

Transfusion Reactions

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November/December 2012 Blood Bank Guy Podcast

www.bbguy.org

A. Scope of the problem

1. Transfusions still harm, despite great reductions in transfusion-transmitted diseases

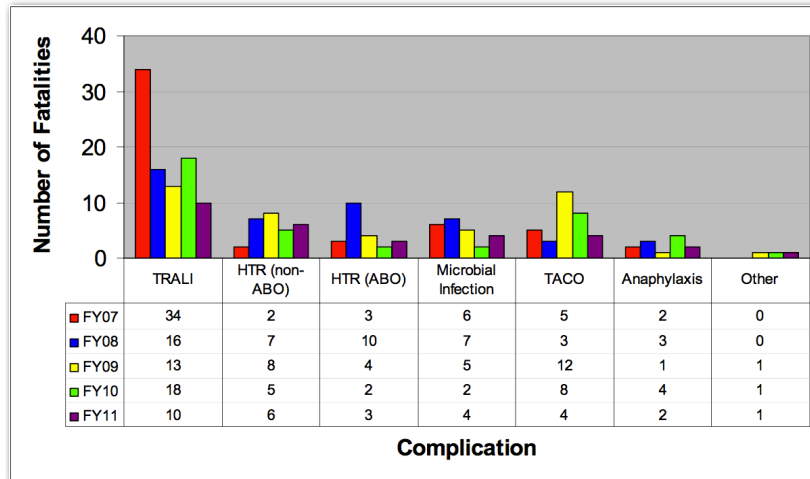


Figure 1: FDA Transfusion Fatalities FY 2007-2011

(Source: <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/ucm302847.htm>)

B. Suspected reaction workup

1. When?
 - a. Indicated when possible reaction is suspected by a combination of signs/symptoms
 - b. Just a few:
 - 1) Inflammatory:
 - a) Fever/chills
 - b) Skin changes
 - c) Pain at infusion site
 - 2) Circulatory:
 - a) Blood pressure changes
 - b) Shock
 - c) Hemoglobinemia/uria
 - 3) Pulmonary:
 - a) Dyspnea, orthopnea, wheezing
 - b) Full respiratory failure
 - 4) Coagulation:
 - a) Unexplained increase in bleeding
 - b) DIC
 - 5) Psychological:
 - a) Sense of unease or impending “doom”!
2. General philosophy (my opinions):
 - a. Opinion 1: Assume all suspected reactions are hemolytic, and work to disprove your assumption
 - 1) A high index of suspicion is much better than low
 - 2) You will be wrong in your assumption almost every time, but the one time that you are right will be life-saving!

- b. Opinion 2: Anyone involved in a transfusion should be allowed to initiate a transfusion reaction workup
- 1) Nurses, perfusionists, and other transfusing staff should be empowered to contact the blood bank directly if suspicious findings occur during transfusion
 - 2) This is from hard experience, with suspected reactions being under-reported (including the worst acute HTR of my professional life)
3. **STEP ONE: STOP THE TRANSFUSION!**
- a. Don't disconnect the unit (though that will eventually happen); at least stop the incoming flow of blood.
 - b. **Main indicator of survival of an acute HTR: amount of incompatible blood infused**; as a result, the obvious thing to do if you are assuming hemolysis is to stop the transfusion
 - c. Leave the line open with saline.

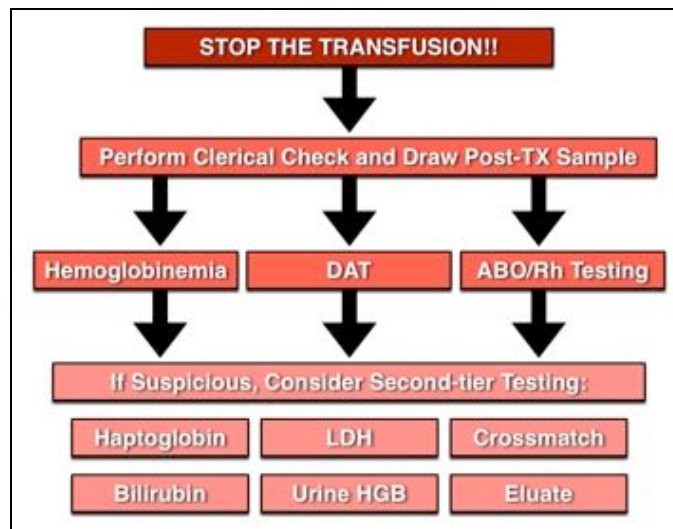


Figure 2: Transfusion Reaction Workup

4. Necessary parts of workup (things everyone should do):
- a. **Clerical check**
 - 1) Bedside paperwork and bag check to ensure right unit went to right patient
 - 2) Blood bank paperwork and computer check to answer same question
 - 3) Should include a basic inspection of the unit for discoloration or obvious issues
 - a) Darkened color in unit: Suspicious for bacterial contamination
 - b) Check for clots, aggregates, or anything out of the ordinary
 - b. **Visible hemoglobinemia check**
 - 1) Spin a post-transfusion EDTA sample and examine visually for a pink-red color change indicative of free hemoglobin in the plasma
 - a) Best to use EDTA because you can then use the same sample for the tube DAT
 - 2) Compare to pretransfusion sample if abnormal.
 - 3) Detects as little as 2.5 to 5 ml of hemolysis occurring anywhere in the body
 - 4) Most sensitive way to detect intravascular hemolysis; not specific, though
 - a) Some causes of false-positive visible plasma hemoglobin:
 - Poor phlebotomy technique (traumatic stick, drawing through IV line)
 - Nonimmune hemolysis (infusion with 0.45 NS, faulty blood warmers, etc.)
 - Autoimmune hemolysis
 - G6PD deficiency and hemoglobinopathies
 - b) Some causes of false-negative visible plasma hemoglobin:
 - Delay in drawing sample (with functioning kidneys, hemoglobin may be cleared in several hours)
 - Sample collected from IV line (dilution of blood)

c. **Direct antiglobulin (Coombs) test (DAT)**

- 1) Demonstrates coating of RBCs with antibody and/or complement *in-vivo* (see figure 3 below)
- 2) Most commonly done with polyspecific method (IgG + C3d)
- 3) If positive, must compare to pretransfusion DAT (automatically done in most places)
- 4) Note that a positive DAT does not prove an acute hemolytic reaction
 - a) Other causes include nonspecific positives in hospitalized patients (20%), autoantibodies, drugs, passive administration of other things like RhIG or IVIG
- 5) Also note that a negative DAT does not disprove an acute hemolytic reaction
 - a) If donor RBCs are completely destroyed by brisk hemolysis, DAT will be negative (especially seen with ABO incompatible transfused RBCs)
 - b) Small amounts of residual donor RBCs (<10% of circulating RBCs) may give false negative tube DAT; gel DAT may help if strongly suspected

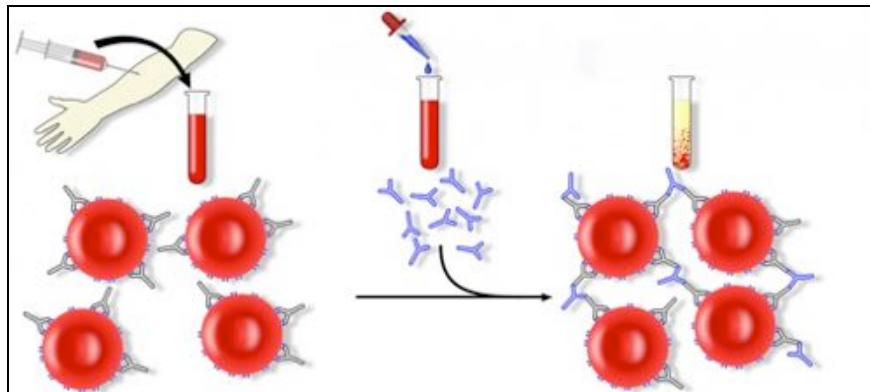


Figure 3: Direct Antiglobulin Test (DAT)

Image credit: A Rad 2006

d. **Repeat ABO/Rh testing**

- 1) Another check for right patient, right blood
 - 2) Check both pre- and post-reaction specimens
5. Other things that may be done (but are not required as a part of every workup)
- a. Facilities must define triggers for when they would do additional testing
 - b. Additional testing for suspected hemolysis:
 - 1) Repeat antibody screen (on both pre- and post-transfusion samples); consider different enhancement (PEG, LISS, cold/warm incubation, etc) or platform
 - 2) Repeat crossmatch with pre- and post samples
 - a) If no serologic crossmatch was done (i.e., if computer crossmatch used), it should be done if there is suspicion on first-tier investigation
 - b) Best done with tube technique including immediate spin and IAT phase readings +/- 37 C reading (gel does not necessarily detect ABO incompatibility)
 - 3) Elution studies if DAT is positive to determine specificity of the antibody
 - 4) Haptoglobin
 - a) Haptoglobin binds to free hemoglobin molecules, facilitating their clearance from the circulation by monocytes and macrophages in the RE system
 - This interaction prevents iron from escaping through the kidneys
 - Also lessens any toxic effect of hemoglobin in the kidneys
 - b) Levels decrease sharply in acute intravascular hemolysis (traditional belief; more current data suggests that it decreases in extravascular hemolysis as well)
 - c) Long turnaround time and acute phase reaction make for limited usefulness in acute setting.
 - If you must use, compare pre- and post levels.
 - 5) Direct and indirect bilirubin

- a) Really more useful to *confirm*, not *make* diagnosis
- b) Both will rise quickly, peak in less than 10 hours, may be normal within 24 hours (if liver is OK)
- c) This is in contrast to traditional teaching that acute hemolysis does not elevate direct bilirubin
- 6) Lactate dehydrogenase (LDH)
 - a) Another marker of hemolysis, as LDH is abundant in RBCs (especially LD2 and LD1 isoenzymes)
 - b) Not specific for intravascular hemolysis (+/- in extravascular, too)
- 7) Urine hemoglobin
 - a) Not as sensitive or as fast as hemoglobinemia for intravascular hemolysis
 - b) Really only useful if testing for visible hemoglobin has been delayed or if there is doubt about a positive visible hemoglobin check
 - c) Remember that hematuria does not equal hemoglobinuria!
- c. Additional testing for suspected septic reactions:
 - 1) Not done routinely on all reaction workups by most facilities
 - 2) Should be done if suggested by clinical data, for example:
 - a) Temperature greater than 102 F
 - b) Temperature increase greater than a specified amount (2 or 3 degrees F)
 - c) Severe rigors
 - d) Clinical septic shock-type findings (marked hypotension, gastrointestinal complaints, later findings of multi-organ failure, DIC, etc.)
 - 2) Both patient and product must be evaluated
 - a) Patient:
 - Blood cultures (drawn as soon as possible from a different site than the infusion); aerobic and anaerobic
 - Consider culture of all intravenous fluids running at the time of reaction if clinically suspicious of sepsis
 - b) Product:
 - Gram stain and culture of actual residual product in the bag (don't culture a segment unless there are absolutely no other options!)
- d. Additional testing for suspected respiratory reactions (see details in TRALI/TACO sections):
 - 1) Chest X-ray
 - 2) BNP levels
 - 3) ABG
 - 4) Donor testing for anti-HLA/HNA antibodies
- e. Additional testing for suspected severe allergic reactions:
 - 1) Serum IgA levels (performed on pretransfusion sample!)
 - 2) Consider serum anti-IgA detection if serum IgA is non-detectable

C. Classification of reactions

1. Worldwide, there is a movement to standardize the definitions of transfusion reactions as well as to improve reporting
2. In the US, this movement is led by the CDC National Healthcare Safety Network (NHSN) and is known as "Biovigilance" (more specifically as "hemovigilance")
3. This lecture includes entities defined in the hemovigilance module (found at http://www.cdc.gov/nhsn/TOC_BIOManual.html)
4. Below is an approach to screening transfusion reactions based on the presence or absence of fever and the timing of the reaction (Acute = during or < 24 hrs after transfusion, Delayed = > 24 hrs after transfusion)

Presenting <i>With</i> Fever	
<u>Acute</u> Acute Hemolytic Febrile Non-hemolytic Transfusion-related Sepsis TRALI	<u>Delayed</u> Delayed Hemolytic TA-GVHD
Presenting <i>Without</i> Fever	
<u>Acute</u> Allergic Hypotensive Tx-associated Dyspnea TACO	<u>Delayed</u> Delayed Serologic Post-transfusion Purpura Iron Overload

D. Acute reactions presenting with fever

1. Acute hemolytic transfusion reactions (AHTRs)

- a. Incidence: 1:76,000 transfusions, (1:1.8 million transfusions fatal HTR)
- b. Clerical errors (both in transfusion service and at bedside) are most common cause
- c. RBC destruction may be intravascular or extravascular
 - 1) ABO-related, intravascular usually more severe
 - 2) 2009-11: More US non-ABO-related than ABO-related fatal HTRs
- d. Signs/symptoms
 - 1) Timing
 - a) Severe reactions may occur early in transfusion (first 15 minutes; see figure 4)
 - b) Milder reactions may present later, but usually before end of transfusion

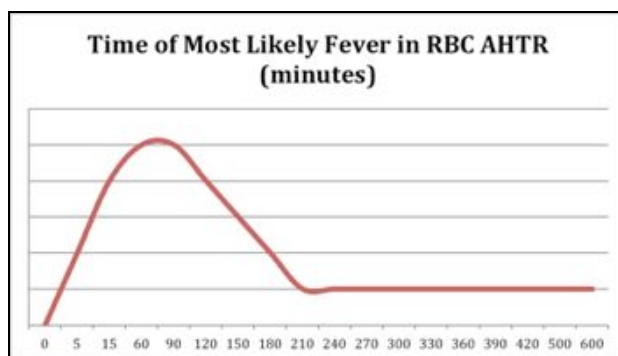


Figure 4

- 2) Specific signs/symptoms:
 - a) Fever and chills
 - Most common presenting symptom (> 80%)
 - b) Back or infusion site pain
 - c) Hypotension/shock
 - d) Hemoglobinuria (may be first indication of hemolysis in anesthetized patients)
 - e) DIC/increased bleeding (also important in anesthetized patients)
 - f) Sense of “impending doom”
- e. Lab findings
 - 1) Hemoglobinemia (pink or red serum/plasma); lasts several hours in those with adequate renal function
 - 2) Hemoglobinuria (typically clears by the end of one day)
 - 3) Positive DAT (unless all donor cells destroyed); may be “mixed field”

- 4) Elevated indirect and direct bilirubin
- 5) Lab findings of DIC (D-dimers, decreased fibrinogen, etc.)
- 6) RBC abnormalities
 - a) Schistocytes: Intravascular hemolysis
 - b) Spherocytes: Extravascular hemolysis



f. Pathophysiology

- 1) Intravascular hemolysis due to ABO incompatibility typifies these reactions
 - a) ABO antibodies fix complement well (high antigen density, potent IgM/IgG antibodies), and this leads to membrane attack complexes and rapid RBC lysis
 - b) Other antibodies (especially Kidd) may also fix complement and lyse RBCs
 - c) Seen much less commonly with incompatible donor plasma (e.g., platelet transfusions from group O donor with high-titer anti-A to group A recipient)

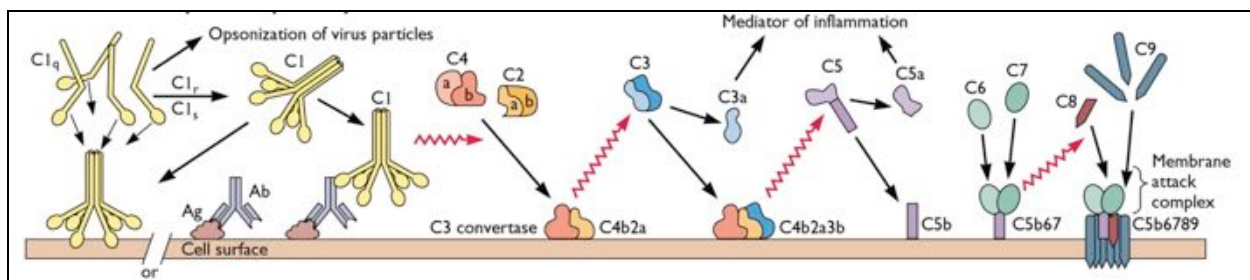


Figure 5: Classical Complement Pathway

Image credit: <http://www.twiv.tv/classical-complement.jpg>

- 2) Hemolysis leads to a complex array of events, including:
 - a) Release of free HGB and HGB-free RBC stroma into circulation
 - b) Stimulation of intrinsic coag pathway and bradykinin via Ag-Ab complexes
 - c) C3a and C5a generation (“anaphylatoxins”)
 - d) Production of several very important cytokines:
 - Tumor necrosis factor (TNF- α)
 - Interleukin-1 β (IL-1 β)
 - Interleukin-6 (IL-6)
 - Interleukin-8 (IL-8, aka CXCL8)

Substance	Effect
C3a/C5a	Increases: Nitric Oxide (NO), cytokines, histamine, leukotrienes
TNF-α	Increases: NO, tissue factor expression (extrinsic) Decreases: Thrombomodulin (anticoagulant; assists protein C)
Interleukin-1 (IL-1β)	Increases: NO Decreases: Thrombomodulin
Free Hemoglobin	Scavenges NO (local, ?global decrease)
Bradykinin	Transient hypotension
RBC Stroma	Direct renal tubular damage

Table 1: Substances generated during acute HTRs and their effects

- 3) Net effects on various systems:
 - a) Inflammatory consequences:
 - TNF- α , IL-1 β , and IL-6 strongly promote fever
 - WBCs activated and stimulated by all of above as well as IL-8 and CCL-5
 - b) Coagulation consequences:
 - Direct intrinsic path activation by Ag-Ab complex interaction with factor XII

- Indirect activation of extrinsic path by *TNF- α* stimulation of *tissue factor*
 - Decreased protein C inhibition via decreased *thrombomodulin*
 - Tissue factor activation also predisposes to DIC (10% of patients)
- c) Circulatory consequences:
- Increased *C3a/5a*, *IL-1 β* , and *TNF- α* stimulate increased *nitric oxide (NO)* levels, which leads to systemic vasodilation
 - *Bradykinin* generation from antigen-antibody complexes likewise promotes transient systemic hypotension
 - On the other hand, massive *free hemoglobin* release may reduce local NO, leading to at least localized vasoconstriction
- d) Renal consequences:
- *Sympathetic response* to hypotension leads to renal vasoconstriction
 - *Free hemoglobin* scavenges renal NO, promoting vasoconstriction
 - Renal *microthrombi* from diffuse coagulation also decrease renal blood flow
 - Hemoglobin-free *RBC stroma* also damages renal tubules directly
 - All of above contribute to risk for acute tubular necrosis, with resultant oliguric renal failure in about 1/3 of confirmed acute HTRs
- e) Respiratory consequences:
- *Anaphylatoxins* promote bronchoconstriction from histamine release, with resultant wheezing/dyspnea
 - Aggressive hydration during resuscitation gives pulmonary edema risk
- 4) Extravascular hemolysis (e.g., Rh/Kell/Duffy, etc.) is usually but not always less severe due to lack of systemic complement and cytokine activation
- g. Treatment
- 1) Hydration and diuresis are critical early components for hypotension treatment and renal function preservation
 - a) Maintain urine output > 1 mL/Kg/hr with saline +/- furosemide
 - b) Low-dose dopamine use is controversial (may not preserve function)
 - 2) Consider DIC; some use heparin during hypercoagulable phase of DIC
 - 3) Consider early exchange transfusion, esp. for high-volume incompatible transfusion
- h. Prevention possibilities
- 1) Training and careful attention to phlebotomy, labeling, issue, and administration
 - 2) Some require two separate ABO/Rh types before transfusion
 - 3) Advanced methods (RFID, bar codes, etc) will likely be helpful in future
2. **Febrile nonhemolytic transfusion reactions (FNHTRs)**
- a. Historically most frequently reported reaction
 - 1) Incidence decreased since “universal” leukoreduction (0.1 to <1%)
 - 2) Still more common than any reaction in heme-onc and transplant patients, especially with platelet transfusion (before LR, as many as 1/3 in some studies!)
 - b. Unexplained increase in temperature of 1C or 2°F
 - 1) Not intended to be a strict cut-off; i.e., don’t require it to diagnose or work up rxn
 - c. Cause: Increased pyrogenic substances (e.g., *TNF- α* , *IL-1 β* , *IL-6*), mostly from WBCs
 - 1) Cytokines may be produced before transfusion
 - Donor WBCs secrete while in the storage bag.
 - Transfusion simply infuses pre-formed fever-inducing substances
 - More common in platelet transfusions
 - 2) OR, cytokines may be produced after transfusion
 - Recipient anti-HLA/HNA antibodies attack donor WBCs, or (less commonly) donor antibodies attack recipient WBCs
 - This action leads to fever-inducing substance release after transfusion
 - More common with RBC transfusions

- d. Signs/symptoms
- 1) Transient fever and chills (+/- rigors?) during or up to 2 hours after transfusion
 - 2) Symptoms tend to occur later in transfusion; if very early, be suspicious of transfusion-related sepsis
 - 3) Note that chills may be first; fever may be delayed up to one hour or more after transfusion in up to 10% of cases
 - 4) Variant versions in premedicated or head injury patients may never have fever

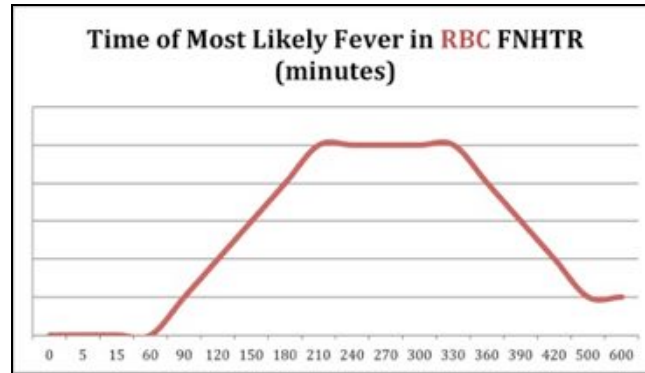


Figure 6

- e. Differential diagnosis:
- 1) Acute HTR
 - a) Remember the above caveat that most AHTRs present with fever/chills alone
 - b) Impossible to distinguish early AHTR from FNHTR clinically, though most fevers in transfusion will NOT be AHTR
 - 2) Transfusion-related sepsis
 - a) Especially sepsis from PLT transfusions (RBC-related sepsis usually presents earlier in transfusion)
 - b) Timing may be identical, mild temperature elevations may mean underdiagnosis of PLT-related septic reactions
- f. Lab findings
- 1) None; negative hemolysis workup (diagnosis of exclusion)
- g. Treatment
- 1) Antipyretics (acetaminophen)
 - 2) Meperidine (Demerol) for more severe chills; use with caution!
- h. Prevention
- 1) Acetaminophen premedication may prevent fever, but is not reliable
 - 2) **Preventing FNH during RBC transfusions**
 - a) Most are due to post-transfusion WBC production of pyrogenic cytokines.
 - b) Leukocyte reduction works extremely well to prevent vast majority of these reactions; nearly all blood banks leukoreduce using pre-storage timing (during or very shortly after collection)
 - 3) **Preventing FNH during platelet transfusions**
 - a) Most are due to pre-transfusion cytokine production by WBCs
 - b) Bedside leukoreduction is ineffective; substances are already in the bag!
 - c) Pre-storage leukoreduction best, but reactions in ~0.1 to 1% of PLT transfusions
 - Exception: Soluble CD40 ligand is PLT-derived and causes fever, so LR wouldn't prevent reactions caused by sCD40L (minority)
3. **Transfusion-related sepsis (septic transfusion reaction, bacterial contamination)**
- a. General statements
- 1) Bacterial contamination is the #1 infectious risk from transfusion, much more common than viruses

- 2) Some sources: As many as 1 in 3000 platelet units are contaminated (many fewer reactions, however)
 - 3) Most contaminated products that cause reactions are closer to their expiration date than their collection date (gives bacteria time to proliferate and enter log phase)
- b. How does it happen?
- 1) Platelets tend to be contaminated by skin contaminants from collection process
 - a) Scarred collection sites (>20 donations) can harbor organisms
 - b) Diversion pouches that accept the first 30-50 mL or so of collected blood in a donation are meant to harvest potentially contaminated skin plugs
 - 2) RBCs more commonly contaminated by an organism growing in the donor's blood (often asymptomatic)
 - a) Surprising amount of silent bacteremia is seen
 - b) *Yersinia enterocolitica* historically most common (large case series from CDC showed most bacteremic donors had mild GI symptoms before or after donation)
- c. Organisms identified depend on product.
- 1) Red cells
 - a) Gram-negative rods (endotoxin-makers that like growing in cold temperatures):
 - *Yersinia enterocolitica* (**most common historically**)
 - *E. coli*
 - *Enterobacter/Pantoea sp*
 - *Serratia marcescens* and *S. liquifaciens*
 - *Pseudomonas* species
 - b) Gram-positive cocci (much less commonly)
 - *Staph. Epidermidis*
 - Propionibacteria
 - *Staph aureus*
 - 2) Platelets
 - a) Vast majority are gram-positive cocci (skin contaminants including those listed above); majority result in only mild reactions (if at all)
 - b) Gram negative rods can also contaminate and are much more likely to cause fatalities than gram-positives (reported examples include *Serratia*, *E. coli*, and *Klebsiella* species)
 - 3) Plasma products
 - a) Uncommonly contaminated
 - b) Few reports involving water bath contamination with *Pseudomonas* species
- d. Signs/symptoms
- 1) Earlier symptoms seen in more severe reactions and more often with RBC transfusions (may occur within the first few minutes of transfusion; see fig 7)
 - 2) Rapid onset high fever (often greater than 4°F/2C)
 - 3) Rigors (true shaking chills with rigidity)
 - 4) Abdominal cramping, nausea/vomiting
 - 5) Hypotension/shock
 - 6) DIC
- e. Differential diagnosis:
- 1) Acute HTR (always!); Severe septic reactions, however, usually are more “acute” and dramatic in presentation than the typical AHTR
 - 2) Anaphylactic transfusion reaction: Can also be dramatic and very early in the transfusion. Usually NOT febrile.
 - 3) Febrile nonhemolytic transfusion reaction (FNHTR): Milder septic reactions and many PLT contaminations can overlap with FNHTR significantly (as a result, many culture units as part of FNHTR workup protocol)

- 4) Sepsis from non-transfusion source (infected lines and/or fluids, coincidental presentation)

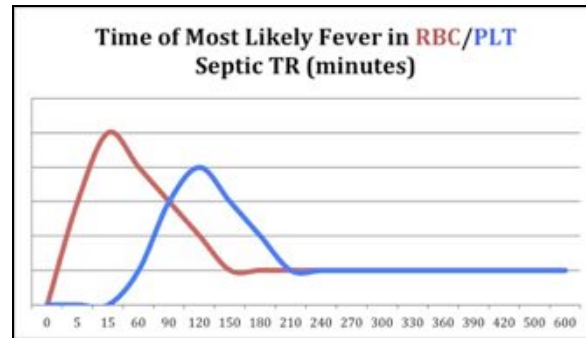


Figure 7

f. Lab findings

- 1) Discolored RBC product (+/-); contaminated RBCs may turn **DARK** or **purple**
- 2) May have hemoglobinemia/uria (non-immune)
- 3) DAT negative (unless coincidental)
- 4) Gram stain positive in only *half to 2/3* of proven cases!
 - a) Source of the gram stain and culture is very important
 - b) Avoid culturing or staining a segment (unless nothing else is available); false negatives when culturing segs only have been described
 - c) Remember to also culture associated IV fluids and consider that an indwelling IV catheter may be a source of contamination
- 5) Culture is proof positive (when same organism is cultured from both unit and recipient; even better if from the donor as well!)

g. Treatment

- 1) Immediate IV antibiotics; treat presumptively with broad spectrum coverage, then adjust as necessary
- 2) Pressure/respiratory/general support as needed
- 3) **Don't forget:** Quarantine all other products from the same donation if a reaction suspicious for sepsis occurs! Notify blood collection agencies promptly!

h. Prevention

- 1) Careful donor history
- 2) Proper phlebotomy technique; use of diversion pouches (mandatory now), strict attention to possible site contaminants
- 3) Leukocyte reduction filters may decrease risk (decrease in *Yersinia* concentration)
- 4) Routine detection of platelet contamination required by *AABB Standard*
 - a) Culture-based methods (culture taken 24 hours after collection):
 - BacT/ALERT system: Microbiology standard blood culture equipment that is most commonly used method; detects decrease in pH from production of CO₂ by growing organisms
 - Pall enhanced bacterial detection system (eBDS): Detects bacterial use of oxygen
 - b) Pre-issue methods (performed shortly before issue)
 - Neither approved system is widely used as of this writing
 - VeraxPGD system (approved for detection in leukocyte reduced apheresis PLTs and pooled whole blood derived PLTs); detects bacterial cell wall antigens
 - Recent report: approximately 1 in 3000 culture-negative apheresis PLTs are Verax-positive before issue (confirmed by second culture of unit)
 - Problem: Cost is direct to transfusion service; resistance
 - BacTx system (approved only for pooled whole blood derived PLTs)

- 5) Despite detection methods, false negatives occur, and pathogen reduction may be the ultimate answer
4. **Transfusion-related acute lung injury (TRALI)**
- Currently the **#1 cause of transfusion-related fatality in the US!** (see pg 1)
 - Incidence varies widely: 1:1200 to 1:190,000 transfusions
 - Two almost identical standard definitions:
 - National Heart, Lung, and Blood Institute (NHLBI) Working Group and Canadian Consensus Conference Panel
 - New acute lung injury within 6 hours of a transfusion; ALI defined:
 - Hypoxemia with $\text{PaO}_2/\text{FiO}_2 \leq 300$ mm Hg (or O_2 sat $< 90\%$) and bilat CXR infiltrates
 - Lack of other risk factors for pulmonary edema
 - No pre-existing acute lung injury
 - Usually also with fever, chills, transient hypertension then hypotension
 - Platelets/plasma transfusions most often, but also with RBCs/whole blood

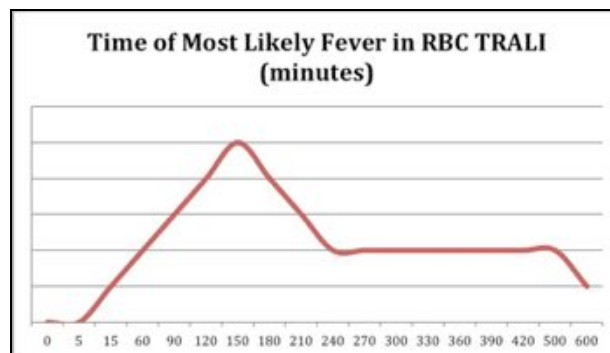


Figure 8

- Clinical differential diagnosis:
 - ARDS**: TRALI may look exactly like ARDS, but TRALI usually resolves in 24-48 hours.
 - Transfusion-associated circulatory overload (TACO)**: May be identical clinically, complete with a “wet” chest x-ray, but TRALI is usually associated with fever (unlike TACO) and does not respond to diuretics
 - Anaphylactic reactions (generally afebrile)
 - Acute pulmonary and myocardial disorders
- Pathophysiology: Two currently accepted pathways that are very closely intertwined
 - The neutrophil is the villain in the pathophysiology of TRALI!
 - Regardless of the “pathway” taken (outlined below), secretion of toxic oxygen free radicals and other substances by the PMN damages pulmonary endothelial cells and capillaries and leads to vascular leakage and TRALI
 - This is merely an exaggeration of normal PMN activity in killing and neutralizing bacterial infections (esp. secretion of reactive oxygen species)
 - The lung is a HUGE sink for PMNs; almost 30% of body PMNs live in the lungs at all times!
 - Donor antibody pathway for TRALI (See Figure 9 on next page)**
 - Anti-HLA or anti-neutrophil antibodies **from the donor** bind to antigens on the recipient neutrophils (see image below)
 - Antibody-PMN complexes deposit in pulmonary vasculature and activate the PMN bactericidal response.
 - Secretion of toxic oxygen radicals and bactericidal enzymes leads to damage to pulmonary endothelial cells lining capillaries, with resultant leakage of fluids into the alveolar spaces (pulmonary edema).

- d) This mechanism may also occur with **recipient** antibodies against **donor** WBCs, but this is less common.
- e) Problem: This mechanism alone does not explain all demonstrated TRALI reactions, nor does it explain why TRALI does NOT occur in settings where it SHOULD (donors with antibodies against recipient antigens that do not have reactions at all)

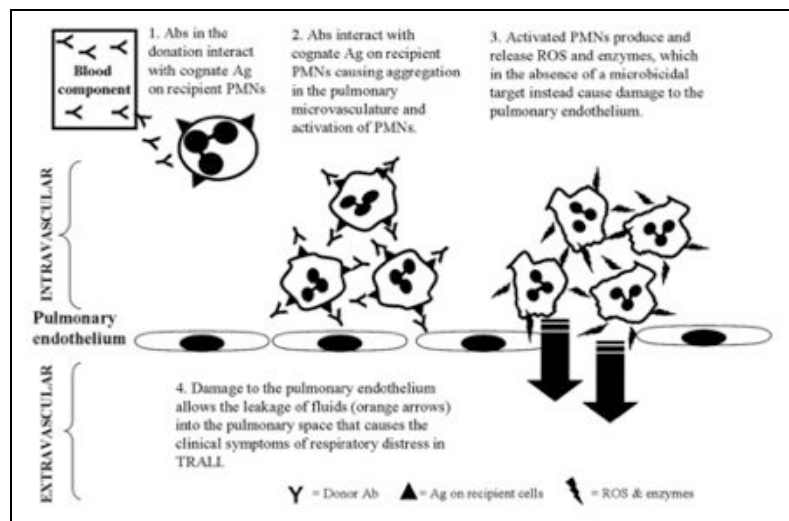


Figure 9: Donor Antibody-mediated TRALI

(Image courtesy of Dr. Chris Silliman)

- 3) **“Two-event” pathway for TRALI (see Figure 10 on next page)**
- First event: Pre-transfusion condition that activates lung endothelial cells and primes PMNs (prepares them for microbicidal action)
 - Examples include sepsis, major surgery, massive transfusion
 - The activation puts the patient in a state where an additional “push” could start the process of
 - Second event: Transfusion of stored blood product (+/- antibodies)
 - Stored blood products accumulate substances called “biologic response modifiers” (BRMs) that can prime/activate destructive neutrophils (bioactive lipids such as lyso-phosphatidylcholines or “lyso-PCs”, soluble CD40 ligand).
 - Either BRMs or antibodies mentioned in the first hypothesis may induce capillary damage by activating the primed PMNs to secrete toxic substances
 - Combination of these events leads to capillary damage and subsequent pulmonary edema.
 - This mechanism helps explain the inconsistencies with the donor antibody pathway and synthesizes the two pathways nicely; still controversial though!
- e. Diagnosis
- Difficult, as it is often confused for something else
 - Typical early findings: bilateral CXR infiltrates, oxygen saturation less than 90%, no evidence of volume overload (no jugular venous distention, normal wedge pressure, normal BNP levels)
 - Lab findings may include demonstration of anti-HLA and/or anti-neutrophil antibodies, and possibly increased biologic response modifiers in the bag.
 - Remember, this is a clinical and radiographic diagnosis; confirming the presence of donor antibodies may take days or weeks!
- f. Treat with respiratory support (oxygen, maybe intubation).
- Mortality reported between 5 and 25%
 - 80% recover quickly

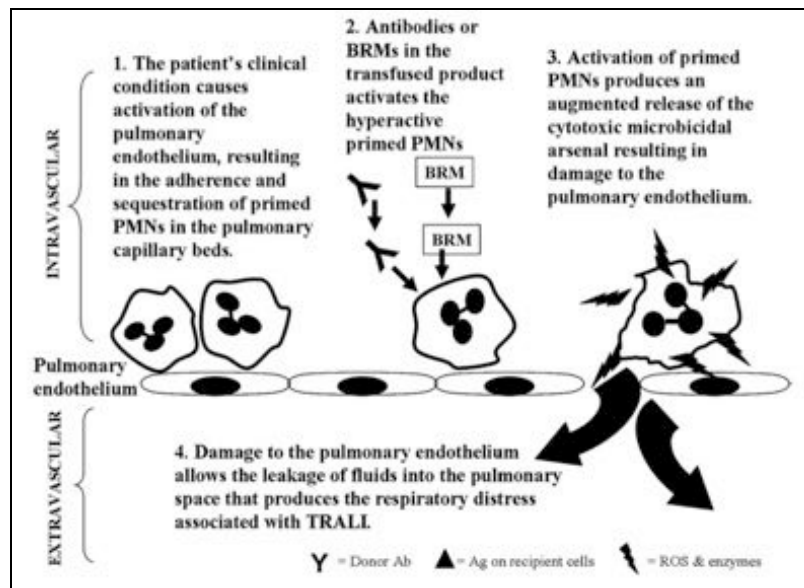


Figure 10: "Two-event" Synthesized Model for TRALI
(Image courtesy of Dr. Chris Silliman)

g. Prevention

- 1) Current AABB mandate for transfusion centers to reduce TRALI risk
- 2) Implicated donors (with antibodies found) should be deferred from donation
- 3) Use of all (or mostly) male plasma has been shown to decrease the risk of TRALI (females have more anti-HLA and anti-neutrophil antibodies because of pregnancy).
- 4) Some centers have begun testing parous female PLT donors for anti-HLA +/- neutrophil antibodies and deferring those who have antibodies
- 5) Strategies only address antibody-formers and ignore two hit model

E. Acute reactions presenting without fever

1. Allergic reactions

a. Mild allergic (urticarial, cutaneous) transfusion reactions

- 1) Very commonly reported reaction (1-3%)
- 2) Usually localized hives, but may have more severe swelling around eyes and lips (angioedema), mild respiratory symptoms, and laryngeal edema (see moderate reactions below)
- 3) Mechanism
 - a) Type I (IgE-mediated) hypersensitivity to transfused plasma proteins (not usually a specific, identifiable allergen)
 - b) Mast cell secretion of histamine and resultant cytokines and other mediators of allergic reactions
- 4) Prevention and treatment options
 - a) Diphenhydramine (Benadryl) IV 25-50 mg as treatment, may use PO form (same dose) as pre-transfusion prophylaxis
 - Probably not cost-effective or advisable for routine transfusions, but may be useful in those with a history of reactions
 - b) Washed products work too (not usually done)
 - c) **May restart transfusion** after hives clear.

b. Moderate allergic (anaphylactoid) transfusion reactions

- 1) Some allergic reactions fall between the two classic categories
- 2) May present with upper/lower airway obstruction +/- cutaneous manifestations
 - a) Upper airway:
 - Stridor, hoarseness, "lump" in throat
 - b) Lower airway:
 - Wheezing, chest tightness, dyspnea

- 3) Some of these patients may respond to IV diphenhydramine and not require epinephrine, while others will need epinephrine
- c. **Severe allergic (anaphylactic) transfusion reactions**
 - 1) Opposite end of hypersensitivity reaction spectrum
 - 2) Uncommon (1:20,000 to 50,000 transfusions)
 - 3) Presentation
 - a) Anaphylactic shock **very early** in the transfusion
 - b) Acute hypotension, lower airway obstruction, abdominal distress, systemic crash
 - c) **Virtually all of these patients have skin findings** (urticaria, angioedema, generalized pruritis)
 - 4) What's the allergen?
 - a) Classic history: IgA deficient recipient who has formed an anti-IgA of the IgE class (which induces a severe type I hypersensitivity reaction)
 - Seen only in those with undetectable IgA levels (lower than what the allergists define as IgA deficient; i.e. $\text{IgA} \leq 0.05 \text{ mg/dL}$)
 - Problem: It's easy to detect IgG anti-IgA, but REALLY hard to detect IgE anti-IgA!
 - Vast minority of patients with anaphylactic-type reactions have demonstrable IgA deficiency with detectable anti-IgA
 - b) Haptoglobin deficiency in Asian patients; anti-haptoglobin in a recipient can give same type of severe reaction as anti-IgA
 - c) Latex, drugs, foods in donors can lead to severe reactions in susceptible recipients (recent report of patient with nut allergy having anaphylaxis after plasma transfusion from donor who ingested peanuts before donation)
 - d) Scattered reports of donors with IgE antibodies transmitting a temporary hypersensitivity to the recipient, with resultant severe allergic reactions
 - e) **BOTTOM LINE:** While all of the above are *possible*, it is very uncommon to find a specific reason why a patient suffered a severe allergic reaction
 - 5) Differential diagnosis:
 - a) Acute HTR
 - Typically febrile
 - Most acute HTRs don't present this early
 - Must rule out nonetheless
 - b) Septic transfusion reaction
 - High fevers and lack of skin findings in septic reactions may be only ways to distinguish early
 - If unclear, give epinephrine anyway
 - c) Acute hypotensive reactions
 - These reactions (see below) have hypotension only, without respiratory or skin findings
 - 6) Confirmation
 - a) ALL patients with a severe allergic reaction should have, at minimum, a check of their pretransfusion sample for serum IgA levels
 - b) Those with very low/undetectable IgA levels ($<0.05 \text{ mg/dL}$) should be tested for anti-IgA (detects IgG antibody but could predict the possibility of IgE)
 - 7) Prevention
 - a) IgA-deficient (IgAD) products traditionally given for those with demonstrated antibodies, but sometimes given for those with low IgA alone
 - IgAD options: Washed cellular products (RBCs, PLTs), or products from IgA-deficient donors (All products)
 - If possible for future transfusions, may also back autologous units

- b) Washed cellular products for those with demonstrated severe allergic reactions and no demonstrable IgA deficiency
 - While this is fairly common practice, MOST patients with history of severe allergic reactions can get future untreated transfusions without harm (they should be monitored VERY carefully however!)
- c) Benadryl probably insufficient by itself for prevention or treatment; if necessary, may use corticosteroids +/- additional histamine blockers
- 8) Treatment
 - a) Epinephrine immediately (0.2-0.5 ml of 1:1000 IM/SQ)
 - b) SQ or IM preferred, but may give IV if already crashed.
- 2. **Acute hypotensive reactions**
 - a. Reactions that are similar to severe allergic reactions but ONLY have severe hypotension (no skin symptoms, no GI complaints, no respiratory issues)
 - 1) CDC definition:
 - a) Over 30 mm Hg drop in systolic BP with diastolic \leq 80 mm Hg
 - b) Occurs less than 15 minutes after the start of transfusion
 - c) Resolves within 10 minutes after transfusion stopped
 - b. Classically associated with two situations (and often with both in the literature)
 - 1) **Patients taking angiotensin-converting enzyme inhibitors (ACEi)**
 - a) Rapid onset of flushing and hypotension in transfused patients who are on ACEi (e.g., Vasotec, Lotensin, Zestril, Capoten).
 - b) Probably caused by accumulation of increased bradykinin or bradykinin metabolites generated during storage
 - ACE inhibitors prevent full metabolism of bradykinin (actually stops at a potent metabolite with a longer half-life)
 - Bradykinin/metabolite causes marked but transient hypotension (bradykinin half-life is on the order of seconds, metabolite mentioned above longer but still only minutes)
 - 2) **Patients receiving blood through negatively charged filters**
 - a) Seen historically with certain negatively charged bedside leukoreduction filters
 - b) Also seen in therapeutic apheresis procedures such as LDL apheresis (due to interaction with negatively charged filters) and plasma exchange with albumin replacement (especially if on ACEi)
 - c) Most concerning, reported with reinfusion of intraoperative blood (cell saver) that is filtered before infusion
 - c. Diagnosis
 - 1) Clearly a diagnosis of exclusion
 - 2) Rule out:
 - a) Acute HTR by workup and lack of fever
 - b) Severe allergic reaction by lack of skin and respiratory findings (as well as transient nature of process)
 - c) Septic reaction by lack of high fever and other clinical findings (GI complaints, transient nature of process)
 - d. Management
 - 1) STOP the transfusion! (short half life of bradykinin leads to rapid resolution)
 - 2) Give fluids, consider epinephrine if not resolved promptly
 - e. Prevention
 - 1) No routine prophylactic measures necessary
 - 2) Avoid bedside leukoreduction filters (not really a problem in most places, as most leukocyte reduction is done in blood centers or transfusion services)
 - 3) Stop ACEi before therapeutic apheresis procedures

3. **Transfusion-associated dyspnea (TAD)**
 - a. A total garbage can diagnosis, in my view!
 - b. Definition:
 - 1) Acute onset of respiratory distress less than 24 hours after transfusion
 - 2) TRALI, TACO, and allergy ruled out
 - c. Should not be a common diagnosis!
4. **Transfusion-associated circulatory overload (TACO)**
 - a. Acute onset of congestive heart failure as a direct result of blood transfusion
 - 1) **Dyspnea**, orthopnea, bilateral rales, with **hypoxia**
 - 2) **Systolic hypertension** (widened pulse pressure), tachycardia, jugular venous distension, pedal edema, headache
 - 3) Usually afebrile
 - 4) X-rays with bilateral predominantly basilar infiltrates, widened cardiac silhouette
 - 5) Proposed diagnostic criteria include some of the above signs/symptoms PLUS:
 - a) Hypoxemia (<90% saturation on room air)
 - b) Bilateral CXR infiltrates
 - c) Reaction occurring within 6 hours of transfusion
 - b. Patients most at risk (though any patient may get TACO if transfused rapidly):
 - 1) Patients with pre-existing CHF
 - 2) Very old (>85% occur in patients over age 60) and very young (to a lesser extent)
 - 3) Renal failure
 - 4) Chronic anemias (e.g., sickle cell, thalassemias), due to compensation for anemia with increased plasma volume
 - c. Differential diagnosis:
 - 1) TRALI
 - a) May be clinically and radiographically identical (though cardiac silhouette widening may not be present in TRALI)
 - b) See distinctions below
 - 2) Allergic/anaphylactic reactions
 - a) May present VERY early in transfusion (first few drops)
 - b) Not responsive to diuretics or positional changes
 - 3) Coincidental cardiac or pulmonary issues unrelated to transfusion
 - a) Acute MI or pulmonary embolism
 - b) Valvular heart disease with decompensation
 - d. Distinguishing from TRALI
 - 1) Clinical (response to diuretics/positional changes in TACO, fever in TRALI)
 - 2) Lab: Elevated brain natriuretic peptide (BNP) suggests TACO (some use ratio of pre- to post-transfusion >1.5 AND elevated post-transfusion)
 - 3) Finding anti-HLA and/or -HNA antibodies as above establishes TRALI
 - e. Treatment
 - 1) Stop the transfusion, evaluate, sit patient up
 - 2) Give supplemental oxygen
 - 3) Diuretics to decrease blood volume
 - 4) In severe cases, therapeutic phlebotomy may be indicated
 - f. Prevention in at-risk patients
 - 1) Control infusion rates (1 mL/Kg/hour).
 - 2) Split units into aliquots when possible.
 - 3) Consider lower volume units (using CPD-RBCs rather than AS-RBCs, for example) or volume reduction of certain products.
5. **Acute Pain Reactions (not discussed in podcast)**
 - a. Sudden onset pain in trunk/extremities
 - b. No predictable risk factors, no way to prevent

- c. Lab workup is negative, and symptoms resolve shortly after transfusion
- d. May require narcotics to relieve pain

F. Delayed reactions presenting with fever

1. Delayed hemolytic transfusion reactions (DHTRs)

- a. Hemolysis occurring at least 24 hours but less than 28 days after transfusion (CDC definition, but rare reports up to 6 weeks).
- b. Pathophysiologic possibilities
 - 1) Anamnestic response
 - a) Mechanism:
 - Patient exposed to non-ABO red cell antigen not present on own RBCs
 - Antibody is formed but fades from detection over time (if patient is not retested after transfusion, which is common, antibody might never be known)
 - Patient is re-exposed to antigen in a future transfusion (because antibody screen is negative for the offending antibody)
 - Anamnestic rapid production of IgG antibody vs. target antigen
 - b) This mechanism is typical for Kidd, Duffy, Kell antibodies
 - 2) Primary response
 - a) Mechanism:
 - Patient exposed to non-ABO red cell antigen not present on own RBCs
 - Antibody is formed quickly
 - Antibody attacks still-circulating transfused red cells carrying target antigen
 - b) MUCH less common than anamnestic mechanism, but possible
- c. Classically leads to extravascular hemolysis
 - 1) IgG antibodies coat red cells and lead to their removal in the liver/spleen
 - 2) Peripheral smear will commonly show spherocytes in this setting
 - 3) NOTE: Delayed HTRs due to Kidd (Jk) antibodies may be intravascular and severe (these antibodies are capable of fixing complement).
- d. Signs/symptoms
 - 1) Often completely asymptomatic
 - 2) Fever and anemia of unknown origin
 - 3) Mild jaundice/scleral icterus may be seen
- e. Lab findings
 - 1) Icteric serum
 - 2) DAT positive (classically “mixed field”)
 - 3) Anemia
 - 4) Newly identified red cell antibody
 - 5) Spherocytes on peripheral smear
 - 6) Elevated LDH and indirect (and often direct) bilirubin, decreased haptoglobin (even if hemolysis is extravascular)
- f. Treatment
 - 1) As for AHTR if severe and intravascular
 - 2) Often no treatment necessary
- g. DHTR vs. “delayed serologic transfusion reaction” (DSTR)
 - 1) These two terms used interchangeably historically (has led to some confusion)
 - 2) Official definition of DSTR:
 - a) The presence of a new, clinically significant red cell antibody in a patient transfused > 24 hours and < 28 days ago without evidence of that antibody, **AND:**
 - b) Complete lack of evidence of hemolysis after careful evaluation
 - 3) Don’t diagnose DSTR without studying the patient carefully (repeat antibody screen on pretransfusion sample if possible; evaluate bilirubin, haptoglobin, LDH, peripheral smear, etc).

- a) Any evidence of hemolysis in study above changes the diagnosis from DSTR to DHTR
2. **Transfusion-associated graft-vs-host disease (TA-GVHD)**
- a. A nearly-always fatal transfusion complication resulting from an attack on recipient cells by viable T-lymphocytes in a transfused blood product
- b. TA-GVHD sequence/requirements:
- 1) Viable, active T-lymphocytes are transfused.
 - a) Minimum number needed to cause TA-GVHD unknown.
 - 2) Donor and recipient are not HLA-identical.
 - 3) Recipient is unable to respond to neutralize the effect of the transfused WBCs.
 - c. The normal response:
 - 1) Transfused T-lymphocytes (CD4, CD8, and NK cells) mount an immune response against foreign HLA host tissues (top left of figure 11 below).
 - 2) Normally, host lymphs (CD8 and NK cells especially) counterattack and neutralize the response (top right of figure 11 below).

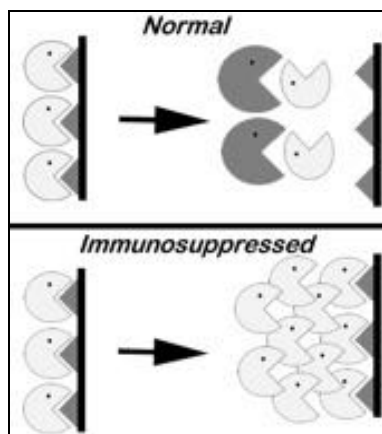


Figure 11: Basic Mechanism of TA-GVHD

- d. Lack of host neutralization (bottom right of figure 11 above) may lead to TA-GVHD, with continued T-lymphocyte attack on host tissues
- 1) Almost uniformly fatal, so thankfully rare
 - 2) Patients present with:
 - a) Fever 7-10 days post-transfusion
 - b) Face/trunk rash that spreads to extremities
 - c) Mucositis, nausea/vomiting, watery diarrhea
 - d) Hepatitis
 - e) **Pancytopenia and subsequent marrow aplasia**
 - This is what leads to the fatal consequences, with most patients dying from overwhelming infections
 - e. Radiation is used to deactivate the T-lymphocytes in transfused blood products
 - 1) 2500 cGy (“rad”) dose required targeted to center of bag, with at least 1500 cGy in all parts of the bag
 - 2) Irradiation dose deactivates lymphocytes without significantly damaging anything else (including PMNs).
 - 3) Why not leukocyte reduction?
 - a) Minimum threshold for TA-GVHD prevention is not known
 - b) Case reports of TA-GVHD from leukoreduced units
 - f. Patients at-risk for TA-GVHD:
 - 1) **Immunosuppressed patients**
 - a) Congenital T-cell deficiencies (DiGeorge’s, SCID, Wiskott-Aldrich)
 - b) Stem cell or marrow transplant recipients

- c) Patients taking chemo agents that attack T-cells (Fludarabine, purine analogs)
- d) Aplastic anemia patients
- e) Patients with solid tumors getting intensive chemotherapy/radiation
- 2) **Intrauterine transfusions, premature neonatal transfusions, and neonatal exchange transfusions**
- 3) **Hematologic malignancies (esp. Hodgkin's)**
 - a) Hodgkins seems to have an inherent cellular immune defect that puts these patients at risk
 - b) Patients with other heme malignancies are more at risk due to intensive treatment regimens
- 4) **Patients with solid tumors undergoing intensive treatment**
- 5) **Granulocyte transfusion recipients**
 - a) Viable, fresh T-lymphocytes present in this short-shelf life product
- 6) **Receiving blood from a first-degree relative donor or receiving HLA-matched units**
 - a) Specific risk: HLA-heterozygous recipient from an HLA-homozygous donor ("One-way HLA match"); see Figure 12 below
 - Child 2 gets blood from child (child 1 is HLA homozygous, while child 2 shares one haplotype with child 1)
 - Child 1 attacks and sees child 2 as "non-self" (due to the non-shared haplotype), but child 2 does NOT see child 1 as "non-self" due to the shared HLA haplotypes

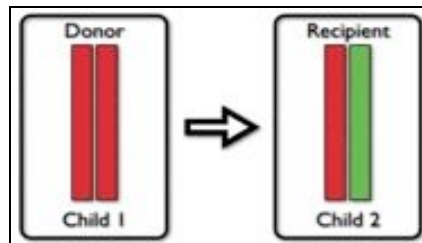


Figure 12: One-way HLA Match

- b) As a result, there is an "attack" (transfused child 1 T-lymphs vs child 2 HLA-bearing cells) but no "counterattack" by child 2 T-lymphs vs. child 1 T-lymphs.
- c) This occurs most frequently in families, but also occurs in less HLA-diverse populations (most famously in Japan)
- d) This interaction can lead to TA-GVHD in a completely immunocompetent recipient
- g. Patients probably NOT at risk (but often get irradiated products anyway).
 - 1) Solid organ transplant recipients
 - 2) Term neonates
 - 3) AIDS patients (CD8 cells that counterattack preserve function until late in disease).
 - 4) Patients receiving previously frozen plasma products (FFP, cryoprecipitate)
 - a) Frozen/thawed/deglycerolized RBCs should be irradiated if recipient is at risk for TA-GVHD; since they were cryopreserved, viable T-lymphs can survive.
- h. Don't use irradiation for:
 - 1) Preventing CMV transmission (leukocyte reduction)
 - 2) Peripheral progenitor cell infusions (think about it)
- i. Gamma irradiation (stand-alone units, usually in transfusion service) and x-ray irradiation (commonly performed in radiology or radiation oncology areas) are used interchangeably and are equally effective
- j. Maximum storage: 28 days after irradiation or regular expiration date, whichever comes first
 - 1) K+ and free hemoglobin increase in plasma

G. Delayed reactions presenting without fever

1. **Delayed Serologic Transfusion Reaction (DSTR)**
 - a. Described above in the DHTR section
 - b. A new antibody in a recently transfused patient, without evidence of hemolysis
2. **Post-transfusion Purpura (PTP)**
 - a. Rare reaction, with marked thrombocytopenia and increased risk of bleeding about ten days following transfusion (may be below 10,000/ μ L)
 - 1) Bleeding is often mucocutaneous (mouth and nose, GI tract); intracranial hemorrhage is possible but occurs in less than 10% of cases typically
 - 2) Triggering transfusion platelets **or** RBCs (more commonly RBCs/whole blood)
 - 3) RBC products contain substantial amounts of platelets and soluble platelet antigens
 - b. Multiparous females especially at risk (5:1 female-male ratio)
 - c. Caused by antibody vs common PLT antigen
 - 1) Anti-HPA-1A (PL^{A1}; present in 98%) most common culprit (70-80% of cases)
 - 2) HPA-1A negative patients are exposed through pregnancy or transfusion.
 - 3) Transfusion after antibody is formed leads to devastating destruction of platelets.
 - 4) **HPA-1A-positive transfused platelets *and* HPA-1a-negative patient platelets are both destroyed, which is weird, right?**
 - a) Most likely because antibody has autoantibody activity
 - b) Passive adsorption of Ag/Ab complexes or soluble PLT Ags also suggested
 - d. Differential diagnosis is challenging and difficult
 - 1) TTP, ITP, DIC, HIT all can share features
 - 2) Even more difficult in patients already thrombocytopenic
 - e. IVIG reverses the process and normalizes platelet count in about 3-5 days
 - 1) Due to this, plasma exchange is uncommon today (only if IVIG doesn't work)
 - 2) Mortality historically 10% without treatment; now near 0% with treatment.
 - f. Platelet transfusion should be avoided if possible (ineffective, may worsen?)
 - g. Future platelet transfusions should be negative for target antigen
3. **Iron overload**
 - a. Each unit of RBCs: 200-250 mg iron (generally, 1 mg iron per 1 mL RBCs)
 - b. Lifetime load of ~50-100 transfusions in 70 Kg person = risk for overload.
 - 1) Hepatic, cardiac, endocrine organ, RE system deposition is especially damaging
 - 2) May present with hepatic or cardiac failure, diabetes, thyroid abnormalities
 - 3) Big risk in chronically transfused patients
 - c. Exchange transfusions reduce risk
 - d. Iron chelators (deferoxamine, deferiprone, deferasirox) may remove iron from hepatic stores and from RE system

H. Consequences of significant reactions

1. FDA requirements
 - a. If there is **suspicion** that a death is transfusion-related, FDA requires notification "as soon as possible" by phone, fax, or e-mail (formerly 24 hours, and most try to comply)
 - 1) Official rule says "confirmed" death, but FDA cites facilities regularly for not reporting deaths that are "suspicious" for being caused by transfusion
 - 2) It's ok to report a death that is suspicious (even a little), then follow-up as below
 - b. Initial report with a full investigation and written report within 7 days
2. JCAHO
 - a. Acute hemolytic transfusion reactions are "sentinel events" and require intensive investigation (Root Cause Analysis) and reporting to JCAHO.

ACUTE FEBRILE REACTIONS (during or <24 hrs from transfusion; presenting with fever)

Reaction/Incidence	Presentation; <i>Diagnosis</i>	Common Mechanism	Treatment	Prevention
Acute Hemolytic (AHTR); <i>1:76,000, 1 in 1.8 million are fatal</i>	Fever/chills (most common), back/flank pain, HGBemia/uria, bleeding, DIC, “doom”; <i>clerical errors, free HGB, repeat x-match</i>	ABO-incompatible red cells given to patient (rarely from incompatible plasma hemolyzing patient RBCs)	Pressure and volume support, fluids, diuretics if necessary (urine output > 1 mL/Kg/hr); may need PLT/FFP/Cryo if DIC	Careful attention to detail and processes
Febrile Nonhemolytic (FNHTR); < 1%	Fever/chills only (>1 C/2°F); <i>negative workup</i>	Cytokines (e.g., IL-6, TNF) from unit or recipient; HLA antibodies	Antipyretics; meperidine if chills are violent	Leukoreduction. Pretransfusion antipyretics used but may not work.
Bacterial Contamination (Septic reaction); 1:3000 PLTS (much fewer reactions)	Rapid high fever, rigors, shock, GI symptoms; gram stain (50%), culture is conclusive	Bacteria in donor’s blood or through collection site	As for sepsis; antibiotics and pressure support as necessary	Donor Center precautions, possible leukoreduction contribution
Transfusion-related Acute Lung Injury (TRALI); 1:1300-1:190,000 (obviously, unclear)	Acute lung injury <6 hours after transfusion. Bilateral CXR infiltrates, hypoxemia. No cardiac dysfunction. <i>Difficult; donor HLA/HNA abs, consensus criteria</i>	1. Transfused anti-HLA and/or anti-HNA Abs activate PMNs or 2. Lung endothelial and PMN priming by physiologic stress, then activation by blood substances	Aggressive supportive care (may include intubation); most resolve but close to 20% fatal	Don’t transfuse! Preferential male plasma use for decreased HLA/HNA antibodies. HLA antibody screening of female PLT donors. If + antibodies in implicated donor, donor should be deferred.

ACUTE AFEBRILE REACTIONS (during or <24 hrs from transfusion; presenting WITHOUT fever)

Reaction	Presentation/ <i>Diagnosis</i>	Common Mechanism	Treatment	Prevention
Urticarial (mild allergic reaction); 1-3%	Localized or diffuse hives/redness; <i>if localized, no workup necessary</i>	IgE-mediated hypersensitivity to transfused protein	Antihistamines	Pretransfusion antihistamine; may wash product if necessary
Anaphylactic/-oid (severe allergic reaction); 1:20,000-50,000	Severe hypotension very early in transfusion, GI symptoms, rare fever; <i>anti-IgA, check IgA levels</i>	Recipient IgA deficiency with anti-IgA antibodies, haptoglobin deficiency, latex or PCN allergy	Epinephrine (0.2-0.5 mL of 1:1000 given IM or SC; use IV if necessary), pressure support	Washed RBCs/PLTs or IgA deficient donor-derived products
Transfusion associated circulatory overload (TACO); 1:350-5000 reported	Dyspnea, hypoxia during or after transfusion; <i>+/- elevated BNP, JVD, hypertension</i>	Cardiopulmonary disease with too rapid blood infusion; very old and very young most at risk	Diuretics, slow infusion	Divide products into aliquots, slow infusion, monitor I/O’s
Premedicated Febrile	Chills; occurs in premedicated pts	As for FNHTR; fever is blocked	Meperidine if chills are violent	As for febrile nonhemolytic

DELAYED FEBRILE REACTIONS (>24 hrs from transfusion; presenting with fever)

Reaction	Presentation/ <i>Diagnosis</i>	Common Mechanism	Treatment	Prevention
Delayed Hemolytic (DHTR); 1:2500-11,000	Fever, anemia ≥ 1 week after transfusion; <i>+DAT, hyperbili, new antibody (Jk, Fy, K especially)</i>	Anamnestic response to re-exposure to red cell antigen; rarely 1° response	Supportive; as for acute hemolytic if severe	Previous records (honor previous antibodies), patient history, some use ID tags/cards
TA-GVHD; Risk varies widely by locale, but is generally rare	Fever, diarrhea, skin rash 7-10 days post transfusion; <i>skin biopsy, bone marrow, flow cytometry, molecular</i>	Cellular immune response by transfused T-lymphocytes vs host	Supportive, immunosuppress; usually in vain (>90% fatal)	Irradiation of cellular products transfused to at-risk recipients

DELAYED AFEBRILE REACTIONS (>24 hrs from transfusion; presenting WITHOUT fever)

Reaction	Presentation/ <i>Diagnosis</i>	Common Mechanism	Treatment	Prevention
Post-transfusion Purpura (PTP); rare	Dec PLTS +/- bleeding 1 week after transfusion (RBCs +/- PLTs); <i>clinical dx, platelet antibodies</i>	Recipient antibody vs. absent PLT antigen (HPA-1a 70%)	IVIG 1 st choice, plasma exchange second; avoid platelet transfusion	Antigen-negative platelet transfusions if necessary
Iron Overload; typically after >100 units received	Liver, pancreas, cardiac dysfx; <i>serum iron/ferritin, LFTs</i>	Iron deposition from multiple Tx	Iron chelators like deferoxamine, deferasirox	Judicious transfusion