How Will You React?

A Look at Transfusion Reactions

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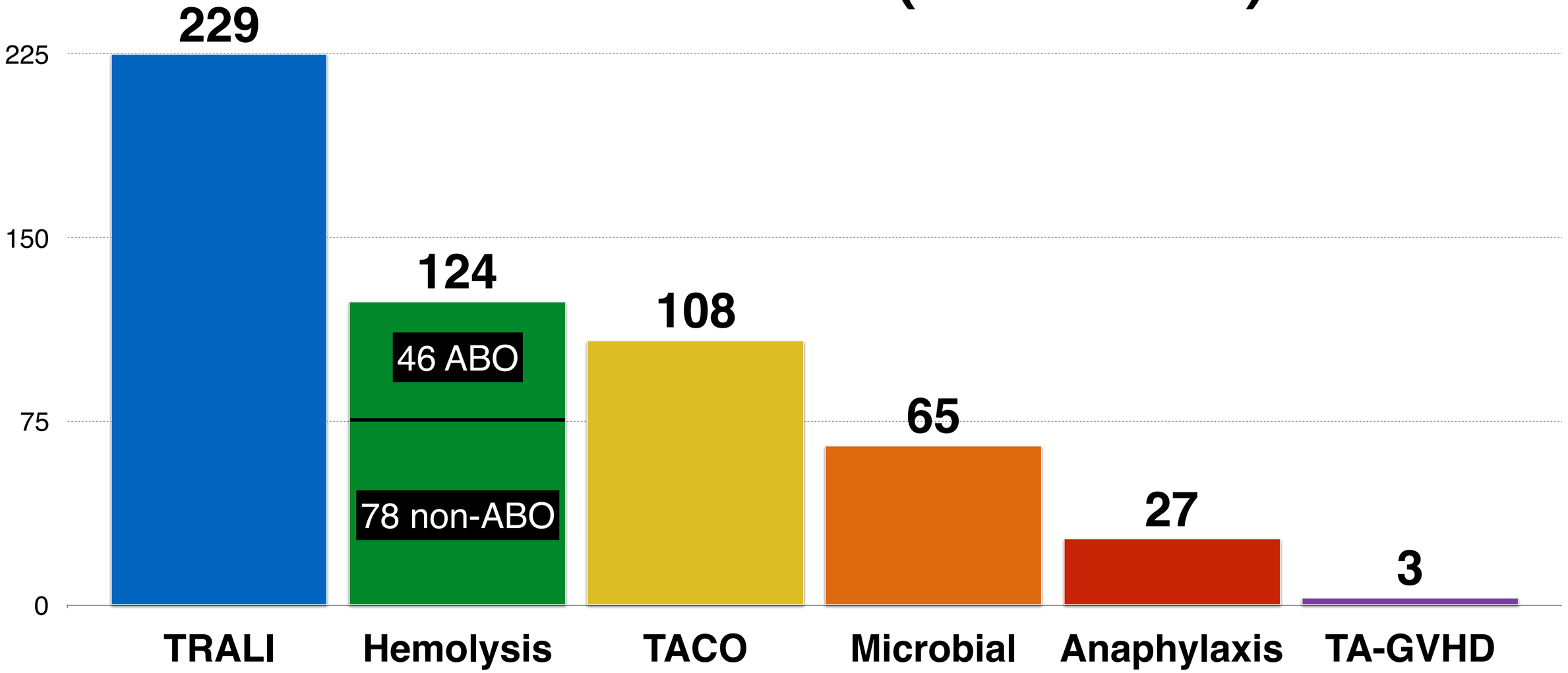
LifeStream Blood Bank, San Bernardino, CA

May 21, 2019
June 18, 2019

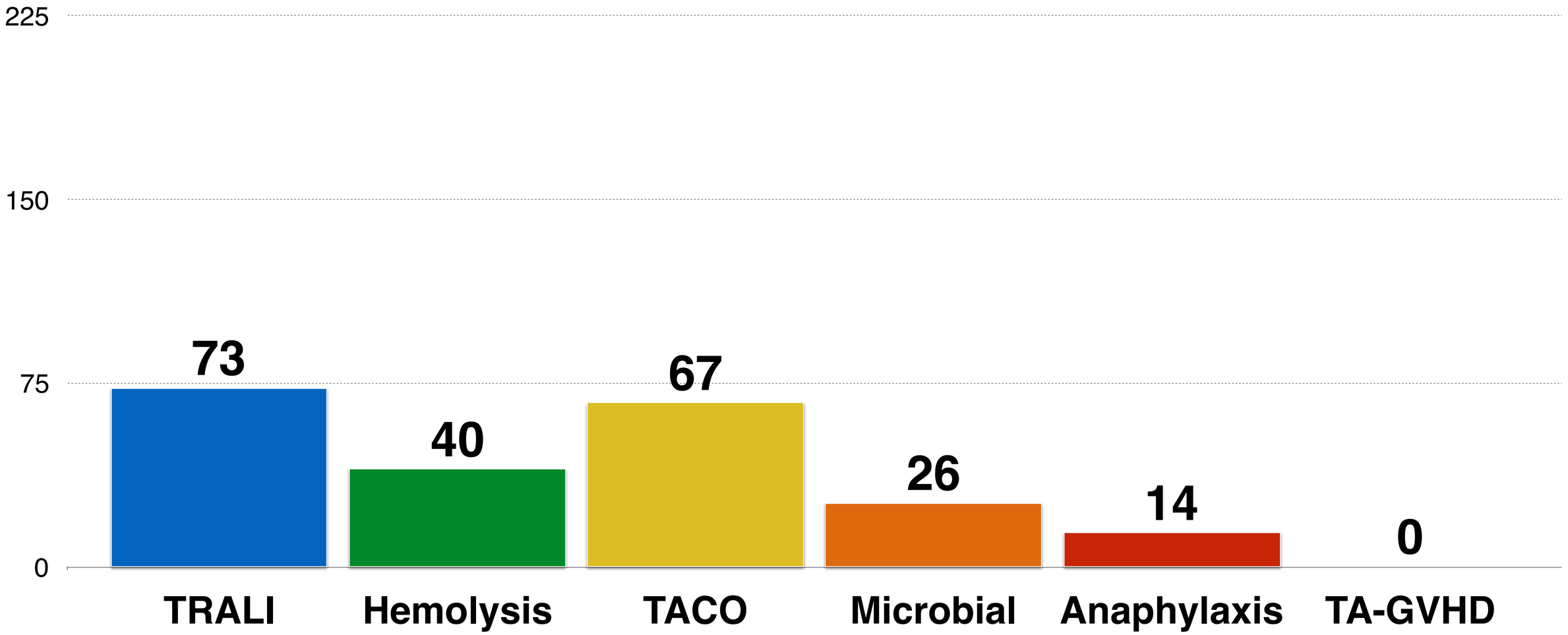
Let’s Do This!

1. Learn what to do in the face of suspected transfusion reactions
2. Learn to categorize transfusion reactions starting with a single vital sign
3. Learn details about pathophysiology, presentation, management, and prevention of common reactions

FDA Fatalities (2005-17)



FDA Fatalities (**2012-17**)



AABB Standards, 31st Ed.

7.3 Classifying Adverse Events

The BB/TS shall use nationally recognized classifications for donor and patient adverse events. The medical director shall participate in the development of protocols used by the staff to identify, evaluate, and report adverse events.

National Healthcare Safety Network
Biovigilance Component
Hemovigilance Module
Surveillance Protocol

12 Defined Reactions

TACO

TRALI

~~Tx-associated Dyspnea~~

Allergic

~~Hypotensive~~

Febrile Non-hemolytic

Acute Hemolytic

Delayed Hemolytic

Delayed Serologic

TA-GVHD

Post-transfusion Purpura

Tx-related Sepsis (TTI)

What to Look For

*Signs and symptoms, laboratory: (check all that apply)

Cardiovascular:	Cutaneous:	Pain:
☐ Blood pressure decrease	☐ Edema	☐ Abdominal pain
☐ Shock	☐ Flushing	☐ Back pain
Hemolysis/Hemorrhage	☐ Jaundice	☐ Flank pain
☐ Disseminated intravascular coagulation	☐ Other rash	☐ Infusion site pain
☐ Hemoglobinemia	☐ Pruritus (itching)	**Respiratory:**
☐ Positive antibody screen	☐ Urticaria (hives)	☐ Bilateral infiltrates on chest x-ray
Generalized:	**Renal:**	☐ Bronchospasm
☐ Chills/rigors	☐ Hematuria	☐ Cough
☐ Fever	☐ Hemoglobinuria	☐ Hypoxemia
☐ Nausea/vomiting	☐ Oliguria	☐ Shortness of breath

☐ Other: (specify) _____

Assurance of Confidentiality: The voluntarily provided information obtained in this surveillance system that would permit identification of any individual or institution is collected with a guarantee that it will be held in strict confidence, will be used only for the purposes stated, and will not otherwise be disclosed or released without the consent of the individual, or the institution in accordance with Sections 304, 306 and 308(d) of the Public Health Service Act (42 USC 242b, 242k, and 242m(d)).

Public reporting burden of this collection of information is estimated to average 15 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to CDC, Reports Clearance Officer, 1600 Clifton Rd., MS D-74, Atlanta, GA 30333 ATTN: PRA (0920-0666).

CDC 57.304 Rev. 4, v8.1

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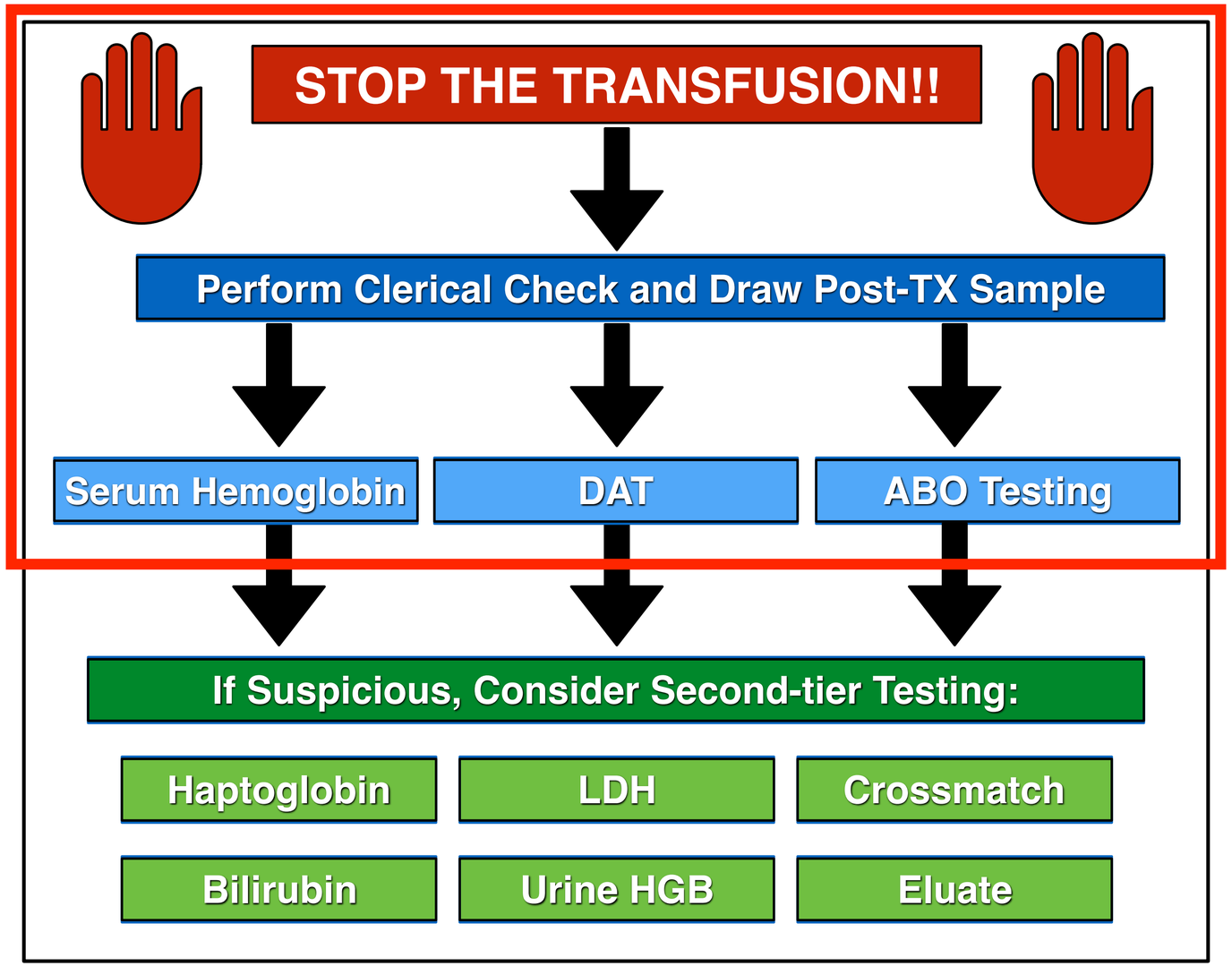
Basic Reaction Workup

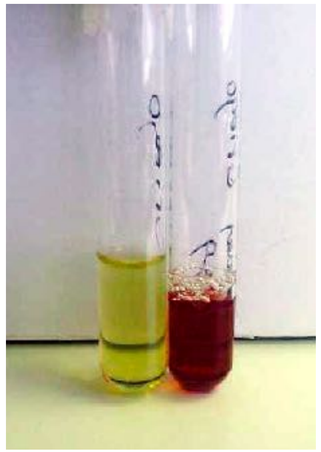


Four CORE Tests

Clerical Check

Image: http://intranet.tdmu.edu.ua/

Visible HGB



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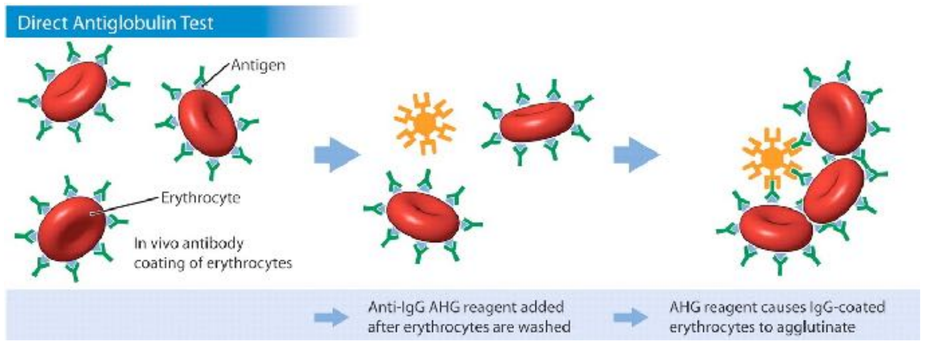
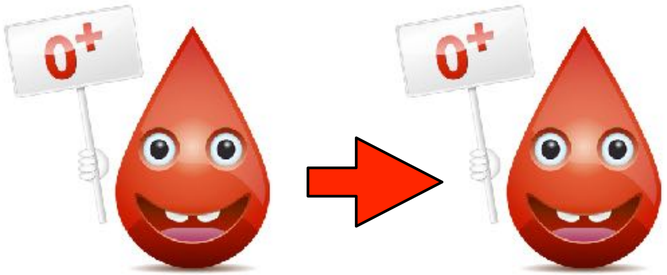


Repeat ABO/Rh



Pre Post

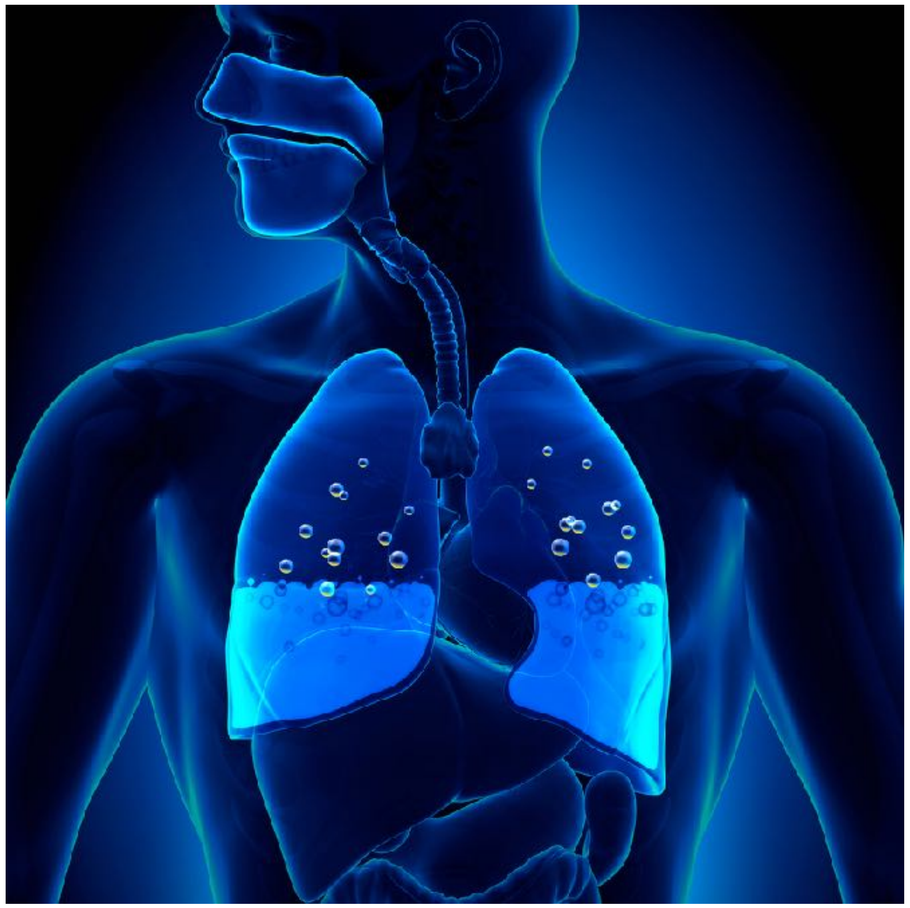
Other Tests to Consider

- **If hemolysis is likely:**
  - Urine hemoglobin
  - Bilirubin
  - LDH
  - Haptoglobin

Other Tests to Consider

- **With high fever (e.g., >2°C):**
  - Gram stain of unit
  - Culture:
    - Patient
    - Unit
    - Donor if possible

Other Tests to Consider



- **With respiratory symptoms:**
  - **Chest x-ray**
  - pBNP levels
  - Fluid I/O for patient
  - HLA/HNA testing for donor
  - IgA/haptoglobin levels if anaphylactic

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Presenting WITH Fever	
Acute (< 24 hrs)	**Delayed (> 24 hrs)**
Acute Hemolytic Febrile Non-hemolytic Tx-related Sepsis (TTI) TRALI	Delayed Hemolytic TA-GVHD

Presenting WITHOUT Fever	
Acute (< 24 hrs)	**Delayed (> 24 hrs)**
Allergic Hypotensive TACO Tx-associated Dyspnea	Delayed Serologic Post-transfusion Purpura

Acute Hemolytic Reactions

- Potentially catastrophic destruction of incompatible RBCs
- Incidence: 1:76,000 (1/1.8 M fatal)
- Clerical errors (~60% at bedside)

Acute Hemolytic Reactions

4 of 5!

*Signs and symptoms, laboratory: (check all that apply)

Cardiovascular:	Cutaneous:	Pain:
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☐ Other: (specify) _____		

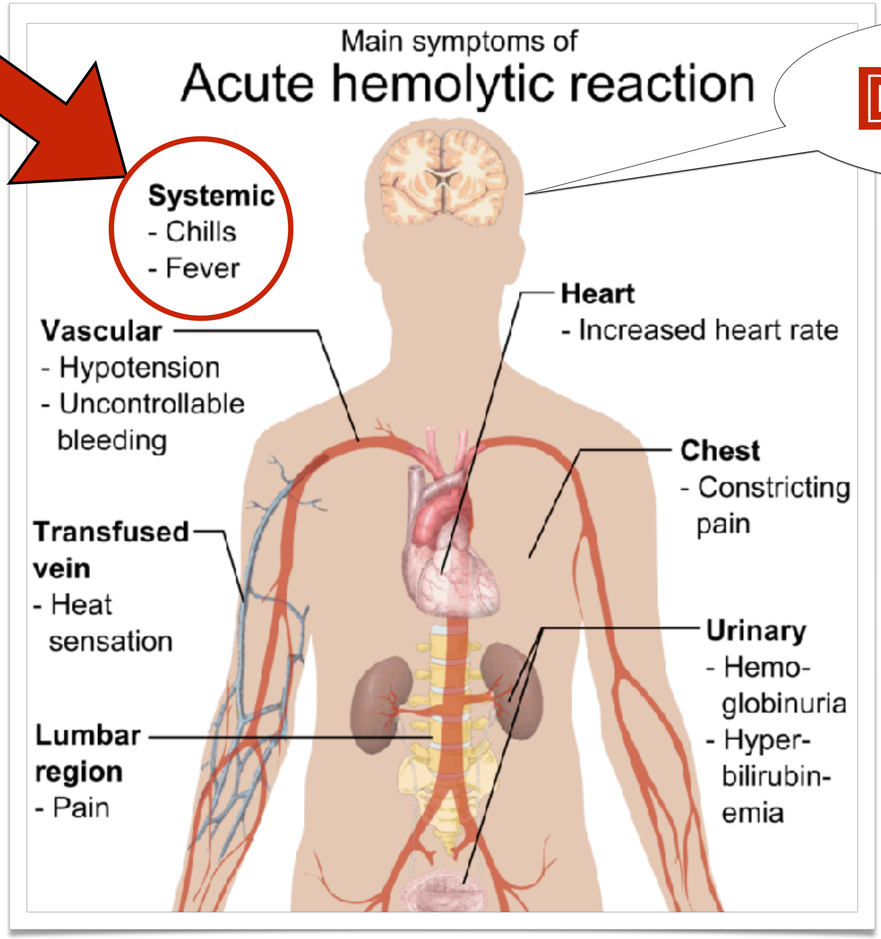


Image: Public Domain

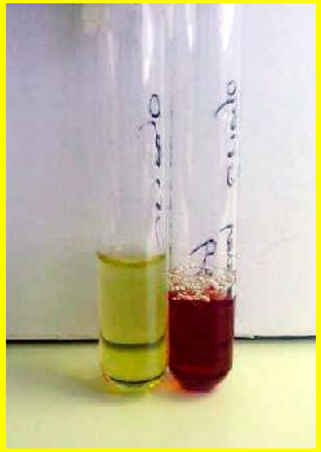
Four CORE Tests

Clerical Check

Image: http://intranet.tdmu.edu.ua/

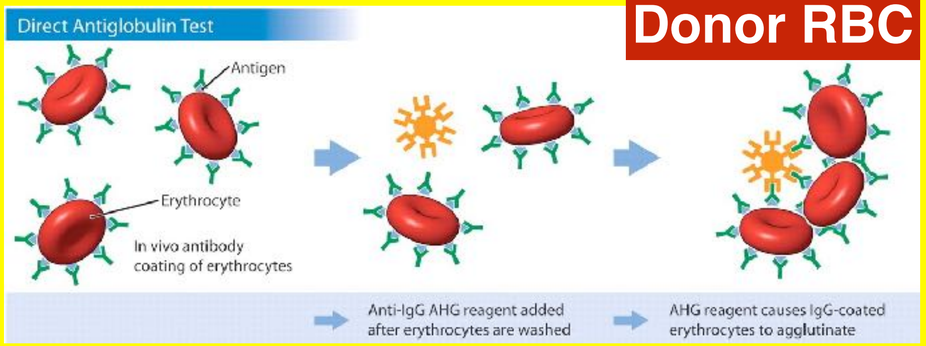
-Mislabel
-Wrong Pt

Visible HGB



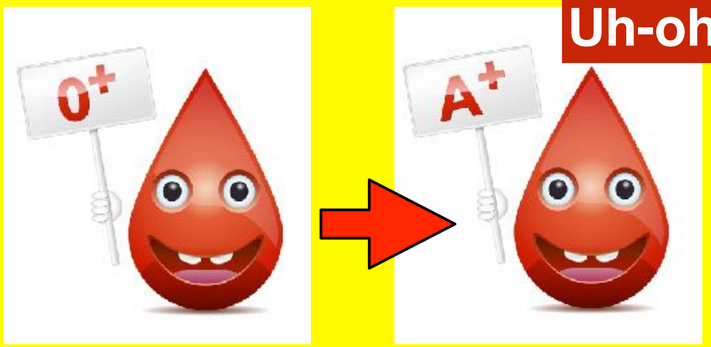
5 mL
Lasts ~1 day

DAT



Donor RBC

Repeat ABO/Rh



Uh-oh!

Pre Post

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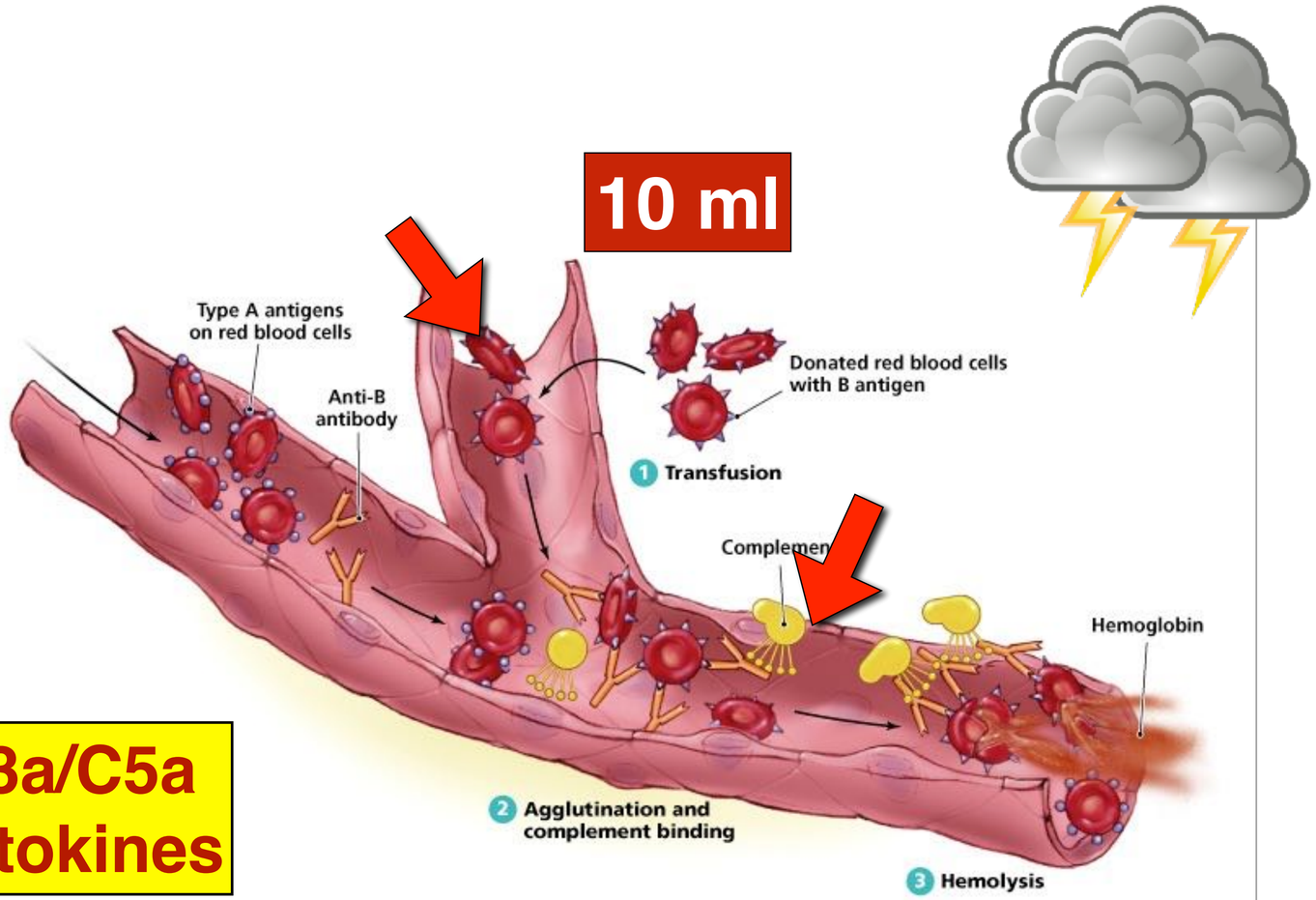
  - Bilirubin ☝🏻
  - LDH ☝🏻
  - Haptoglobin 👇🏻

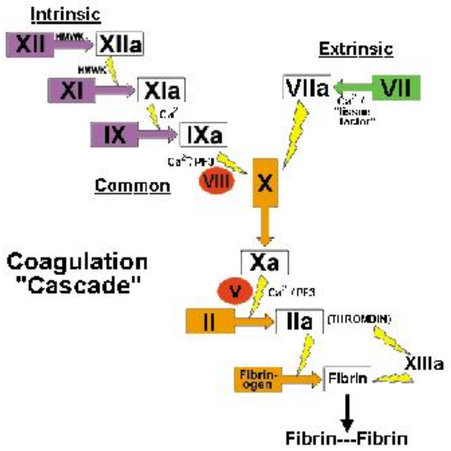


C3a/C5a Cytokines

Intravascular Hemolysis

Storm!

- Inflammatory
  - TNF-α, IL-1β, IL-6 cause fever
- Coagulation
  - Activation of both clotting and lysing
  - DIC!

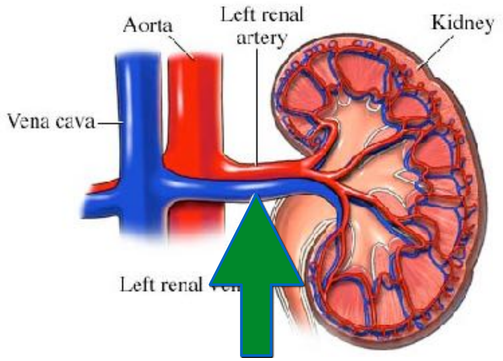


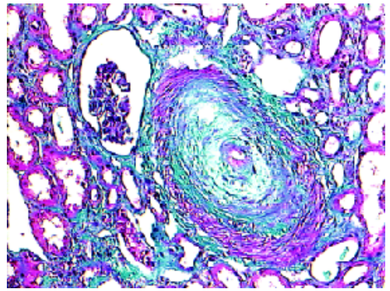
Storm!

- Circulatory:
  - Cytokine Nitric Oxide generation
  - Bradykinin from antigen-antibody
  - Hypotension/shock

Storm!

- <u>Renal damage:</u>
  - Vasoconstriction (reflex, from NO:HGB complex)
  - Microthrombi
  - Acute tubular necrosis
  - Oliguric renal failure





Acute Hemolytic Rxns

- Treatment
  - Support circulation and renal function (fluids and diuresis)
  - Heparin for early DIC controversial
  - RBC exchange if stable (unlikely)

Acute Hemolytic Rxns

- Prevention
  - Details, details, details!
    - ✓ Phlebotomy
    - ✓ Labeling
    - ✓ Issue
    - ✓ Administration
  - Two separate types for confirmation
  - Technology (RFID, bar codes, etc)

Febrile non-Hemolytic Rxn

- Most reported reaction
- Definition:
  - 1°C or 2°F; no other explanation
    - ✓ Diagnosis of exclusion

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Four CORE Tests

Clerical Check

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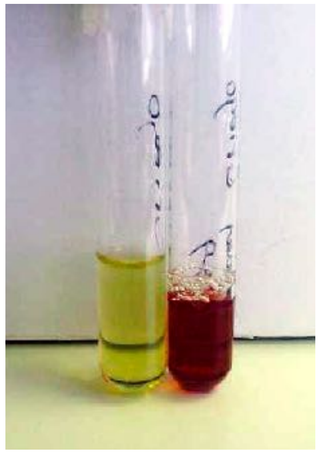

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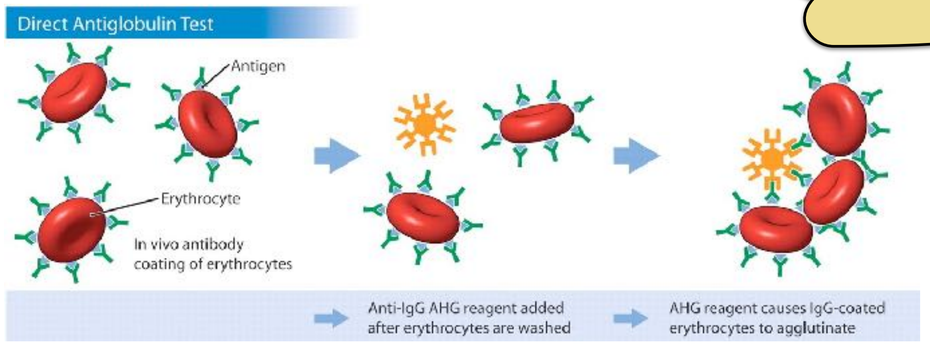
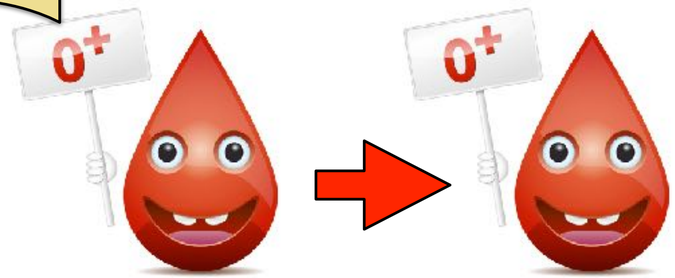
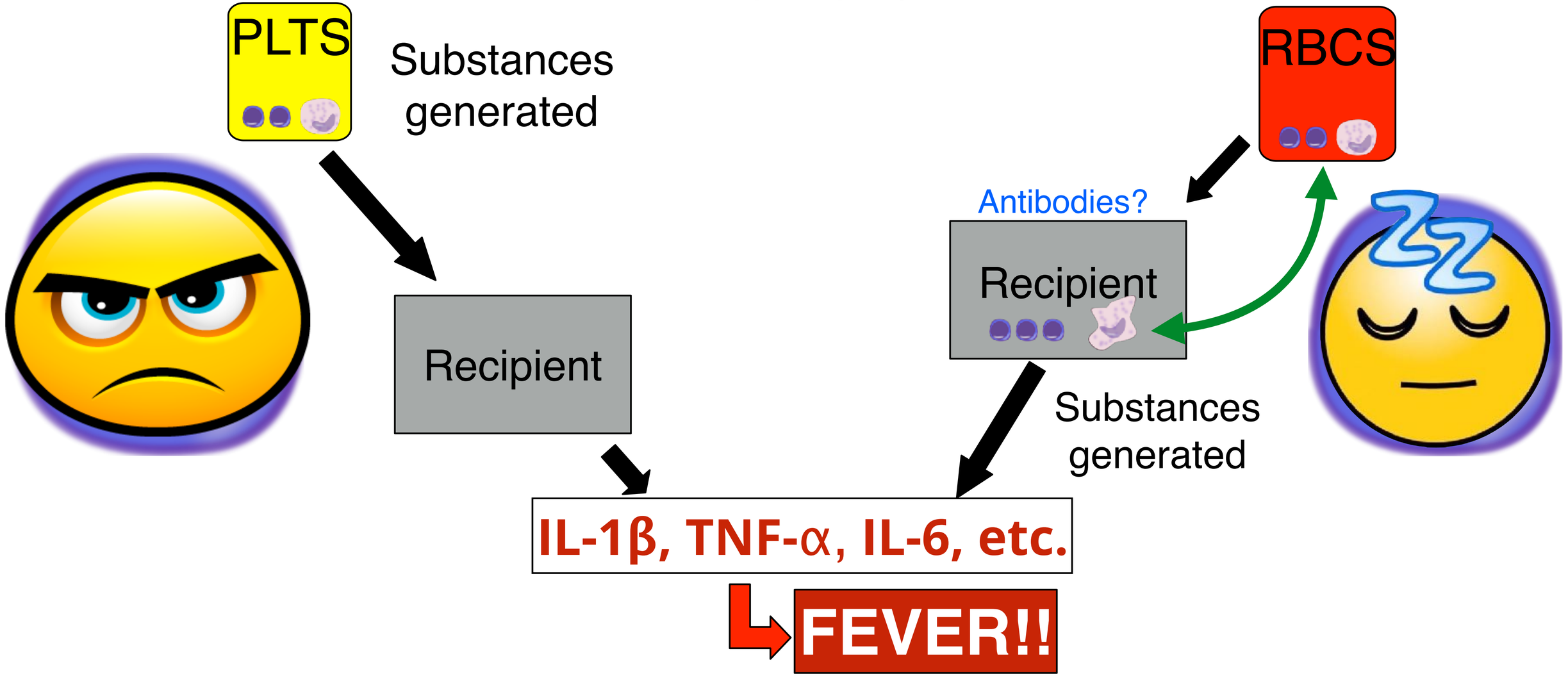




Pre Post

Repeat ABO/Rh

Fever!


PLTS
Substances generated
RBCS
Antibodies?
Recipient
Recipient
Substances generated
IL-1β, TNF-α, IL-6, etc.
FEVER!!

FNHTR

- Management
  - Stop transfusion, do workup
  - Acetaminophen or other antipyretic
- Prevention: Leukoreduction (premedication does not work)

Transfusion-related Sepsis

- Number one infectious risk from transfusion today; by FAR!
- 1 in 3000 contaminated
- FAR fewer cause harm
  - ARC: 1:108,000

Transfusion-related Sepsis

- Timing: ≤ 4 hours, but may be immediate
- Signs/symptoms (endotoxin effect)

*Signs and symptoms, laboratory: (check all that apply)

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Generalized:	**Renal:**	☐ Bronchospasm
☑ Chills/rigors (Severe)	☐ Hematuria	☐ Cough
☑ Fever (High)	☐ Hemoglobinuria	☐ Hypoxemia
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Four CORE Tests

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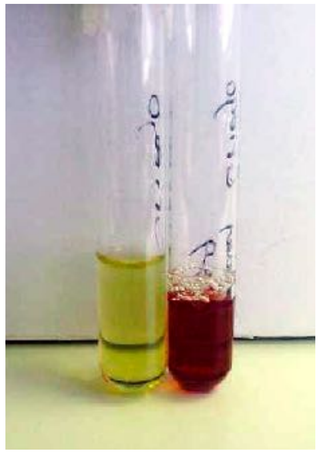

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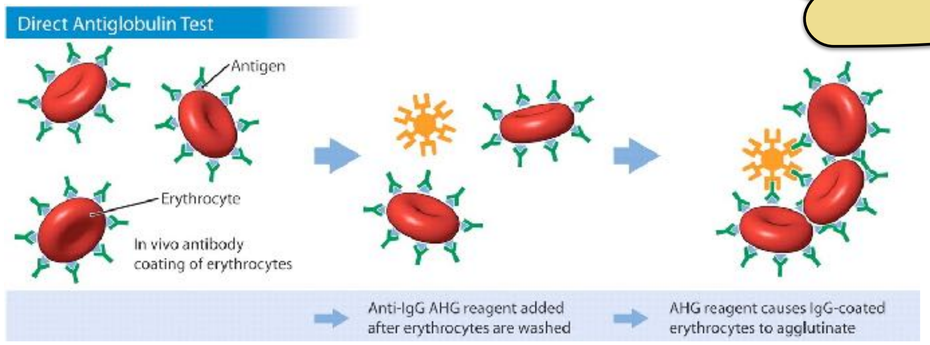
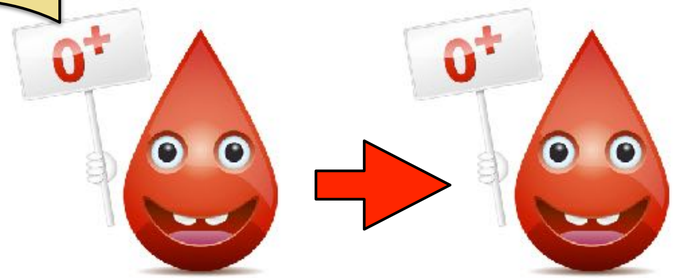
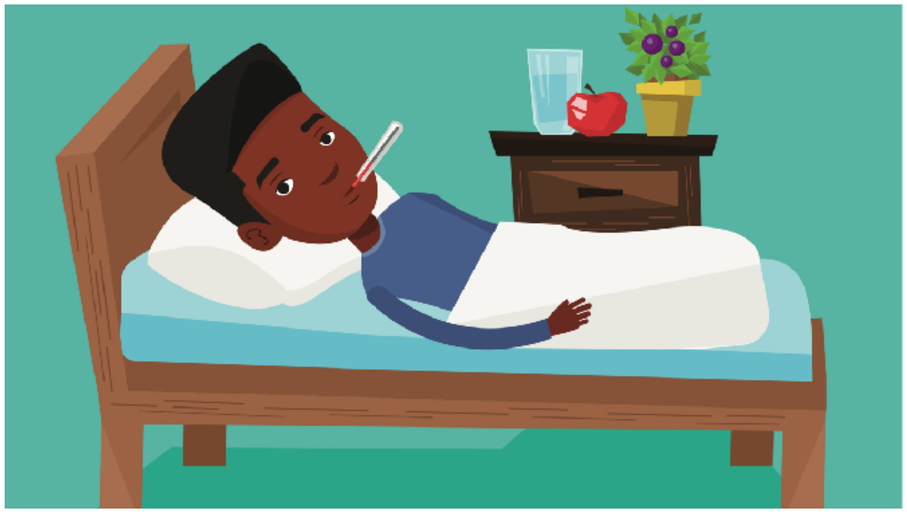




Pre Post

Repeat ABO/Rh

Other Tests to Consider



- **With high fever (e.g., >2°C):**
  - Gram stain of unit (50%)
  - Culture:
    - Patient
    - Unit
    - Donor if possible

Transfusion-related Sepsis

- Product inspection
  - Dark RBC unit
    - Classic: Dark unit, light seg
  - Junk in platelets
    - Can look like clots/fibrin

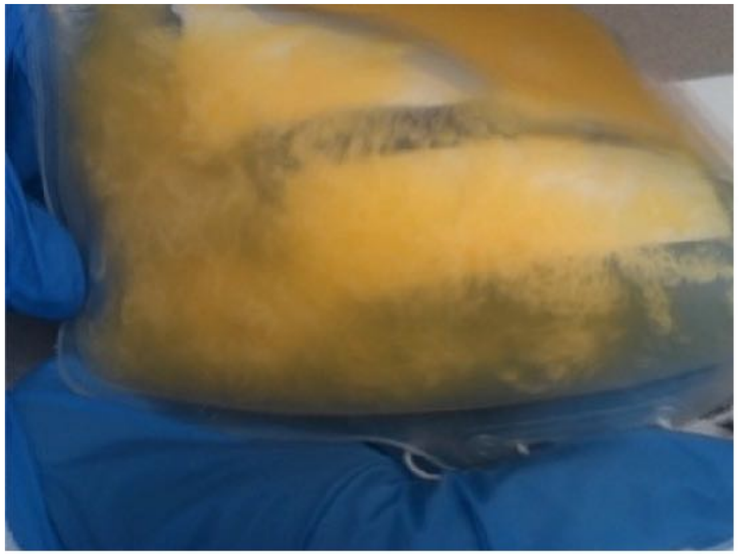


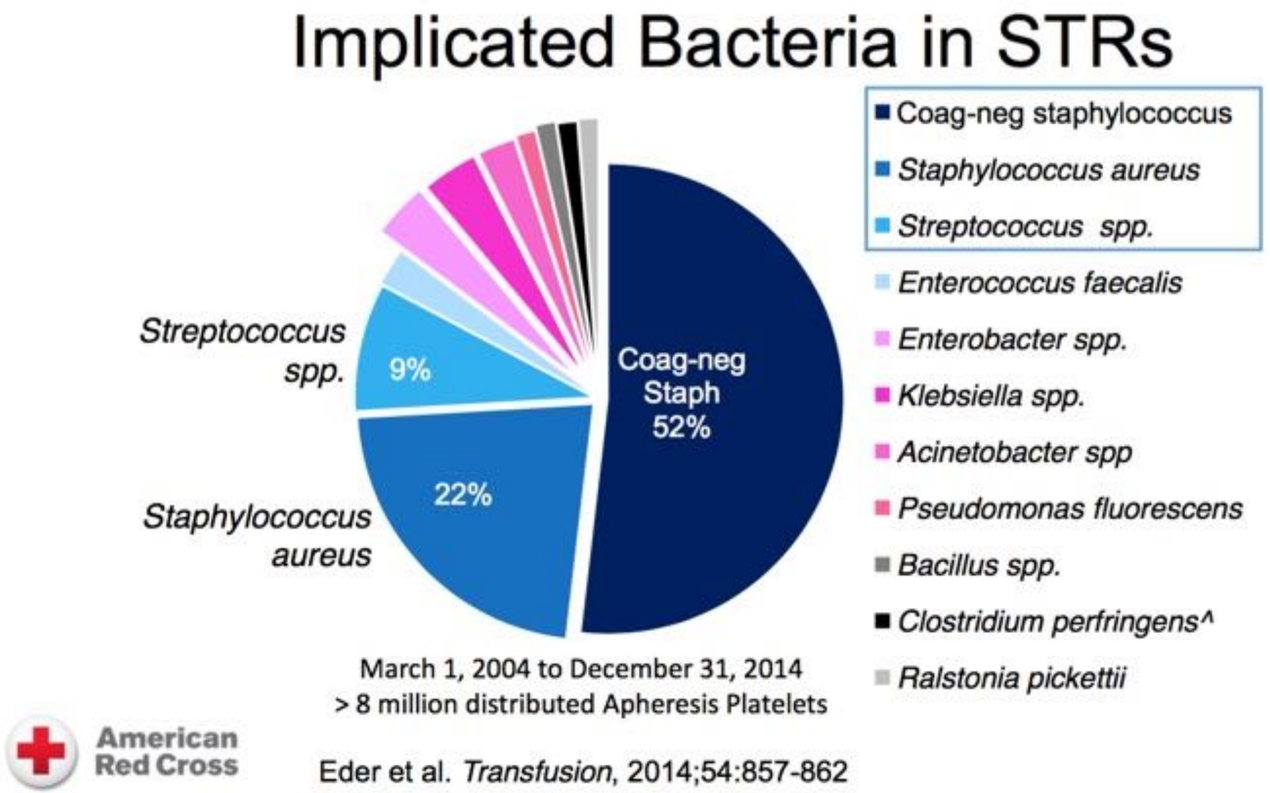
Image courtesy Anne Eder, MD

Transfusion-related Sepsis

- RBCs
  - Gram-neg rods:
    - ✓ *Yersinia enterocolitica*
    - ✓ *E.coli*
    - ✓ *Enterobacter/Pantoea*
    - ✓ *Serratia*
    - ✓ *Pseudomonas*
  - Staph. epidermidis

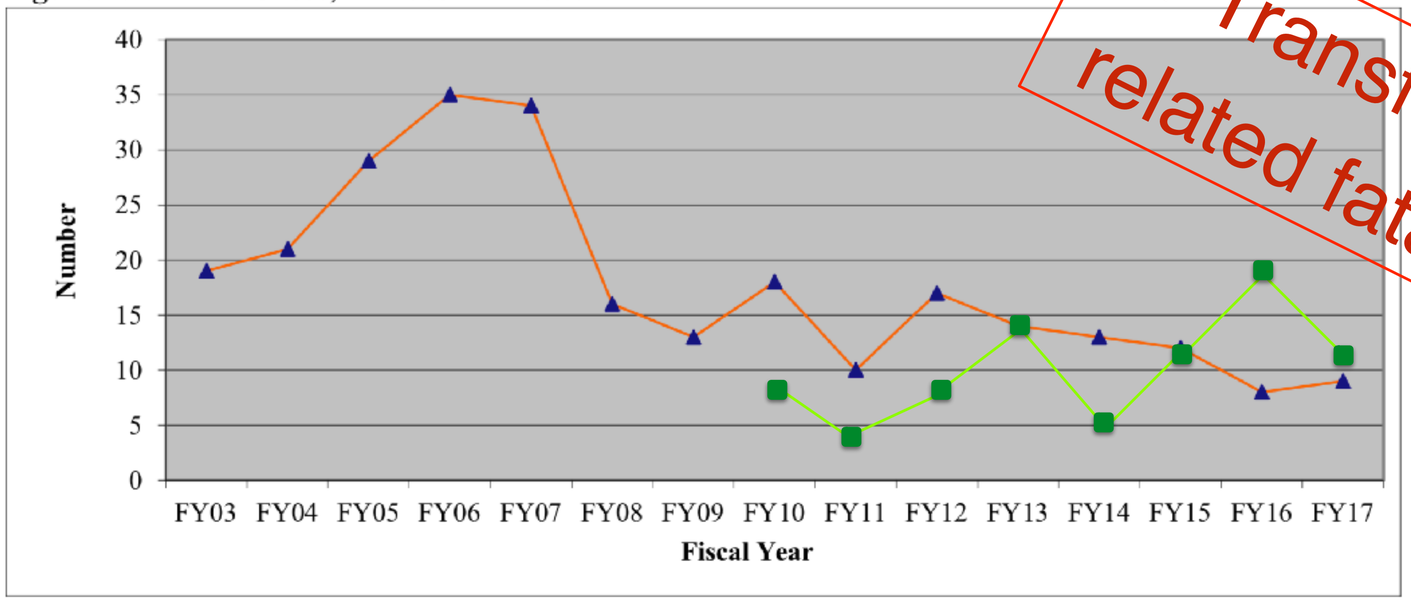
Transfusion-related Sepsis

- Platelets



Transfusion-related Acute Lung Injury

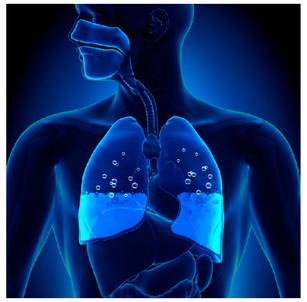
Figure 1: TRALI Cases, FY2003 - FY2017



#1 Transfusion-related fatality

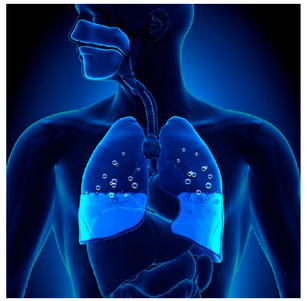
- Fatal TACO Cases

Source: www.fda.gov (FY 2017 Fatalities)

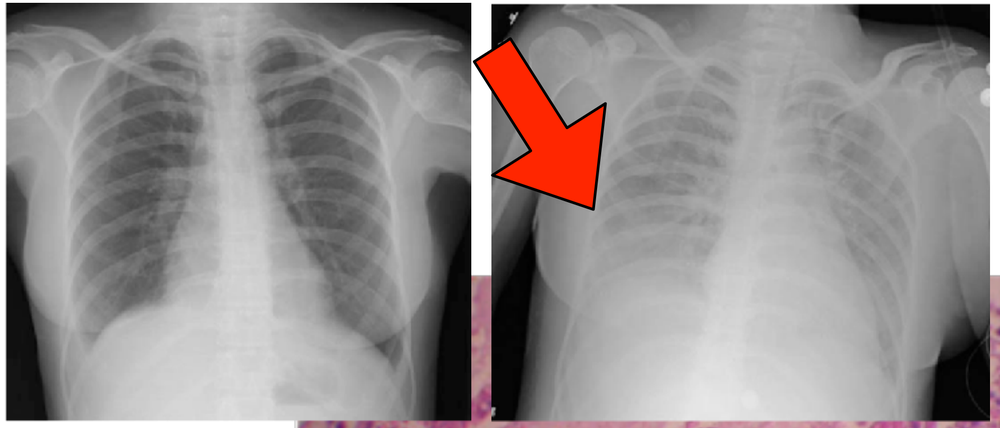


TRALI Definition

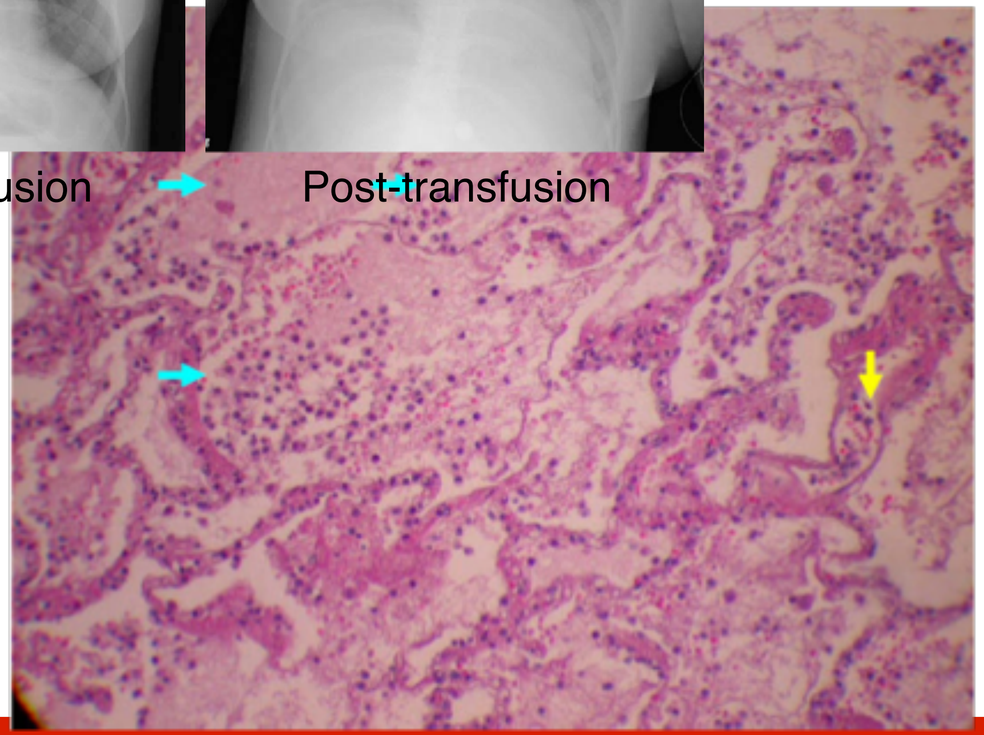
- New Acute Lung Injury <6 hrs after transfusion ends
  - Acute Lung Injury:
    - ✓ Hypoxemia (O2 sat <90%), **AND**
    - ✓ Bilateral chest x-ray infiltrates, **AND**
    - ✓ No left atrial hypertension

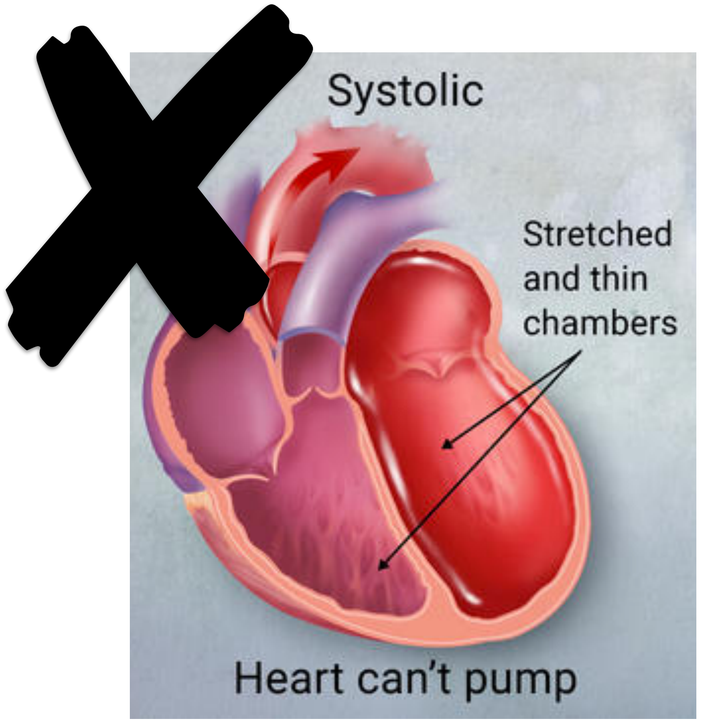


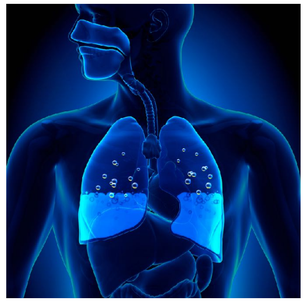
TRALI



Pretransfusion → Post-transfusion







TRALI

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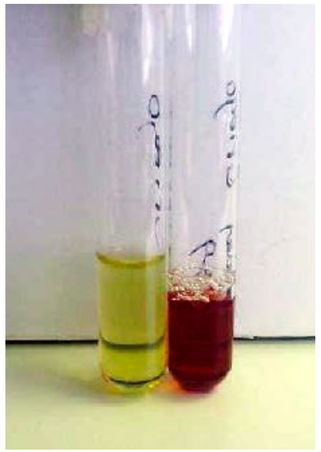
☑ Fever	☐ Hemoglobinuria	☑ Hypoxemia
☐ Nausea/vomiting	☐ Oliguria	☑ Shortness of breath
☑ Other: (specify) Frothy, pink sputum		

Four CORE Tests

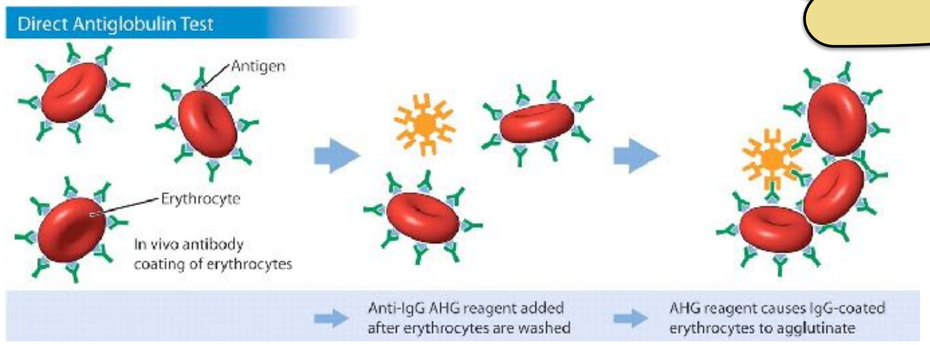
Clerical Check

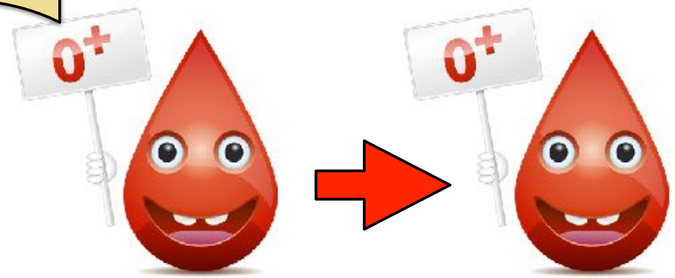
Image: http://intranet.tdmu.edu.ua/



Visible HGB

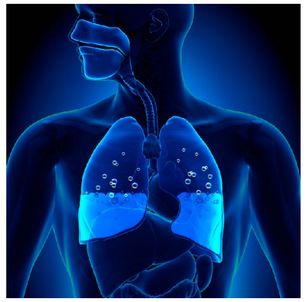
DAT





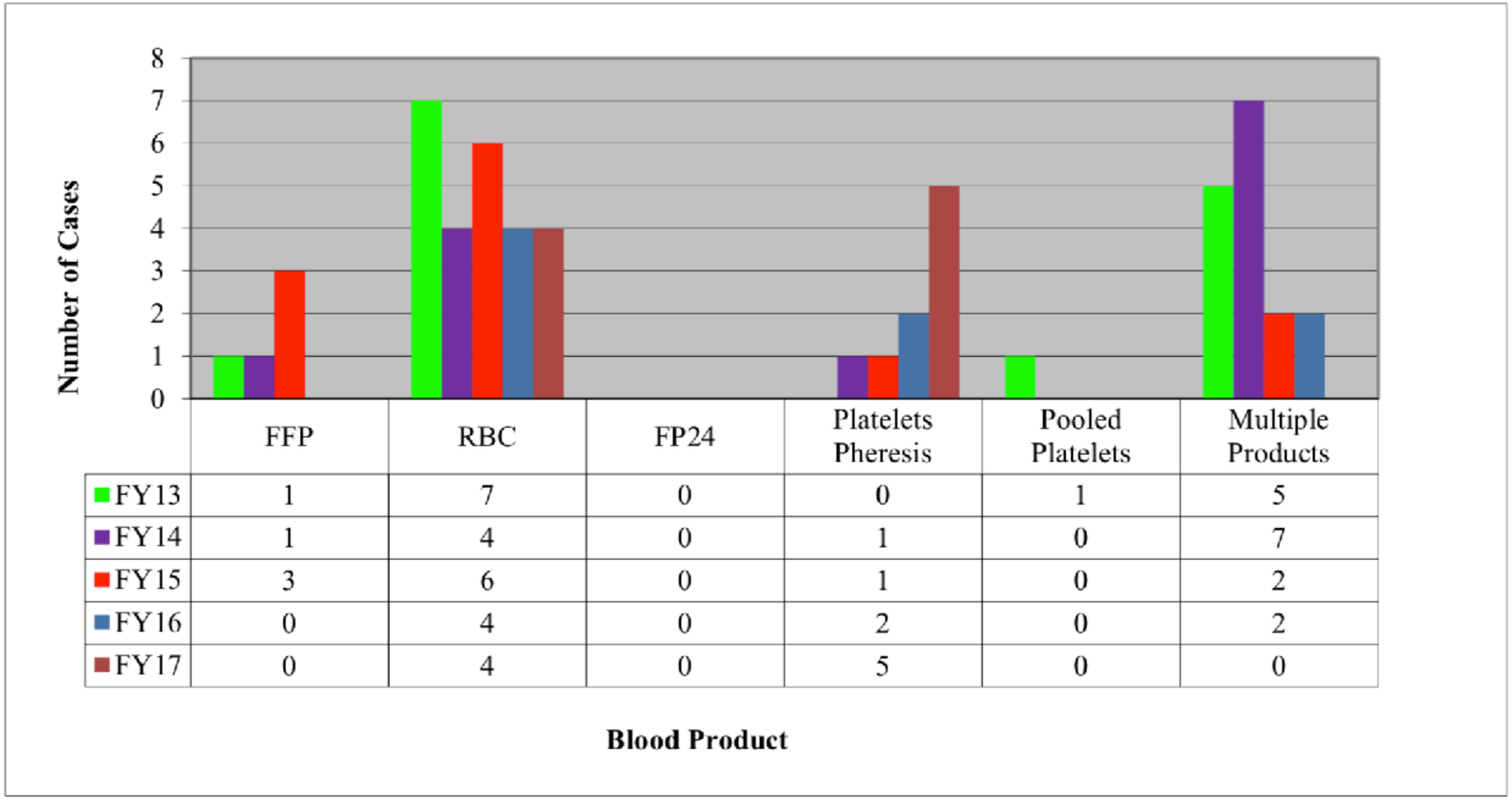
Pre Post

Repeat ABO/Rh

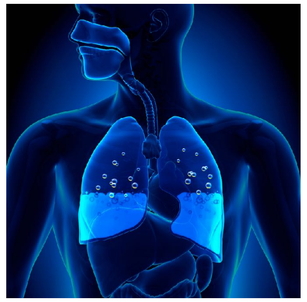


TRALI

Figure 2: Reports of TRALI Cases by Implicated Blood Product, FY2013 – FY2017



	FFP	RBC	FP24	Platelets Pheresis	Pooled Platelets	Multiple Products
FY13	1	7	0	0	1	5
FY14	1	4	0	1	0	7
FY15	3	6	0	1	0	2
FY16	0	4	0	2	0	2
FY17	0	4	0	5	0	0



TRALI

- Two main pathways
  - **“Donor antibody”**
    - ✓ Transfused anti-HLA/HNA
  - **“Two-event”**
    - ✓ Patient susceptibility comes first
    - ✓ Antibodies +/–

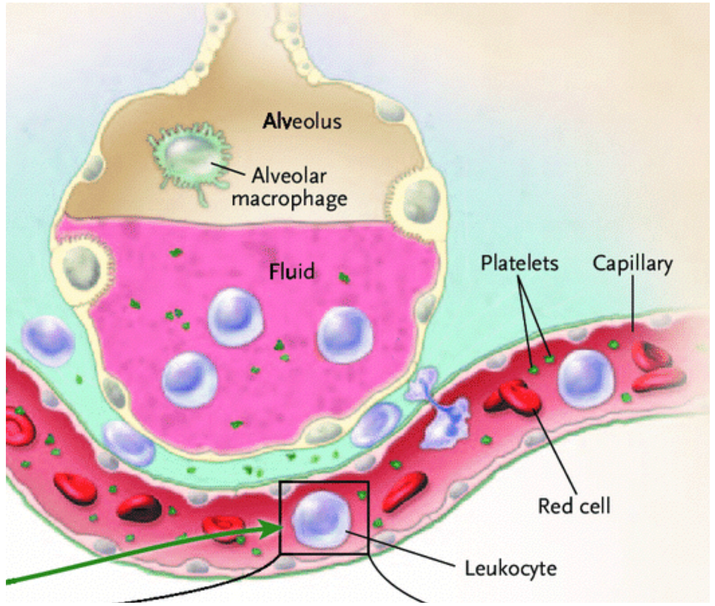
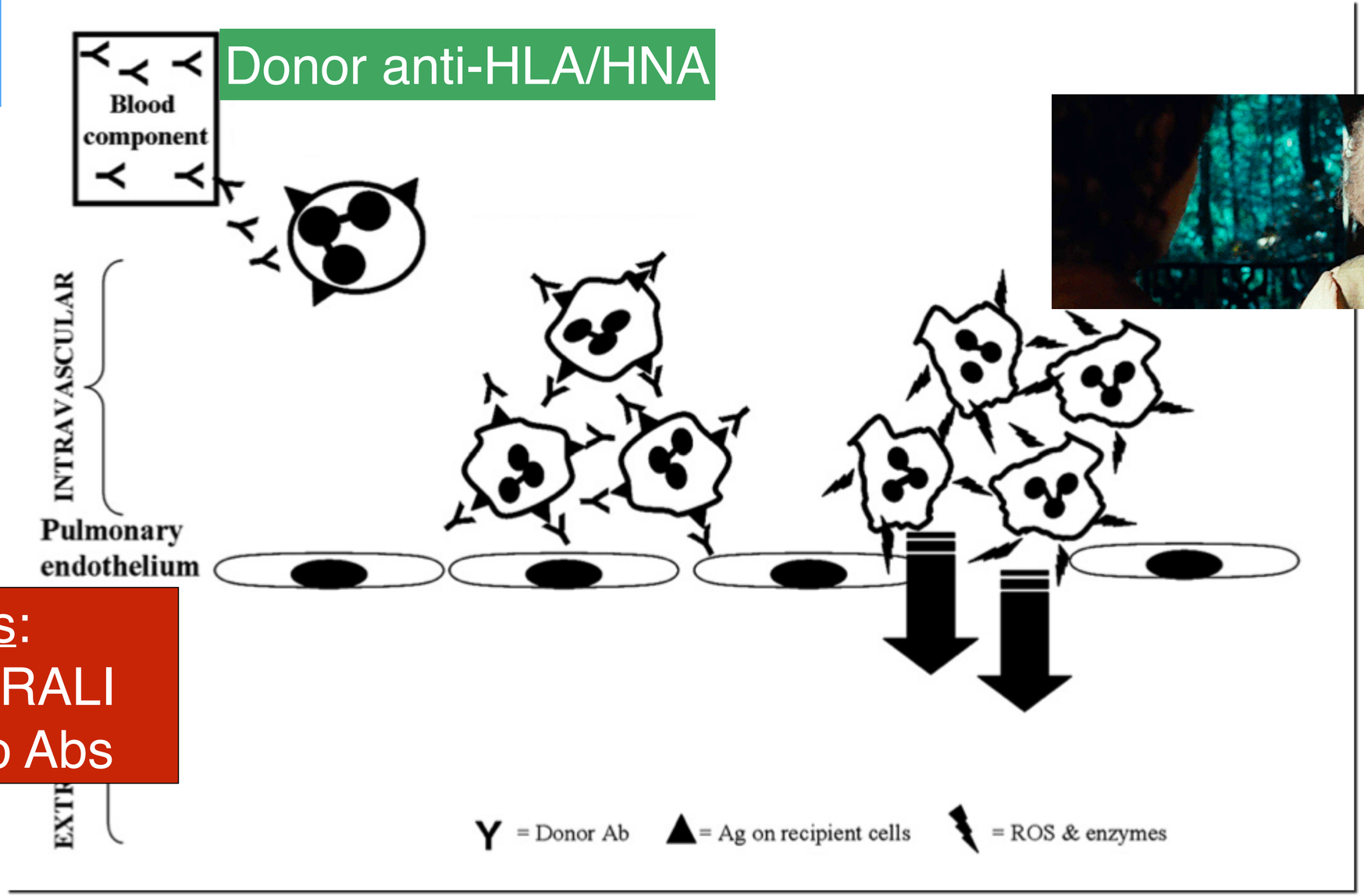


Image: Suter PM, *New Engl J Med* 2006;354(16):1740

1

Donor anti-HLA/HNA



Flaws:

1. Abs, no TRALI
2. TRALI, no Abs

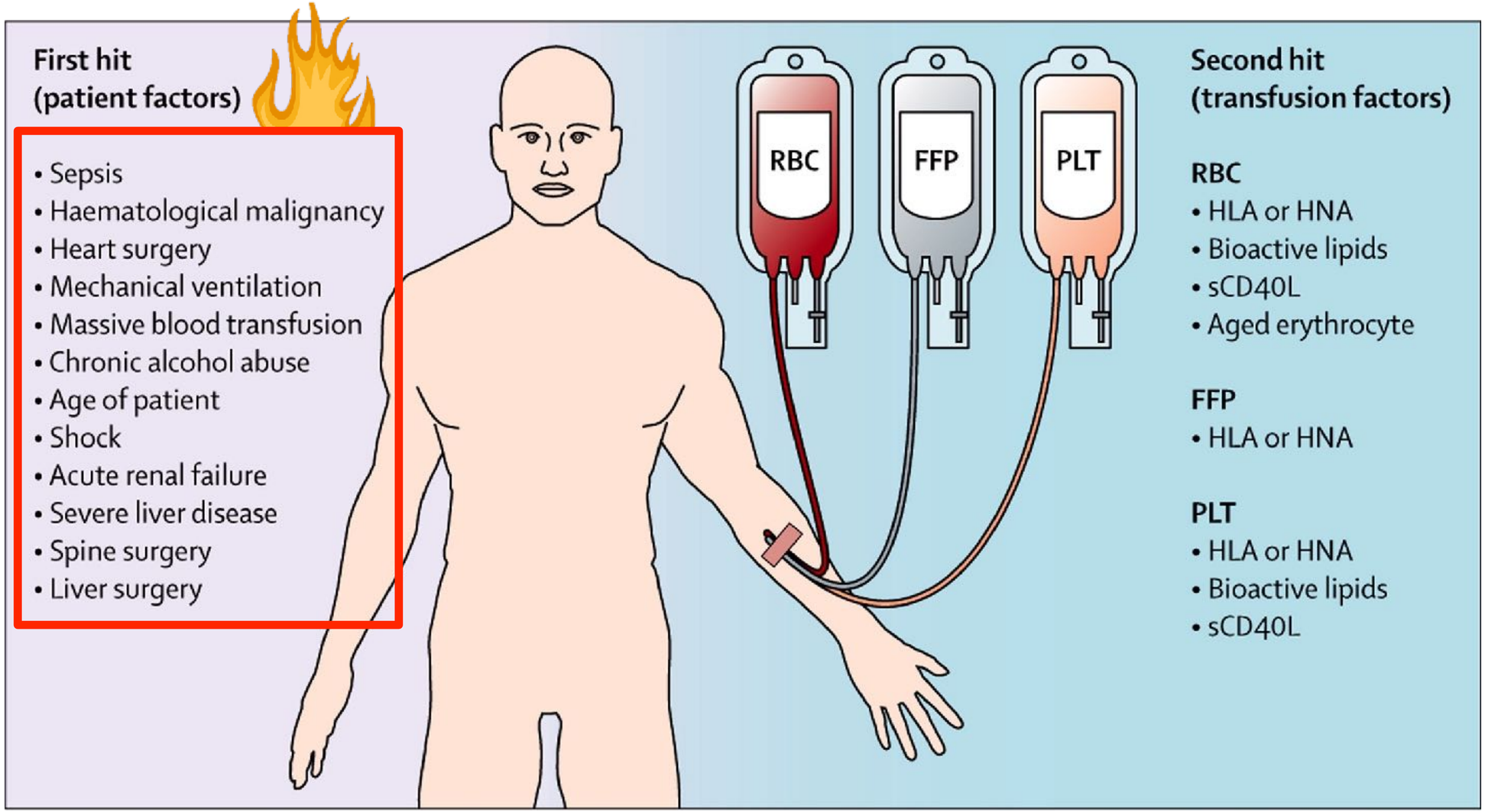
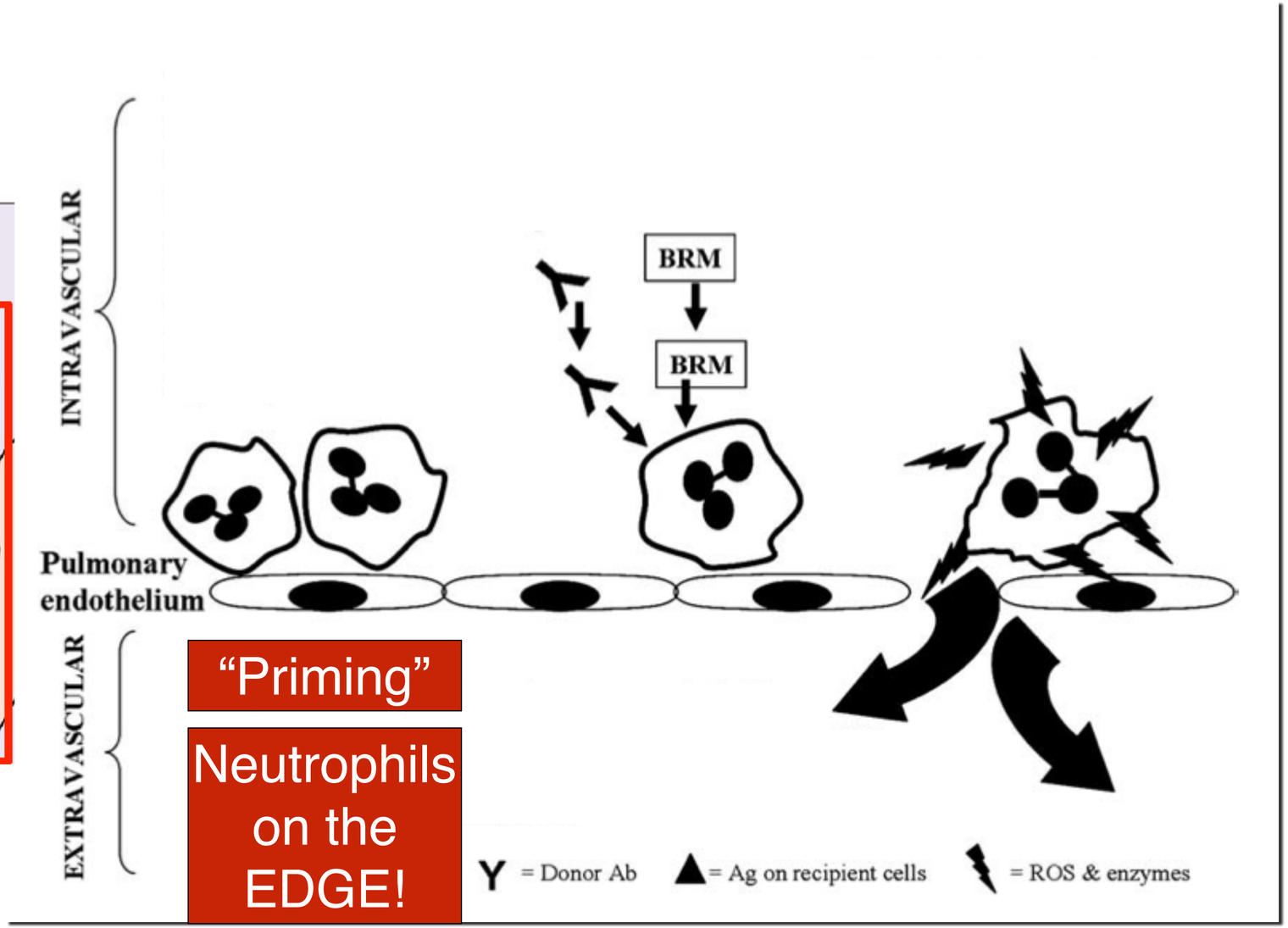


Image: Vlaar APJ et al. Lancet 2013;382(9896):984-94

2

First hit
(patient factors)

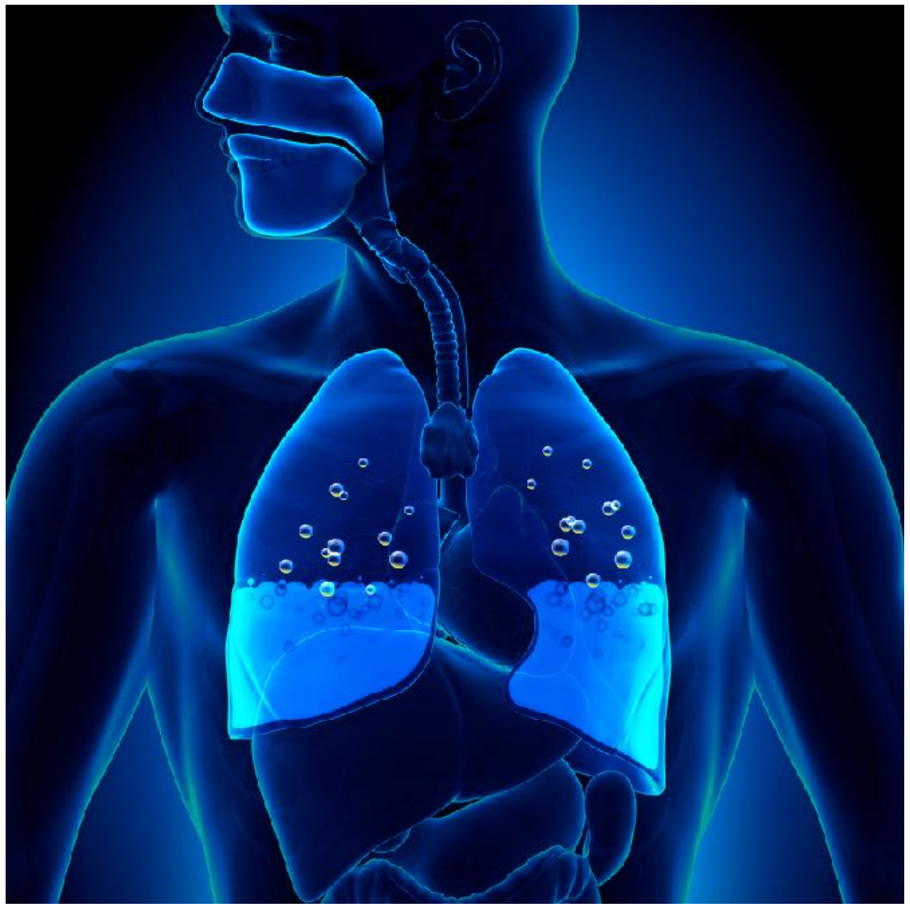
- Sepsis
- Haematological malignancy
- Heart surgery
- Mechanical ventilation
- Massive blood transfusion
- Chronic alcohol abuse
- Age of patient
- Shock
- Acute renal failure
- Severe liver disease
- Spine surgery
- Liver surgery



"Priming"

Neutrophils on the EDGE!

Other Tests to Consider



- **With respiratory symptoms:**
  - **Chest x-ray**
  - pBNP levels
  - Fluid I/O for patient
  - HLA/HNA testing for donor
  - ~~IgA/haptoglobin levels if anaphylactic~~

TRALI Diagnosis

- TRALI IS A CLINICAL DIAGNOSIS!!
- Proving with lab tests is usually difficult
  - TACO, ARDS, non-tx stuff
- Fever, hypotension may help distinguish from TACO
  - Normal pBNP levels may help
- HLA type for patient
- Anti-HLA (maybe anti-HNA) for donors involved

TRALI

- Prevention
  - Predominantly male plasma (2006-8)
  - Screen parous female PLT donors for HLA Abs (16)
  - All have decreased TRALI frequency greatly
    - ✓ <1:100,000 transfusions

Presenting WITH Fever	
Acute (< 24 hrs)	**Delayed (> 24 hrs)**
Acute Hemolytic Febrile Non-hemolytic Tx-related Sepsis (TTI) TRALI	Delayed Hemolytic TA-GVHD
Presenting WITHOUT Fever	
Acute (< 24 hrs)	**Delayed (> 24 hrs)**
Allergic Hypotensive TACO Tx-associated Dyspnea	Delayed Serologic Post-transfusion Purpura

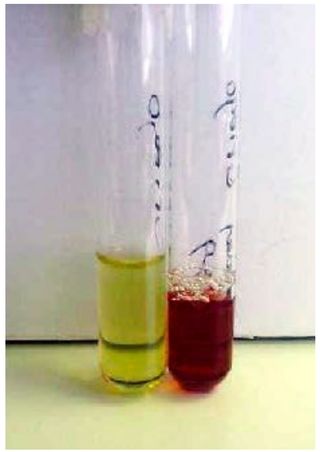
Mild Allergic Reactions

- 1-3% incidence
  - May not report
- Urticaria (hives); local
  - Angioedema
- Type I hypersensitivity
- Diphenhydramine treats, may not prevent
- May restart transfusion

Four CORE Tests

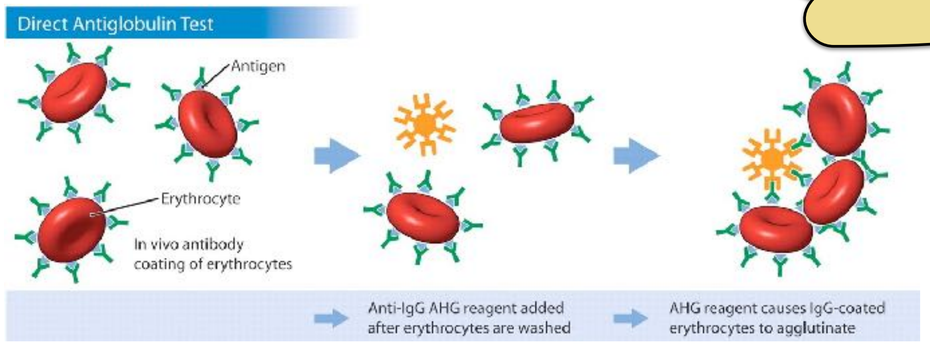
Clerical Check

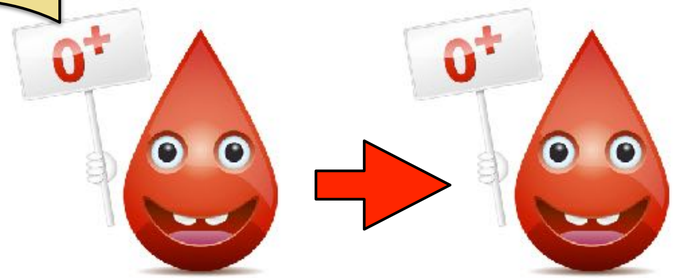
Image: http://intranet.tdmu.edu.ua/



Visible HGB

DAT



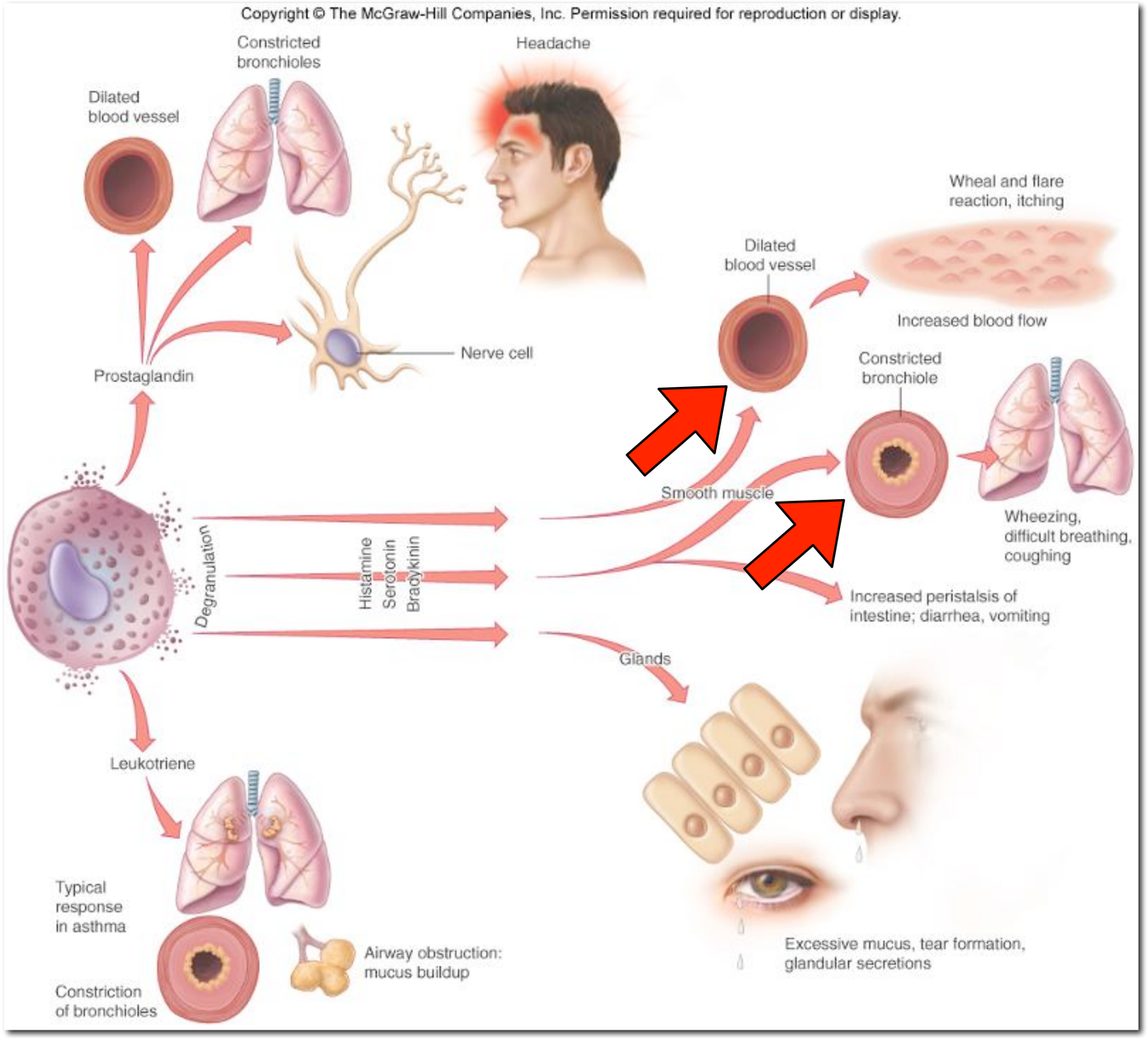


Pre Post

Repeat ABO/Rh

Severe Allergic RXNs

- Extreme opposite of urticarial
- Classic: Anaphylaxis early in TX
  - Acute hypotension, abdominal distress, systemic crash
  - Almost always have skin findings!


Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.
Constricted bronchioles
Headache
Dilated blood vessel
Wheal and flare reaction, itching
Dilated blood vessel
Increased blood flow
Nerve cell
Prostaglandin
Constricted bronchiole
Smooth muscle
Wheezing, difficult breathing, coughing
Degranulation
Histamine
Serotonin
Bradykinin
Increased peristalsis of intestine; diarrhea, vomiting
Glands
Leukotriene
Typical response in asthma
Airway obstruction: mucus buildup
Constriction of bronchioles
Excessive mucus, tear formation, glandular secretions

Severe Allergic RXNs

- Classic: **IgA-deficiency**
  - Severely decreased/absent IgA (<0.05 mg/dl)
  - Anti-IgA; anaphylaxis with exposure
- Anti-IgA is difficult to detect (specialty labs)
  - Further, may not be predictive!
  - VERY few with RXN have anti-IgA

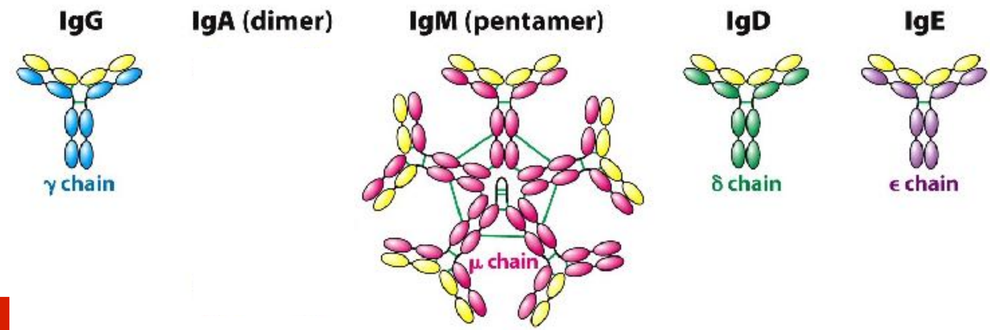


Figure 34.8
Biochemistry, Seventh Edition
© 2012 W. H. Freeman and Company

Severe Allergic RXNs

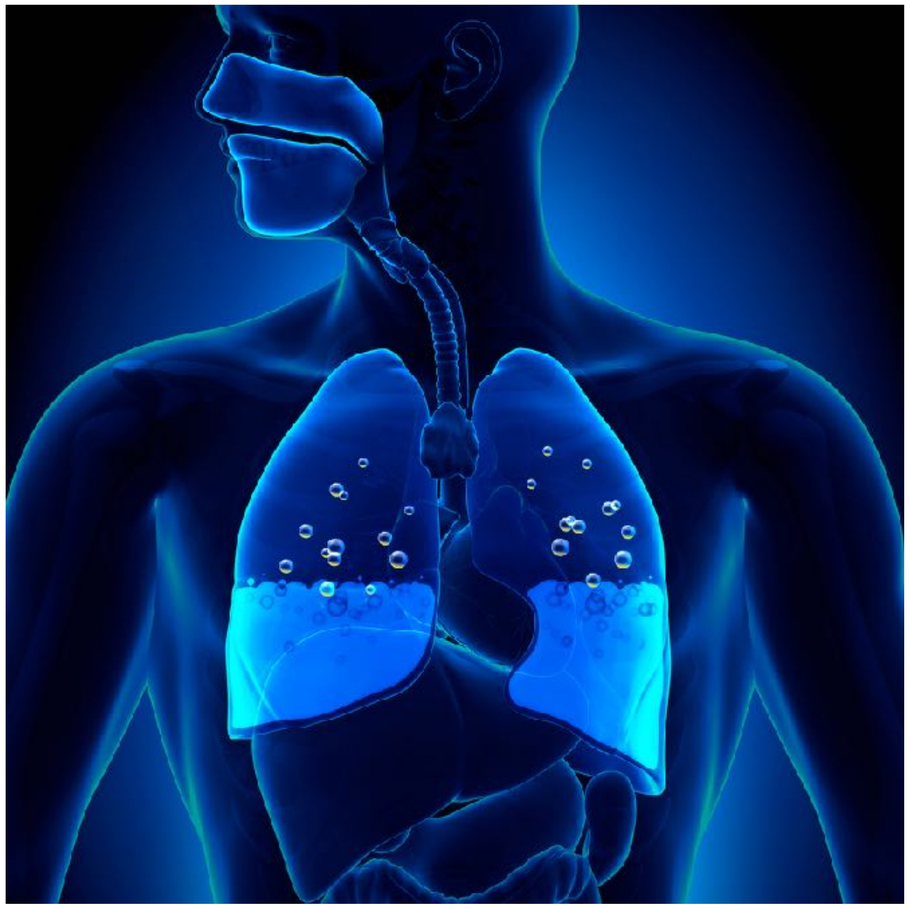
- Others:
  - Haptoglobin deficiency
  - Latex
  - Drugs
  - Foods eaten by donors
  - Donors passing on severe allergies?
- <u>Most RXNs do NOT have explanation!</u>

Anaphylactic Rxn DDX

- Acute hemolytic reaction (not exactly)
- Septic transfusion reaction
- TRALI/TACO
- Coincidental anaphylactic RXN
- Pulmonary embolus, acute MI, others

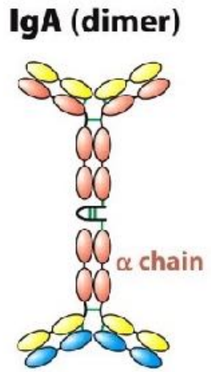
- NOTE: No fever + skin findings VERY helpful

Other Tests to Consider



- **With respiratory symptoms:**
  - **Chest x-ray**
  - pBNP levels
  - Fluid I/O for patient
  - HLA/HNA testing for donor
  - IgA/haptoglobin levels if anaphylactic

Diagnosis



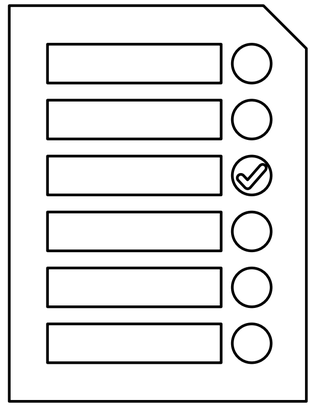
- Upon presentation, consider IgA-deficiency (possibly haptoglobin)
  - Test <u>pretransfusion</u> sample
    - ✓ Screen for IgA level
    - ✓ Do anti-IgA test if IgA is very low/absent
    - ✓ Understand limitations (not predictive)
- Rare to pursue other etiologies

Treatment

- Diphenhydramine (Benadryl) not enough!
- Epinephrine…RIGHT NOW!!
- Bronchodilator (e.g., aminophylline)

Prevention

- IgA-deficient with anti-IgA and Hx of reaction:
  - "IgA-deficient" products
    - ✓ IgA-deficient donors of RBCs, PLTs, plasma
    - ✓ Washed RBCs, PLTs (2 L NaCl)
  - Autologous donations
- If IgA-deficient but no anti-IgA/reaction: No wash
- If Rxn, not IgA-deficient, use washed or autologous
  - May re-try "normal" transfusion later



Transfusion-associated Circulatory Overload

- Acute congestive heart failure due to transfusion

*Signs and symptoms, laboratory: (check all that apply)

Cardiovascular:	Cutaneous:	Pain:
☐ Blood pressure decrease	☐ Edema	☐ Abdominal pain
☐ Shock	☐ Flushing	☐ Back pain
Hemolysis/Hemorrhage	☐ Jaundice	☐ Flank pain
☐ Disseminated intravascular coagulation	☐ Other rash	☐ Infusion site pain
☐ Hemoglobinemia	☐ Pruritus (itching)	**Respiratory:**
☐ Positive antibody screen	☐ Urticaria (hives)	☑ Bilateral infiltrates on chest x-ray
Generalized:	**Renal:**	☐ Bronchospasm
☐ Chills/rigors	☐ Hematuria	☑ Cough
☐ Fever	☐ Hemoglobinuria	☑ Hypoxemia
☐ Nausea/vomiting	☐ Oliguria	☑ Shortness of breath

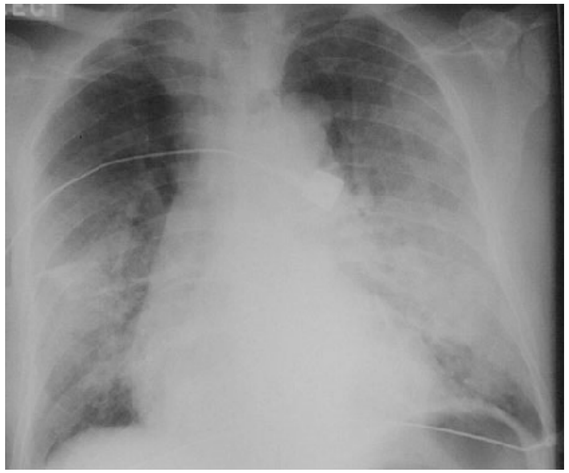
☑ Other: (specify) **Blood pressure INCREASE, headache, JVD, elevated BNP**

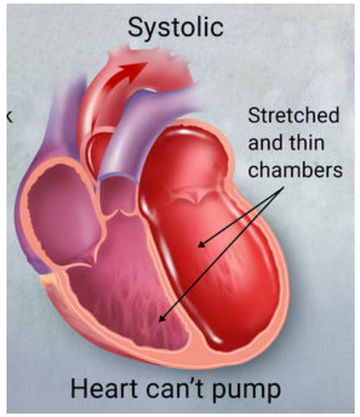
Image source: James Heilman, MD (via Wikipedia)

TACO Definition

3 or more within 6 hours after transfusion end:

- Acute respiratory distress (dypnea, cough)
- Elevated Brain Natriuretic Peptide (BNP)
- Elevated central venous pressure
- Evidence of left heart failure
- Evidence of positive fluid balance
- Chest x-ray with pulmonary edema



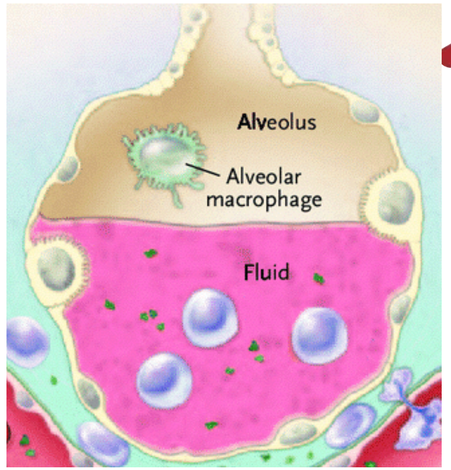


TACO

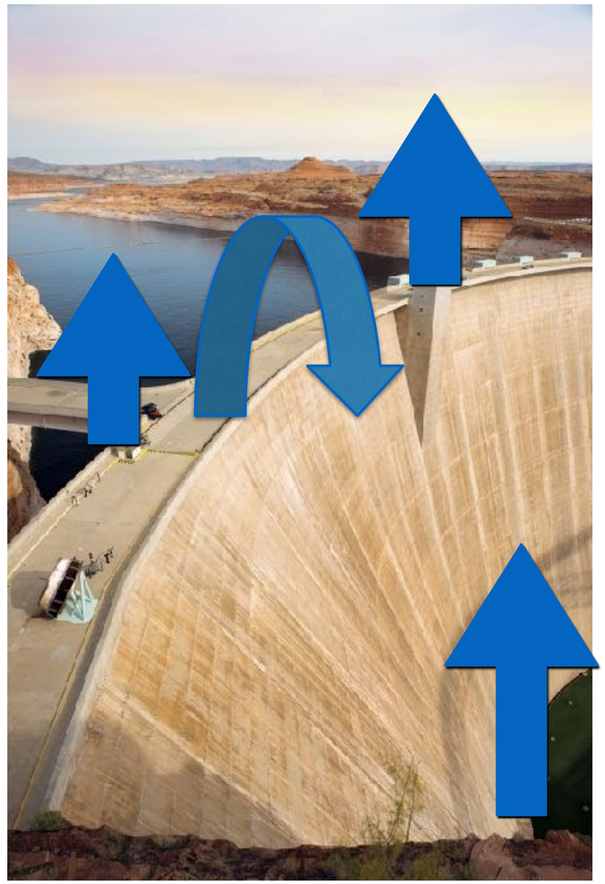
- At-risk:
  - Those already with CHF
  - Older patients (85% over 60)
  - Very young patients
  - Renal failure patients
  - Chronic compensated anemias

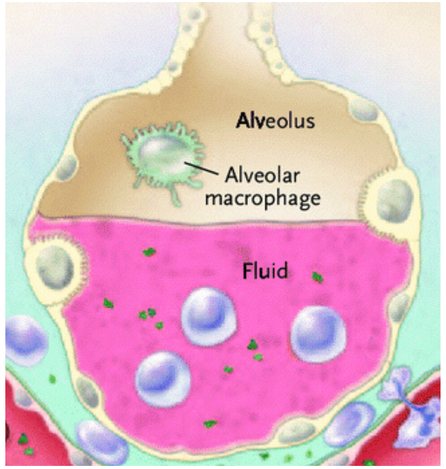
Image: pngtree.com

TRALI vs TACO

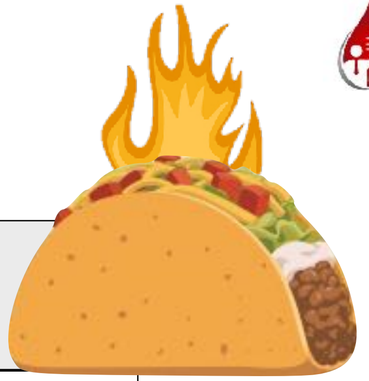


Vs.





TRALI	TACO
Fever	No fever
Hypotension	Hypertension
No diuretic effect	Dramatic diuretic effect
Normal BNP	Elevated BNP*
Transient leukopenia	No leukopenia
+/- anti-HLA/HNA Abs	No antibodies



"Hot TACO"

[Eye Roll]

TACO

- Treatment
  - Stop transfusion, sit patient up, diuretics, oxygen
- Prevention
  - Slower infusion rates (1 ml/Kg/hr)
  - Split units/aliquots
  - Volume reduction

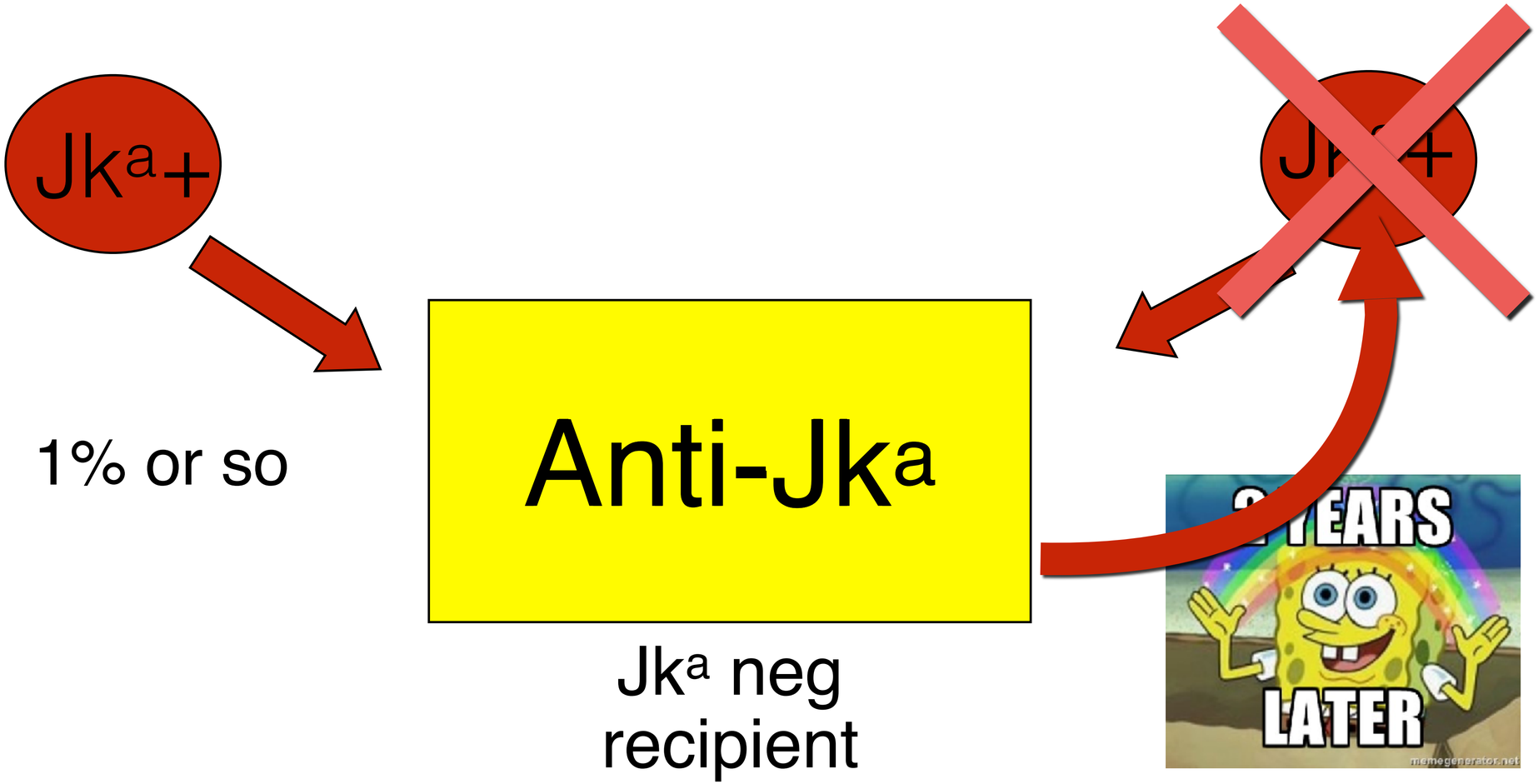
Presenting WITH Fever	
Acute (< 24 hrs)	**Delayed (> 24 hrs)**
Acute Hemolytic Febrile Non-hemolytic Tx-related Sepsis (TTI) TRALI	Delayed Hemolytic TA-GVHD

Presenting WITHOUT Fever	
Acute (< 24 hrs)	**Delayed (> 24 hrs)**
Allergic Hypotensive TACO Tx-associated Dyspnea	Delayed Serologic Post-transfusion Purpura

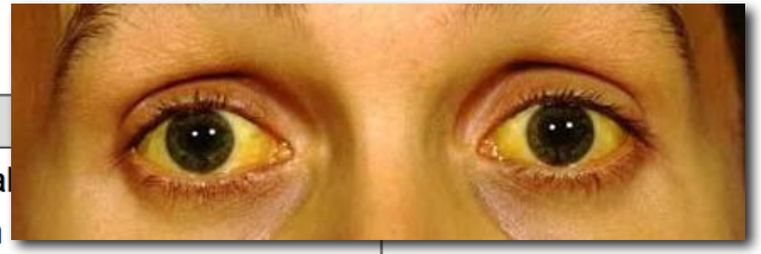
Delayed Hemolytic Rxns

- Hemolysis occurring >24 hrs to <28 days after transfusion
- Almost always a previously present antibody that reappears after exposure
  - Kidd, Duffy, Kell most common

Mechanism of DHTR



DHTR Signs & Symptoms



*Signs and symptoms, laboratory: (check all that apply)

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☐ Shock	☐ Flushing	☐ Back pain
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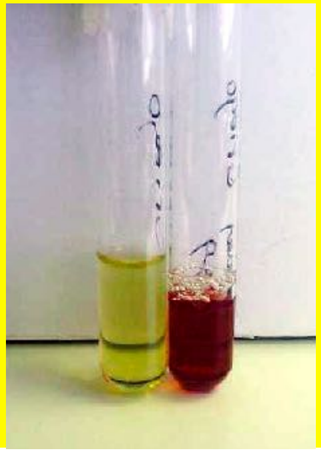
Generalized:	**Renal:**	☐ Bronchospasm
☐ Chills/rigors	☐ Hematuria	☐ Cough
☒ Fever	☐ Hemoglobinuria	☐ Hypoxemia
☐ Nausea/vomiting	☐ Oliguria	☐ Shortness of breath
☑ Other: (specify) Scleral icterus		

Four CORE Tests

Clerical Check

Image: http://intranet.tdmu.edu.ua/

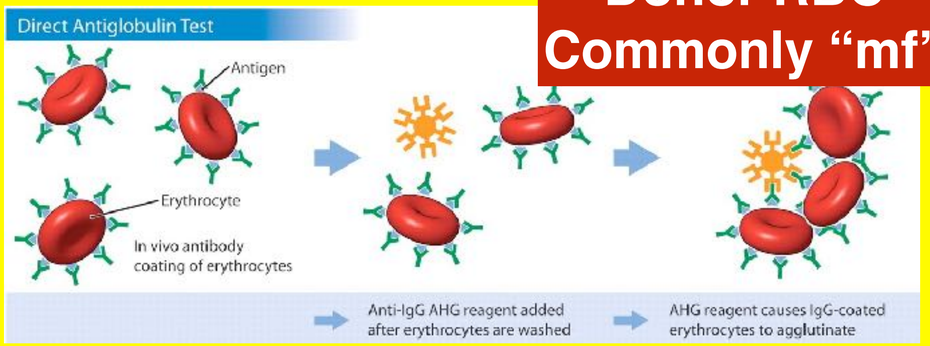


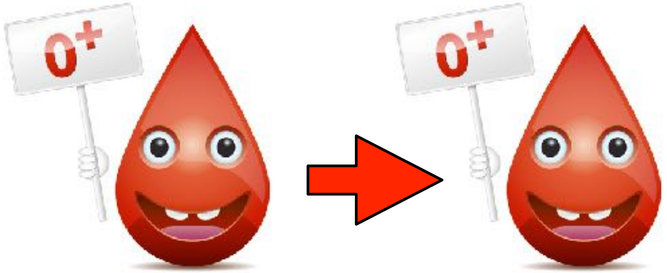
Visible HGB

Serum dark

DAT

Donor RBC Commonly “mf”



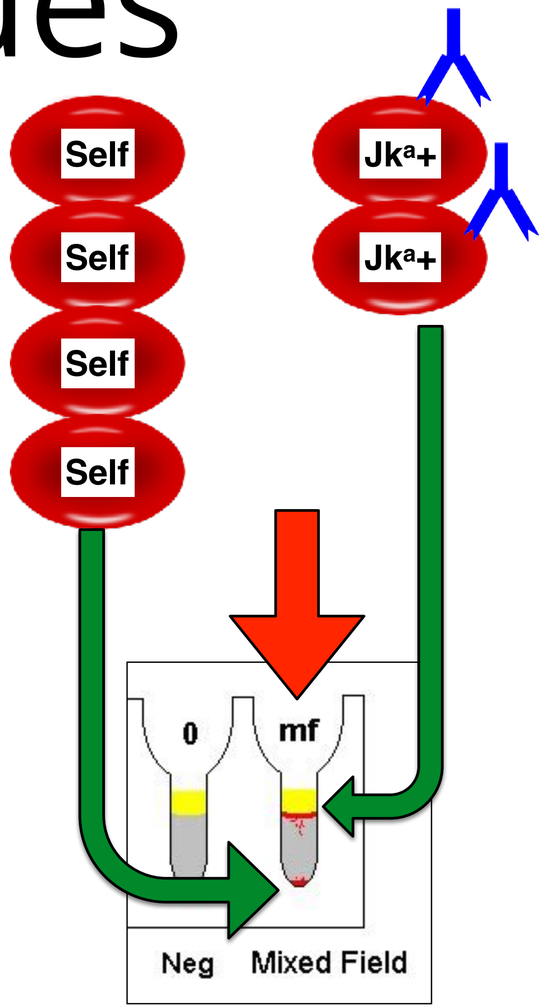


Pre Post

Repeat ABO/Rh

DHTR Lab Clues

- “Mixed field” DAT
- Newly identified antibody
- Eluate with antibody
- Spherocytes (extravascular hemolysis)
- Expected LDH/bili, haptoglobin changes



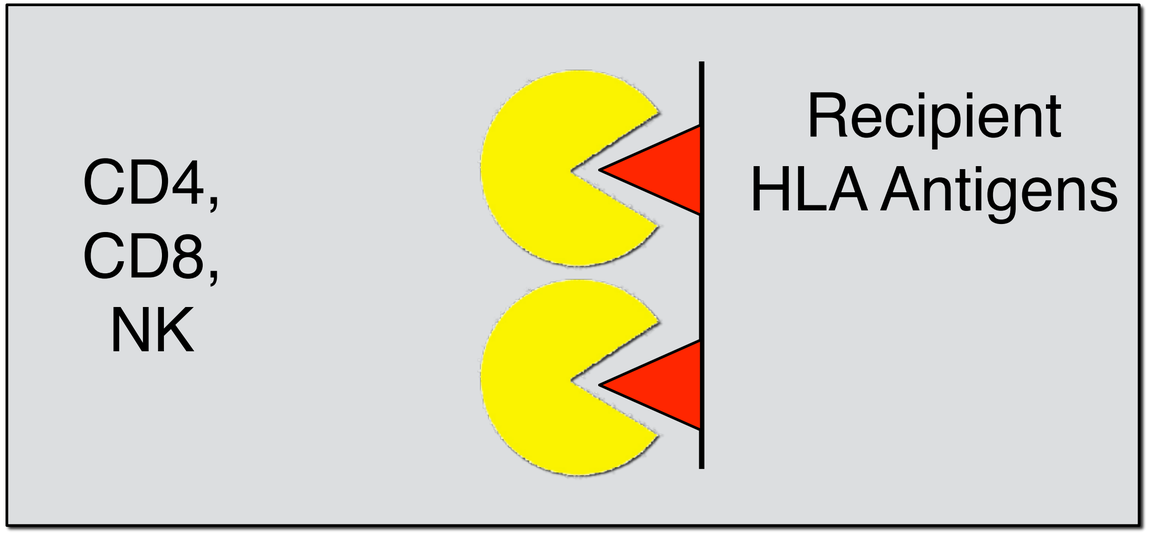
DHTR Treatment

- Often not required
- If severe, treat as AHTR
  - Volume and pressure support

Transfusion-associated GVHD

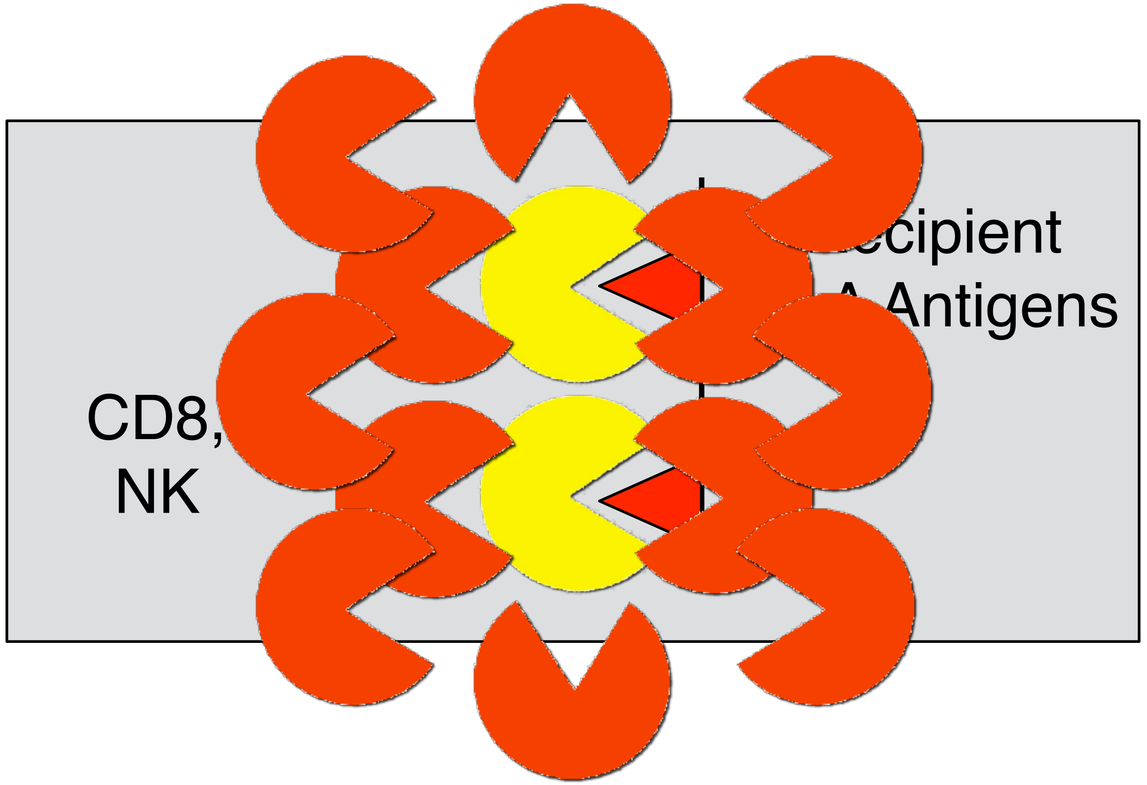
- Attack on host HLA antigens on tissues by transfused T-lymphocytes
  - "TA" part distinguishes from GVHD from stem cell and organ transplant
- Rare, but nearly always fatal
  - 3 fatals reported to FDA since 2005
  - 66 cases in literature 2000-13

Normal Activity

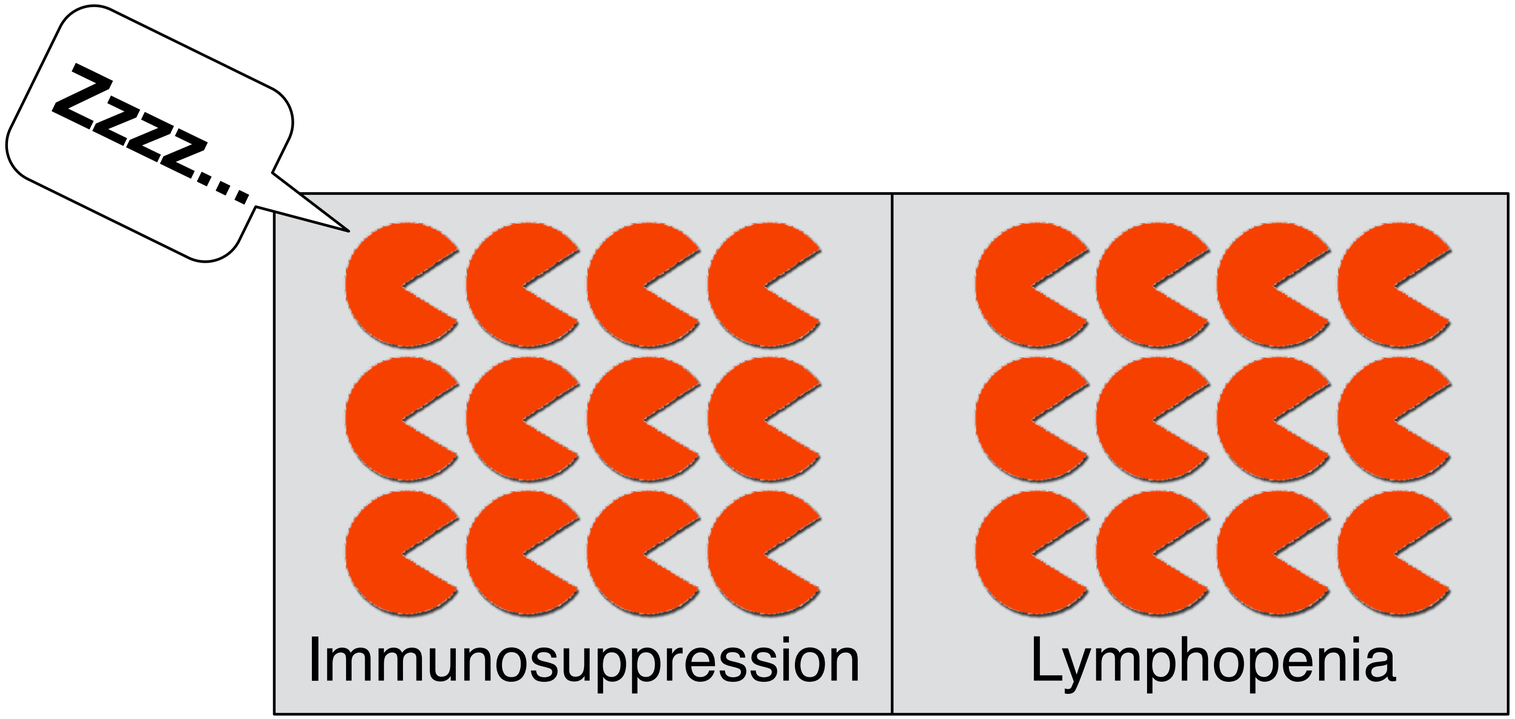


Attack!

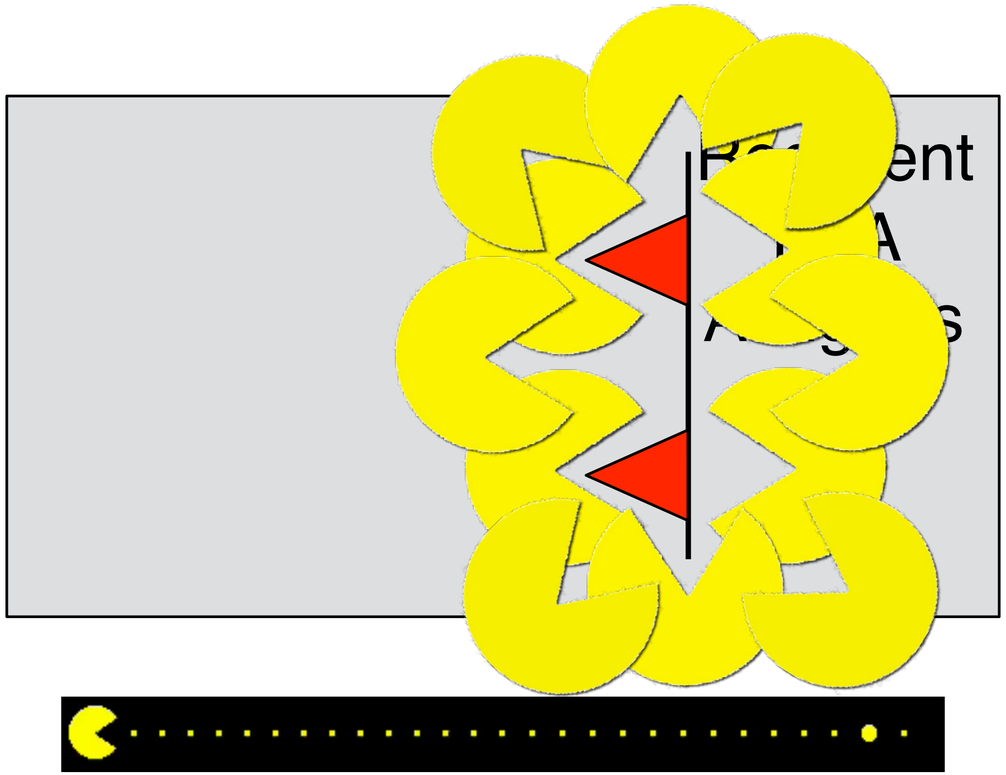
Counter-Attack



But, What If There Is….?



TA-GVHD

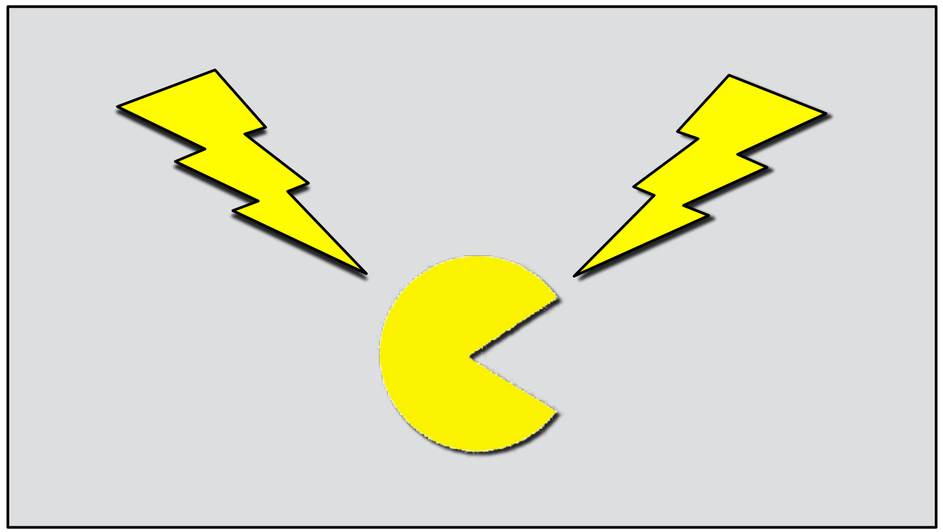


7-10 days: Skin, liver, GI tract

<u>Bone marrow</u>

Prevention

2500 cGy targeted to center of bag,
1500 cGy to all parts

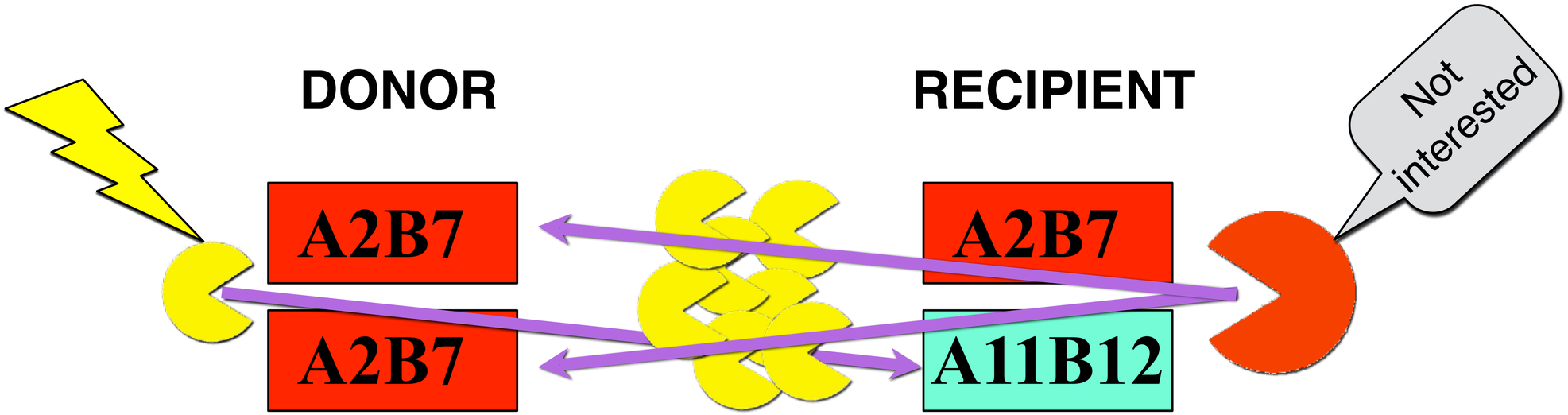


Irradiation!!

Indications

- Immunosuppression
  - T-cell defects (including drugs)
  - Stem cell/marrow transplants
  - Aplastic anemia
- Intrauterine/preemie transfusions
- Heme malignancies (esp HD)
- Granulocytes
- 1st-degree relatives or HLA-matched

One-Way HLA Match



Highest risk:

- Family members
- HLA-selected products
- Genetically non-diverse populations

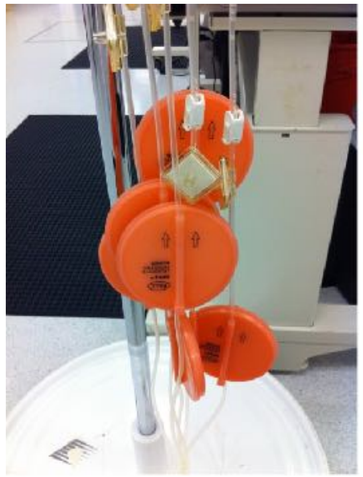
Probably NOT at risk

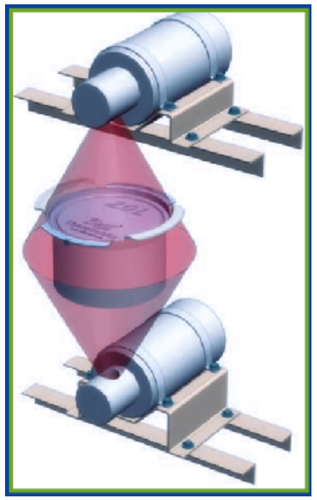
- Organ transplant recipients
- Term neonates
- AIDS patients
- Previously frozen products

Miscellaneous

- Not for CMV prevention
- Not for stem cell infusions (duh!)
- LR is NOT interchangeable!
  - We don't know minimum threshold

Not Good Enough!





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Acute Hemolytic Febrile Non-hemolytic Tx-related Sepsis (TTI) TRALI	Delayed Hemolytic TA-GVHD

Presenting WITHOUT Fever	
Acute (< 24 hrs)	**Delayed (> 24 hrs)**
Allergic Hypotensive TACO Tx-associated Dyspnea	Delayed Serologic Post-transfusion Purpura

Post-transfusion Purpura

- Severe thrombocytopenia (< 10K) about 10 days post-transfusion
  - Platelet or RBC transfusion
- Females 5:1
  - Especially with pregnancy history

Post-transfusion Purpura

HPA-1a + PLTs

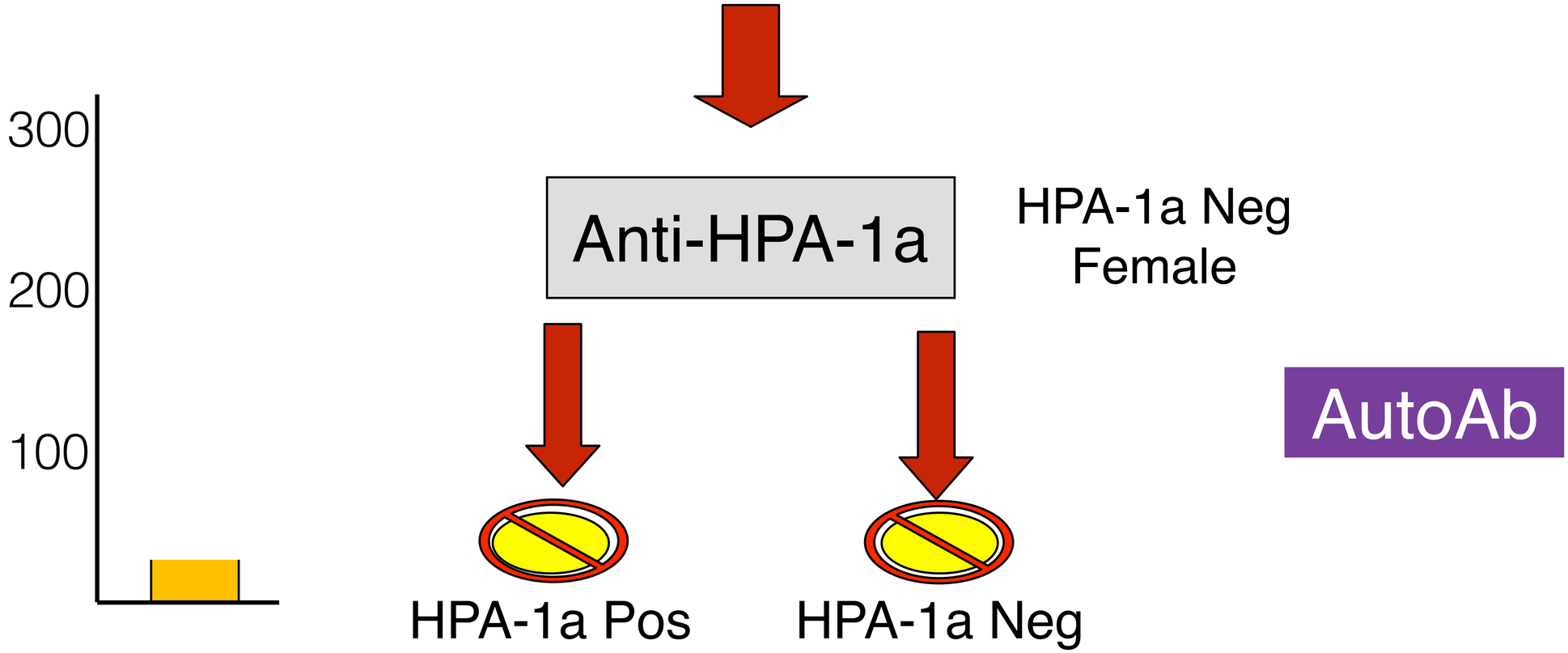
Pregnancy/Transfusion

HPA-1a Neg Female

Anti-HPA-1a

Post-transfusion Purpura

Future Platelet or RBC transfusion (HPA-1a Pos)



Post-transfusion Purpura

- Treat with IVIG
  - Formerly plasma exchange
- Mortality 10% without treatment, rare with IVIG
- Avoid platelet transfusion if possible
- Future PLTs should be Ag-matched