Fred Hutch Cancer Center

Transfusion Medicine: Pretransfusion Testing, Blood Component Therapy and Adverse Reactions

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University of Washington

Land Acknowledgement

Fred Hutchinson Cancer Center acknowledges the Coast Salish peoples of this land, the land which touches the shared waters of all tribes and bands within the Duwamish, Puyallup, Suquamish, Tulalip and Muckleshoot nations.

Table of Contents

1. Analyze the basis of pre-transfusion testing with a type and screen
2. Explain the risks of transfusing uncrossmatched blood products
3. Describe the various blood components available for transfusion and their indications
4. Analyze the pathophysiology and mitigation strategies of the most common and severe transfusions

Pre-Transfusion Testing

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(5.06.01)
Which of the following tests are required prior to a red cell transfusion? (select all that apply)?

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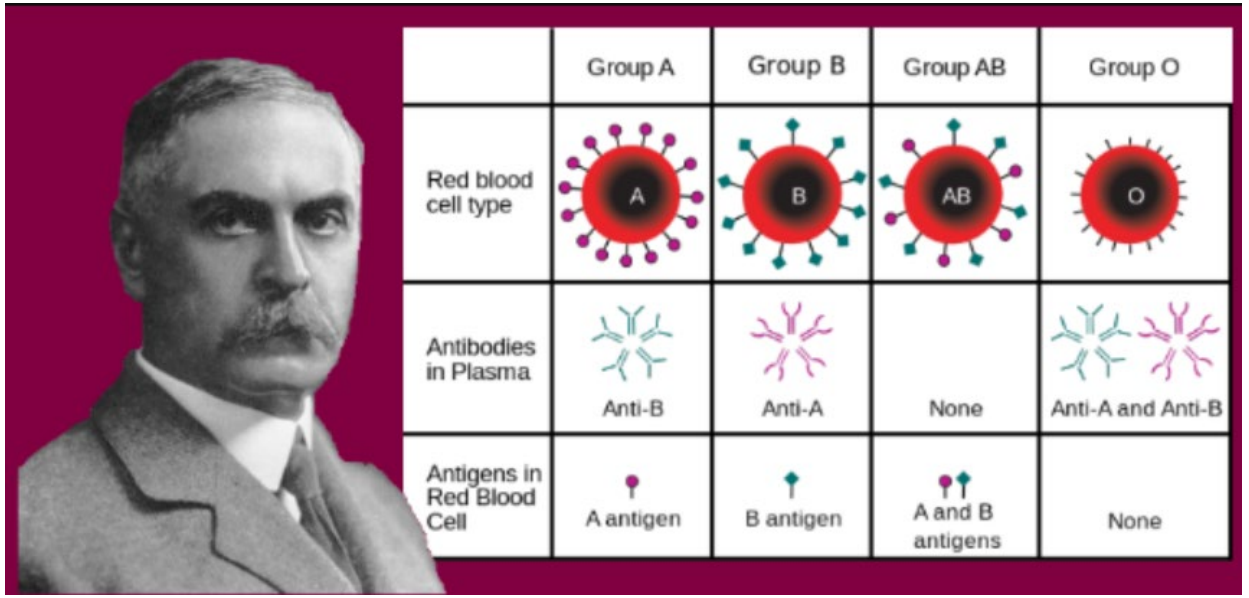
Which of the following tests are required prior to a red cell transfusion? (select all that apply)?

- **A) A blood type**
- **B) A second confirmatory blood type**
- **C) A crossmatch**
- D) A second confirmatory crossmatch
- **E) An antibody screen**
- F) A direct antiglobulin test

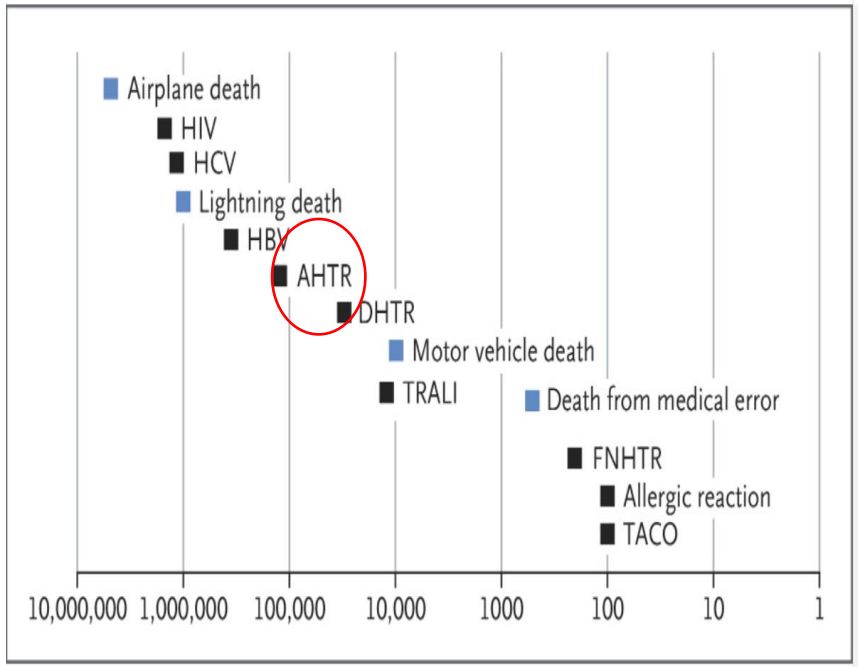
“Type and Screen”

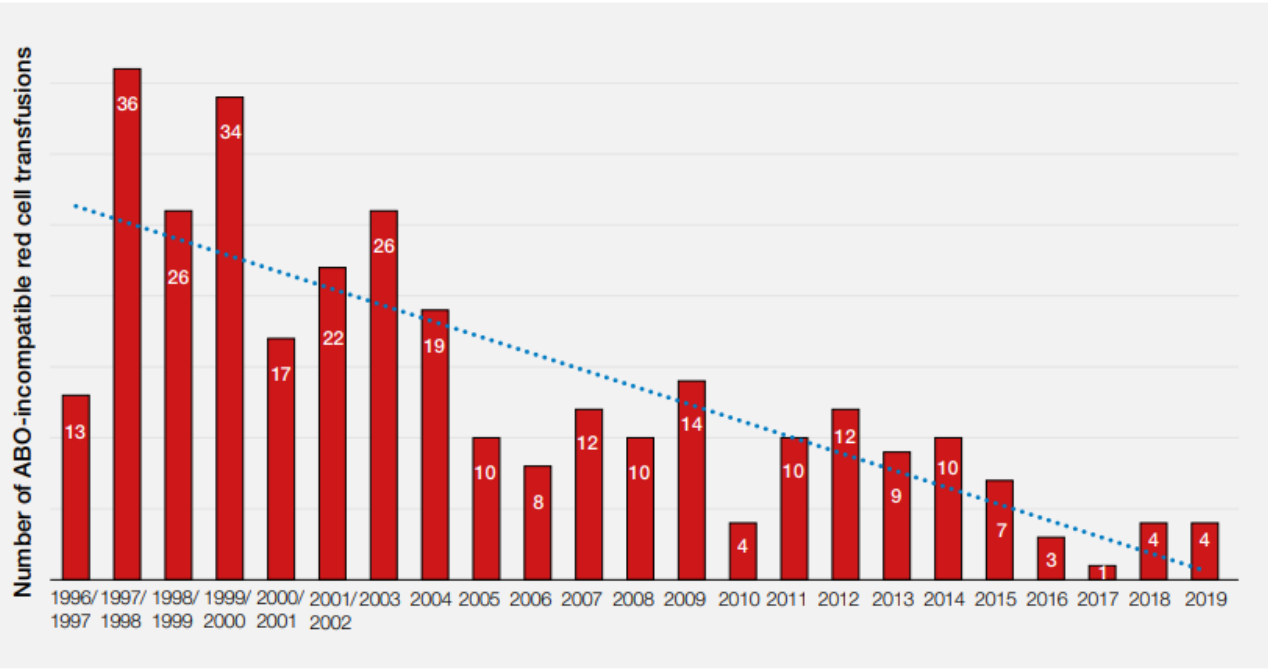
Blood Type



- ABO and RhD typing
  - Forward type: RBC Antigen (A, B, RhD
  - Reverse type: Antibodies (anti-A, anti-B)
- Need a second confirmatory blood type for a new patient
  - Reduced wrong blood in tube errors leading to acute hemolytic transfusion reactions

ABO incompatible Red Cell Transfusions: Never Event





Reducing the Incidence of Acute Hemolytic Transfusion Reactions

- Almost always due to error at bedside (>99%)
  - Wrong patient label on patient sample
    - 2 Samples for Type are required for every new patient
    - All samples for blood bank MUST be verified by 2 different providers
  - Wrong unit started on a patient
    - Double verification: Prior to starting a transfusion, 2 different nurses must verify the product and patient

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(5.06.02)
Type O RhD negative (O neg) red blood cells are universally safe in all patients.

ⓘ Start presenting to display the poll results on this slide.

Type O RhD negative (O neg) red blood cells are universally safe in all patients.

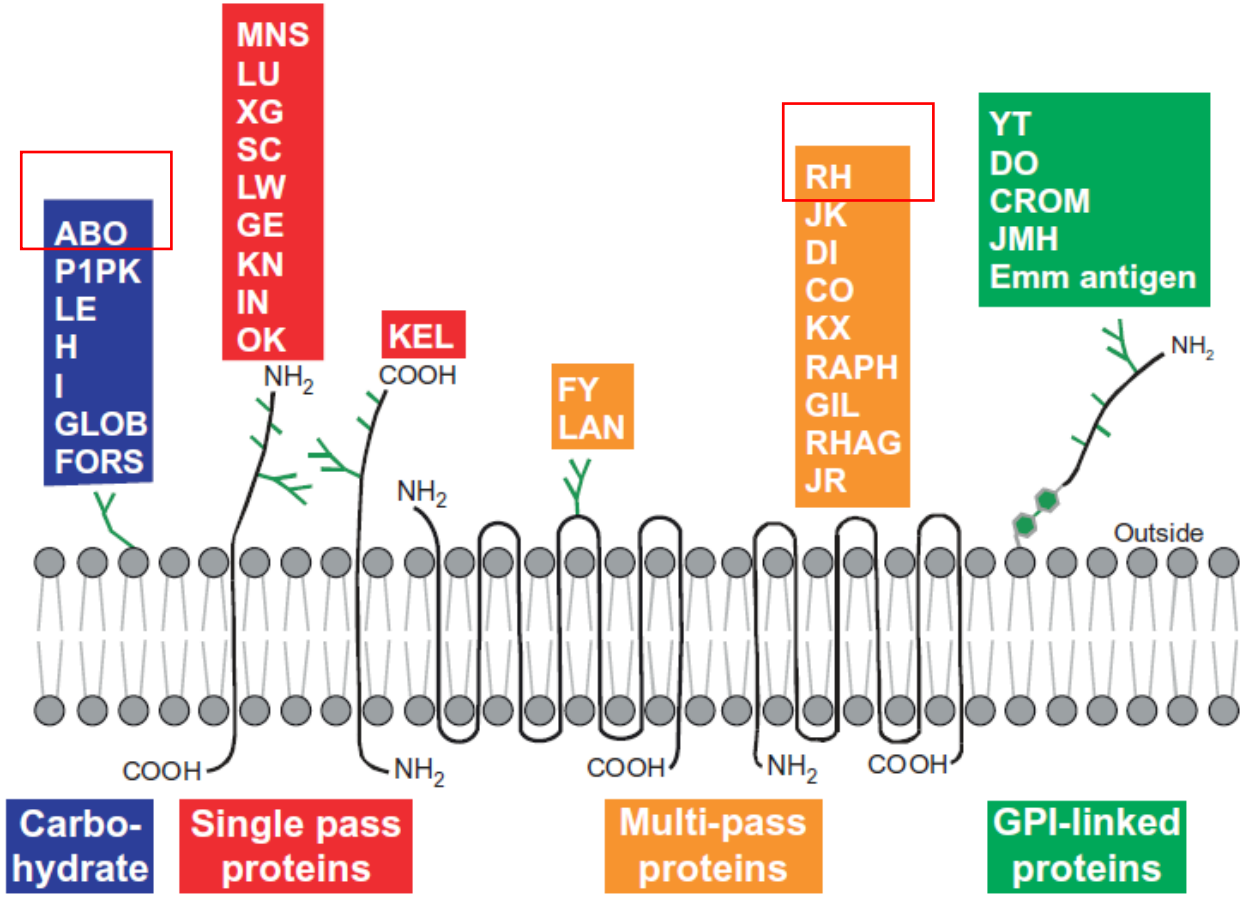
- A) True
- **B) False**

“Type and **Screen**”

Antibody Screen

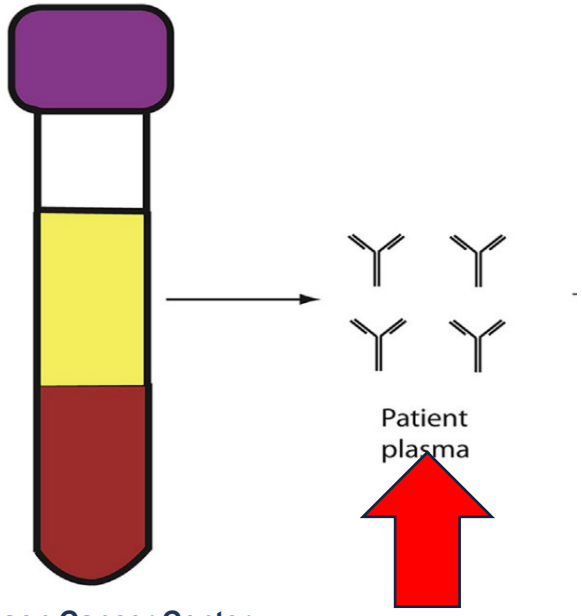
- Test patient plasma for presence of red cell *allo*antibodies
  - NOT Anti-A or anti-B
  - Anti-D, Anti-E, Anti-e, Anti-C, Anti-c, Anti-K, Anti-Jka, etc….
- Ab screen positive = universal supply of O negative RBC may not be safe

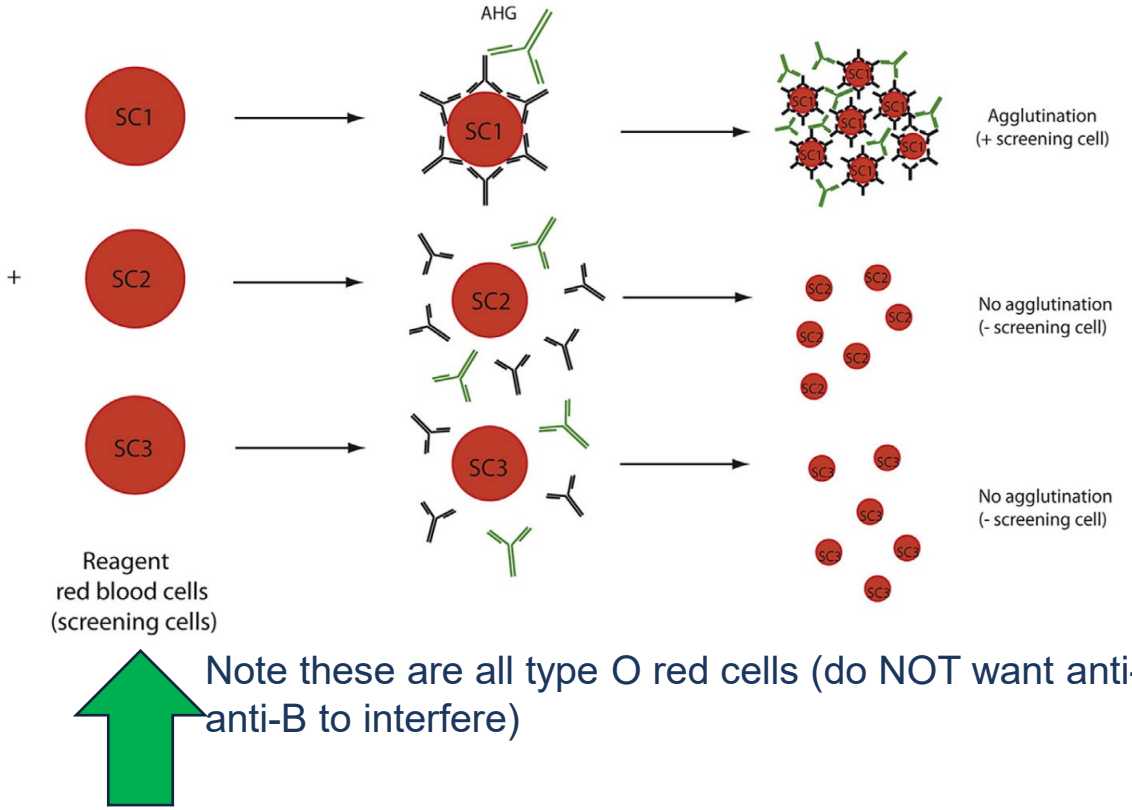
Blood Groups



Why is an antibody screen needed?

- Screen: Presence of unexpected antibodies *(anti-K, anti-E, anti-e, etc)*
  - *Not naturally occurring*
  - *Expected result: negative screen*



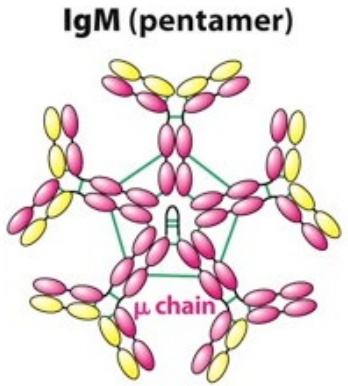


Note these are all type O red cells (do NOT want anti-A, anti-B to interfere)

Immunoglobulin Class: ABO and alloantibodies antibodies

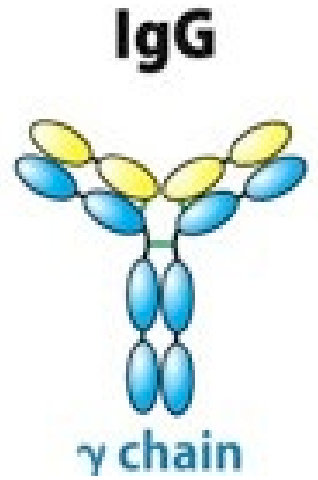
ABO Antibodies (Reverse type)

- Naturally occurring (expected antibodies)
- Cold reacting, No incubation needed (5-10 minutes)
- Strong activators of complement pathway
- Intravascular hemolysis (hemoglobinuria, hemoglobinemia)



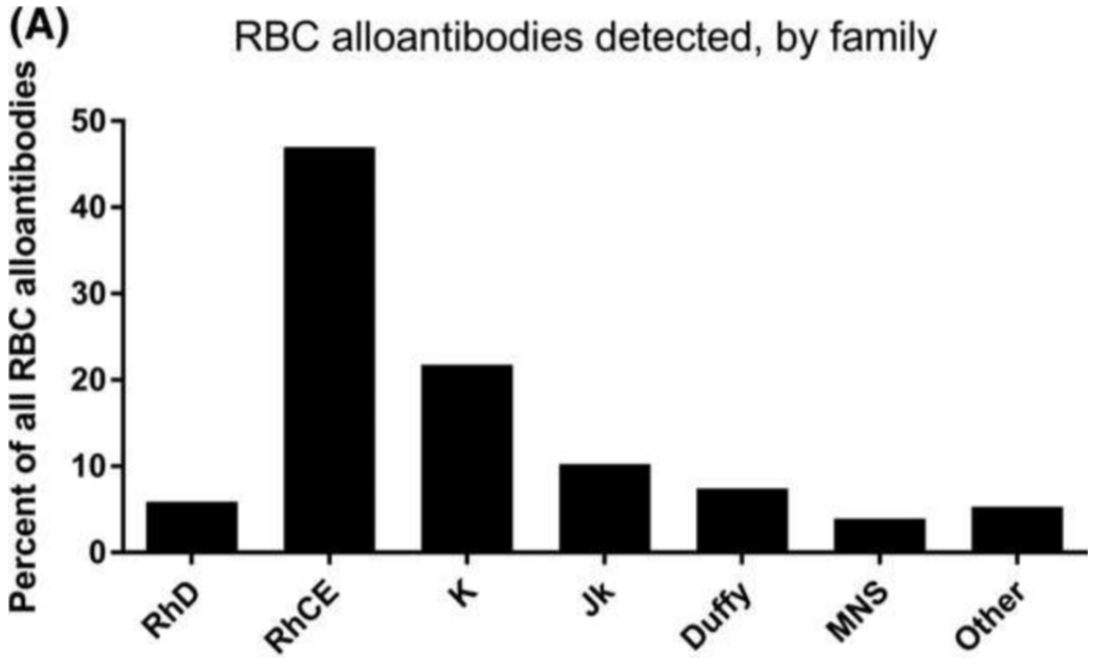
Alloantibodies (antibody screen)

- After alloimmunizing event (unexpected antibodies)
- Warm reacting, Incubation needed at 37C with AHG (30-60 minutes)
- Weaker activators of complement pathway
- Extravascular hemolysis (hyperbilirubinemia, slowly declining Hg)



RBC antigen alloimmunization

- Rate of RBC antigen allo-immunization in the US: 2-6%
- SCD, SLE, MDS, other diseases, are associated with higher rates of RBC allo-immunization



How to transfuse patient without alloantibodies?

- Example: Patient is A positive with a negative antibody screen
- Transfuse: Type O or A (Rh positive or Rh negative) RBC
    - Universal type O RBCs are safe

How to transfuse patient with alloantibodies?

- Example: Patient is A positive with a positive antibody screen
  - Antibody Identification: anti-Fy(a)
- Transfuse: Type O or A (Rh positive or Rh negative) RBC that is negative for Fy(a) antigen
  - Units are not routinely tested to determine if positive/negative for blood group antigens outside of ABO (Fy, Jk, K, etc)
  - Need specific units that are tested to be Fy(a) negative
  - Universal type O RBC units available in hospitals for emergency release are generally NOT tested for these antigens
    - May not be safe to transfuse

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(5.06.03)
In patients with a negative antibody screen, a crossmatch is not required for red cell transfusions.

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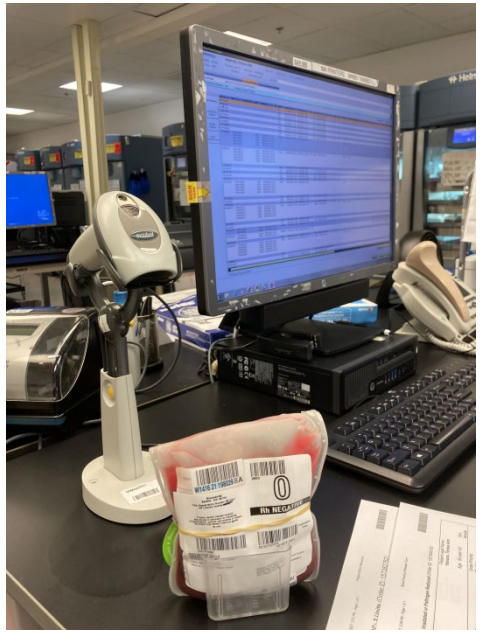
In patients with a negative antibody screen, a crossmatch is not required for red cell transfusions.

- **A) True**
- B) False

All Products With > 2mLs of RBCs are Required to Be Crossmatched (RBC, Whole Blood, Granulocytes)

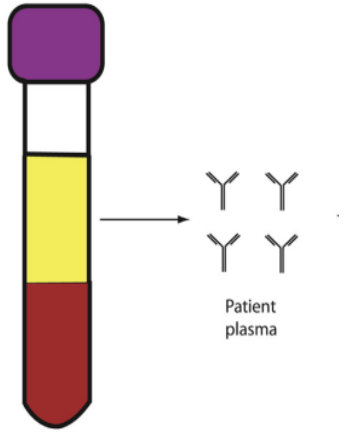
Electronic Crossmatch

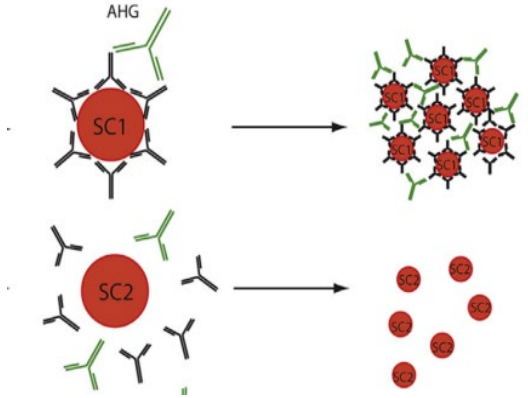
- Negative antibody screen
- ABO compatibility
- 5 minutes



Serologic Crossmatch

- Positive antibody screen
- Minor antigen compatibility
- 45-60 minutes

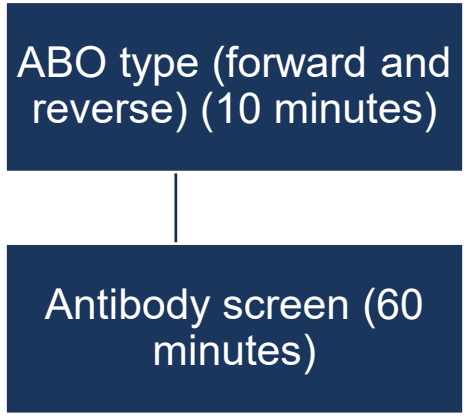




Turn around time for completion of testing and proving crossmatched products:

ABO type (forward and reverse) (10 minutes)

Turn around time for completion of testing and proving crossmatched products:



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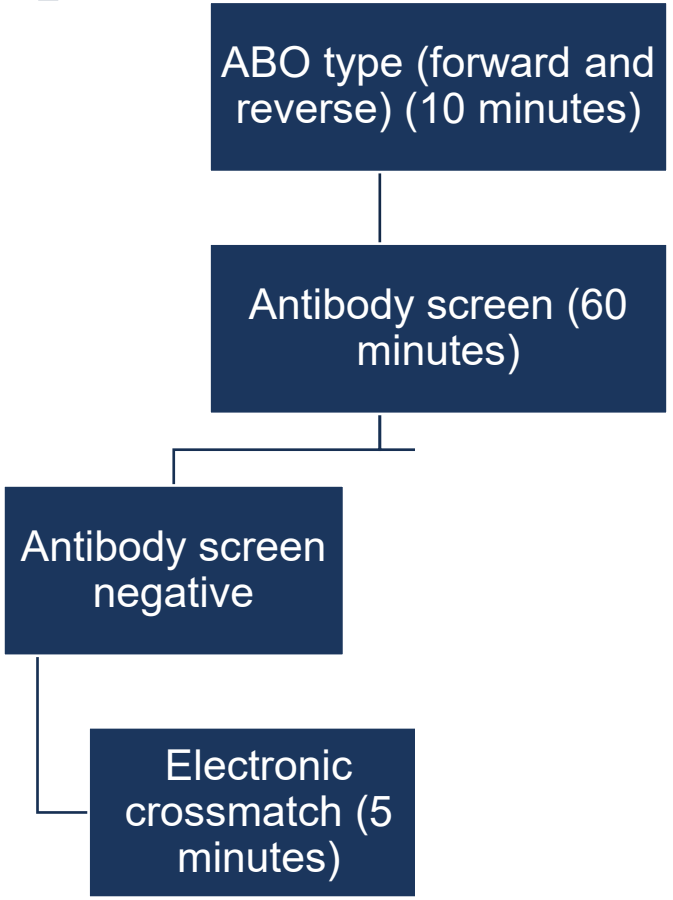

Time to crossmatch compatible blood products:
1-2 hours

If patient has active T&S → electronic CXM RBC have same turn around time as uncrossmatched products

Turn around time for completion of testing and proving crossmatched products:

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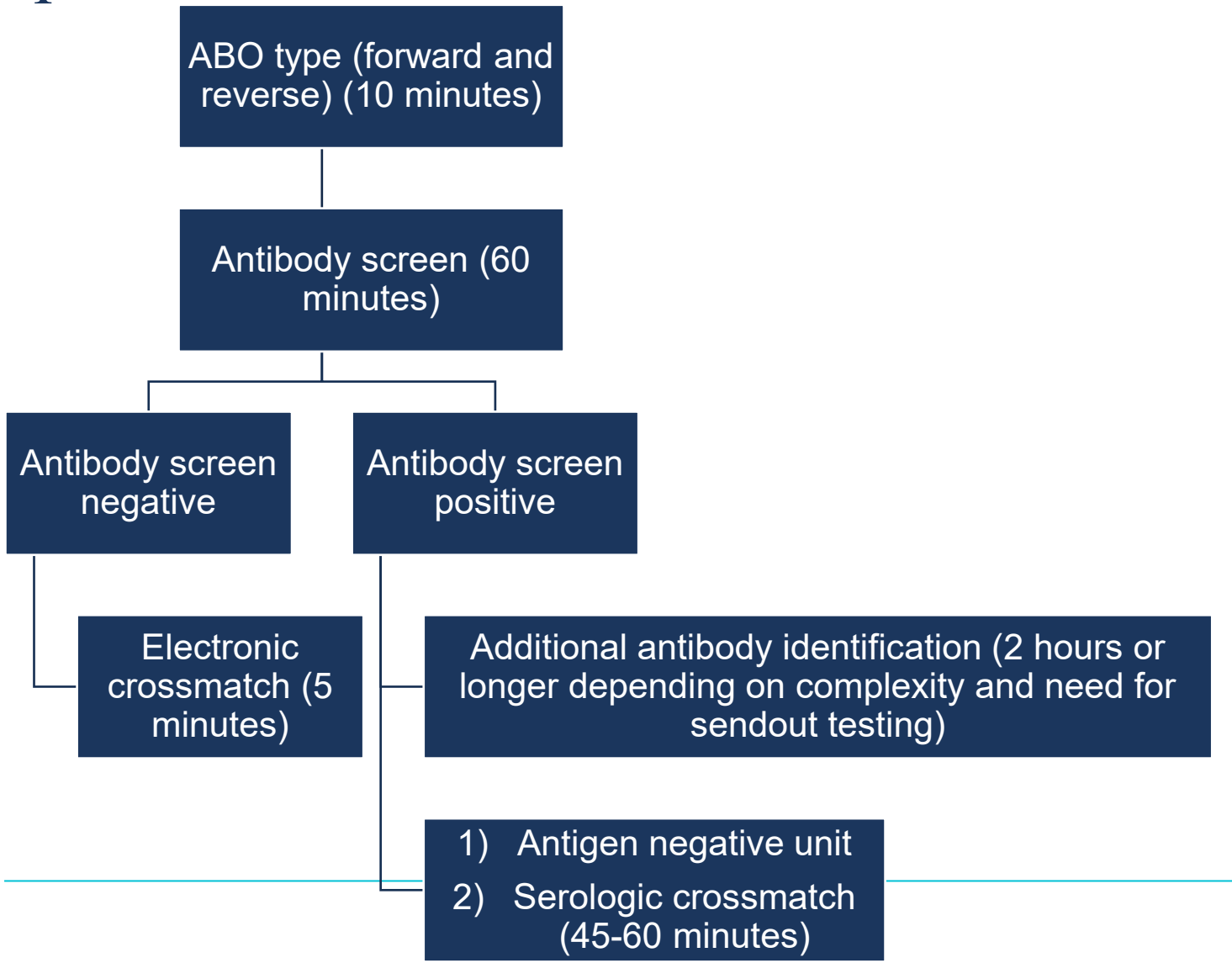

If patient has active T&S → electronic CXM RBC have same turn around time as uncrossmatched products

Time to crossmatch compatible blood products:
3-4 hours or longer (up to days in complex cases)

BLOOD PRODUCTS

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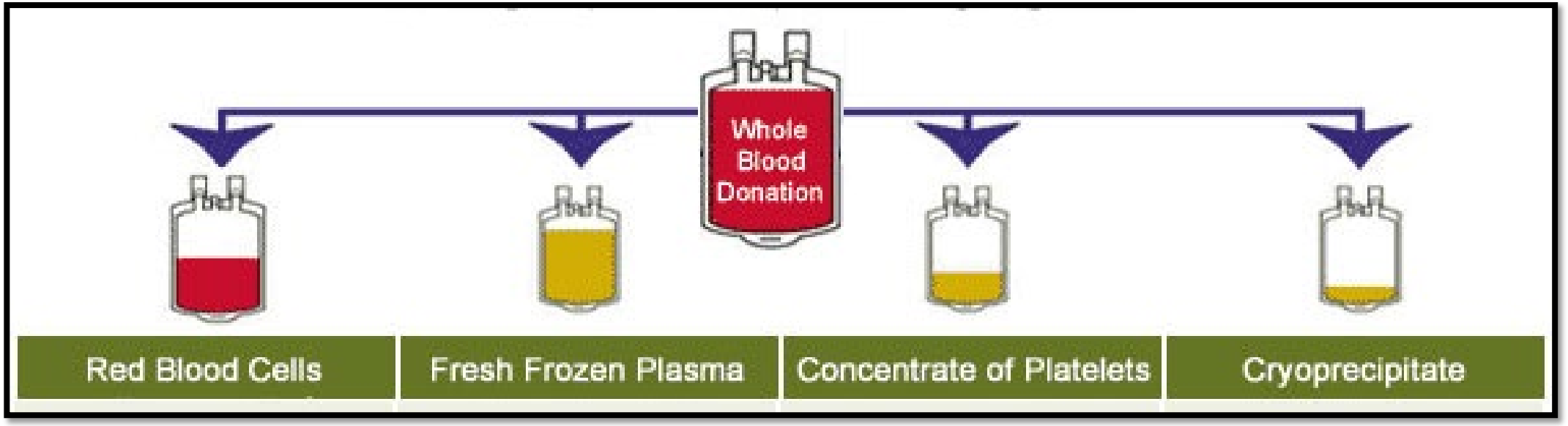
(5.06.04) Which of the following blood products has the most limited supply?

ⓘ Start presenting to display the poll results on this slide.

Which of the following blood products has the most limited supply?

- A) Whole Blood
- B) Red Blood Cells
- **C) Platelets**
- D) Plasma
- E) Cryoprecipitate

Whole blood donation



Whole Blood

The Evolution of Blood Transfusion in the Trauma Patient: Whole Blood Has Come Full Circle

Jonathan A. Black, MD[1] Virginia S. Pierce, MD[1] Jeffrey D. Kerby, MD, PhD[1] John B. Holcomb, MD[1]

- Characteristics
  - Low Titer Type O Whole Blood
  - Titer of anti-A and anti-B to make sure below certain threshold (can give to patients who are A and B)
  - 35 days shelf life
- Indication:
  - Trauma resuscitation (patient's blood type is unknown)
  - Pediatric surgery, ECMO priming

Semin Thromb Hemost 2020;46:215–220.

One Red Blood Cell Unit

- Content:
  - 200 mL Red blood cells (Hct of unit is about 55-65%)
  - 100 mL storage solution (anticoagulant and additive)
  - 30 mL plasma
- Testing:
  - ABO/Rh crossmatched compatible
- Effect: Increase hemoglobin 1g/dL (or 3% increment)
- Storage: 42 day shelf life, 2-6C (refrigerator)

Transfusion Thresholds

JAMA | Special Communication

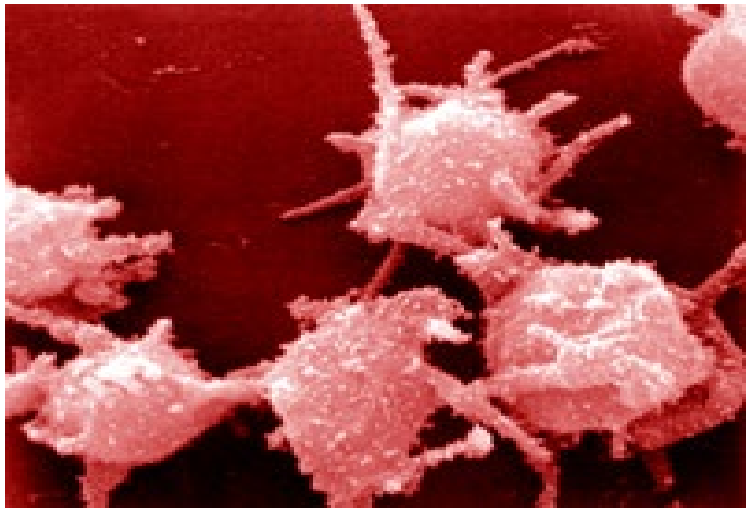
Red Blood Cell Transfusion
2023 AABB International Guidelines

- Systematic review of 45 RCT on adults and 7 RCT in pediatrics
- 1) Hospitalized and hemodynamically stable Hg <7g/dL
  - Cardiac Surgery: <7.5g/dL
  - Orthopedic surgery or cardiac disease: <8g/dL
- 2) Heme/Onc: <7g/dL
- 3) Hospitalized pediatric patients without hemoglobinopathy, cyanotic heart disease <7g/dL
- 4) Pediatric patients with congenital heart disease 7-9g/dL depending on cardiac abnormality and stage of repair

Carson et al, *JAMA* 2023

Platelets

- Testing:
  - Do not have to be crossmatched
  - Consider Plasma compatible (Out of Group Platelets practices are common!)
- Storage:
  - room temperature (20-24C with gentle agitation)
    - Highest risk of infectious contamination
  - Shelf life: 5 days (up to 7 with delayed sampling)



Activated Platelets

Platelet Transfusion Thresholds

JAMA | Special Communication

Platelet Transfusion
2025 AABB and ICTMG International Clinical Practice Guidelines

Platelet Count ($\times 10^9$/L)	Indication	Certainty of Evidence	Strength of Recommendation
<150	Accepted definition of thrombocytopenia		
<100	Adult patients with spontaneous or traumatic, nonoperative intracranial hemorrhage, including those receiving antiplatelet agents	Low/very low	Conditional
<50	Adult patients undergoing major nonneuraxial surgery	Very low	Conditional
<50	Adult patients undergoing interventional radiology, high-risk procedures	Very low	Conditional
<25	Preterm neonates without major bleeding	High	Strong
<20	Lumbar puncture (BSH[28] recommends 40 $\times 10^9$/L)	Moderate	Strong
<20	Adult patients undergoing interventional radiology, low-risk procedures	Very low	Conditional
<10	Nonbleeding patients with hypoproliferative thrombocytopenia actively receiving chemotherapy or undergoing allogeneic stem cell transplantation	Moderate	Strong
<10	Adult patients with consumptive thrombocytopenia due to critical illness (nondengue) and without major bleeding	Very low	Conditional
<10	Adult patients undergoing CVC placement at anatomic sites amenable to manual compression	Moderate/very low	Conditional
None	Dengue-related consumptive thrombocytopenia in the absence of major bleeding	Moderate	Strong
None	Nonbleeding adult patients with hypoproliferative thrombocytopenia undergoing autologous stem cell transplantation or with aplastic anemia	Very low	Conditional
None	Nonthrombocytopenic patients undergoing cardiovascular surgery in the absence of major hemorrhage, including those undergoing cardiopulmonary bypass	Very low	Conditional
Platelet Count ($\times 10^9$/L)	**Indication**	**Certainty of Evidence**	**Strength of Recommendation**

Adapted from Metcalf et al, *JAMA* 2025

Platelet Transfusion Thresholds

JAMA | Special Communication

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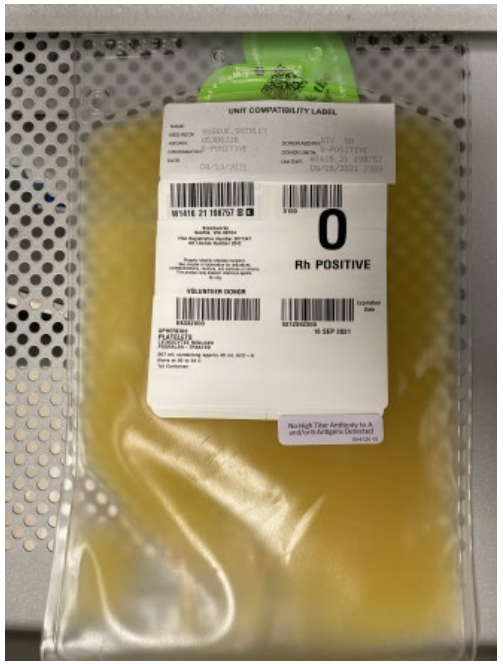
None	Nonthrombocytopenic patients undergoing cardiovascular surgery in the absence of major hemorrhage, including those undergoing cardiopulmonary bypass	Very low	Conditional

Adapted from Metcalf et al, *JAMA* 2025

Type of Platelet Products

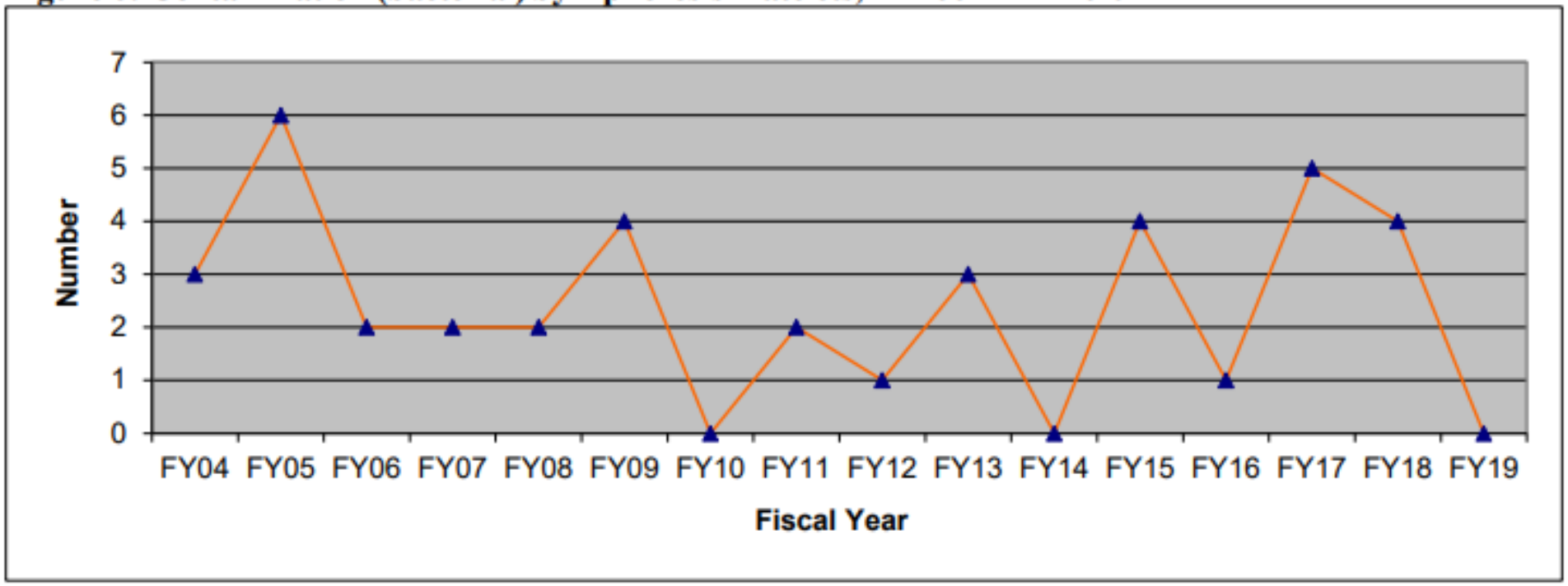


- Source:
  - Apheresis (single donor) vs. Pooled (whole blood from 4-6 donors)
- Storage solution
  - Plasma vs. Platelet additive solution (PAS)
- Storage temperature
  - Room temperature versus cold stored
- Bacterial testing
  - Bacterial culture vs. Pathogen inactivated (psoralen treatment)

Transfus Med Rev 2020 Oct;34(4):207-208

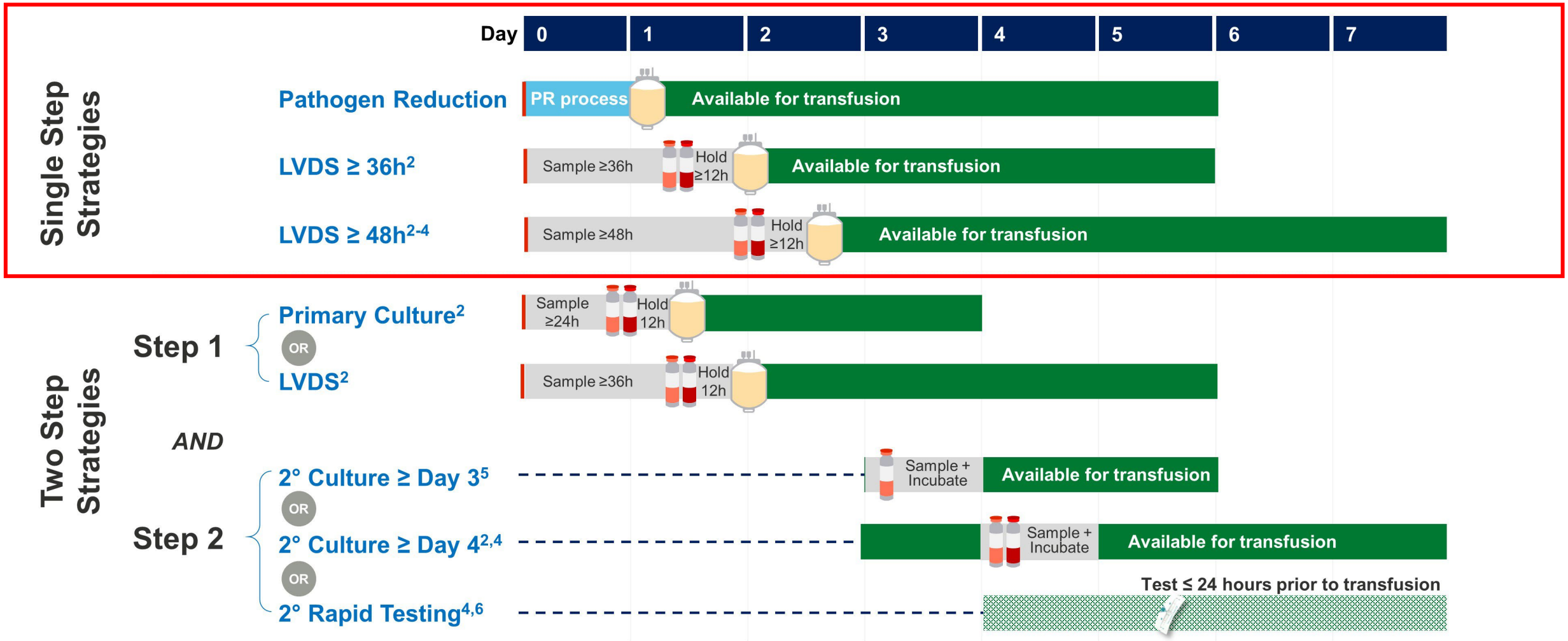
FDA Reported Fatalities from Bacterial Contamination

Figure 6: Contamination (bacterial) by Apheresis Platelets, FY2004 – FY2019



- ~4 deaths per year due to bacterial contamination of apheresis platelets
- ~1:500,000 platelet transfusions may result in fatality due to contamination
- ~1:1500 to 1:3000 non-fatal septic transfusion reaction rate with passive surveillance

FDA Guidance on Bacterial Safety September 2019[1]



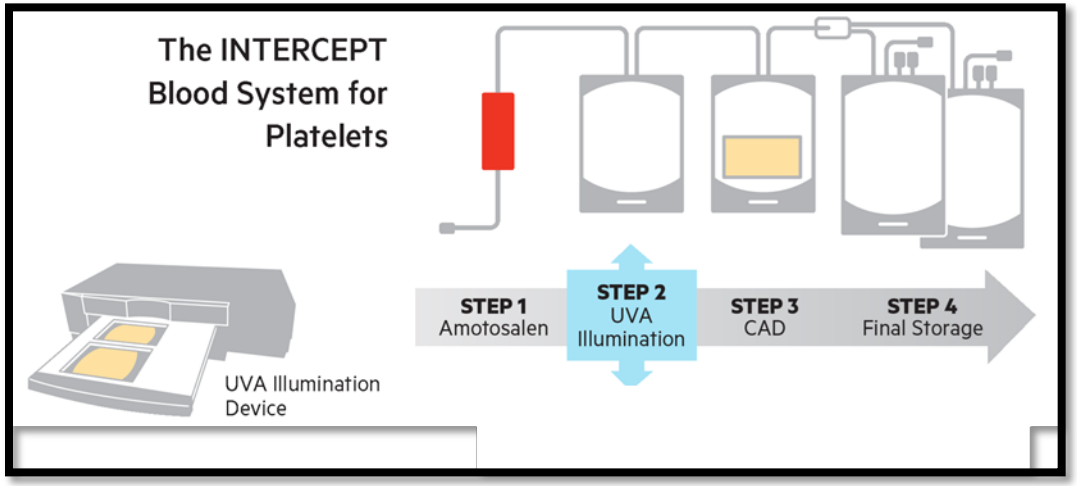
1. Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion: Guidance for Industry. US FDA; Sept 2019. 2. Aerobic and Anaerobic, 3. At the time of the finalization of this guidance, the instructions for use of the culture-based device currently labeled as a "safety measure" require a primary culture and secondary test to extend dating of platelets. Therefore, the LVDS no sooner than 48 hours strategy for a 7-day dating period cannot be implemented until appropriately labeled devices are available. 4. Platelets may only be stored beyond day 5 and up to day 7 if each component is tested using a bacterial detection device cleared by FDA and labeled for use as a "safety measure" according to its instructions for use, and if the platelet storage container has been cleared or approved for 7-day storage. 5. Aerobic. 6. Rapid testing practices vary and should be performed according to bacterial testing device instructions for use. Institutions may test daily to ensure availability of units (non-reactive test valid 24 hours prior to transfusion) or may choose to quarantine unit then test within 24 hours of transfusion. (Harm SK, et al. Transfusion. 2018 Apr;58(4):938-942. Ruby KN, et al. Transfusion. 2018 Jul;58(7):1665-1669).

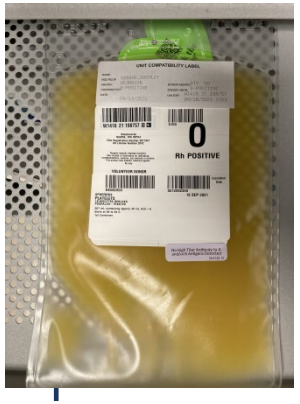
cerus

Pathogen Inactivation – Amotosalen treatment

- Only FDA approved method for pathogen inactivation (PI)
- Can be used for Platelets
- Platelet shelf life is 5 days
- PI can replace irradiation to prevent TA- GVHD
- Questionable hemostatic equivalence between treated and non-treated platelets

Spring Trial Transfusion 2005 Dec;45(12):1864-75.



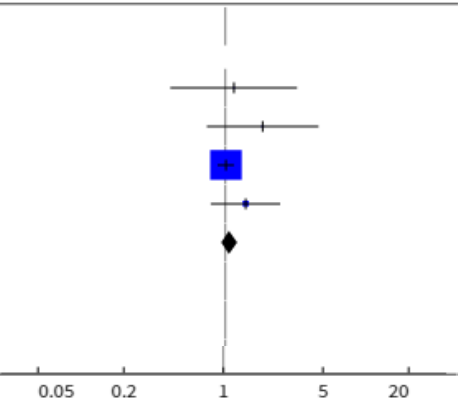


- Enveloped viruses
- Non-enveloped viruses
- Gram-negative bacteria
- Gram-positive bacteria
- Spirochetes
- Protozoa
- Leukocytes

Efficacy of Psoralen Treated Platelets – No increase in significant bleeding events

Analysis 1.4. Comparison 1 Pathogen-reduced platelets versus standard platelets for the prevention of bleeding, Outcome 4 Number of participants with 'clinically significant' bleeding (WHO grade ≥ 2 or equivalent) - follow-up more than 7 days.

Study or subgroup	PCT Plts n/N	Standard Plts n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Intercept plts vs standard plts - multiple platelet transfusion studies					
Janetzko 2005	6/22	5/21		2.2%	1.15[0.41,3.19]
Kerkhoffs 2010	11/85	7/99		2.79%	1.83[0.74,4.51]
McCullough 2004	186/318	190/327		80.68%	1.01[0.88,1.15]
Rebulla 2016	24/109	17/107		7.39%	1.39[0.79,2.43]
Subtotal (95% CI)	**534**	**554**		**93.06%**	**1.06[0.94,1.21]**
Total events: 227 (PCT Plts), 219 (Standard Plts)					
Heterogeneity: $Tau^2=0$; $Chi^2=2.96$, df=3(P=0.4); $I^2=0\%$					



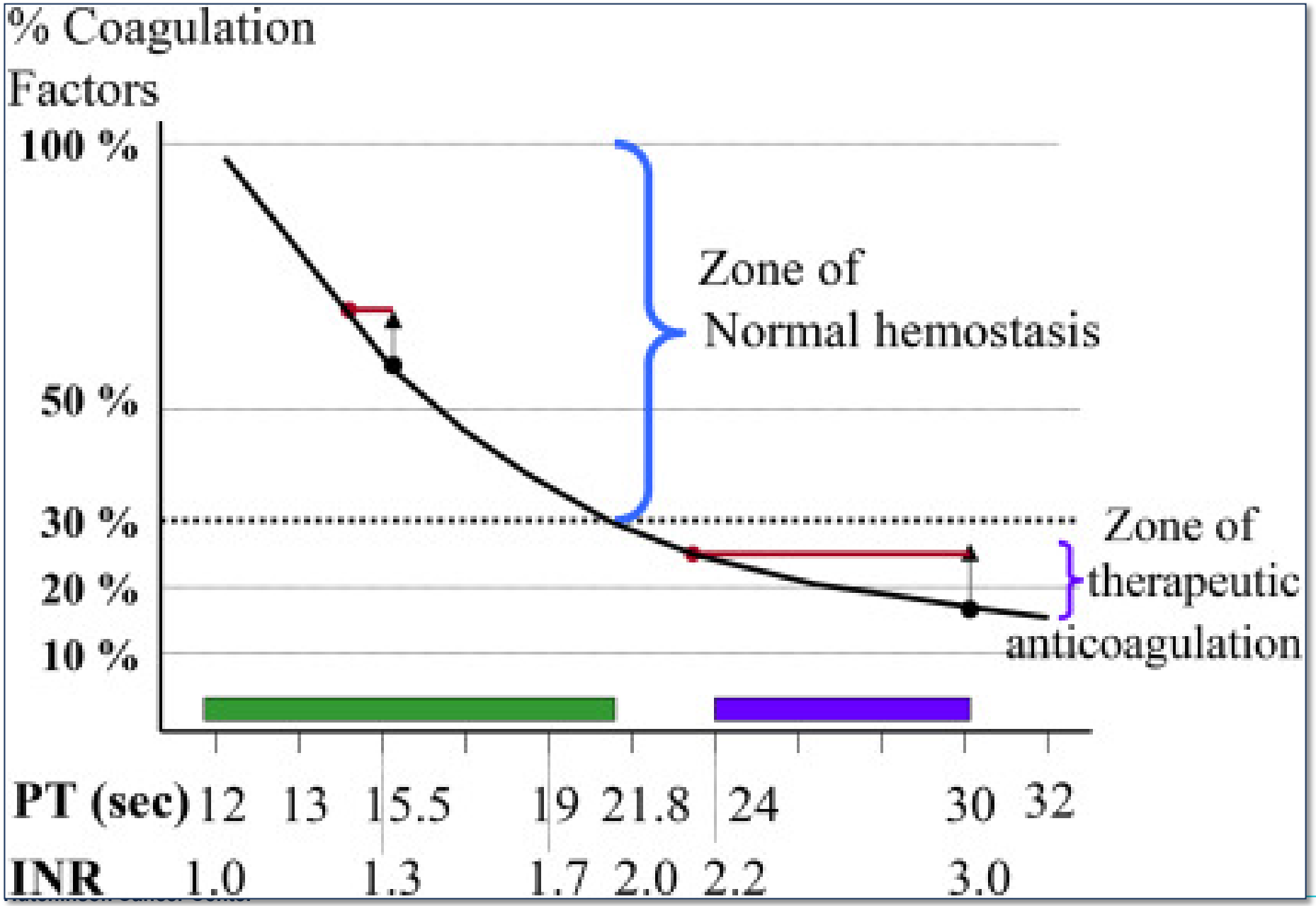
- 2017 meta-analysis of Intercept psoralen-treated platelets vs standard platelets
  - Majority Adult Hem/Onc patients
  - Moderate-quality evidence psoralen-treated platelet transfusion does not affect the risk of clinically significant or severe bleeding

Estcourt et al. Cochrane Database of Systematic Reviews 2017

Fresh Frozen Plasma

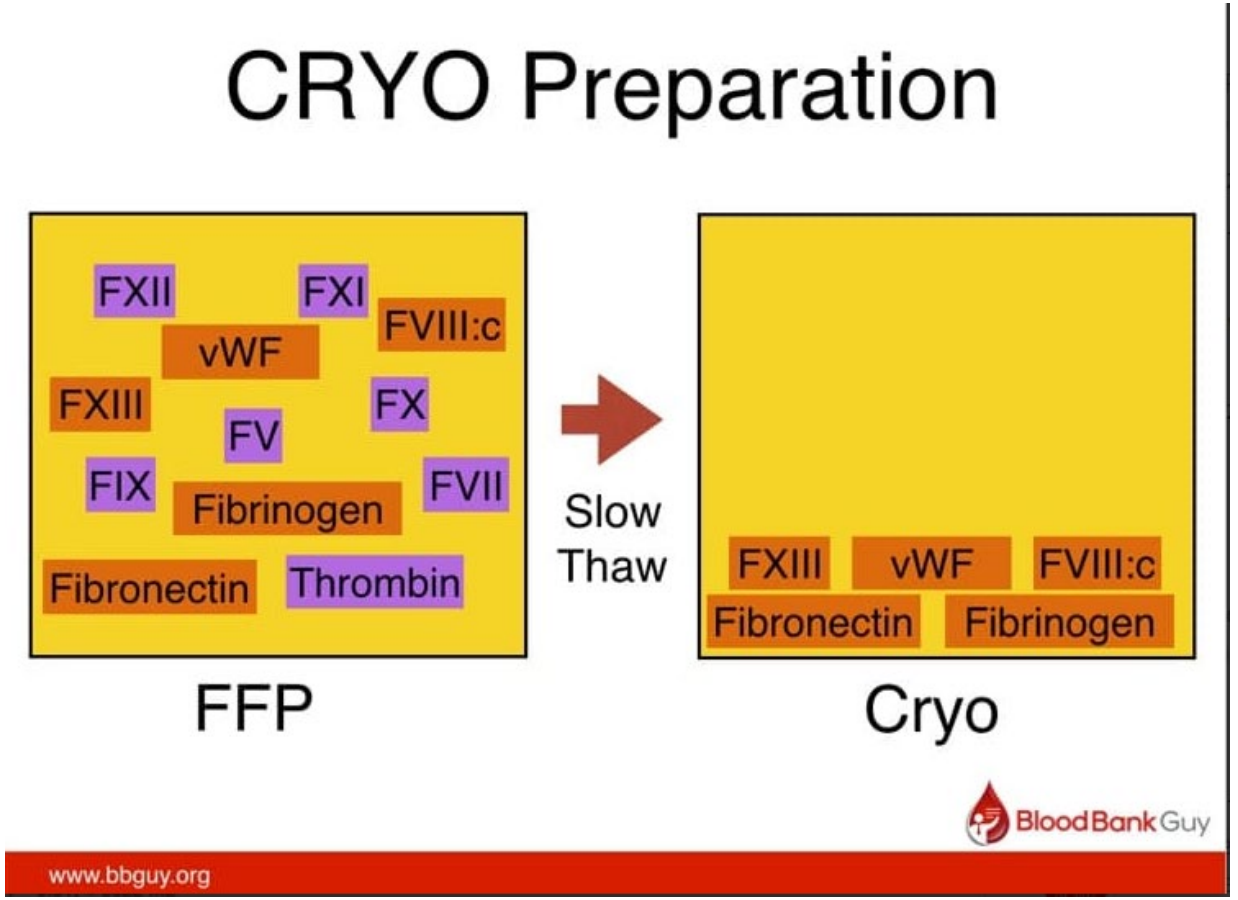
- All coagulation factors including fibrinogen
- 200-250ml volume/unit
- Dose: 10-15 mL/kg

Indication	Grade of recommendation
Liver disease with active bleeding	1C+
Warfarin reversal (If PCC unavailable)	1C+
DIC with active bleeding	1C+
Massive transfusions	1C+
Clotting factor deficiency in the absence of recombinant products	1C+
Plasmapheresis in TTP	1A+
Bleeding ppx/INR decrease prior to surgery/procedure*	2C
Volume expander	2C


% Coagulation Factors
100 %
50 %
30 %
20 %
10 %
Zone of Normal hemostasis
Zone of therapeutic anticoagulation
PT (sec) 12 13 15.5 19 21.8 24 30 32
INR 1.0 1.3 1.7 2.0 2.2 3.0

Cryoprecipitate

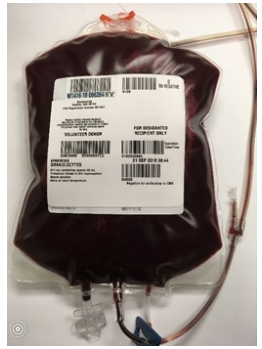
- Prepared by slowing thawing FFP in the cold
  - Insoluable precipitate: Factors VIII, XIII, vWF, fibronectin, **fibrinogen**



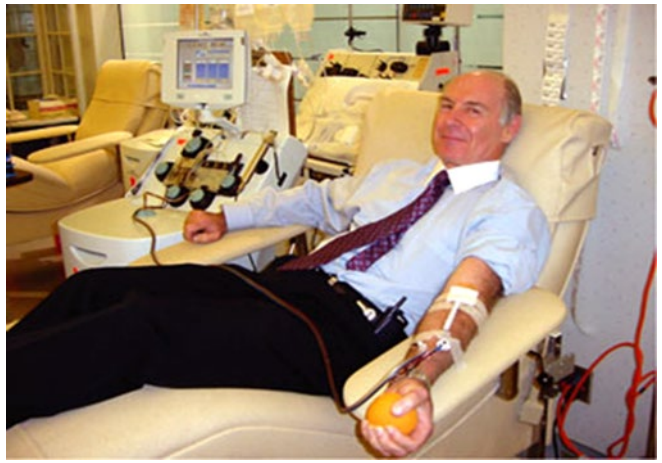
Cryoprecipitate

- Dosing
  - Dose: 1 unit/10 kilo will increase fibrinogen ~100 mg/dL
  - One cryoprecipiate bag/unit= 1 donor
  - One Cryoprecipiate pool= 5- 6 donor units
  - **Two Cryoprecipiate pools = ~ 1 adult patient dose**
- Indicated:
  - Hypofibrinogenemia (< 100 - 150 mg)
  - Disseminated Intravascular Coagulation (DIC)
  - Obstetrical bleeding

Granulocytes



- Unit:
  - > 1 x 10^{10} granulocytes
  - Shelf-life 24 hours
- Indicated
  - To treat severe and refractory fungal infections in neutropenic patients
  - Controversial efficacy due to underpowered studies
- Not indicated
  - To prevent infections in neutropenic patients



- ✓ A donor receives stimulation with steroids and/or G-CSF
- ✓ Granulocytes are collected through apheresis procedure (~ platelets)

Estcourt LJ,. Cochrane Database of Systematic Reviews 2016, Issue 4.

Adverse Reactions

slido

Please download and install the Slido app on all computers you use

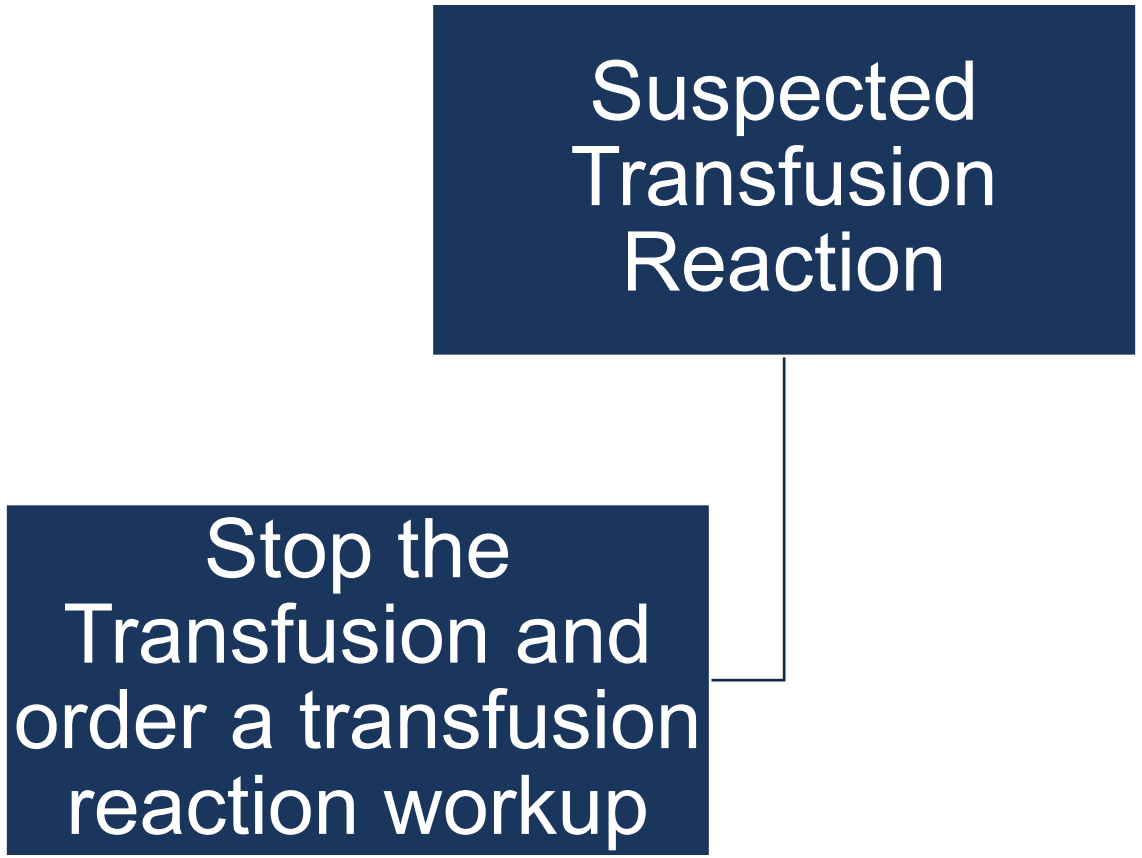
(5.06.05)
Which of the following is done in a transfusion reaction investigation? (select all that apply)

ⓘ Start presenting to display the poll results on this slide.

Which of the following is done in a transfusion reaction investigation? (select all that apply)

- **A) Stop the transfusion**
- **B) Clerical Check**
- **C) Return the unit to the blood bank**
- **D) Draw a post transfusion sample**
- E) Restart the unit once workup is negative

Transfusion Reaction Workflow



Transfusion Reaction Workup: Nursing Workflow

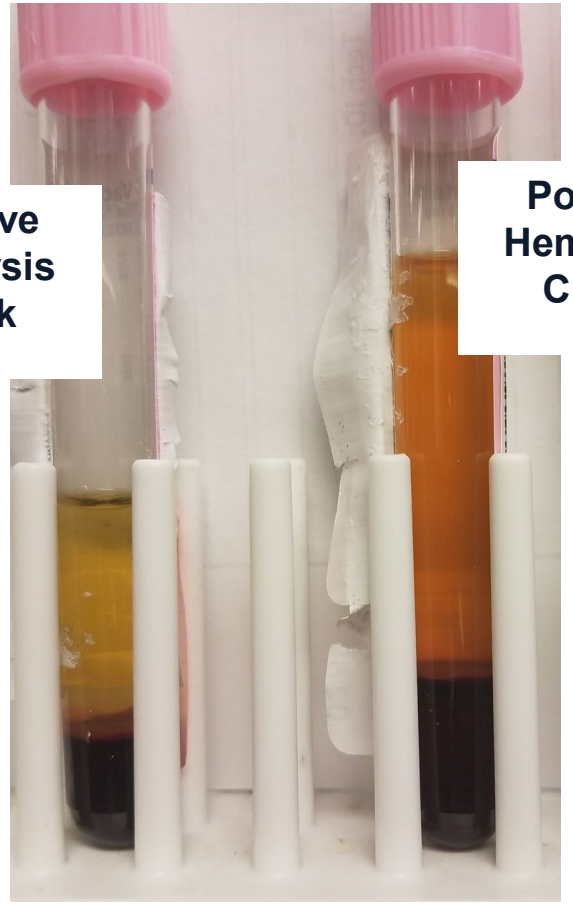
1. STOP transfusion but keep the IV open with IVF.
2. Notify Clinical Team
3. Monitor vital signs.
4. Clerical Check- right unit to right patient?
5. Notify the Blood Bank
6. Send a post-transfusion sample and remainder of unit/tubing
7. Document.

Transfusion Reaction Workup: Blood Bank Workflow

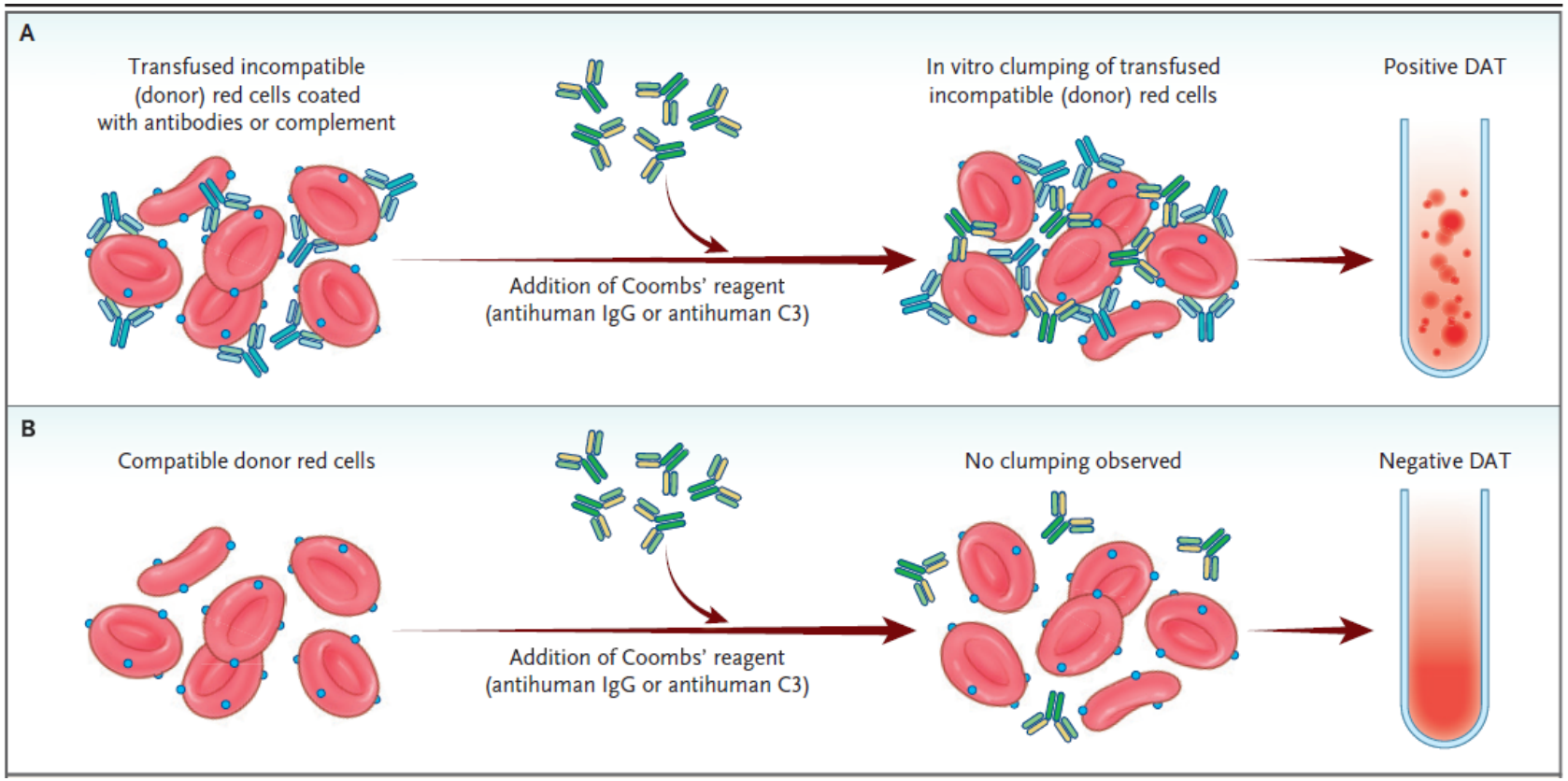
Clerical Check (Right unit for right patient?)

Post-Transfusion Sample

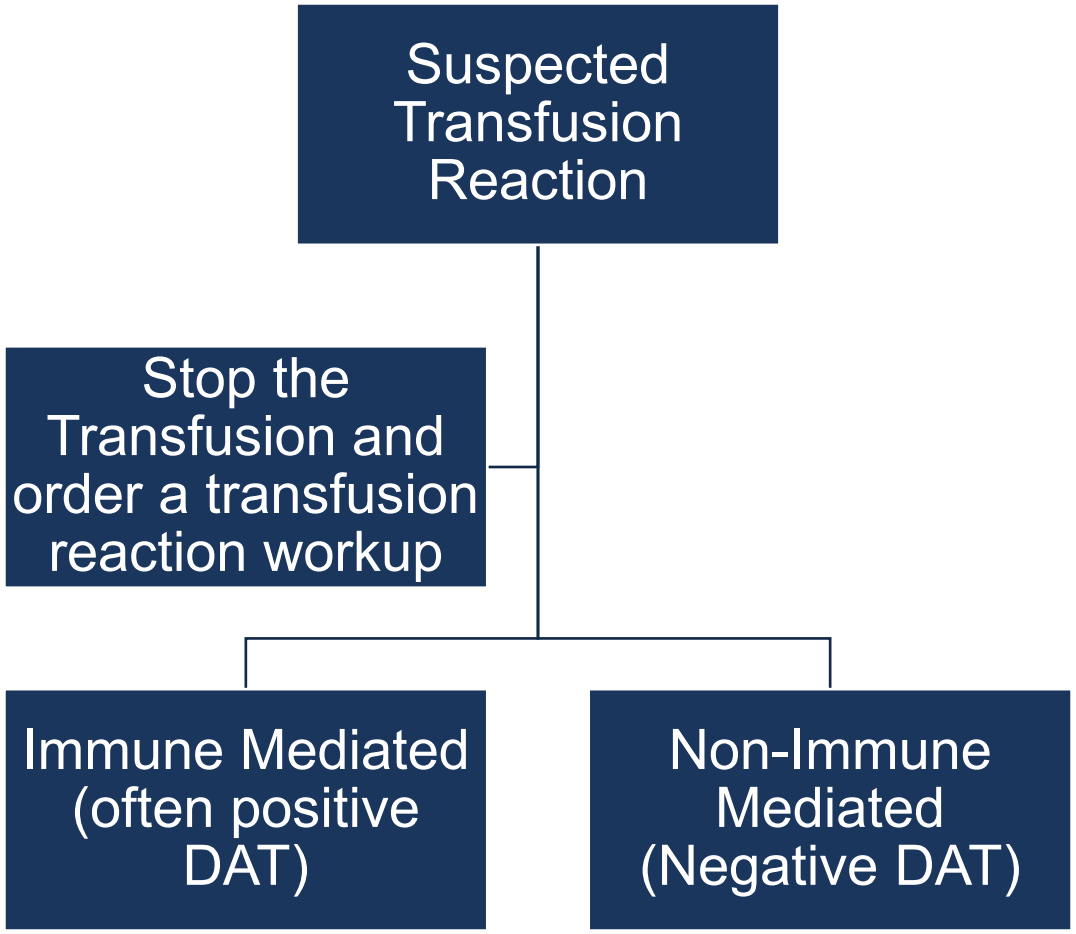
- Hemolysis check (hemoglobinemia, red plasma → intravascular hemolysis)
- Repeat ABO type (right sample sent for right patient?)
- Direct antiglobulin test (Coomb's test)



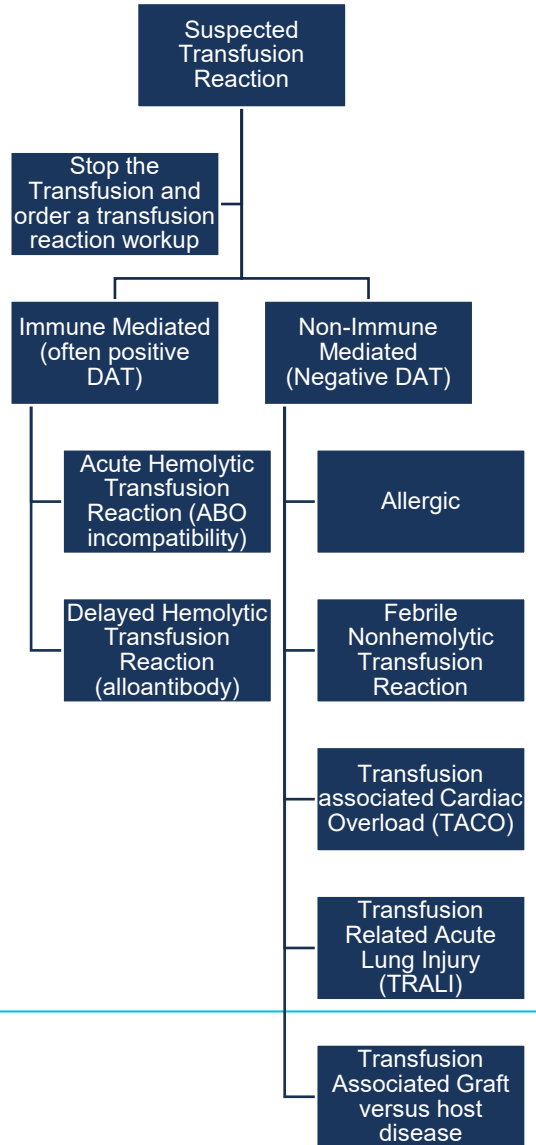
DAT (Direct Antiglobulin Test)



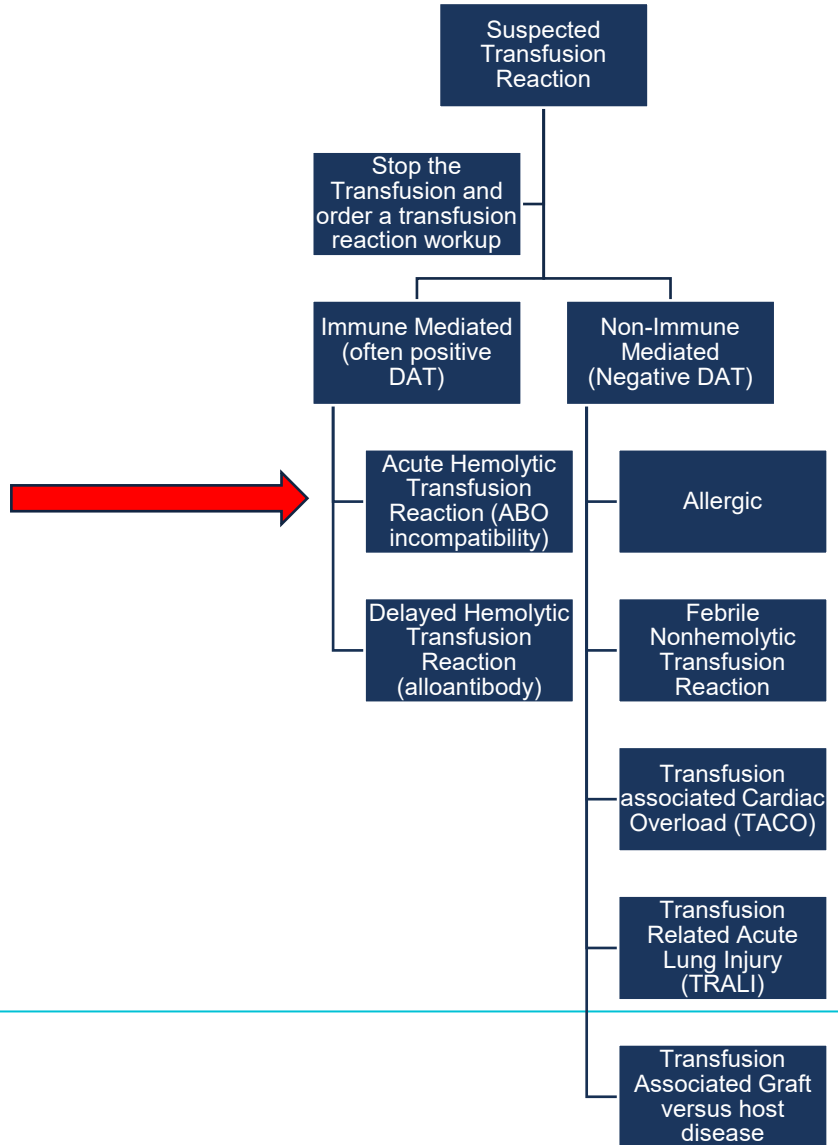
Transfusion Reaction Workflow



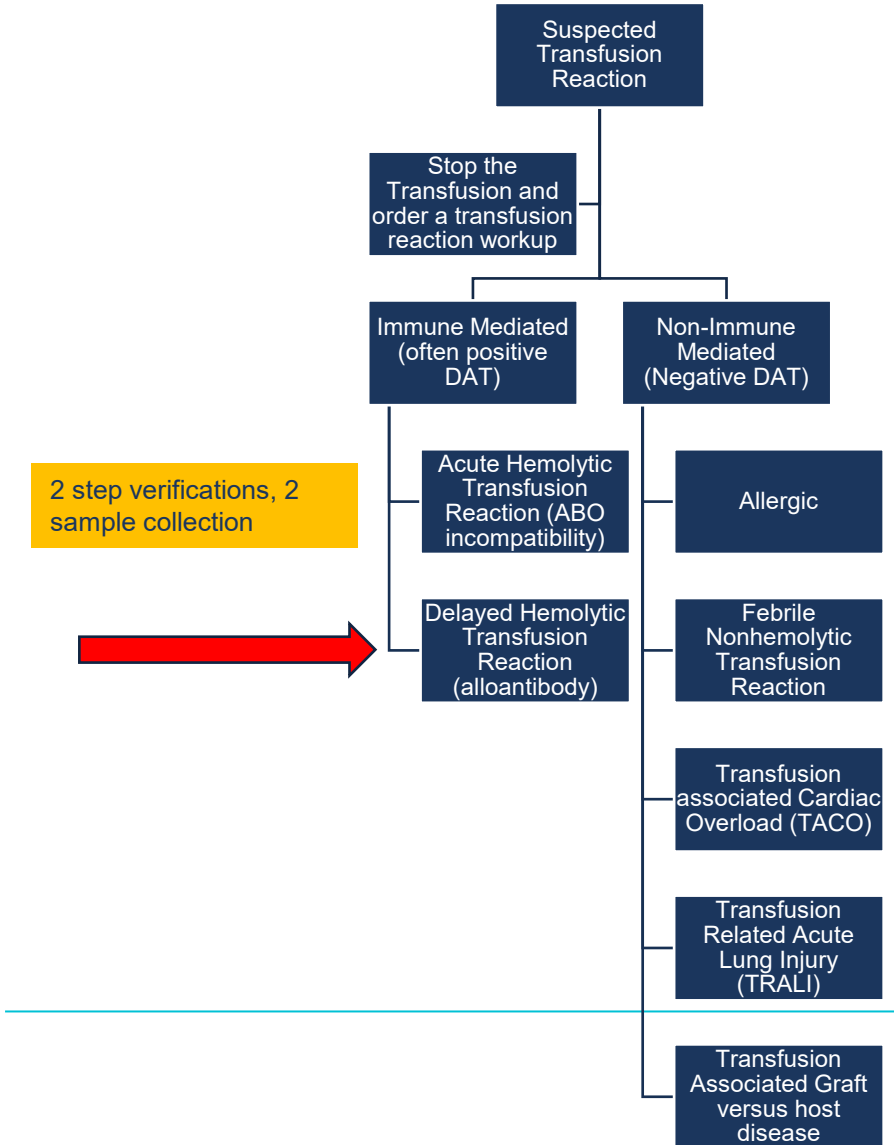
Transfusion Reaction Workflow



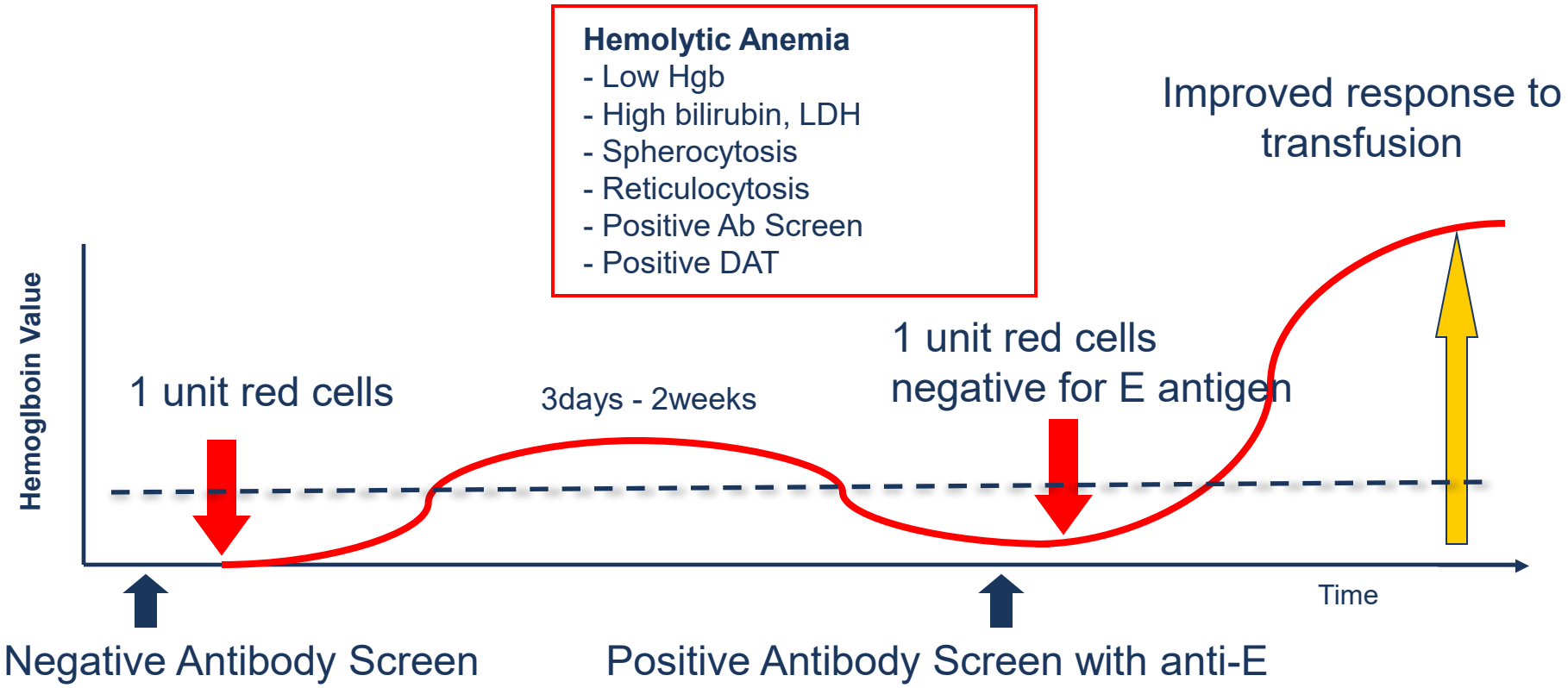
Transfusion Reaction Workflow



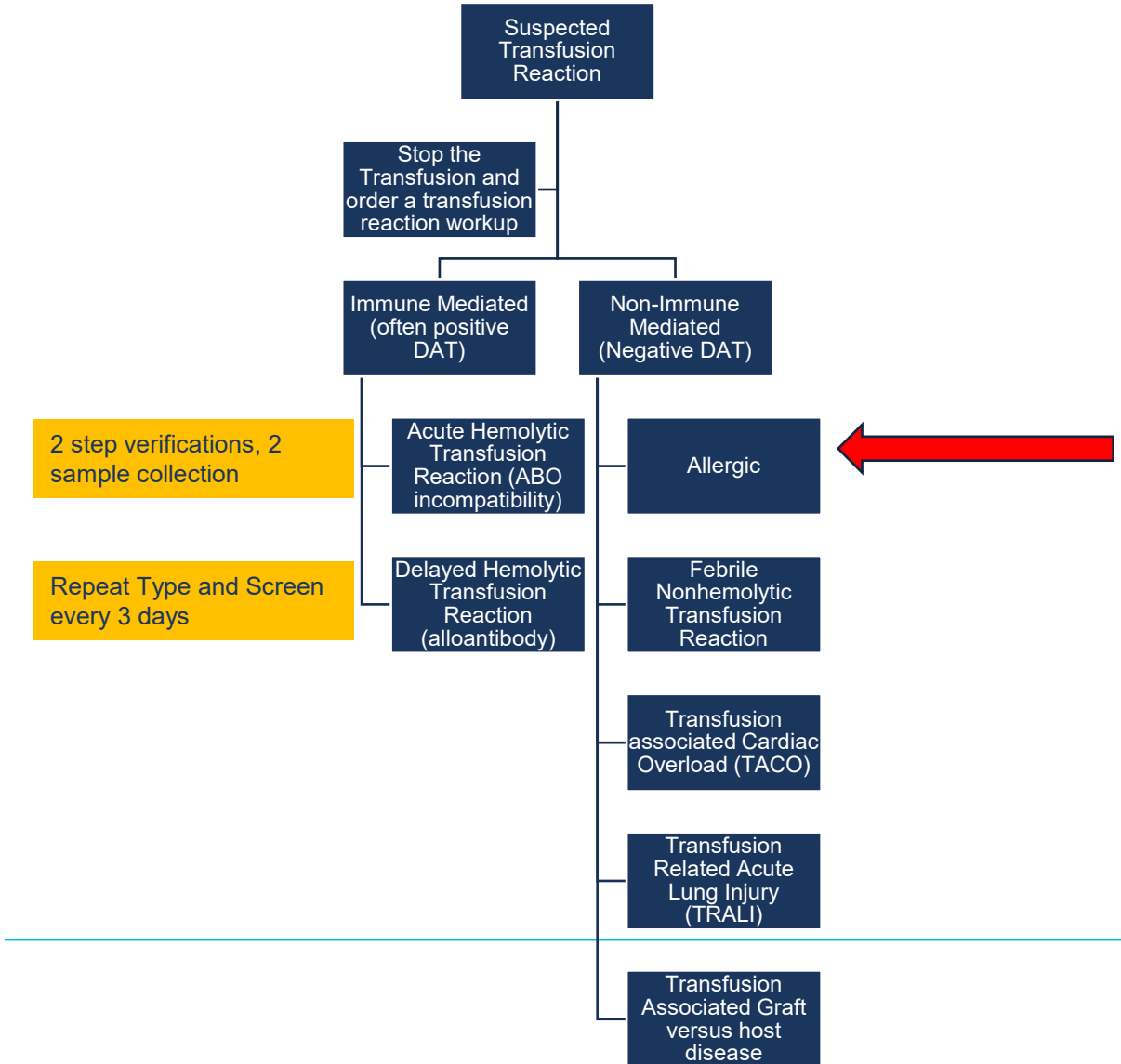
Transfusion Reaction Workflow



Delayed Hemolytic Transfusion Reaction (DHTR)



Transfusion Reaction Workflow



Allergic Transfusion Reactions

Urticarial reactions

- Unknown cause, though to be IgE-mediated or independent
- Symptoms: Mild, flushing, pruritis, urticaria
- Management:
  - Treat with anti-histamines
  - Ok to re-start transfusion at slower rate if symptoms subside or stabilize

Anaphylactic reactions

- IgE mediated histamine release in patient
- Symptoms: Severe, Hypotension, dyspnea, airway edema, anaphylaxis
- Management:
  - Requires emergent care
  - Epinephrine, corticosteroids, antihistamines, pressors and intubation if necessary

Preventing Allergic Transfusion Reactions

Things that are known to decrease risk of allergic reactions

- Less plasma in the product (Plasma > Platelets > RBC)
  - Volume Reduction (remove 2/3 of plasma)
  - Platelets in additive solution (replaces 2/3 of plasma)
  - Washing RBC + Platelets (remove > 99% of plasma)
    - A lot of resources, expiration < 24 hours

Things that have not been proven to decrease risk of allergic reactions

- Premedication with anti-histamines, steroids

Allergic Transfusion Reactions: Note on IgA Deficiency

THE JOURNAL OF AABB
transfusion.org
TRANSFUSION

COMMENTARY

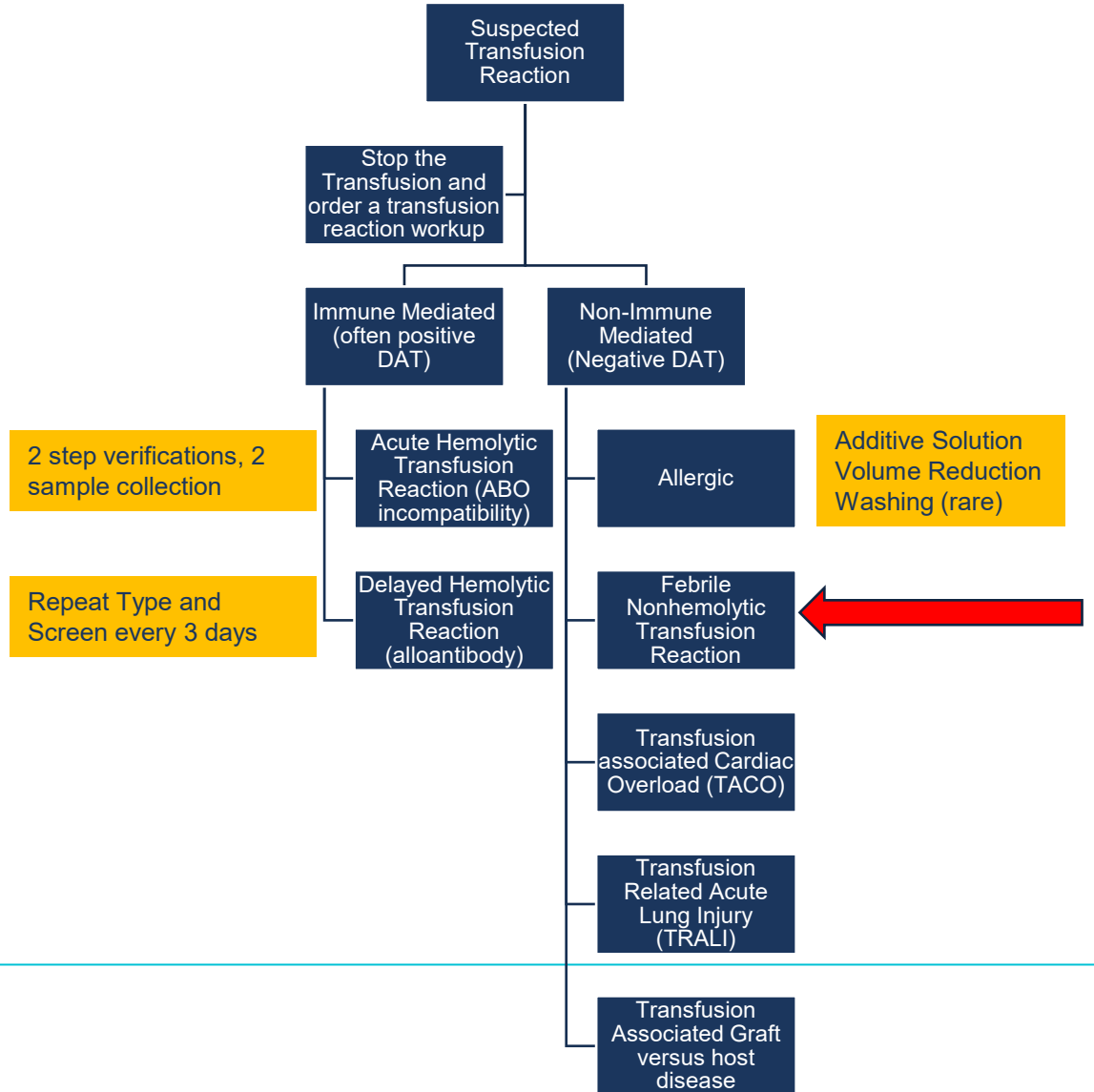
The entity of immunoglobulin A–related anaphylactic transfusion reactions is not evidence based

S. Gerald Sandler, Anne F. Eder, Mindy Goldman, Jeffrey L. Winters

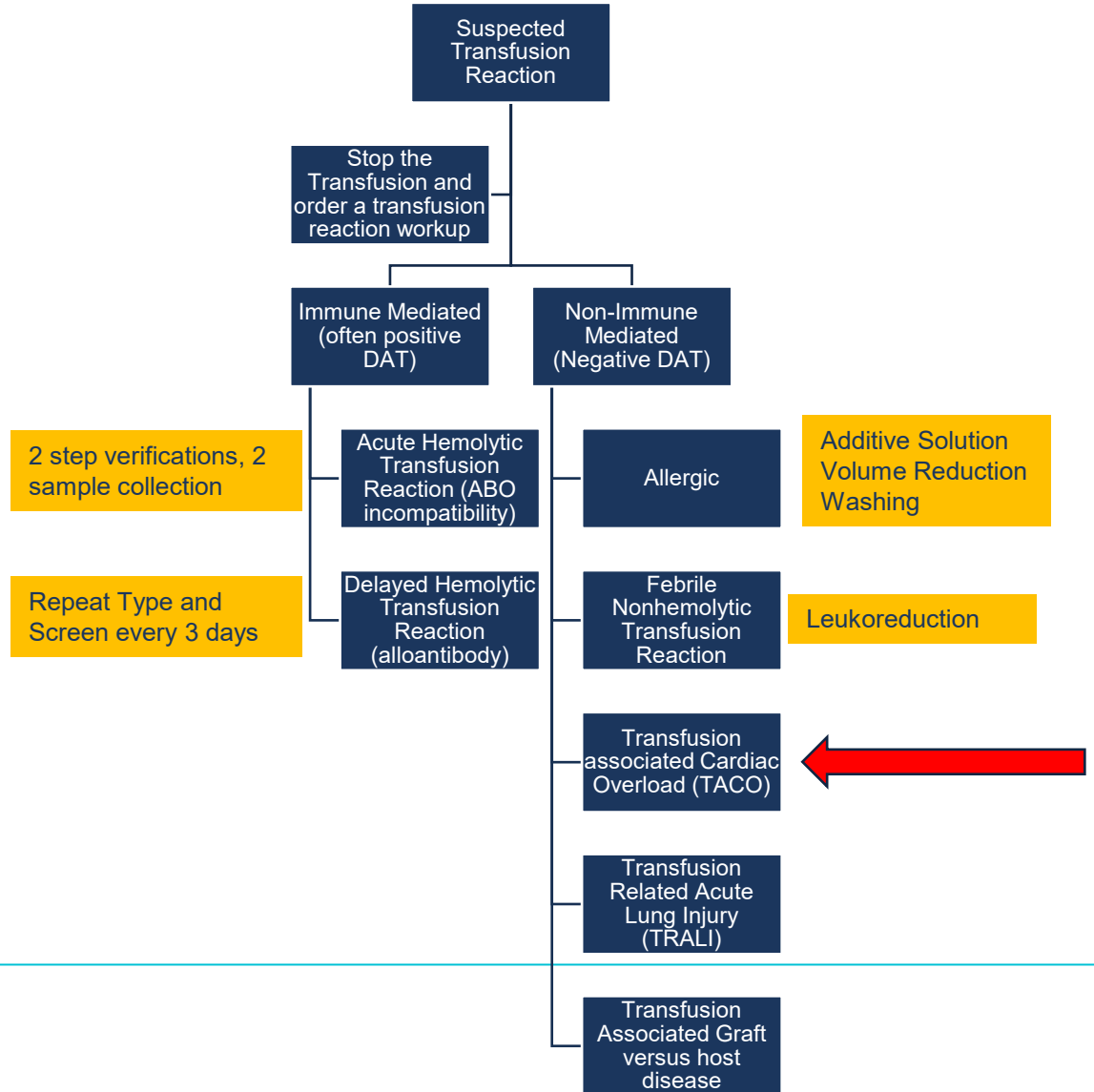
First published: 28 July 2014 | https://doi.org/10.1111/trf.12796 | Citations: 41

- Prevalence of IgA deficiency with anti-IgA ~ 1 in 1200 donors (American Red Cross)
- Assuming the same frequency of IgA deficiency with anti-IgA in transfused patients as donors, would expect at least 48 anaphylactic transfusion reactions from anti-IgA/day in the US
- Winters, et.al. - transfusion of 25 plt products from four IgA-deficient donors with class-specific high-titer anti-IgA --> 22 recipients w/o IgA deficiency
  - no allergic or anaphylactic reactions in patients receiving platelet products from these donors

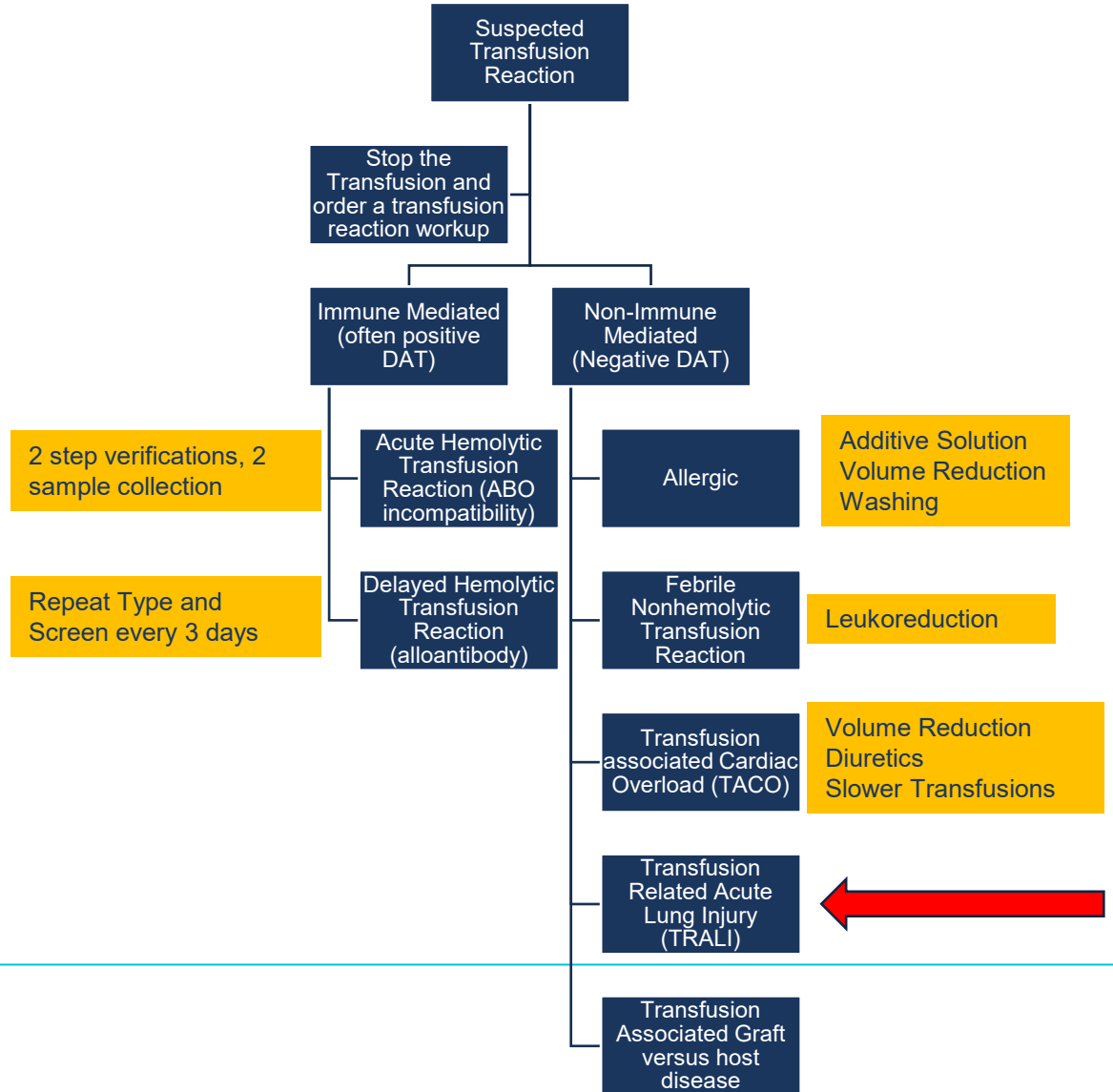
Transfusion Reaction Workflow



Transfusion Reaction Workflow

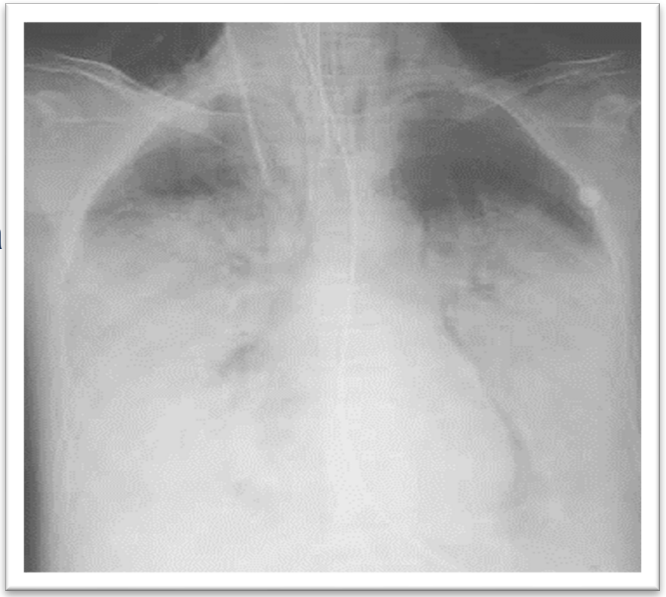


Transfusion Reaction Workflow

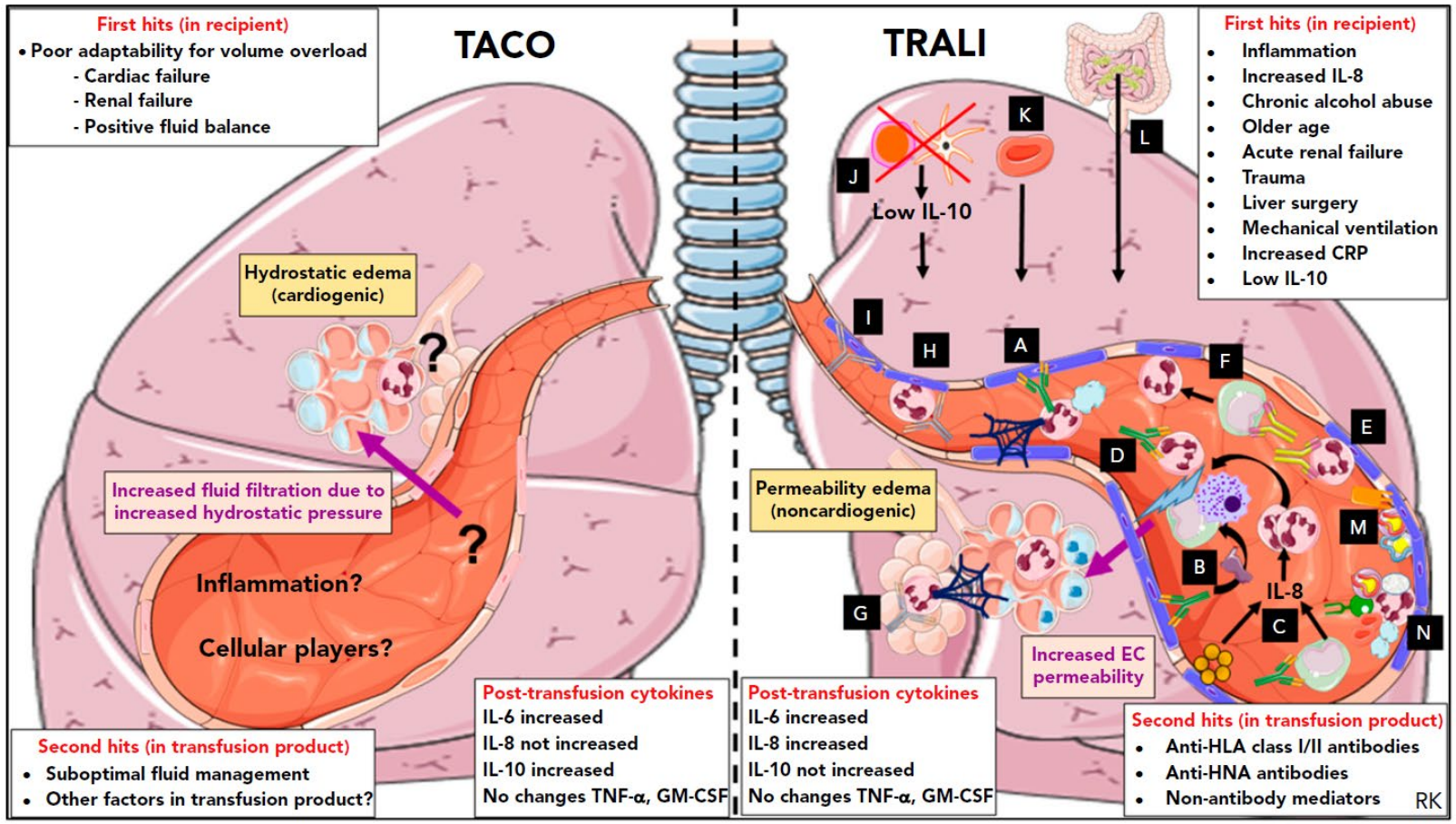


Transfusion Related Acute Lung Injury (TRALI)

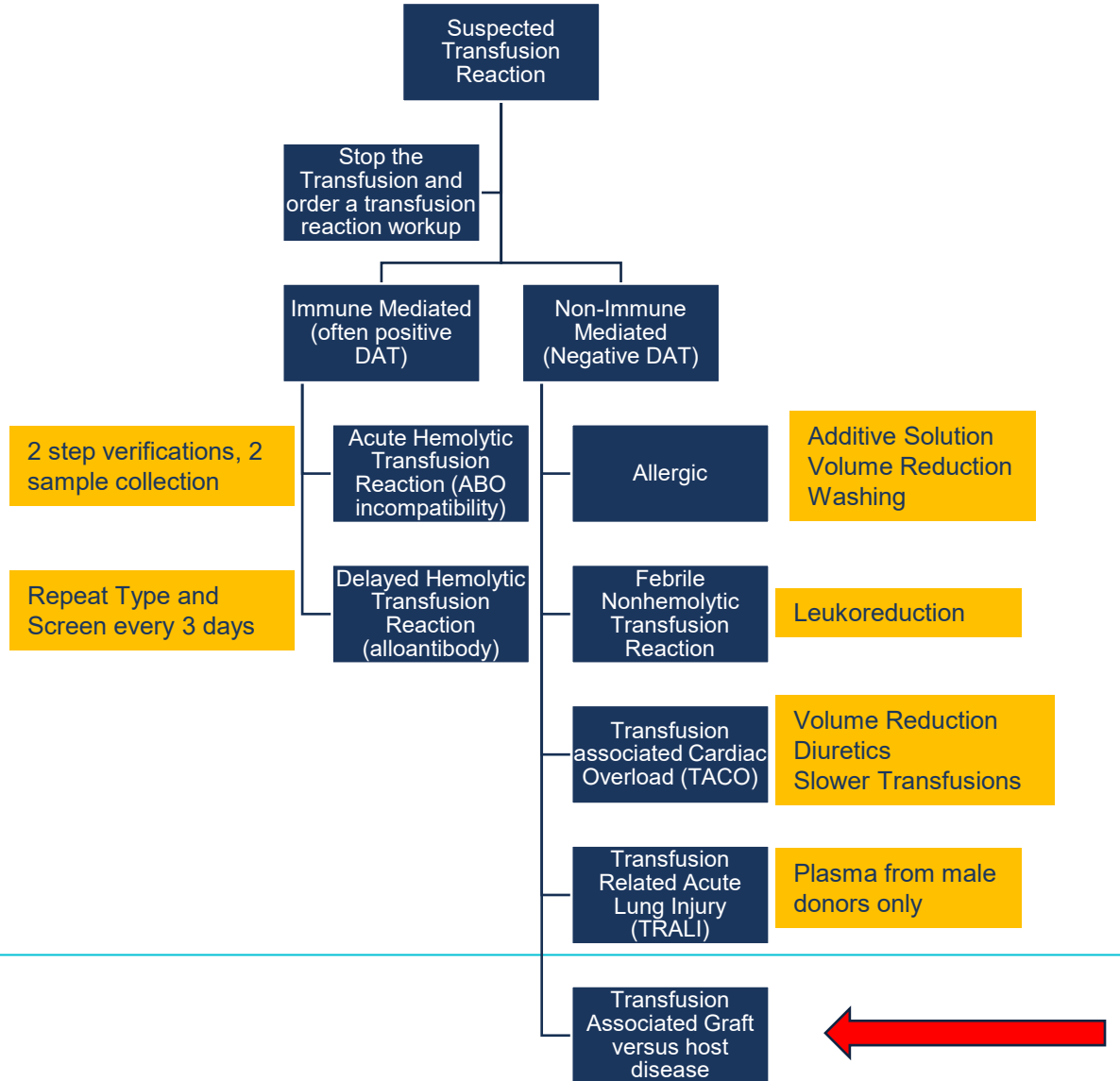
- Acute respiratory distress syndrome (ARDS) within 6h of transfusion
- Cause: not well understood
  - donor HLA and HNA antibodies
  - Lipid activations of neutrophils in donor plasma
- Clinical findings: respiratory symptoms, chest x-ray findings (bilateral pulmonary edema
- Treatment:
  - supportive care, improve after 72 hours, 5-10% mortality
- Prevention:
  - Use of plasma from male donors only (lower incidence of HLA/HNA antibodies)



Blood Component Risks: TACO vs. TRALI



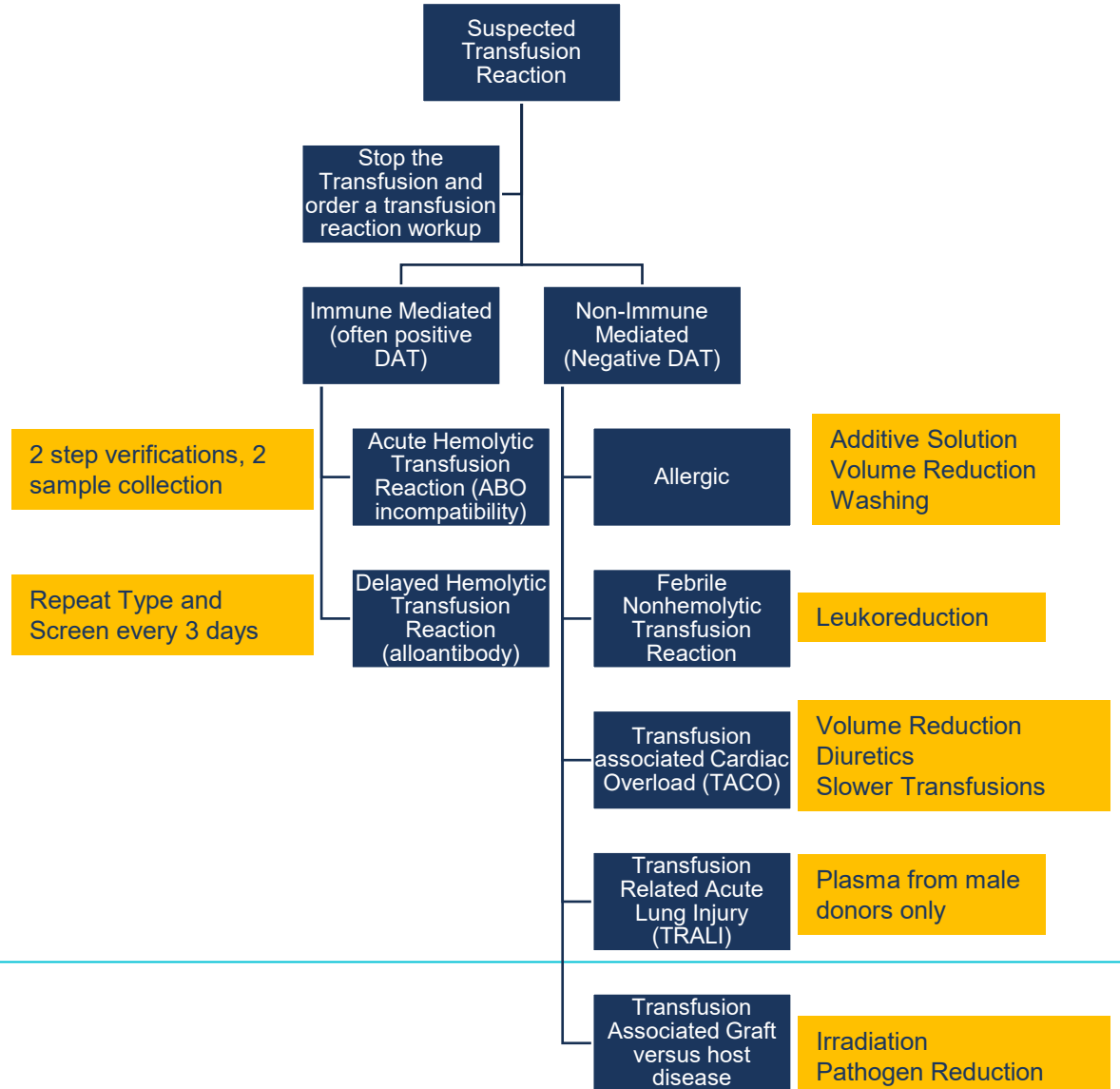
Transfusion Reaction Workflow



Transfusion Associated Graft Versus Host Disease (TA-GVHD)

- Risk Factors: Patient with decreased T cell response to attack donor lymphocytes
  - Hematologic malignant
  - Bone marrow transplant
  - High dose chemotherapy
  - Premature infants
  - Immunodeficiencies
  - Patients and donors with shared HLA antigens
    - Directed donations from blood relatives
- Most people are not at risk!

Transfusion Reaction Workflow



Team Bios

Rida Hasan

Associate Medical Director, Transfusion Services

Clinical interests include: Pediatric hematology, transfusion support for neonatal patients, immune hemolytic anemias

Current research projects: Evaluation the utility of DAT in cord blood testing

Fred Hutch
Cancer Center

Thank you