Educational Case

Educational Case: Transfusion reactions: Transfusion associated circulatory overload vs transfusion-related acute lung injury

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme.1

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Primary objective

Objective TM1.2: Transfusion Reactions. Compare and contrast the pathophysiology, presentations, prophylaxis, and acute management of the different types of transfusion reactions.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic: Transfusion Medicine (TM); Learning Goal 1: Concepts of Blood Transfusion.

Patient presentation

A 61-year-old otherwise healthy man with a past medical history of osteoarthritis is admitted for a bilateral total hip replacement. During the surgery, the patient experiences significant intraoperative blood loss of approximately 0.6 L, and is transfused four units of packed red blood cells (RBCs). Two of the four units are transfused during the surgery, while the two additional units are administered immediately following the surgery when a post-operative CBC reveals a hemoglobin of 5.8 g/dl. Approximately 1 hour following transfusion of the final RBC unit, the patient complains of sudden onset of difficulty breathing and requires intubation.

Diagnostic findings, Part 1

The patient’s pre- and post-transfusion vital signs are in Table 1. His pre- and post-transfusion blood sample is submitted to the blood bank for further investigation, with results shown in Table 2. There is no evidence of clerical error or serological incompatibility. A chest radiograph shows diffuse bilateral pulmonary infiltrates with a normal sized cardiac silhouette.

Questions/discussion points, Part 1

How do you interpret the changes in vital signs in Table 1?

From the information provided, it is apparent that there are significant changes in this patient’s vital signs when compared to baseline (pre-transfusion) values. The patient has experienced a fever. In addition, he is tachycardic, tachypneic (increased respiratory rate), and has a significantly decreased oxygen saturation level. Finally, his blood pressure dropped following transfusion.
A blood transfusion is a routinely performed procedure in the hospital setting. The decision to transfuse a patient is made following a careful assessment of the risks and benefits of blood transfusion therapy which includes thorough evaluation of the patient’s clinical condition and laboratory findings. A transfusion reaction is any adverse reaction associated with the transfusion of blood products. It is important to recognize transfusion reactions, as their clinical severity ranges from mild to life-threatening complications of transfusion. The initial transfusion reaction workup assists in the evaluation of hemolysis, which is characteristic of hemolytic transfusion reactions, one of the most life-threatening complications of transfusion. The workup in Table 2 is negative in all types of transfusion reactions except those involving hemolysis of red blood cells (RBC).

The ABO/Rh type and clerical check are performed to ensure that the correct component was administered to the correct patient. Human errors are the most common cause of an acute hemolytic transfusion reaction (AHTR) resulting from improper identification of the patient, patient sample, or the donor unit.

The pre-and post-transfusion samples are visually analyzed for evidence of hemoglobinemia by examining the color of plasma after centrifugation. Clear or yellow is the expected color of normal plasma whereas the finding of a pinkish/red tinge to the plasma indicates hemoglobinemia seen during hemolysis. In fact, hemoglobinemia is the most sensitive indicator of intravascular hemolysis, which is observed in ABO-incompatible transfusions.

A DAT detects if a patient’s red blood cells have been coated with an antibody, or complement, or both, in vivo. There are many causes of a positive DAT, one of which is a hemolytic transfusion reaction, where a patient has anti-red blood cell antibodies to a particular antigen on the transfused donor red blood cells. The binding of patient anti-RBC antibodies to transfused donor red cells results in RBC hemolysis. A negative DAT helps us rule out a hemolytic transfusion reaction.

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Acute hemolytic transfusion reactions (AHTR) are Type 2 hypersensitivity reactions from the transfusion of incompatible ABO group red blood cells. Naturally occurring pre-formed IgM antibodies in the recipient bind to the transfused ABO (major blood group) incompatible red blood cells causing immune mediated acute intravascular hemolysis. Patients present with fever, chills, back pain, epistaxis, pain at IV site, hypotension, and renal failure. Laboratory findings that support intravascular hemolysis include elevated LDH (lactate dehydrogenase), elevated bilirubin, hemoglobinemia, hemoglobinuria, decreased haptoglobin and spherocytes on peripheral blood smear. The most common causes of AHTR are mismatches (wrong blood being given to wrong patient) due to human errors involving misidentification of specimen, blood product or patient.

No, this patient is not demonstrating laboratory or clinical signs suggestive of an AHTR. This patient has a negative initial blood bank transfusion reaction workup shown in Table 2, which helps to rule out AHTR. The DAT is negative, indicating that there is no evidence of immune mediated hemolysis (acute and/or delayed hemolytic transfusion reaction). These reactions are rare, but can be fatal, hence the importance of early recognition.

### Table 1

| Pre-transfusion | Post-transfusion |
|----------------|-----------------|
| Temperature (degrees Celsius) | 37.2 | 38.9 |
| Heart rate (beats/min) | 90 | 110 |
| Respiratory rate (breaths/min) | 14 | 21 |
| Blood pressure (mm Hg) | 142/88 | 120/72 |
| O₂ saturation | 99% | 86% |

### Table 2

| Pre-transfusion | Post-transfusion |
|----------------|-----------------|
| ABO/Rh type | O+ | O+ |
| Clerical check | Ok | Ok |
| Visual hemoglobin check | Clear | Clear |
| DAT/Direct coombs test | Negative | Negative |

* DAT = Direct antiglobulin test.

**Given the changes in vital signs, physical exam findings, and radiologic findings, what diagnoses should be considered as an explanation for this patient’s symptoms?**

Some pathologies to consider in the differential diagnoses include pulmonary embolism, acute respiratory distress syndrome, pneumonia, acute on chronic congestive heart failure, and transfusion reaction.

**What are the most common clinical signs and symptoms of a transfusion reaction?**

Fever, chills, and hives are commonly reported sequelae of transfusions. The patient in this case has developed a fever following transfusion of red blood cells, as depicted in Table 1.

**What other parts of this patient’s clinical work-up and vital sign derangements suggest that this patient may be experiencing a transfusion reaction as opposed to another condition?**

The patient’s chest x-ray shows evidence of bilateral pulmonary infiltrates. Furthermore, he is experiencing fever, significantly increased work of breathing, a precipitous decline in oxygen saturation, and hypotension. Importantly, these findings occurred within an hour of the fourth RBC transfusion, suggesting that the patient’s respiratory distress is likely a consequence of his recent transfusions.

**What is a transfusion reaction and what are some common types of transfusion reactions?**

A blood transfusion is a routinely performed procedure in the hospital setting. The decision to transfuse a patient is made following a careful assessment of the risks and benefits of blood transfusion therapy which includes thorough evaluation of the patient’s clinical condition and laboratory findings. A transfusion reaction is any adverse reaction associated with the transfusion of blood products. It is important to recognize transfusion reactions, as their clinical severity ranges from mild to life-threatening. While infectious complications from blood transfusions (transmission of HIV, hepatitis B, hepatitis C) have been decreasing, noninfectious hazards of transfusion are now the most common complications of transfusions and it is important to distinguish amongst the different subtypes. Transfusion reaction subtypes include acute hemolytic, febrile non-hemolytic, allergic (from mild allergic to anaphylactic), septic, transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO).

**What is the first step in managing a possible transfusion reaction?**

STOP the transfusion. This helps avoid any further negative clinical consequences resulting from transfusion of additional volume of the potentially offending blood product. Until proven otherwise through a transfusion reaction investigation, the transfusion is assumed to be the cause for the patient’s symptoms. Notify the treating physician and initiate a transfusion reaction workup with the blood bank.

**What is the significance of the initial blood bank transfusion reaction workup shown in Table 2?**

The initial transfusion reaction workup assists in the evaluation of hemolysis, which is characteristic of hemolytic transfusion reactions, one of the most life-threatening complications of transfusion. The workup in Table 2 is negative in all types of transfusion reactions except those involving hemolysis of red blood cells (RBC).

The ABO/Rh type and clerical check are performed to ensure that the correct component was administered to the correct patient. Human errors are the most common cause of an acute hemolytic transfusion reaction (AHTR) resulting from improper identification of the patient, patient sample, or the donor unit.

The pre-and post-transfusion samples are visually analyzed for evidence of hemoglobinemia by examining the color of plasma after centrifugation. Clear or yellow is the expected color of normal plasma whereas the finding of a pinkish/red tinge to the plasma indicates hemoglobinemia seen during hemolysis. In fact, hemoglobinemia is the most sensitive indicator of intravascular hemolysis, which is observed in ABO-incompatible transfusions.

**What is a direct antiglobulin test (DAT) and what is the significance of a negative DAT in this context?**

A DAT detects if a patient’s red blood cells have been coated with an antibody, or complement, or both, in vivo. There are many causes of a positive DAT, one of which is a hemolytic transfusion reaction, where a patient has anti-red blood cell antibodies to a particular antigen on the transfused donor red blood cells. The binding of patient anti-RBC antibodies to transfused donor red cells results in RBC hemolysis. A negative DAT helps us rule out a hemolytic transfusion reaction.

**What is an acute hemolytic transfusion reaction and is this patient experiencing this type of reaction?**

Acute hemolytic transfusion reactions (AHTR) are Type 2 hypersensitivity reactions from the transfusion of incompatible ABO group red blood cells. Naturally occurring pre-formed IgM antibodies in the recipient bind to the transfused ABO (major blood group) incompatible red blood cells causing immune mediated acute intravascular hemolysis. Patients present with fever, chills, back pain, epistaxis, pain at IV site, hypotension, and renal failure. Laboratory findings that support intravascular hemolysis include elevated LDH (lactate dehydrogenase), elevated bilirubin, hemoglobinemia, hemoglobinuria, decreased haptoglobin and spherocytes on peripheral blood smear. The most common causes of AHTR are mismatches (wrong blood being given to wrong patient) due to human errors involving misidentification of specimen, blood product or patient.

No, this patient is not demonstrating laboratory or clinical signs suggestive of an AHTR. This patient has a negative initial blood bank transfusion reaction workup shown in Table 2, which helps to rule out AHTR. The DAT is negative, indicating that there is no evidence of immune mediated hemolysis (acute and/or delayed hemolytic transfusion reaction). These reactions are rare, but can be fatal, hence the importance of early recognition.
Given the above findings, what is your differential diagnosis for this transfusion reaction?

The diagnosis of Transfusion-related acute lung injury (TRALI) or transfusion associated circulatory overload (TACO) must be explored in a patient who develops sudden onset respiratory compromise following a transfusion. However, hemolytic transfusion reactions, septic transfusion reactions, and allergic/anaphylactic reactions may also cause significant respiratory distress, and these other diagnoses must be appropriately excluded.

Of note, a febrile non-hemolytic transfusion reaction (FNHTR) is unlikely, as this patient is experiencing significant respiratory distress in addition to fever. Those experiencing a FNHTR do not typically experience respiratory complications; rather the symptoms are limited to fever, chills, and/or rigors. These reactions are often self-limited, and do not require ventilatory support.

Septic transfusion reactions result from bacterial contamination of a transfused blood product. These are seen more commonly with platelet transfusions than RBC transfusions because platelets are stored at room temperature as opposed to RBCs, which are refrigerated.2 Patients demonstrate a significantly elevated post-transfusion temperature, as well as a markedly increased white blood cell count, and positive blood cultures. These reactions are characterized by shock like symptoms, including significant respiratory distress, high fever, hypotension, and tachycardia.2 A Gram stain and blood cultures should be performed on the unit in question as well as on the patient. In the event that a septic transfusion reaction is confirmed, administration of broad-spectrum IV antibiotics is the appropriate next course of action. The absence of high fever as well as the normal WBC count post-transfusion argues against a septic transfusion reaction as the cause for this patient’s symptoms.

Anaphylactic (severe allergic) transfusion reactions are type I hypersensitivity reactions to donor plasma proteins. They result from IgE mediated mast cell degranulation in response to plasma donor proteins, causing systemic release of histamine and other inflammatory mediators. Anaphylaxis is characterized by hypotension, hypoxia, shortness of breath, urticaria, flushing, laryngeal edema, and wheezing.2 Fever is notably absent. These reactions occur within seconds or minutes upon initiation of transfusion. In most cases, the specific protein in the donor’s plasma is not identified. However, this phenomenon is well documented in IgA deficient patients who have developed an anti-IgA antibody.2 They develop symptoms of anaphylaxis upon exposure to IgA containing blood products. Laboratory tests have limited utility in this setting, and the diagnosis is therefore a clinical one. The chest x-ray is typically negative in this setting. Treatment includes rapid administration of epinephrine. The presence of fever in the patient, as well as the positive chest x-ray findings, make this diagnosis less likely.

TACO is also referred to as cardiogenic pulmonary edema resulting from transfusion. The recipient cannot appropriately respond to the volume and/or rate of transfusion. Elderly patients with reduced cardiac or renal function or neonates are at greatest risk for TACO.2 Physical exam findings include volume overload/positive fluid balance, elevated jugular venous pressure, dyspnea, peripheral edema, an S3 gallop, and elevated blood pressure. BNP (brain natriuretic peptide) levels, commonly performed in the diagnosis of congestive heart failure, are characterizedly increased in patients with TACO. Patients with TACO demonstrate a significant and rapid improvement in respiratory function following diuresis. Similar to TRALI, patients that experience TACO have imaging findings demonstrating diffuse bilateral pulmonary edema. In contrast to TACO, chest x-rays of patients experiencing TRALI do not demonstrate any evidence of cardiomegaly.

Define TRALI and describe its typical clinical presentation

TRALI is defined as acute lung injury occurring within 6 h of a blood transfusion, with the absence of any other plausible alternative.2 It most commonly occurs in the setting of transfusions containing high volumes of plasma and is characterized by sudden onset respiratory distress. Acute lung injury is defined as new onset hypoxemia with bilateral pulmonary infiltrates in the absence of cardiac failure.

TRALI results in non-cardiogenic exudative pulmonary edema as a consequence of increased vascular permeability from inflammatory injury to pulmonary endothelium.3 Cardiogenic pulmonary edema (TACO), fluid overload, and acute respiratory distress syndrome may demonstrate similar findings of bilateral pulmonary infiltrates on imaging.3 Both TRALI and TACO are associated with risk of mortality. TACO was the most common and TRALI was the second most common cause of transfusion related fatalities reported to the FDA in 2017.4

What additional testing would you perform on this patient?

TRALI is a clinical diagnosis, and while there is no single definitive laboratory test available to confirm the diagnosis of TRALI, it would be appropriate to examine the following: BNP, patient blood cultures, and, if available, pulmonary capillary wedge pressure (PCWP). Also, blood cultures on each of the transfused RBC units could be considered.

Diagnostic findings, Part 2

Blood cultures collected on the patient and the pRBC products are negative. The patient’s BNP is 99 pg/ml (normal < 100 pg/ml). The patient’s pulmonary capillary wedge pressure (PCWP) is 14 mm Hg (normal < 16 mm Hg).

Questions/discussion points, Part 2

Given the additional findings, what is the most likely diagnosis?

The additional findings show blood cultures are negative, arguing against a septic transfusion reaction. The BNP and PCWP is normal, arguing against TACO. Additionally, this patient does not demonstrate cardiomegaly on chest-x-ray. Clinical signs of TACO include hypoxemia and absence of fever. Of note, the patient experienced a fever and experienced a drop in blood pressure post-transfusion, making the

Table 3 Distinguishing transfusion-related acute lung injury and transfusion-associated circulatory overload.

|                      | TRALI                              | TACO                                |
|----------------------|------------------------------------|-------------------------------------|
| Clinical presentation| Respiratory distress, hypoxia,      | Respiratory distress, hypoxia,      |
|                      | hypotension, fever, pulmonary edema| hypertension, tachycardia,          |
| Laboratory           | No elevation in BNP, may see       | Significant elevation in BNP        |
|                      | transient decrease in neotrophil   |                                     |
|                      | count                              |                                     |
| Chest X-ray          | Diffuse bilateral pulmonary         | Alveolar and interstitial           |
|                      | infiltrates (‘white out’), no       | edema, pleural effusions,           |
|                      | evidence of cardiomegaly           | response to volume and/or rate of   |
|                      |                                    | transfusion                         |
| Pleural effusion      | Transudate                         | Exudate                             |
| Pathogenesis          | Immune mediated; donor anti-leukocyte (HLA or neutrophil) antibodies that attack recipient cells | Insufficient compensatory response to volume and/or rate of transfusion |
| Treatment             | Immediately stop transfusion, Support with supplemental oxygen, and intubation, if required. | Immediately stop transfusion. Rapid improvement following treatment with diuretics. |
| Prevention            | Accepting plasma products from male only donors or previously pregnant women that have tested negative for anti-leukocyte antibodies | Consider treatment with diuretics prophylactically. Transfuse future units with caution at a slower rate of infusion |

TACO: Transfusion-related acute lung injury, TACO: Transfusion-associated circulatory overload, BNP: B-type natriuretic peptide, HLA: Human leukocyte antigen.
required intubation. Chest-x-ray showed diffuse bilateral pulmonary infiltrates without an enlarged cardiac silhouette. There are no clinical signs of fluid overload. While there is no single definitive laboratory test available to confirm the diagnosis of TRALI, the constellation of these findings in this patient are most consistent with TRALI.

**How would you manage this patient acutely?**

Management is to provide supportive care with oxygen supplementation, IV fluids, hemodynamic monitoring.

**What is the pathophysiology of TRALI?**

The pathophysiology of TRALI is not completely understood, however studies have proposed antibody mediated and non-immune theories to explain this phenomenon, both of which involve a “two-hit” model:

The “first hit” primes the pulmonary endothelium and leukocytes in the recipient as a consequence of their underlying medical condition.

The “second hit” occurs as a consequence of the blood transfusion via one of the following mechanisms

1. Immunologic: Donor derived HLA or granulocyte specific antibodies (anti-human neutrophil antigen, i.e., HNA), present in the plasma of transfused blood products, may react with HLA or HNA antigens present on primed recipient neutrophils (see above). Subsequently, these neutrophils become activated and sequestered in the lung. They then release toxic metabolites and vasoactive substances into the pulmonary vasculature, causing increased vascular permeability, capillary leak, and pulmonary edema. Alternatively, donor derived anti-HLA antibodies may attack HLA antigens located directly on the pulmonary interstitial cells. These donors derived anti-HLA antibodies are most commonly found in multiparous women, and thus patients receiving blood components from this subset of donors are at increased risk for development of TRALI.

2. Non-Immunologic: Involves the accumulation of bioactive lipids and cytokines during storage of the transfused component. Once this component is transfused, the previously primed recipient leukocytes become activated and aggregate in the lung, triggering the release of proteases that result in capillary leak and subsequent pulmonary edema

**How is the risk of TRALI mitigated? Is pharmacologic prophylaxis needed for future transfusions?**

Regulations require that blood collection centers have strategies in place to mitigate the risk of TRALI. Multiparous women donors are more likely to have antibodies implicated in TRALI thus mitigation strategies focus on the blood donor. These strategies include using plasma from male only donors or women who have never been pregnant, or women who have tested negative for HLA antibodies. It is worthwhile to note that these strategies mitigate the risk of immunologic mediated TRALI but does not address the non-immunologic mechanisms that may contribute to TRALI. Prophylactic pre-transfusion treatment (e.g., antihistamine or acetaminophen) of patients plays no role in prevention of TRALI.

**How can the risk for TACO be mitigated?**

The key to prevention of TACO is to decrease the rate of transfusion of a specific blood component. Prophylactic treatment with diuretics may also be considered.

**What are the other common transfusion reactions? Discuss their pathophysiology**

See Table 4. Febrile non-hemolytic transfusion reaction (FNHTR) and mild allergic transfusion reactions are the two most common types of transfusion reactions.

FNHTR is defined as fever or chills/rigors occurring within 4 hours of a transfusion. FNHTR is caused by accumulation of cytokines produced by white blood cells during product storage. These reactions can be treated with administration of acetaminophen or meperidine for severe chills/rigors.

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### Table 4

Clinical presentation and pathophysiology of transfusion reactions.

| Transfusion reaction | Mechanism | Clinical presentation | Comments |
|----------------------|-----------|-----------------------|----------|
| Febrile nonhemolytic | Accumulation of cytokines released from donor WBCs during blood product storage | Fever (>1-degree Celsius increase in temperature), chills, or rigors | One of the most common transfusion reactions; treat with acetaminophen |
| Allergic (mild)      | Type 1 hypersensitivity. Recipient has IgE antibodies to donor plasma proteins which cause mast cell degranulation and release of histamine. | Dyspnea, wheezing, angioedema, hypotension, shock | Rapid clinical improvement upon treatment with Epinephrine. Can be seen in IgA deficient patients that have anti-IgA antibodies |
| Anaphylactic         | Type 1 hypersensitivity. Recipient has IgE antibodies to donor plasma proteins which cause mast cell degranulation and release of histamine. | Fever, chills, back pain, hypotension, pain at IV site, and renal failure | Most common cause is human error (misidentified specimen or patient) leading to wrong blood given to wrong patient. Lab findings support intravascular hemolysis (elevated LDH, bilirubin, hemoglobinemia, hemoglobinuria, and decreased haptoglobin). Pulmonary infiltrate is exudate. Mitigation involves using male donor plasma or previously pregnant females who have tested negative for anti-leukocyte antibodies. |
| Acute hemolytic      | Type 2 hypersensitivity; naturally occurring preformed IgM antibodies in recipient bind to the transfused ABO-incompatible donor red cells causing complement mediated intravascular hemolysis | Fever, chills, hypotension, shock | Pulmonary infiltrate is transudate. Rapid improvement following diuresis. Most common cause of transfusion related mortality in the U.S. |
| Transfusion-related  | Donor anti-leukocyte (anti-human leukocyte antigen or anti-neutrophil) antibodies to recipient white blood cells | Dyspnea, hypoxemia, fever, hypotension, bilateral pulmonary infiltrates with a normal cardiac silhouette. | Pulmonary infiltrate is transudate. Rapid improvement following diuresis. Most common cause of transfusion related mortality in the U.S. |
| acute lung injury     | Rapid volume expansion by transfusion of large volumes over a short time or to those with underlying cardiovascular or renal disease. | Dyspnea, headache, hypertension, jugular venous distension. Signs of positive fluid balance. Bilateral pulmonary infiltrates with an enlarged cardiac silhouette. | More common with platelet products. Storage of platelets at room temperature provides a favorable environment for bacterial proliferation. |
| Transfusion-         | Bacterial sepsis due to transfusion of bacterially contaminated blood product | Fever, chills, nausea, vomiting, tachycardia, hypotension, shock, multi-organ failure | |
| associated           | circulatory overload | | |
| infection            | | | |
Mild allergic transfusion reactions are type 1 hypersensitivity reactions in which the patient has pre-existing IgE antibodies to plasma proteins found in the donor blood product. Patients present with urticaria, pruritus, flushing or localized edema. If respiratory symptoms such as tightness in throat, dyspnea, wheezing, or if systemic symptoms such as hypotension or syncope are present, the patient should be evaluated for anaphylaxis. Mild allergic reactions can be treated with an antihistamine.

A meta-analysis analyzing over 4000 red blood cell and platelet transfusion events found that routine prophylactic premedication with acetaminophen and antihistamines did not prevent these non-hemolytic transfusion reactions. Thus, routine premedication is not indicated to prevent FNHTR or allergic transfusion reactions.

Teaching points

- Timely recognition of transfusion reactions is critical to patient safety, as reactions can range from mild to life threatening.
- Once a transfusion reaction is suspected, the first step is to stop the transfusion.
- Febrile non-hemolytic transfusion reactions present with fever (and/or chills and rigors) without evidence of hemolysis or respiratory compromise.
- Fever is characteristically absent in allergic and anaphylactic transfusion reactions.
- High fever is characteristic of septic transfusion reactions. The primary treatment for this type of reaction is intravenous antibiotics.
- Appropriate classification of transfusion reactions allows for proper management of patients and guides future transfusion procedures in order to prevent such occurrences.
- TRALI is most commonly caused by donor anti-leukocyte antibodies to recipient white blood cells, specifically anti-HLA or anti-HNA antibodies.

- TRALI mitigation strategies focus on the donor and include using plasma from male donors.
- TACO occurs when the recipient cannot appropriately respond to the volume and/or rate of transfusion.

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