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Transfusion-related immunomodulation: review of the literature and implications for pediatric critical illness

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Abstract

Transfusion-related immunomodulation (TRIM) in the intensive care unit (ICU) is difficult to define and likely represents a complicated set of physiologic responses to transfusion, including both proinflammatory and immunosuppressive effects. Similarly, the immunologic response to critical illness in both adults and children is highly complex and is characterized by both acute inflammation and acquired immune suppression. How transfusion may contribute to or perpetuate these phenotypes in the ICU is poorly understood, despite the fact that transfusion is common in critically ill patients. Both hyperinflammation and severe immune suppression are associated with poor outcomes from critical illness, underscoring the need to understand potential immunologic consequences of blood product transfusion. In this review we outline the dynamic immunologic

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CONFLICT OF INTEREST

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response to critical illness, provide clinical evidence in support of immunomodulatory effects of blood product transfusion, review preclinical and translational studies to date of TRIM, and provide insight into future research directions.

Defining transfusion-related immunomodulation (TRIM) in critically ill patients is complicated by the underlying dynamic nature of the immune response to critical illness, variation in the timing of transfusion, number of transfusions received, variation in blood products transfused, and a myriad of additional immunomodulatory treatments often received in the intensive care unit (ICU). Early reports of TRIM in the 1970s stemmed from the observation that red blood cell (RBC) transfusion was associated with fewer episodes of organ rejection in renal transplant patients, implying an immunosuppressive effect of transfusion.[1] On the other hand, subsequent studies have attributed a number of proinflammatory effects to blood transfusion.[2–4] These seemingly incompatible findings may be explained by blood product–specific, host-related, and other contextual influences at the time of transfusion including the highly dynamic immunologic response to acute illness itself. Changes in blood banking practices over the last decade, including the adoption of near-universal prestorage leukoreduction, have likely changed the epidemiology and indeed the pathophysiology of TRIM. Furthermore, inflammation and immune function in pediatric and adult critical illness is now known to be more complex and dynamic than previously thought. Together, these observations provide impetus for a reevaluation of TRIM, both to place transfusion immunobiology in a modern ICU context and to highlight important research priorities in this rapidly changing field.

The dynamic immune response to critical illness

The need for a more comprehensive understanding of the immunologic effects associated with transfusion in critically ill children is underscored by recent data that suggest that the immunobiology of critical illness is far more variable than previously thought. Many of the events inciting critical illness are rooted in an amplified inflammatory response—or systemic inflammatory response syndrome. It is increasingly apparent, however, that this initial response is commonly accompanied by an overly robust compensatory anti-inflammatory response syndrome, which leads to a significant critical illness-induced immune suppression. Restoration of immunologic homeostasis, with resolution of both the systemic inflammatory response syndrome and the compensatory anti-inflammatory response syndrome states, is an important goal of treatment (Fig. 1). This is evidenced by the fact that high systemic levels of proinflammatory mediators such as interleukin (IL)-6 and IL-8 and elevations in anti-inflammatory cytokines such as IL-10 have all been associated with increased risks for secondary infection or death from critical illness in both adults and children.[5–10]

Critical illness-induced immune suppression, termed “immunoparalysis” in its most severe form, can affect both the innate (e.g., neutrophil, monocyte, macrophage) and the adaptive (e.g., lymphocyte) arms of the immune system. This form of acquired immunodeficiency can be quantified with laboratory measures that have been used in single- and multicenter studies of immune function in critical illness. From the innate immune perspective, the two

assays most often associated with ICU outcomes are monocyte human leukocyte antigen (HLA)-DR expression and ex vivo lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF)-α production capacity. HLA-DR is an important antigen presenting molecule that should be highly expressed on more than 90% of circulating monocytes. In the immunoparalyzed state, monocyte HLA-DR expression is markedly down regulated.[11–14] Another characteristic of the immunoparalyzed monocyte is diminished proinflammatory cytokine response to a standardized ex vivo LPS challenge. Healthy innate immune cells should produce large quantities of TNF-α upon ex vivo LPS stimulation. Markedly and persistently reduced whole blood ex vivo LPS-induced TNF-α production capacity predicts increased risks for secondary infection or death in the adult and pediatric ICU (PICU).[6,8,12,15,16]

Adaptive immune suppression has also been clearly identified as a risk factor for adverse ICU outcomes. Severe and prolonged lymphopenia, along with lymphocyte apoptosis in lymphoid organs such as the spleen, are strongly associated with adverse outcomes in adult and pediatric sepsis.[17–19] Further, lymphocyte hyporeactivity to ex vivo stimulation, with reduced interferon (IFN)-γ production in response to incubation with phytohemagglutinin or anti-CD3, has been demonstrated in adult sepsis nonsurvivors as well as in children with adverse infectious outcomes from sepsis.[17,20]

Mechanisms of critical illness-induced immune suppression are unclear, but are almost certainly multifactorial with host, environmental, and treatment-related factors all likely contributors. For instance, while specific genotypes have not been identified that confer increased risk for immunoparalysis in the setting of critical illness, strong evidence for both heritable and epigenetic factors exist.[15,21] Interplay between proinflammatory and anti-inflammatory mediators likely exists, wherein immunoparalysis has been reported in patients with many forms of “proinflammatory” critical illness including sepsis, trauma, multiple organ dysfunction syndrome (MODS), critical viral infections, cardiopulmonary bypass, and pancreatitis. It appears, however, that certain inflammatory insults, such as *Staphylococcus aureus* infection, confer particularly high risk for development of immune suppression.[6] Additionally, many of the treatments employed in the PICU are intentionally immunosuppressive, including glucocorticoids, antineoplastic agents, and transplant rejection prophylaxis. Moreover, immunomodulatory side effects are common in the ICU pharmacopeia, including antimicrobials, catecholamines, sedatives, and diuretics, with the bulk of these effects being immunosuppressive.[22]

It is in this context that TRIM in the ICU must be considered, with weight being given to both proinflammatory and immunosuppressive effects of transfusion. Depending on the patient’s genetic background, diagnosis, comorbidities, severity of illness, and timing of transfusion, the immunologic effects of a given transfusion may be difficult to predict. However, it can be expected that ICU patients may be more sensitive to immunomodulatory mediators in blood products because of their background immune dysregulation. As transfusion remains a common occurrence in the PICU, particularly in children with high severity of illness, it is important to understand the contribution of transfusion to systemic inflammation and to critical illness-induced immune suppression.

Epidemiology of transfusion in the PICU

Published rates of RBC transfusion among critically ill children vary from 49% among children admitted to the PICU for more than 48 hours to between 6.8 and 17% when considering all PICU admissions.[23–26] Compared to nontransfused patients, those receiving RBC transfusion tend to be sicker, with higher pediatric logistic organ dysfunction (PELOD) scores and incidence of multiple organ dysfunction being independently predictive of transfusion status.[24,25]

Regarding plasma transfusion, Karam and colleagues[27] recently published the most comprehensive-to-date study of the epidemiology of plasma transfusion in critically ill children. Among all children admitted to 103 included PICUs over 6 study weeks, a relatively low percentage of children (3.4%) received plasma. However, the mortality rate for the 443 children who received at least one plasma transfusion was as high as 27%, suggesting that children who receive plasma represent a cohort with high severity of illness. Very little is known about the epidemiology and outcomes associated with platelet (PLT) transfusion in the PICU, representing an important gap in the literature.

Clinical evidence suggesting TRIM in the ICU

In multiple observational studies, RBC transfusion is independently associated with adverse outcomes in hospitalized patients.[28] However, because sicker patients tend to receive transfusions, these observational studies are often limited by confounding by indication. Consequently, several prospective randomized controlled trials in adults across a variety of clinical settings have compared restrictive versus liberal transfusion strategies and have demonstrated either improved outcomes in restrictive-group subjects or lack of benefit in the liberally transfused.[29–34] Several meta-analyses have since been performed and support the finding that a restrictive transfusion strategy appears to be safe in most settings, with no obvious benefit to liberal transfusion practices.[35–38]

Similar to adult studies, retrospective studies in critically ill children identify RBC transfusion as an independent risk factor for morbidity and mortality.[39,40] In prospective, multicenter observational study by Bateman and colleagues,[23] after controlling for age and severity of illness, RBC transfusion was independently associated with longer mechanical ventilation, cardiopulmonary dysfunction, PICU stay, and mortality. In 2007 Lacroix and coworkers[41] published a prospective randomized controlled trial of transfusion strategies in pediatric critically ill patients that demonstrated that a restrictive transfusion strategy decreased RBC transfusions without increasing the incidence of new or progressive MODS.[41] Subgroup analyses from this trial showed similar results in children after surgery or cardiac surgery and those with sepsis.[42–44] Two additional prospective randomized trials in pediatric cardiac surgery, also examining hemoglobin (Hb) thresholds, found no benefit to liberal transfusions even in this high-risk population.[45,46] Whether the lack of apparent benefit from liberal transfusion strategies stems from a lack of efficacy or from an increase in transfusion-related risk remains unclear and continues to be a topic of debate.[47–50]

Potential risk may arise from immunomodulation related to RBC transfusion. Multiple analyses link RBC transfusion to infection risk in the ICU, suggesting that RBC transfusion may be associated with immune suppression. Earlier adult studies identified an association between infections and nonleukoreduced RBC transfusions, with more recent studies—using leukoreduced transfusions—confirming these results.[28,51–55] Variations in storage duration and volume transfused drew criticism of these studies.[56] However, when volume of transfusion is controlled for, the association between postoperative infection and RBC transfusion is supported.[57,58] Meta-analyses in postoperative and medical patients comparing transfused versus nontransfused adults demonstrates increased risk for nosocomial infections in transfused patients.[59–62] Large meta-analyses of medical and surgical patients randomized in restrictive versus liberal RBC transfusion trials demonstrate significantly reduced risks for health care–associated infections in those managed with a restrictive transfusion strategy.[37,38,63]

Critically ill children are also at risk for hospital-acquired infections, and RBC transfusions may increase this risk.[64,65] Critically ill children with sepsis managed with a restrictive transfusion strategy had significantly fewer cases of nosocomial infection than liberally managed patients.[42] Children with significant burn injuries receiving high numbers of blood transfusions were at increased risk for development of sepsis.[66] Additionally, transfused children after cardiac surgery had higher incidence of ventilator associated pneumonia and postoperative infections.[67,68]

RBC transfusions in critically ill children are also associated with MODS and transfusion-associated respiratory complications, including respiratory dysfunction, transfusion-related acute lung injury, and transfusion-associated circulatory overload.[69–73] Like TRIM, these transfusion complications are likely the result of transfusion in a susceptible host under certain circumstances (two-hit phenomenon). They are also likely to be mediated by immunologic mechanisms.

Storage duration of the RBC unit may impact immune function in critically ill children, with longer storage duration of transfused RBCs associated with increased risks for postoperative infection, MODS, and hospital length of stay.[74–76] While transfusion with shorter-storage RBCs has not been shown to improve outcomes in randomized trials in adults, premature neonates, or children with severe anemia, the ongoing Age of Blood in Children in Pediatric ICU (ABC-PICU) trial (NCT01977547) may shed light on this question in critically ill children.[77–80] Notably, in the only studies to date evaluating immune function after RBC transfusion in critically ill or injured children, older prestorage leukoreduced RBCs were associated with persistent immune suppression and systemic inflammation compared to fresher RBCs.[8,81]

Taken together, these clinical studies strongly suggest some immunomodulatory effect of transfusion. Consequently, several preclinical and translational studies have been performed to try to define and clarify these effects.

Proinflammatory versus immune suppressive effects of transfusion

Preclinical studies demonstrate mixed immunomodulatory effects of RBC exposure, with results suggesting both proinflammatory and immune-suppressive effects (Table 1). Investigations to date are heterogeneous with variation in blood product studied and model utilized, limiting direct comparison of effects. In studies suggesting a proinflammatory effect using murine and in vitro neutrophil models, stored RBCs resulted in greater induction of proinflammatory cytokines compared to fresh RBCs, with effects more often seen when nonleukoreduced RBCs were used.[76,82–85,87] Studies evaluating immune-suppressive effects are more heterogeneous. Studies to date have used various in vitro immune cell models (including monocytes, lymphocytes, natural killer [NK] cells, and neutrophils), neutrophil chemotaxis models, and murine tumor models.[88–95] These studies likewise suggest that suppression of immune cell function may be associated with RBCs of longer storage duration or nonleukoreduced RBCs. For instance, murine tumor suppression models suggest that there is less tumor progression after exposure to fresh RBCs or leukoreduced RBCs when compared to stored RBCs.[94,95] On the other hand, more recent studies suggest that even when leukoreduced, stored RBC products can directly suppress monocyte or lymphocyte function in vitro.[90,93] However, findings are not consistent, as some murine and ex vivo studies report mixed or even no effect on inflammatory markers.[76,86] In this way TRIM may be analogous to RBC alloimmunization, whereby immunologic consequences of transfusion are highly variable and likely host and/or context specific. Overall, the evidence to date suggests that RBC transfusion has important immune modulatory effects in vitro and in animal models, but the clinical impact of these experimental effects remains to be determined.

Studies investigating immunomodulatory effects of PLT and plasma products are fewer and mostly limited to preclinical models. Similar to RBC studies, PLT products have demonstrated both proinflammatory and immune-suppressive effects. This is perhaps not surprising given emerging evidence that PLTs themselves may play important roles in activating and modulating the innate inflammatory response.[96,97] On the proinflammatory side, PLT products may increase immune cell cytokine production and neutrophil activity.[98,99] By contrast, Aslam and colleagues[100] demonstrated an immunosuppressive phenotype dependent on PLT major histocompatibility complex Class I expression with fresh but not 72-hour-stored PLTs in a murine transfusion model. Similarly, PLT products have been shown to suppress dendritic cell function in in vitro models.[101] Limited data suggest that pathogen reduction technologies may mitigate some PLT-associated TRIM effects, although further study in this area is certainly needed.[99,102] Data regarding immunomodulatory effects of plasma products are even fewer. In a single in vitro study, allogeneic fresh-frozen plasma suppressed innate immune cell function as measured by LPS-induced cytokine production.[103]

Clinical studies on immunologic effects of RBC transfusion have been executed in a variety of patient populations (Table 2). The majority of studies have limited sample size and are observational, describing effects of RBC transfusion in a “before–after” design. Contrasting results are reported, including both immune-stimulatory as well as immune-suppressive effects. On the proinflammatory side, nonleukoreduced RBC products were used in most

studies demonstrating increases in posttransfusion cytokine levels.[106–109] One observational study in neonates using leukoreduced RBC found mildly elevated plasma levels of select proinflammatory cytokines 2 to 4 hours posttransfusion.[105] Notably, a relatively large randomized controlled trial comparing leukoreduced with white blood cell (WBC)-containing, buffy coat–depleted RBCs in adult cardiac surgery patients suggested that in the heavily transfused patients (needing > 4 units), WBC-containing blood products induced a stronger proinflammatory response.[107] Taken together, these data suggest that proinflammatory responses observed after RBC transfusion may be largely mitigated by leukoreduction.

By contrast, the studies that found no effect, mixed effects, or immune-suppressive effects associated with RBC transfusion largely employed leukoreduced RBC products.[8,81,110–112,114,115] Immunosuppressive effects of transfusion have been studied most often in surgical patients.[51,113,115] Whether these patients are more prone to immunosuppressive effects of RBC transfusion, or that other patient populations are understudied, is not clear. Different immunosuppressive effects of transfusion have been observed, including decreased ability of immune cells to produce proinflammatory cytokines, increased production of anti-inflammatory cytokines, and decreased function of T lymphocytes and NK cells.[8,51,113–115] Effects of storage duration in the context of RBC TRIM are unclear, with some studies indicating a storage effect, while others do not. Among critically ill children, observational data suggest that transfusion with RBCs of longer storage duration may be immunosuppressive, although these studies are currently limited by small sample size.[8,81] Further delineating potential storage-related effects on transfusion-related immune suppression remains an active area of investigation. Similarly, the precise mechanisms of immunosuppressive effects of RBC transfusion are not well understood and require further study.

Does TRIM exist in the ICU population?

Answering the question of whether or not TRIM exists is not an easy task. An in-depth review of epidemiologic, preclinical, and clinical studies reveal conflicting evidence for the existence of TRIM. Clearly one of the major obstacles to measuring effects of TRIM is the magnitude and variability of background immune modulation seen in ICU patients, independent of transfusion. Several (but not all) studies point to increased risk of infection after RBC transfusion, and while these data support an immunosuppressive TRIM effect, increased non–transferrin-bound iron may also provide an alternative explanation for increased infection after RBC transfusion, particularly after receipt of older units.[87] Animal models show varied effects of TRIM depending on the model or immune cell tested. In our review, approximately twice as many animal studies showed immune-suppressive effects of transfusion compared to immune activation, although approximately one-third of published studies showed mixed or no immune effects of transfusion. Human studies showed a more balanced pro- vs. anti-inflammatory effect of transfusion, again with approximately one-third of published studies showing mixed or no immune effects of transfusion. Given the mixed results of both preclinical and clinical studies, it is tempting to conclude that TRIM does not exist or if it does occur the effects must be small compared to other insults patients face in the ICU setting. The answer is probably more complex, as there are likely both

proinflammatory and immune-suppressive effects mediated by transfusion, and the balance of how these forces influence an individual patient will depend on the underlying physiology, age and comorbidities of the patient, the timing of transfusion, and the individual blood product(s) used. Understanding these interactions is important because RBC transfusion represents a potentially modifiable factor among the many potential mediators of immunologic dysregulation in the PICU.

Not all blood components are equivalent

Confounding most studies examining the potential immune modulatory activity of blood components is the growing recognition that blood donor variability (age, sex, race) and differences in blood component manufacturing can have a significant impact on the levels of pro- and anti-inflammatory molecules in transfused products.[116–119] When different methods for the production of a RBC product were directly compared, enormous variability in immune modulatory agents including residual PLTs and WBCs, free Hb levels, extracellular vesicles, cell-free DNA, cytokines, growth factors, and lipid mediators were seen.[117,119] While the length of storage of RBC products continues to be explored in randomized clinical trials, studies are now under way to examine the effect that donor factors and RBC component manufacturing may have on patient outcomes.[120] In addition, plasma components have also been shown to have significant differences in levels of residual cells and extracellular vesicles depending on the method of manufacturing, and it is not inconceivable that similar observations will be made when different PLT products are evaluated.[121] What is becoming clear is that it is no longer appropriate to consider all RBC, PLT, or plasma products used in transfusion as being equivalent, and care should be taken to understand which products are being used when evaluating the immune modulatory effect of transfused blood components.

Can studies be performed to measure immunologic consequences in the transfused critically ill child?

As noted, one of the biggest impediments to measuring immune-modulatory effects of transfusion is the heterogeneity of transfused patient populations and their underlying state of immune activation and competence. Indeed, a given blood product that may confer minimal risk in one critically ill child has the potential to confer substantial risk in another. Our understanding of how this risk is mediated, however, and how to mitigate it at the ICU bedside is rudimentary at best. Observational studies comparing transfused to nontransfused populations are limited by the fact that patients who receive transfusions are likely sicker than those who do not, introducing a confounding by indication bias which is difficult to overcome. However, the field of transfusion medicine may face an opportunity to study TRIM effectively in the near future. Further formal study of appropriate RBC transfusion “thresholds” for various patient populations are planned, as noted at the recent NIH State of the Science Symposium.[122] Collection of biologic specimens in patients randomized to receive RBC transfusions or not would allow objective laboratory comparisons of immune function in these subjects, data that have been lacking to date. Incorporating comprehensive, longitudinal immunophenotyping into such a randomized trial would provide valuable

information that could never be obtained through observational studies. Ideally, the design of these trials would be informed by greater understanding of TRIM mechanisms, including patient-related and individual blood product–related risk factors. This therefore demands a more comprehensive understanding of the fundamental biology of TRIM, importantly placing transfusion in the physiologic context of the critically ill child. Only in this way can we begin to identify which blood products may have the potential for harm in a given individual. A multidisciplinary approach, spanning the spectrum of basic, translational, and clinical research methodologies, may well be required to accomplish this important task.

How does one define TRIM in the PICU? The answer to this question will likely be complex. In fact, immunomodulation associated with transfusion may not be a single entity, but may represent multiple context-specific effects—both proinflammatory and/or immunosuppressive. As stated, much more work is needed to understand the full spectrum of immunologic consequences in the transfused critically ill child.

ABBREVIATIONS:

ICU	intensive care unit
LPS	lipopolysaccharide
MODS	multiple organ dysfunction syndrome
PICU	pediatric intensive care unit
TRIM	transfusion-related immunomodulation

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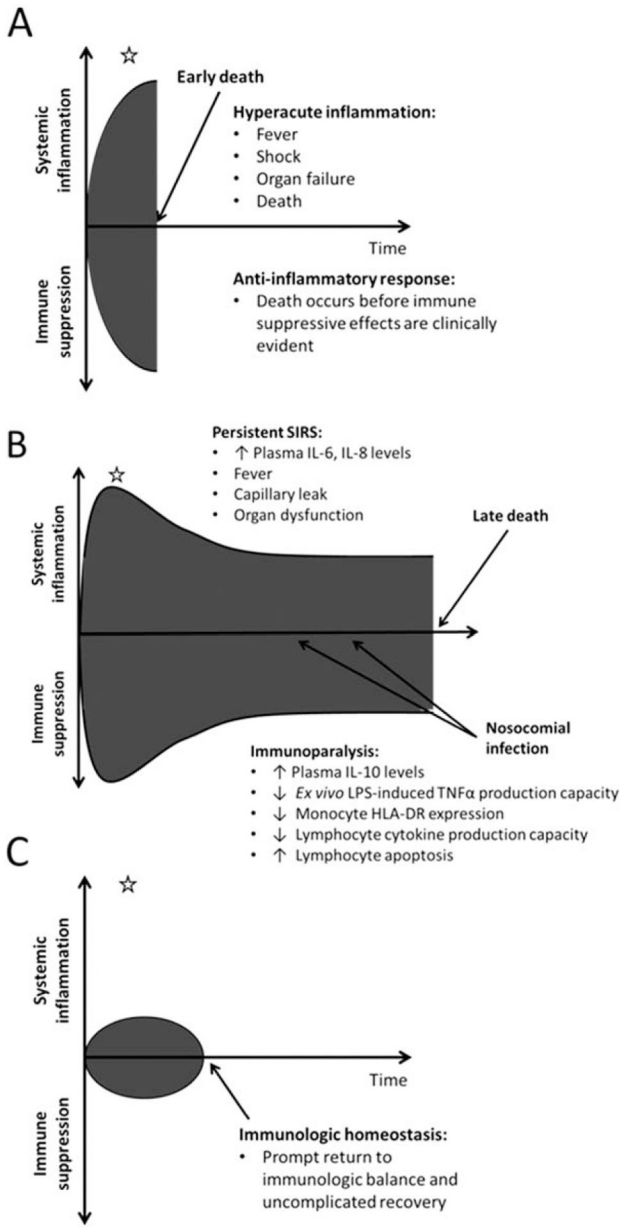

Fig. 1.

The dynamic immune response to critical illness. Some patients experience severe hyperacute inflammation that results in early death before the immunosuppressive effects of the compensatory anti-inflammatory response can become clinically evident (A). Those who survive the initial proinflammatory insult can develop severe persistent immune suppression that is associated with increased risks for nosocomial infection and late death (B). An important goal of critical care management is to promote prompt restoration of immunologic homeostasis through resolution of systemic inflammation and normalization of immune function (C). The immunologic effects of a transfusion at a given point in time (white star) have the potential to be quite variable depending on the context, with some subjects being too ill to detect an effect (A), others being too well to have a clinical impact (C), and others

in a highly dynamic state where pro- or anti-inflammatory effects of transfusion could greatly influence overall immune function. SIRS = systemic inflammatory response syndrome.

TABLE 1.

Selected preclinical studies evaluating RBC TRIM

Model	Blood product(s)	Findings	Storage effect	Reference(s)
Proinflammatory effects				
Human cells				
In vitro neutrophil priming	RBCs, buffy coat–poor RBCs, LR	SN from RBCs but not buffy coat–poor or LR RBCs primed neutrophils, effect increased with storage time.	Yes	Sparrow et al.[82]
In vitro neutrophil priming and in vitro monocyte	Washed RBCs vs. LR RBCs	Neutrophil CD11b expression and monocyte IL-8 production increased. Mitigated by LR but not by RBC washing.	Not evaluated	Cardo et al.[83]
Animal models				
Murine transfusion	LR RBCs	Stored, but not fresh, RBCs induced IL-6, CXCL1, and MCP-1, reversed by concurrent fresh RBCs.	Yes	Hendrickson et al.[84]
Murine hemorrhagic shock and transfusion	Non-LR RBCs	Unwashed, stored RBCs induced IL-6, KC, MIP-1α, and MIP-2.	Yes	Belizaire et al.[85]
Mixed effects or no effect				
Human cells				
LPS-stimulated whole blood	Non-LR RBCs	RBC supernatant decreased LPS-induced TNF-α and increased IL-8 response.	Not evaluated	Patel et al.[86]
Ex vivo T-cell activation	LR RBC supernatants, variable storage duration	Increased IL-6, IL-10, decreased TNF-α. No change in CD25 expression.	Yes	Karam et al.[76]
Animal models				
Murine transfusion	LR RBCs	Stored but not fresh RBCs induced IL-6, KC, MCP-1, TNF-α, and MIP-1β and enhanced growth of *Escherichia coli*. No change in plasma IL-10 or IFN-γ.	Yes	Hod et al.[87]
Immunosuppressive effects				
Human cells				
Anti-CD3–stimulated PBMNCs	RBCs and LR RBCs	Supernatant from fresh and stored RBCs with or without LR induced Tregs and decreased cytokine response in CD3-stimulated PBMNCs.	No	Baumgartner et al.[88]
NK cells	RBCs	SN from stored but not fresh RBCs decreased NK-cell activity.	Yes	Ghio et al.[89]
LPS-stimulated monocytes	LR RBCs	RBCs and RBC supernatant decreased LPS-induced TNF-α but not IL-10 production.	Yes	Muszynski et al.,[90] Mynster et al.[91]
Ex vivo neutrophils	Non-LR vs. LR RBCs	Inhibition of neutrophil chemotaxis via synthesis of TGF-β after exposure to non-LR RBCs.	Not evaluated	Ottonello et al.[92]
Stimulated T cells	Older vs. fresh LR RBCs	Decreased T-cell proliferation, IL-10, IL-17a, IFN-γ, TNF-α, GM-CSF production with stored RBC exposure.	Yes	Long et al.[93]
Animal models				

Model	Blood product(s)	Findings	Storage effect	Reference(s)
Murine tumor model	Whole blood vs. LR RBCs	Mice receiving whole blood but not LR blood had more tumors. Pre- but not post-storage LR removed the tumor enhancing effect of WB transfusion in rabbits.	Not evaluated	Bordin et al.[94]
Rat mammary adenocarcinoma model and leukemia model	RBCs	Aged RBCs promoted cancer progression.	Yes	Atzil et al.[95]

CXCL1 = chemokine (C-X-C motif) ligand 1; KC = keratinocyte chemoattractant; LR = leukoreduced; MCP = monocyte chemoattractant protein; MIP = macrophage inflammatory protein; PBMNC = peripheral blood mononuclear cell; PHA = phytohemagglutinin; SN = supernatant; TGF = transforming growth factor; Treg = regulatory T cell; WB = whole blood.

TABLE 2.

Selected clinical studies evaluating RBC TRIM

Population	Study design	Number	Blood product(s)	Findings	Storage effect	Reference
Proinflammatory effects						
Pediatric studies						
Critically ill children	Observational pre- vs. posttransfusion	100	LR RBCs	Overall no change in markers of inflammation, but elevated CRP in children with elevated markers of hemolysis posttransfusion	No	L'Acqua et al.[104]
Neonatal	Observational pre- vs. posttransfusion	28	LR RBCs	Increased plasma IL-1β, TNF-α, MCP-1, and IL-8 2 to 4 hr posttransfusion	Not evaluated	Keir et al.[105]
Adult studies						
Adult cardiac surgery	Observational	114	Non-LR RBCs	Higher postoperative plasma IL-6 and BPI levels in transfused vs. nontransfused	Not evaluated	Fransen et al.[106]
Adult cardiac surgery	Randomized controlled trial	346	Buffy coat–poor vs. LR RBCs	IL-6 levels higher in non-LR group only in those with >3 RBC units	Not evaluated	Bilgin et al.[107]
Nonhemolytic febrile reaction	Observational pre- vs. posttransfusion	81	Non-LR RBCs	IL-8 and IL-6 increased but not IL-1 and TNF-α	Not evaluated	Lin et al.[108]
Critically ill adults	Observational before and after transfusion	96	LR vs non-LR RBCs	RBC but not LR RBC induced leukocytosis, associated with increased IL-8 levels in product	Yes	Izbicki et al.[109]
Mixed effects or no effect						
Pediatric studies						
Neonatal	Observational	9	LR RBCs	No change in plasma IL-1β, IL-6, or IL-10 pre- vs. posttransfusion	Not evaluated	Locke et al.[110]
Critically ill children	Observational pre- vs. posttransfusion	31	LR RBCs	No difference in plasma cytokines, Treg, or monocyte function pre- vs. 24 hr posttransfusion. Suppressed monocyte function after older vs. fresher RBCs.	Yes	Muszynski et al.[81]
Adult studies						
Healthy adult subjects	Observational	14	LR RBCs	No change in plasma IL-6 or CRP with fresh or stored RBCs. Increased in vitro proliferation of *E. coli* after stored RBCs	Not evaluated	Hod et al.[111]
Adult cardiac surgery	Observational	29	LR RBCs	No difference in gene expression of 114 cytokines between transfused vs. nontransfused patients	Not evaluated	Sitniakowsky et al.[112]
Immunosuppressive effects						
Pediatric studies						
Pediatric trauma	Observational fresh vs. older RBCs	29	LR RBCs	Suppressed monocyte function over time in patients transfused older vs. fresher RBCs	Yes	Muszynski et al.[8]
Adult studies						

Population	Study design	Number	Blood product(s)	Findings	Storage effect	Reference
Adult postoperative colorectal	RCT unfiltered whole blood vs. LR blood	104	Whole blood vs. LR blood	Whole blood but not LR blood decreased NK-cell function	Not evaluated	Jensen et al.[51]
Adult abdominal surgery	RCT, liberal vs. restrictive transfusion	20	Non-LR RBCs	Higher IL-10 1 day postoperatively in liberal group	Not evaluated	Theodoraki et al.[113]
Adult trauma	Observational fresh vs. older RBCs	64	LR RBCs	Decreased IL-12, IL-23, RORγt gene expression with older RBCs	Yes	Torrance et al.[114]
Adult abdominal surgery	Observational	119	LR RBCs	Decreased TNF-α, IL-12, IL-23, RORγt gene expression; more infections in transfused	Yes	Fragkou et al.[115]

BPI = bactericidal permeability-increasing protein; CRP = C-reactive protein; LR = leukoreduced; MCP = monocyte chemoattractant protein; RORγt = retinoic acid-related orphan receptor-γt; Treg = regulatory T cell.