Transfusion reactions and cognitive aids

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Purpose of review
Although the overall safety of blood transfusion is high, adverse events do still occur. Much research on transfusion reactions was done in nonperioperative patients. Fortunately, important contributions to the perioperative literature have been made in the last several years, specifically in the areas of transfusion-associated circulatory overload and transfusion-related acute lung injury (TRALI).

Recent findings
An unfavorable reaction occurs in as many as 1% of transfusions overall, although the risk of death with each unit given is between 0.002 and 0.0005%. Specific, modifiable factors exist, however, of which the anesthesiologist should be aware. A 2017 article by Clifford *et al.* is the first to examine risk factors and outcomes for transfusion-associated circulatory overload in a high-risk noncardiac surgery population undergoing anesthesia and surgery. In recent years, limiting plasma donors to males only resulted in an approximately 50% decrease in TRALI.

Summary
The current article explores new research on the topics of transfusion-associated circulatory overload and transfusion-related lung injury.

Keywords
fresh frozen plasma, packed red blood cells, platelets, surgical blood loss, transfusion-associated circulatory overload, transfusion reaction, transfusion-related lung injury

INTRODUCTION

Although the overall safety of blood transfusion is high, adverse events do still occur. An unfavorable reaction occurs in as many as 1% of transfusions overall [1], although the risk of death with each unit given is between 0.002 and 0.0005% [2]. Compared with transfusion in the hospital or clinic setting, transfusion reactions in the perioperative period may be more challenging to prevent, detect and treat. For example, the rapid nature of blood loss during some surgeries makes rapid transfusion necessary, meaning that a greater quantity of blood products might be inadvertently received prior to detecting an adverse reaction. In addition, an anesthetized patient is not able to verbalize symptoms such as itching or shortness of breath, and signs such as a rash or bronchospasm may be more difficult to detect in a patient who is covered in surgical drapes. Much research on transfusion reactions was done in nonperioperative patients. Fortunately, important contributions to the perioperative literature have been made in the last several years, specifically in the areas of transfusion-associated circulatory overload and transfusion-related acute lung injury (TRALI).

Transfusion-associated circulatory overload

Surgery is frequently associated with absolute and relative hypovolemia due to surgical blood loss, and this hypovolemia is a common cause of perioperative hypotension and decreased end-organ perfusion. Treatment of brisk surgical blood loss via rapid transfusion makes the perioperative patient particularly susceptible to transfusion-associated circulatory overload and its associated morbidity and mortality. Indeed, in 2016 (most recent data available), in a report from the United States Federal Drug Administration, transfusion-associated circulatory overload was the second-most common cause of death related to transfusion [3].

The build-up of hydrostatic transudate in the lungs is the proximate cause of transfusion-related

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KEY POINTS

- An unfavorable reaction occurs in as many as 1% of transfusions overall, although the risk of death with each unit given is between 0.002 and 0.0005%.
- In recent years, limiting plasma donors to males only resulted in an approximately 50% decrease in TRALI.
- Checklists and cognitive aids can be beneficial for assisting anesthesiologists with treating rare events such as transfusion-associated respiratory distress, and can be in paper or electronic form.

circulatory overload. In the anesthetized patient, symptoms include jugular venous distension, and tachycardia. In contrast, an awake patient may suddenly additionally suffer from shortness of breath.

When perioperative transfusion is indicated, maintaining the careful balance between adequate perfusion and avoiding hypervolemia is informed by knowledge of the risk factors for transfusion-associated circulatory overload. A 2017 article by Clifford *et al.* [4▪▪] is the first to examine risk factors and outcomes for transfusion-associated circulatory overload in a high-risk noncardiac surgery population undergoing anesthesia and surgery. Their method was a case–control study, matching 163 adults who suffered from transfusion-associated circulatory overload with 726 transfused controls who did not develop respiratory complications in the setting of transfusion. A multivariable analysis looked for independent predictors and found that risk factors included increasing administration of fluids during surgery, left ventricular dysfunction, previous β-adrenergic receptor antagonist use, emergency surgery, chronic kidney disease, fresh frozen plasma transfusion by itself in comparison with packed red blood cell transfusion by itself, transfusing more than one blood component in comparison to only transfusing packed red blood cells, and mixed product transfusion (vs. isolated erythrocyte transfusion). In those patients who suffered from transfusion-associated circulatory overload, additional days in the ICU (11.1 vs. 6.5 days) and hospital (19.9 vs. 9.6 days) as well as postoperative mechanical ventilation (73 vs. 33%) were more likely. One year survival was 72% in those who developed transfusion-related circulatory overload versus 84% in those who did not [4▪▪]. Awareness of these factors may assist the anesthesiologist with preventing transfusion-related circulatory overload.

There is overlap between the risk factors for transfusion-associated circulatory overload in the perioperative and critically ill populations. A 2018 multivariate analysis compared patients with transfusion-associated circulatory overload and two control groups, one who had been transfused without pulmonary complications and one who had not been transfused but still developed circulatory overload [5]. This study found that renal failure and cardiac failure were risk factors for transfusion-associated circulatory overload [5], which was also found in the paper by Clifford *et al.* [4▪▪] in the perioperative population.

In addition to being aware of these risk factors, practical steps to decrease the risk of transfusion-associated circulatory overload and its sequelae can be taken. Boucek points out in a 2018 editorial that signs that mimic transfusion-associated circulatory overload may in some cases actually be caused by outgassing of blood from several sources [6]. The necessary refrigeration of packed red blood cells and fresh frozen plasma means that additional dissolved gas is contained in these blood products in their stored state, which will enter the bloodstream if these blood products are not sufficiently warmed [6]. In addition, use of a mechanical infusion device may be useful to decrease outgassing, as manual compression of the blood unit by a pressure bag leads to turbulent flow though a drip chamber [6]. Lastly, washing blood will also have a degassing effect [6].

Transfusion-related acute lung injury

TRALI occurs when a patient has the sudden onset of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) in the setting of transfusion. The onset of TRALI is always within six, but more commonly in less than 2 h after transfusion. Pulmonary symptoms of transfusion-related lung injury range along the spectrum from mild shortness of breath to pulmonary edema that is severe, of a noncardiogenic nature, and necessitating mechanical ventilation. Hypotension and fever are concomitant symptoms, along with chills in awake patients. If other causes of ALI or ARDS are feasible, the diagnosis is then referred to as 'possible transfusion-related acute lung injury' or 'transfused acute respiratory distress syndrome' [7].

In the united states, for the years 2012–2016 (most recent data available), confirmed or possible TRALI was the most common cause of death related to transfusion [3]. The mechanisms underlying TRALI are incompletely understood. It is a rare event, however, occurring in 1/10 000 [8] to 1/100 000 [9] transfusions, with the lower frequency reported in more recent perioperative data. The leading theory for the development of TRALI, which is that it requires two distinct pathogenic processes, is consistent with its infrequent occurrence [10].

First, neutrophils must be primed, which is hypothesized to occur as a result of an insult such as major surgery or sepsis, then these neutrophils are sequestered in the lung tissue. Second, antibodies against the neutrophils, specifically antihuman leukocyte antigen or antihuman neutrophil antigen, which occur in donors who have been pregnant, are introduced to activate these neutrophils. The latter theory is supported by the finding that limiting plasma donation to males only resulted in an approximately 50% decrease in TRALI [11]. One article reviewing 14 studies showed that donor leukocyte antibodies were present in 86% of donors (24/28) in confirmed transfusion-related lung injury cases [12].

The fact that the rate of transfusion-related lung injury is not zero, as well as the fact that leukocyte antibodies are not found in all donors in cases of transfusion-related lung injury, however, means that the search for other causative factors must continue. The latest evidence suggests that incompatible plasma is not a contributing factor to transfusion-related lung injury. Stevens *et al.* [13] published an article including 1536 patients (study and control group) from eight trauma centers after type A plasma was given as part of a massive transfusion protocol to patients with blood types AB and B. This study showed no increase in the incidence of transfusion-related lung injury (or other measures of morbidity and mortality) compared with patients who received compatible plasma [13].

Although not specifically looking at TRALI, a 2018 study took steps toward addressing this issue by examining the strategy of leukocyte filtration for improving pulmonary function after surgery. Specifically, the study prospectively divided patients undergoing lumbar spine surgery and autologous cell salvaged blood into a control group and a group who would additionally have their blood undergo leukocyte filtration [14]. A definitive benefit, in the form of decreased respiratory complications or decreased adverse transfusion reactions was not seen. Nevertheless, physiologic signs were improved, such as the oxygenation index at 1 and 6 h after transfusion and dynamic respiratory system compliance at 1 h after transfusion, and inflammatory markers such as the white blood cell count, IL-6, IL-8, and TNF-α were lower in the study group at 1, 6, and 12 h after transfusion, pointing to leukocyte filtration as a promising avenue for future research with larger study groups and broader populations. Although the cost and increased labor needed for leukocyte filtration may hinder its routine use at many centers without additional definitive evidence, the results found in this study are another factor in favor of pursing research in this area.

Another essential step toward decreasing the incidence of transfusion-related lung injury is accurate reporting. In a 2018 article, Peters *et al.* [15] surveyed all hospitals in the Netherlands with the capacity to care for five or more intensive care patients, using clinical vignettes, and the question 'would you report this case as TRALI'? The authors has a 74% response rate, and discovered that the likelihood that a case would be reported as transfusion-related lung injury was less in younger patients, after transfusion of only one unit of a blood product, or if the hypothesized patient had an added risk factor for ALI or had sepsis [15].

Transfusion-related lung injury and transfusion-associated circulatory overload in pediatrics

Obtaining information on the incidence, risk factors, and strategies for prevention of transfusion-related lung injury and transfusion-associated circulatory overload in the pediatric population is in the beginning stages of the comprehensive research that needs to be done on this topic. A 2018 article looking at 411 pediatric patients who were transfused intraoperatively showed that 3.6% developed either transfusion-related lung injury or transfusion-associated circulatory overload [16▪▪]. These complications showed a nonstatistically significant trend toward being more common in younger patients. Transfusion-related circulatory overload was more common, occurring in 3.4%, with transfusion-related lung injury in 1.2%, and both in 1.0% [16▪▪].

Transfusion-associated respiratory distress and cognitive aids

Checklists and cognitive aids can be beneficial for assisting anesthesiologists with treating rare events such as transfusion-associated respiratory distress, and can be in paper or electronic form. For example, malignant hyperthermia is a rare event, and the cognitive aid pertaining to its treatment is widely accepted [17]. Incorporating principles from human factors can increase the usefulness of cognitive aids [18]. A 'transfusion-associated respiratory distress' checklist is shown here, with similar information to established checklists [19], but in a human factors format (Fig. 1). When acting in response to a critical event such as transfusion-associated respiratory distress, anesthesiologists often do not seek out a cognitive aid at the beginning of the event. Instead, oftentimes, they first perform initial treatment actions to stabilize and later seek a cognitive aid for specific information

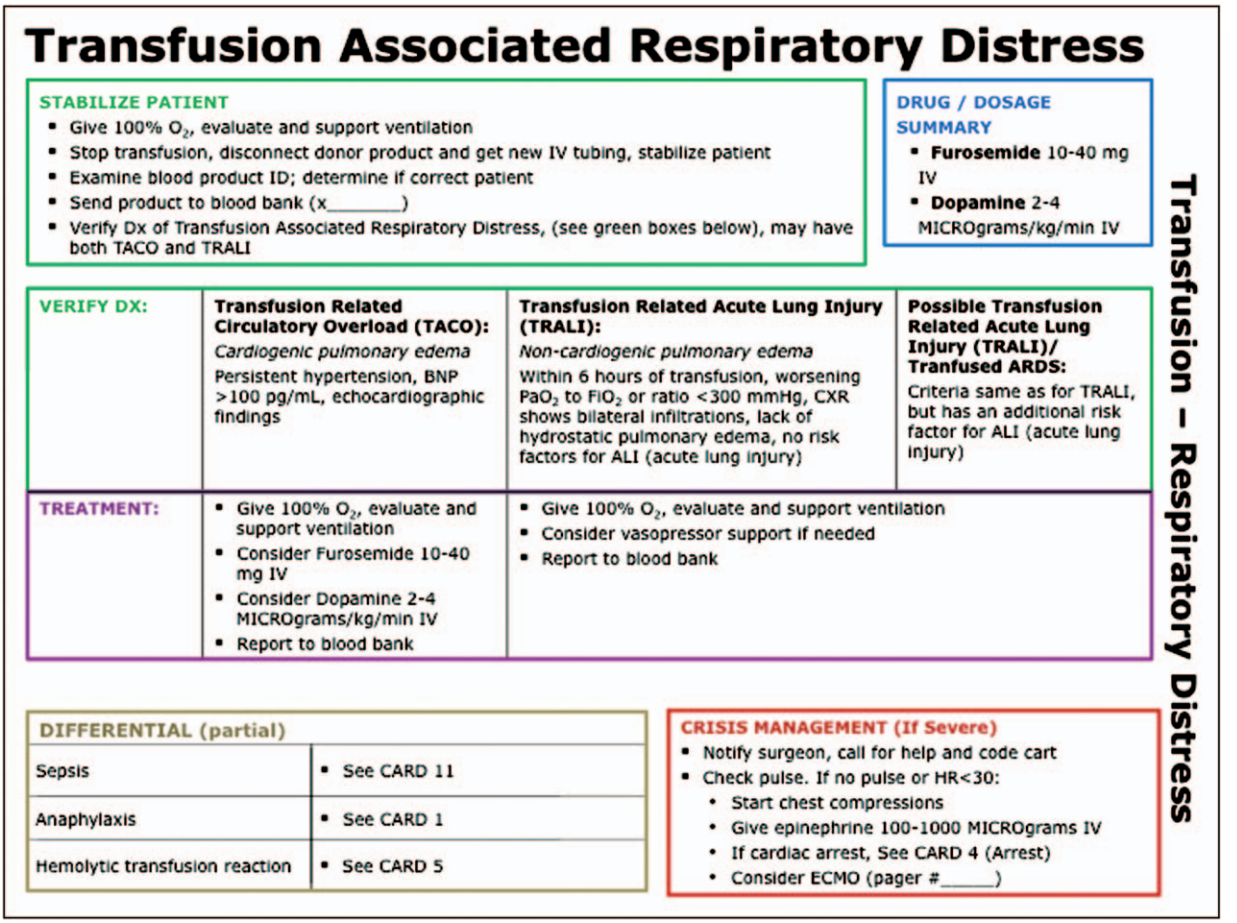

FIGURE 1. Transfusion-associated respiratory distress. In this checklist in the 'sampling' design, content is divided into five blocks to facilitate searching for specific information [18]. This checklist could be used from the beginning of the event starting in the STABILIZE PATIENT block and going down, or the physician could go directly to specific information, such as the VERIFY DIAGNOSIS AND TREATMENT block, DRUG/DOSAGE SUMMARY block, or to the CRISIS MANAGEMENT block. The contents of the massive transfusion protocol will vary by institution. Clinical judgment, verification of appropriateness for patient and situation, and expert review must be used for this and all checklists. Reproduced with permission [18].

such as additional treatment ideas, a drug dose, a differential diagnosis, or to make sure that nothing was missed [18]. This type of checklist use is called 'sampling' and Fig. 1 shows a design that supports accessing a checklist for these specific uses during an episode of 'transfusion-associated respiratory distress' [18].

Adverse neurologic sequalae

Uncommonly, the neurologic system can be adversely impacted by transfusion of blood products. In one case report, rapid transfusion of 14 units of blood products (4 U of packed red blood cells and 10 U of fresh frozen plasma) may have led to the development of posterior reversible encephalopathy syndrome due to a quick upspike in cerebral blood flow, and resultant vasogenic edema and altered mental status [20].

Uncrossmatched blood and transfusion reactions

Uncrossmatched blood products are frequently needed in emergency trauma surgery. In patients with alloantibodies to red blood cells that are pre-existing from previous red blood cell transfusion, a risk for hemolytic transfusion reaction exists. A 2018 literature review, however, found this risk to be low, 0.06% after emergency transfusion of packed red blood cells that are not crossmatched [21].

CONCLUSION

The current article details important contributions to the perioperative literature that have been made in the last several years, specifically in the areas of transfusion-associated circulatory overload and TRALI. Much research is still needed in the adult and pediatric perioperative populations to decrease

the incidence, morbidity, and mortality from transfusion-associated circulatory overload and TRALI overall.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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