Transfusion-related acute lung injury (TRALI): Clinical presentation, treatment, and prognosis

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The term transfusion-related acute lung injury (TRALI) was coined in 1983 to describe a constellation of clinical and laboratory features seen within 6 hrs of the transfusion of plasma-containing blood products. These products contain antibodies directed to human leukocyte antigens (and subsequently described to nonhuman leukocyte antigens) found on white blood cells. In the intervening 2 decades, other cases not associated with antibodies have been reported as TRALI and an association with passive infusion of lipids accumulated in stored cellular blood products has been made in those cases. This has led to confusion as to what should be considered to constitute TRALI. Therefore, the true incidence of this pulmonary reaction to blood products is currently conjectural at best. Recent consensus development conferences have been held to develop and standardize definitions of TRALI so that epidemiologic and research aspects of this condition can be explored in a scientific manner. These conferences have set out criteria by which TRALI is distinguished from other causes of acute lung injury. This review outlines the widely accepted clinical (mainly pulmonary) features of TRALI, the treatment options, and the excellent long-term prognosis for patients who survive the initial pulmonary insult.

Key Words: transfusion reaction; acute lung injury; pulmonary reaction; human leukocyte antigen antibodies; blood storage lipids

One of the problems now encountered by those wishing to study the entity known since 1983 as transfusion-related acute lung injury (TRALI) is that this term has since been used to describe some clinical situations with certain associated laboratory findings that significantly differ from the original constellation of findings we described in 1983 and 1985 (1, 2). Our original definition outlined not only the clinical findings in our cases but also some associated laboratory findings. Since neither the spectrum of clinical manifestations nor the associated laboratory findings could be claimed to be independently pathogenomic for TRALI, the somewhat nebulous nature of the entity or syndrome we were describing virtually invited other interpretations of the pathogenesis of what we described and the inclusion, under the term TRALI, of combinations of clinical and laboratory findings that were somewhat at variance with our original description. At this point, >20 yrs later, one is at a loss to decide whether there is one entity or several similar clinical pictures and whether the originally described laboratory findings are a sine qua non for the diagnosis or merely interesting and perhaps pathogenetic “clues” in some, or even most cases. Because of this confusion and the need to reach consensus about what should and should not be included under the heading of TRALI, a number of groups of experts have recently met to try to establish a working definition and to suggest reasonable avenues of research (3–5). In addition, largely due to heightened interest in this condition, numerous review papers have been published in recent years (6–8). The recent increase in interest has been largely spurred by the emergence of TRALI as one of the most frequent causes of transfusion-related mortality or severe morbidity. Many of the more “classic” and previously recognized causes of transfusion-related mortality are diminishing in frequency, and, in particular, the transfusion transmission of viruses has become a vanishingly small problem in developed countries with well-regulated and effectively tested blood donation programs. Because of the varied nature of the laboratory findings described in cases reported in the literature to be TRALI, it has been difficult to develop a consensus view on which, if any, laboratory anomaly (5) should be considered to be the sine qua non for a diagnosis of TRALI. However, at least two theories of pathogenesis have been propounded: a) passive infusion of antileukocyte antibodies (as in our original description) (1, 2); and b) passive infusion of blood storage-related lipids (7). Naturally, the reported studies of TRALI have tended to emphasize particular laboratory abnormalities depending on the theories of pathogenesis of the respective authors. Although, our original description of TRALI included a delineation of associated human leukocyte antigen antibodies (1, 2), I focus my comments here on the clinical aspects of the condition and leave the discussion of various constellations of diagnostic laboratory findings to other articles in this supplement.

To facilitate definition of TRALI cases for descriptive or research purposes, most authorities and recent consensus statements have emphasized that there should be no evidence for the presence of acute lung injury (ALI) due to other known risk factors. That is not to say that patients with ALI due to any of the myriad of known causes, could not, in addi-
tion, develop TRALI after transfusions. However, to establish both the clinical manifestations as well as the pertinent laboratory and other test associations, it will be necessary, for descriptive purposes, to exclude cases with any of the other well-known causes of ALI. We must first recognize what occurs in “clean,” uncomplicated cases of TRALI before we attempt to study it in cases that are already complicated by the likely presence of ALI due to other causes.

Clinical Features

Despite the confusion about many aspects of TRALI, there is general agreement that respiratory distress symptoms appear within the first 2–6 hrs from the initiation of the relevant blood transfusion. A few cases of apparent TRALI have been reported to occur much later, even up to 48 hrs (9) My personal experience has been that, like most reactions caused by intravenous infusion of causative agents, the clinical manifestations are usually seen within minutes to just a few hours. Intuition is certainly not a science, but I am always intuitively skeptical of a manifestation that it is not clinically suspected that a serious pulmonary change has indeed occurred until 5 or 6 hrs hours have elapsed. It is not uncommon for my anesthesia colleagues to relate that they have retrospectively appreciated that the changes that they now clearly see, in fact, probably began perhaps with some subtlety, several hours previously. Although approximately 50% of blood product transfusions at our institution have traditionally been transfused to patients in surgical settings (operating rooms or postanesthesia recovery rooms), we have long noted (1, 2) that the great majority of our cases of TRALI have occurred in this surgical setting. It is certainly possible that this particular clinical setting is one in which some other pathogenetic factor is preferentially found. As is outlined elsewhere in this supplement, experimental data have demonstrated a predisposing role for relative hypoxemia, which is not an uncommon occurrence in patients under general anesthesia.

Nevertheless, the surgical setting per se tends to restrict the spectrum of clinical manifestations (particularly symptoms) seen in patients. Those who are anesthetized, emerging from that state, intubated, or otherwise less than fully alert obviously will not be as clear in their articulation of symptoms as patients who are fully alert. In this situation, one has to rely on clinical signs augmented by objective measures of the oxygenation status and pulmonary functions.

Apart from the caveat noted here, the signs and symptoms of TRALI and their relative frequencies in most studies are outlined as in Table 1. Patients most frequently experience dyspnea or are observed to have acute respiratory distress. The onset of these manifestations is often strikingly abrupt, with exchanges sometimes observed to occur over a matter of minutes. These initial symptoms are caused by the onset of pulmonary edema. This edema may be first seen in the dependent areas of the lungs, or sometimes perihilar, but is often more generalized within a few hours. The florid radiologic picture is often described as “white out.” We have seen cases where patients who were lying in a right- or left-dependent position, rather than prone or supine, had the pathologic evidence of the edema seen only in the lung that was most dependent. In other cases, it was first seen in the dependent lung but was later seen equally in both lungs after the patient was no longer in a right- or left-dependent position. Like most clinical conditions, a spectrum of severity is seen in cases. It is likely that there are cases mild enough that the only manifestation is dyspnea that is so transient that the subsequently performed chest radiograph is clear by the time that test is performed. Such cases may well not even be attributed by clinicians to TRALI because of the paucity of clinical or radiographic findings. An interesting early finding in some of our cases has been transient neutropenia that was initially detected by serendipity in patients in intensive care areas who were tested for peripheral blood white cell count during the most fulminating clinical manifestation. Others have corroborated these findings (10). In most cases, one does not have the good fortune to have an immediately prereaction white cell count to compare with the postreaction count.

Another interesting finding has been the remarkable dichotomy between the often florid pulmonary radiologic findings accompanying significant oxygen desaturation and the paucity of auscultatory findings. On one occasion, this finding was so remarkable to me that I questioned whether I was examining the correct patient! In situations where pulmonary problems (with prominent radiologically evident infiltrates) are caused by volume overload or cardiac failure, there are virtually always abundant moist lung (crepitations) sounds that are readily detectable by auscultation. A possible explanation for the lack of prominent moist lung sounds in TRALI might simply be that in this latter condition, the excess pulmonary fluid is largely interstitial whereas in congestive cardiac failure relatively more fluid is intra-alveolar. However, I am unaware of data that would support or refute this theory! Particularly in cases with a rapid onset while the patient is under general anesthesia, copious frothy edema fluid can ooze from the endotracheal tube. The anesthesiologists often comment that they first notice that the lungs “feel heavy” and are difficult to ventilate as the systemic blood pressure simultaneously begins to decrease, occasionally quite precipitously. Sometimes a high protein content in the fluid from the endotracheal tube helps differentiate TRALI from cardiogenic pulmonary edema (11).

Despite the differentiating features noted here, it is quite often difficult to make the distinction between TRALI and ALI due to a variety of conditions such as sepsis, trauma, gastric fluid aspiration,

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Frequency</th>
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<tr>
<td>Dyspnea/respiratory distress requiring oxygen support</td>
<td>Virtually all</td>
</tr>
<tr>
<td>Requiring mechanical ventilation</td>
<td>~70%</td>
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<tr>
<td>Documented hypoxemia</td>
<td>Virtually all</td>
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<tr>
<td>Cyanosis</td>
<td>Very common</td>
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<tr>
<td>Hypotension</td>
<td>Majority</td>
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<tr>
<td>Fever</td>
<td>Very common</td>
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<tr>
<td>Hypertension</td>
<td>Unusual</td>
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disseminated intravascular coagulopathy, or ventilator-associated lung injury.

Definitions

A Working Party on Definitions of Adverse Transfusion Events was established by the European Haemovigilance Network (EHN). This group has suggested that the following be the minimum requirements for a clinical diagnosis of TRALI: 1) the occurrence of acute respiratory distress during or within 6 hrs of transfusion; 2) absence of signs of circulatory overload; 3) radiographic evidence of bilateral pulmonary infiltrates. Bux (8) noted that these criteria are basically the same as those which Popovsky and I proposed in 1985 (2).

The Canadian Consensus Conference in Toronto in 2004 suggested a somewhat more restricted definition. This group included the criteria of the EHW Working Party Group but added the following criteria for TRALI (4): 1) hypoxemia: \( \text{PaO}_2/\text{FiO}_2 \geq 300 \text{ mm Hg} \) regardless of positive end expiration pressure level or oxygen saturation of \( \leq 90\% \) on room air; 3) bilateral infiltrates on frontal chest radiograph; 4) pulmonary artery occlusion pressure \( \leq 8 \text{ mm Hg} \) when measured or lack of clinical evidence of left atrial hypertension.

The NHLBI clinical definition of TRALI was as follows. 1) Patients without ALI risk factors other than transfusion. In patients with no ALI immediately before transfusion, a temporal association of transfusion and ALI is made if the following is present: new ALI; onset of symptoms or signs during or within 6 hrs after the end of transfusion of one or more plasma-containing blood products. As there is no other ALI risk factor, the new ALI is inferred to be mechanistically related to transfusion, that is, TRALI. 2) Patients with ALI risk factors other than transfusion.

In patients with no ALI immediately before transfusion, a temporal association of transfusion and ALI is made if the following is present: new ALI; onset of symptoms or signs during or within 6 hrs after the end of transfusion of one or more plasma-containing blood products. By assessing the patient’s clinical course, the new ALI is either of the following: a) TRALI, and the new ALI is inferred to be mechanistically related to the transfusion, or both the transfusion and the alternative risk factor; b) not TRALI, and the new ALI is mechanistically related to the alternative ALI risk factor alone, whereas the transfusion is coincidental.

As pointed out in Reference 12, these definitions are largely if not completely clinical in nature and do not depend on any particular type of laboratory test result indicating the presence of antibodies to white cell antigens or the involvement of cellular storage-related lipids. Indeed, as we have found at Mayo Clinic, the involvement of clinicians with expertise in critical pulmonary care is often required to sort out the likelihood of TRALI against a background of cases of ALI due to other causes. In addition, the prevalence of volume-related hydrostatic pulmonary edema in complex cases seen in intensive care units further complicates the establishment of a diagnosis of TRALI. As outlined previously, the coexistence of multiple types of acute lung injury of diverse etiology must also be considered at times. It is also worth noting that both the NHLBI and Canadian Consensus definitions do not attempt to separate out the presence of massive transfusions as a cause of acute lung injury separate from TRALI and suggest that in the absence of other cases of ALI, massive transfusion associated with ALI should be considered to be TRALI.

It is obvious that the real incidence of TRALI is not established at this time because the definition of what is included in the designation has been somewhat muddled and is only now being redefined by consensus. The two most widely pronounced theories of etiology are those of passive antibody transfusion and passive transfusion of cell-derived lipids accumulated in stored cellular blood components. These theories are discussed in other articles in this supplement.

Treatment

As is generally true in all areas of clinical medicine, making the correct diagnosis is the first step. This seemingly trite comment emphasizes that distinguishing TRALI from other causes of acute respiratory decompensation can be quite difficult. It is not uncommon for other diagnoses to be initially made and even acted on before the true nature of the patient’s condition becomes clear. A second problem has been that, until recently, there were merely case reports or relatively small series of cases in the literature. The therapeutic approaches reported were based on general principles and intuitive reasoning by pulmonary experts with the wisdom gleaned from anecdotal accounts. In fact, to date, no formally structured, prospective trials of different treatments have been reported. Perhaps one of the features of TRALI played a role in this paucity of data-based therapeutic options! The fact that episodes of TRALI are generally limited to 24–28 hrs may be associated with the fact that, in many cases, the patient’s condition has spontaneously resolved before the diagnosis is clearly established. Of course, this brief clinical course contrasts with ALI that is not transfusion related. In addition, in all series so far reported, the mortality rate in TRALI has been much lower (~10%) than that for ALI.
that is not transfusion related (40–50%). Bux (8) and others have also pointed out that, from published reports, it would appear that TRALI that is antibody mediated tends to be more clinically florid and severe than that reported for those cases thought to be due to lipids in stored components.

Management of TRALI is supportive, as it would be for any patient with pulmonary edema that is permeability in type. In our experience and that of many others, this has included intubation and mechanical ventilation in a high proportion of patients (~72%) (1, 2). It has become increasingly clear that “lung-protective,” small tidal volume settings should be used for optimum ventilatory care (13). Because of the ubiquitous finding of hypoxemia in reported cases, it is reasonable to assume that essentially all patients will require oxygen support even if they do not require intubation. In our experience, the generally present arterial hypotension is often managed with intravenous fluids alone, but occasionally pressor agents are also needed especially when the hypotension is profound, prolonged, or unresponsive to intravenous fluid infusions. The recommendation to use intravenous fluids highlights the importance of distinguishing congestive cardiac failure or transfusion overload from TRALI. Naturally, aggressive fluid therapy would be expected to worsen the former two conditions. In patients with TRALI and concomitant fluid overload, the use of diuretics is often efficacious but, in the absence of overload, there is no evidence to indicate a benefit. Indeed, their use is somewhat controversial and is considered by some to be contraindicated since patients who are significantly hypotensive and need fluid support may experience worsening of their condition after vigorous diuretic treatment (14). The use of corticosteroids has often been reported in anecdotal case reports and we have used them empirically. However, there are no convincing data to support or indeed to refute the value of such therapy. One can certainly understand the rationale that the use of steroids in these patients may even increase their risk of developing nosocomial infections since the patients are often on ventilatory support in intensive care units. Where patients have TRALI in addition to other serious medical conditions, it is often necessary to employ invasive hemodynamic monitoring to guide safe fluid management.

Prognosis

In contrast with ALI in general, the mortality rate in cases of TRALI is relatively low (~6–10%). For patients who survive the initial episode and recover their pulmonary function in a couple of days, the long-term function of the lungs seems to be essentially the same as that for patients who never experience TRALI. This is no apparent late occurrence of fibrosis or other structural damage to the lung parenchyma as a result of TRALI.

REFERENCES


