Advancing Transfusion and Cellular Therapies Worldwide

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To: AABB Members

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Re: Transfusion-Associated Circulatory Overload (TACO)

Summary
The AABB Clinical Transfusion Medicine Committee has developed this bulletin to provide background information and guidance to members regarding transfusion-associated circulatory overload (TACO). The bulletin includes recent information on proposed definitions for TACO and recommendations for its prevention and treatment.

Association Bulletins, which are approved for distribution by the AABB Board of Directors, may include announcements of standards or requirements for accreditation, recommendations on emerging trends or best practices, and/or pertinent information. This bulletin contains information and recommendations regarding TACO recognition, prevention, and treatment. No new standards are proposed.

Background
TACO remains a leading cause of transfusion-related morbidity and mortality, accounting for 27% of the transfusion-related fatalities reported to the United States Food and Drug Administration (FDA) for fiscal year (FY) 2020.[1] The 2021 Serious Hazards of Transfusion (SHOT) Hemovigilance report from the United Kingdom observed that TACO may have contributed to 21.2% of transfusion-related deaths and major morbidity.[2] In addition to its associated mortality, TACO results in substantial resource utilization and associated health-care cost. Clinical evidence demonstrates that up to 21% of TACO cases are life-threatening with associated increases in the duration of time in the intensive care unit (ICU) and hospital stay.[3-7]

Although TACO symptoms have been recognized for more than half a century, the epidemiology, mechanisms, and attributable burden of TACO are incompletely understood. Indeed, multiple recent reports highlight concerns related to under-recognition and underreporting of TACO episodes.[6,8-10] The failure to recognize the association of transfusion with the onset of respiratory distress is presumed to be at least partially responsible for the lack of effective clinical evaluation, prevention, and therapeutic interventions for at-risk patients.

The primary pathophysiologic process underlying TACO pathogenesis is believed to be fluid overload with resulting hydrostatic (cardiogenic) pulmonary edema.[3,11] An intriguing question is

whether circulatory overload due to transfusion of blood components involves other physiologic mechanisms in addition to those associated with fluid overload from excessive administration of crystalloids (eg, normal saline, dextrose). Recently, additional and potentially synergistic mechanisms have been proposed in diverse physiologic domains including inflammation and altered vasoreactivity (eg, nitric oxide scavenging).[12-17] Although the roles of these alternate mechanisms remain incompletely defined, it is clear that a number of patient and transfusion characteristics have been consistently identified as risk factors for development of TACO.[6,7,13,18,19] Improved understanding of these risk factors as well as the mechanisms underlying TACO may provide opportunities for risk modification.

This bulletin reviews TACO incidence and risk factors, diagnosis, treatment, and prevention in adult and older pediatric patients. TACO has been recognized as a possible adverse transfusion reaction in neonates, as this patient population is vulnerable to volume overload due to their small circulatory volumes.[20] However, TACO features are not well-described enough at this time in neonatal patients (particularly premature neonates) to make consensus recommendations for recognition, treatment, and prevention.[21]
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Incidence and risk factors

TACO incidence, as determined by passive reporting to national hemovigilance systems, varies substantially across countries and over time within the same country. Although incidence appears to be increasing in some hemovigilance systems, this is most likely due to increased recognition and reporting rather than a true increase in case rate. However, even with increased recognition of TACO morbidity, recent studies using active surveillance continue to document substantial under-reporting to hospital transfusion services.[9]

More accurate incidence numbers have been obtained in focused clinical studies, albeit in specific hospitals with a tertiary-care patient population. Recent studies have documented a per-patient TACO incidence at 2-6%.[6,22,23] These reports are also consistent with several older patient-centered reports in elderly orthopedic patients.[24,25] TACO can occur after transfusion of Red Blood Cells (RBCs), platelets, or plasma.[4,5,9,10]

TACO risk factors were initially identified through descriptive case series, as with transfusion related acute lung injury (TRALI), following one of its first descriptions in 1943.[26] Older publications state that recipient age (<3 years or >60 years) is a risk factor. In the last decade, several case-control studies have reported associations with preexisting recipient conditions and/or transfusion characteristics (eg, transfusion volume and infusion rate). A case control study examined risk factors for TACO in transfused hospitalized patients older than 6 months of age, using a combination of electronic medical record surveillance and physician case review.[7] Of 47,783 patients receiving transfusion, 166 distinct cases (0.34%) of TACO were identified. Multivariate analysis found statistically significant associations between TACO and chronic renal failure [odds ratio (OR), 27.0], congestive heart failure (CHF) (OR, 6.6), number of blood products transfused (OR, 1.11 per unit), fluid balance per hour (OR, 9.4 per liter), and age (inversely; OR, 0.78 per 10 years).

Critically ill adult patients appear to have increased vulnerability to TACO. A retrospective nested case-control study examined the prevalence of risk factors in critically ill patients who developed TACO as compared to matched controls.[22] Of 1351 transfused patients, 25 (1.9%) developed TACO, yielding a per patient incidence of 1.9%; on a per unit transfused basis, the incidence was 0.18%. Transfusion volumes and 24-hour fluid balance were significantly higher in those patients developing TACO. A single center prospective cohort study observed medical intensive care unit (MICU) patients over a 2-year period for respiratory complications following transfusion.[23] Of the 901 transfused MICU patients, 51 (6%) developed TACO. Significant baseline risks for TACO determined by multivariate analysis included left ventricular dysfunction [OR, 8.23; range, (3.36-21.97)] and transfusion of plasma for anticoagulant reversal [OR, 4.31; range, (1.45-14.30).] When compared to matched controls, those patients developing TACO had significantly higher fluid balances, larger plasma transfusion volumes, and faster transfusion rates.[23]

The epidemiology of TACO in the perioperative setting was discussed in a single-center cohort study examined the incidence of TACO in 4070 adult noncardiac surgical patients receiving intraoperative transfusion.[6] Of those patients, 176 [4.3%; 95% confidence interval (CI), 3.7 to 5.0%] experienced TACO; multivariate analysis showed a significant reduction in the rate of TACO between 2004 and 2011, from 5.5% to 3.0% ($p<0.001$). Vascular, transplant, and thoracic surgeries were found to have the highest TACO rates, with obstetric and gynecologic surgeries showing the lowest rates.

Similar to nonsurgical settings, the elderly appeared most vulnerable to TACO; those patients 80 years or older had a nearly fourfold higher rate than patients younger than age 50 (7.4% vs 2.0%, respectively). Increasing transfusion volumes and positive fluid balances were also significantly associated with TACO ($p<0.001$ for both).

A retrospective case series of 100 TACO patients at two Canadian hospitals reported that CHF was present before transfusion in 41% of cases, renal function was compromised in 44%, and 56% of patients were older than age 70.[27] Furthermore, 73% of patients were judged to have fluid overloaded before the transfusion that preceded the TACO diagnosis.

It is not surprising that both CHF and fluid overload appear as risk factors for TACO in multiple studies, as both of these are included as contributing elements to the diagnosis of TACO (see below). Although one should be cautious in comparing TACO risk factors across studies due to differences in case ascertainment and diagnostic criteria, it is notable that case-control studies and descriptive case series have identified similar TACO risk factors (**Table 1**).

Hemovigilance systems definitions

Hemovigilance systems worldwide have established diagnostic criteria for definitions of TACO. Two hemovigilance system definitions—from the International Society for Blood Transfusion (ISBT) and the Centers for Disease Control and Prevention (CDC)—are summarized in **Table 2**;

both require that symptoms occur within 12 hours of the transfusion.[28,29] These hemovigilance systems, among others, provide clinical, radiographic, and laboratory criteria for diagnosis of TACO. The current ISBT diagnostic criteria for TACO are employed by other hemovigilance systems (i.e., as the Serious Hazards of Transfusion in the UK).

Differential diagnosis

TACO must be distinguished from other pulmonary syndromes that may occur during or shortly after transfusion. The most important alternate diagnosis is TRALI. Distinguishing TACO from TRALI can be challenging, and these entities sometimes co-occur (**Table 3**).[30] On chest radiograph, diffuse bilateral infiltrates are seen in both conditions. The critical distinction is whether the observed pulmonary edema is noncardiogenic (TRALI) or cardiogenic (TACO) in nature. Today, Swan-Ganz catheterization is rarely performed, but in cases of severe respiratory decompensation, echocardiography may be available, allowing an assessment of whether left ventricular function is normal (as in uncomplicated TRALI) or abnormal (TACO). Brain natriuretic peptide (BNP) and N-terminal proBNP levels are established noninvasive markers of CHF and have been shown to be elevated in TACO.[31-33] However, based on the sparse available literature, these tests may have limited predictive value in distinguishing TRALI from TACO.[34,35] In most cases, the diagnosis of TACO is made clinically, based on the medical history, an assessment of the patient's fluid volume status, baseline cardiac function, and response to diuretic challenge. Diuretic administration is ineffective in treating TRALI, but will often produce rapid improvement in oxygenation status in cases of TACO. Hypertension is characteristically seen in cases of TACO. In TRALI, either hypertension or hypotension may be seen, but hypotension is more common. A transient, precipitous decline in total peripheral leukocyte count is sometimes observed in cases of TRALI[36]; this would not be expected in TACO cases. Finally, acute respiratory distress syndrome (ARDS) entirely unrelated to transfusion may occur in a transfused patient. Thus, other etiologies of ARDS need to be considered when the diagnosis of TRALI or TACO is being entertained.

The other main diagnosis that should be considered in cases of suspected TACO is an allergic reaction with a pulmonary component. Here, the presence or absence of other clinical features consistent with a hypersensitivity reaction (eg, urticarial rash) may be helpful. On lung auscultation, the presence of expiratory wheezing is suggestive of an allergic reaction (bronchospasm), although this is not a specific finding. In TACO, inspiratory crackles are typically heard. Response to antihistamines can often help support the diagnosis of an allergic reaction, although in some situations both diuretics and antihistamines will be given simultaneously.

Air embolism is an extremely rare but potentially devastating cause of cardiopulmonary decompensation in a transfusion recipient. Other causes of respiratory compromise that are unrelated to transfusion include pulmonary syndromes such as acute asthma, pulmonary embolism, and pneumothorax. Finally, a variety of cardiac syndromes may manifest as "flash" pulmonary edema in a transfusion recipient, including entities such as acute myocardial infarction and arrhythmia.

Prevention

An effective prevention strategy for TACO, as with other adverse transfusion reactions, is to avoid unnecessary transfusion by transfusing patients only when the benefits outweigh the risks. Another key step in TACO prevention is identification of underlying risk factors (**Table 1**). However, the ideal prevention strategy for TACO has yet to be determined. Very few studies are available to assess the prevalence of prevention strategies. No controlled studies are available to compare the effectiveness of different strategies, but several approaches have been proposed and implemented for patients worldwide when deemed necessary by clinicians.

Use of diuretics

The first approach is to administer diuretics to potentially susceptible patients before transfusion. There is little information on how frequently diuretics are used for this purpose. Fry et al, reported minimal use of diuretics before transfusion in their observational retrospective review.[37] However, they audited only the first transfusion of the day, which would result in missing any premedications for TACO that were given in between units. Two studies found that, as expected, pretransfusion diuretic therapy was not protective against TRALI.[23,38] However, based on the potential for confounding factors in these studies (ie, higher use of diuretics in patients at increased TACO risk), it is difficult to draw conclusions about the effectiveness (or lack thereof) of this approach. Sarai and Tejani performed a Cochrane review to determine if the prophylactic administration of loop diuretics provides a therapeutic advantage for blood transfusion recipients vs placebo, no treatment, or general fluid restriction measures, but concluded there was insufficient evidence available to answer the question.[39] Although premedication with diuretics may be helpful for at-risk patients, insufficient data are available to either support or refute this practice. It is worth noting that the use of diuretics is not without adverse effects, including hypovolemia and hypokalemia.

Decrease in transfusion volume and/or infusion rate

Decreasing the transfusion rate and the volume of the blood components infused may also be beneficial. Li et al found that the mean transfusion rate in patients who developed TACO was 225 mL/hour compared to 164 mL/hour in matched controls in their prospective observational study.[23] Decreasing the volume of the transfusion and/or the infusion rate may be achieved in multiple ways. One can perform a single unit transfusion and then assess efficacy before transfusing additional units (eg, transfusing one unit of RBCs, then checking the hemoglobin level before ordering a second unit). Second, a unit can be volume-reduced to remove unnecessary plasma from cellular components. Third, a unit can be split using a sterile method to allow two smaller dose transfusions, each of which can be infused at a slower rate than could be achieved if the unit were not split. Finally, a hospital could choose to establish prescriptive guidelines in the hospital's blood administration policy. This could be in the form of a consistent hospital-wide protocol for infusion of fluids and blood components (e.g., a controlled and precise blood component infusion rate through the use of computerized infusion pumps) [18] or a guideline could be targeted to patients with, or at risk for, TACO.

Warfarin reversal

One specific clinical scenario merits mention in consideration of TACO prevention: warfarin reversal. Four-factor prothrombin complex concentrate (4-PCC) is approved by the FDA for emergent warfarin reversal in patients with acute major bleeding or those who require urgent surgery or an invasive procedure.[40] In the United States, warfarin reversal has traditionally been performed using plasma; however, the infused volume necessary for a therapeutic effect may place patients at risk for TACO. A Phase IIIb, open label, non-inferiority randomized trial compared 4-PCC to plasma in patients experiencing major bleeding, with primary outcomes of hemostatic response and achievement of an international normalized ratio (INR) <1.3 within 30 minutes of infusion completion.[41] Median volume administrations for 4-PCC and plasma were 99.4 and 813.5 mL, respectively, with 4-PCC demonstrating non-inferiority to plasma in achieving effective hemostasis within 24 hours (72.4% vs 65.4%, p=0.0045). Accordingly, 4-PCC can provide warfarin reversal with significantly smaller infusion volumes. Furthermore, the *Circular of Information for the Use of Human Blood and Blood Products* notes that plasma transfusion is contraindicated when warfarin reversal can be corrected more effectively by prothrombin complex concentrates.[42]

Careful monitoring

Prevention through early recognition by careful monitoring of vital signs may also be an option for preventing TACO. Andrzejewski et al found that although no single vital sign value was diagnostic of TACO, the absolute and delta changes for pulse pressure at the different time points of transfusion may be predictors for the development of TACO.[13] Lieberman et al also reported increases in mean systolic, diastolic, and pulse pressure.[27] If these vital sign changes are identified in real time, an intervention may be possible to prevent TACO.[13]

Physician education

Once risk factors and prevention strategies have been identified, the education of clinicians in TACO risk-identification is an important step in preventing this reaction. If clinicians are unaware of the risk and prevalence of TACO, they are less likely to take the needed steps to prevent TACO. Traditional lectures and interactive education modules focused on the recognition, prevention, and treatment of TACO can be helpful in educating physicians. In addition, clinical decision support software during physician order entry for blood products may assist clinicians as they make transfusion decisions.[18] Important reminders about a patient's underlying risk factors (i.e., heart failure) for TACO during the order process may cause a provider to reconsider the medical necessity of a transfusion, consider premedication with a diuretic, or remember to instruct nurses to transfuse the minimum acceptable dose slowly.

Treatment

Once TACO is suspected or diagnosed, the transfusion should be immediately stopped and reported to the transfusion service for investigation of other transfusion reactions associated with respiratory distress (such as TRALI and anaphylaxis). The patient should be monitored by pulse oximetry and appropriate oxygen therapy provided. The patient should be placed in an upright posture, if possible, to promote oxygenation via maximum chest expansion.

Additional infusions that exacerbate volume overload should be halted when clinically appropriate. Loop diuretics, such as furosemide, are usually given to reduce cardiac preload via diuresis and direct venodilation.

In more severe cases of TACO, ventilator support or intensive care may be needed. As with other etiologies of hydrostatic lung edema (i.e., CHF), non-invasive approaches to mechanical ventilation such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) should be considered. These less invasive modes of mechanical ventilation have been shown to reduce the need for endotracheal intubation as well as mortality in patients with acute hypoxemic respiratory insufficiency resulting from cardiogenic pulmonary edema.[43-45] Of note, caution should be used when considering the initiation of non-invasive ventilator support in those with concomitant respiratory or metabolic acidosis or associated shock as these factors have been shown to predict failure with less invasive approaches to respiratory support.[46] When invasive mechanical ventilation is required, lung protective strategies should be implemented using low-tidal volume ventilation (< 6 mL/kg of ideal body weight) while maintaining an inspiratory plateau pressure of < 30 cm H_2O.[47-49] At the present time, data are insufficient to provide definitive guidance on the optimal management of positive end-expiratory pressure (PEEP) levels in patients with TACO who are requiring full ventilator support.

Some reports have found that TACO may have an associated inflammatory component,[12,13] in which case the addition of an anti-inflammatory agent, such as steroids, may be of benefit. However, this is purely hypothetical and has never been shown in a well-designed study. For refractory cases, hemodialysis may be required.

Key points and recommendations

TACO prevention strategies

Hospitals should consider the following strategies to help prevent TACO:

1. Transfuse blood components only when the benefits outweigh the risks of transfusion.
2. Educate clinicians on recognition of risk factors: elderly patients, left ventricular dysfunction, congestive heart failure, pretransfusion fluid overload, large transfusion volumes, and infusion rate.
3. Transfuse at-risk patients at slower infusion rates.
4. Hospital-wide infusion protocols and, when possible, and use of rate-controlled transfusion via infusion pump.
5. When possible, and clinically indicated, perform emergent warfarin reversal using 4-PCCs instead of plasma
transfusion.
6. Modify blood components with volume reduction or split large-volume units for patients at risk of TACO.

TACO Treatment Recommendations

In treating patients with TACO, providers should consider the following:

1. Stop transfusion upon recognition of possible TACO

2. Provide supplemental oxygen, place patient in an upright position and monitor oxygen saturation levels by pulse oximetry.
3. Consider non-invasive ventilation such as CPAP or BiPAP, if not clinically contraindicated, as well as early cardiopulmonary or critical care consultation.
4. Consider diuretics for TACO treatment, if not clinically contraindicated.
5. Consider patient transfer to ICU and need for mechanical ventilator support in severe cases of TACO.
6. Educate clinicians on the importance of reporting suspected cases of TACO immediately to the transfusion service.

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Table 1. Risk factors for Transfusion-Associated Circulatory Overload (TACO)

Patient demographics
Age (elderly patients)
Medical conditions
Left ventricular dysfunction/congestive heart failure
Chronic renal failure
Transfusion and fluid therapy
Infusion rate
Number of blood products administered/total transfused volume
Positive fluid balance prior to transfusion

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Table 2. Comparison of ISBT and CDC Hemovigilance system diagnostic criteria for TACO[28,29]

	ISBT	CDC
Timing of respiratory distress onset	Occurring during or within 12 hours of transfusion	Within 12 hours of cessation of transfusion
Surveillance Diagnostic criteria	REQUIRED CRITERIA A. Acute or worsening respiratory compromise B. Evidence of acute or worsening pulmonary edema based on: 1. Clinical physical examination, and/or 2. Radiographic chest imaging and/or other non-invasive assessment of cardiac function e.g. echocardiogram ADDITIONAL CRITERIA C. Evidence for cardiovascular system changes not explained by the patient's underlying medical condition D. Evidence of fluid overload E. Supportive result of a relevant biomarker eg. increase of B type natriuretic peptide level	REQUIRED CRITERIA • Evidence of acute or worsening respiratory distress and/or • Radiographic or clinical evidence of acute or worsening pulmonary edema; or both AND ADDITIONAL CRITERIA • Elevated brain natriuretic peptide (BNP) or NT-pro BNP relevant biomarker • Evidence of cardiovascular system changes not explained by underlying medical condition • Evidence of fluid overload
Confirmed/definite case definition	At least 1 required criterion (A and/or B) and a total of 3 or more criteria (A to E)	Three or more of the surveillance diagnostic criteria with at least one of the required criteria
Possible/Probable case definition	Not applicable	Probable: Transfusion is a likely contributor to volume overload *and either* the patient received other fluids *or* the patient has a history of cardiac insufficiency

		Possible: Patient history of cardiac insufficiency that most likely explains volume overload.

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Table 3. Clinical features of TRALI versus TACO [Adapted from Skeate and Eastlund[30] (30)]

	TRALI	**TACO**
Similar features		
• Chest X-ray	Diffuse bilateral infiltrates	Diffuse bilateral infiltrates
• Respiratory symptoms	Acute dyspnea	Acute dyspnea
• Auscultation	Rales	Rales, occasionally S3
Disparate features		
• Temperature	Often elevated	Often unchanged
• Blood pressure	Hypotension	Hypertension
• Pulmonary artery • occlusion pressure	≤18 mmHg	>18 mmHg
• Response to diuretic	Minimal	Significant
• Pulmonary edema fluid	Exudate	Transudate
• WBC count	May have transient leukopenia	Unchanged
• Fluid balance	Positive, even, negative	Positive

TRALI = transfusion-related acute lung injury, TACO = transfusion-associated circulatory overload.

Note: Readers are cautioned that patients with either TRALI or TACO may lack some typical features of these adverse reactions. Furthermore, patients with TRALI may have some features suggestive of TACO (or vice versa). Lastly, TRALI and TACO can on occasion present concurrently.