Distinguishing between transfusion related acute lung injury and transfusion associated circulatory overload
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Purpose of review
The purpose of this review is to provide an overview of concepts recently presented in the literature that impact our understanding of transfusion related acute lung injury (TRALI) and transfusion associated circulatory overload (TACO), and how to distinguish between the two disorders.

Recent findings
An exceptionally clear review article by Brux and Sachs clarified the two-hit model of TRALI pathogenesis. The TRALI definition developed at the 2004 consensus conference helped demonstrate that TRALI is likely underreported. Brain natriuretic peptide can be useful in distinguishing cardiogenic from noncardiogenic pulmonary edema. Blood centers are implementing male predominant plasma programs to limit TRALI, and preliminary evidence suggests that this is a useful intervention.

Summary
TACO and TRALI have emerged as important causes of posttransfusion morbidity and mortality. As understanding of their pathogenesis improves, incidence, risk factors, differences, and possible preventive interventions are becoming clearer. There is no sentinel feature that distinguishes TRALI from TACO. Developing a thorough clinical profile including presenting signs and symptoms, fluid status, cardiac status including measurement of brain natriuretic peptide, and leukocyte antibody testing is the best strategy currently available to distinguish the two disorders.

Keywords
circulatory overload, diagnosis, TACO, TRALI, transfusion

Introduction
Transfusion reactions can be difficult to evaluate [1*]. Determining the correct diagnosis is important because there are implications for the patient, the donor, and the other products associated with the involved donation [2*]. Pulmonary transfusion reactions can be especially difficult to investigate. The differential diagnosis includes allergic/anaphylactic reactions, transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), bacterial contamination, and hemolytic transfusion reaction [3*]. Particularly troublesome is the scenario wherein the patient presents with acute respiratory distress due to pulmonary edema, and the transfusing physician suspects TRALI versus TACO [4*]. The clinical features are similar, and there are no diagnostic tests that reliably discriminate. The fact that a patient could have both simultaneously only adds to the complexity [5*,6,7*]. Yet the therapy and management of the patient, and the implications for the donor of the two different reactions are completely different.

This paper will review recent articles in the scientific literature relevant to diagnosing TRALI and TACO, and to distinguishing between them.

Transfusion associated circulatory overload
Despite the fact that circulatory overload has been a recognized complication of transfusion for decades, it still receives relatively little attention in the scientific literature [8].

There is no universally agreed-upon definition for what constitutes TACO [9]. During or within several hours of transfusion, patients develop respiratory distress, and may develop orthopnea, cyanosis, tachycardia, and hypertension. Rales can be identified on auscultation, and some patients may have jugular venous distention, an S3 on cardiac auscultation, or lower extremity edema. A chest radiograph can reveal cardiomegaly and interstitial infiltrates, but not all patients with heart failure will have these abnormalities [10].

TACO incidence estimates have ranged from one in approximately 3000 transfusions to 8% of transfusions depending upon patient population and reporting method [5*,11]. In a recent retrospective review of 8902 transfusions in 1351 consecutive ICU patients, TACO was identified in one in 356 transfusions [12*]. Patients at the
highest risk for TACO include those younger than 3 and those older than 60 years of age, particularly those with underlying cardiac dysfunction [13].

The pathogenesis of TACO is felt to be similar to other causes of acute congestive heart failure: an increase in central venous pressure and pulmonary blood volume causes an increase in hydrostatic pressure leading to fluid extravasation into the alveolar space [8].

Treatment of TACO starts with discontinuing any ongoing transfusion. Respiratory distress is treated with the degree of respiratory support needed to maintain the patient’s oxygenation. Diuretics are administered to remove excess fluid. It is common to infuse subsequent transfusions slowly, but no formal evidence exists that this is an effective intervention [9].

**Transfusion related acute lung injury**

TRALI is acute lung injury (ALI) that occurs during or following transfusion. It has emerged as the leading cause of transfusion-related fatality reported to the United States Food and Drug Administration [14].

Recently transfused patients present with respiratory distress, hypoxemia, rales on auscultation, and diffuse bilateral infiltrates on chest radiograph. The respiratory distress can be severe enough to require mechanical ventilation. Other features include hypotension, fever, and transient leukopenia. Treatment is with increasingly aggressive respiratory support depending on the degree of respiratory distress. Five to 25% of cases are fatal, but most patients fully recover within 3 days [15*,16*].

TRALI results from neutrophil-mediated damage to the pulmonary microvasculature. The current proposed model is a ‘two-hit hypothesis’ wherein a primary stimulus causes neutrophil sequestration in the pulmonary capillaries, and a secondary stimulus causes the neutrophils to ‘activate’, damaging the endothelial layer such that fluid and protein leaks into the alveolar space [17**]. Neutrophils can be first ‘primed’ and subsequently ‘activated’ by pro-inflammatory stimuli present either in patients with certain disease states, or infused with blood products.

Patient exposures that can lead to neutrophil priming include surgery, tissue injury, and infection. Pro-inflammatory stimuli that can be infused with blood products include neutrophil-specific or anti-human leukocyte antigen (HLA) antibodies, or bioactive lipids. The requirement for both priming and activation of neutrophils explains why a product from a donor with HLA antibodies may induce TRALI in a surgical patient, and cause no clinical reaction in a relatively healthy anemic patient, even if both patients are positive for the relevant HLA antigens. Neutrophil-specific antibodies appear to be capable of both priming and activating neutrophils, and can cause TRALI in even healthy recipients [17**].

In April of 2004, an international consensus conference was convened to develop a definition of TRALI [18]. Participants felt that a useful definition of ALI had already been proposed [19], and they decided to use this as the basis for establishing the presence of ALI in candidate TRALI patients. ALI was defined as acute onset hypoxemia with bilateral infiltrates on chest radiograph, and with no evidence of circulatory overload [20]. Because patients with other risk factors for ALI often receive transfusions, they created a two-tiered definition: TRALI and possible TRALI. TRALI is ALI that occurs during or within 6 h of transfusion, and with no temporal relationship to an alternative risk factor for ALI (risk factors for ALI are summarized in [21]). Possible TRALI is used when there is a clear temporal relationship to an alternative risk factor for ALI. An important limitation of this definition is that patients with circulatory overload cannot be defined as having ALI or TRALI.

Because a usable case definition was developed only recently, earlier estimates of the incidence of TRALI have varied widely [18]. The retrospective review referred to earlier [12**] used the consensus conference definition of TRALI, and the investigators reported a TRALI incidence of one in 1271 units transfused, and a possible TRALI incidence of one in 534 units transfused. This is a higher incidence than that seen in other studies, but the authors point out that they investigated each transfusion event for the possibility of TRALI rather than depending on the typical passive reporting strategy. They conclude that their results suggest that TRALI is an underreported disorder.

The case definition presented above describes a clinical syndrome. Laboratory studies are available to investigate TRALI cases, but the participants in the conference felt they were not specific enough to be included in the definition [21]. The laboratory tests (testing donors for neutrophil and HLA antibodies, antigen typing recipients to demonstrate the presence of cognate antigen, performing donor–recipient leukocyte crossmatches, testing residual product for bioactive lipids) can be expensive, are not universally available, and are difficult to arrange [22**]. While results are often not available in a clinically relevant timeframe for an individual case, they are very important for the evaluation of the eligibility of the implicated donor [16*], and are proving useful for efforts to identify and evaluate possible TRALI prevention interventions [23**].

The United Kingdom’s Serious Hazards of Transfusion (SHOT) hemovigilance system was founded in 1996 as a
way of tracking transfusion-related complications [24*]. Their earlier data suggested that the most frequent products associated with TRALI were plasma-containing products from female donors who were positive for leukocyte antibodies [25]. In 2003, SHOT recommended using only male plasma for plasma products and platelet pools whenever possible. By 2005, male donors provided 90% of frozen plasma and 84% of the plasma for platelets. TRALI cases dropped from 22 in 2003 to six in 2005, deaths from TRALI dropped from seven to two, and the number of cases of TRALI from plasma containing leukocyte antibodies dropped from 10 to zero [25]. The authors admit that this was not a controlled experiment, but the data do suggest that use of predominantly male plasma might decrease TRALI rates.

Investigators from the American Red Cross recently performed a retrospective review of all TRALI cases reported to their surveillance system from 2003 to 2005 [25**]. Five hundred and fifty cases were examined including 72 fatalities. A female, leukocyte antibody-positive donor was involved in 71% of the fatalities. The authors conclude that converting to predominantly male plasma could be a prudent step towards limiting TRALI. The American Red Cross and other United States blood centers are currently involved in efforts to convert to predominantly male plasma, and this should be a useful first step in limiting TRALI [26*].

Antileukocyte antibodies do not always cause TRALI. A recent report describes reactions in both recipients of a split platelet product from a donor who was subsequently shown to be positive for an antibody directed against one of the neutrophil-specific antigens (HNA-2a) [27*]. One patient developed dyspnea, chills, and rigors, the other developed chills and headache, and both developed significant, transient leukopenia. A lookback was performed on the donor’s previous 26 donations that resulted in 39 transfusions. There were 12 mild to moderate reactions in nine patients. Seventy-five percent of the transfusions with reactions resulted in leukopenia, and 35% of those without reactions resulted in leukopenia. This article highlights the fact that antileukocyte antibodies can cause no reaction, or a mild reaction with or without transient leukopenia. Transient leukopenia is also seen in severe TRALI related to antileukocyte antibodies [28*].

**TRALI versus TACO**

While it is clear from the above discussion that our knowledge of TRALI and TACO is improving, it is still the case that distinguishing between the two can be quite difficult. There are features, however, that can help to discriminate (Table 1).

**Clinical presentation**

Both TRALI and TACO are clinical diagnoses, and clinical features can sometimes distinguish between them. With both, patients present with respiratory distress due to acute onset pulmonary edema. With TRALI, patients also often have hypotension and fever, and can have transient leukopenia. With TACO, one would typically expect hypertension and a lack of fever and leukopenia. Features sometimes seen with TACO that would not be expected in TRALI include jugular venous distention, an S3 heard on cardiac auscultation, and peripheral edema.

**Fluid balance**

A careful investigation of the patient’s fluid balance can sometimes provide a clue to the underlying diagnosis. In

<table>
<thead>
<tr>
<th>Feature</th>
<th>TRALI</th>
<th>TACO</th>
</tr>
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<tbody>
<tr>
<td>Body temperature</td>
<td>Fever can be present</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Hypotension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Acute dyspnea</td>
<td>Acute dyspnea</td>
</tr>
<tr>
<td>Neck veins</td>
<td>Unchanged</td>
<td>Can be distended</td>
</tr>
<tr>
<td>Auscultation</td>
<td>Rales</td>
<td>Rales, S3 may be present</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Diffuse, bilateral infiltrates</td>
<td>Diffuse, bilateral infiltrates</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>Normal, decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>PA occlusion pressure</td>
<td>18 mmHg or less</td>
<td>Greater than 18 mmHg</td>
</tr>
<tr>
<td>Pulmonary edema fluid</td>
<td>Exudate</td>
<td>Transudate</td>
</tr>
<tr>
<td>Fluid balance</td>
<td>Positive, even, negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Response to diuretic</td>
<td>Minimal</td>
<td>Significant</td>
</tr>
<tr>
<td>White count</td>
<td>Transient leukopenia</td>
<td>Unchanged</td>
</tr>
<tr>
<td>SNP</td>
<td>&lt;200 pg/ml</td>
<td>&gt;1200 pg/ml</td>
</tr>
<tr>
<td>Leukocyte antibodies</td>
<td>Donor leukocyte antibodies present, crossmatch incompatibility between donor and recipient</td>
<td>Donor leukocyte antibodies may or may not be present, positive results can suggest TRALI even with true TACO cases</td>
</tr>
</tbody>
</table>

The typical patterns that would be expected for cases of transfusion related acute lung injury (TRALI) or transfusion associated circulatory overload (TACO) are represented. Readers are reminded that a given case of TRALI or TACO may lack some of the typical features. Also, a case of TRALI may have some features suggesting TACO or vice versa, and TRALI and TACO can be present together. The best strategy is to develop a full clinical profile of the case using the feature list above, and determine which diagnosis is most supported. BNP, brain natriuretic peptide; PA, pulmonary artery.
a patient with excess fluid intake pretransfusion [9] or significant diuresis postreaction [29]. TACO should be carefully considered. A normal fluid balance does not rule out TACO or rule in TRALI.

**Cardiac function**

Evidence of a new myocardial infarct can suggest that pulmonary edema may not be transfusion related. Patients with known preceding congestive heart failure are at risk for TACO [33,36]. Systolic dysfunction identified on echocardiography is also suggestive of TACO [5**, but does not rule out TRALI.

Pulmonary artery occlusion pressure can distinguish cardiogenic (greater than 18 mmHg) from noncardiogenic (18 mmHg or less) pulmonary edema [30]. There is much debate in the literature, however, concerning the utility of pulmonary artery catheters (PACs) [31*,32*]. A report from the Acute Respiratory Distress Syndrome Network (ARDSN) of a clinical trial comparing the utility of PAC monitoring versus central venous catheter (CVC) monitoring in patients with ALI found increased complications and no significant benefit to PAC over CVC [33**]. As has been noted before in the literature [34], the ARDSN found that some of their ALI patients had pulmonary artery occlusion pressures of greater than 18 mmHg, suggesting that one can not rely solely on PAC monitoring when trying to distinguish TRALI from TACO.

Elevated levels of brain natriuretic peptide (BNP) and n-terminal pro-brain natriuretic peptide (NT-proBNP) are established markers for congestive heart failure [35*,36]. Investigators recently reported evidence that BNP levels can be used to distinguish between cardiogenic and noncardiogenic pulmonary edema in patients presenting with acute respiratory failure [37**]. BNP levels were measured in 80 respiratory failure patients who also underwent PAC placement. BNP levels of 200 pg/ml or less were 91% specific for ALI, and BNP levels of 1200 pg/ml or greater were 92% specific for cardiogenic pulmonary edema.

Analogously, case reports have been published that suggest that elevated levels of BNP can imply TACO [29], and normal levels of BNP can support a diagnosis of TRALI [38*]. Zhou and colleagues [13] measured pretransfusion and posttransfusion BNP levels in 21 patients with suspected TACO and 19 transfused controls. BNP change was considered significant if the posttransfusion to pretransfusion ratio was 1.5 or greater, and the posttransfusion BNP was 100 pg/ml or greater. A significant change in BNP was 81% sensitive and 89% specific for TACO, and had a positive predictive value of 89% and a negative predictive value of 81%. While not conclusive, these papers suggest that BNP has a role in distinguishing TACO from TRALI.

**Pulmonary edema fluid**

With TACO the pulmonary edema fluid is a low-protein plasma filtrate, and with TRALI the pulmonary edema fluid is relatively high in plasma proteins. The edema fluid to serum protein ratio has been used clinically to suggest the presence of noncardiogenic edema (ratio \( \geq 0.75 \)) and therefore more likely TRALI [28*]. The utility of this metric for distinguishing TRALI from TACO has not been evaluated in a formal experiment, and there are aspects to the technique (e.g., sample timing, can be used only in intubated patients) that limit its utility [5**].

**Leukocyte antibody testing**

Depending upon gender and pregnancy history, between seven and 25% of donors are positive for leukocyte antibodies [22**]. Given the low incidence of TRALI, the majority of transfusions from leukocyte alloimmunized donors must be uneventful. Also, there are TRALI cases reported in the literature in which leukocyte antibodies were not detected [15*,22**]. These findings must be kept in mind when interpreting leukocyte antibody results. For example, one or more donors to a multiply transfused patient who is experiencing TACO could be positive for leukocyte antibodies, and these results would obscure rather than confirm the correct diagnosis. Despite these concerns, leukocyte antibody testing should be performed where possible for cases with a strong clinical suspicion of TRALI, and the test results can support the diagnosis. Demonstration of cognate antigen in the recipient, or crossmatch incompatibility between donor and recipient makes the case for TRALI even more credible [22**].

**Overall profile**

There is no one feature that discriminates TRALI and TACO. A true case of TRALI may have some of the features typical of TACO, and vice versa. The best strategy is to evaluate all of the features available from the above discussion (Table 1), and determine which diagnosis best fits the scenario in question.

**Conclusion**

As our understanding of TRALI and TACO improves, it becomes clear that both are significant risks to transfusion recipients. Unfortunately, there is no single feature that distinguishes TRALI from TACO. Developing a thorough clinical profile including presenting signs and symptoms, fluid status, cardiac status including measurement of BNP, and leukocyte antibody testing is the best strategy currently available to distinguish the two disorders.
Transfusion medicine and immunohematology

Acknowledgements
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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
• • of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 705).


This is an excellent review article on TRALI including sections on historical background, definition, clinical presentation, incidence, the two-hit model of pathogenesis, and animal models.


This is a review of the English language literature published since 1990 on noninfectious complications of transfusions. The authors focus on the incidence per transfusion and the prevalence in transfusion recipients, and on the cause, management, and prevention of each complication.


This is the most thorough review article on the pathogenesis of TRALI available.


This recent review article gives a concise and effective description of the phenomenology of TRALI and TACO.


This article describes the differences in diagnostic tools that are available to distinguish between hydrostatic and permeability pulmonary edema including pulmonary artery catheterization, pulmonary edema fluid protein content, chest radiography and echocardiography, B type natriuretic peptide, and biomarkers of acute lung injury. They also present an algorithm for evaluating posttransfusion acute pulmonary edema.


This is the most up-to-date and comprehensive of the current case definitions for TRALI.


This editorial describes the limitations of the current case definition for TRALI and the factors that contribute to the development of acute lung injury after transfusion.


The authors performed a retrospective review of consecutive patients newly requiring ventilatory support posttransfusion in four intensive care units at one institution in an effort to determine the incidence of TRALI and TACO. A total of 8600 units were transfused to 1351 patients, 49 of whom developed acute pulmonary edema. The incidence of TRALI was one in 1271 units transfused, possible TRALI was one in 534 units transfused, and TACO was one in 356 units transfused. The consensus conference definition was used to identify TRALI and possible TACO cases.


This is an excellent review article on TRALI including sections on historical background, definition, clinical presentation, incidence, the two-hit model of pathogenesis, and animal models.


26 Stroncek DF, Klein HG. Heavy breathing in the blood bank: is it transfusion-related acute lung injury, our anxiety, or both? Transfusion 2007; 47:559–562.

In this editorial, the authors caution that interventions to limit TRALI need to be evaluated for their effect on the adequacy of the blood supply before being implemented, and that because there are multiple factors that can lead to TRALI, a multimodal approach will be required to eliminate TRALI altogether.


This case report describes relatively mild reactions and transient leukopenia in both recipients of a split platelet product from a donor who was positive for a neutrophil-specific antibody. A check on the donor’s previous 26 donations demonstrated 12 mild to moderate reactions in nine patients, and instances of leukopenia not associated with a clinical reaction. The authors conclude that neutrophil antibodies do not always cause severe reactions, and cause leukopenia with or without a clinical reaction.
In this editorial, the authors argue that use of pulmonary artery catheters (PACs) will likely continue. They argue that the clinical trials that have shown no benefit or a central venous catheter. The authors showed no benefit to pulmonary artery catheters over a central venous catheter to guide treatment of acute lung injury. N Engl J Med 2006; 354:2213–2224.

This is a report of a prospective clinical trial performed by the Acute Respiratory Distress Syndrome Network that compared outcomes for 1000 patients with acute lung injury randomized to receive care guided by either a pulmonary artery catheter or a central venous catheter. The authors showed no benefit to pulmonary artery catheter over central venous catheter, but did identify more complications in the pulmonary artery catheter group.

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This article presents two cases of pediatric TRALI and a review of the literature on pediatric TRALI. The authors highlight the fact that TRALI patients can experience transient, profound leukopenia, and that the protein content of pulmonary edema fluid can help distinguish cardiogenic from noncardiogenic pulmonary edema.


In this editorial, the author argues that use of pulmonary artery catheters (PACs) will likely decrease if not cease. His key arguments include that multiple clinical trials have been performed showing that management of patients using PACs does not improve outcomes, and that a few of these studies have shown an increased risk of complications with PACs.


In this editorial, the authors argue that use of pulmonary artery catheters (PACs) will likely continue. They argue that the clinical trials that have shown no benefit to PACs are misleading because they have been performed with the wrong types of patients, and because the physicians who were using the PACs in the studies did not have a standardized algorithm of practice guiding how they used the PAC data.


This is a report of a prospective clinical trial performed by the Acute Respiratory Distress Syndrome Network that compared outcomes for 1000 patients with acute lung injury randomized to receive care guided by either a pulmonary artery catheter or a central venous catheter. The authors showed no benefit to pulmonary artery catheter over central venous catheter, but did identify more complications in the pulmonary artery catheter group.


The authors compared the diagnostic accuracy of brain natriuretic peptide (BNP) and amino-terminal proBNP (NT-proBNP) for the diagnosis of mild heart failure by measuring plasma NT-proBNP and BNP in 182 healthy controls and in a prospective cohort of 620 heart failure patients. They conclude that monitoring BNP or NT-proBNP enabled identification of asymptomatic patients at risk for the development of heart failure, but that NT-proBNP showed better accuracy than BNP.


This is a report of a prospective study wherein brain natriuretic peptide (BNP) levels were measured in 80 ICU patients with acute hypoxic respiratory failure and bilateral pulmonary infiltrates on chest radiograph in an effort to determine the utility of BNP for discriminating cardiogenic versus noncardiogenic pulmonary edema. BNP levels of 200 pg/mL or less were 91% specific for noncardiogenic pulmonary edema, and BNP levels of 1200 pg/mL or greater were 92% specific for cardiogenic pulmonary edema.


This is a case report of a patient who experienced acute respiratory distress due to pulmonary edema and who was demonstrated to have had normal levels of brain natriuretic peptide (BNP) posttransfusion. The authors felt the normal BNP levels were supportive of a diagnosis of TRALI.