American Red Cross

Investigations of Suspected Transfusion Reactions by Blood Collection Establishments

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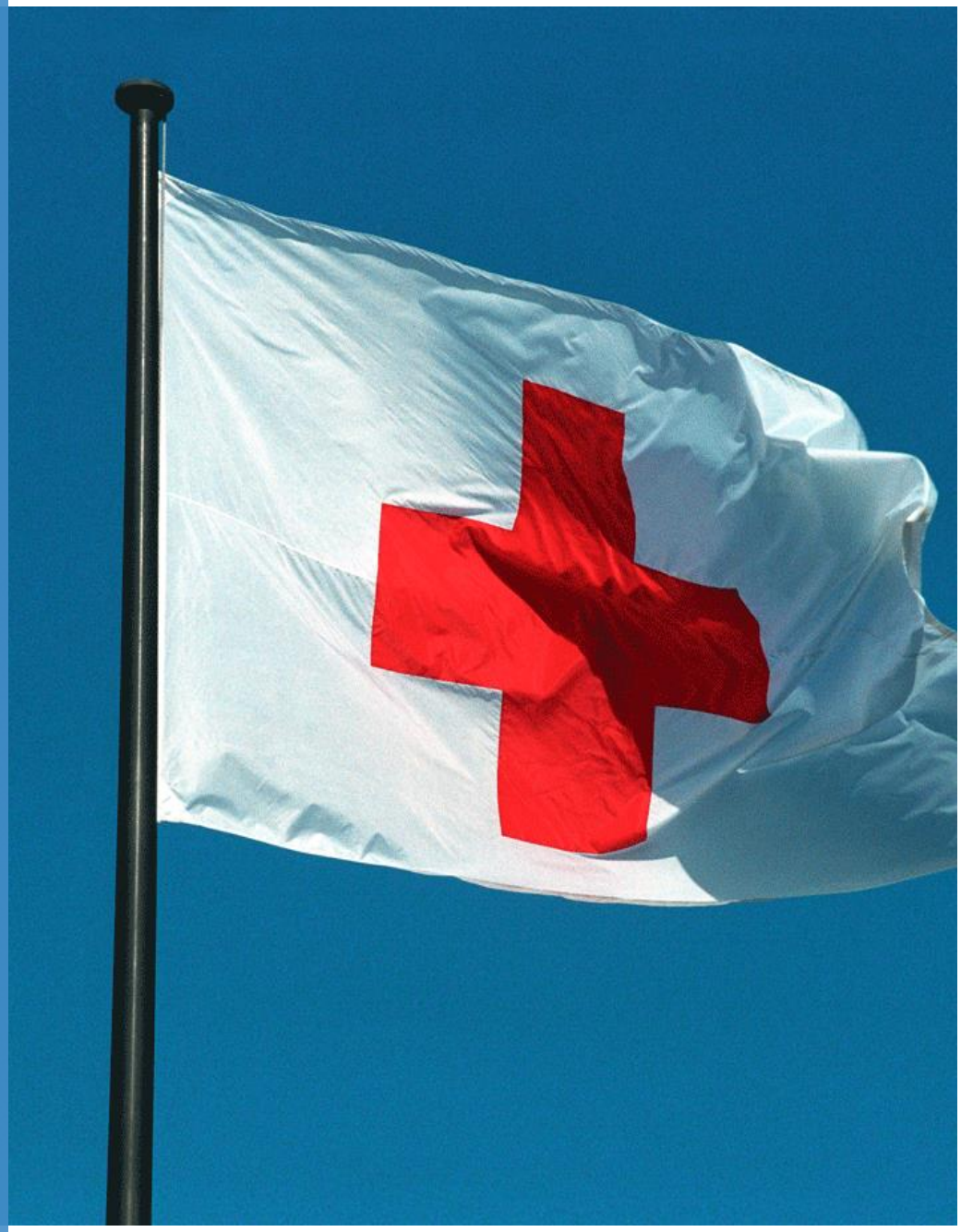

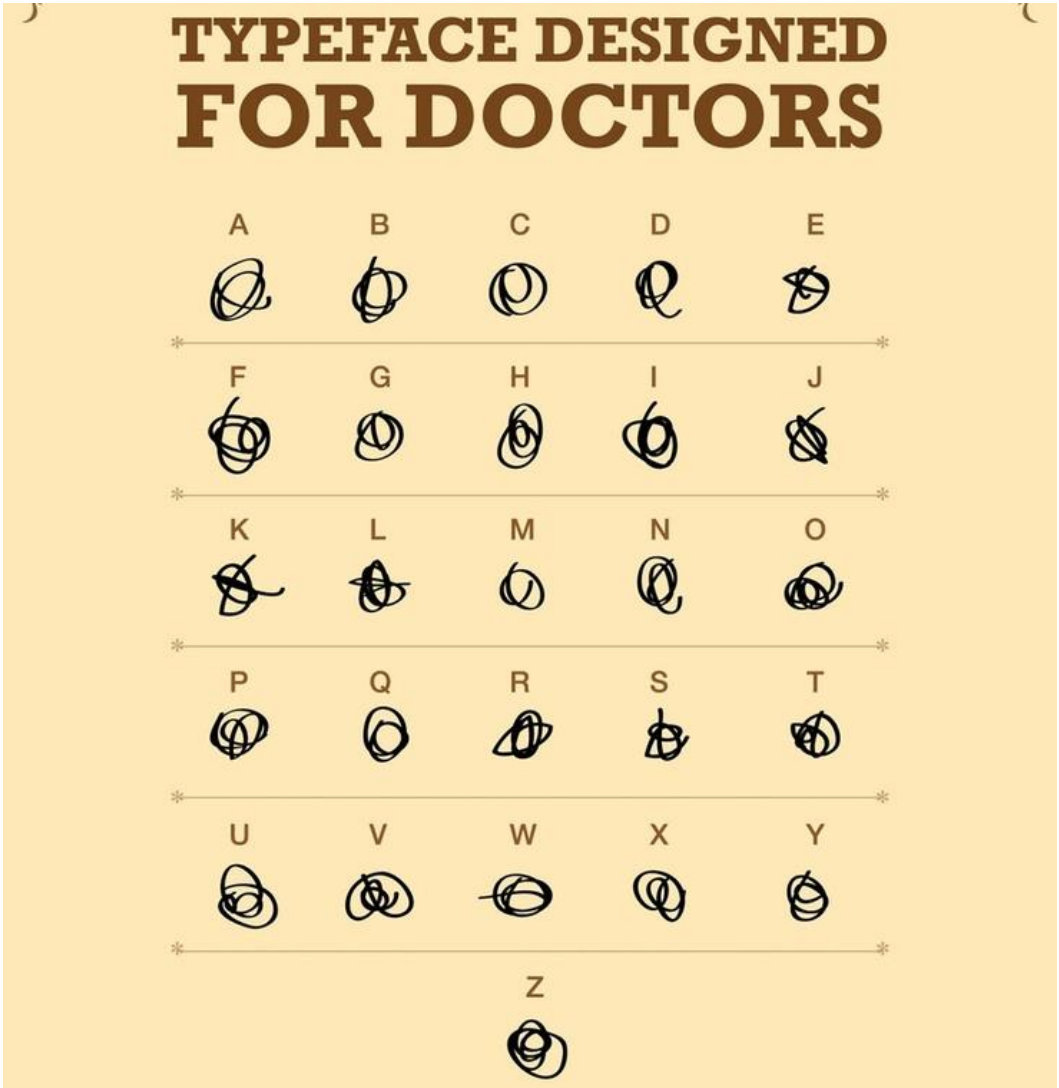
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Disclosures

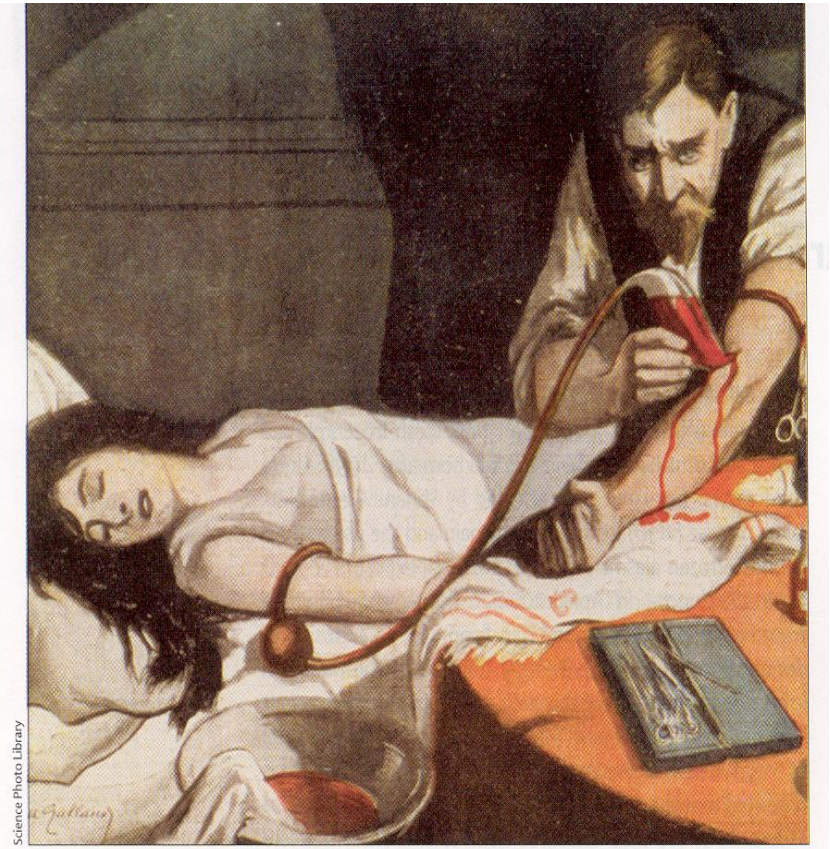
- I have no financial disclosures
- I will not discuss any off label use and/or investigational use in my presentation

Transfusion Reactions

- Objectives:
  - Recognize the initial signs and symptoms of a transfusion reaction
  - Understand the basic work up for a transfusion reaction
  - Understand the importance of reporting a suspected transfusion reaction to the Blood Collection Establishment

History of Blood Transfusions

- 1667
  - Lamb-to-human blood transfusion
- 1816
  - 1st successful human-to-human transfusion
- 1900
  - ***Discovery of the first blood groups (ABO)***
- 1907
  - Pre-transfusion cross match

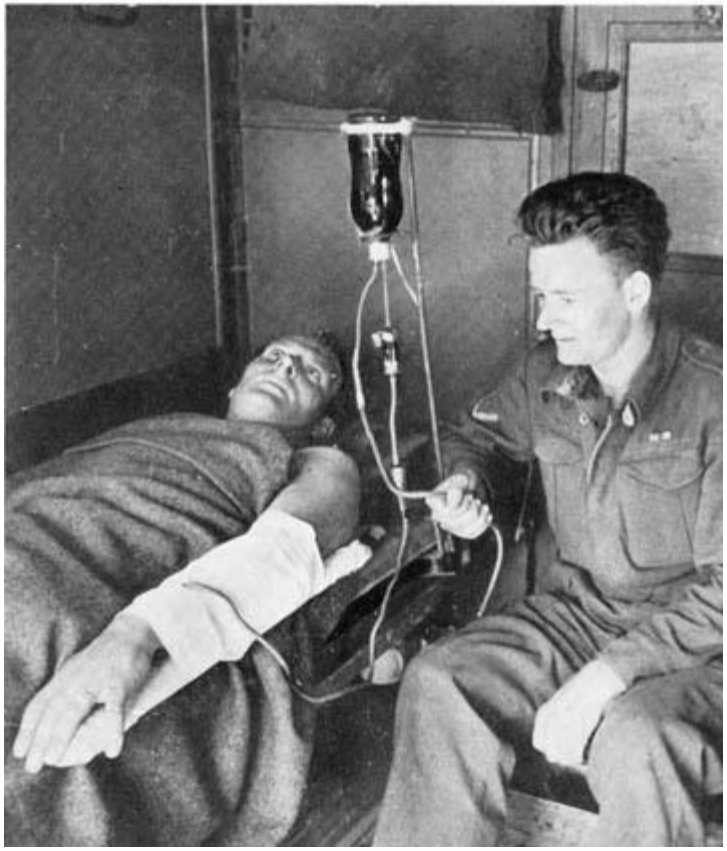


Doctor transfusing patient with his own blood
From a French maqazine, 1922.

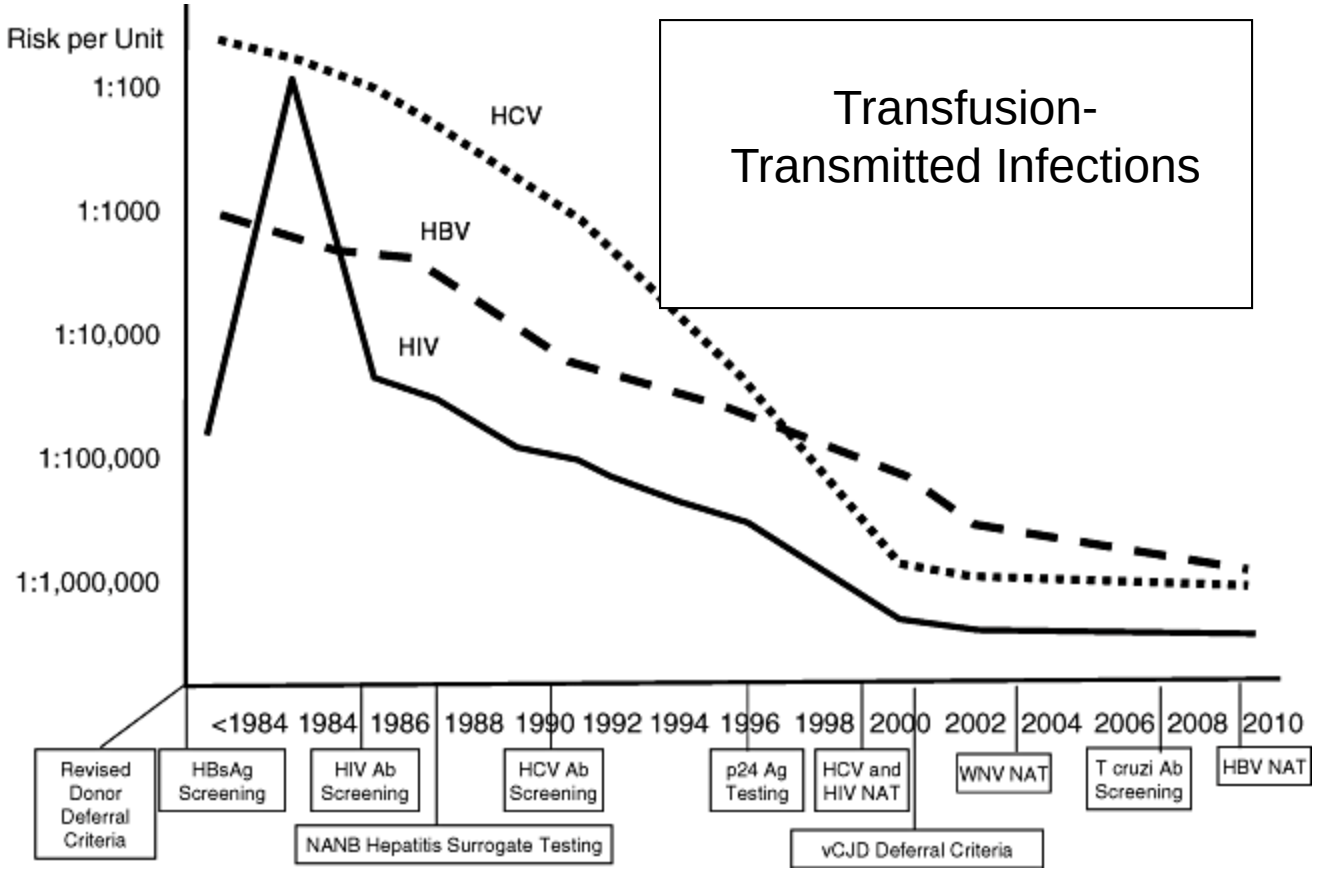
History of Blood Transfusions

- 1930s – 1950s
  - Blood banks
  - Blood fractionation
  - Plastic blood bags
- 1960s
  - AABB publishes *Transfusion*
- 1970s
  - Hepatitis B testing
- 1980s
  - HIV testing
- 1990s
  - Hepatitis C testing
- 2000s
  - “Zero risk” blood (NAT testing)

Blood transfusion in Ambulance Car



“Zero Risk” Blood



Perkins et al. *Transfusion* 2010;50:2080

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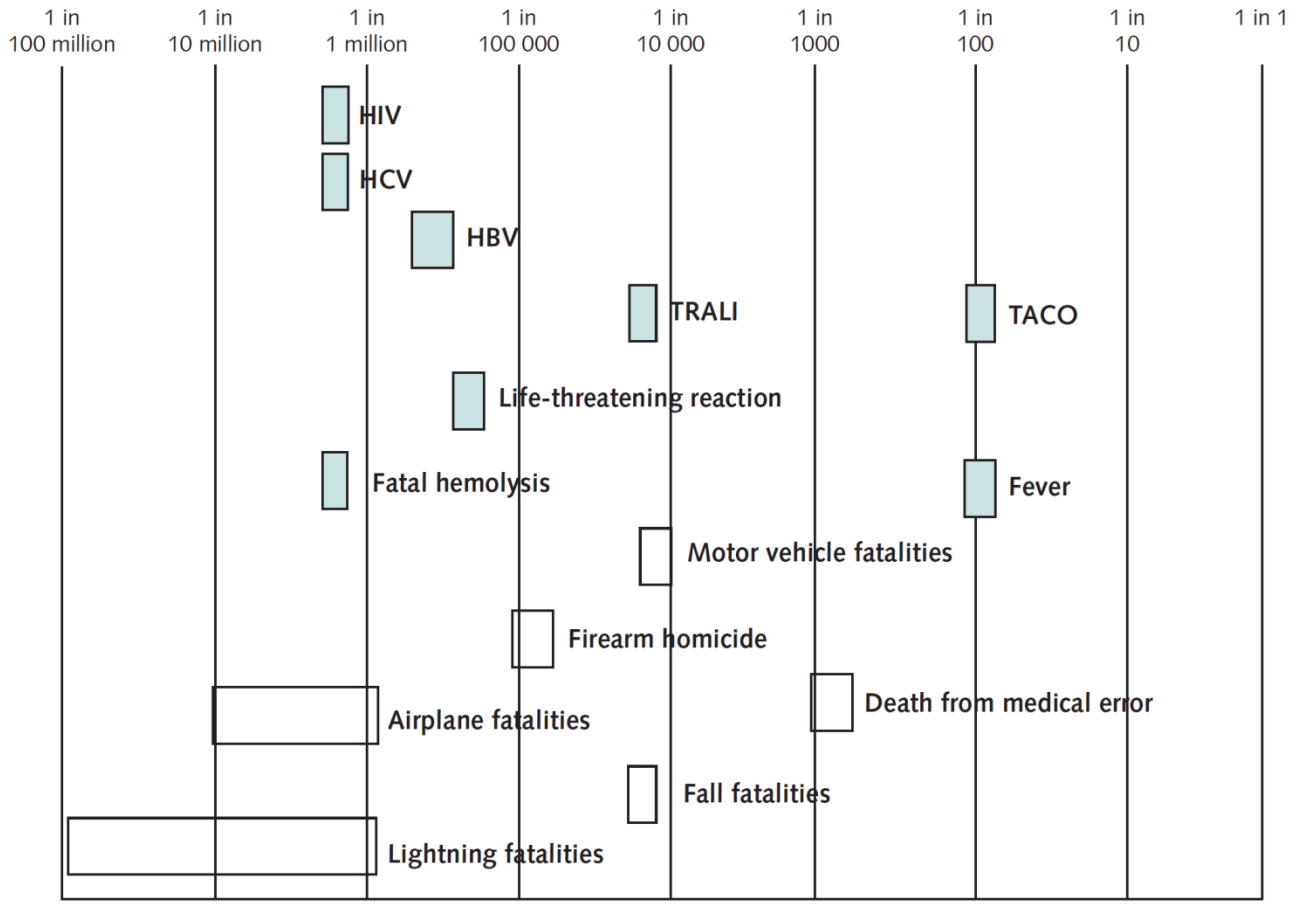
Relative Risk



Carson et al. *Ann Intern Med*. 26 March 2012

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Transfusion Reactions

- AABB Technical Manual, 19th Edition:
  - Greatest risk of morbidity and mortality is from non-infectious complications of blood transfusions
  - Most commonly reported causes of transfusion-related mortality:
    - Transfusion-related acute lung injury
    - Transfusion-associated circulatory overload

Transfusion-Associated Fatalities, FY2012-FY2016

COMPLICATIONS	FY2012	FY2013	FY2014	FY2015	FY2016	TOTAL
Anaphylaxis	2	0	2	2	5	11 (6%)
Contamination	3	5	1	5	5	19 (10%)
HTR (ABO)	3	1	4	2	4	14 (8%)
HTR (non-ABO)	5	5	4	4	1	19 (10%)
Hypotensive Reaction	0	0	1	1	1	3 (2%)
TACO	8	13	5	11	19	56 (30%)
TRALI	17	14	13	12	8	64 (34%)

Transfusion Reactions

- Recognizing signs and symptoms of adverse reactions - with timely lab evaluation - is essential due to the potentially life-threatening nature of acute transfusion reactions
- ***Assume all reactions are hemolytic until proven otherwise***

Transfusion Reactions

	Immune	Non-immune
Acute During or < 24 hours	AHTR TRALI* Allergic FNH	TACO Septic Hypotensive Non-immune hemolysis Air embolism
Delayed > 24 hours	DHTR/DSTR TA-GVHD PTP TRALI*	Infection (TTI) Iron Overload

Symptoms?

- Fever, chills/rigors
  - AHTR
  - FNH
  - Septic
  - TRALI
- Itching, rash/hives
  - AHTR
  - Allergic reaction
  - Anaphylaxis
- Respiratory distress
  - AHTR
  - TRALI
  - TACO
  - Anaphylaxis
- Shock
  - AHTR
  - Sepsis
  - Anaphylaxis

Basics

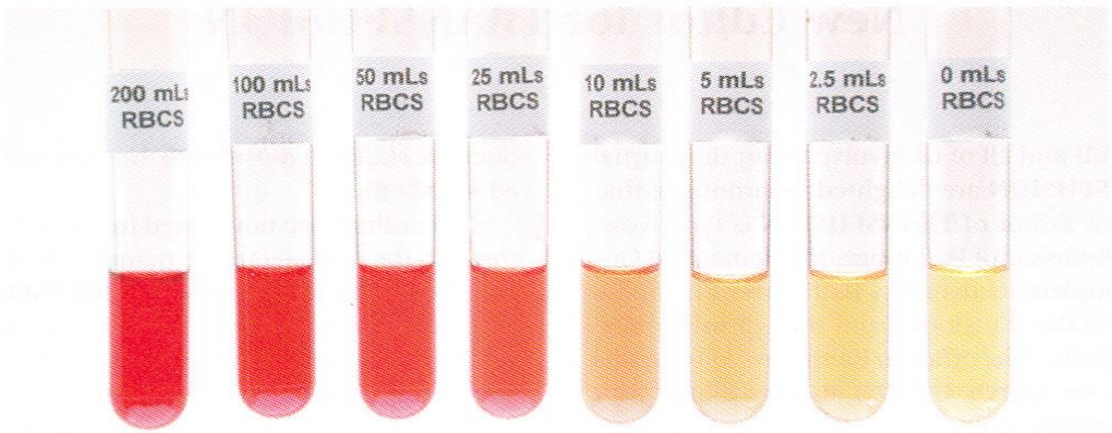
- ***Stop the transfusion!!!***
- Treat symptoms
  - Keep the line open
  - Monitor vital signs and symptoms
- Report the reaction to the physician, transfusion service, and blood center
- Collect appropriate specimens and send to laboratory
  - Return blood product bag with administration tubing set, all attached bags to Blood Bank

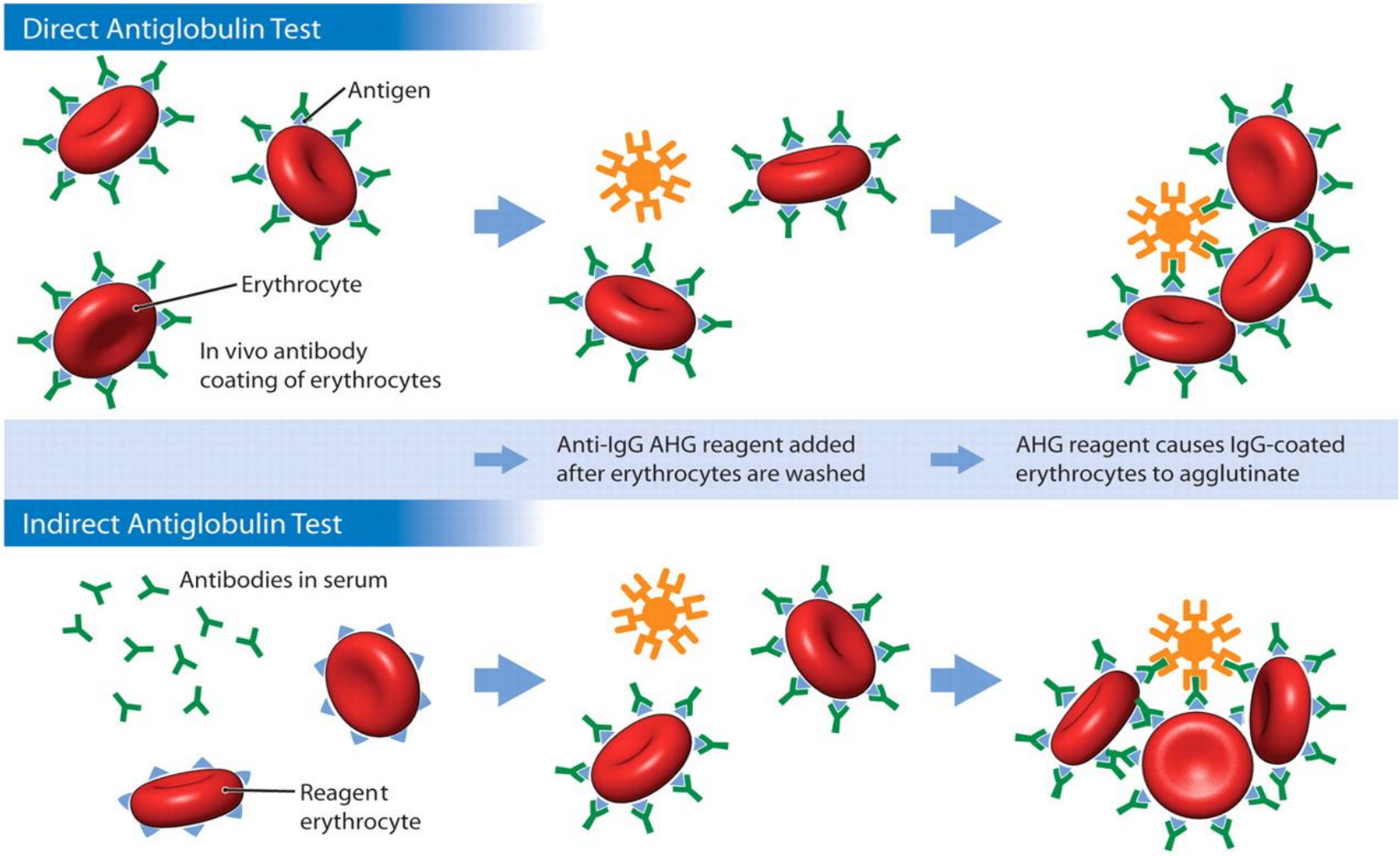
Initial Laboratory Evaluation

- Blood Bank
  - Immediate visual checks for hemolysis
  - Clerical check
  - ABO/Rh of patient
  - Direct antiglobulin test (DAT)
  - Examine blood bag, administration set, IV fluid bags

Initial Laboratory Evaluation

- Immediate visual check for hemolysis
  - Can detect free hemoglobin with lysis of as little as 5-10cc red cells





http://crashingpatient.com/wp-content/images/part1/coombs.jpg

Direct Antiglobulin Test

- Compare to pre-transfusion DAT:
  - Positive DAT
    - Change from baseline?
    - Antibody coated RBCs
  - Negative DAT
    - Non-immune mediated hemolysis
    - Transfused cells already destroyed

Acute Hemolytic Transfusion Reaction

- Acute hemolysis of transfused red cells due to presence of preformed antibody
- Usually due to ABO incompatible RBCs
- Majority due to clerical error:
  - ***Misidentification of patient/sample***
    - Phlebotomy
    - Blood bank
    - Transfusion administration

AHTR

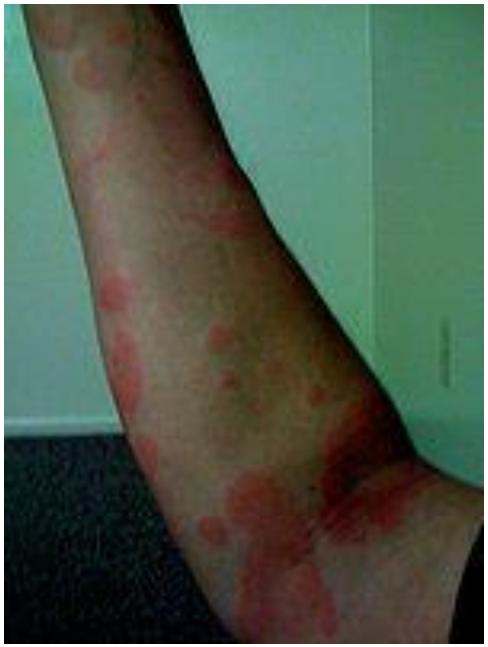
- Usually occurs ***early*** in transfusion
- ***5 – 10 ml***
- Severity related to amount of blood transfused: value of early recognition/stopping transfusion!
  - Fatality rate 15-20%
  - AHTR rate 1:76,000
  - Fatal AHTR 1:1,800,000

Febrile Non-Hemolytic Reaction

- 0.1 – 1% or all transfusions
  - 1º C or greater temp increase within 4 hours
  - ***Must rule out:***
    - AHTR
      - Evidence of hemolysis
    - Septic TR
      - Higher fever, systemic symptoms
    - TRALI
      - Respiratory symptoms

Allergic Reaction

- 1 – 3% or transfusions
  - *Usually* plasma or platelet products
- Symptoms:
  - Pruritis/hives
  - Localized or widespread
  - Angioedema
- If effective in relieving symptoms, *restart component slowly*



Anaphylactic Reaction

- 1:20,000 – 1:50,000
- Hypersensitive reaction to allergens in donor plasma
  - IgA deficient recipient with anti-IgA antibodies
  - Haptoglobin (and other plasma proteins) deficiency
- Symptoms:
  - Respiratory distress, laryngeal edema
  - Hypotension/shock
- Order products from IgA-deficient donor
- Wash products

Reporting Form

Section I: Clinical Information		
Recipient ID (patient #):	Age or DOB:	Gender: ☐ Female ☐ Male
Primary diagnoses:		
Attending physician:	Phone:	
Transfusion service medical director:	Phone:	
Contact for additional information:	Phone:	

Date and time evidence of reaction began: _____

Fatality? ☐ No ☐ Yes ► Date and time of death: _____

If yes, will autopsy be performed? ☐ No ☐ Yes

Transfusion fatalities must be investigated urgently and are reportable to the Food and Drug Administration (FDA) by the transfusion service.

Which of the following developed during or within 6 hours following transfusion? *(Note: The signs/symptoms of a septic reaction may be delayed for as long as 24 hours post transfusion).* **Check all that apply:**

☐ Fever (≥39°C or ≥2°C rise)	☐ Hematuria	☐ Rigors
☐ Hypoxemia (PaO_2<60, O_2 sat. <90%)	☐ Hemoglobinuria	☐ Abdominal pain
☐ Tachycardia (>120/min or >40/min rise)	☐ Nausea or vomiting	☐ Lumbar pain
☐ Rapid breathing (>28/min)	☐ Bronchospasm/wheezing	☐ Chest pain
☐ Rise in systolic BP of >30 mmHg	☐ Jugular venous distension	☐ Cardiac arrhythmia
☐ Drop in systolic BP of >30 mmHg	☐ Pulmonary edema	☐ Other:

Describe reaction in more detail: _____

Reporting Form

Section II: Transfusion History
Did the patient receive any non-Red Cross-provided products? ☐ No ☐ Yes
Did the Red Cross perform the compatibility testing of record? ☐ No ☐ Yes

List transfusions of Red Cross-provided products that are suspected to have been involved with the reaction.

For Transfusion Service Use						For Red Cross Use		
Unit number	Product name	Transfusion		Volume transfused	Residual product available	*Unit involved	Cleared	
		Date	Time					
					☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ N/A
					☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ N/A
					☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ N/A
					☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ N/A
					☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ N/A
					☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ N/A
					☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ N/A
					☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ N/A
					☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ N/A
					☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ N/A
						***Unit involvement recorded by:** ____________ (Identity/date)		

Reporting Form

Section II: Transfusion History (continued)

Previous transfusion history in this patient (summarize, including types of products and nature of prior reactions):

Was a post-transfusion chest X-ray performed? ☐ No
If yes, please attach copy of radiology report. ☐ Yes ► Result: _____

Summary of treatment, response, and patient status at the time of this report: _____

Were any of the involved products modified by the transfusion service or in the clinical care area?
(pooled, aliquoted, warmed, irradiated, washed, leukocyte-reduced by filtration, or other):

Routine transfusion reaction workup (or ☐ Not done)

Clerical check of transfusion (right unit, right recipient?):	☐ Correct	☐ Incorrect	
Appearance of returned blood bag and contents:	☐ Normal	☐ Abnormal	☐ Not returned
Appearance of returned solutions, tubing, and filters:	☐ Normal	☐ Abnormal	☐ Not returned
Describe any problems:			

Confirmation of compatibility

	Pre-transfusion	Post-transfusion
ABO/RH type		
Antibody screen		
Crossmatch (if applicable)		
Direct antiglobulin test		

How Do We Work Up Reactions?

- ***Protect the safety of the blood supply!***
- Temporarily defer all involved donors
- Gain control of all associated products
  - Hemolytic reactions:
    - Check ABO and clerical check of donor/product
    - Check antibody screen – did we miss something?
  - Transfusion-transmitted infections:
    - Donors must provide samples for testing to determine if they have infection – if yes, permanently deferred

Reporting Form

For potential septic reactions due to bacterial contamination of the blood product:

Residual product/blood bag			
Sample source:	☐ Bag	☐ Segment	☐ Infusion set/tubing
Sample collection:	☐ Aseptic	☐ Clean	☐ Retrieved from trash
Gram stain:	☐ Negative	☐ Not done	☐ Positive
Culture:	☐ Negative	☐ Not done	☐ Positive

Patient blood cultures			
Pre-transfusion	☐ Not done	Date:	☐ Negative ☐ Positive for:
Post-transfusion	☐ Not done	Date:	☐ Negative ☐ Positive for:

What other event could explain the findings in this patient other than the transfusion?

☐ Sepsis	☐ Drug reaction	☐ Volume overload
☐ Heart failure	☐ Hemorrhagic shock	☐ Allergic or anaphylactic reaction
☐ Other:		

Transfusion Service: Medical Director's Summary

Suspect Cause: (check appropriate box)

☐ Septic reaction
☐ Hemolytic reaction
☐ Transfusion-related acute lung injury (TRALI)
☐ Electrolyte abnormality (K+, Ca++)
☐ Anaphylaxis
☐ Volume overload
☐ Other: _____

From your perspective, what is the likelihood that the transfusion caused this event?

☐ Certain ☐ Likely ☐ Possible ☐ Cannot exclude ☐ Unlikely

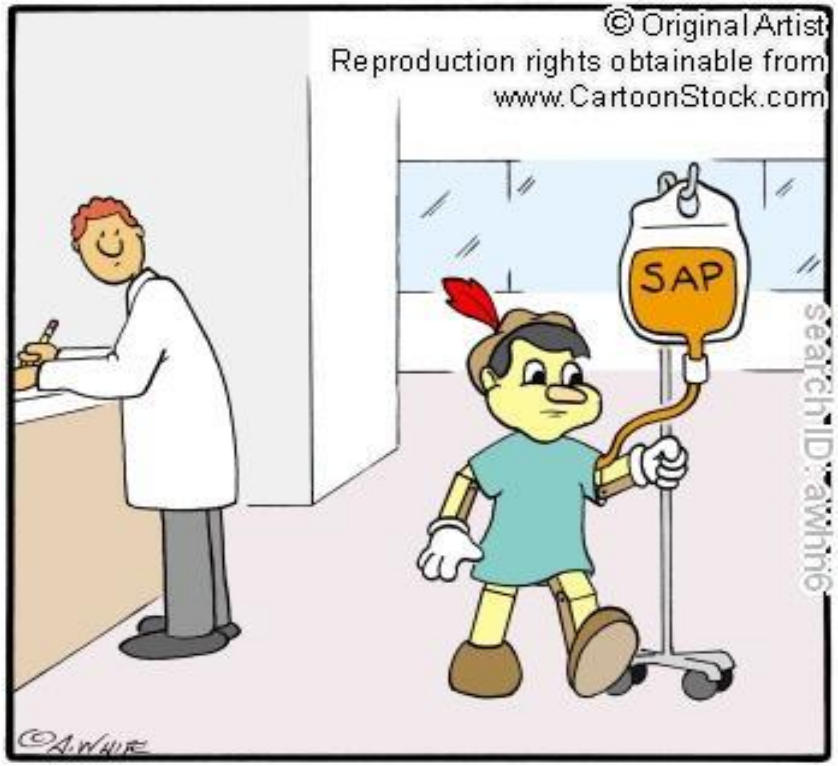
How Do We Work Up Reactions?

- Septic/Bacterial contamination:
  - Determine the causative organism
    - Was in-house sample positive
    - Did it match with patient/blood product result
  - Interview donor
    - Health issues – possible transient bacteremia
    - Arm issues – unable to get adequate arm scrub
  - Review processing records to locate source
    - Collections – inadequate arm scrub/break sterility
    - Manufacturing – accidently create an open system

How Do We Work Up Reactions?

- TRALI (vs TACO):
  - Donor allo-immunization risk
    - Prior transfusions, transplants or pregnancies
    - If yes to any, order HLA and HNA workup
  - Recipient HLA typing
  - Test results
    - Positive for HLA antibodies – defer if match with recipient
    - Positive for HLA antibodies, no match – defer from plasma (may redirect to RBC)
    - Positive for HNA antibodies – defer

The End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Investigation of Suspected Septic Transfusion Reactions by Blood Collection Establishments

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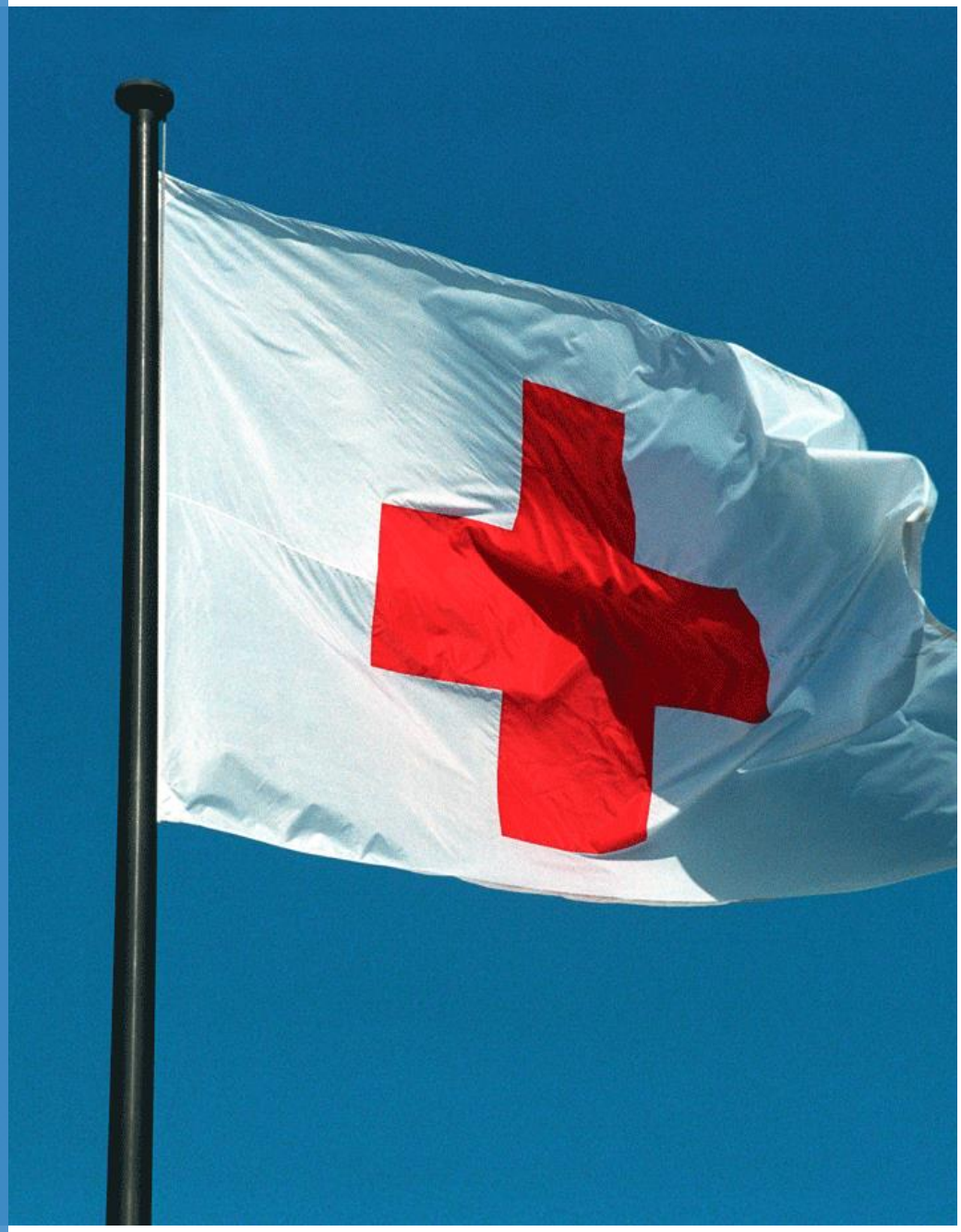
East Division Blood Services



Disclosures

- Fenwal
- Cerus
- No commercial support was received for this activity.

Septic Transfusion Reactions

- Objectives:
  - List the initial signs and symptoms of a suspected septic transfusion reaction.
  - State why a suspected septic transfusion reaction should be reported (to the Blood Center).
  - Name the most common causes of fatal septic reactions as reported to the FDA in 2016.
  - Summarize the approach to a septic transfusion reaction by our Blood Center.

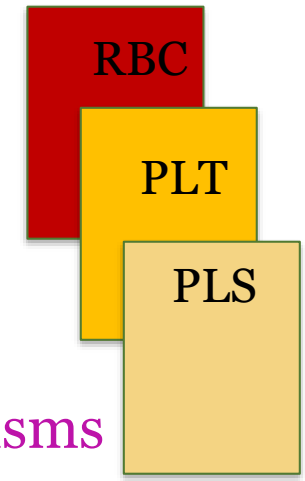
Septic Transfusion Reaction

AABB Standards 31st Ed. Effective April 1, 2018 (Glossary)

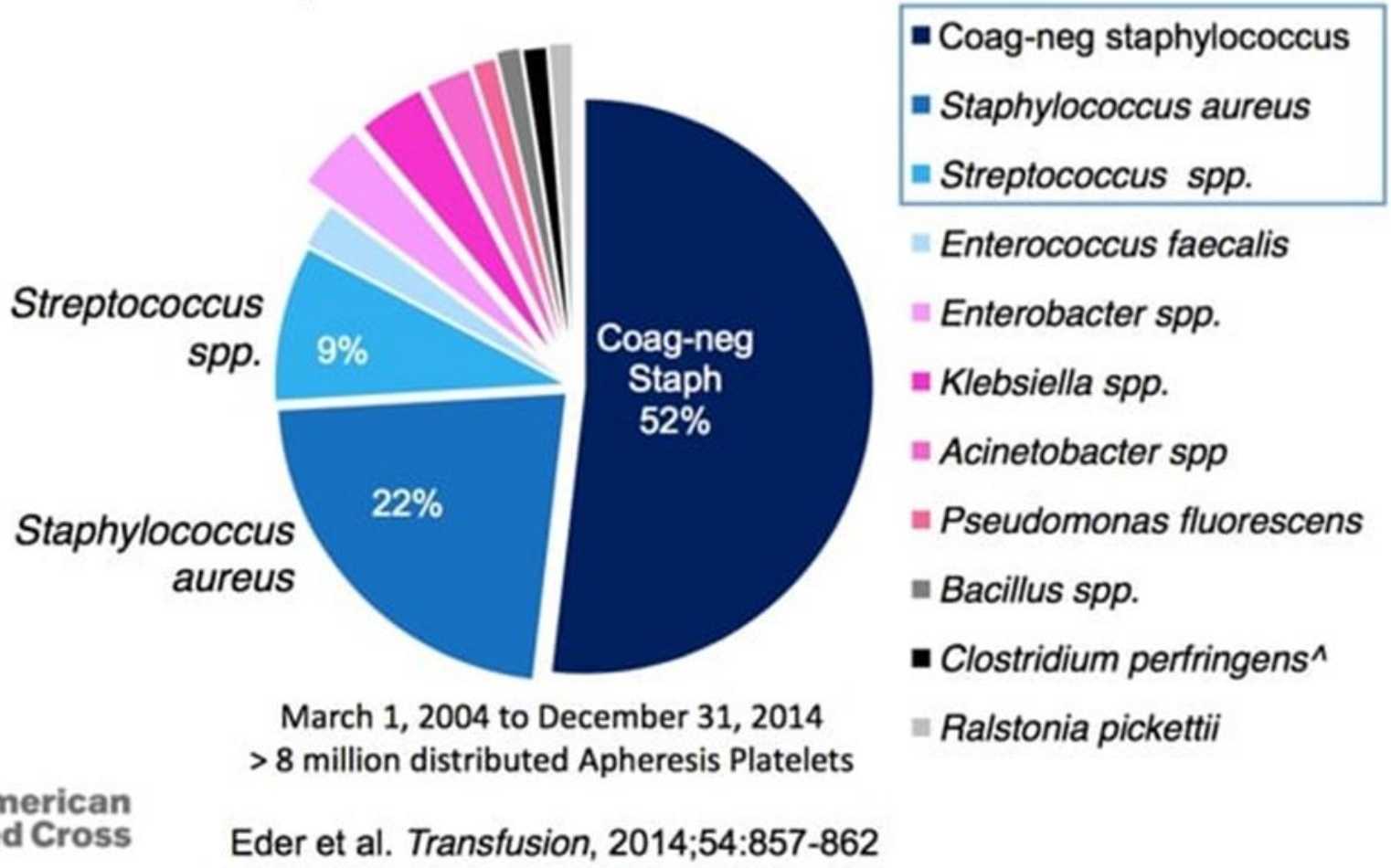
Transfusion-Transmitted Infection: A disease or condition caused by a virus, bacteria, fungus, parasite, or agent of transmissible spongiform encephalopathy that may be transmitted by transfusion of blood or blood components or by tissue implantation or transplantation or administration of derivatives.

- Septic Transfusion Reaction (AABB TM 19th Ed.)
  - **Fever** > or = 38.5C (101F)
  - Chills
  - Rigors
  - Hypotension (but could see hypertension)
  - **Shock**
  - **Renal failure**
  - **DIC**

Esp. gram negative organisms



Implicated Bacteria in STRs



March 1, 2004 to December 31, 2014
> 8 million distributed Apheresis Platelets

Eder et al. *Transfusion*, 2014;54:857-862

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FY2012-FY2016 Fatalities Reported to FDA

Table 3: Transfusion-Associated Fatalities by Complication, FY2012 – FY2016

Complication	FY12 No.	FY12 %	FY13 No.	FY13 %	FY14 No.	FY14 %	FY15 No.	FY15 %	FY16 No.	FY16 %	Total No.	Total %
Anaphylaxis	2	5%	-	0%	2	7%	2	5%	5	12%	**11**	**6%**
Contamination	3	8%	5	13%	1	3%	5	14%	5	12%	**19**	**10%**
HTR (ABO)	3	8%	1	3%	4	13%	2	5%	4	9%	**14**	**8%**
HTR (non-ABO)	5	13%	5	13%	4	13%	4	11%	1	2%	**19**	**10%**
Hypotensive Reaction	-	0%	-	0%	1	3%	1	3%	1	2%	**3**	**2%**
TACO	8	21%	13	34%	5	17%	11	30%	19	44%	**56**	**30%**
TRALI*	17	45%	14	37%	13	43%	12	32%	8	19%	**64**	**34%**

Note: FY2015-FY2016 only includes cases with an imputability of *Definite/Certain, Probable/Likely*, or *Possible*.

FY2012-FY2014 only include cases classified as transfusion-related.

*FY2012-FY2016 numbers combine both *TRALI* and *Possible TRALI* cases[22,23]

Fatalities Reported to FDA Following Blood Collection and Transfusion Annual Summary for FY2016

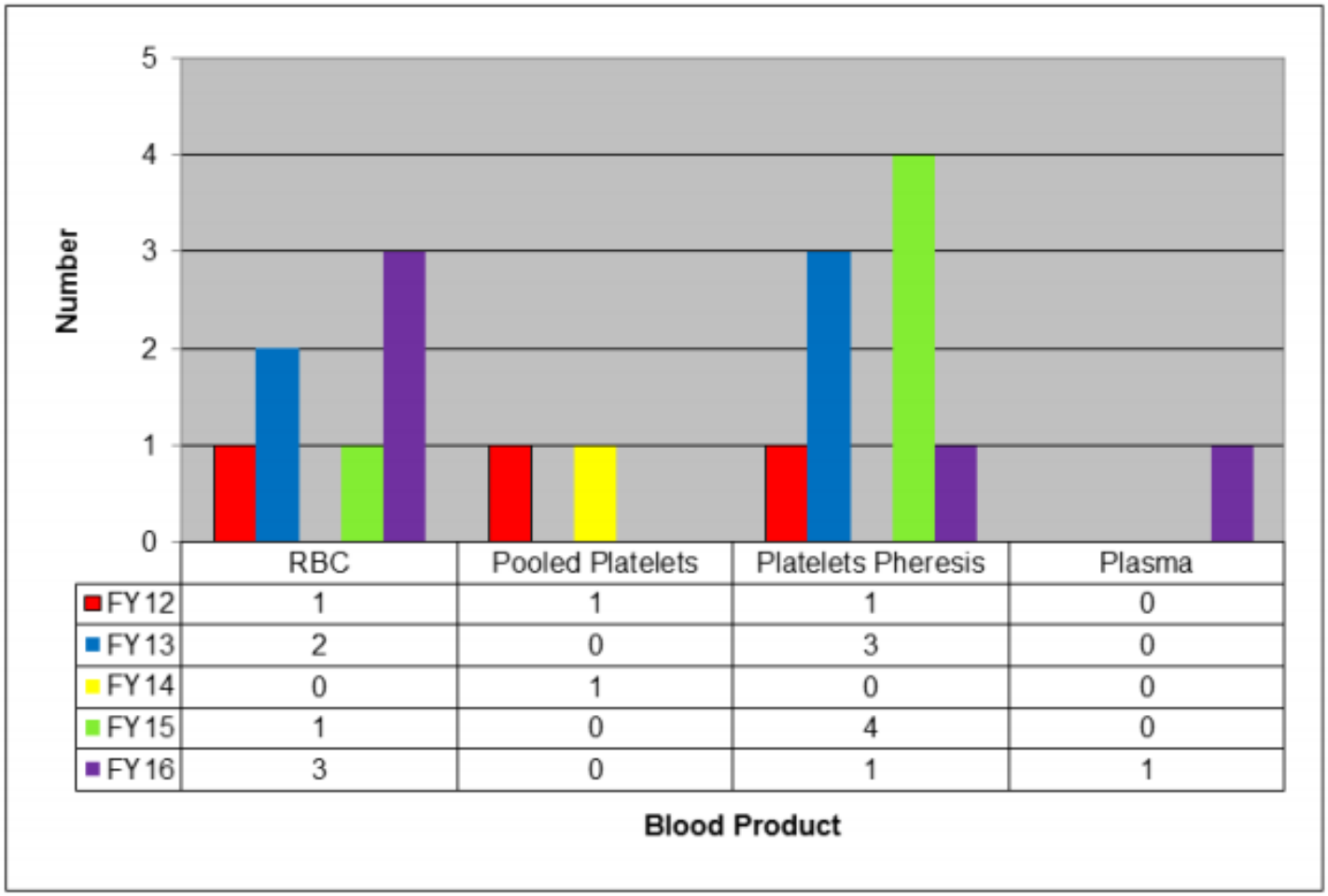
Table 6: Contamination by Implicated Organism, FY2012 - FY2016

Organism	FY12	FY13	FY14	FY15	FY16	TOTAL
Staphylococcus aureus	1	-	-	3	-	**4**
Babesia microti	1	1	-	-	2	**4**
Serratia marcescens	1	-	1	-	-	**2**
Coagulase-negative staphylococci	-	-	-	1	1	**2**
Pseudomonas fluorescens	-	1	-	-	1	**2**
Staphylococcus epidermidis	-	1	-	-	-	**1**
Acinetobacter species	-	1	-	-	-	**1**
Enterococcus faecium	-	-	-	1	-	**1**
Enterobacter aerogenes	-	-	-	-	1	**1**
West Nile virus	-	1	-	-	-	**1**
TOTAL	**3**	**5**	**1**	**5**	**5**	**19**

Table 5: Contamination Breakdown, FY2016

Product	Organism
Apheresis platelets	*Enterobacter aerogenes*
Plasma (TPE)	Coagulase-negative staphylococci
Red Blood Cells	*Pseudomonas fluorescens*
Red Blood Cells	*Babesia microti*
Red Blood Cells	*Babesia microti*

Figure 4: Contamination by Implicated Blood Product, FY2012 – FY2016



	RBC	Pooled Platelets	Platelets Pheresis	Plasma
FY 12	1	1	1	0
FY 13	2	0	3	0
FY 14	0	1	0	0
FY 15	1	0	4	0
FY 16	3	0	1	1

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

Focusing on Platelets
morbidity and mortality from septic risk

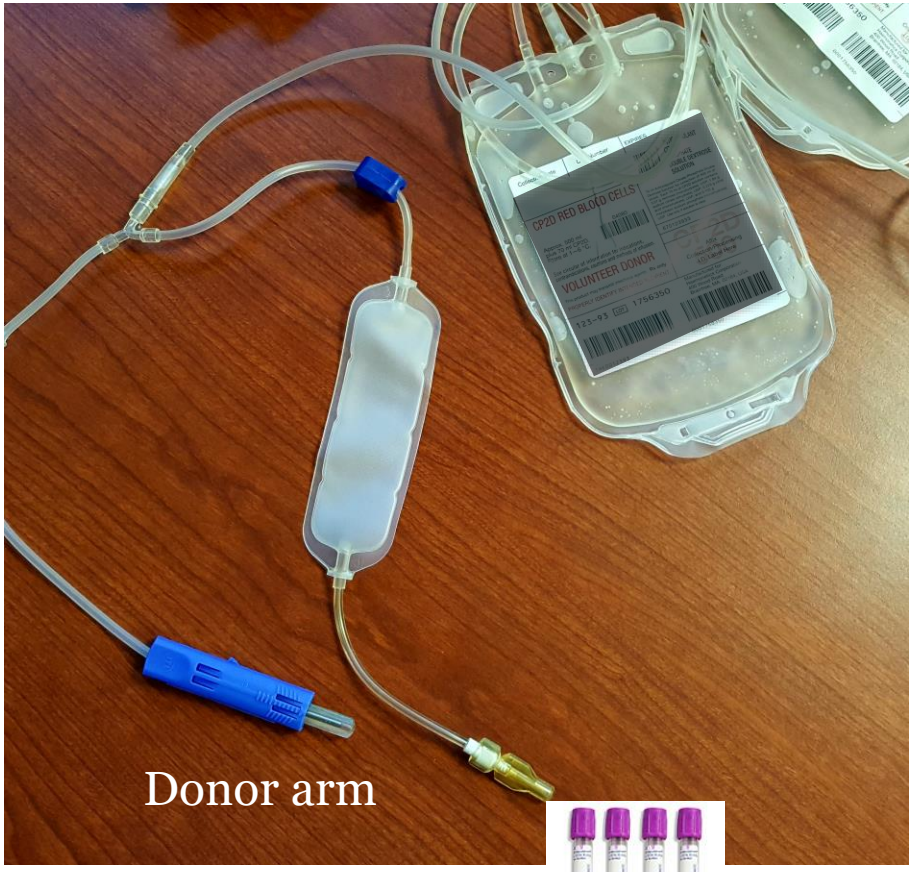
- Greater risk of sepsis than other blood products
- Platelets in:
  - 100% plasma
  - Platelet additive solution
  - Pools of 5-6
- Stored at 20C-24C
- Continuous, gentle agitation
- Oxygen-permeable bag
- 5-7d storage

Title 21: Food and Drugs
PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS
Subpart F—Dating Period Limitations

Platelets		
Platelets	Between 20 and 24 °C	5 days from date of collection.
Platelets	Other temperatures according to storage bag instructions	As specified in the instructions for use by the blood collection, processing and storage system approved or cleared for such use by FDA.

Reducing Risk *Pre-collection: protecting the patient*

- Donor
  - Reading materials
  - Health history
  - Mini-physical
  - Chlorhexidine-based
  - Iodine-based
  - Diversion pouch
  - Routine ID testing



Electronic Code of Federal Regulations

e-CFR data is current as of October 9, 2018

Title 21 → Chapter I → Subchapter F → Part 606 → Subpart H → §606.145

Browse Previous | Browse Next

Title 21: Food and Drugs
PART 606—CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS
Subpart H—Laboratory Controls

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§606.145 Control of bacterial contamination of platelets.

(a) Blood collection establishments and transfusion services must assure that the risk of bacterial contamination of platelets is adequately controlled using FDA approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose by FDA.

Options

Standards for Blood Banks and Transfusion Services, 31st edition, effective April 1, 2018

5.1.5.2 The BB/TS shall have methods to detect bacteria or use pathogen reduction technology in all platelet components.*

*21 CFR 606.145.

Reducing Risk *Post-collection: protecting the patient*

- Blood Center
  - Visual inspection
  - Environment
  - Product sampling and volume
  - Culture samples since 2004
    - Rest 24hrs
    - Sample culture
    - 12hr hold prior to release
    - False negatives and false positives

Reducing Risk *Post-collection: protecting the patient*

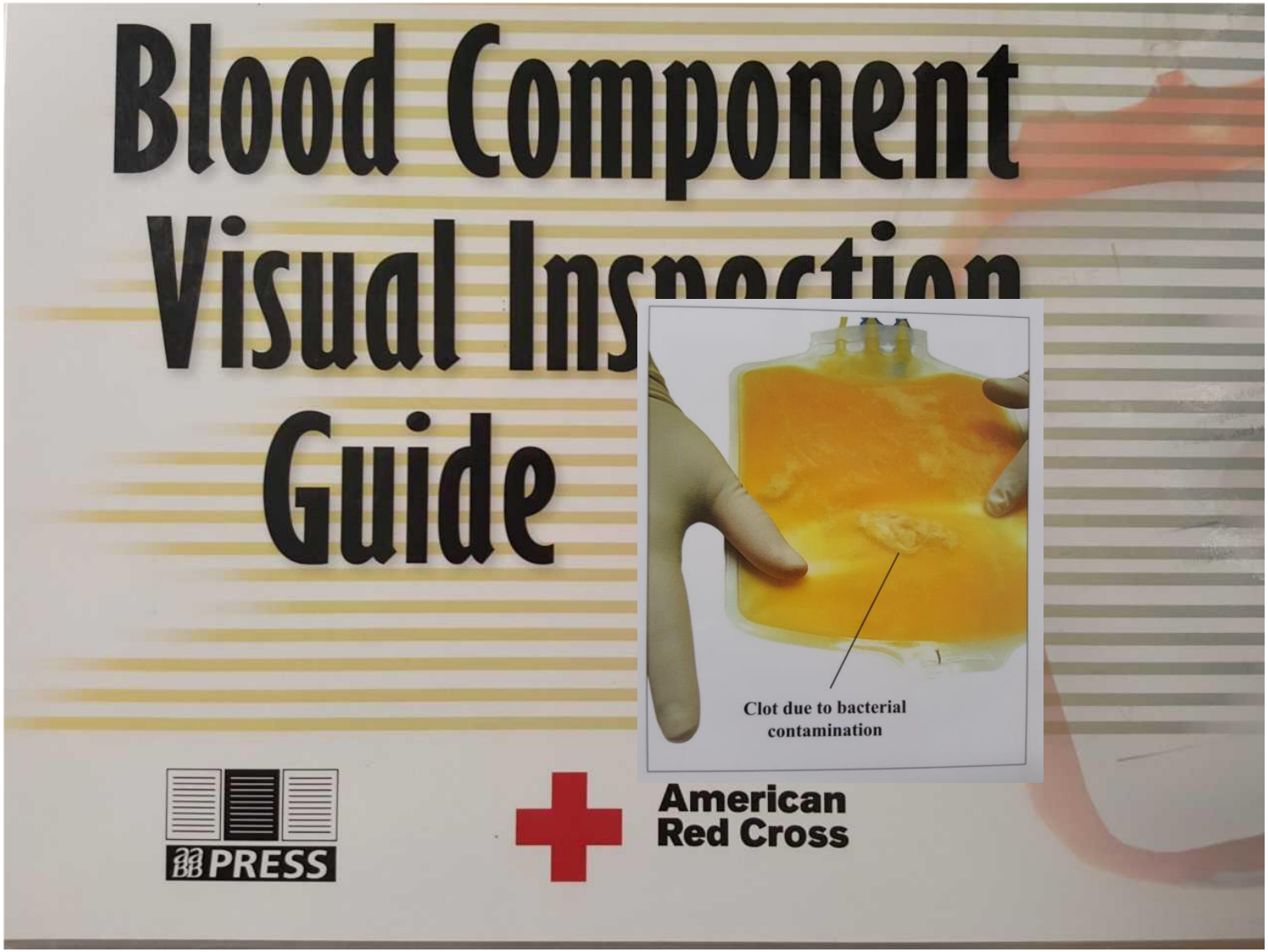
- Blood Center
- Pathogen reduction technology

  Chemical, UV, both
  - Currently only 1 FDA approved device
  - PAS-collected unit
  - Amotosalen +UVA technology
  - Reduces risk of TTI from many organisms
  - (Not all bacteria are detectable)

Intercalates into DNA and RNA, inactivates a broad spectrum of organisms

Reducing Risk *Post-collection: protecting the patient*

- Hospital
  - Visual inspection
  - Environment
  - Point of issue testing
    - High false positive rate
    - Possible false negatives
    - Not effective with all bacterial strains
    - Challenge for some hospitals to adopt


Blood Component
Visual Inspection
Guide
Clot due to bacterial contamination
PRESS
American Red Cross

Septic Transfusion Reaction

- Septic Transfusion Reaction (AABB TM 19th Ed.)
  - **Fever** > or = 38.5C (101F)
  - Chills
  - Rigors
  - Hypotension
  - Shock
  - Renal failure
  - DIC

Why Report the Reaction?

- Prevent transfusion of any other co-components.
- Donor is temporarily deferred during investigation.

§606.145 Control of bacterial contamination of platelets.

(c) In the event that a transfusion service identifies platelets as bacterially contaminated, the transfusion service must not release the product and must notify the blood collection establishment that provided the platelets. The transfusion service must take appropriate steps to identify the organism; these steps may include

How We Work Up A Suspected Septic Transfusion Reactions

- Hospital Blood Bank calls Donor Client Support Center
  - Donor is immediately temporarily deferred.
  - Products are recalled/quarantined, disposition determined.
- Hospital BB Medical Director → ARC Medical Director
- Review reaction paperwork and hospital lab. results
    - In-house modifications?
    - Gram stain, culture of donor and product.
- Request additional information as needed.
- Write an initial report within 24 hours of receipt.

Positive Results

- Both blood center and hospital attempt to determine the causative organism
- Original sample (in bottle) from parent bag
  - If positive then determine organism
  - Gram stain
  - Sample ‘daughter’ bags.
    - Confirmatory test is positive (with the same organism).
  - Review hospital reports of patient blood cultures pre/post.
  - Hospital may also culture the product bag(s).

True Positive: A positive result on both the initial test and the confirmatory test. Specifically for bacteria detection, a confirmatory test is a culture-based test performed on a different sample than the blood culture bottle or other sample used for the initial test. For example, a sample source for the confirmatory test could be the original platelet component. A subculture of the initial positive culture is not an adequate sample for this purpose. If initial testing was culture based, the confirmatory test can use the same method applied to the alternate sample source.

Donor

- Talk with donor to determine risk factors.
  - Any remarkable issues during donation?
  - Recent illness or symptoms of illness
  - Recent procedures
  - Contact with soil, certain animals, water, etc.

ORIGINAL ARTICLE BRIEF REPORT

Salmonella Sepsis Caused by a Platelet Transfusion from a Donor with a Pet Snake

Mehrdad Jafari, M.D., Ph.D., Jean Forsberg, M.D., Ronald O. Gilcher, M.D., James W. Smith, M.D., Ph.D., James M. Crutcher, M.D., M.P.H., Michael McDermott, B.S., Brent R. Brown, M.D., and James N. George, M.D.

Article Figures/Media

15 References 31 Citing Articles

October 3, 2002
N Engl J Med 2002; 347:1075-1078
DOI: 10.1056/NEJMoa021050

Donor

- Review donor records from day of donation.
- Review history of donations.
- Look for medical or other previous deferrals.

Review Processing Records

Review of:

- Apheresis or other collection records.
- Instrumentation or lab equipment.
- Observation of staff.
- Manufacturing records.

Fatalities 21CFR Sec 606.170(b)

- The transfusion service (who performed the compatibility testing) must report fatalities to FDA.
  - As soon as possible after confirming the fatality as being linked to the transfusion.
  - Submit a written report within 7 days.
    - Full report may take longer.
- The Blood Establishment can assist with information as needed.
- fatalities2@fda.hhs.gov and other methods of contact on FDA website.

Finalizing the Process

- Internal report
- Hospital report
- Letter to donor
- Call to donor
- Call to hospital
- Health Department or any other entity as required by law

Thank you