Transfusion Reactions

Adverse Effects of Blood Transfusion

- Transfusion-Transmitted Infectious Disease (ie, "aftermath")
- "Transfusion Reactions" (acute/subacute)

Introduction of ID Testing for Blood

Date	Test	Date	Test
c. 1910	Syphilis	1987	HIV-2
1970	HBV by ID	1988	HTLV I & II
1972	HBV by CIE	1991	HCV
1975	HBV by RIA	1995	HIV p24 Ag
1981	HBV by RIA	1995	NAT (HCV/HIV)
1985	HIV-1		

Transfusion-Transmitted Agents Not Tested For

- Malaria
- Trypanosoma cruzi
- Babesia
- Miscellaneous bacteria
- Miscellaneous viruses (eg CMV, Parvovirus)

Risk Estimate/Unit Transfused (approximate)

Agent	Estimate
HAV	1: 1 million
HBV	1:100,000
HCV	1:360,000
HIV	1: 1 million
Bacteria/platelet	1:10-20,000
T cruzi	1:42,000
ABO incompatible	1:12,000

Transfusion Reactions

- Allergic
- Hemolytic (Acute; Delayed)
- Bacterial
- Febrile non-hemolytic
- TRALI
- Volume Overload

Transfusion Reactions: Signs & Symptoms

- Fever
- Hypotension
- Chest Tightness/Dyspnea
- Nausea/Vomiting
- etc

Allergic Transfusion Reactions - Etiology

- Anti-IgA in an IgA deficient patient (18%)
- Antibodies to polymorphic forms of serum proteins (IgG, albumin, haptoglobin, α-1 antitrypsin, transferrin, C3, C4, etc)
- Transfusion of allergen in a sensitized patient (eg Penicillin, ASA, etc consumed by donor)
- Passive transfer of IgE (to drugs, food)
- <u>MOST COMPLETELY UNEXPLAINED</u>

Immuno-Hemolytic Transfusion Reactions

- Intravascular vs Extravascular

- Immediate vs Delayed

Immunohematological Testing for Safety

- Imminent Importance – ABO Typing

- Anticipatory/Prophylactic Importance – Rh Typing

RE: Transfusion Safety (Serological)

- "Given the distribution frequency of ABO groups, the chances of major incompatibility are *one in three*"

Acute Hemolytic Reactions - Etiology

- 1 in 38,000 Red Blood Cell Transfusions
- Usually ABO incompatibility
  - Sample or transfusion error 65%
  - Blood Bank error 35%
- Other red cell antigen – K, Jk-a/b, Fy-a
- Mortality dependent on amount transfused
  - 0% < 500 ml, 25% 500-1000 ml, 44% > 1000 ml
- Non-immune hemolysis – hypotonic fluid, overheating or freezing, cell saver

Acute Hemolytic Reactions - Management

- STOP the transfusion
- Keep IV open
- *Report immediately!!!*
- Blood samples (T&S, DAT, lytes, creat, PT/aPTT, fibrinogen)
- Support BP
- Transfuse to correct coagulopathy
- ↑ K, metabolic acidosis common; dialysis as needed
- Return units to Blood Bank
- *Often another patient at risk*

Case #2 – Patient History

- 38 year old man with AML admitted with febrile neutropenia post-chemotherapy
- On cefazolin & tobramycin
  - Blood cultures negative
  - Afebrile
  - Tongue swelling since day 2 with airway compromise
- Taken to OR for awake intubation and possible tracheostomy if oral intubation failed
- Pre-intubation:
  - Plt count 7×10^9/l; Temp 37.4° C, BP 140/80

Case #2 – Patient History Cont'd

- Transfused 5 units of pooled random donor platelets (including the implicated platelet)
  - The pool is infused over 10 minutes
- During platelet transfusion patient is intubated
- Patient develops immediate cardiac ischemia & hypotension
  - BP 95/60, O_2 Sat 91% (temp not monitored)
- Patient sedated & paralyzed
- Transfusion reaction not included in the differential diagnosis of the acute clinical change

Case #2 – Patient History Cont'd

- On arrival to the Critical Care Unit
  - Temp 40° C
  - BP 70/58
- Blood cultures taken at admission to ICU grow *Serratia marcescens* within 24 hours despite Cipro/tobramycin administered pre-transfusion
- Renal & hepatic failure ensue
  - Death within 18 hours of transfusion
- Platelet pool discarded; no cultures performed
- RBC positive culture for *Serratia marcescens*

Bacterial Contamination Etiology

- Donor bacteremia, skin plug, processing
- Organisms PRBC = *Yersinia enterocolitica, Serratia marcescens, Serratia liquefaciens*
- Organisms PLTs = *Staph aureus, Klebsiella pneumoniae, Serratia marcescens, Staph epidermidis*

Incidence of Bacterial Contamination and Septic Transfusion Reactions

- Incidence of bacterial contamination
  - 1 in 2000-3000 platelet units
  - 1 in 30,000 RBC units
- Prevalence of severe episodes of transfusion-associated bacterial sepsis not clearly established; estimated to occur in about 1/6 contaminated units

Febrile Transfusion Reactions Differential Diagnosis

- Bacterial contamination/septic transfusion reaction
- Acute hemolytic transfusion reaction
- Febrile non-hemolytic transfusion reaction (although such a reaction may actually occur without fever!)

Febrile Transfusion Reaction - Approach
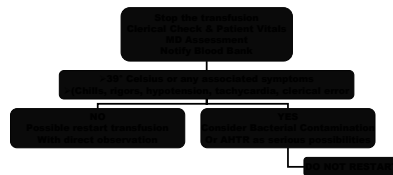
Transfusion Related Acute Lung Injury - Definition

- A syndrome of acute respiratory distress with hypoxia and bilateral pulmonary edema, without evidence of congestive heart failure
  - Within 6 hours of transfusion
  - May be indistinguishable from ARDS (from other causes)
  - Usually resolves in 24-72 hours

Case #1 – Patient History

- 51 year old female
- Diagnosis – T-Cell Lymphoma
- Chemotherapy – 2nd cycle
- CBC
  - Hemoglobin 87 gm/l
  - Platelet count 10 x 10^9/l
  - WBC 14.9 x 10^9/l

Case #1 – Reaction Details

- Transferred to ICU
- Intubated & ventilated
- Temperature 38.4° C (37.9° pre-transfusion & normal 6 hours later
- Antihistamines, acetaminophen, antibiotics
- CXR
- Patient and product culture negative
- Extubated 6 hours later
- Up walking 2 days later

Case #1 – Transfusion Details

- Patient transfused 5 units pooled platelets over 30 minutes
- 15 minutes after completion of platelet transfusion:
  - Not feeling well
  - Rigors
  - Rapidly progressive dyspnea
  - Tachycardic (pulse 170/min)
  - Reduced level of consciousness – Cardiac arrest code called

Transfusion Reaction Manifestation

Pulmonary Edema

- **Circulatory Overload**

- **TRALI**

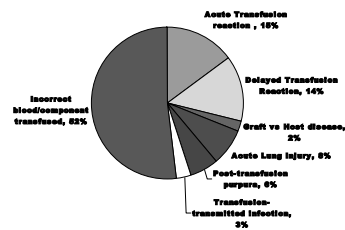
Suspected Transfusion Reaction Clinical Management

1. **STOP THE TRANSFUSION**
2. Maintain IV access; administer 0.9% saline
3. Treat reaction symptoms
4. Report reaction to transfusion service
5. Perform bedside clerical check
6. Continue to monitor vital signs
7. Obtain blood and urine samples, if indicated
8. Complete transfusion reaction form
9. Send transfusion reaction form, patient specimens, and blood bag with attached administration set to the Blood Bank
10. Document the transfusion reaction in the patient's chart

Risks of Transfusion Complications

Frequency per million units transfused

| 0 | 5000 | 10000 | 15000 | 20000 |

-25   25   75   125
Frequency per million units transfused
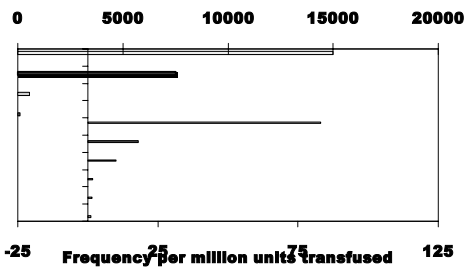
BMJ 1999 "SHOT" [Serious Hazards of Transfusion] Study

Acute Transfusion reaction , 15%
Delayed Transfusion Reaction, 14%
Graft vs Host disease, 2%
Acute Lung Injury, 6%
Post-transfusion purpura, 6%
Transfusion-transmitted infection, 3%
Incorrect blood/component transfused, 52%

Acute Transfusion Reactions

Type	Signs and Symptoms	Usual Cause	Treatment	Prevention
Intravascular Hemolysis (immune)	Hemoglobinemia and hemoglobinuria, fever, chills, anxiety, shock, DIC, dyspnea, chest pain, flank pain, oliguria	ABO incompatibility (clerical error) or other complement-fixing antibody causing antigen-antibody incompatibility	Stop transfusion; hydrate, support blood pressure and respiration, induce diuresis, treat shock & DIC	Avoid clerical error; ensure proper sample and recipient identification
Extra-vascular hemolysis (immune)	Fever, malaise, indirect hyperbilirubinemia, increased urine urobilinogen, falling hematocrit	IgG non-complement-fixing antibody – more often associated with delayed hemolysis	Monitor hematocrit, renal function, coagulation profile; no acute treatment generally required	Avoid clerical errors
Febrile	Fever, chills, rarely hypotension	Antibodies to leukocytes or plasma proteins; rule out hemolysis; consider sepsis. Commonly due to patient's underlying condition	Stop transfusion; give antipyretics, acetaminophen (or aspirin, if not thrombocytopenic	Pretransfusion antipyretic; leucocyte-reduced blood components, if recurrent
Allergic (mild to severe)	Urticaria (hives), rarely hypotension or anaphylaxis	Antibodies to plasma proteins including antibodies to IgA	Stop transfusion; give antihistamine (PO or IM); if severe, epinephrine and/or steroids	Pretransfusion antihistamine; washed red cell components, if recurrent or severe
Hypervolemic	Dyspnea, hypertension, pulmonary edema, cardiac arrhythmias	Too rapid and/or excessive blood transfusion	Induce diuresis; phlebotomy; support cardiorespiratory system as needed	Avoid rapid or excessive transfusion
Transfusion-related acute lung injury (TRALI)	Dyspnea, pulmonary edema, normal pulmonary capillary wedge pressure	HLA or leukocyte antibodies; usually donor antibody transfused with plasma in component	Support blood pressure and respiration (may require intubation)	Leukocyte-reduced RBCs if recipient antibody; notify blood supplier, to quarantine remaining components from donor
Bacterial sepsis	Rigors, chills, fever, shock	Contaminated blood component	Stop transfusion; support blood pressure; give antibiotics	Care in blood collection and storage

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Workup of an Acute Intravascular Hemolytic Transfusion Reaction

If an acute transfusion reaction occurs:
1. Stop blood component transfusion immediately.
2. Maintain IV access with an appropriate crystalloid or colloid solution
3. Maintain blood pressure, pulse
4. Maintain adequate ventilation
5. Give a diuretic and/or institute fluid diuresis
6. Obtain blood/urine for transfusion reaction workup
7. Perform blood bank workup of suspected transfusion reaction
   - Check paper work to ensure correct blood component was transfused to the right patient
   - Evaluate patient for hemoglobinuria
   - Perform direct antiglobulin test
   - Repeat compatibility testing (crossmatch)
   - Repeat other serologic testing as needed (ABO, Rh)
   - Analyze urine for hemoglobinuria

If intravascular hemolytic reaction is confirmed:
8. Monitor renal status
9. Monitor coagulation status (prothrombin time, partial thromboplastin time, fibrinogen, platelet count
10. Monitor for signs of hemolysis (LDH, bilirubin, haptoglobin, plasma hemoglobin)
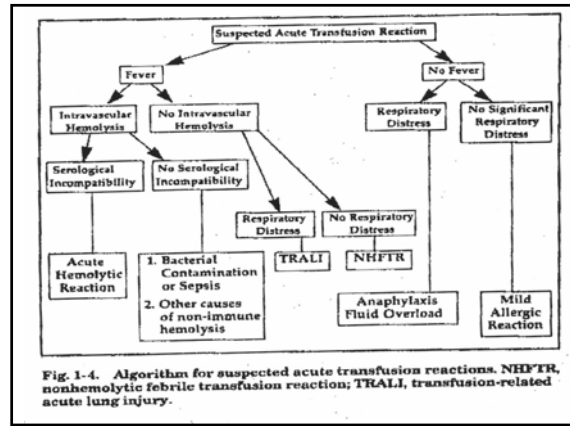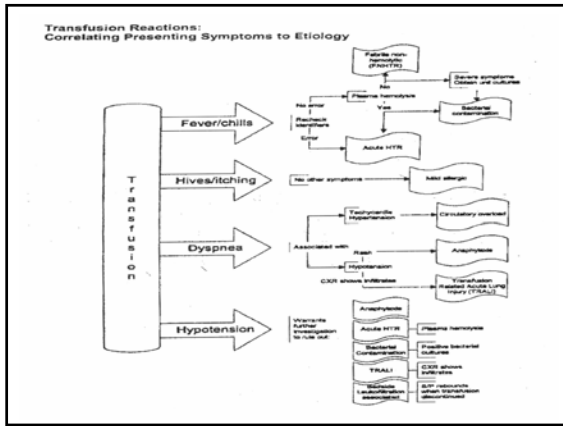11. If sepsis is suspected, culture and treat as appropriate

Transfusion Reactions: Correlating Presenting Symptoms to Etiology

Fig. 1-4. Algorithm for suspected acute transfusion reactions. NHFTR, nonhemolytic febrile transfusion reaction; TRALI, transfusion-related acute lung injury.

Table 1-11. Common signs and symptoms of acute transfusion reactions

Signs and symptoms	Types of Acute Transfusion Reactions					
	Circulatory Overload	AHTR	FNHTR	Allergic Mild/Severe	TRALI	Bacterial Contamination
Fever	-	+	+	-/-	+	+
Chills	-	+	+	-/-	+	+
SOB	+	+	+	-/+	+	-
Hypotension and Shock	-a	+	-b	-/+	+	+
DIC	-	+	-	-/-	-	+
N&V	-	+	+	-/+	-	+
Hgb-emia	-	+	-	-/-	-	+
Hgb-uria	-	+	-	-/-	-	+
DAT	-	+	-	-/-	-	-

AHTR, acute hemolytic transfusion reaction; DAT, direct antiglobulin test; DIC, disseminated intravascular coagulation; FNTHR, febrile non-hemolytic transfusion reaction; Hgb-emia, hemoglobinemia; Hgb-uria, hemoglobinuria; N/V, nausea and vomiting; SOB, shortness of breath; TRALI – transfusion related acute lung injury.

aCirculatory overload is associated with *hyper*tension and signs of congestive heart failure

bHypotension is unusual in FNHTR

Case #1

At 11:40 pm on January 7, 1975 a unit of blood was requisitioned from the blood bank for patient A, who was being prepared for plastic surgery on the following day. A cross-matched specimen compatible Group A Rh negative was released to be picked up by the requisitioning physician (Dr. X).

This unit of blood was (incorrectly) administered to patient B, for whom no blood had been ordered, by Dr. X, who signed the mandatory bedside identification documents for the blood and the patient (patient B was Group B Rh positive).

Patient B's hospital record reveals that the transfusion ran from 12:30 am to 4:00 am on January 8. During this period the patient complained of fever and abdominal cramps. At approximately 5:30 am the patient voided urine which was dark Coca-Cola in color. Shortly thereafter his blood pressure dropped markedly. Despite numerous efforts at resuscitation, the patient was pronounced dead at 6:45 am.

A blood specimen taken from the patient after resuscitation had begun showed visible evidence of marked hemolysis. Additionally, the dark-colored urine already mentioned was demonstrated to be due to the presence of free hemoglobin. Blood bank serologic investigations revealed a positive direct antiglobulin (Coombs) test (normally negative) and an AB blood grouping.

Case #2

A 74 year old female had undergone aortic valve replacement for aortic stenosis when she was 68 years old. Seven units of blood were utilized during this open heart surgery, which was accomplished with the use of the heart-lung machine (extracorporeal circulation).

The patient required reoperation for a leak which developed in the replacement valve. This procedure was carried out on 6/3/91 without any complications. She received multiple units of several, completely compatible, blood components (packed red cells, platelets, and fresh frozen plasma) with no untoward effects in the course of the surgery. Her hematocrit immediately following surgery was 35, and remained at approximately that level for the next ten days.

Her post-operative course was uneventful until 6/14/91, when it was noted that her hematocrit had abruptly fallen to 25. A blood transfusion was ordered, and her physician requested a type and crossmatch for four units.

At that time both her direct and indirect antiloulin tests (Coombs tests) were found to be positive (they were both negative at the time of surgical transfusion). This prompted additional testing and it was discovered that her total bilirubin had risen to 4.0 (normal 1.3), with 90% of this being of the indirect reacting type. In addition, her serum lactic dehydrogenase enzyme level had risen to 2390 units (from 750 at time of surgery) [normal up to 625].

Additional testing in the blood bank then revealed that an antibody of specificity "little s" could be eluted from the patient's circulating red cells. Moreover, an indirect Coombs test disclosed that the patient now had two "irregular" antibodies in her circulating plasma (of specificities "little f" and "Kidd-B").

Testing on 6/18/91 showed that the direct antiglobulin test on the red cells had become negative, but the indirect Coombs test remained positive. At that time also, the patient's reticulocyte count was reported as 5.8% (normal < 1.6%).