ANESTHESIOLOGY

Transfusion-related Acute Lung Injury in the Perioperative Patient

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ANESTHESIOLOGY 2019; 131:693–715

ABSTRACT

Transfusion-related acute lung injury is a leading cause of death associated with the use of blood products. Transfusion-related acute lung injury is a diagnosis of exclusion which can be difficult to identify during surgery amid the various physiologic and pathophysiologic changes associated with the perioperative period. As anesthesiologists supervise delivery of a large portion of inpatient prescribed blood products, and since the incidence of transfusion-related acute lung injury in the perioperative patient is higher than in nonsurgical patients, anesthesiologists need to consider transfusion-related acute lung injury in the perioperative setting, identify at-risk patients, recognize early signs of transfusion-related acute lung injury, and have established strategies for its prevention and treatment.

(ANESTHESIOLOGY 2019; 131:693–715)

Transfusion of blood products remains a crucial intervention for critically ill patients. Although administered to improve oxygen delivery to tissues or to restore hemostatic capacity, transfusion can lead to considerable morbidity or even death. Albeit generally relatively rare among all transfused patients, transfusion-related acute lung injury is an important consideration in perioperative patients, due to at-risk surgical patients being frequently exposed to blood products capable of eliciting transfusion-related acute lung injury reactions while in parallel being more susceptible for the development of transfusion-related acute lung injury.

Transfusion-related acute lung injury during the perioperative period causes considerable morbidity and mortality. The pathophysiology of transfusion-related acute lung injury is incompletely understood, and specific therapies beyond supportive measures are lacking, which adds challenges to effective diagnosis and management in the perioperative setting. As a result, anesthesiologists may benefit from a framework to approach perioperative patients suspected of having or being at risk for the development of transfusion-related acute lung injury that outlines available tools and strategies for diagnosis, prevention, and treatment. This review provides an overview of transfusion-related acute lung injury and recommendations for its detection, prevention, and management in the perioperative patient.

Transfusion-related Acute Lung Injury Epidemiology

Transfusion-related acute lung injury is defined as onset of lung injury usually within 6 h of transfusion of plasma-containing blood products.[1,2] Early accounts of transfusion-related acute lung injury–like presentations fitting this criterion, often referred to as pulmonary hypersensitivity reactions, date back to the 1950s, although cases were not labeled as transfusion-related acute lung injury until the 1980s.[3] Transfusion-related acute lung injury has an estimated incidence of 0.02 to 1.12% per transfused blood product but can exceed 5 to 8% in critically ill patients.[4–7] Similar to adults, children have comparable reported incidences of transfusion-related acute lung injury with increased risk among patients in the intensive care unit (6.9%).[8,9] Estimates of perioperative transfusion-related acute lung injury incidence vary but range from approximately 0.1 to 2%.[10–12] Of all transfusion-associated complications, transfusion-related acute lung injury has one of the highest mortalities (up to 43% in high-risk patients)[2,4,13–15] with more than one blood product implicated for every 100 transfusions.[4,7,13,16–18] Beyond mortality, transfusion-related acute lung injury affects patient morbidity as its treatment often requires positive pressure ventilation with endotracheal intubation, which leads to unscheduled or prolonged intensive care unit stays and overall longer hospital lengths of stay.[10] An important limitation to interpreting the above epidemiologic rates is the complexity pertaining

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Submitted for publication July 8, 2018. Accepted for publication February 6, 2019. From the Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, Canada (M.J.M., J.W.S., W.M.K); Departments of Physiology and Anesthesia (M.J.M.), Pharmacology (J.W.S.), Laboratory Medicine–Pathobiology (C.C.-G.), Medicine–Division of Hematology (C.C.-G.), Anesthesia and Pain Management, University Health Network (K.K.), and Physiology and Surgery (W.M.K.), University of Toronto, Toronto, Canada (C.C.-G.); Sickkids Department of Anesthesia and Pain Medicine (M.J.M.), and Division of Hematology and Transfusion Medicine (R.K., J.W.S.), Lund University, Lund, Sweden; Department of Experimental Immunohematology, Sanquin Research, and Landsteiner Laboratory, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands (R.K.); Departments of Laboratory Hematology (Blood Transfusion Laboratory), Laboratory Medicine Program (C.C.-G.), and Medical Oncology and Hematology (C.C.-G.), University Health Network, Toronto, Canada (K.K.); Department of Clinical Pathology, Blood and Tissue Bank, Sunnybrook Health Sciences Centre, Toronto, Canada (C.C.-G.); and Institute of Physiology, Charité University Berlin, Berlin, Germany (W.M.K.).

 Anesthesiology 2019; 131:693–715. DOI: 10.1097/ALN.0000000000002687

<zdoi;10.1097/ALN.0000000000002687>

to transfusion-related acute lung injury definitions and its diagnosis based on exclusion of other causes. This may result in both over- and underestimation of transfusion-related acute lung injury results, as true cases of transfusion-related acute lung injury may be attributed to other evident risk factors, while unawareness of known or unknown pathomechanisms may result in false-positive transfusion-related acute lung injury diagnosis. This ambiguity is further amplified by differences between medical centers in terms of hemovigilance, diagnostic prowess/compliance, and use of definitions/diagnoses, as well as patient populations.

Transfusion-related Acute Lung Injury Definitions

Defining transfusion-related acute lung injury involves a complex nomenclature of terms. As a means to organize these definitions, a hierarchical approach can be taken.

Transfusion-associated Dyspnea

Pulmonary complications related to transfusion can be situated within a broad spectrum of lung pathologies of varying severity, which are often referred to globally as "transfusion-associated dyspneas."[19] Transfusion-related acute lung injury represents a severe presentation of a transfusion associated dyspnea. Transfusion-associated dyspnea can be stratified for severity of injury at least in part using criteria from definitions established for transfusion-related acute lung injury. For example, perioperative patients with documented Pa_{O_2}/fraction of inspired oxygen (F_{IO_2}) ratios less than 300 but no chest radiograph transfusion-related acute lung injury–associated consolidation do not fully meet criteria for transfusion-related acute lung injury but still represent transfusion-associated dyspnea.[20]

Classic Transfusion-related Acute Lung Injury

Within the transfusion-associated dyspnea spectrum, transfusion-related acute lung injury represents one of if not the highest risk transfusion-related pulmonary complications due to its high morbidity and mortality. Different transfusion-related acute lung injury definitions have evolved over time with most incorporating all or many facets of expert consensus definitions.[1,21] The "classic" definition of transfusion-related acute lung injury requires onset of acute lung injury (oxygen saturation measured by pulse oximetry < 90% ± Pa_{O_2}/F_{IO_2} < 300 on room air ± clinical evidence of hypoxemia) including bilateral infiltrates on chest radiograph within 6 h of transfusion of blood products in the absence of preexisting acute lung injury, acute lung injury risk factors, or left atrial hypertension (cardiac confounders).

Possible Transfusion-related Acute Lung Injury

Considering that cardiac disease, acute lung injury, or factors that predispose for acute lung injury are common especially among high-acuity perioperative patients, a compromise diagnosis of possible transfusion-related acute lung injury is often entertained.[1] Similarly, in pediatric patients in the intensive care unit, investigators have created a novel diagnostic category of patients referred to as "respiratory distress associated with transfusion," which are similar to possible transfusion-related acute lung injury but capture additional information such as Pa_{CO_2} as well as treatment with increased F_{IO_2} and/or mechanical ventilation.[22]

Transfused Acute Respiratory Distress Syndrome

A competing diagnosis, somewhat similar to, and suggested by some to replace possible transfusion-related acute lung injury is "transfused acute respiratory distress syndrome (ARDS)" as it insinuates that possible transfusion-related acute lung injury cases may not be transfusion-dependent but rather that coincident ARDS is the cause of respiratory dysfunction.[23] The transfused ARDS definition has not been widely adopted, in part due to underaddressing potential non–antibody-mediated transfusion-related acute lung injury in at-risk ARDS populations such as those in the intensive care unit and incompletely recognizing the potential of ARDS to increase the risk for possible transfusion-related acute lung injury.[24]

Delayed Transfusion-related Acute Lung Injury

Besides transfusion-related acute lung injury definitions that consider ARDS risks or preexisting comorbid cardiac or lung injuries, variations in the timing of transfusion-related acute lung injury onset are accommodated with additional subcategorization. As the name implies, delayed transfusion-related acute lung injury incorporates a longer window of time, extending the definition to up to 72 h from time of transfusion until onset of symptoms as opposed to the classic 6 h time window for classic transfusion-related acute lung injury.[25] Delayed transfusion-related acute lung injury is noteworthy for its smoldering insidious onset (as opposed to a rapid sudden onset with classic transfusion-related acute lung injury), higher frequency of presentation in intensive care unit/critically ill patients, lower likelihood of being antibody-mediated transfusion-related acute lung injury, high associated mortality (35 to 45%) and its inability, unlike classic transfusion-related acute lung injury, to completely resolve within 5 days but rather may progress to fibroproliferative ARDS.[25]

Perioperative Transfusion-related Acute Lung Injury

Currently there is no specific definition pertaining to transfusion-related acute lung injury in the perioperative patient. The perioperative period is characteristically associated with specific confounding factors that make diagnosing transfusion-related acute lung injury more challenging, such as preexisting pulmonary injuries, challenges in imaging lungs due to limitations in patient positioning, chest tubes and or pleural effusions, high amounts of perioperative iatrogenic fluid administration,

lung atelectasis and/or consolidation, and blood or secretions in airways.[14,26] Further, transfused and nontransfused cardiac surgery patients both commonly have Pao_2/Fio_2 ratios less than 300, which complicates criteria for classic transfusion-related acute lung injury as a diagnosis of exclusion (therefore more resembling possible transfusion-related acute lung injury), which is further complicated with perioperative positive pressure ventilation, which may obscure the presentation of transfusion-related acute lung injury in terms of Pao_2/Fio_2 ratios and chest radiograph findings.[27] Previous investigations of perioperative transfusion-related acute lung injury have relied on individual or combinations of the above transfusion-related acute lung injury definitions, which have both strengths and weaknesses (table 1).[9–12,16,20,26,28–63] Patients undergoing major surgeries resemble intensive care unit patients and, as such, delayed transfusion-related acute lung injury–like presentations may be fairly common but frequently unrecognized among transfused surgical patients. Specifically, for perioperative transfusion-related acute lung injury, a particular challenge is to discriminate whether any emerging lung injury is the direct result of surgery or a potential underlying disease, transfusion of blood products, or a combination of these factors. Alam *et al.* defined the perioperative period as 72 h from the onset of surgery (similar time frame as delayed transfusion-related acute lung injury).[46] Combining aspects of both possible transfusion-related acute lung injury and delayed transfusion-related acute lung injury definitions provides a means of capturing perioperative transfusion-related acute lung injury cases.

Clinical Presentation of Transfusion-related Acute Lung Injury

The diagnosis of transfusion-related acute lung injury is established by a combination of physical examination, history, imaging, and laboratory findings.

Physical Examination

When patients present with acute lung injury after recently being transfused, their physical examination and vital signs are key to narrow the differential diagnosis. The key features of transfusion-related acute lung injury are exudative pulmonary edema as a result of barrier failure within the endothelial, interstitial, and epithelial layers of the lung leading to extravasation of proteinaceous fluid into the airspace. Autopsy findings have corroborated these key features by demonstrating pulmonary edema, neutrophil infiltration, lung hyaline membrane formation, platelet aggregates, and destruction of normal lung parenchyma similar to presentations of ARDS.[15,57] Loss of alveolo-capillary barrier function results in a series of clinical symptoms that can be detected by physical examination, including the presence of pulmonary edema, bronchorrhea, dyspnea, hypoxemia, respiratory failure, bilateral consolidations on chest radiograph (similar to ARDS), fever, cyanosis, tachypnea, hypovolemia, and hypertension or more commonly hypotension, albeit none of these signs alone are either specific or a requirement for the diagnosis of transfusion-related acute lung injury.[1,37,64] Several perioperative accounts have associated transfusion-related acute lung injury with pulmonary hypertension, although pulmonary pressures are often not elevated[28,32,34] (table 1). In some cases, onset can be rapid and volumes of pulmonary edema copious, making it challenging to manage, as in a perioperative case report describing suctioning in excess of 1,700 ml of bronchial fluid.[31]

Although physical examination and imaging (chest radiograph findings) are helpful for diagnosing transfusion-related acute lung injury, they are not always conclusive, especially in perioperative patients in whom transfusion-related acute lung injury can be masked or obscured by confounders such as anesthesia or mechanical ventilation. Some surgical interventions bear a specifically high risk for transfusion-related acute lung injury, namely those involving the use of mechanical ventilation, elevated fractions of inspired oxygen, cardiopulmonary bypass, or high-volume fluid administration. In addition, medications such as immunomodulating glucocorticoids, diuretics, and anesthetic agents may prevent, delay, or even worsen presentations of perioperative transfusion-related acute lung injury (table 1). Especially in these instances, a patient history can establish a potentially causal relationship and thus aid in the diagnosis of perioperative respiratory failure in the context of recently transfused patients during surgery.

History

Supplementing the physical examination, a focused preoperative history can help identify patients at high risk for transfusion-related acute lung injury based on (1) preexisting patient-related risk factors, (2) anticipated transfusion requirements (increasing volume of transfusion correlates with the risk of transfusion-related acute lung injury), and (3) surgical procedure–related risks. Beyond these preoperative factors, carefully recording the timing of perioperative transfusions relative to suspected transfusion-related acute lung injury presentation can help establish important timelines that may help rule transfusion-related acute lung injury in or out (fig. 1).

Laboratory Investigations

Without the context provided by history and physical examination, laboratory investigations in isolation have a relatively low utility in confirming transfusion-related acute lung injury. Yet when the history and physical examination are suggestive of transfusion-related acute lung injury, laboratory findings are a useful adjunct for confirming the diagnosis. Laboratory abnormalities associated with but not specific for transfusion-related acute lung injury include hypoalbuminemia, thrombocytopenia, neutropenia (from immune complex effects of passively acquired human leukocyte antigens and human neutrophil antigens leukoagglutinins) in the context of a nonelevated brain natriuretic peptide.[1,44,64,65]

Table 1. Summary of Published Accounts of Perioperative Transfusion-related Acute Lung Injury

Population	No. of Patients	Risk Factors/Comorbidity	Presentation	Treatments	Reference
Surgical (nonspecified)	218	Cardiac surgery (CPB) General surgery Orthopedic surgery Gynecological surgery Liver surgery Male sex ↑Volume TXN ↑ASA score Hypertension Thoracic surgery Transplantation Vascular surgery ↑Volume blood products Intraoperative transfusion Trauma surgery RBC, FFP, PLT, CRYO, Ab Preoperative liver dysfunction Immune thrombocytopenia ↑PAP ↑Fluid balance	CXR + hypoxemia Onset 1–7 h ↓O_2Sat (lowest 68%) Pulmonary edema ↓BP Neutrophilia Hypoalbuminemia Resolution < 72 h	ETT/PPV Diuretics Oxygen Steroids	10,20,44–49
Liver surgery	23	Liver transplantation Transfusion of RBC, FFP, PLT Smoking	CXR + hypoxemia Onset < 6 h, often < 3 h Pulmonary edema Resolution < 96 h	ETT/PPV Diuretics Oxygen	26,38,39
Cardiac surgery	78	Coronary artery bypass grafting ↑Age ↑CPB time ↑Cytokines (IL-8, IL-6) Repeat/emergency-surgery ↑Antibodies ↑ASA scores ↑Respiratory comorbidity RBC, PLT, FFP, WB, Ab, BRM Smoking	CXR + hypoxemia Onset < 1 h to 24 h Pulmonary edema ↓BP Pulmonary hypertension Coagulopathy ↓Fibrinolysis ↓Lung compliance ↑RR Dyspnea ↓O_2Sat (lowest 78%) Resolution < 96 h but some as late as 168 h	iNO PPV/ETT PEEP Vasopressors Diuretics Hydrocortisone CPB RVAD Inotropes iABP	11,16,28-37
Orthopedic surgery	4	Femur trauma Spine laminectomy Coronary artery disease Lupus Orthopedic surgery RBC, FFP, PLT, WB Massive transfusion Hip surgery Juvenile arthritis	CXR + hypoxemia Onset < 1–6 h Pulmonary edema PAWP > 10 mmHg ↑BP, ↑HR DHR delayed hemolytic reaction ↓O_2Sat (lowest 82%) Resolution < 120 h	ETT/PPV Diuretics Oxygen Steroids Vasopressors	40–43
Obstetrics and gynecological surgery	5	Hysterectomy RBC, FFP, PLT, CRYO ↑Antibodies Repeat/emergency surgery Preeclampsia Cesarian delivery Massive transfusion Congenital ↓fibrinogen	Onset 1 h ↓O_2Sat (lowest 77%) CXR + pulmonary edema ↓BP, ↑HR Leukocytosis ↑CRP ↑Respiratory rate PEA arrest Resolution < 96 h	ETT/PPV Diuretics Oxygen Vasopressors Steroids CPR VA ECMO iNO	50–54
Pediatrics	16	Spine surgery RBC, FFP, PLT, WB, ↑antibodies Cardiac surgery Liver surgery Craniofacial surgery CPB ↓Age Neurosurgery Orthopedic surgery	CXR + hypoxemia Onset < 1 h ↓O_2Sat (lowest recorded 50%) Pulmonary edema ↑PAP (45 cmH_20) Lactic acidosis Leukopenia Monocytopenia Cyanosis, ↓BP Resolution < 96 h	Inotropes ETT/PPV/PEEP iNO Oscillator CPB CPB Bronchodilators Diphenhydramine Vasopressors	9,12,55-63

Upward arrow denotes increase, *downward arrow* denotes decrease. Ab, antibodies; ASA, American Society of Anesthesiologists; BP, blood pressure; BRM, biologic response modifier; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; CRP, c-reactive protein; CRYO, cryoprecipitate; CXR+, chest radiograph findings of transfusion-related acute lung injury; ETT, endotracheal tube; FFP, plasma; HR, heart rate; iABP, intraaortic balloon pump; IL, interleukin; iNO, inhaled nitric oxide; O_2Sat, oxygen saturation; PAP, peak airway pressure; PAWP, pulmonary artery wedge pressure; PEA, pulseless electrical activity; PEEP, positive end expiratory pressure; PLT, platelet; PPV, positive pressure ventilation; RBC, red blood cell; RR, respiratory rate; RVAD, right ventricular assist device; TXN, transfusion; VA ECMO, venous arterial extracorporeal membrane oxygenation; WB, whole blood.

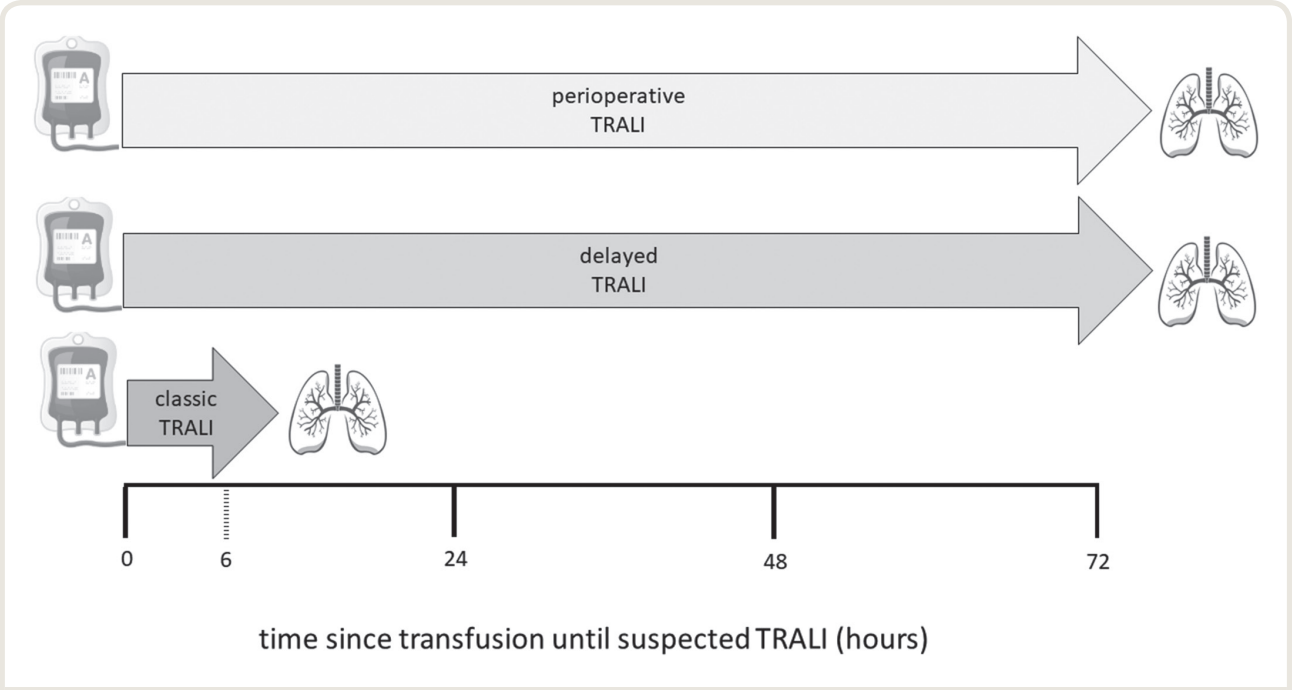

Fig. 1. Time of onset of transfusion-related acute lung injury (TRALI) relative to transfusion of blood products.

Transfusion-related Acute Lung Injury Pathophysiology

Transfusion-related acute lung injury is an indirect (*i.e.*, triggered by systemic rather than pulmonary events) form of acute lung injury that can be severe enough to meet the criteria of the ARDS involving hypoxemia, excess inflammation, lung vascular barrier disruption, and formation of edema. The mechanisms of transfusion-related acute lung injury are not completely understood but are thought to be mediated by either pathogenic antibodies[66] or non–antibody-dependent factors typically referred to as biologic response modifiers such as lipids, extracellular vesicles, or soluble CD40 ligand (fig. 2).[67] In general, the development of transfusion-related acute lung injury is considered to work through a two-hit model. The first hit (mediated by preexisting patient risk factors) recruits primed neutrophils into the lungs, where they only elicit full blown transfusion-related acute lung injury by damaging barrier integrity resulting in pulmonary edema formation when combined with a second hit, which is either transfusion of pathogenic antibodies or biologic response modifiers from blood products (fig. 3).

Antibody-mediated Transfusion-related Acute Lung Injury

Estimates of pathogenic antibodies being implicated in antibody-mediated transfusion-related acute lung injury cases have historically ranged from 72 to 89%, in part influenced by differing sensitivity of antibody detection tools.[3,33,66,68–71] Antibodies within blood products directed against select human leukocyte antigens and human neutrophil antigens are capable of eliciting rapid immune responses culminating in complement activation, pulmonary neutrophil infiltration, and vascular barrier disruption.[17,66,72,73] Antibody-mediated transfusion-related acute lung injury has been reproduced experimentally with mouse models involving transfusion of monoclonal antibodies directed against major histocompatibility complex class I antigens[66,74–79] and was evidenced clinically in a single lung transplant patient with antibody-mediated transfusion-related acute lung injury present in only the transplanted lung from graft human leukocyte antigen cognate responses, emphasizing the specificity of antibody-mediated transfusion-related acute lung injury.[80] Mitigation strategies to reduce exposure of recipients to pathogenic antibodies in blood products by using nonalloimmunized male donors have reduced but not eliminated the incidence of antibody-mediated transfusion-related acute lung injury.[5]

Non–Antibody-mediated Transfusion-related Acute Lung Injury

Despite reduced antibody exposures, emerging evidence shows that the critically ill or those with chronic inflammation even in an era of antibody mitigation strategies face transfusion-related acute lung injury risks in excess of 5% per transfused patient.[4,81] Further, accounts of documented positive titers of pathogenic antibodies have not consistently led to

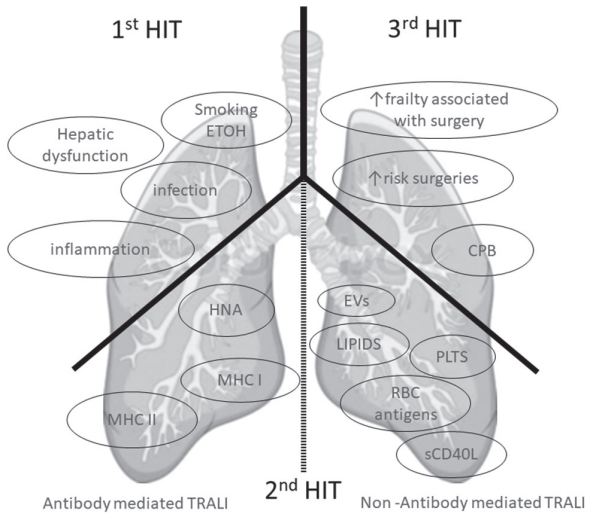

Fig. 2. Examples of transfusion-related acute lung injury (TRALI) first (patient-related), second (antibody- and non–antibody-mediated—separated by *dashed vertical line*) and third (perioperative) hits. CPB, cardiopulmonary bypass; ETOH, ethanol; EV, extracellular vesicle; HNA, human neutrophil antibody, MHC, major histocompatibility complex; PLT, platelet, RBC, red blood cell; sCD40L, soluble CD40 ligand.

antibody-mediated transfusion-related acute lung injury reactions.[13,66,82,83] Conversely, transfusion-related acute lung injury reactions are documented where no pathogenic antibodies are detected within the donor, blood product, or recipients.[3,33,84] These cases provide proof-of-concept that not all transfusion-related acute lung injury cases are mediated by antibodies, and non–antibody-dependent transfusion-related acute lung injury mechanisms may elicit significant transfusion-related acute lung injury in at least 20% of transfusion-related acute lung injury cases where no antibodies are implicated.[3,33,66,68–70] Importantly, this number may be a gross underestimate as non–antibody-dependent transfusion-related acute lung injury mechanisms may partially or even exclusively contribute to disease severity in cases where antibodies are detected but may not necessarily or only partially contribute to disease, but which are nevertheless by convention classified as "antibody-mediated transfusion-related acute lung injury."[3,66] This notion is supported by investigations documenting the presence of pathogenic antibodies in as few as 3.7% of transfusion-related acute lung injury patients.[33] Hence, beyond antibodies, other blood product related factors emerge as relevant to the presence and severity of transfusion-related acute lung injury. Among those, the age of stored transfused blood products has received particular interest over recent years. However, recent meta-analyses did not reveal an increased risk of death with the use of older/standard storage duration erythrocytes

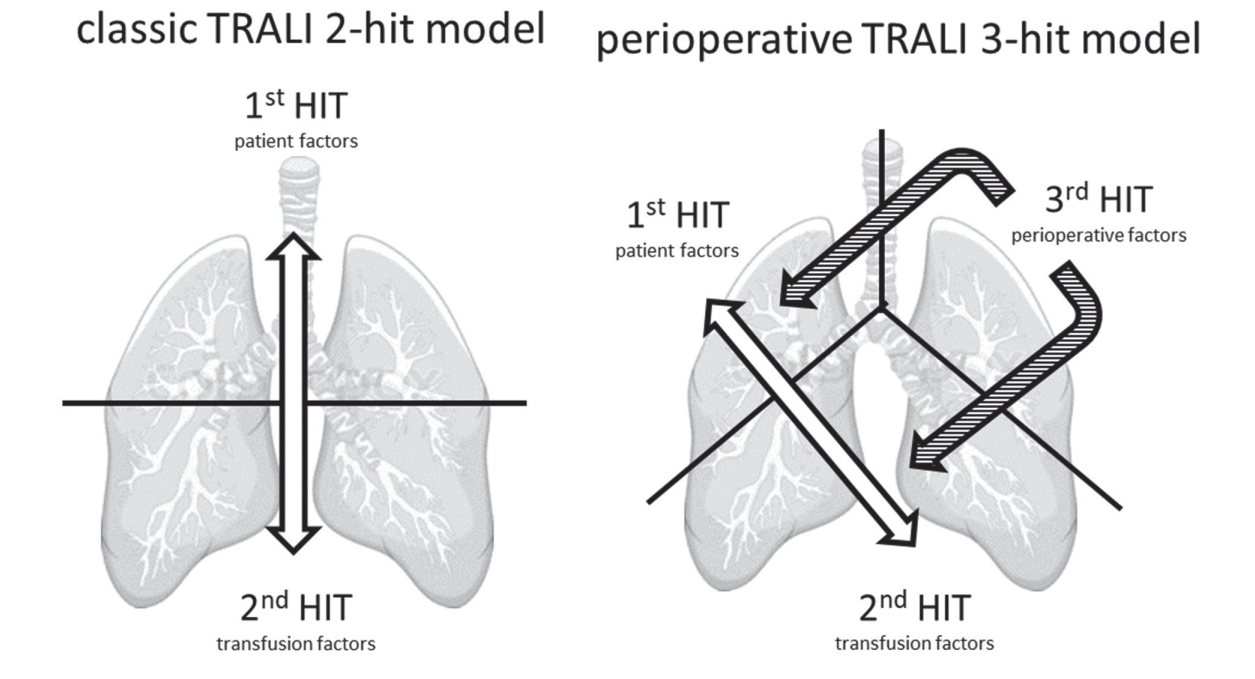

Fig. 3. Classic and perioperative transfusion-related acute lung injury (TRALI) involves two or three hits, respectively. Classic two-hit model (*left*) with first hit triggering susceptibility and vulnerability for development of TRALI if combined (*white arrow*) with the second hit (blood products). Perioperative three-hit model (*right*), where the third (perioperative hit) amplifies (*hashed arrows*) both the first and second hits (of the classic TRALI model), increasing the likelihood of TRALI above when solely the first and second hits combine (*white arrow*).

compared with fresher (less than 7 days [pediatric] or less than 8 to 21 days [adult]) erythrocytes, and a convincing erythrocyte storage duration effect for transfusion-related acute lung injury was only seen when the recipient was primed with inflammation.[85–89] Yet, although stored erythrocytes have often been suggested to be able to cause transfusion-related acute lung injury, in part due to their frequency of use, it is actually platelets that have a higher per-product risk.[4] In contrast to erythrocytes, the risk of transfusion-related acute lung injury is increased 5.8-fold with aged platelet products (stored 4 to 5 days) or 6.3-fold higher with older platelets (stored 6 to 7 days) compared with fresher platelets (stored less than 4 days).[85] The association of transfusion-related acute lung injury with aged platelets has been replicated in preclinical rodent and sheep studies.[90–93] In these models of non–antibody-mediated transfusion-related acute lung injury, biologic response modifiers, which often accumulate throughout storage of blood products, were considered critical for the induction of transfusion-related acute lung injury.[84] As such, experimental xenobiotic animal studies have shown supernatants of aged human platelets and erythrocytes to cause transfusion-related acute lung injury in two-hit models.[90,91,94–99] Similarly, lipopolysaccharide-primed rats transfused with aged yet not fresh rat platelets or erythrocytes develop lung inflammation and coagulopathy.[92,100] Among the various lipids contained in stored platelets, the sphingolipid ceramide specifically accumulates throughout storage of mouse and human platelets and seems to play a key role as mediator of antibody-independent transfusion-related acute lung injury in that lipopolysaccharide-primed mice transfused aged ceramide-enriched platelets develop transfusion-related acute lung injury.[93] Lysophosphatidyl choline, damage associated proteins, neutrophil extracellular traps, and soluble CD40 ligand are further examples of biologic response modifiers that are either contained in or released after contact with aged blood products that have been documented to contribute to transfusion-related acute lung injury.[77,84,93,98,101,102] A particular field of recent interest in this context is extracellular vesicles, *i.e.*, small subcellular bilipid membrane extracellular vesicles (50 to 1,000 nm) that are released from blood cells when stressed or apoptotic.[103] Notably, extracellular vesicles have been associated with transfusion complications,[104,105] inflammation, and lung injury,[103] and may thus pose an important yet poorly characterized or targeted mechanism of non–antibody-mediated transfusion-related acute lung injury.

Cell Types that Mediate Transfusion-related Acute Lung Injury

Despite different mechanisms of action (antibody *vs.* nonantibody), there is a convergence on a similar transfusion-related acute lung injury phenotype with contributions from key cell types that mediate the injury. As discussed before, donor cells (erythrocytes, platelets, leukocytes) and cell fragments (extracellular vesicles) are considered as the initial trigger, at least in non–antibody-mediated transfusion-related acute lung injury.[93,106,107] Beyond donor cells, recipient immune cells ($CD4^+$ regulatory T-cells, dendritic cells, monocytes, and neutrophils) as well as parenchymal cells such as pulmonary microvascular endothelial cells also contribute relevantly to the disease process. In transfusion-related acute lung injury, neutrophils accumulate and become activated in the pulmonary vasculature and finally extravasate into interstitial and airspace compartments within the lungs, causing injury through mechanisms such as reactive oxygen species formation.[108–111] Beyond neutrophils, experimental models of antibody-mediated transfusion-related acute lung injury have shown macrophages and monocytes to act as agonists, whereas $CD4^+$ regulatory T-cells and dendritic cells reduce transfusion-related acute lung injury severity.[75,76,111,112] The extent and exact mechanisms by which these cells contribute to transfusion-related acute lung injury and their intercellular crosstalk remain poorly understood, and their individual contributions may not always be mandatory. An example of this is the development of transfusion-related acute lung injury in neutropenic patients[113] or in highly immunocompromised patients with anergic immune cell responses (where the above stated cells are present but highly dysfunctional) such as oncology patients or those receiving high doses of glucocorticoids and other antirejection medications such as for hematological or solid organ transplantation.[39,114–116] Beyond inflammatory and immune-mediated responses, barrier disruption leading to enhanced permeability and extravasation of exudative fluid into the airspace is a key feature of transfusion-related acute lung injury. During transfusion-related acute lung injury reactions, barrier-forming cells such as endothelial and epithelial cells become damaged, leading to fluid leak from the circulation into lung tissue and airspaces.[117–120]

Transfusion-related Acute Lung Injury Risk Factors

As outlined above, classic transfusion-related acute lung injury is typically described as a two-hit model where the patient's preexisting vulnerability (first hit) primes for an excessive injury response to subsequent transfusion (second hit). Although Silliman *et al.* previously described transfusion-related acute lung injury in proximity to surgery as a patient-related risk factor synonymous with a first hit, the argument can be made that recent or ongoing surgery is a distinct hit in itself (third hit), which deviates from the classic two-hit model (fig. 3).[33] Therefore, one could consider the pathophysiologic changes seen in perioperative patients with transfusion-related acute lung injury reactions as the combined result of three major contributions comprised of patient (first hit), blood product (second hit), and surgical procedure (third hit)–related factors (fig. 2). Teasing out surgery-related risk factors (third hits) for transfusion-related acute lung injury from typically patient-related factors (first hits) can help identify specific perioperative, potentially modifiable transfusion-related acute lung injury risks.

First Hits

Recipient-related risk factors (first hits) for transfusion-related acute lung injury are typically preexisting proinflammatory pathologic conditions. Examples of transfusion-related acute lung injury first hits include chronic liver, heart, kidney and lung diseases, cancer, chronic alcohol abuse, positive pressure ventilation with high peak airway pressures (greater than 30 cm H_2O), smoking, inflammation, circulating interleukins (increased interleukin-6, increased interleukin-8, decreased interleukin-10), circulating increased C-reactive protein, pneumonia, multiple fractures, pancreatitis, extremes of age (elderly/neonates), previous transfusion-related acute lung injury, shock, and a relevant positive fluid balance.[5,49,121,122]

Second Hits

Blood product–related factors (second hit) reflect contributions from the transfusion donor that then combine with first (± third) hits to culminate in transfusion-related acute lung injury. Blood products transmit antibodies against recipient antigens or cells (anti–human leukocyte antigen class I/II ± anti–human neutrophil antigen) or non–antibody-mediated factors such as biologic response modifiers, *e.g.*, bioactive lipids) that exacerbate neutrophil activation that initiates or worsens lung injury, which in turn drives systemic responses such as inflammation and hypotension. Essentially all plasma-containing blood products, except albumin, can potentially trigger transfusion-related acute lung injury. Even pooled plasma products produced from many donors (leading to very low or undetectable dilution of titers of pathogenic antibodies received from potential at-risk donors), such as IV immunoglobulin, have been implicated in transfusion-related acute lung injury reactions.[123] An interesting exception is the use of solvent-detergent plasma (thought to reduce transfusion-related acute lung injury risk due to washing and being formed form large pools of donors), which, since its clinical adoption in Norway in 1993, has seemingly eliminated transfusion-related acute lung injury associated with this product's use.[124,125] Blood product–specific risks for transfusion-related acute lung injury may include high volumes of plasma-containing blood products, platelets, and alloimmunized donors (nonnulliparous females or those who have elevated titers of antibodies capable of causing reactions).[5,85,126] In addition, risk factor prevalence and transfusion-related acute lung injury rates are affected by how blood products such as platelets are processed postdonation (pooled platelets greater than apheresis) and stored (platelet additive solutions less than plasma or fresh less than prolonged duration).[126,127]

Third Hits

While transfusion-related acute lung injury is often thought to be a disease of two hits, perioperative transfusion-related acute lung injury may involve contributions from a distinct third hit. This third hit represents surgical-procedurally related risks that synergize or at a minimum contribute additively with first and second hits. Although third hits may not be absolutely required for transfusion-related acute lung injury, as appears to be the case with first and second hits in classic transfusion-related acute lung injury, they likely increase first and second hit risks further in keeping with "threshold" and "sufficient cause" models of transfusion-related acute lung injury, which both emphasize the requirement for adequate exposure or magnitude of risk factors regardless of type (first, second, or third) to actually clinically develop lung injury.[128] Some third hits are comprised of perioperative factors that overlap with first hits such as requirement for positive pressure ventilation or elevated airway pressures. Admission anemia, thrombocytopenia, prolonged partial thromboplastin time, pulmonary comorbidities, and higher American Society of Anesthesiologists scores are risk factors previously reported for transfusion-related acute lung injury at the time of surgery.[35] In keeping with second hits, major surgeries requiring frequent and sometimes sizeable transfusions involving erythrocytes, plasma, and platelets are commonly associated with perioperative transfusion-related acute lung injury.[10] Beyond these risk factors arguably shared by the classic two-hit model, there are other, more discrete perioperative (third hit) transfusion-related acute lung injury risks. Examples are intermittent deflation of lungs (as during some surgeries, cardiopulmonary bypass, or one-lung ventilation).[129] Surgical procedures can cause release of proinflammatory cytokines due to incisions or endothelial trauma from minimally invasive procedures involving wires and cannulas, negative pressure pulmonary edema, or extracorporeal circuit use such as cardiopulmonary bypass (with increased transfusion-related acute lung injury risk with longer cardiopulmonary bypass durations), which each can promote inflammation.[16,27,129] Cardiac surgery itself is a risk factor, and specifically longer cases with longer cardiopulmonary bypass durations were significantly associated with possible transfusion-related acute lung injury in a single-center prospective study examining nearly 800 patients with an incidence of 12.2% for possible transfusion-related acute lung injury.[35] Cardiac surgery, due to many of the third-hit factors listed above, is also associated with increased inflammation, which—similar to first hits—increases the risk for transfusion-related acute lung injury upon second-hit exposures.[130] Further examples of synergy between third and first hits for increased perioperative transfusion-related acute lung injury risk include, *e.g.*, the fact that complex surgeries such as liver transplantations can lead to increased plasma levels of lipopolysaccharide-binding protein (third hit), which in turn upregulates lipopolysaccharide-mediated inflammatory responses (infection; first hit) worsening systemic inflammation, thereby again increasing the risk for transfusion-related acute lung injury.[131] The presence of third hits described above in transfused perioperative patients may, at least in part, be responsible for the higher incidences of

transfusion-related acute lung injury associated with surgery and/or in critically ill patients.

Approach to Transfusion-related Acute Lung Injury in the Perioperative Patient

If transfusion-related acute lung injury is anticipated, highly suspected, or diagnosed perioperatively, a systematic approach to preparation (teaching, consultation, patient/procedure optimization), recognition of risk factors, prevention, prognostication (biomarkers, vital signs, physical examination findings), treatment (supportive care or emerging strategies), and follow-up (blood bank, anesthesia, hematology) are recommended to improve care and prevent harm to other patients.

Preoperative Preparation and Prevention

Anesthesiologists can anticipate transfusion-related acute lung injury and screen for transfusion-related acute lung injury risks in perioperative patients before surgery, initiate preoperative strategies to minimize intraoperative transfusion requirements, and facilitate interdisciplinary communication. Transfusion-related acute lung injury is a relatively rare event, and as such, ubiquitous use of resource-, personnel-, and cost-intensive preemptive transfusion-related acute lung injury risk mitigation may not be effective or practical for all surgical patients. Therefore, to ration resources, anticipating who is at greatest risk for transfusion-related acute lung injury during surgical admissions becomes an important goal for anesthesiologists.

Screening for Risk Factors

Although currently, a validated and accepted perioperative transfusion-related acute lung injury risk assessment tool is lacking, anesthesiologists can screen for preexisting transfusion-related acute lung injury–relevant risk factors (first hits) and transfusion-related acute lung injury risks related to the proposed surgery (third hits) such as preexisting or anticipated surgery-related lung injuries, coagulopathies, anemia, and inflammatory conditions. Considering that transfusion (second hits) is a *conditio sine qua non* for the occurrence of transfusion-related acute lung injury, estimation of expected surgical bleeding is of central importance for appropriate risk stratification. Existing bleeding risk scores and assessment tools can predict transfusion requirements in select surgical populations.[132,133]

Prevention of Transfusion

Based on the accumulation of risks (first, second, and third hits) and in surgical cases likely associated with bleeding requiring transfusion, patients may benefit from primary prevention strategies intended to reduce the need for perioperative transfusions. In these select cases, patient blood management strategies can be applied such as discontinuation of antiplatelet, herbal (with known anticoagulant or antiplatelet function), or anticoagulant medications, or boosting of blood cell production, *e.g.*, by prescription of oral or IV iron, erythropoietin, thrombopoietin, folate, and autologous directed donations of blood, as well as detailed plans to limit iatrogenic or "hospital acquired anemia" such as minimizing the number and volume (ml) of perioperative blood-based investigations.[134–139] Analogous to preparations for caring for Jehovah's Witness patients, anesthesiologists may initiate preoperative case conferences with surgeons, perfusionists, intensivists, recovery teams, and blood bankers. Potential strategies include organizing restrictive thresholds for transfusion relevant to the particular patient and procedure, resultant types and amounts of blood products that may be required (if high-risk, consider washed erythrocytes, solvent-detergent plasma, prospective antibody screening of products, and additive solution–containing products). Surgical strategies and techniques associated with minimal blood loss (use of minimally invasive techniques, use of tourniquets, neoadjuvant treatments such as chemotherapy or sclerotherapy, preemptive elective embolization of vessels before excision of vascular lesions such as tumors) reduce bleeding and subsequent need for transfusion. Use of cell-saver devices, patient- and blood-warming devices, use of antifibrinolytics, and use of surgical site hemostatic agents such as thrombin-based topical procoagulants also comprise secondary preventions for transfusion-related acute lung injury.[124,125,134–136,140–143]

Preoperative Communication

One of the unique strengths of anesthesiology in advocating for primary and secondary transfusion-related acute lung injury prevention strategies is familiarity and connectivity with other, often siloed, members of the perioperative care team, which allows for improved coordination of planning, education, and logistical alignment of resources, recruitment of specialized team members (hematology/transfusion medicine/intensivists), and interventions (such as patient blood management) to help reduce the need for transfusions. Preemptive discussion of anticipated transfusion can help alert postoperative teammates such as recovery room nurses and intensivists to early signs of transfusion-related acute lung injury.[41] Beyond the perioperative team, anesthesiologists can educate about, clarify expectations of, and discuss with patients and their families the intended benefit but also possible risks (such as transfusion-related acute lung injury) of transfusion.

Perioperative Transfusion-related Acute Lung Injury Identification and Prognostication

Beyond screening for preexisting or anticipated risks, it is critical/essential to acutely monitor for and promptly diagnose transfusion-related acute lung injury in the perioperative period. However, transfusion-related acute lung injury is challenging as it is a rare diagnosis of exclusion.

Anesthesiologists should be familiar with the differential diagnosis surrounding perioperative transfusion-related acute lung injury and consider available and emerging biomarkers for diagnosis, prognosis, and longitudinal tracking of transfusion-related acute lung injury.

Differential Diagnosis of Perioperative Transfusion-related Acute Lung Injury

The differential diagnosis for transfusion-related acute lung injury is extensive. During the perioperative period, various confounding conditions share phenotypes similar to transfusion-related acute lung injury (table 2). Specifically, patients may be afflicted with preexisting conditions sharing features of transfusion-related acute lung injury such as heart failure or noncardiac conditions such as ARDS, high-altitude pulmonary, neuroendocrine, and near drowning edema or pulmonary emboli. Similarly, trauma, and primary and secondary injuries, as well as their treatments, can cause lung injury. Trauma may also frequently cause symptoms of acute lung injury, either by directly affecting the lung, *e.g.*, in pulmonary contusion, or indirectly as a consequence of shock and systemic ischemia, fat emboli from fractured long bones, or aspiration during periods of diminished consciousness and emergency airway management. Such a primary hit may be further aggravated by barotrauma, hyperventilation, and sustained 100% oxygen administration during prehospital airway management, making it difficult to discriminate from transfusion-related acute lung injury in any trauma patient who has received a transfusion. Negative pressure or reexpansion pulmonary edema as well as immune reconstitution syndrome represents additional transfusion-related acute lung injury first hits or confounders to the diagnosis of perioperative transfusion-related acute lung injury. In addition to mechanical ventilation, sudden deflation from positive-pressure ventilation may worsen lung injury.[129] Finally, surgery-related complications such as emboli may initially present similar to transfusion-related acute lung injury.

Specifically, among transfusion related complications, presentations similar to transfusion-related acute lung injury include transfusion-associated circulatory overload and transfusion-related immunomodulation as well as severe bacterial contamination reactions, most frequently seen with platelet units, which is relevant as platelets are the most implicated cellular product for triggering transfusion-related acute lung injury.[85,144–146]

Transfusion-associated Circulatory Overload

Within the transfusion-associated dyspnea spectrum, transfusion-associated circulatory overload poses diagnostic challenges when attempting to diagnose transfusion-related acute lung injury. The precise definition of transfusion-associated circulatory overload is controversial, but most authors focus on acute generation of cardiogenic pulmonary edema in association with volume overload from rapid transfusion of high volumes of blood. Transfusion-associated circulatory overload and transfusion-related acute lung injury share many similarities in presentation, response to treatment, and timing. They both can present with hemodynamic instability and pulmonary edema; however, in transfusion-related acute lung injury, the resultant permeability leads to exudative

Table 2. Differential Diagnosis of Presentations Resembling Perioperative Transfusion-related Acute Lung Injury

Respiratory Failure Related To
Surgery
Liver surgery: ischemia reperfusion injury, hepatopulmonary syndrome, shunts, graft rejection
Orthopedic surgery: fat embolus, pulmonary embolism
Neurosurgery: neuroendocrine pulmonary edema
Cardiac surgery: cardiopulmonary bypass, emboli, deflated lungs, cardiac edema, ischemia reperfusion injury, shunts, protamine, sepsis, tamponade, acute coronary syndrome, myocardial infarction
Obstetrical surgery: amniotic fluid embolism, preeclampsia, postpartum hemorrhage, myocardial infarction, high regional anesthesia block height
Other: renal failure, sepsis, pneumonia, ventilator associated pneumonia, pulmonary embolism, acute respiratory distress syndrome, high airway pressures, ventilator induced lung injury, reexpansion and negative pressure–related pulmonary edema, immune reconstitution syndrome
Trauma
Primary injury: chest contusion, pulmonary hemorrhage, rib fractures, pneumothorax, bronchopleural fistula
Secondary injury: shock, systemic ischemia, fat emboli, aspiration
Resuscitation-related: barotrauma, hyperoxia, hyperventilation, ventilator induced lung injury, lung deflation injury, large volume fluid management
Transfusion
Transfusion-associated circulatory overload
Bacterial contamination
Delayed hemolytic transfusion reaction
Hemolysis
Transfusion-related immunomodulation
Anesthesia
Equipment failure: ventilator/circuit/oxygen
Secretions: respiratory/cardiogenic
Obstruction: displaced endotracheal tube/airway, pneumothorax, inadvertent extubation, extrinsic compression/kinking of circuit/endotracheal tube
Other: malignant hyperthermia, aspiration, anaphylaxis, ventilator-induced lung injury

edema, while transfusion-associated circulatory overload is characterized by hydrostatic (cardiogenic) edema. Key differences between the diagnoses include that transfusion-associated circulatory overload is by definition strongly associated with volume overload (increased edema, increased jugular vein pressures, increased central venous pressure, increased brain natriuretic peptide), and is more likely to be associated with hypertension, transudative (*i.e.*, protein-poor and cell-free) pulmonary edema, medical comorbidities (cardiac and renal failure), and beneficial responses to diuretics in comparison to transfusion-related acute lung injury.[10,146,147] Importantly, transfusion-associated circulatory overload (general incidence of 1%) is just as, if not more, common than transfusion-related acute lung injury, and hence should be routinely considered and ruled out when a diagnosis of transfusion-related acute lung injury is suspected.[148] However, the occurrence of transfusion-associated circulatory overload does not reduce the risk or eliminate the possibility of transfusion-related acute lung injury. In contrast, transfusion-associated circulatory overload may contribute to inflammatory priming—a retrospective study showed transfusion associated circulatory overload associated with fever in 42% of recorded cases—which may in turn increase the risk of transfusion-related acute lung injury.[149]

Transfusion-related Immunomodulation

Transfusion-related immunomodulation represents a posttransfusion transient immune suppression thought to be mediated by allogeneic leukocytes (from nonleukoreduced blood) that leads to perioperative morbidity and mortality from conditions such as infections.[150] Just as seen with transfusion-related acute lung injury, transfusion-related immunomodulation can present with inflammation, neutrophil activation, leukopenia, hypotension, and fever.[151,152] The prevalence of transfusion-related immunomodulation varies around the world, as in countries such as Canada where blood is universally leukoreduced (making transfusion-related immunomodulation highly unlikely), whereas in the United States or Africa, there are considerable variations within hospitals in terms of availability of leukoreduced products. A useful distinction of transfusion-related immunomodulation's pulmonary complications from transfusion-related acute lung injury is the delayed onset and often infectious (pneumonia) etiology.[153]

Bacterial Contamination

Early signs of severe bacterial contamination that can progress to sepsis can resemble transfusion-related acute lung injury presentations in terms of hemodynamic and inflammatory responses such as hypotension, tachycardia, and respiratory distress as well as cytokine release, neutrophil activation, leukopenia, and fever. Similar to transfusion-related immunomodulation, bacterial contamination's pulmonary complications are often infectious, while transfusion-related acute lung injury is often a noninfectious pulmonary injury.

Perioperative Transfusion-related Acute Lung Injury Diagnostic Challenges

In addition to difficulties in differentiation from other transfusion-related complications, diagnosis of transfusion-related acute lung injury during surgery is further complicated due to patients commonly being on positive pressure ventilation with elevated F_{IO_2}, which can delay or alter the typical presentation of transfusion-related acute lung injury such as lung edema or hypoxemia while patients are directly under the care of anesthesiologists. In the recovery room or critical care unit, often anesthesiologists have handed over care and do not directly monitor the patient, yet this is potentially when the first signs and symptoms of transfusion-related acute lung injury will present. Hence, changes in care givers and location common with surgery in combination with transfusion-related acute lung injury's potentially delayed onset greater than 6 h increase the risk for missing a diagnosis of transfusion-related acute lung injury or possible transfusion-related acute lung injury as it is often low on the differential diagnosis.

Strategies for Perioperative Transfusion-related Acute Lung Injury Reporting

Monitoring for and accurate detection of relatively rare cases of perioperative transfusion-related acute lung injury is a major challenge. Recommended strategies include active (medical team discovers and reports perioperative transfusion-related acute lung injury) clinical monitoring (such as imaging, physical examination, vital signs), which gets incorporated into databases such as Serious Hazards of Transfusion (United Kingdom), Federal Drug Administration (United States), Canadian Blood Services (Canada), or automated means (such as computer algorithms).[10,154–156] Voluntary case tracking, both retrospective and prospective, may underestimate transfusion-related acute lung injury rates due to missed cases, ambiguity around definitions, or poor compliance recording suspected transfusion-related acute lung injury cases.[10] Passive electronic algorithms require recordable data at the time of reaction and also may underreport cases due to their inability to accommodate subtle differences in transfusion-related acute lung injury definitions, potentially leading to lumping or splitting of diagnoses.[47,157] Both active and passive strategies are considerably complicated by the complexity and pace of changes in physiology and pathophysiology due to, *e.g.*, ischemia/reperfusion injuries, trauma, or use of extracorporeal life support in patients undergoing major surgeries.

Transfusion-related Acute Lung Injury Biomarkers

An ideal biomarker for perioperative transfusion-related acute lung injury would be highly sensitive and specific and help rule out confounding diagnoses. Currently, however, available biochemical and cellular markers are not

particularly sensitive or specific for transfusion-related acute lung injury but do help rule out close imitators of transfusion-related acute lung injury such as transfusion associated circulatory overload. In particular, brain natriuretic peptide or N-terminal pro-brain natriuretic peptide are typically more elevated in transfusion-associated circulatory overload than transfusion-related acute lung injury, with one study clearly differentiating transfusion-related acute lung injury patients with brain natriuretic peptide less than 400 pg/ml from transfusion-associated circulatory overload patients who had brain natriuretic peptides greater than 500 pg/ml.[146,158] It should, however, be taken into consideration that factors such as obesity or liver cirrhosis can create falsely low or elevated brain natriuretic peptide levels, respectively, which may lead to diagnostic ambiguity to decipher between transfusion-associated circulatory overload and transfusion-related acute lung injury in these populations.[159,160] Although many reports of transfusion-related acute lung injury describe changes in peripheral platelet and neutrophil counts, these are not consistently seen, nor are the type of changes, as neutrophils can be acutely elevated or decreased in transfusion-related acute lung injury.[64,161]

Beyond biochemical and hematological markers, vital signs offer important diagnostic cues to transfusion-related acute lung injury. Tachycardia and hypotension are commonly seen, with or without acute signs of pulmonary hypertension. Similar to vital signs, pulmonary function can provide early insight into transfusion-related acute lung injury reactions. Serial perioperative Pao_2/Fio_2 ratio monitoring, which—not surprisingly in patients commonly on mechanical ventilation at supranormal Fio_2—is more sensitive than measurement of changes in O_2 saturations, may be an alternative biomarker for transfusion-related acute lung injury.[35] Yet this technique may bias to sicker patients and exclude milder or emerging transfusion-related acute lung injury reactions which do not (yet) have extreme changes in Pao_2 requiring elevated Fio_2.[162] Although potentially less accurate than Pao_2/Fio_2 ratios, oxygen saturations/Fio_2 ratios have the advantage of being more universally available, as they can be calculated without requirement for arterial blood gas sampling. In addition to measures of hypoxemia, although not commonly available unless complex surgery is being undertaken, monitoring pulmonary artery and wedge pressures may help discriminate between transfusion-associated circulatory overload (high wedge pressure, low transpulmonary gradient) *versus* transfusion-related acute lung injury (low wedge pressure, with frequently higher transpulmonary gradient). Another often overlooked, but useful, monitor is edema fluid itself. Although often present and abundant during acute transfusion-related acute lung injury presentations, alveolar edema fluid is rarely collected and assayed for protein content. Testing of edema fluid for protein concentration within the first 15 min of presentation of suspected transfusion-related acute lung injury is useful to determine if it is transudative (more in keeping with cardiac edema or transfusion-associated circulatory overload) as opposed to exudative (in line with transfusion-related acute lung injury).[38,40,58] In addition to invasive diagnostics, echocardiography may provide for a more globally accessible monitoring of pressures and flows. Transthoracic and esophageal echocardiography are useful adjuncts that offer opportunity to guide resuscitation and assess for elevated circulating volume status (transfusion associated circulatory overload ± cardiogenic edema greater than transfusion-related acute lung injury). Although not commonly accessible, a recent prospective study examining effects of washing erythrocytes on perioperative transfusion-related acute lung injury incidence shows association with biomarkers such as interleukin-6, interleukin-8, cytokines (Chemokine (C-C motif) ligand 5), coagulation mediators (plasminogen activator inhibitor 1, von Willebrand factor), cell surface antigens (intercellular adhesion molecule-1, receptor for advanced glycation endproducts, soluble CD40 ligand), pulmonary markers (surfactant D), lipids, erythrocyte-derived extracellular vesicles, erythrocyte breakdown products including cell-free hemoglobin, heme, and N-terminal pro-brain natriuretic peptide.[140] Certain biomarkers also help to determine the mechanism of action of transfusion-related acute lung injury: Detection of antihuman leukocyte antigen class I/II or antihuman neutrophil antigens in patients or transfusion products as well as experimental assessment of their potencies to elicit transfusion-related acute lung injury (*in vitro* [cell culture], *in situ* [isolated lung models], or *in vivo* [animal models]) is valuable for stratifying antibody from non–antibody-mediated transfusion-related acute lung injury.[161] Serum tryptase (if sampled less than 2 h from onset of symptoms) is another biomarker worth considering in order to rule out differential diagnoses such as anaphylaxis or allergic transfusion reactions.[163]

Experimental Perioperative Transfusion-related Acute Lung Injury Biomarkers

Biologic response modifiers represent biomarkers for monitoring non–antibody-mediated transfusion-related acute lung injury and include soluble CD40 ligand, lipids (such as lysophosphatidyl choline and ceramide), donor-derived extracellular vesicles, or elevated levels of damage-associated proteins such as mitochondrial DNA, while biomarkers such as C-reactive protein and interleukin-8 or deficiency of interleukin-10 are likely common to both antibody- and non–antibody-mediated transfusion-related acute lung injury.[93,103,121,122,164] Interleukin-10 deficiency in transfusion-related acute lung injury is an especially interesting candidate biomarker as it appears to offer some specificity from other confounding inflammatory responses associated with lung injuries.[121] An alternative promising yet so far underinvestigated candidate biomarker is extracellular vesicles. Extracellular vesicles accumulate in donor products and are detectable upon transfusion in the circulation of recipients. Extracellular vesicles may thus represent a means

of screening donor product quality and then monitoring for signs of transfusion-related acute lung injury once transfused into recipients. Currently, use of extracellular vesicles is only a research tool and is limited by challenges in acquiring the extracellular vesicles from patients and blood products, handling and processing them, storing them, and then reproducibly assaying them. However, standardization and enhanced procedures for reproducible acquisition and analysis of extracellular vesicles are a rapidly evolving area of research, making utilization of extracellular vesicles as a clinical biomarker an obtainable aim in the near future.[165,166]

Perioperative Transfusion-related Acute Lung Injury Treatment

Currently, there are no specific treatments available for transfusion-related acute lung injury. Once perioperative transfusion-related acute lung injury is suspected, it is important to assess recent and current transfusion, recruit appropriate help, begin treating (tertiary prevention) with supportive measures, and consider opportunities for pharmacologic management (fig. 4).

Reassess Transfusion Products

If transfusions of blood products are still ongoing, they should be stopped immediately, and samples of these or other available recently delivered (within the last 6 to 72 h) products should be sent off for further testing (including microbiologic testing) by the blood bank.[57] The patient should have a new type and screen sent in case of blood group error. If lifesaving transfusion is urgently required, then blood bank policy–specific uncrossmatched components can be delivered. Alternatively, solvent–detergent plasma may be favored on account of its negative association with transfusion-related acute lung injury.[125]

Obtain Expert Consultation

Depending on hospital resources, consultation and involvement of other teammates may increase resources and effectiveness of transfusion-related acute lung injury diagnosis and management. Consultation of intensivists may occur as early as in the operating room, facilitating echocardiographic assessment (for differential diagnosis and to guide fluid management), or patient handover to their care postoperatively.[50,52] The blood bank and or hematologists need to be involved for transfusion logistics and testing. Once the blood bank is aware of a suspected reaction, they take charge of immediately quarantining the suspected products. Next, they investigate implicated donors to make a ruling on the need for deferral of future products, and finally look to the past to link implicated donors to other transfusion reactions, which all contribute to general improvements in safety for future patients.

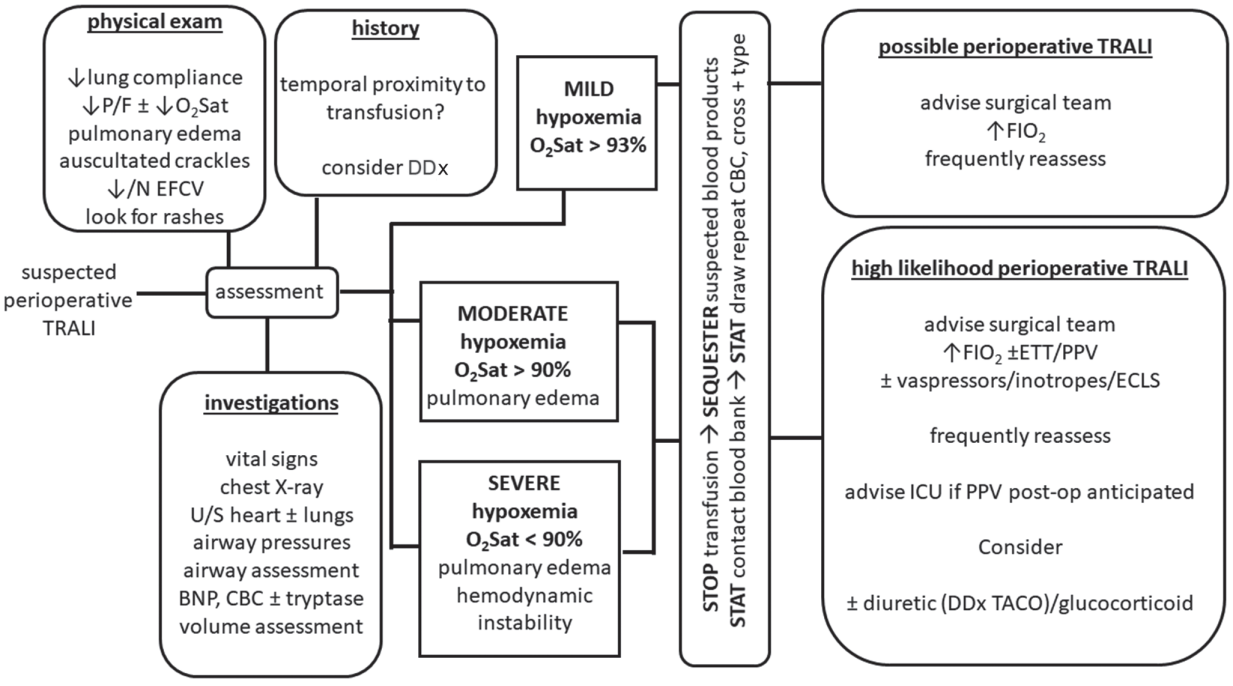

Fig. 4. Diagnostic and treatment algorithm for suspected perioperative transfusion-related acute lung injury (TRALI). BNP, brain natriuretic peptide; CBC, complete blood count; DDx, differential diagnosis; ECLS, extracorporeal life support; EFCV, effective fluid circulating volume; ETT, endotracheal tube; FIO_2, fraction of inspired oxygen; ICU, intensive care unit; N, normal; O_2Sat, oxygen saturation; P/F, arterial oxygen partial pressure/fraction of inspired oxygen; PPV, positive pressure ventilation; TACO, transfusion-associated circulatory overload; U/S, ultrasound.

Perioperative Transfusion-related Acute Lung Injury Supportive Care

Historically, intubation, positive pressure ventilation, and oxygen delivery have been associated with increased perioperative transfusion-related acute lung injury survival (table 1). In extreme cases where gas exchange is severely limited by pulmonary edema, initiation of extracorporeal life support has been life-sustaining.[51] It should, however, be noted that preexisting use of extracorporeal life support can also be a potential source of inflammation, which in turn may be a first hit in transfusion-related acute lung injury. Perhaps in the perioperative setting in particular, starting extracorporeal life support is more feasible, as surgeons and equipment are more immediately available, expediting cannulation and initiation of flows. Rare accounts describe use of plasmapheresis to reduce antibody titers in recipients, yet limited access and speed of initiating this intervention reduce its utility as an elective means of treatment.[56] Patients diagnosed with transfusion-related acute lung injury often require critical care support due to their prolonged requirement for mechanical ventilation. In these cases, intensive care unit settings may allow for additional adjunctive strategies such as establishing parameters (positive end-expiratory pressure, minute ventilation, tidal volumes) for mechanical ventilation driven by ARDS experience/guidelines, prone positioning for improved lung recruitment and ventilation/perfusion ratio matching, and extracorporeal life support.[167]

Pharmacologic Treatment of Transfusion-related Acute Lung Injury

Though pharmacologic strategies are limited currently with no good existing options of medications for transfusion-related acute lung injury beyond oxygen, improved insight into the preclinical mechanisms of transfusion-related acute lung injury has given yield to new therapeutic strategies such as supplementation of interleukin-10 or lowering C-reactive protein, interleukin-8, and reactive oxygen species levels with the use of antiinflammatory agents or reactive oxygen species scavengers.[168] The use of diuretics (likely often due to initial confusion with transfusion-associated circulatory overload or cardiogenic shock) has not been proven to be effective to reduce transfusion-related acute lung injury. If diuretics are used, volume status should be carefully assessed as diuresis may aggravate hypotension commonly seen with transfusion-related acute lung injury. In rodent models of experimental transfusion-related acute lung injury, 2 mg/kg dexamethasone decreased pulmonary levels of tumor necrosis factor-α but did not reduce neutrophil recruitment or other markers of inflammation such as interleukin-1β or macrophage inflammatory protein-2.[169] In line with these ambiguous preclinical data, glucocorticoids have often been given to patients with transfusion-related acute lung injury, but their contribution to lessening disease severity or hastening recovery remains unclear.

Follow-up

Once a transfusion-related acute lung injury reaction has passed, one of two outcomes has happened. The patient is dead, in which case an autopsy should be considered to explore the cellular and organic changes that occurred. If the patient survives, the perioperative team should debrief on aspects of the care provided that could lead to better prevention or treatment of transfusion-related acute lung injury reactions. If not already done, the patient should have a repeat crossmatch conducted if there is an ongoing need for transfusion. The patient should be counseled around the possibility of recurring-transfusion–related acute lung injury.[170,171] Recurrent-transfusion–related acute lung injury is a rare entity and as such is understudied in terms of risk factors or etiology.[171]

Regardless of outcome, the perioperative team should collect all remnant transfusion products such as component segments (small cylindrical infusion tubing attached to the main blood product) from suspected blood products for further testing, which is commonly organized and coordinated by the local blood bank, transfusion medicine physicians, or hematology department.[50,54] The blood bank may request other samples for investigation such as patient blood or bronchorrhea fluid. Notably, a retrospective 3-yr look back on 1,000 adult cardiac surgery patients revealed an incidence of transfusion-related acute lung injury of 2.4% (16 cases) of whom, however, only 1 was reported to the blood bank as a possible transfusion-related acute lung injury,[16] suggesting significant underreporting of transfusion-related acute lung injury and underutilization of blood bank resources for prospective, acute, and retrospective transfusion-related acute lung injury consultation. While blood bank tests to investigate transfusion-related acute lung injury reactions are currently scarce, early involvement of the blood bank in suspected transfusion-related acute lung injury reactions is mandatory so that suspected products may be diverted before affecting more individuals.[52]

Gaps in Understanding Related to Perioperative Transfusion-related Acute Lung Injury: Opportunities for Research

Transfusion-related acute lung injury research up to now has increased our understanding of the incidence, presentation, and mechanisms of transfusion-related acute lung injury. Yet many aspects of transfusion-related acute lung injury remain unclear. Advances in understanding of transfusion-related acute lung injury mechanisms led to antibody mitigation strategies (to reduce second hits), which showed signs of reducing but not eliminating transfusion-related acute lung injury rates.[5] Yet the true impact of antibody mitigation has yet to be determined as certain reports actually show no reductions in transfusion-related acute lung injury rates or 30-day mortality after initiation of antibody-mitigation

efforts.[126] Mediators and cellular targets have not been conclusively confirmed with preclinical models and clinical accounts of transfusion-related acute lung injury, which has limited efforts to create biomarkers and treatments. Transfusion-related acute lung injury may remain underreported in perioperative patients due to confounding or concurrent lung injury diagnoses preventing definitive transfusion-related acute lung injury diagnosis, but also barriers to reporting such as multiple care givers in multiple settings providing care (such as is typical in care for perioperative patients). As our ability to characterize and diagnose transfusion-related acute lung injury improves, there is an ongoing need to revisit the pathophysiology and epidemiology of transfusion-related acute lung injury to reassess risk factors and attempts to prevent and treat transfusion-related acute lung injury. In parallel, investigation of the effects of various anesthesia medicines on transfusion-related acute lung injury remains largely unstudied and may influence transfusion-related acute lung injury in the perioperative period.[172] For example, neuromuscular blockade can inhibit inflammation in the context of ARDS and mechanical ventilation,[172] yet its effect on transfusion-related acute lung injury has so far not been addressed.

Conclusions

Although transfusion-related acute lung injury has one of the highest mortalities of all transfusion adverse events, it is hard to diagnose in the perioperative period and therefore requires vigilance and preparedness to detect and manage effectively. Nearly 50% of all transfusions take place perioperatively, with 41% of these blood products being delivered during surgery.[10,157] Accordingly, Alam *et al.* estimate that 38% of all transfusion-related acute lung injury reactions originate from the perioperative period,[46] and this number is likely to increase further over the coming years. Not only is the diversity of transfused products increasing including new cellular products (T cells, stem cells, bone marrow transplants) but so is the perioperative clinical demand for blood products.[114–116,173] Increasing complexity and duration of surgeries and the increasing severity of illness of patients undergoing surgical interventions requiring transfusions (increased American Society of Anesthesiologists scores known to correlate with transfusion-related acute lung injury risk) further increase the risk of perioperative transfusion-related acute lung injury. Finally, improved recognition and reporting are expected to further increase the incidence of documented or suspected transfusion-related acute lung injury.

Considering the difficult diagnosis of transfusion-related acute lung injury by exclusion and the presence of many confounders especially in the perioperative setting, it is important to have a team approach for predicting, preventing, treating, and following up transfusion-related acute lung injury–like reactions. Regardless of the diagnostic nomenclature used, lung injury rivaling transfusion-related acute lung injury's severity in the context of recent transfusion in the perioperative period has a high mortality, and needs early diagnosis, resource allocation, and prompt treatment. Some aspects of transfusion-related acute lung injury can be predicted (risks/biomarkers), but intense efforts are required to recognize and reduce transfusion-related acute lung injury risks. Anesthesiologists and critical care physicians caring for perioperative patients are uniquely positioned to become leaders in transfusion-related acute lung injury due to their proximity to the patient, their role of directly delivering and monitoring blood products, their ability to arrange rapid testing, and their ability to coordinate teammates, resources (intensive care unit/extracorporeal life support), and follow-up. First steps should consist of increasing awareness and training, perioperative monitoring, and reporting of transfusion-related acute lung injury, to allow more accurate epidemiologic characterization and establishment of risk factors. Development of prospective risk scores to better predict transfusion-related acute lung injury during the perioperative period would help triage at-risk patients who may require additional monitoring or preventative strategies during their hospital stay to minimize transfusion. Last, establishing and testing emerging new therapies from preclinical studies or analysis of large patient databases may offer improved care for those afflicted by transfusion-related acute lung injury; however, it should be kept in mind that prospective randomized trials for treatment of transfusion-related acute lung injury are nearly impossible due to its relatively rare incidence.

Research Support

Support was provided solely from institutional and/or departmental sources. Dr. McVey is supported by a Canadian Institute of Health Research Vanier Scholarship.

Competing Interests

The authors declare no competing interests.

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