TRANSFUSION MEDICINE UPDATE & REVIEW – TOO MUCH OF A GOOD THING?

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DISCLOSURES

No Disclosures/Conflicts of interest

OVERVIEW

- Brief overview of history of transfusion medicine
- Review of blood product manufacturing
- Review of benefits of specific blood components
- Overview of infectious risk
- Transfusion reaction recognition and treatment
- ASH Choosing Wisely Campaign

TRANSFUSION

- Every two seconds someone in the U.S. needs blood
- Approximately 7,000 units of platelets and 10,000 units of plasma are needed daily
- Nearly 21 million blood components are transfused annually in the U.S.
- ~ 85 million units of RBC are transfused annually worldwide

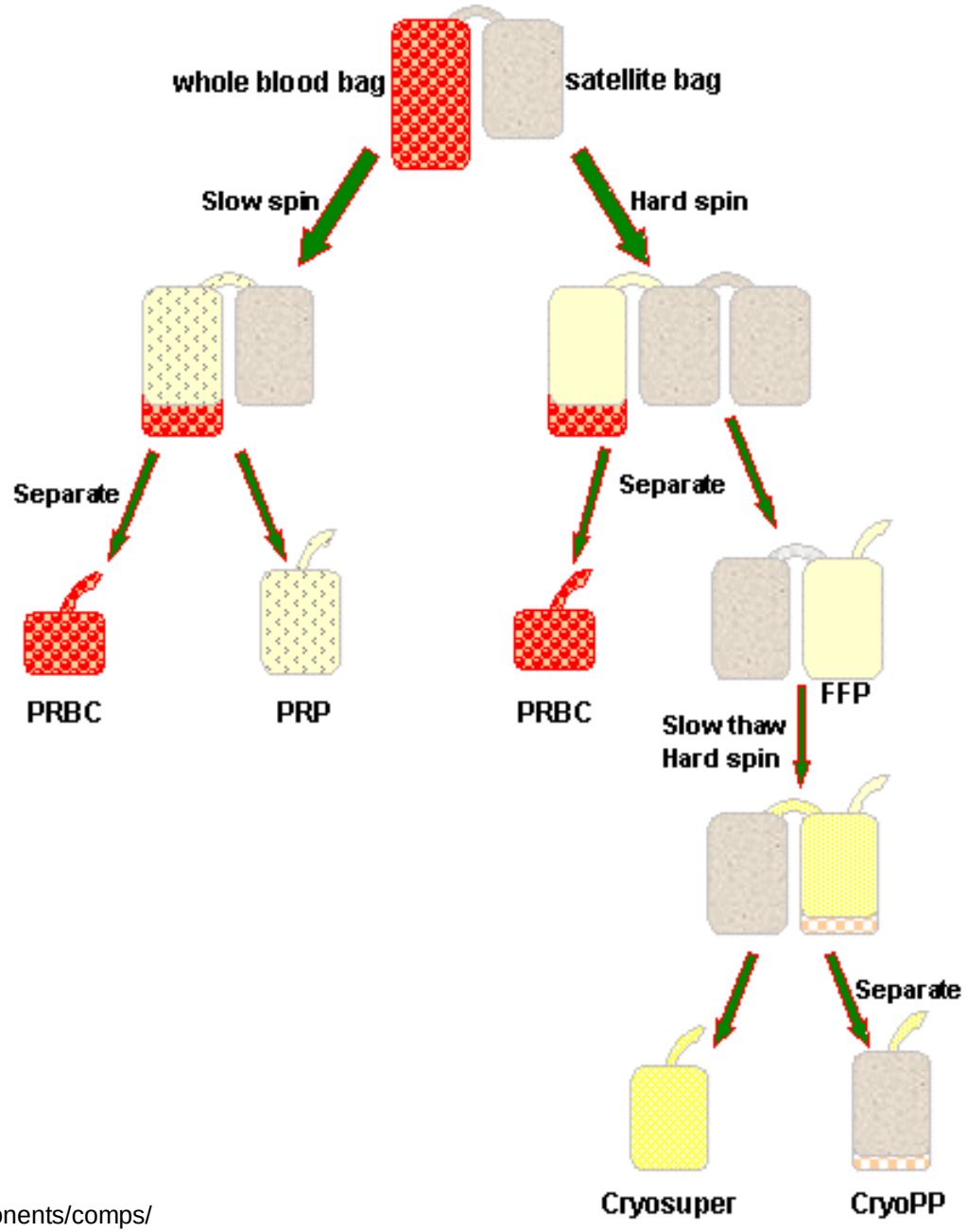
HISTORY OF TRANSFUSION

- 1628 Dr. William Harvey
- 1st animal to animal transfusion February 1665
- Animal to human transfusions 1667 ended poorly
- 1st documented transfusion with human blood September 26, 1818 by Dr. James Blundell
- 1900 Karl Landsteiner identifies blood groups

HISTORY OF TRANSFUSION

- 1914 Long term anticoagulants developed
- 1916 Francis Rous and J.R. Turner introduce citrate-glucose solution
- 1917 – 1st successful blood depot established during World War I
- Today

BLOOD PRODUCT MANUFACTURING



http://www.eclinpath.com/hemostasis/transfusion-medicine/components/comps/

Table 1. Contents of Anticoagulant-Preservative Solutions*

Anticoagulant-Preservative (g/L)	Trisodium Citrate	Citric Acid	Monobasic Sodium Phosphate	Dextrose	Adenine	Shelf Life
Anticoagulant citrate-dextrose A (ACD-A)†	22.0	8.0	0	24.5	0	21 days
Citrate-phosphate dextrose (CPD)	26.3	3.27	2.22	25.5	0	21 days
Citrate-phosphate-dextrose-dextrose (CP2D)	26.3	3.27	2.22	51.1	0	21 days
Citrate-phosphate-dextrose-adenine (CPDA-1)	26.3	3.27	2.22	31.9	0.275	35 days

*63 mL/450 mL collection, 70 mL/500 mL collection
†ACD is used for apheresis components.

Table 1: Storage Details for Various Blood Products			
Product	**Storage**	**Product**	**Storage**
RBCs / Whole blood	21 days (CPD/2D) 35 days (CPDA-1) 42 days (AS) All @ 1-6 C	**Granu-locytes**	24 hrs @ 20-24 C (no agitation)
Frozen RBCs	10 years @ –65 C 24 hours @ 1-6 C after thaw	**Frozen Plasma (FFP, PF24 etc.)**	1 year @ –18 C 7 years @ –65 C; 24 hours at 1-6 C after thaw
Washed RBCs	24 hours @ 1-6 C		
Platelets	5 days @ 20-24 C (gentle agitation); 4 hours if pooled in open system	**CRYO**	1 year @ –18 C 6 hours @ 20-24 C after thaw (4 hrs if pooled in open system)

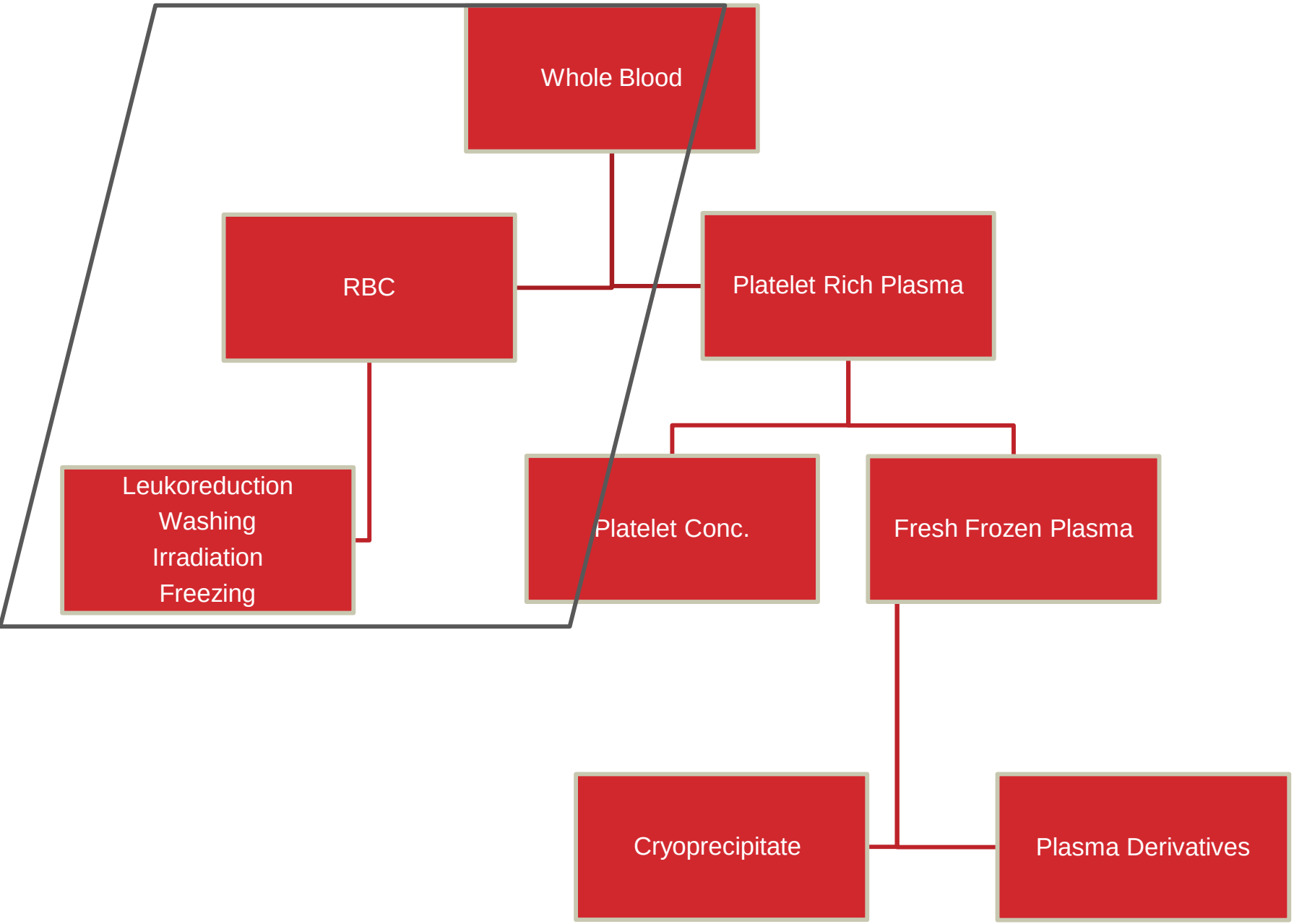
BLOOD PRODUCT ADMINISTRATION

American Society of Hematology Guidelines

American Society of Hematology Choosing Wisely Campaign

American Society of Anesthesiology

American Association of Blood Banks


Whole Blood
RBC
Platelet Rich Plasma
Leukoreduction
Washing
Irradiation
Freezing
Platelet Conc.
Fresh Frozen Plasma
Cryoprecipitate
Plasma Derivatives

WHOLE BLOOD

- **Minimal availability**
- **Potential Indications:**
  - Massive blood loss
  - Autologous transfusions

Volume:	450-500 mL
Contents:	RBCs (200-250 mL)
	Plasma (250-300 mL)
	WBCs (10^9)
	Platelets
	Anticoagulant (63 or 70 mL)

COW BITT

A Randomized Controlled Pilot Trial of Modified Whole Blood Versus Component Therapy in Severely Injured Patients…

Article *in* Annals of surgery · August 2013

DOI: 10.1097/SLA.0b013e3182a4ffa0 · Source: PubMed

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21 code of federal regulations [CFR] 50.24). Primary outcome was 24-hour transfusion volumes.

Results: A total of 107 patients were randomized (55 mWB, 52 COMP therapy) over 14 months. There were no differences in demographics, arrival vitals or laboratory values, injury severity, or mechanism. Transfusions were similar between groups (intent-to-treat analysis). However, when excluding patients with severe brain injury (sensitivity analysis), WB group received less 24-hour RBC (median 3 vs 6, $P = 0.02$), plasma (4 vs 6, $P = 0.02$), platelets (0 vs 3, $P = 0.09$), and total products (11 vs 16, $P = 0.02$).

Conclusions: Compared with COMP therapy, WB did not reduce transfusion volumes in severely injured patients predicted to receive massive transfusion. However, in the sensitivity analysis (patients without severe brain injuries), use of mWB significantly reduced transfusion volumes, achieving the prespecified endpoint of this initial pilot study.

RED BLOOD CELLS

Volume:	350 mL (incl. additive)
Contents:	RBCs (200-250 mL)
	Plasma ($\leq$ 50 mL)
	WBCs (10^9) and PLTs
	Anticoagulant (63 or 70 mL)
	Additive solution
	200-250 mg iron

MODIFICATION OF RBC AND PLATELETS

- Leukocyte reduced products
- Washed products
- Frozen products
- Irradiated products

LEUKOCYTE REDUCTION OF RBC

- Use leukocyte reduction filters

- **Benefits:**
  - Prevention of febrile nonhemolytic transfusion reactions
  - Prevention of HLA immunization
  - Prevention of CMV transmission
  - Reduction of reperfusion injury post cardiac bypass
  - Does NOT prevent transfusion associated graft-versus-host disease (TA-GVHD)

BLOOD. 1995;86,3598-3603 “The Bowden Study”

WASHED RBC

- Shelf life: RBC 24 hrs post wash at 1-6C, 4hrs at 20-24C
- May lose 20% of red cells in washing process

- **Benefits:**
  - Decreases risk of anaphylaxis (IgA deficiency with anti-IgA antibodies)
  - Removal of unwanted antibodies
  - Removal of unwanted electrolytes

FREEZING RBC

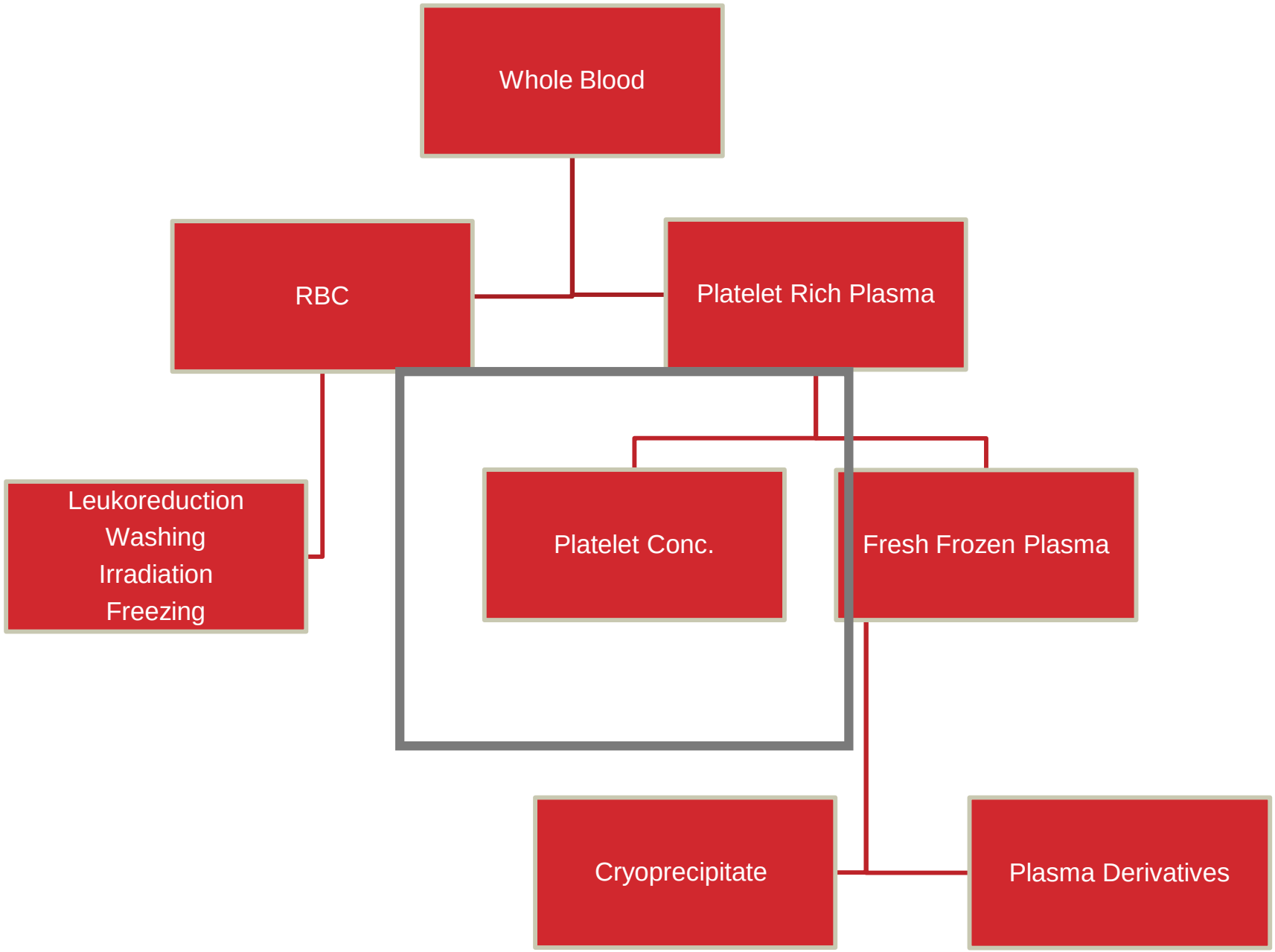
- 10 years at -65C
- 24 hours at 1-6C after thawing/deglycerolizing

- **Benefits:**
  - Storage of rage, autologous, O-negative units
  - Plasma hypersensitivities

IRRADIATION OF RBC

- Deactivation of lymphocytes and prevention of transfusion associated graft vs. host disease (TAGVHD)
- Shelf life: up to 28 days

- **Indication for irradiation:**
  - Immunosuppression
  - Hematologic malignancies
  - Intrauterine transfusion
  - Blood from 1st degree relative or HLA matched unit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PLATELETS

- Platelets do not require pretransfusion crossmatches
- ABO incompatible platelets commonly given
- RhD antigens not present on platelets
  - * May be present on RBCs contained in platelet product
- Storage: 5 days at 20-24C
- **Adults – 1 single donor apheresis unit usually increases platelet count by 25K-35K/µL**

TABLE 61-5 CORRELATION BETWEEN PLATELET COUNT AND INCIDENCE OF BLEEDING

Platelet Count (cells/mm³)	Total No. Patients	No. Patients with Bleeding
>100,000	21	0
75,000-100,000	14	3
50,000-75,000	11	7
<50,000	5	5

Data from Miller RD, Robbins TO, Tong MJ, et al: Coagulation defects associated with massive blood transfusions, Ann Surg *174:794, 1971.*

	Pooled concentrates from whole blood (from 5-6 units)	Single donor apheresis concentrates
Platelet number	$3.0\text{-}4.0 \times 10^{11}$	$3.0\text{-}6.0 \times 10^{11}$
Leukocytes	4×10^{8}	10^{7}
Red cells	< 2 ml	rare
Volume (ml)	225-275	225-275
Donor exposure	5-8	1
Donor available	High	Low
Matching potential	No	Yes
Cost	Moderate	High

LEUKOCYTE REDUCTION OF PLATELETS

- **Prevention of:**
  - HLA alloimmunization
  - CMV infection
  - Febrile nonhemolytic transfusion reactions
  - Reduction of reperfusion injury post cardiac bypass

- Does not prevent transfusion associated GVHD

IRRADIATION PLATELETS

- **Prevention of Transfusion Associated GVHD**
  - Only cellular products require irradiation (RBC, platelets)

HSCT	Leukemia
Lymphoma	Multiple Myeloma
Solid tumor with high intensity chemotherapy	Fludarabine therapy
Congenital deficiency of cellular immunity	Intrauterine Transfusion
Prematurity	Erythroblastosis Fetalis
Recipients of HLA matched donations	Recipients of granulocyte transfusions

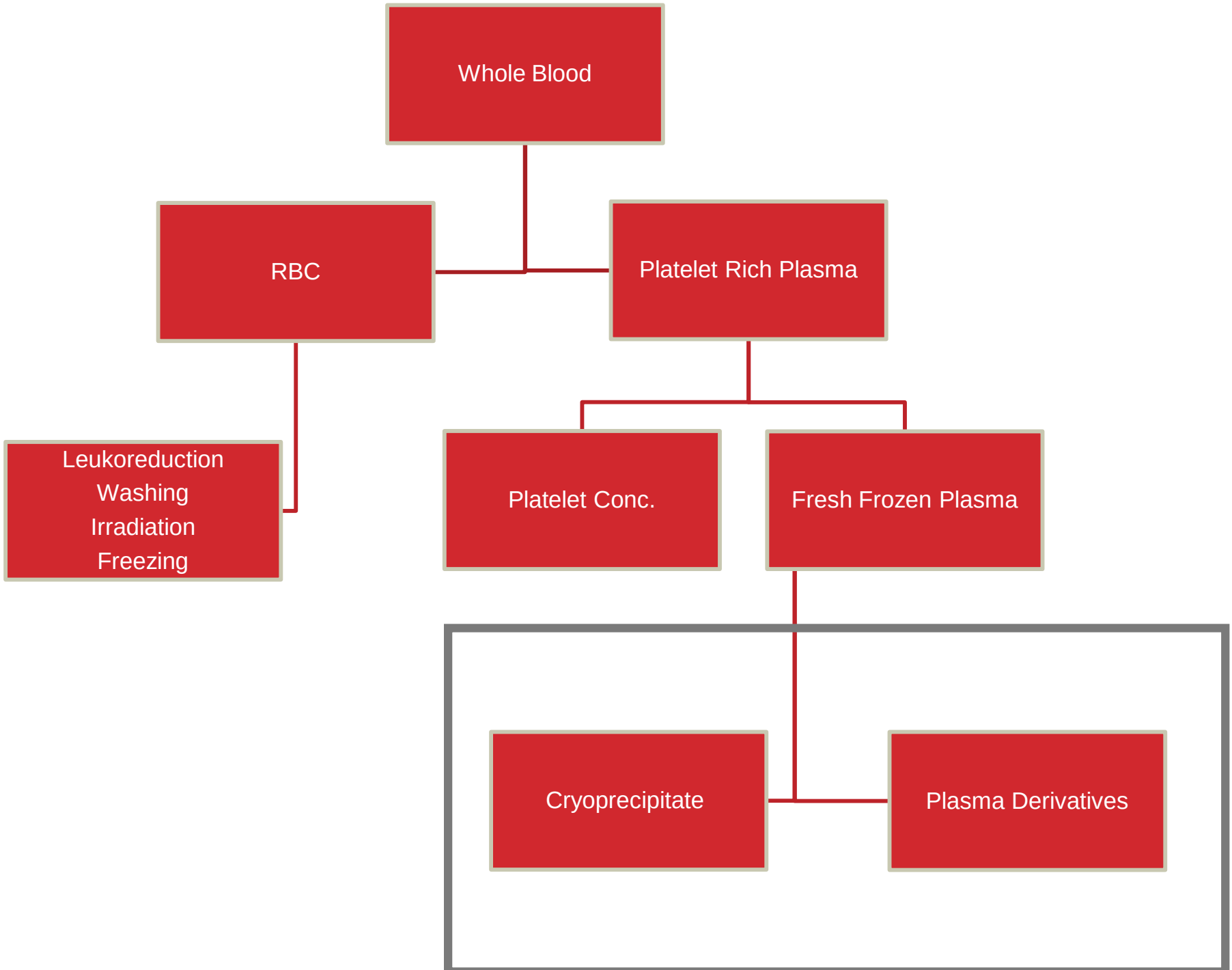
WASHED PLATELETS

- Shelf life: 4 hours post wash

- **Benefits:**
  - Removal of plasma proteins for hypersensitivity
  - Neonatal allo-immune thrombocytopenia (NAIT)
  - Removal of unwanted electrolytes

VOLUME REDUCED PLATELETS

- **Removal of a portion of the plasma associated with platelets**
  - 2 scenarios may necessitate:
    - Neonates
    - Highly volume sensitive adult patients
  - 20% platelets lost during this process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CRYOPRECIPITATE

- Able to deliver large amounts of fibrinogen in a small volume

- **Use:**
  - Fibrinogen deficiency
  - Uremic thrombocytopathy
  - Preparation of fibrin glue
  - When fibrinogen levels are below 100mg/dl

Volume:	15 mL
Contents:	≥ 150 mg fibrinogen
	≥ 80 IU Factor VIII
	80-120 IU vWF
	40-60 IU Factor XIII
	Fibronectin

FRESH FROZEN PLASMA

- May be frozen within 8 hours of collection (Fresh Frozen Plasma) or within 24 hours of collection (FP)
- Standard dose increases levels by 20-30%
- Will not help if INR <1.5-1.6

Volume:	200-250 mL
Contents:	All coag factors - 400 mg fibrinogen - 1 IU/mL of all others Almost no viable WBCs NOTE: No QC testing

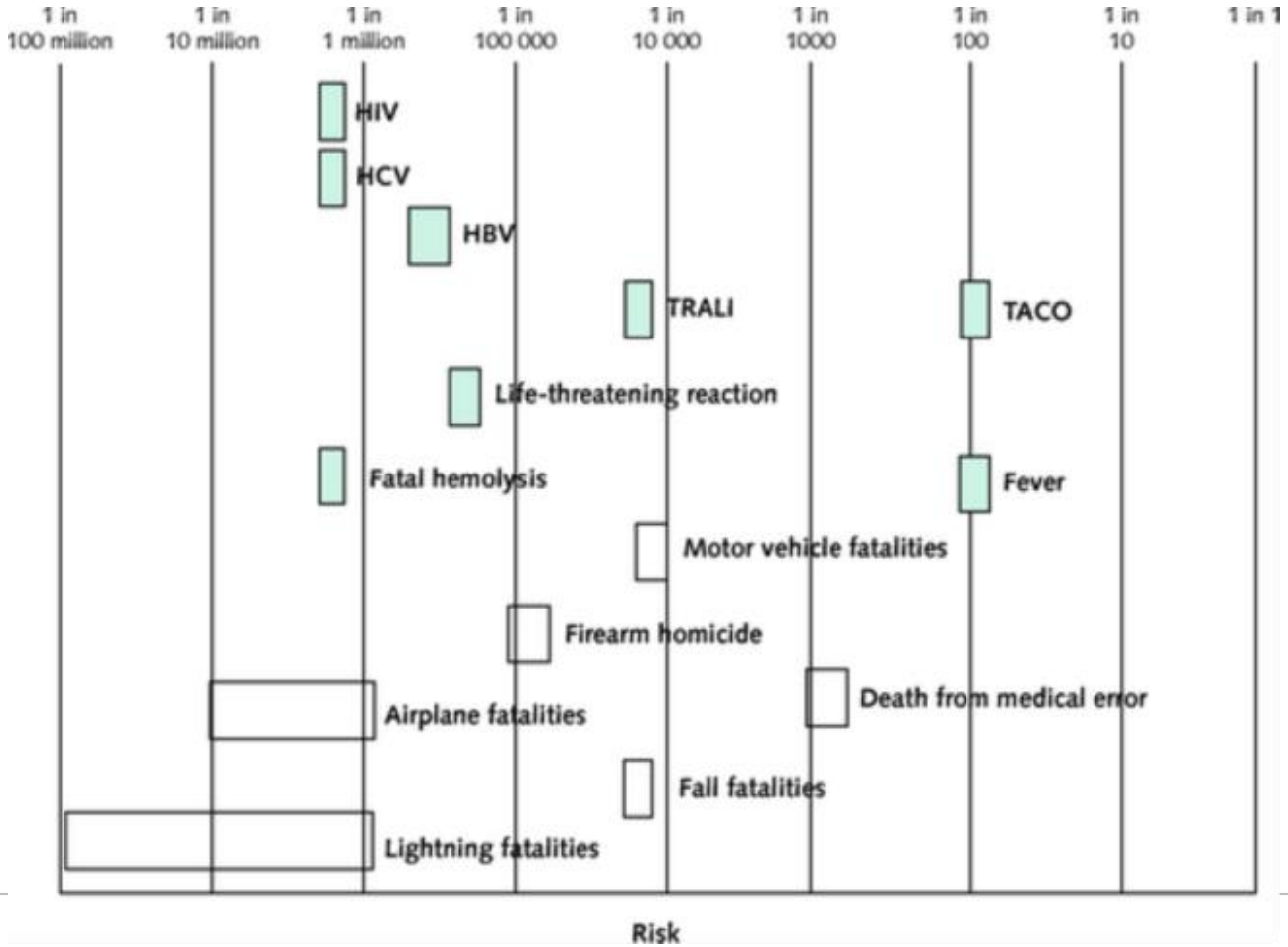
TRANSFUSION REACTIONS

Presenting *With* Fever	
Acute	**Delayed**
Acute Hemolytic Febrile Nonhemolytic Transfusion-related Sepsis TRALI	Delayed Hemolytic TA-GVHD
Presenting *Without* Fever	
Acute	**Delayed**
Urticarial Anaphylactic Anaphylactoid TACO Acute Pain Reaction	Post-transfusion Purpura Iron Overload

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

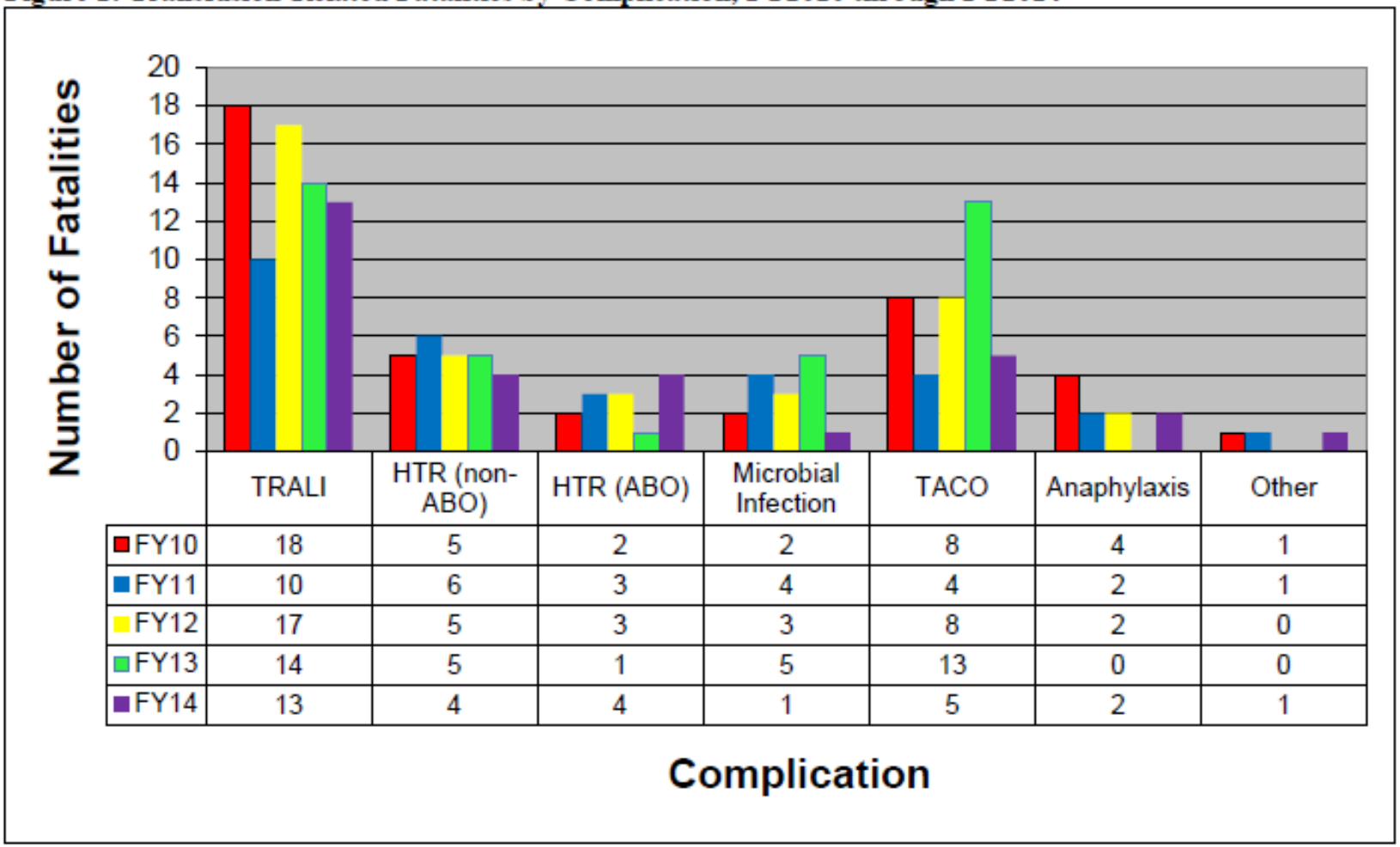
From: Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB*

Ann Intern Med. 2012;157(1):49-58. doi:10.7326/0003-4819-157-1-201206190-00429



TRANSFUSION RELATED FATALITIES BY COMPLICATION 2010-2014

Figure 1: Transfusion-Related Fatalities by Complication, FY2010 through FY2014



	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY10	18	5	2	2	8	4	1
FY11	10	6	3	4	4	2	1
FY12	17	5	3	3	8	2	0
FY13	14	5	1	5	13	0	0
FY14	13	4	4	1	5	2	1

Federal Drug Administration report 2014

Table 2: Fatality Complication Breakdown by Imputability FY2015

CATEGORY	Definite/ Certain	Probable/ Likely	Possible	Doubtful/ Unlikely/ Improbable	Ruled Out/ Excluded	Not Determined/ Assessable/ Evaluable	TOTAL
Transfusion							
Allergy/Anaphylaxis	2	-	-	-	-	-	**2**
Contamination (Bacterial)	3	-	2	-	-	-	**5**
HTR (ABO)	2	-	-	-	-	-	**2**
HTR (non-ABO)	2	1	1	1	-	-	**5**
Hypotensive Reaction[18]	-	1	-	1	-	-	**2**
TACO	3	6	2	-	-	1	**12**
TRALI	5	N/A*	7	1	1	-	**14**
Donation							
Donor Fatality	-	-	1	12	5	2	**20**

*Definitions based on the Canadian Consensus Conference Panel on TRALI.[22,23]

Table 3: Transfusion-Associated Fatalities by Complication, FY2011 – FY2015

Complication	FY11 No.	FY11 %	FY12 No.	FY12 %	FY13 No.	FY13 %	FY14 No.	FY14 %	FY15 No.	FY15 %	Total No.	Total %
Anaphylaxis	2	7%	2	5%	-	0%	2	7%	2	5%	**8**	**5%**
Contamination	4	13%	3	8%	5	13%	1	3%	5	14%	**18**	**10%**
HTR (ABO)	3	10%	3	8%	1	3%	4	13%	2	5%	**13**	**7.5%**
HTR (non-ABO)	6	20%	5	13%	5	13%	4	13%	4	11%	**24**	**14%**
Hypotensive Reaction	-	0%	-	0%	-	0%	1	3%	1	3%	**2**	**1%**
TACO	4	13%	8	21%	13	34%	5	17%	11	30%	**41**	**24%**
TRALI*	10	33%	17	45%	14	37%	13	43%	12	32%	**66**	**38%**
Other	1**	3%	-	0%	-	0%	-	3%	-	0%	**1**	**.5%**

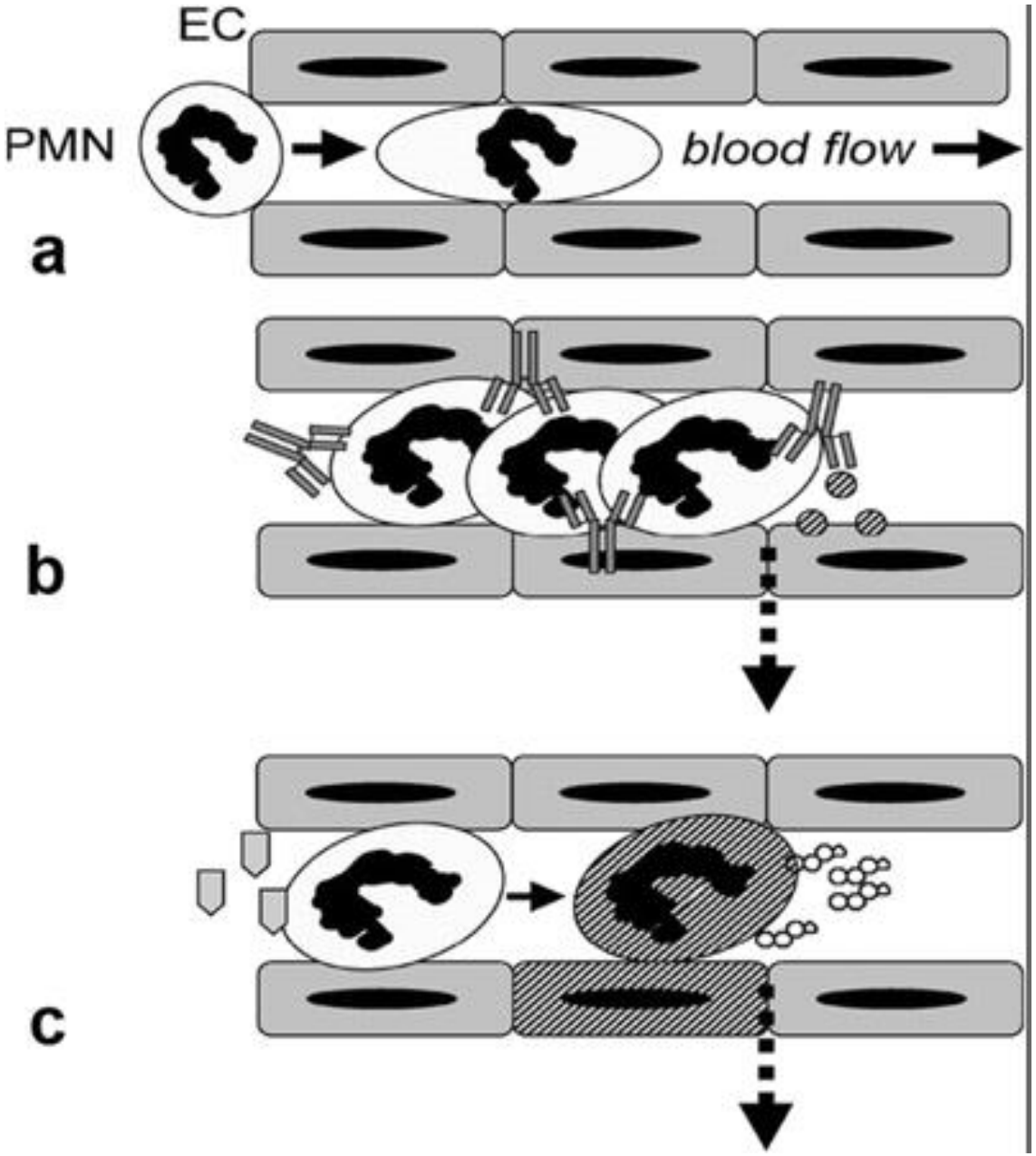
Note: FY15 denotes an imputability of *Definite/Certain, Probable/Likely*, or *Possible*

*FY11-FY14 numbers include both *TRALI* and *Possible TRALI* cases [22,23]

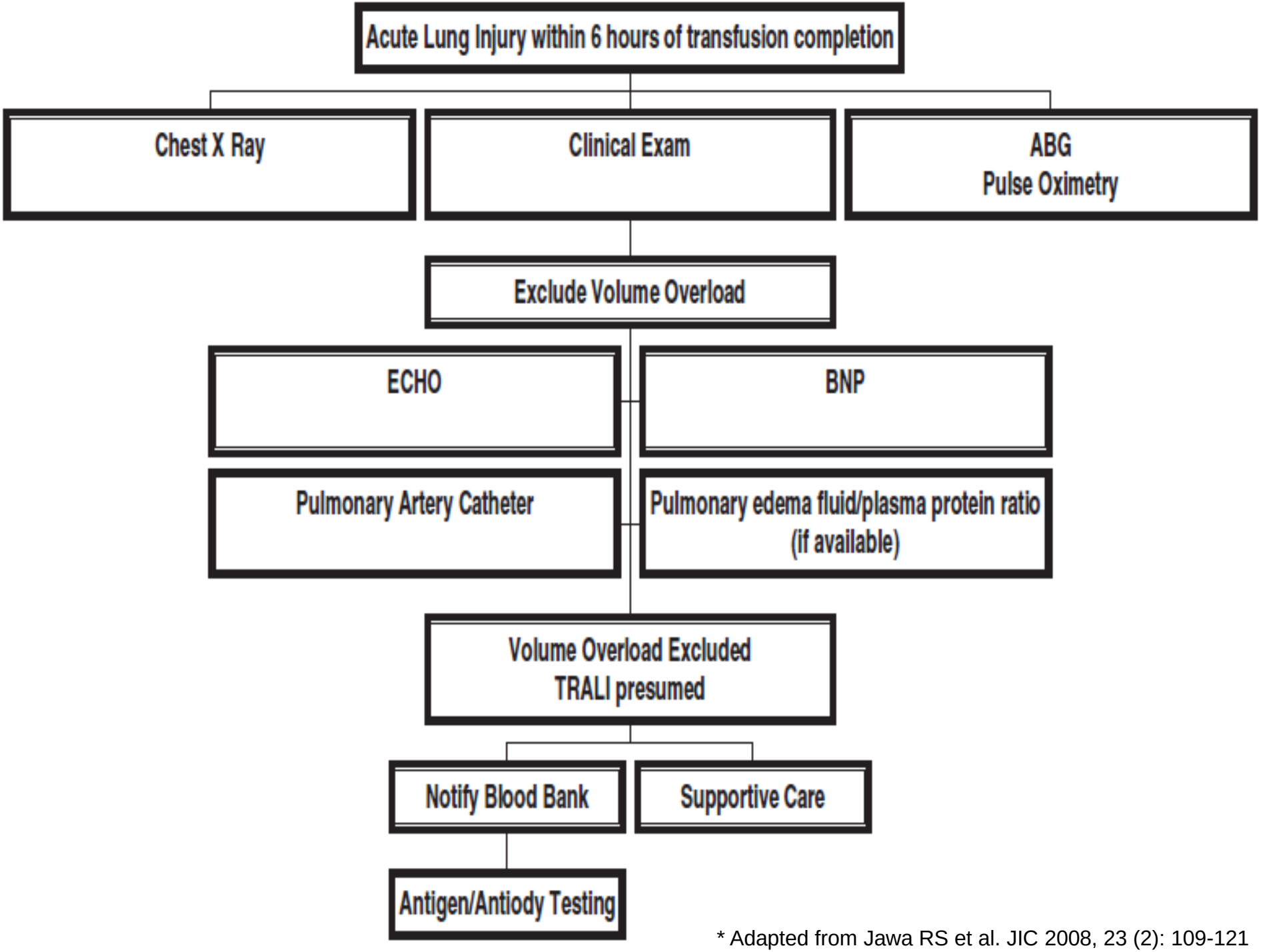
**Other: GVHD (Graft vs. Host Disease)

TRANSFUSION ASSOCIATED LUNG INJURY (TRALI)

- Timing: Acute onset
- Pulmonary artery wedge pressure: ≤ 18 mm Hg when measured, or a lack of clinical evidence of left atrial hypertension
- Chest radiograph: Bilateral infiltrates seen on frontal chest radiograph
- Hypoxemia: Ratio of PaO2/FIO2 ≤ 300 mm Hg regardless of PEEP level



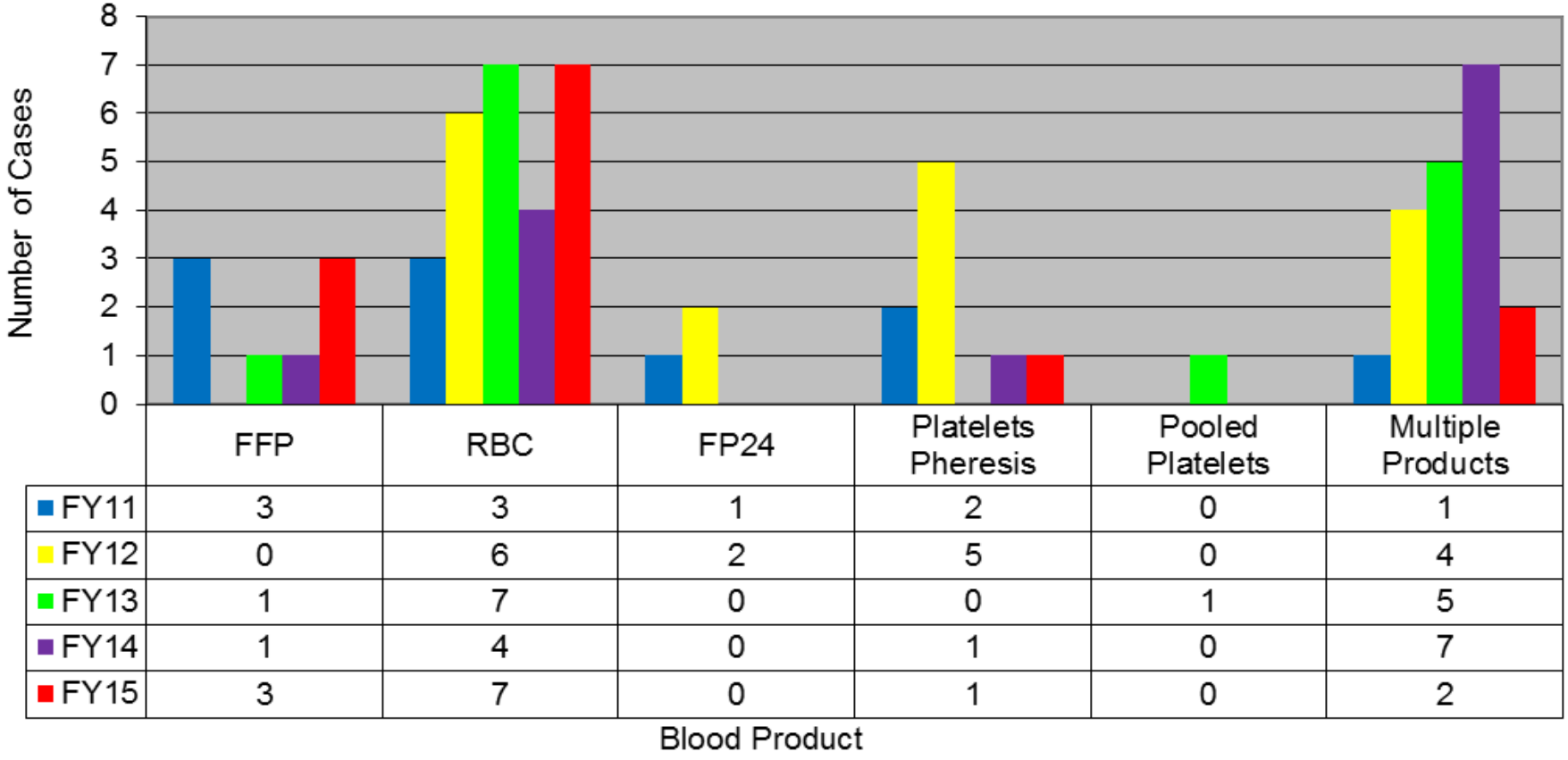
Ref. Triulzi DJ, Anesth Analg 2009; 108:770-6



* Adapted from Jawa RS et al. JIC 2008, 23 (2): 109-121

TRALI CASES BY IMPLICATED BLOOD PRODUCT 2011-2015

Figure 2: Reports of TRALI Cases by Implicated Blood Product FY2011 – FY2015

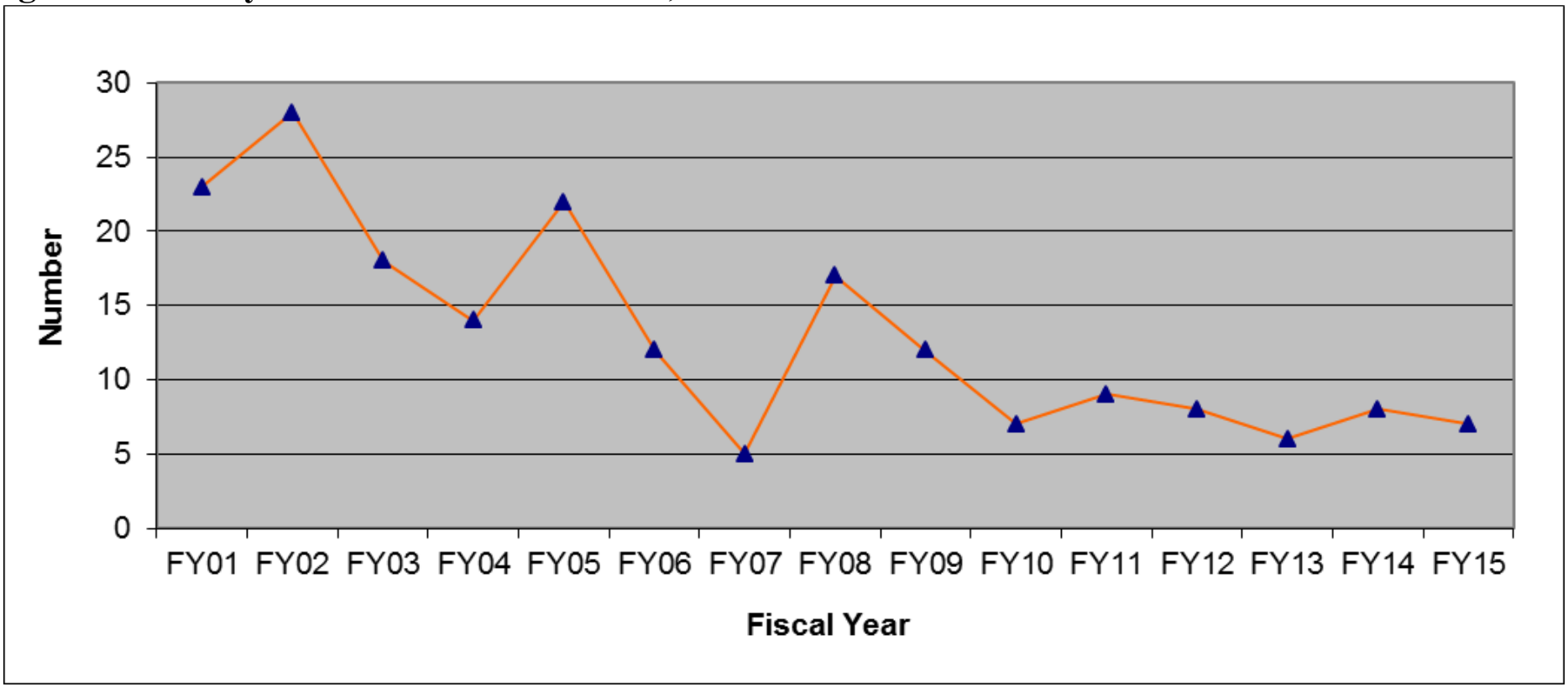


	FFP	RBC	FP24	Platelets Pheresis	Pooled Platelets	Multiple Products
FY11	3	3	1	2	0	1
FY12	0	6	2	5	0	4
FY13	1	7	0	0	1	5
FY14	1	4	0	1	0	7
FY15	3	7	0	1	0	2

FFP – Fresh Frozen Plasma
RBC – Red Blood Cells
FP24 – Plasma Frozen within 24 hours

HEMOLYTIC TRANSFUSION REACTIONS 2001-2015

Figure 3: Hemolytic Transfusion Reactions, FY2001 – FY2015



ACUTE HEMOLYTIC TRANSFUSION REACTION

- **Presentation:**
  - Fever/chills, back pain, hemoglobinemia/uria, bleeding, "impending doom”, nausea/vomiting, dyspnea, hypotension, tachycardia, renal failure, DIC
- **Common Mechanism:**
  - ABO incompatibility or preformed antibodies to incompatible product
- **Prevention:**
  - Careful attention to detail and processes

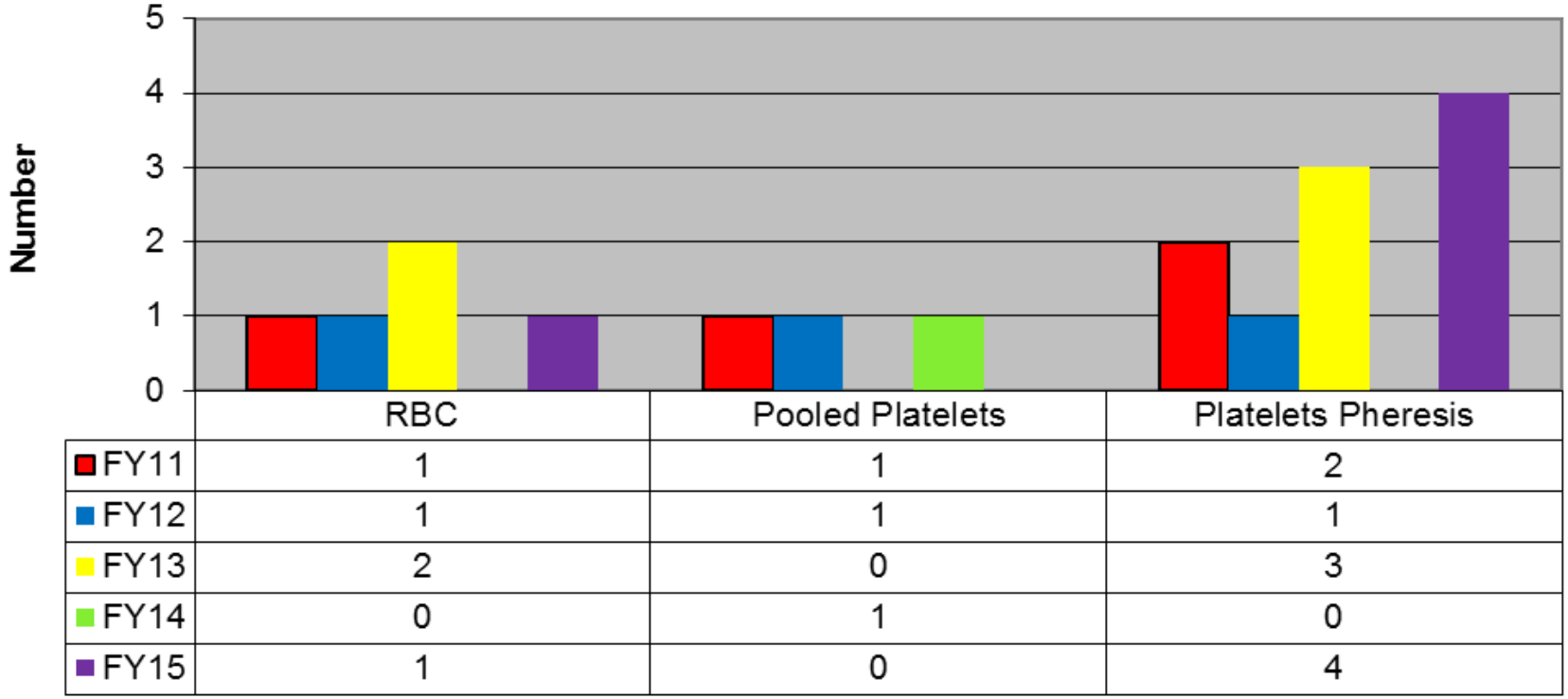
TRANSFUSION RELATED SEPSIS

- **Presentation:**
  - Rapid onset of high fever, chills/rigors, hypotension, nausea/vomiting
- **Common Mechanism:**
  - Bacteria gain entry through donor's blood or through collection site
- **Treatment:**
  - As for sepsis
- **Prevention:**
  - Donor Center precautions and bacterial testing

Table 5: Contamination breakdown for FY2015

Product	Organism	Imputability
Apheresis platelets	*Staphylococcus aureus*	Definite/Certain
Apheresis platelets	*Staphylococcus aureus*	Definite/Certain
Apheresis platelets	*Staphylococcus aureus*	Possible
Apheresis platelets	Coagulase-negative staphylococci	Definite/Certain
Red Blood Cells	*Enterococcus faecium*	Possible

Figure 4: Contamination by Implicated Blood Product FY2011 – FY2015



	RBC	Pooled Platelets	Platelets Pheresis
FY11	1	1	2
FY12	1	1	1
FY13	2	0	3
FY14	0	1	0
FY15	1	0	4

Red Blood Cells microorganisms: *B. microti (3), P. fluorescens (1), E. faecium (1)*
Pooled Platelets microorganisms: *S. aureus (1), S. Marcescens (2)*
Platelets Pheresis microorganisms: *S. aureus (4), S. epidermidis (1),* coagulase-negative staphylococci *(1), M. morganii (1), K. pneumoniae (1),* West Nile virus *(1), Acinetobacter sp. (1)*

Adverse Reaction Case Classification Criteria Tables

Transfusion-associated circulatory overload (TACO)

Case Definition	Severity	Imputability
Definitive: New onset or exacerbation of 3 or more of the following within 6 hours of cessation of transfusion: • Acute respiratory distress (dyspnea, orthopnea, cough) • Elevated brain natriuretic peptide (BNP) • Elevated central venous pressure (CVP) • Evidence of left heart failure • Evidence of positive fluid balance • Radiographic evidence of pulmonary edema **Probable:** N/A **Possible:** N/A	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly, probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** No other explanations for circulatory overload are possible. **Probable:** Transfusion is a likely contributor to circulatory overload **AND EITHER** The patient received other fluids as well **OR** The patient has a history of cardiac insufficiency that could explain the circulatory overload, but transfusion is just as likely to have caused the circulatory overload. **Possible:** The patient has a history of pre-existing cardiac insufficiency that most likely explains circulatory overload. **OPTIONAL** **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Adverse Reaction Case Classification Criteria Tables

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ADVERSE EFFECTS OF TRANSFUSION

Transfusion-Transmitted Infection	Residual Risk Per Transfused Component
HIV	1 in 1,467,000
Hepatitis C	1 in 1,149,000
Hepatitis B	1 in 282,000
West Nile Virus	Uncommon
Cytomegalovirus	50-85% of donors are carriers. Leukocyte reduction is protective.
Bacterial Infection	1 in 2-3,000 (mostly platelets)
Parasitic Diseases Babesiosis, Chagas, Malaria	Relatively uncommon

BLOOD PRODUCT ADMINISTRATION

- **American Society of Hematology Guidelines**
  - **Uses of RBC transfusion**
    - Treatment of symptomatic anemia
    - Prophylaxis of life-threatening anemia
    - Restoration of oxygen-carrying capacity
    - Exchange transfusion
  - **RBC Transfusion is not routinely indicated for *pharmacologically treatable anemia***

ASH CHOOSING WISELY CAMPAIGN

- Do not transfuse more than the minimum number of red blood cell (RBC) units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7 to 8 g/dL in stable, non-cardiac, in-patients).

- Clinicians are urged to avoid the routine administration of 2 units of RBCs if 1 unit is sufficient and to use appropriate weight-based dosing of RBCs in children.

ASH CHOOSING WISELY CAMPAIGN

- Do not administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (i.e. outside of the setting of major bleeding, intracranial hemorrhage or anticipated emergent surgery).

ASH CHOOSING WISELY CAMPAIGN

- Don’t treat patients with immune thrombocytopenic purpura (ITP) in the absence of bleeding or a very low platelet count.

Table 3. RBC Transfusion Recommendations* for Hospitalized, Hemodynamically Stable Patients in Specific Clinical Situations

Clinical Situation	Potential Transfusion Threshold	Evidence Quality	Recommen-dation
ICU Patients (adult or ped)	Hgb** ≤ 7 gm/dL†	High	Strong
Post-Operative	Hgb ≤ 8 gm/dL§ or for symptoms††	High	Strong
Cardiovascu-lar Disease	Hgb ≤ 8 gm/dL‡ or for symptoms††:	Moderate	Weak
Acute Coronary Syndrome	AABB cannot recom-mend for or against a liberal or restrictive RBC transfusion strategy	Very Low	Uncertain
All Patients	Guided by symptoms as well as by Hgb level	Low	Weak

Carson JL, Grossman BJ, Kleinman S et al. Red Blood Cell Transfusion: A Clinical Practice Guideline from the AABB. Ann Intern Med 2012;157:49-58.

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THANK YOU