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NARRATIVE REVIEW

Transfusion in the mechanically ventilated patient

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Abstract

Red blood cell transfusions are a frequent intervention in critically ill patients, including in those who are receiving mechanical ventilation. Both these interventions can impact negatively on lung function with risks of transfusion-related acute lung injury (TRALI) and other forms of acute respiratory distress syndrome (ARDS). The interactions between transfusion, mechanical ventilation, TRALI and ARDS are complex and other patient-related (e.g., presence of sepsis or shock, disease severity, and hypervolemia) or blood product-related (e.g., presence of antibodies or biologically active mediators) factors also play a role. We propose several strategies targeted at these factors that may help limit the risks of associated lung injury in critically ill patients being considered for transfusion.

Keywords: Acute respiratory distress syndrome, Anemia, Hypervolemia, Inflammatory response, Oxygen delivery, Transfusion-associated circulatory overload, Transfusion-related acute lung injury

Introduction

Anemia is a hallmark of critical illness, eliciting the frequent administration of red blood cell (RBC) transfusion to critically ill patients. RBC transfusion in this setting can be beneficial (Table 1). Indeed, as arterial oxygen content (CaO_2) is a primary determinant of oxygen delivery (DO_2), RBC transfusion can be an effective way to increase DO_2 when there is impaired tissue perfusion. A recent review indicated that an increase in DO_2 after transfusion was associated with an increase in oxygen consumption (VO_2) [1]. This effect may also be helpful in severe hypoxemia, including in patients requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [2]. However, blood transfusions can also have important and even life-threatening complications (Table 1). In some patients, the benefits of RBC transfusion may outweigh its adverse effects and improve outcomes, but the conundrum is that there are currently no clear methods to determine which patients will benefit from an RBC transfusion and which patients are at risk of harm [3, 4]. Although the indications for transfusion are less liberal than in the past, one in four patients still receives a RBC transfusion during their intensive care unit (ICU) stay [5, 6]. Thus, RBC transfusion remains an important intervention in the ICU.

Transfusions are more often administered to the sickest patients [5], whom are also the most likely to be mechanically ventilated. Transfusion and mechanical ventilation can both contribute to the risk of acute respiratory distress syndrome (ARDS). These two interventions may be interrelated and act synergistically. This review summarizes this interrelation between mechanical ventilation, transfusion and ARDS and provides recommendations on how to prevent lung injury following transfusion of patients receiving mechanical ventilation. We will also consider some perspectives for the future.

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Table 1 Some of the main beneficial and harmful effects of red blood cell (RBC) transfusion

Benefit of RBC transfusion	Harm of RBC transfusion
Potential for improved oxygen delivery	Acute lung injury
Reduced microcirculatory derangements during shock	Acute fluid overload
Improved subjective wellbeing, decreased fatigue	Acute kidney injury
	Modulate host immune response
	Allergic and hemolytic reactions
	Bacterial contamination
	Transmission of diseases

Transfusion, ARDS and transfusion-related acute lung injury (TRALI)

Observational studies have consistently suggested an association between RBC transfusion and ARDS, in particular in the critically ill and in trauma patients [7, 8], in what appears to be a dose-dependent manner [9, 10], although this dose dependency requires more detailed analysis [11, 12]. In trauma patients, the risk of ARDS following large transfusion volumes has decreased during the past years, most probably due to improved damage control resuscitation strategies and more limited use of fluids. This suggests that the risk of ARDS in transfused patients is not only related to volume infusion, but also includes an interaction between transfusion, fluid resuscitation and other insults, such as mechanical ventilation, in a context of inflammatory lungs with pulmonary capillary leakage.

Take-home message

Along with several host factors, transfusion and mechanical ventilation can both contribute to the risk of acute respiratory distress syndrome (ARDS). Optimizing ventilator settings, avoiding hypervolemia and correctly treating sepsis and shock may help prevent the development of lung injury post transfusion.

The term TRALI is used when lung injury and hypoxemia that cannot be solely attributed to fluid overload develop within 6 h following transfusion. Clinically, TRALI is indistinguishable from ARDS due to other causes. In an effort to distinguish transfusion from other causes of ARDS, the TRALI definition was recently revised [13]. TRALI type I refers to patients in whom no temporal relation to another ARDS risk factor is present, and type II refers to patients in whom either another risk factor for ARDS is present, or who already have some degree of hypoxemia but who were stable for at least 12 h prior to transfusion (Table 2). Although this most recent TRALI classification includes a maximum of 6 h between transfusion and TRALI onset, the possibility of TRALI with a delay of 6 to 72 h after transfusion in mechanically ventilated critically ill patients has been proposed, and termed 'delayed TRALI' [14]. The reported incidence of TRALI in the ICU is around 1–15%, depending on the specific patient population [15, 16]; however, in a broader sense, estimates of the association between transfusion

Table 2 Criteria for transfusion-related acute lung injury (TRALI). Reproduced from [13] under the Creative Commons Attribution-NonCommercial-NoDerivs License

TRALI type I–Patients who have no risk factors for ARDS and meet the following criteria:		
a.	i.	Acute onset
	ii.	Hypoxemia ($PaO_2/FiO_2 \leq 300$[a] or $SpO_2 < 90\%$ on room air)
	iii.	Clear evidence of bilateral pulmonary edema on imaging (e.g. chest radiograph, chest CT, or ultrasound)
	iv.	No evidence of left atrial hypertension (LAH)[b] or, if LAH is present, it is judged to not be the main contributor to the hypoxemia
b.	Onset during or within 6 h of transfusion[c]	
c.	No temporal relationship to an alternative risk factor for ARDS	
TRALI type II–Patients who have risk factors for ARDS (but who have not been diagnosed with ARDS) or who have pre-existing mild ARDS (PaO_2/FiO_2 of 200–300), but whose respiratory status deteriorates[d] and is judged to be due to transfusion based on:		
a	Findings as described in categories a and b of TRALI type I, and	
b	Stable respiratory status in the 12 h prior to transfusion	

[a] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [(PaO_2/FiO_2) × (barometric pressure/760)]

[b] Use objective evaluation when LAH is suspected (imaging, e.g., echocardiography, or invasive measurement using e.g., pulmonary artery catheter)

[c] Onset of pulmonary symptoms (e.g., hypoxemia–lower P/F ratio or SpO_2) should be within 6 h of end of transfusion. The additional findings needed to diagnose TRALI (pulmonary edema on a lung imaging study and determination of lack of substantial LAH) would ideally be available at the same time but could be documented up to 24 h after TRALI onset

[d] Use PaO_2/FiO_2 ratio deterioration along with other respiratory parameters and clinical judgement to determine progression from mild to moderate or severe ARDS

and lung dysfunction in the critically ill appear to be as high as 43% [14, 17–19].

TRALI is mediated by the interaction of neutrophils with pulmonary endothelial cells [20]. TRALI depends on patient-related factors, such as mechanical ventilation and host factors, and blood product-related factors (Table 3). In general, host factors reflect the presence of an inflammatory reaction from any cause, which attracts neutrophils to the pulmonary compartment. These primed neutrophils, trapped in the lung's microvasculature, are functionally hyperactive. The transfusion acts as a second step, activating the primed neutrophils and resulting in endothelial damage, with ensuing pulmonary edema. Antibodies can result in TRALI, but many cases of TRALI are reported in which no antibodies are detected and in which the causative factor is not known.

All types of blood components have been associated with lung injury (Table 3). However, following implementation of "low risk TRALI donor" strategies including a male-only blood donation policy and donor deferral based on antibody screening and past history of pregnancy, TRALI following plasma transfusion has decreased substantially [21], rendering RBC transfusion the most common cause. TRALI mitigation efforts have also reduced the incidence of antibody-mediated TRALI secondary to apheresis platelet concentrate transfusion, and use of platelet additive solution has led to a decrease in TRALI secondary to buffy coat derived platelet concentrate [22]. However, there is evidence suggesting that non-immunologic TRALI following platelet transfusion is likely to remain an issue in the context of a steady increase in platelet concentrate exposure. First, pro-inflammatory biological response modifiers accumulate during platelet storage, which can induce neutrophil activation [23]. Second, an in vivo transfusion model showed that aged platelets induced lung injury [24].

Table 3 Risk factors for lung injury following transfusion reported in observational studies

Patient-related factors	Blood product-related factors
Mechanical ventilation	***Red blood cells***
Large tidal volume	HLA/HNA antibodies
High peak pressure	Biolipids
Duration of ventilation	sCD40L
Host factors	Duffy antigen
Disease severity (e.g., APACHE II score)	Extracellular vesicles
Hypervolemia	***Plasma***
Sepsis	HLA/HNA antibodies
Shock	Large volume
Cardiac surgery	***Platelets***
Hematologic malignancy	Extracellular vesicles
Alcohol abuse	sCD40L
Liver disease	Biolipids
Previous multiple transfusion	

Although the TRALI definition enables surveillance of transfusion reactions and stimulates homogeneity of transfusion research, it is important to understand that transfusion in the critically ill is also associated with pulmonary injury that does not meet full TRALI criteria. In experimental models, transfusion induces a pro-inflammatory and pro-coagulant host response in the lung [24, 25]. These data are underlined by findings in post-cardiac surgery patients, in whom transfusion of just 1–2 RBC units is already associated with increased pulmonary levels of pro-inflammatory cytokines [10]. Using a technique that detects pulmonary vascular permeability by measurement of labelled transferrin, pulmonary vascular permeability was shown to be increased in patients after cardiac surgery, probably due to an inflammatory condition following the use of cardiopulmonary bypass [26]. In these patients, a single RBC transfusion already increased pulmonary vascular permeability, with concomitant decreased oxygenation [26]. This study provides direct evidence that RBC transfusion is associated with increased pulmonary permeability. By contrast, other studies in hemorrhagic shock models suggest that fresh whole blood causes less lung injury and inflammation compared to lactated Ringers [27].

Transfusion and transfusion-associated circulatory overload (TACO) mimicking ARDS

A second transfusion-related respiratory complication that can mimic both TRALI and ARDS is TACO. Like TRALI, TACO appears more common in the critically ill and typically presents with bilateral pulmonary infiltrates with hypoxemia. The incidence of TACO is very difficult to define, but is likely similar to that of TRALI. In contrast to ARDS and TRALI, the pathophysiology underlying the lung edema of TACO is hydrostatic in nature [28–30]. Risk factors are conditions associated with an impaired ability to handle fluid loading with a blood product, including cardiac or renal disease [31]. However, in addition to volume, other aspects of the transfused blood component may also play a role [28]. Importantly, differentiating TACO, TRALI and ARDS remains challenging, particularly considering that more than one of these conditions may co-exist.

Transfusion and mechanical ventilation

Observational studies have suggested that following transfusion, ARDS occurs much more frequently in patients receiving mechanical ventilation than in other patients [17]. This risk of ARDS following transfusion is higher in patients receiving high tidal volumes compared

to patients ventilated with lower tidal volumes [26]. Similar findings were noted in a large observational study that was restricted to TRALI patients, showing that mechanical ventilation with high peak pressures was a risk factor for the development of TRALI [32]. Of note, the interaction between transfusion and mechanical ventilation in the induction of lung injury can occur after just a short period of time. This was shown in a meta-analysis of almost 3,700 patients requiring ventilation for a general surgical procedure, where ventilation with high pulmonary pressures and RBC transfusion were individually associated with occurrence of postoperative ARDS, but their combination was associated with the highest risk of developing ARDS [33]. There was also a significant interaction between transfusion and airway pressure as a risk factor for ARDS. These risks appear to be particularly present in patients undergoing high-risk procedures, such as cardiac, vascular, and thoracic surgeries, as well as those undergoing liver transplantation [22]. These procedures are also characteristically associated with a high risk for allogeneic blood transfusion.

In addition to these observational studies, direct evidence of an interaction between mechanical ventilation and RBC transfusion is present in the experimental setting. In an in vitro model of mechanical ventilation, incubation with RBC products augmented the injury induced by stretching of lung cells [34]. And, in a mouse model, the occurrence of TRALI was enhanced by injurious ventilation settings [35]. Interestingly, in a mouse hemorrhagic shock model, fresh whole blood caused less lung inflammation and capillary permeability compared to lactated Ringers [27]. It is apparent that the risk of blood products compared to crystalloid fluids with respect to lung injury is not straightforward and there may be circumstances where blood products may have less adverse inflammatory effects than crystalloids.

Taking these data together, it is reasonable to assume that mechanical ventilation and transfusion can act synergistically to induce ARDS, with mechanical ventilation promoting pulmonary inflammation and priming pulmonary neutrophils, and transfusion contributing further to the process, resulting in increased pulmonary vascular permeability. Thereby, hypervolemia as a result of liberal fluid loading (transfusion and fluids) will increase the leakage gradient across the hyper-permeable endothelium.

RBC transfusion and ARDS in children receiving mechanical ventilation

ARDS in children, when severe, carries mortality rates of 30–40%, which are similar to those in adults [36, 37]. RBC transfusions are given to 20–40% of children receiving mechanical ventilation and are associated with increased risks of new or worsened lung injury [18, 19], and increased duration of mechanical ventilation [18, 19, 38–43]. In studies including a total of more than 489,000 children, RBC transfusion was independently associated with ARDS development or with longer duration of mechanical ventilation, after accounting for baseline differences [18, 19, 38, 44, 45] (Table 4). While these studies suggest that RBC transfusion may be harmful in patients with severe pediatric ARDS (PARDS), these retrospective analyses are likely confounded by indication and most analyses to date have been insufficient to understand variation in risk based on patient-specific pathophysiology.

Prevention of lung injury in mechanically ventilated patients in need of blood product transfusion

Patient-related factors

The treating physician can potentially decrease the risk of lung injury developing following transfusion via several actions. The evidence for these measures is

Table 4 Observational studies demonstrating adverse respiratory effects associated with red blood cell (RBC) transfusion in critically ill and injured children

Population	*N*	Design	Findings	References
Children with PARDS	353	Single center retrospective	RBC transfusion independently associated with longer time to extubation (aSHR 0.65 [0.51, 0.83])	[44]
Traumatically injured children	488,381	Registry study (NTD)	Transfusion independently associated with ARDS development (aOR 4.7 [4.3, 5.2])	[45]
Critically ill children	842	Single center retrospective	43% rate of new or worsened respiratory dysfunction associated with RBC transfusion; RBC transfusion independently associated with longer duration of MV (aHR 0.59 [0.45, 0.79])	[19, 38]
Critically ill children with ALI	79	Single center retrospective	RBC transfusion associated with increase in OI (11.7–18.7 vs. 12.3–11.1 in non-transfused) and longer duration of MV (15.2 vs. 9.5, $p < 0.001$)	[18]

NTD National Trauma Database; *aSHR* adjusted subdistribution hazard ratio; *aOR* adjusted odds ratio; *OI* oxygenation index; *MV* mechanical ventilation; *PARDS* pediatric acute respiratory distress syndrome; *ALI* acute lung injury

not substantiated by a large body of evidence, but they largely follow from known pathophysiologic mechanisms (Fig. 1).

Application of a restrictive RBC transfusion trigger should be considered, although transfusions should not be withheld if patients require transfusion based on the available evidence [4]. Assessing the balance between oxygen delivery and consumption may provide a more personalized approach to identifying patients who may benefit from transfusion [46]. Lung protective ventilation, with limited tidal volumes and plateau pressures, should be applied not only in those patients who already have ARDS, but also in patients without ARDS who require mechanical ventilation. Based on the pathophysiology of the interaction between transfusion and vascular leakage, avoiding fluid overload and administering diuretics when needed, can be considered, because reducing volume will reduce the leakage gradient in the lung. As shock is a risk factor for TRALI, probably via the induction of an inflammatory response, it may be beneficial to administer vasopressors prior to a blood transfusion; however, the possible benefits of such an approach are unknown. Of interest, a recent single center trial showed that early administration of low-dose arginine vasopressin (AVP) during the resuscitation of trauma patients with hemorrhagic shock significantly decreased the amount of blood products used and improved fluid balance without increasing overall complications [47]. AVP may promote hemostasis by inducing von Willebrand factor exocytosis from endothelial cells, increasing the procoagulant capacity of platelets. Whether this intervention also reduces the risk of ARDS remains to be determined. Experimental research in TRALI models has suggested a beneficial effect of aspirin on lung injury development [48]; however no benefit was found in observational studies in critically ill patients [49] or in patients with a risk factor for ARDS [50].

Although TRALI patients have increased levels of pro-inflammatory cytokines, including interleukin (IL)-6 and IL-8 [51], we do not support modulating inflammation with corticosteroids during transfusion, because this is not supported by the current evidence. Of note, levels of the anti-inflammatory cytokine IL-10 are reduced in TRALI [52], and there is experimental evidence that boosting the anti-inflammatory response by injection of IL-10 abrogates TRALI [53]. However, boosting the anti-inflammatory response with IL-10 prior to a transfusion seems rather excessive.

Blood product-related factors

The contribution of antibodies to TRALI due to plasma rich products has been largely eliminated by implementation of male donor only strategies. The causative factor in blood products that contributes to non-immune mediated lung injury, is largely unknown. It may be related to cellular debris, vesicles or other biologically active mediators that accumulate during storage, such as lysophosphatidylcholines, soluble CD40 ligand and extracellular

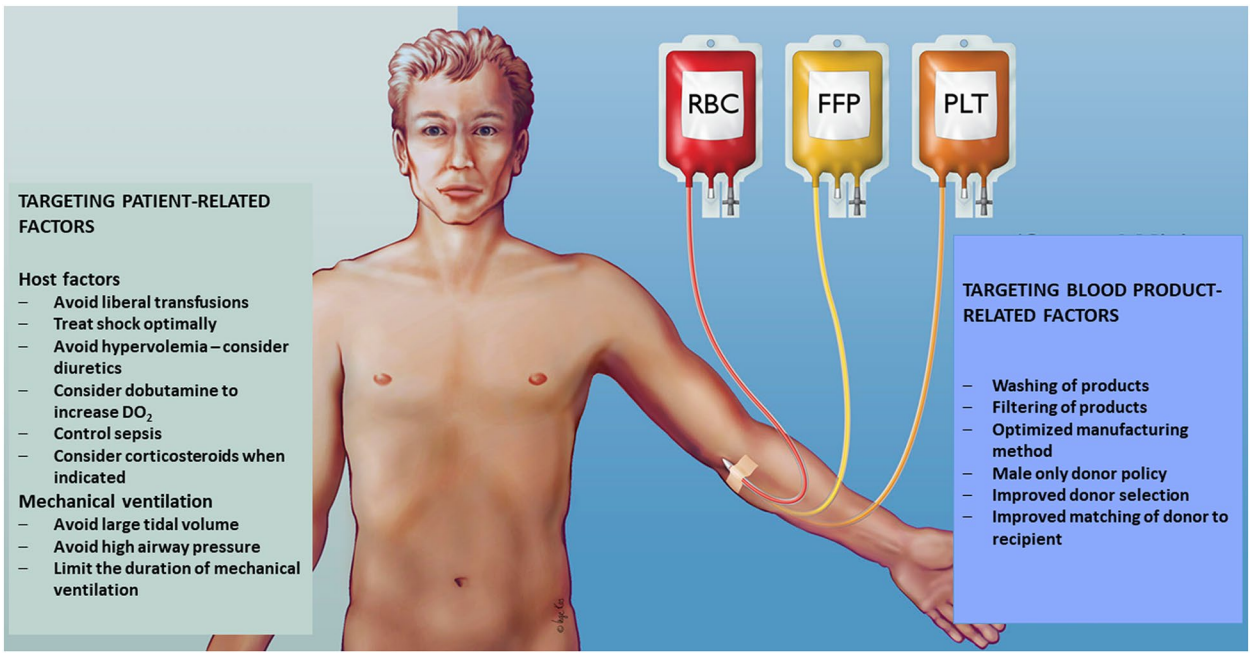

Fig. 1 Some suggested methods to limit the risks of lung injury associated with transfusion, based on pathophysiological concepts

vesicles. These mediators have various pro-inflammatory actions, including the priming of neutrophils. From this, it may be inferred that the age of the RBCs being transfused may be a factor in TRALI. However, although acute lung injury has not been the primary outcome of studies investigating the impact of the age of RBCs on outcome of critical illness, several trials did not detect any benefit from the use of fresh RBCs [54], which implies age has only a very modest effect, if any. The same holds true for platelet storage duration [55]. Other measures are under investigation. These include washing or filtering of RBCs, as washing of RBCs prior to transfusion was found to reduce markers of inflammation in experimental settings [56] and in children undergoing cardiac surgery [57], although this effect was not confirmed in adults [58]. A randomized trial of point-of-care washing of RBCs to prevent both TRALI and TACO in cardiac surgery patients is currently ongoing [59]. Another aspect that is currently receiving attention is the way in which blood products are manufactured. In an in vitro model of mechanical ventilation, apheresis-derived RBC products induced lung injury, whereas filtered RBC products did not, suggesting that manufacturing method has an impact on the safety of a blood product [34]. Improvement in storage solutions for RBCs may improve quality, which may lead to improved outcomes. For example, a new RBC storage solution that mitigates oxidative injury has been shown to reduce inflammation and organ injury in an animal model of hemorrhagic shock [60]. Solvent detergent treated plasma may be associated with a lower risk of TRALI without impairment of efficacy compared to the use of non-pathogen reduced frozen plasma [61].

Finally, we may need to think about blood transfusion as a 'mini-transplantation', implying that we may need to match the recipient to the donor in a more detailed way than just checking the blood type. In this regard, male recipients of female RBC products (sex-mismatched transfusion) had increased mortality compared to recipients of a sex-matched transfusion [62]. In relation to ARDS, the risk was only noted with donor blood from women who had been pregnant [63], suggesting that antibodies associated with TRALI may have played a role. Although not all studies concur [64], this finding requires further study.

Conclusions

Mechanically ventilated patients are the sickest critically patients with the highest exposure to blood component transfusion. Mechanical ventilation and the underlying condition of ICU patients may play key roles in the relationship between transfusion and ARDS. This review highlights several preventive measures that may potentially minimize the risk of ICU patients developing transfusion-associated ARDS.

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Author contributions

NPJ and JLV drafted the manuscript; CA, JD, APJV, DJK, JAM, and PCS revised the manuscript for critical content; all authors read and approved the final version.

Compliance with ethical standards

Conflicts of interest

NPJ receives research support from CSL Behring and Octapharma. CA has no conflicts of interest to declare. JD has no conflicts of interest to declare. APJV has no conflicts of interest to declare. DK received RO1 funding to study TRALI/TACO from the National Institutes of Health; is a consultant for the REDS-IV-P study network for the National Institutes of Health; is on the Advisory Committee for Blood and Tissue Safety and Availability for the Department of Health and Human Services; is on the Scientific Advisory Board for Terumo BCT; and wrote the chapter on TRALI for UpToDate. JAM has no conflicts of interest to declare. PCS is a consultant for Hemanext, Entegrion, Secure Transfusion Services. JLV has no conflicts of interest to declare.

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