize an elevated preprocedural international normalized ratio (INR) [29]. Importantly, available evidence does not support this practice. In contrast, FFP administration in the setting of massive bleeding is often delayed and inadequate, promoting dilutional coagulopathy, need for massive transfusion, and potentially catastrophic consequences [27].

In the ICU, the three primary indications for FFP include the replacement of multiple coagulation factor deficiencies with associated severe bleeding, disseminated intravascular coagulation, and the prevention of dilutional coagulopathy in patients with major trauma who require massive transfusion (discussed below) [25]. FFP is not indicated in patients with isolated coagulation factor deficits for which specific factor concentrates are available. Additionally, the use of FFP to reverse the effect of anticoagulation is generally not recommended [30]. In the absence of bleeding or need for emergent
This discordance is largely explained by the nonlinear, exponential relationship between clotting factor levels and coagulation test results (Fig. 2) [29]. As the ability to form in-vivo thrombus is dependent on actual coagulation factor levels, these finding are significant. One must also appreciate that whereas FFP administration often normalizes a markedly elevated INR, coagulation factor levels rise and associated bleeding risk falls only modestly (Table 1) [34]. Furthermore, multiple studies have noted an inability of FFP to correct INR values ranging from 1.1 to 1.85 [28,32]. This lack of efficacy is in part explained by the INR of an FFP unit, which is frequently on the upper limits of normal or even beyond the normal range [28]. Thromboelastography (TEG) is an attractive alternative to traditional coagulation screening tests which may better reflect in-vivo clotting activity [35].

**Fresh frozen plasma: risks**

The three most notable complications with plasma transfusion include allergic reactions, TACO and TRALI. Allergic reactions can vary in severity from mild pruritus to anaphylaxis with the latter being extremely rare. Although also believed rare, TACO has an estimated incidence of 1–11% of patients transfused. This incidence is almost certainly an underestimate due to poor syndrome recognition and under-reporting. TACO develops quickly, typically within minutes to hours of transfusion and usually in patients with already compromised cardiac function and volume overload. Prompt volume reduction with diuresis typically results in rapid improvement, but ventilatory support may be needed. The associated mortality is reported between 5 and 15% [36]. In patients at risk for TACO (e.g. reduced left ventricular systolic function, diastolic dysfunction, renal failure, pre-existing volume overload), reduced transfusion rates and diuretic administration are recommended. TRALI will be discussed in detail later in this review.

### Table 1 Changes in the vitamin K-dependent clotting factors and international normalized ratio following the administration of approximately 800 ml fresh frozen plasma in warfarin-treated patients

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All clotting factor values in IU/dl. Modified from Makris et al. [34].
Platelets
This section of the review will address platelet use in the ICU. We will specifically focus on indications, transfusion thresholds, and risks associated with platelet component therapy.

Platelets: indications
Indications for platelet transfusion include thrombocytopenia and platelet function disorders [37]. Although inherited disorders are very rare, thrombocytopenia is frequently encountered in the ICU. It has been estimated that more than 40% of patients requiring ICU care will have a platelet count below 150 × 10⁹/l at some point during their ICU stay and greater than 25% will have a platelet count below 100 × 10⁹/l [38,39]. Furthermore, the presence of thrombocytopenia in the ICU has been associated with major bleeding, increased ICU and HOS length of stay, and mortality.

The most frequent clinical indication for platelet transfusion in the ICU is prophylaxis for presumed bleeding risk in the setting of thrombocytopenia [40,41]. This is followed closely by transfusion for active bleeding and prophylaxis for a planned invasive procedure. Whereas evidence suggests bleeding risk is minimal when the platelet count exceeds 50 × 10⁹/l, risk is believed to increase dramatically when platelet counts fall below 10 × 10⁹/l [37]. Importantly, the characterization of bleeding risk associated with thrombocytopenia has been performed primarily in patients with bone marrow failure and compromised thrombopoiesis. This precludes an accurate estimation of bleeding risk in most ICU populations and presents an opportunity for meaningful future research.

Platelets: transfusion thresholds
Although evidence suggests that the platelet count triggering platelet transfusion in the ICU most often ranges from 40 to 50 × 10⁹/l [39], Cameron et al. [41] described a more liberal transfusion practice in the perioperative setting with an average pretransfusion platelet count of 85 × 10⁹/l in patients having noncardiac surgery and 102 × 10⁹/l in patients undergoing cardiopulmonary bypass. We emphasize that whereas platelet dysfunction is clearly present in patients undergoing cardiopulmonary bypass surgery, it is not believed to increase their risk of bleeding when compared to other surgical populations [41]. Indeed, with the exception of patients with massive bleeding, higher transfusion thresholds (> 50 × 10⁹/l) are generally difficult to justify.

Randomized controlled trials provide guidance on appropriate platelet transfusion thresholds in patients with leukemia or bone marrow failure due to chemoradiation or other hematologic disorders [42]. In this setting, a transfusion threshold of 10 × 10⁹/l has been shown to be well tolerated. Unfortunately, the presence of multiple comorbid conditions, coexisting bleeding diatheses, and need for invasive procedures in ICU populations prevents generalization of these study results. Furthermore, the available evidence evaluating prophylactic platelet transfusion in the critically ill are conflicting [38,43], further preventing definitive recommendations.

While recognizing these limitations, current guidelines for patients with disseminated intravascular coagulation (DIC), massive bleeding, or need for invasive procedures suggest a platelet transfusion threshold of 50 × 10⁹/l. Still higher thresholds (100 × 10⁹/l) are recommended for specific surgeries with heightened concern for perioperative bleeding (neurosurgery and ophthalmic surgery) [44]. We emphasize that these thresholds are based primarily on expert opinion and the treatment of bleeding or its prophylaxis in patients with disorders of platelet number or function remains a matter of debate [37]. Indeed, it maybe prudent to avoid prophylactic strategies altogether, transfusing platelets for thrombocytopenic patients only when there is evidence of active bleeding [45,46]. If prophylactic platelet transfusion is pursued, recent data suggest low-dose transfusion can reduce the quantity of platelets transfused without increasing bleeding risk [47].

Platelets: risks
Importantly, platelet transfusions have been associated with worse outcome in certain critically ill populations [43]. As with FFP, platelets are high plasma volume products and share many of the same risks, including TRALI, TACO, acute hemolysis, and anaphylaxis [48]. A unique concern with platelet administration is transfusion-related sepsis [49] with bacterial contamination of platelets being the third leading cause of transfusion-related mortality [50]. Storage of platelets at room temperature provides a favorable environment for bacterial contamination with resultant septic transfusion [49]. This risk increases with duration of storage [49] and whereas more effective microbial testing strategies [48] have reduced the rate of this complication, a substantial false-negative testing rate persists [49]. Finally, platelet component therapy has also been associated with thrombotic complications such as acute in-stent thrombosis [51].

Massive transfusion
Hemorrhage lags only neurologic injury as the second leading cause of death in patients sustaining major trauma [52]. Importantly, uncontrolled hemorrhage can propagate the lethal triad of coagulopathy, acidosis, and hypothermia and each of these abnormalities can exacerbate the others. If left uncorrected, there is a progressive deterioration in each parameter leading to additional bleeding, greater transfusion requirements, and ulti-
recently noted a substantial fall in lung ne-

Intravenous fluids

10

TRALI is defined as new acute lung injury (ALI) occur-

Transfusion-related acute lung injury

TRALI is defined as new acute lung injury (ALI) occurring within 6 h of transfusion, with clear temporal relationship to transfusion, in patients with (possible TRALI) or without (TRALI) additional risk factors for ALI [61]. It is now recognized as the leading cause of mortality associated with blood transfusion [62]. Although all blood products can lead to this serious complication, high plasma volume products such as FFP and platelets carry the greatest risk [62,63]. Stainsby and colleagues [64] recently noted that TRALI occurs 5–6 times more frequently with high plasma volume components when compared to RBCs. Interestingly, the majority of reported deaths resulting from TRALI follow administration of a single unit of FFP [65].

The association of platelet administration with TRALI is also strongly supported by both preclinical [66] and clinical data [62,67–69]. The intriguing work of Looney et al. [66] recently noted a substantial fall in lung neutrophil sequestration and subsequent TRALI when animals were rendered thrombocytopenic prior to lipopolysaccharide (LPS) priming and an antimajor histocompatibility complex class I monoclonal antibody (anti-MHC I mAb) challenge (two-hit model of TRALI). In this same investigation, administration of antplatelet therapy prior to insult also provided lung protection. Of note, the liberal use of platelet components in patients requiring massive transfusion has not been consistently associated with increased risk of TRALI [3,54].

In 2001, Palfi and colleagues [70] noted a greater degree of hypoxemia and elevated levels of the inflammatory marker, tumor necrosis factor α, in critically ill patients who received plasma from multiparous female donors when compared to those who received male-donor plasma. We subsequently published similar findings [71] and multiple additional investigations have confirmed the association between alloimmunized donor status and risk of TRALI in the transfusion recipient [68,69,72,73]. Due to the primary role of antileukocyte antibodies in TRALI, new blood banking strategies have been adopted. In October of 2003, the UK National Blood Service recommended use of FFP and buffy coat-derived pooled platelet components from male donors only. Similar policy changes were subsequently introduced in the Netherlands and the US. Recently, Chapman and colleagues [62] reported the UK experience with their male-only donor policy. The results note an impressive fall in highly likely/probable TRALI due to both FFP and platelet transfusion. In contrast, a recently published retrospective database investigation challenges the change in plasma procurement strategy noting a lower frequency of respiratory complications in cardiac surgery patients receiving exclusively female donor plasma transfusion compared to a matched cohort who received exclusively male donor plasma [74]. A National Institutes of Health (NIH)-sponsored, prospective investigation being performed at the University of
California—San Francisco and Mayo Clinic will further define TRALI mechanisms and the effects of recent changes in donor procurement strategies.

Conclusion

The past two decades have witnessed an extensive re-evaluation of transfusion therapy in the ICU. Accumulating evidence refutes the efficacy of RBC, plasma, and platelet transfusion in the majority of critically ill patients. Simultaneously, investigations have increasingly exposed previously under-recognized transfusion risks such as nosocomial infection and TRALI. With the notable exception of acute blood loss, this improved understanding has led to recommendations for more conservative RBC, plasma, and platelet transfusion strategies. Importantly, numerous knowledge gaps persist. Well-designed prospective studies are needed to better define and characterize important issues such as the impact of RBC storage duration, transfusion-related immune modulation, and donor procurement procedures. Different transfusion strategies with particular focus on the timing of intervention and specific clinical endpoints need to be investigated in patients with major trauma and acute local or global tissue ischemia.

References


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