I. Acute Hemolytic Transfusion Reactions
   A. Incidence: 1:38,000 to 1:70,000
   B. Etiology/Pathophysiology
      o RBC antigen–RBC antibody reaction usually due to ABO incompatibility
      o Other commonly implicated alloantibodies: Kell, Kidd, Rh
      o Usually due to mistransfusion or clerical errors
      o Ag-Ab activates the following systems:
         ♦ Neuroendocrine: Ag-Ab → XIIa → production/activation of Bradykinin → Hypotension → sympathetic vasoconstriction of renal, splanchnic, pulmonary and cutaneous vascular beds
         ♦ Complement: Ag-Ab → activated complement on RBCs → intravascular hemolysis with free Hgb and RBC stroma (contributes to ATN?) or C3b → RE system
         ♦ Coagulation:
            - Intrinsic cascade by XII or RBC stroma → DIC → consumption → coagulopathy with bleeding
            - Production of anaphylatoxins → degranulation of mast cells → release of histamine and serotonin
      o Primary concerns:
         ♦ Renal ischemia due to hypotension, renal vasoconstriction and intravascular thrombi which may lead to ATN
         ♦ DIC
   C. Signs/Symptoms
      o Usually occur early during the transfusion. Onset of symptoms may not necessarily by sudden; may be mild and vague
      o Fever or fever and chills (most common presenting sign, >80%): increase in body temperature by 1°C
      o Others signs/symptoms: chest pain, back pain, pain at infusion site, nausea, flushing, dyspnea, hemoglobinuria, oliguria, anuria, bleeding, hypotension, shock
      o Difficult to recognize in anesthetized patient – may manifest as hypotension, hemoglobinuria, and evidence of DIC
   D. Action/Therapy
      o Stop transfusion immediately, keep IV line open and administer saline to maintain BP
      o Clerical check at bedside
      o Notify blood bank, send appropriate specimens
      o Primary goals of therapy:
         ♦ Treat hypotension
Promote renal blood flow (in adults: maintain urine output at 100ml/hr for 18–24 hrs)
Use of osmotic or diuretic agents (furosemide)
Low dose dopamine to increase CO, dilate renal vasculature
If DIC develops – treat with blood products for bleeding, ?anti-coagulation

E. Lab evaluation
  o Clerical check
  o Evaluation of patient’s pre- and post- transfusion specimens
    ♦ Look for free Hgb or bilirubin
    ♦ Visual check for hemolysis valuable: eye can detect 5-10 ml of hemolysis
    ♦ Repeat ABO, Rh
    ♦ DAT, eluate and compare with pre-transfusion specimen if positive
    ♦ Repeat crossmatch with RBC unit or segment
    ♦ If immune mediated hemolysis suspected, perform antibody screen on new specimen and phenotype segment retained from the transfused unit.
  o Laboratory evaluation of patient
    ♦ Follow Hgb and Hct
    ♦ Look for free Hgb in free urine, r/o intact RBCs
    ♦ Check unconjugated bilirubin (5 to 7 hours post reaction)
    ♦ Haptoglobin on patient’s pre- and post- transfusion specimens
    ♦ Urine hemosiderin
    ♦ Coagulation labs to monitor for DIC
  o If bacterial contamination suspected, gram stain/culture unit and patient
  o **If clerical check not OK, free Hgb present, post DAT positive, or patient’s condition suspicious, further investigation is warranted**
  o If DAT negative, no evidence of clerical error, and no new alloantibody identified , immune mediated hemolysis unlikely. consider non-immune hemolysis (differential)
    ♦ Bacterial contamination of donor unit
    ♦ Sepsis with Clostridia. Spp.
    ♦ Mechanical damage of donor unit
    ♦ Heat damage due to faulty blood warmer
    ♦ Mechanical damage due to pressure infusion pump, small bore needle, extracorporeal circulation
    ♦ Hemolysis due to hypotonic solutions, dextrose solutions, medications
    ♦ R/O myoglobinemia
    ♦ Drug-induced hemolysis: penicillin, quinidine, α-methyldopa, cephalosporins, sulfonamines, rifampicin (DAT+ but eluate negative)

II. Febrile Non-Hemolytic Transfusion Reaction (FNHTR)
A. Incidence: 1:17 to 1:200 in RBCs, 1:3 to 1:100 in platelets (most frequently reported reaction)

B. Etiology/Pathophysiology
   - Due to elevated levels of pyrogenic cytokines (IL-1β, IL-6, TNF-α) in the transfusion recipient.
     - Possible mechanisms:
       - Recipient cells (leukocytes, endothelial cells, etc.) may be stimulated directly or indirectly by infused foreign cells or plasma constituents to produce pyrogenic cytokines
       - Donor leukocytes may be stimulated in vivo to produce cytokines upon infusion into the recipient
       - Donor leukocytes in the component bag may be stimulated to produce pyrogenic cytokines during storage

C. Signs/Symptoms
   - Temperature rise of 1°C/2°F or more in associated with transfusion (usually during or shortly after transfusion, but may occur up to 2 hours after completion of transfusion)
   - May be associated with chills and rigors, or chills and rigors without fever
   - Fever may be blunted with premedication
   - Not life threatening, but causes patient discomfort

D. Action/Evaluation
   - Diagnosis of exclusion
   - Patients respond to antipyretics (severe rigors may require Demerol)
   - Usual evaluation required; important to r/o HTR or bacterial contamination
     - If the fever is quite high or accompanied by hypotension, or if the clinical picture is very suspicious for sepsis, make sure the blood bag and the patient are cultured.
   - Prevent with leukocyte-reduced blood products for patients with two FNHTRs or a more severe first reaction; consider premedication with antipyretics

III. Transfusion Related Acute Lung Injury (TRALI)
A. Incidence: 1:5,000 to 1:190,000

B. Etiology/Pathophysiology
   - Donor antibodies to HLA or granulocyte antigens of the recipient leading to increase in permeability of the pulmonary microcirculation (capillary leakage) – rarely antibodies in the recipient’s circulation interact with the transfused granulocytes
   - Multiparous female donors are at high risk for developing anti-HLA
   - Possible “two-hit” model:
     - First hit is recipient condition such as sepsis or trauma that activates pulmonary capillary endothelium and primes recipient neutrophils, both resulting in sequestration of these cells in the pulmonary vasculature
Second hit is a donor factor – either specific antibody or another factor such as a lipid agent of cytokine which triggers the sequestered neutrophils to damage the endothelium, leading to capillary leak.

C. Signs/Symptoms
- Acute respiratory distress during or shortly after transfusion (1–6 hours but has been reported within 24 hours) – can be fatal
- Can be accompanied by fever, chills, and hypotension (hypertension seen less frequently)
- CXR: pulmonary edema/diffuse bilateral pulmonary interstitial infiltrates
- Normal CVP, normal/low pulmonary wedge pressure
- Diagnosis of exclusion – must rule out cardiogenic pulmonary edema
- May look like ARDS, but usually resolves in 24–48 hours

D. Action/Evaluation
- Stop transfusion immediately
- Respiratory support to maintain oxygenation – intubation may be required
- Patient should not be diuresed – diuresis can further complicate the patient’s clinical status
- Usual blood bank evaluation (consider assessing patient and/or unit segment for HLA and granulocyte antibodies)
- Prevention:
  - None generally necessary since the donor is usually the problem
  - Consider removing implicated donors from the donor pool and quarantine other products from the donor
  - Other measures donor centers can take: No consensus yet.
    - Using only male plasma (UK, American Red Cross)
    - Deferring donor with anti-HLA antibodies from donating plasma or platelets

IV. Allergic (Urticarial) Transfusion Reaction
A. Incidence: 1:33 to 1:100 (second most frequently reported reaction)
B. Etiology/Pathophysiology
- Due to soluble products/proteins in donor plasma
- Type I hypersensitivity
- Dose dependent: more common secondary to FFP and platelet apheresis product than RBCs due to the greater volume of plasma
- Usually not dangerous but may cause patient discomfort and anxiety
C. Signs/Symptoms
- Hives or pruritic rash during or shortly after transfusion
- Usually without fever or other symptoms
D. Therapy/Evaluation
- If localized, can momentarily stop transfusion and administer antihistamine (i.e. Benadryl). If hives/itching abate, can restart transfusion (only transfusion reaction in which transfusion can be safely restarted)
- Routine blood bank evaluation if reported
Prevention: consider premedication if repeated allergic reactions or reactions are particularly severe

V. **Anaphylactic Transfusion Reactions**
   A. Incidence: 1:20,000 to 1:50,000
   B. Etiology/Pathophysiology
   o About 50% reported cases occur in patients who are IgA deficient with anti-IgA Abs due to transfusion or pregnancy
     ♦ IgA deficiency: 1 in 700 individuals – but this includes many individuals with low levels of IgA
     ♦ For clinically significant anti-IgA to develop in an individual, IgA levels must be absent, not simply decreased levels,
   o Some reported cases have been attributed to antibodies to drugs
   C. Signs/Symptoms
   o Coughing, bronchospasm, dyspnea, vomiting, diarrhea, hypotension, shock, LOC
   o Symptoms may be seen after infusion of only a few mls of blood or plasma
   D. Therapy/Evaluation
   o Stop transfusion immediately; keep IV open
   o Treat anaphylaxis with sub-Q epinephrine, IV steroids, etc.
   o Usual blood bank evaluation, r/o HTR
   o Sensitive quantitative assays for IgA and anti-IgA Abs not readily available (send to National Red Cross)
   o Sensitized IgA deficient patients should be transfused with components lacking IgA
     ♦ Rare donor file must be consulted for IgA deficiency plasma/platelets
     ♦ Deglycerolized/washed RBCs can be used for red cell transfusion
     ♦ Autologous donation provides the safest transfusion

VI. **Bacterial Contamination** (Septic Unit)
   A. Incidence: 1:2,000 to 1:4,000
   B. Etiology/Pathophysiology
   o Bacteria proliferate during storage
   o Organisms depends on the product, and therefore storage temperature
     ♦ **RBCs** (iron-loving organisms)
       - *Yersinia enterocolitica*
       - *Citrobacter Freundii*
       - *E. coli*
       - *Pseudomonas* species
     ♦ **Platelets**
       - Gram-positive cocci, skin contaminants
   C. Signs/Symptoms
   o Rapid onset of high fever, rigors, abdominal cramping, nausea/vomiting
   o May have hemoglobinemia/hemoglobinuria
   D. Action/Evaluation
   o Stop transfusion immediately
Immediate wide-spectrum antibiotics and pressure support

Usual blood bank evaluation (plus culture both the unit and the recipient)
- Discolored product
- Gram stain/culture of product not segment (unless only segment available)

Prevention
- Careful donor history
- Proper phlebotomy technique
- Bacterial detection systems of platelets

VII. Circulatory Overload
- Volume sensitive patients
- CHF symptoms during or after transfusion
- Treatment: oxygen +/- diuresis