Blood Centers *of the* Pacific

Bacterial Contamination of Blood Products

Suchi Pandey, MD

BCC Board Meeting

9/23/2013

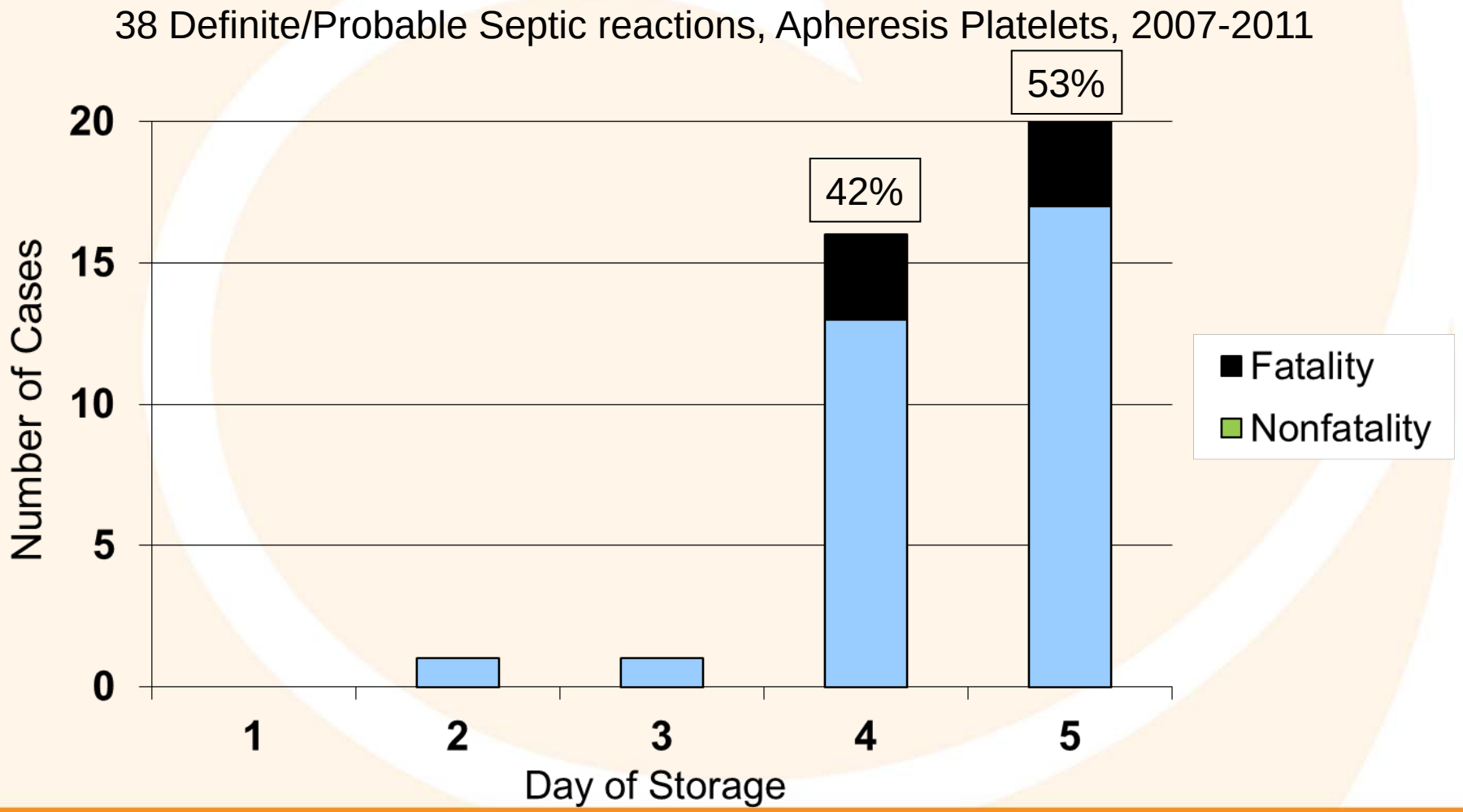
Objectives

- Define methods for decreasing risk of bacterial contamination.
- Identify the residual risk of contamination in platelets that test negative in culture systems.
- Discuss additional strategies to ↓risk

Platelet Contamination

- PLT storage at room temperature (20-24C) → promotes bacterial growth
- At the time of collection, number of bacterial organisms may be very low
- During storage → bacteria proliferate
- Reason for short shelf life (5 days) of PLTs
  - Higher risk of reaction on Day 4 or 5 of transfusion

Septic Reactions – Day of Storage



Benjamin R et al. Vox Sang 2013; 1-5

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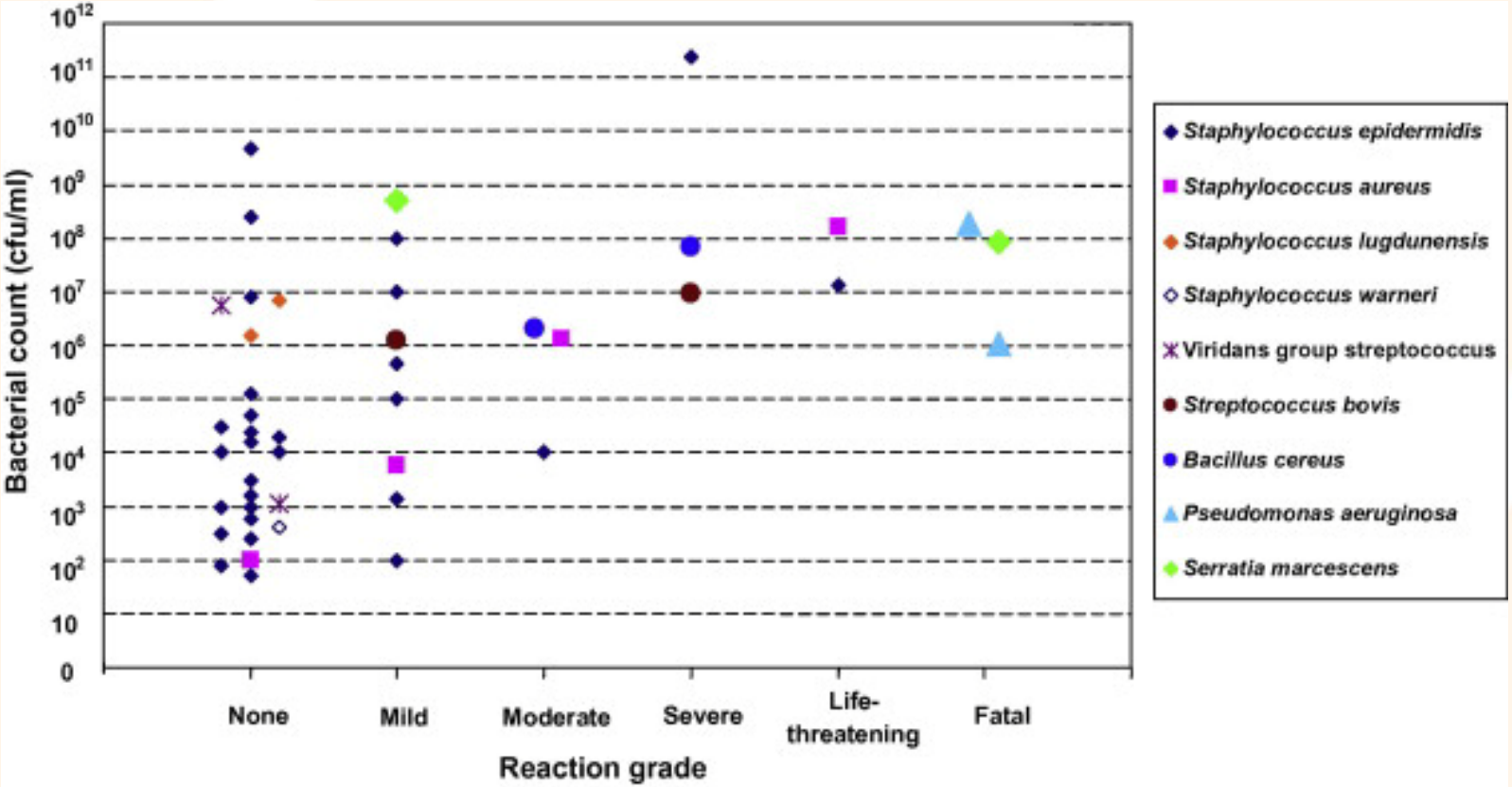
Clinical Presentation

- Wide range of clinical sequelae from transfusion of contaminated platelets:
  - Asymptomatic
  - Fever, rigors, tachycardia, hypotension
  - Acute sepsis, DIC, lung injury, organ failure, death

Septic Reactions (PLTs)

- Reaction in patient depends on virulence of bacterial species, inoculum and patient factors



Statistically significant correlation between severity of reaction and bacterial counts of $>10^5$ CFU/ml

Jacobs et al. Clin Infect Dis 2008; 46: 1214-20

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US Platelet Transfusions

- Over 2,169,000 apheresis-equivalent units are transfused annually in the form of 1.97 million apheresis units + 199,000 pools (933,000 WBP)[1]
- California – Only apheresis platelets are collected and transfused.[2]

1. Whitaker, 2011 NBCUS
2. Medical Technical Advisory Committee Meeting 4/2013

Contaminated platelet outcomes

- Estimated by passive surveillance, 188/million apheresis units annually are contaminated[1]
- Based on utilization data (1,970,000), approximately 370 bacterially contaminated units are transfused annually[2]
- Surveillance data suggest a rate of septic reactions at 9.4/million, translating to about 19 septic reactions expected annually[1,2]
- Fatality rate associated with bacterial contaminated platelets is estimated to be 0.98/million for a fatality total of about 2/year[1,2]

1 Benjamin R et al. Vox Sang 2013; 1-5
2 Whitaker, 2011 NBCUS

Sources of Bacterial Contamination

- Skin Surface Contamination
- Phlebotomy Core
- Donor Bacteremia (occult)
- Containers and Disposables - Rare

Heltberg et al. transfusion 1993; 33:221-7

Organisms

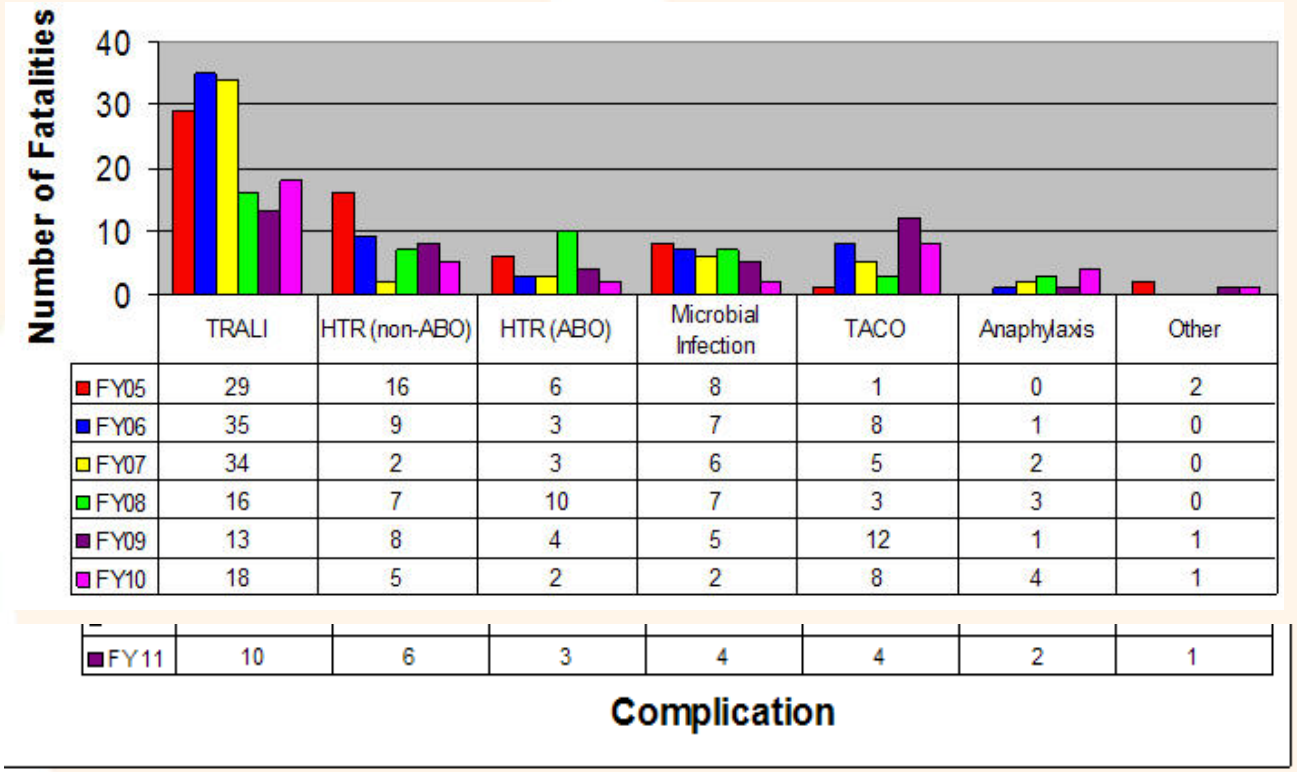
- Gram positive bacteria on skin are the most frequent contaminants of platelet units.
  - Coag negative *Staphylococcus*
  - *Streptococcus species*
  - Initial lag phase of growth
  - Asymptomatic to severe reactions
- Gram negative organisms
  - Usually cause severe rxns

ARC data: 2007-2011

Bacterial isolate	Hemovigilance data Septic reactions	(%)	BacT/Alert Culture Data Confirmed positive	(%)
Coag. negative *Staphylococcus*	22 (1)	58	141	33·8
Streptococcus spp.	4	11	127	30·5
Staphylococcus aureus	8 (3)	21	39	9·4
Bacillus spp.			6	1·4
Corynebacterium spp.			3	0·7
Micrococcus spp.				
Enterococcus spp.			6	1·4
Clostridium perfringens	1	3		
Escherichiae coli			32	7·7
Klebsiella spp.	1	3	20	4·8
Listeria spp.			5	1·2
Proteus mirabilis			1	0·2
Serratia spp.			15	3·6
Pseudomonas spp.			2	0·5
Citrobacter spp.			2	0·5
Haemophilus spp.				
Salmonella spp.			2	0·5
Enterobacter spp.	1	3	8	1·9
Acinetobacter spp.	1	3	1	0·2
Other			7	1·7
Total	38		417	

Benjamin R et al. Vox Sang 2013; 1-5

Transfusion-Related Fatalities by Complication, FY2005 through FY2011



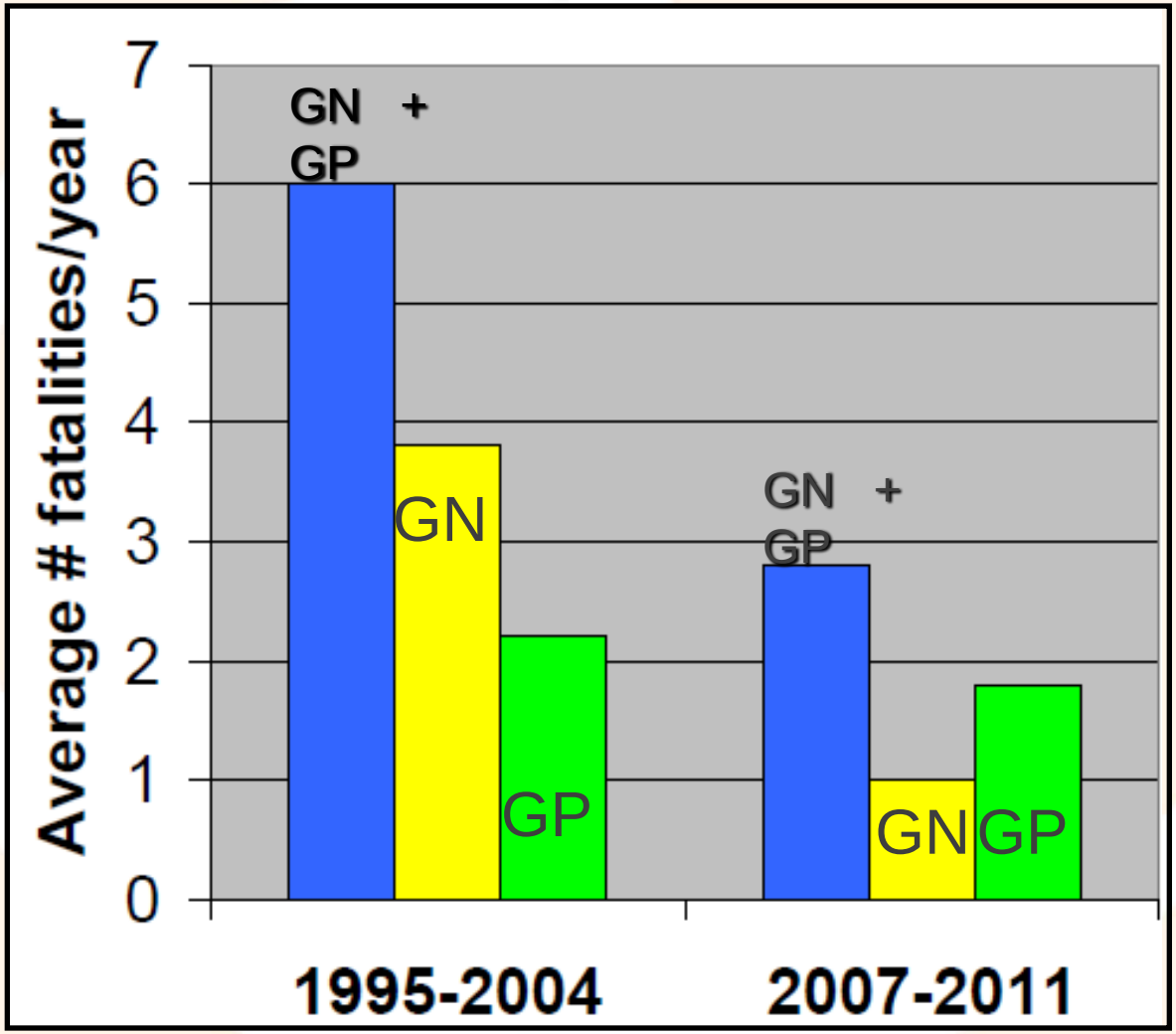
	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY05	29	16	6	8	1	0	2
FY06	35	9	3	7	8	1	0
FY07	34	2	3	6	5	2	0
FY08	16	7	10	7	3	3	0
FY09	13	8	4	5	12	1	1
FY10	18	5	2	2	8	4	1
FY11	10	6	3	4	4	2	1

Since 2004:

Babesia is #1 (12 fatalities)

Staphylococcus aureus is #2 and accounted for 20% (7 fatalities)

Fatalities reported to FDA associated with Bacterial Contamination of Platelets



N=60 N=14

Courtesy Dr. Salim Haddad
FDA/CBER

Platelet bacterial contamination risk mitigation strategies

AABB Standard: Require methods to limit, detect, or inactivate bacteria in PLTs. Detection methods shall be FDA approved (or have equivalent sensitivity).

Methods to Limit Contamination

- Pre-phlebotomy disinfection of phlebotomy site
- Diversion of the 1st 10-40mL of the collection to a satellite pouch can significantly reduce bacterial load
  - American Red Cross: Rates of contamination of apheresis platelets decreased with diversion pouch (27.2/100,000 →14.7/100,000)

Goldman et al. Transfusion 1997; 37:309-312
Eder et al. Transfusion 2009; 49: 1554-63

Methods to Detect Contamination

What FDA approved detection methods are available?

Culture based methods

- Pall eBDS (2002)
- Bio-Merieux BacT/Alert 3D (2003)
- Acrodose PL system (WB-derived PLTs)

Point-of-Issue tests

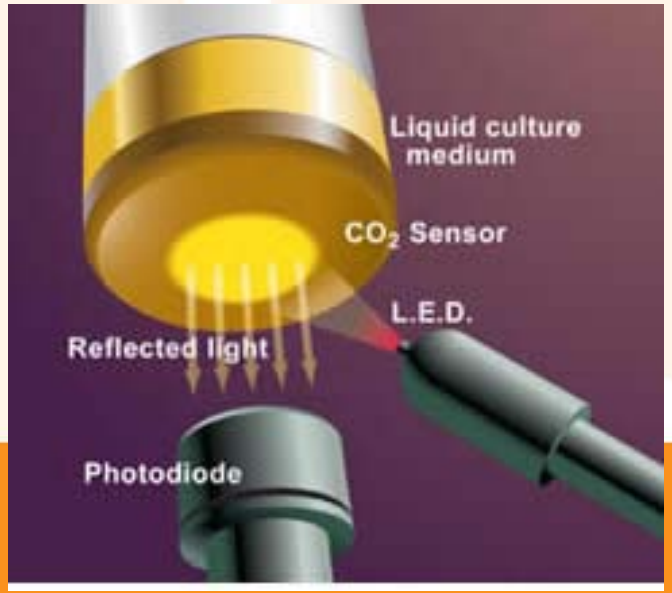
- Verax PGD (2009)
- Immunetics BacTx (2012)

FDA-cleared Culture-based Methods

- Cleared for quality control (QC)
- Most commonly used by most collection centers as a release test.
- Analytical sensitivity 1-10 CFU/mL

bioMeriuex BacT/Alert System (used at BCP)

- Microorganisms multiply in the media, generating CO2. As CO2 increases, the sensor in the bottle turns yellow.
- Measuring reflected light, the BacT/ALERT 3D monitors and detects color changes



Bacterial Testing in Platelets

Collection of a SDP unit.

Sampling: Typically 24 hours after collection†

Bottle Incubation:

*Incubation time prior to release varies (0-24 hours)**

If bottle turns positive, bottles and platelet unit are sent for culture.

If unit is negative after initial incubation period unit is split and released

Even after platelet is released, bottles incubate for 5 full days

† Typical sample volume is 8ml (~1.7% of collection volume)

*BSI and ARC use a 12 hour initial incubation period prior to release.

Residual Risk and Post Surveillance Studies

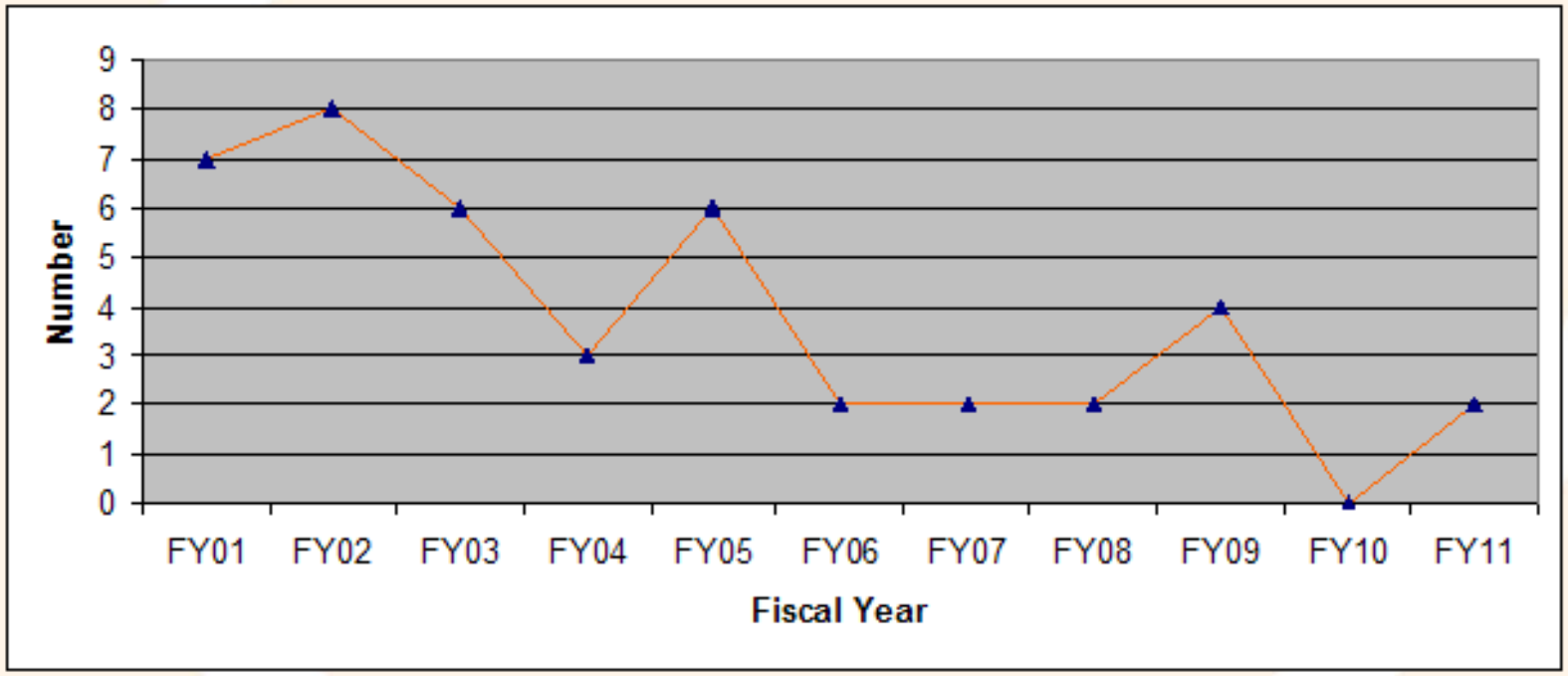
Residual Risk of Reaction Post Screening

	Septic transfusion reaction (STR) rate	Fatality rate from a STR
Pre-screening – ARC	**1:40,000**	**1:240,000**
Post-screening – ARC (2004-2006)	**1:75,000** ***1:193,305 (single needle and diversion pouch)**	**1:500,000**
Post-screening – BSI (2003-2005)	**1:242,786 (mostly single needle with diversion pouch)**	

- Implementation of screening resulted in significant decrease in reported reactions and fatalities.
- American Red Cross: 20 septic reactions and 3 fatalities (2 Staph aureus and 1 Coag Neg Staph) reported during the study period

1. Kleinman et al. Transfusion 2006; 46:1787-1793
2. Eder et al. Transfusion 2007; 47: 1134-1142

2011 FDA Fatality Report:
Bacterial Infection by Apheresis Platelets, FY2001 through FY2011



PASSPORT Study

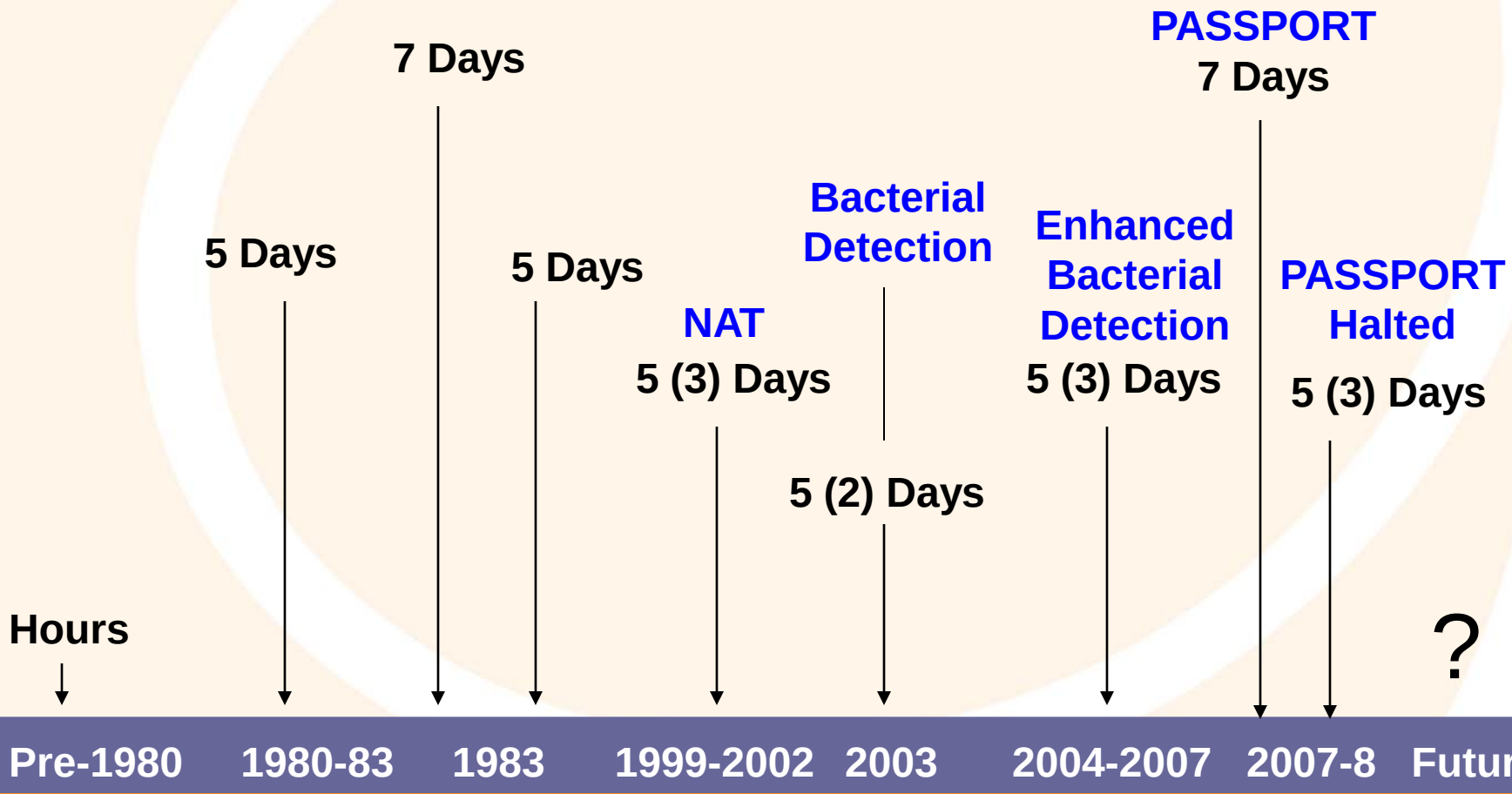
- 2005 FDA approved platelet bags for 7 day storage
- 2005 FDA approves 7 day shelf life for centers in PASSPORT study
  - Culture on Day 1
  - Re-culture on Days 6-7
- Primary endpoint: show that, with 95% CI, culture at Day 1 would decrease contamination rate to ≤1/5,000

Life with 7 Day platelets

- ↓ platelet shortages
- ↓ delays in platelet transfusion
- ↓ need to triage platelet transfusion in hospitals
- Platelet expiration rate: 10% → 2%

- 2008: PASSPORT terminated early due to failure to meet endpoint
  - Return to 5 day platelets

A Brief History of Platelet Shelf Life



Study	Type Platelets	Diversion Pouch?	Bottle type	Sample Day(s)	Inoculum Vol (ml)	Time of Inoculum post collection
PASSPORT[1]	Apheresis	Yes	Aerobic Anaerobic	Day 1 Outdate(8)	8 total	24-36 hr
ARC[2]	Apheresis	Partial	Aerobic	Day 1	8	>24 hr
Blood Systems[3]	Apheresis	Yes	Aerobic	Day 1	8	24 -36 hr
Canadian Blood Services[4]		Yes	Aerobic	Day 1	8	24-48 hr
Irish Blood Services[5]	Apheresis Buffy Coat	Yes	Aerobic Anaerobic	Day 1 Outdate (8)	16-20 total	??
Welch Blood Services[6]	Apheresis Buffy Coat	Yes	Aerobic Anaerobic	Day 2 Outdate (8)	15-20 total	??
NHSBT[7]	Apheresis Buffy Coat	Yes	Aerobic Anaerobic	Day 2	16-48 total	36-48 hr

1. Dumont,Transfusion 2010;50:589
2. Eder, Transfusion 2007;47:1134
3. Tomasulo, Transfusion 2012:52;1576
4. Jenkins, Transfusion 2011;51:2555-2565
5. Vox Sang 2008;95:13-193
6. Pearce, Transf Med 2011:21:25-32
7. McDonald, Vox Sang 2012; 103(suppl1) 176

	TP Rate on Day 1	TP Rate on Day 4	Residual Risk[3]	Test Sens. Day 1 Culture
PASSPORT[1]	1/4,310		1/1,500[4]	26%
ARC[1]	1/5,000			
BSI[1]	1/8,431			
Canada[1]	1/7,800			
IBTS[1,2]	1/3,088	1/3,310	1/1,183[4]	22%
Wales[1,2]	1/1,566		1/1,073[4]	40%
Holme[1]	1/5,133			
Yomtovian[1]	1/7,587			
Jacobs[1]			1/2,302[5]	

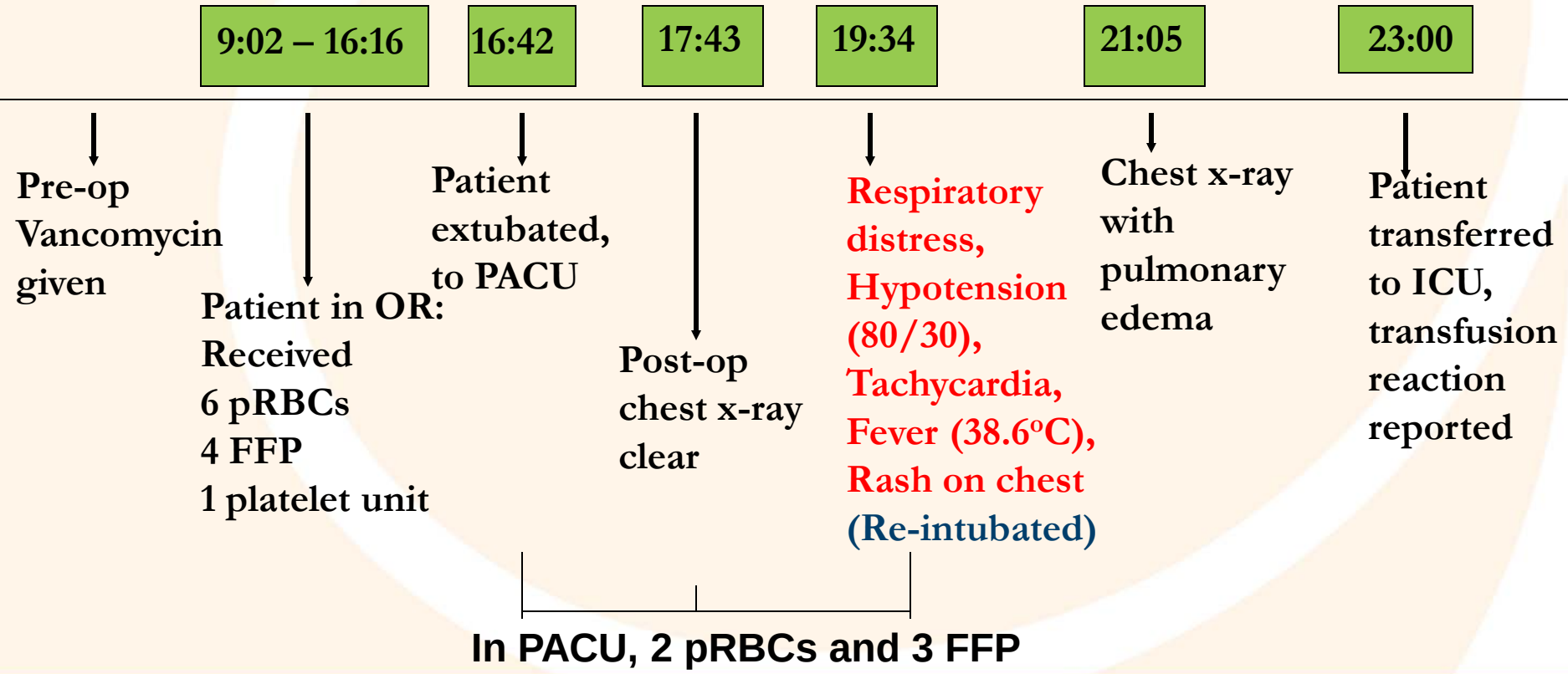
[1]Apheresis [2] WBD pools [3]Majority of G(+) organisms [4]Outdate [5]Day of Transfusion

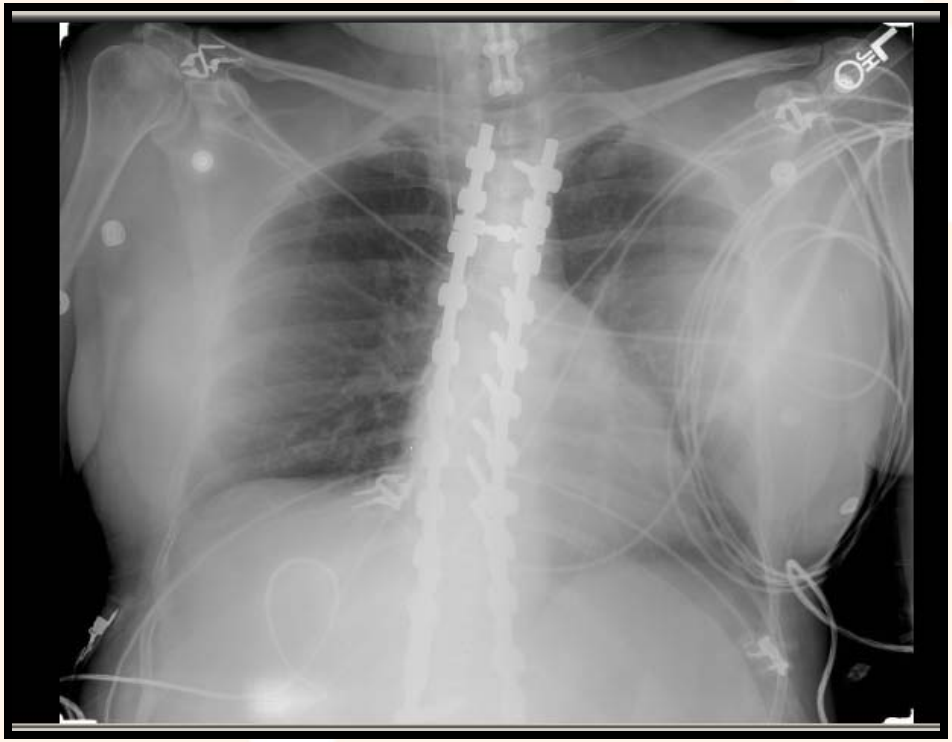
Courtesy Dr. Salim Haddad FDA/CBER

The Case I Will Never Forget….

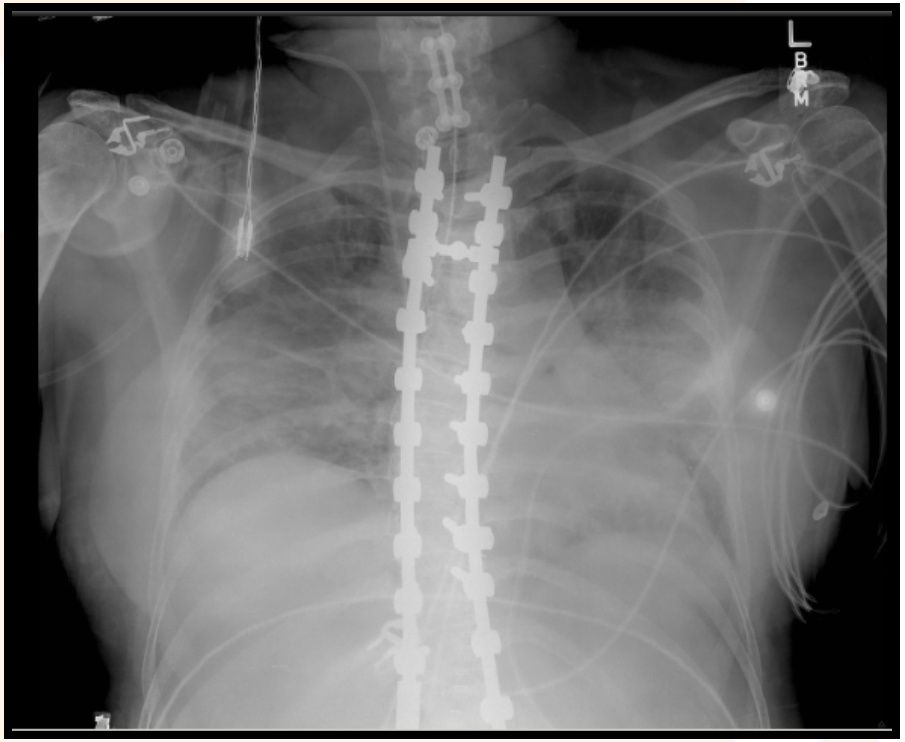
Patient #1 – 47yo female with scoliosis admitted for a posterior spinal fusion

Day 1 – patient admitted for surgery





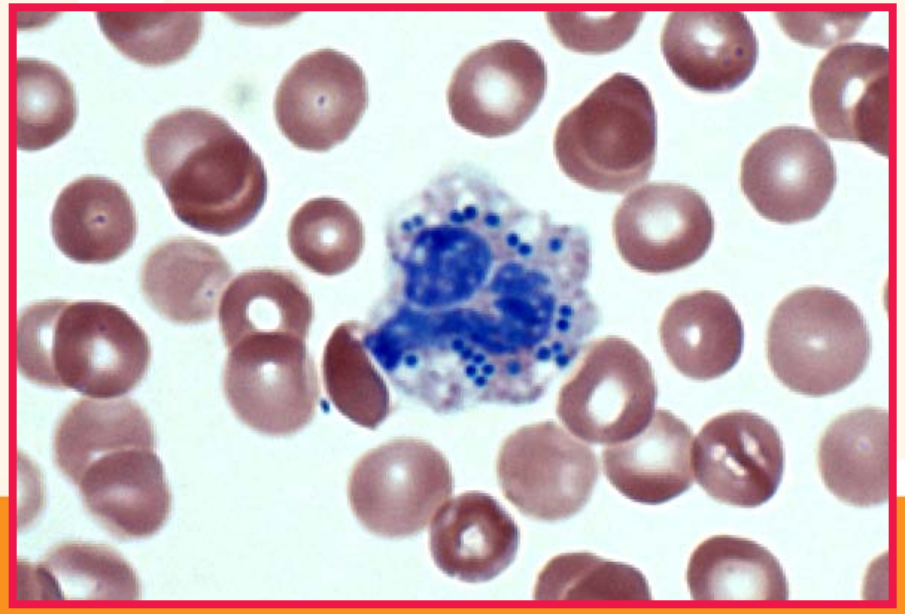
Chest x-ray at 17:43 (immediately post-op)



Chest x-ray at 21:05 (in PACU)

- **Blood gas: severe hypoxemia**
- **Central venous pressure normal**

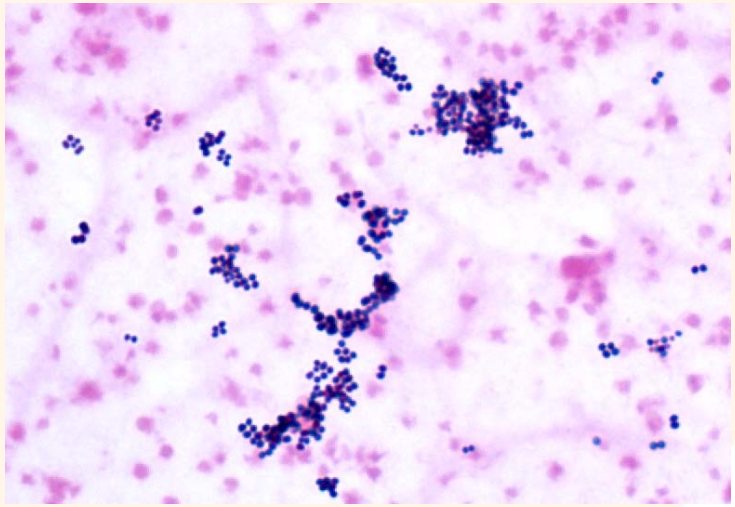
- The case did fit clinical and radiologic criteria for TRALI – initially reported to BCP as possible TRALI
- However, by early morning of day 2, patient still had sustained hypotension despite pressors and multi organ failure (renal failure and liver damage)



Peripheral Blood Smear on Day 2

Microbiology Results

- One PLT was transfused in OR ~8 hours before reaction onset.



Gram stain on empty bag: Gram + cocci in clusters

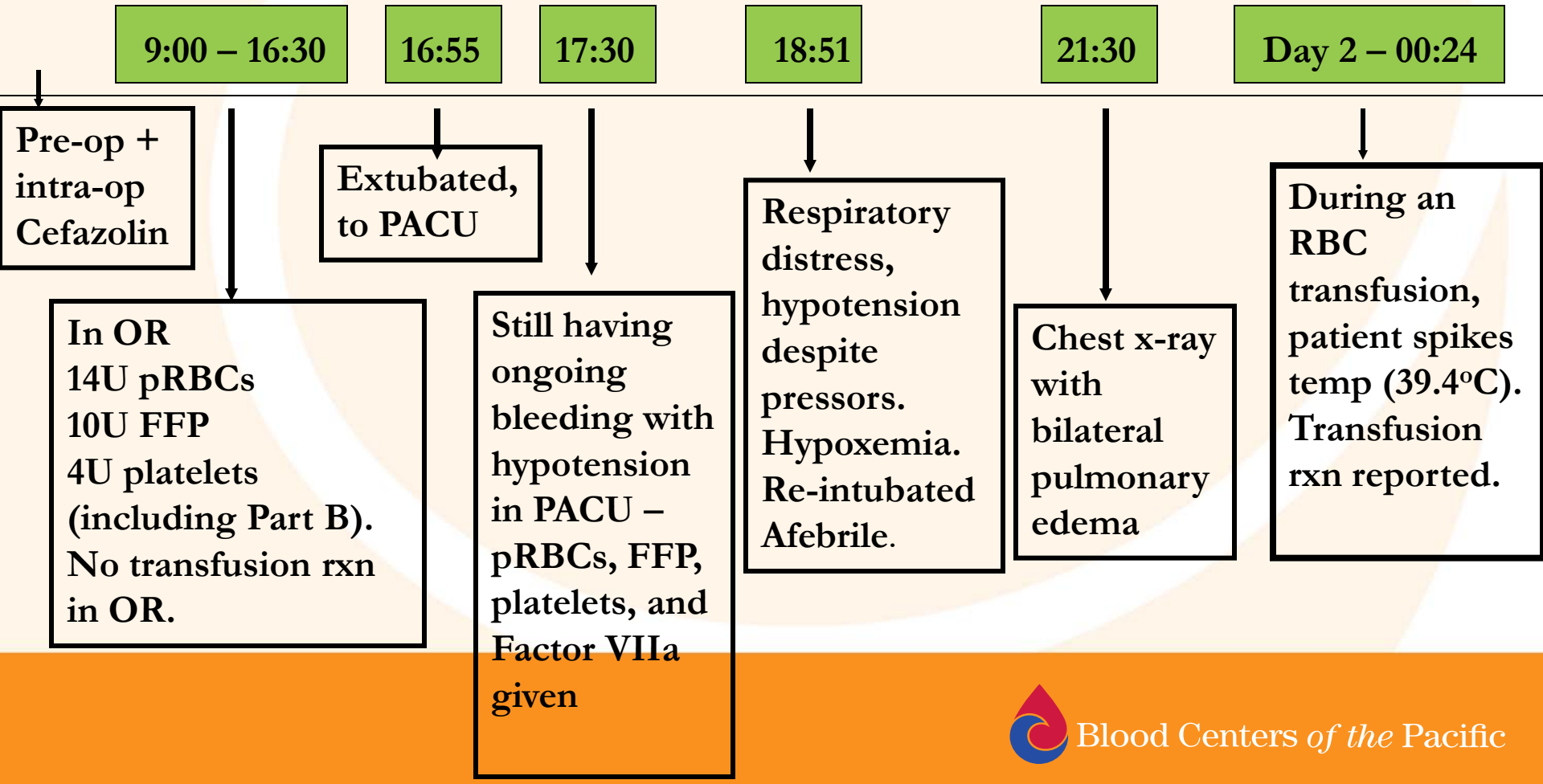
- Blood cultures from empty bag and patient
  - Grew *Staphylococcus aureus*

More bad news….

- That platelet unit had a part B (split component). Part B had been issued around the same time to another patient undergoing spinal surgery (patient #2)

Patient #2 – In the OR Next Door. Admitted for posterior spinal fusion

Day 1 – same day as patient #1's surgery



The story continues…

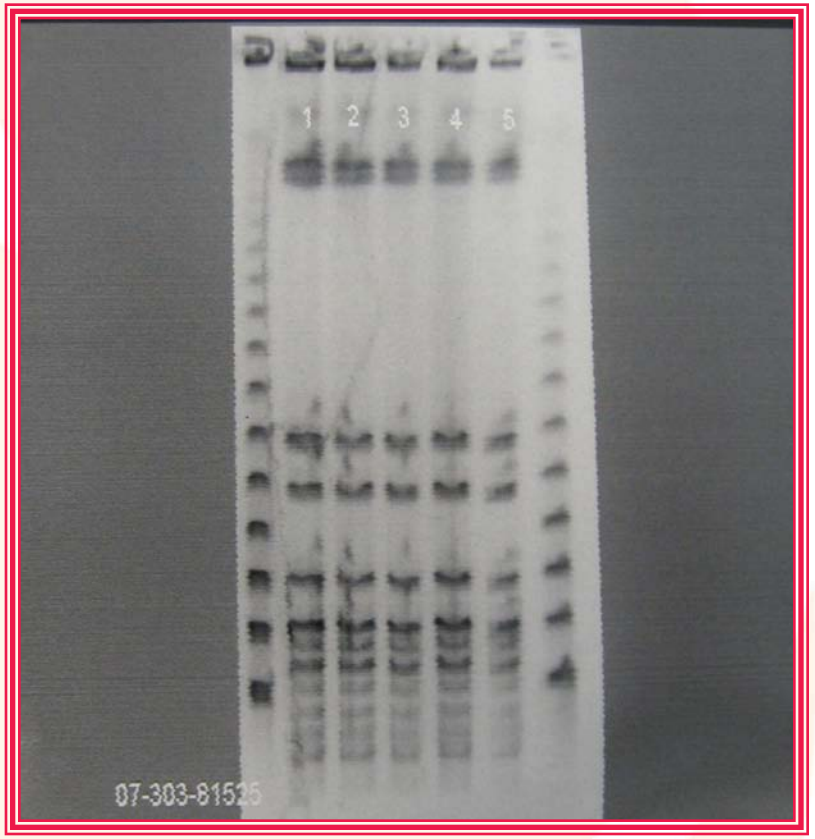
- On Day 2, informed patient # 2's clinical team that the patient had received Part B of a contaminated platelet unit. Patient started on broad spectrum antibiotics.

- Empty PLT bag grew *Staph aureus.* Patient's cultures remained negative

- Both patients remained in ICU for extended period. Eventually recovered.

Blood Center Investigation Summary

- Double PLT was part of PASSPORT study
- Transfused on Day 4 of shelf life
- 8ml sample innoculated (4ml aerobic and 4 ml anaerobic) 24 hours after collection
- BacT bottle remained negative for 7 days
- Donor investigation
  - Asymptomatic, nasal carrier of S. aureus
- Pulse Field Gel Electropheresis of S. aureus
  - Identical among donor, Patient #1, platelets #1 and #2



Conclusion

- False negative BacT result:
  - S. aureus with long lag phase in platelets
  - Missed in 8mL sample at day 1
  - Grew in platelets
- Atypical septic transfusion reaction (delayed, initial symptoms c/w TRALI)
- Severe reaction occurred at Day 4 (what if PLT had been transfused at Day 7?)

Options for Detection Enhancement

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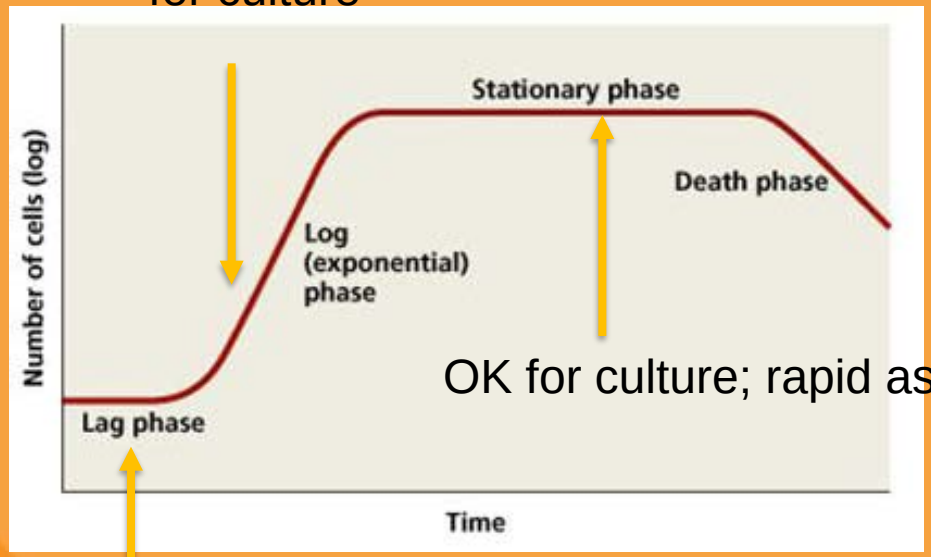
Bacterial Growth and Impact on Detection

Optimal sampling for culture

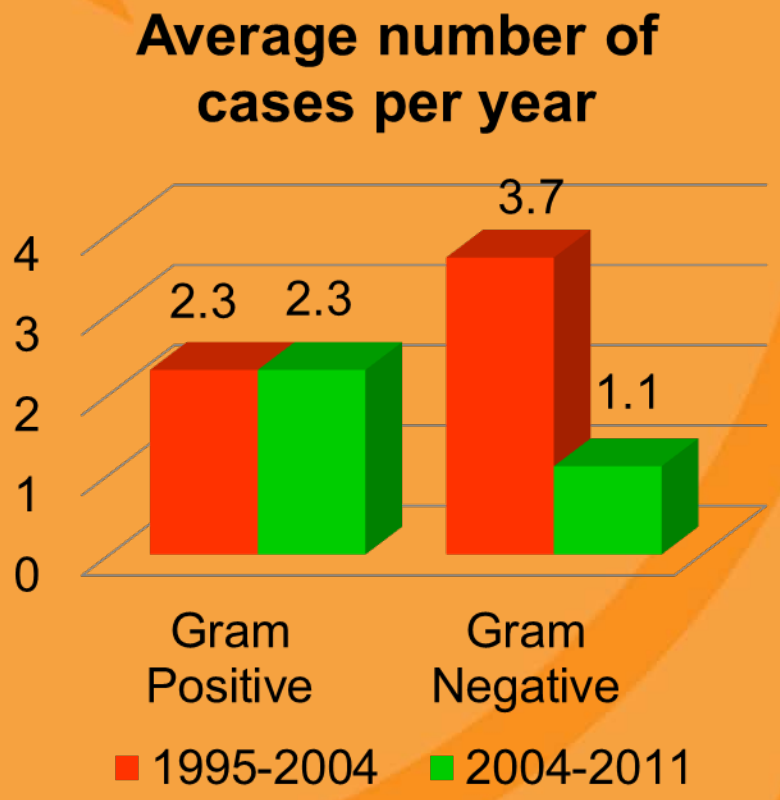


OK for culture; rapid assay

Sampling error

Fatalities reported to FDA and associated with Bacterial Contamination of Platelets

- Early culture of apheresis units appears to be effective at intercepting most Gram negative contaminants but has not effectively addressed Gram positive contaminants



Modified Dr. Michael Jacobs

What can be done to enhance platelet bacterial safety?

Enhanced detection

- Sample greater volume
- Sample later
- Additional point-of-issue testing

Reduce patient risk

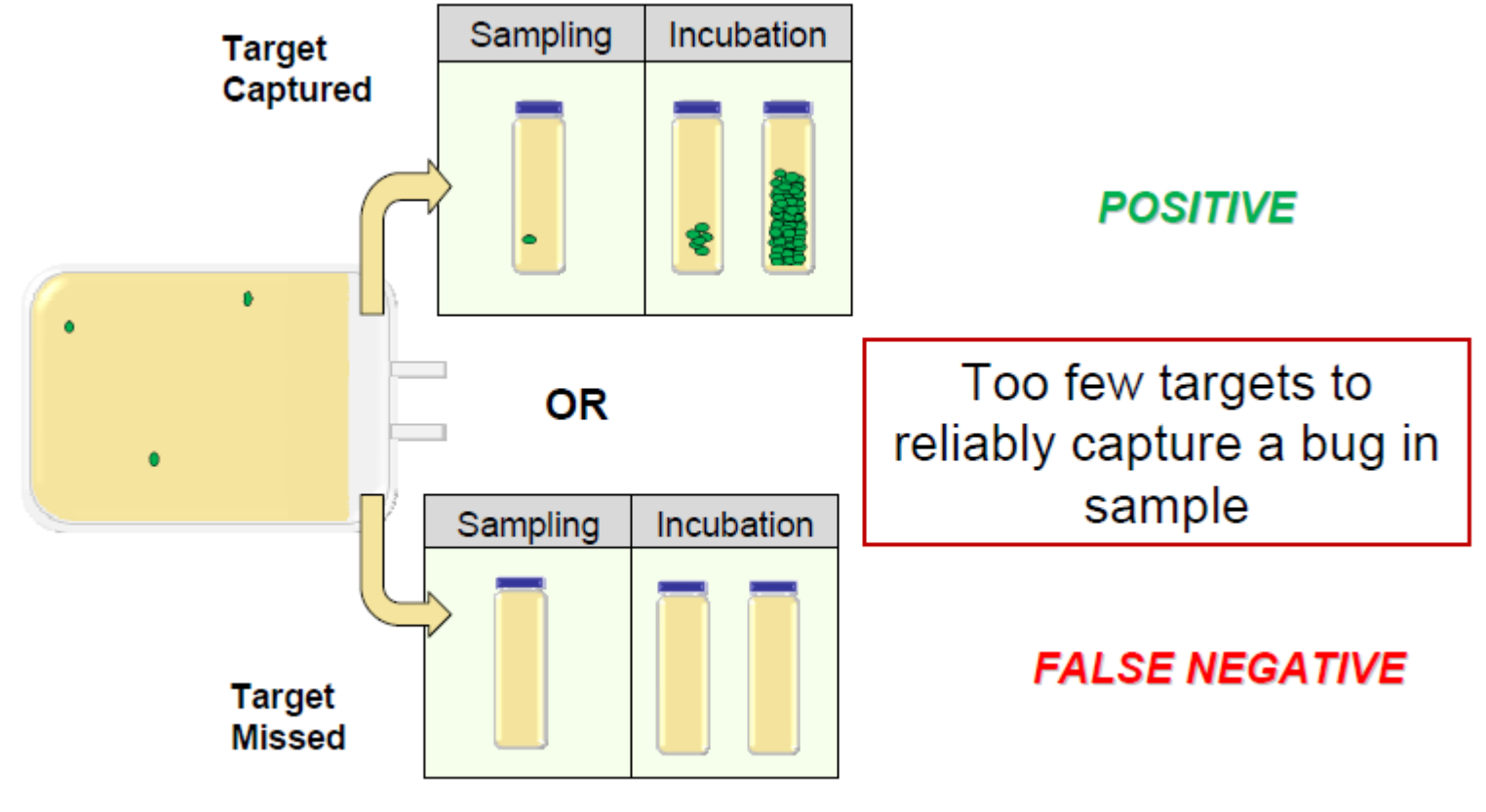
- Shorten shelf-life

Reduce contamination

- Greater “sample” diversion
- Cleaner venipuncture methods

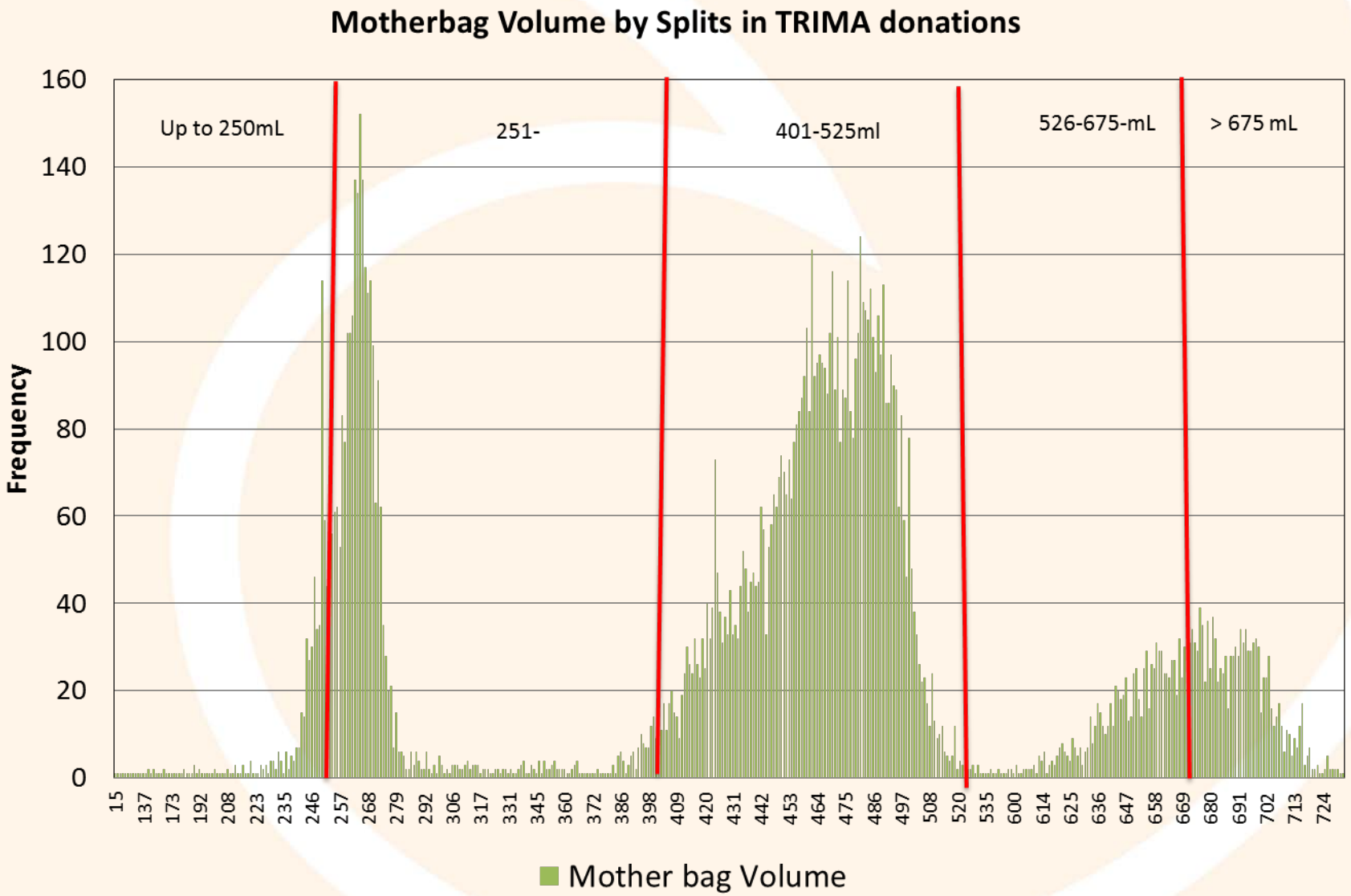
Pathogen inactivation/reduction

Option: Increase volume of inoculum



The concentration of bacteria at the time of sampling can be as low as 1-60 CFU per bag
This represents ~0.002-0.3 CFU/ml which is below the sensitivity of BacT/ALERT system
Increasing sample will increase sensitivity.

Courtesy Dr. Michael Jacobs
Benjamin R et al. Vox Sang 2013; 1-5



~85,000 PLT apheresis procedures at BSI in a 12 month period.

~35% -- 1 unit
~53% -- 2 units
~12% -- 3 units

Fixed Volume vs. Fixed Proportion Sampling

Fixed proportion of sampling for bacterial detection will result in a larger inoculation volume

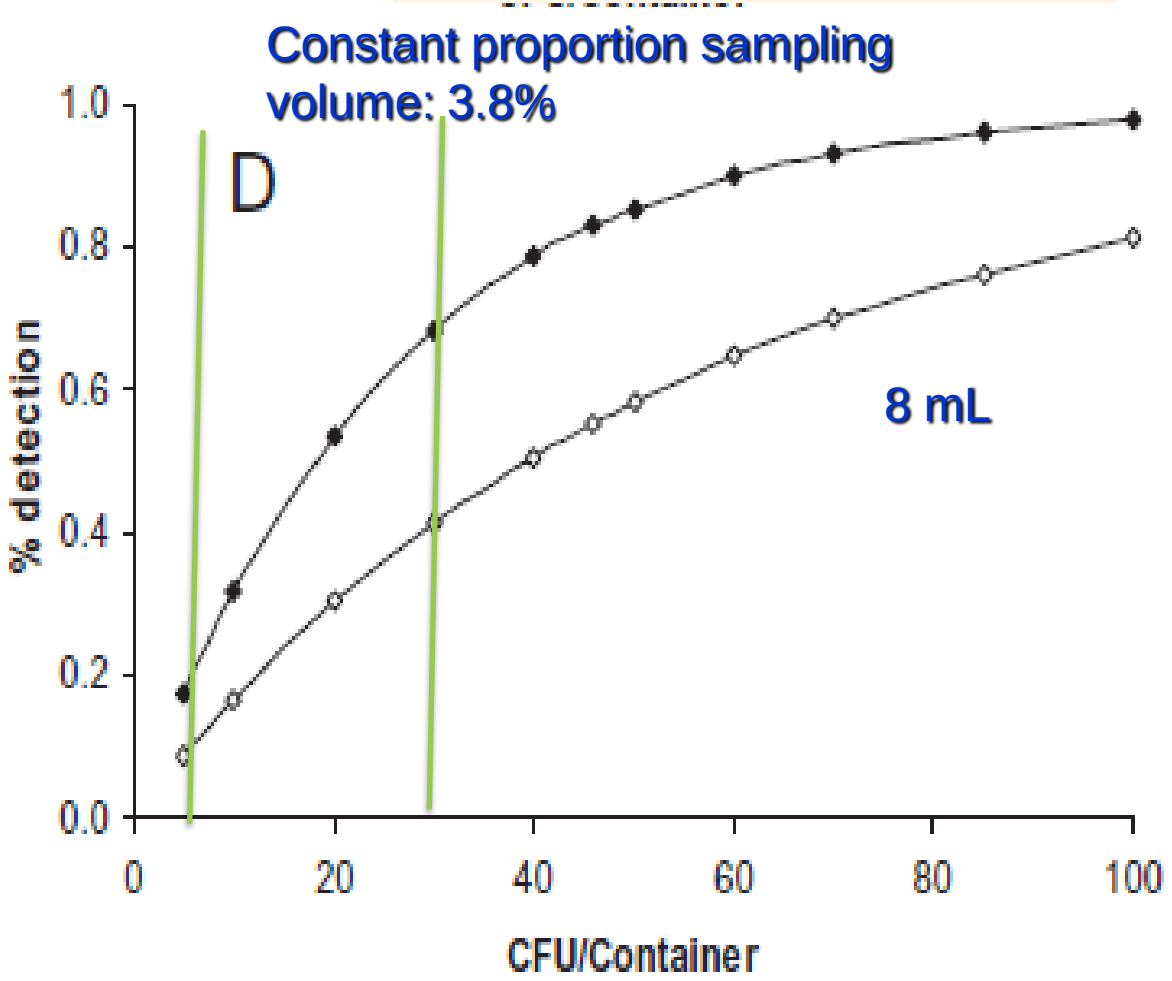
- Constant *volume*
  - **8** mL – single platelet collection (**3.2%**)
  - **8** mL – double platelet collection (**1.6%**)
  - **8** mL – triple platelet collection (**1.2%**)
- Constant *proportion*
  - **9.5** mL – single platelet collection (**3.8%**)
  - **19** mL – double platelet collection (**3.8%**)
  - **25.6** mL – triple platelet collection (**3.8%**)

Current procedure at BSI/BCP: ~10ml for singles, ~20 ml for doubles/triples (2 bottles)

Culture Using a Constant Proportion Sampling Volume[1]

- Poisson distribution modeling[1]

CFU/ bag	8ml sample	Constant 3.8% sample
5	9% detection	17% detection
30	41% detection	68% detection



1. Tomasulo and Wagner Transfusion 2012;53:835-842

BSI BacT Data (True Positives)

True Positive Rate (BSI):

Hours to Positive	Organism	Comment
9.8	Staphylococcus aureus (BCP)	
10.8	Streptococcus viridans	
11.0	Staphylococcus aureus	
13.2	Streptococcus pneumoniae	
12.9	Serratia marcescans (BCP)	
15.6	Enterobacter aerogenes	
17.4	Coagulase negative Staphylococcus	
17.6	Coagulase negative Staphylococcus	
19.4	Coagulase negative Staphylococcus	
21.7	Coagulase negative Staphylococcus (BCP)	
28.08	**Staphylococcus aureus**	
33.0	Staphylococcus epidermidis (BCP) – unit already transfused. No rxn.	

September 2012 - April 2013 (8 months): After increasing sample size

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Cost of intervention

- Cost Items
  - Maintain current dose/bag by decreasing split rate
  - More Bottles
    - Estimated 25,011 bottles vs 19,651
  - New TP and DN rate
  - Total 5% increase in expense
- Select different sampling software and work with vendors/GPOs to improve procedures
- **Total cost increase < 1% and no price increase**

Option: Shorten the shelf-life to 4 days

- Canadian Study[1]
  - Apheresis: 2 STRs (1 fatality): both day 5
  - Apheresis and pooled platelets: 5 STRs: 4 on day 5 (including 1 fatality), 1 on day 3
- Germany[3]: 80% of fatalities were from day 5 platelets
- ARC data[4] :100% fatalities from day 5 platelets
- ARC data[5] :50% fatality day 4, 50% day 5

1. Jenkins, Transfusion 2011;51:2555-2565
2. Dumont,Transfusion 2010;50:589
3. Siries, Vox Sang 2011;101:191
4. Eder, Transfusion 2007;47:1134
5. Benjamin R et al. Vox Sang 2013; 1-5

Option: Shorten the shelf-life to 4 days: availability?

	≤2 days	3 days	4 days	5 days
Jacobs[1] 27,620 units	15%	30%	24%	31%
Welsby[2] 2614 Units	20%	33%	24%	22%
Kleinman[3]				~20-30%
Katz[4]	3%	12%	41%	44%

1.Transfusion 2011;51:2573
2. Transfusion 2010;50:2311
3. Transfusion 2009;49:903
4. Katz, Americas Blood Centers

Option: Repeat/Later samples with Increase Sample volume (Combination of approaches)

- Detect greater proportion of contaminating organisms (those entering growth phase after 24 hr)

- Shorten shelf life when culture @ 24 hours (4 day outdate)

- Inoculate @ 48 hrs to capture late growing organisms (6 day outdate) → Requires FDA approval

OR

- Inoculate @ 72 hrs to capture later growing organisms (7 day outdate) → Requires FDA approval

- Release negative units 12 hrs post inoculation. Interdict transfusion of positive units within 2 hours of machine signal for released platelets

Option: Repeat/Later samples with Increased Sample volume (Combination of approaches)

- **MAJOR Operational Impact**
- Possible Tiered Release Strategy
  - Early culture on 50% of platelets – 3 day
  - 48 hour culture on remaining platelets – 5 day

Surveillance (if mitigation strategy on prior slide is implemented)

- Surveillance culture of outdated platelets
  - Compare surveillance results

Screening Culture	Shelf Life	Outdate	Surveillance Culture
24 Hours	4 Day	Midnight Day 4	≥ Day 5
48 Hours	6 Day	Midnight Day 6	≥ Day 7
72 Hours	7 Day	Midnight Day 7	≥ Day 8

Point-of-issue Assays

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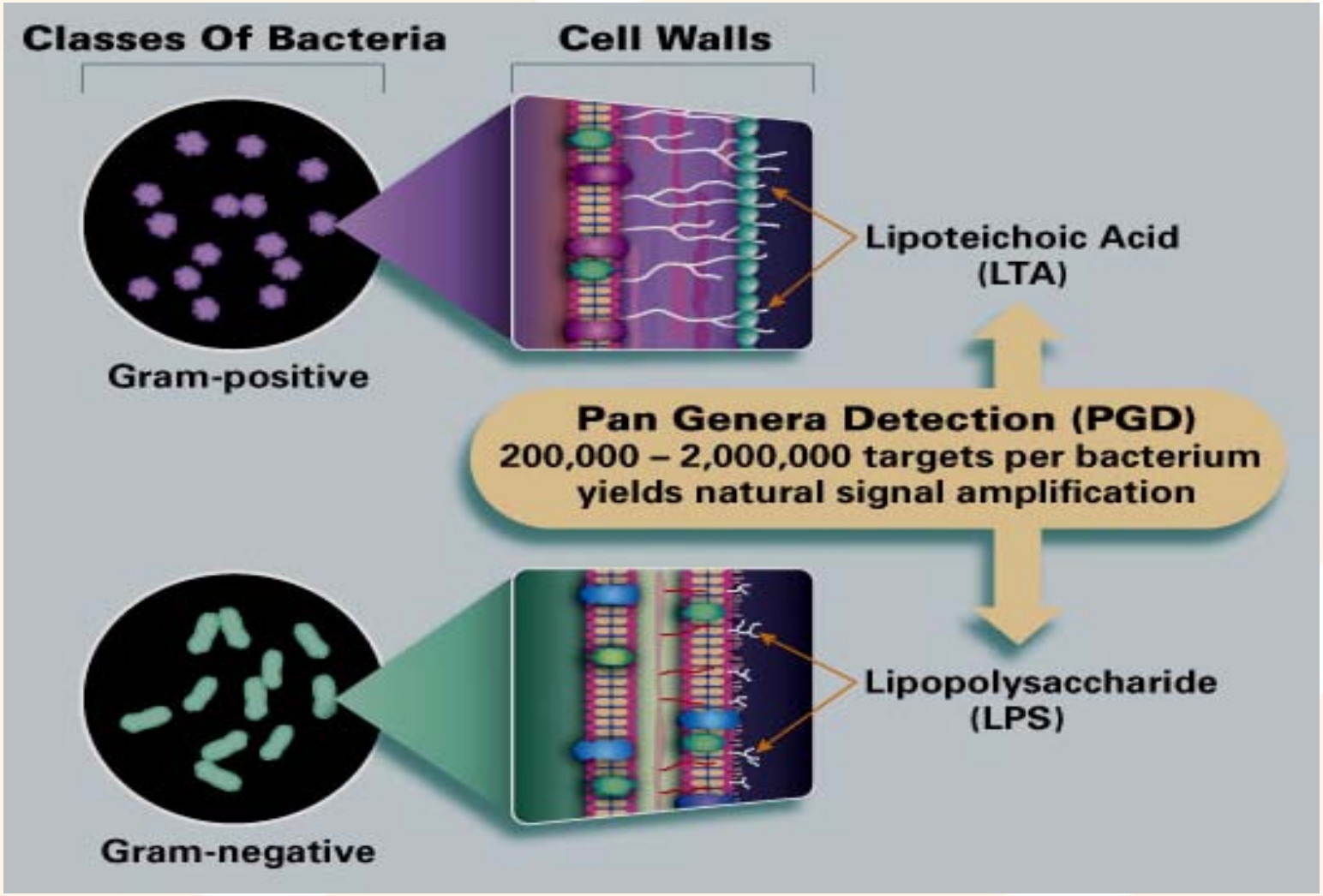
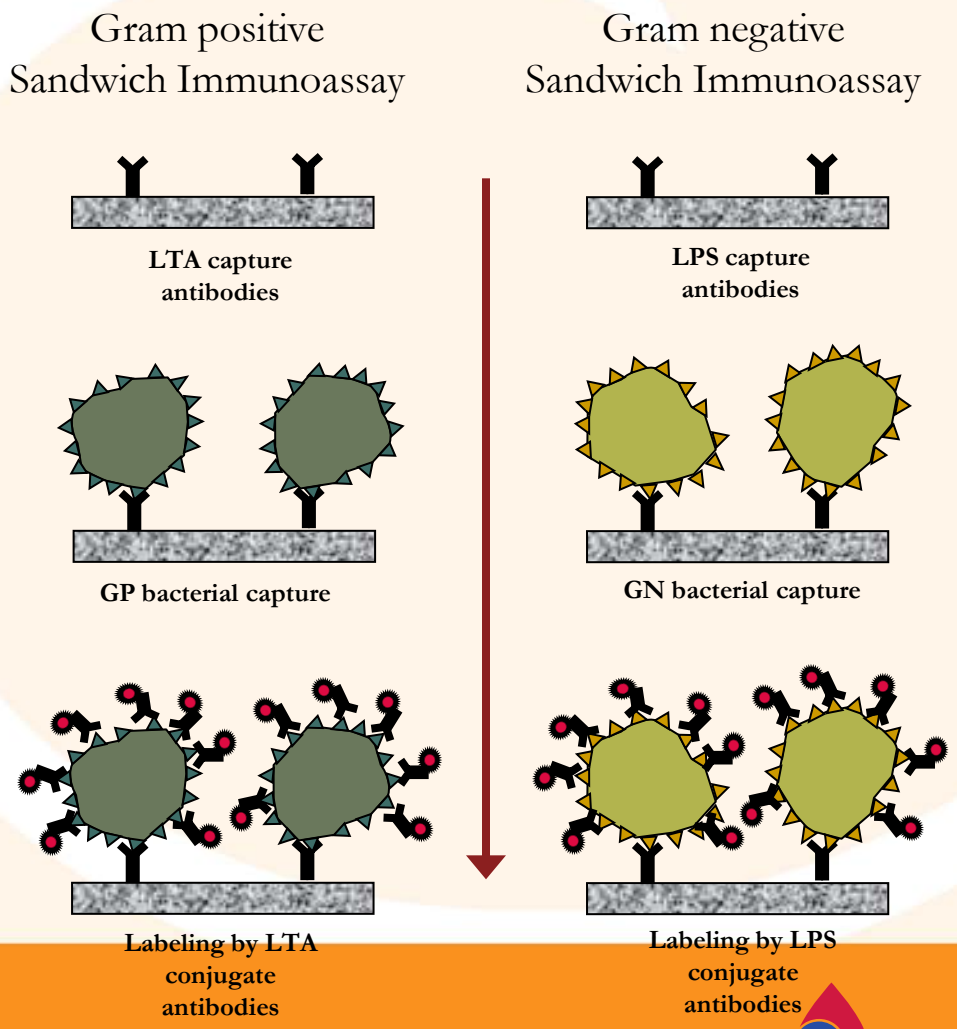
Sensitive Point of Issue Testing

- **Qualitative Immunoassay for detection of GP and GN bacteria.**
- **FDA approved as an adjunct test for apheresis plts.**
- **Approved as stand-alone QC test for WB-derived platelets.**
- **Average sensitivity of approximately 10^3 - 10^4 CFU/mL**
- **Test time: 35-45 minutes Tech time: 5 mnutes**


Classes Of Bacteria
Cell Walls
Lipoteichoic Acid
(LTA)
Gram-positive
Pan Genera Detection (PGD)
200,000 – 2,000,000 targets per bacterium
yields natural signal amplification
Lipopolysaccharide
(LPS)
Gram-negative

PGD Immunoassay Format – two tests run simultaneously

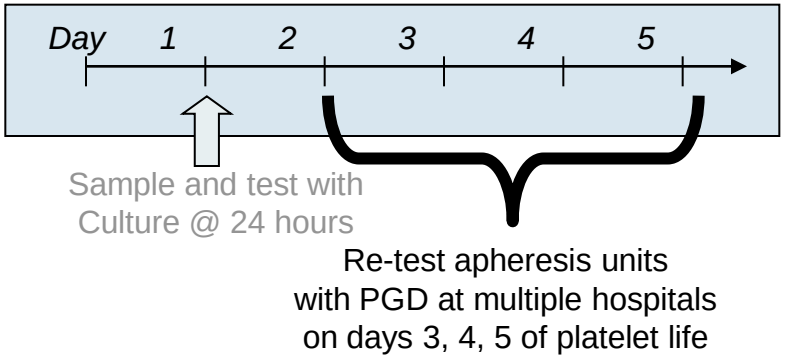


Detection of bacterial contamination in prestorage culture-negative apheresis platelets on day of issue with the Pan Genera Detection test

*Michael R. Jacobs, Daniel Smith, W. Andrew Heaton, Nicole D. Zantek, Caryn E. Good, and the PGD Study Group**

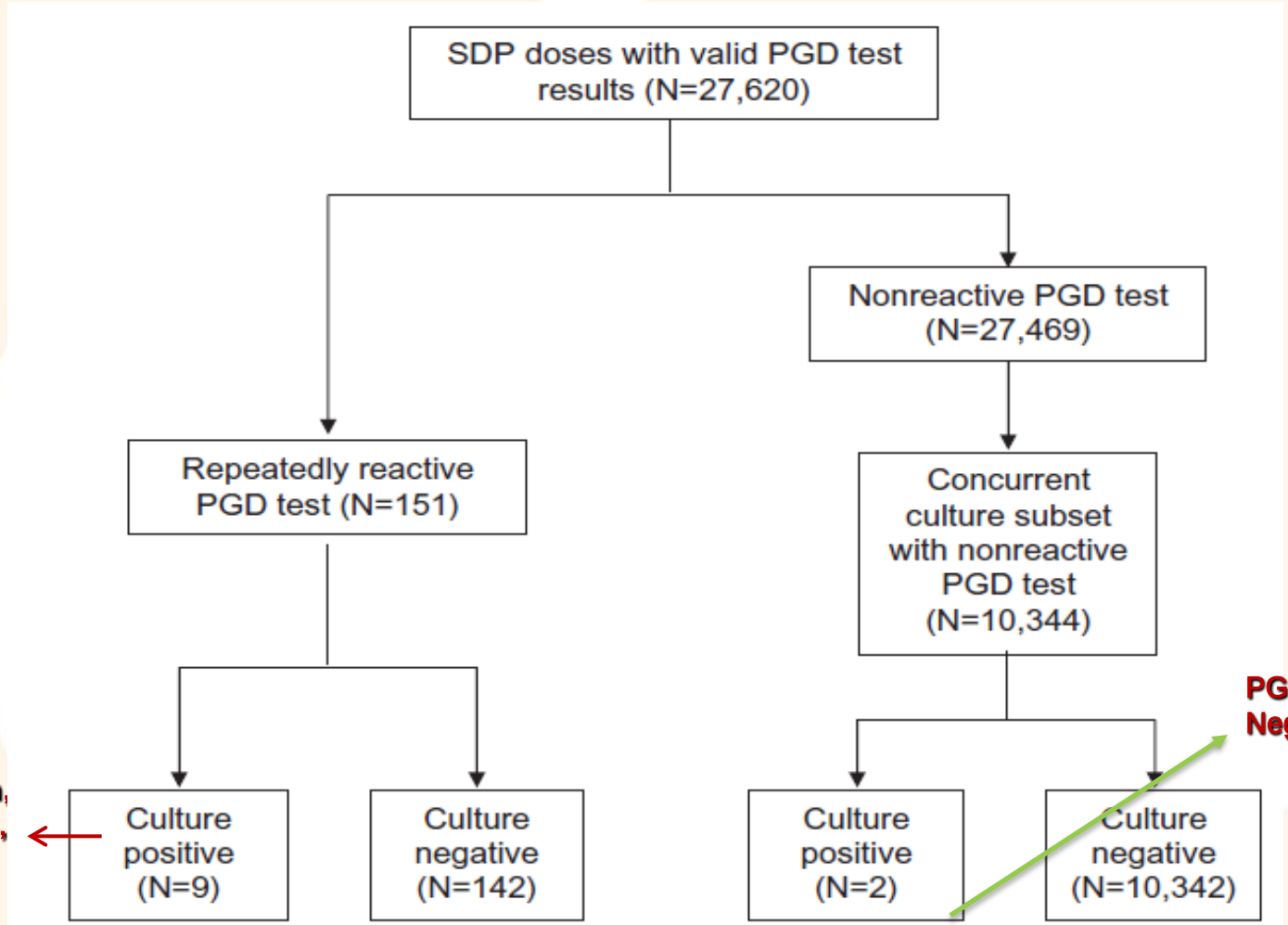
Multi-center Post-Market Surveillance Study

Study: Demonstrate PGDs ability to detect culture FN apheresis units



- Confirm PGD reactives with culture

Study design and results



Rate of FN by culture is 1:3,000

Rate of FP by PGD is 1:200

PGD User Survey – FP Rates are Low in Routine Use

2012 Survey of 50 Existing PGD Users

How often do you observe PGD initial and repeat reactives?

	RDPs	SDPs	Overall
Total Doses Tested	166,282	16,982	183,264
Initially Reactive	0.21%	0.60%	0.25%
Repeat reactive	0.13%	0.37%	0.15%

- IR and RR rates reported by PGD users are lower than those observed during the PGD post market surveillance study (SDP IR: 0.6% vs 0.91%, SDP RR: 0.37% vs 0.51%

Contaminated SDPs Detected BY PGD

Post Market Surveillance (PMSS)

SDP Doses Tested: 27,682 SDPs

PGD True Positives (Culture FN): **10**

- 9 in the study cohort
- 1 (not included in data set)

User Survey Positives

SDP Doses Tested: 16,982

PGD True Positives: **5**

Total = **15 SDPs, 67% were day 3 or Day 4 units**

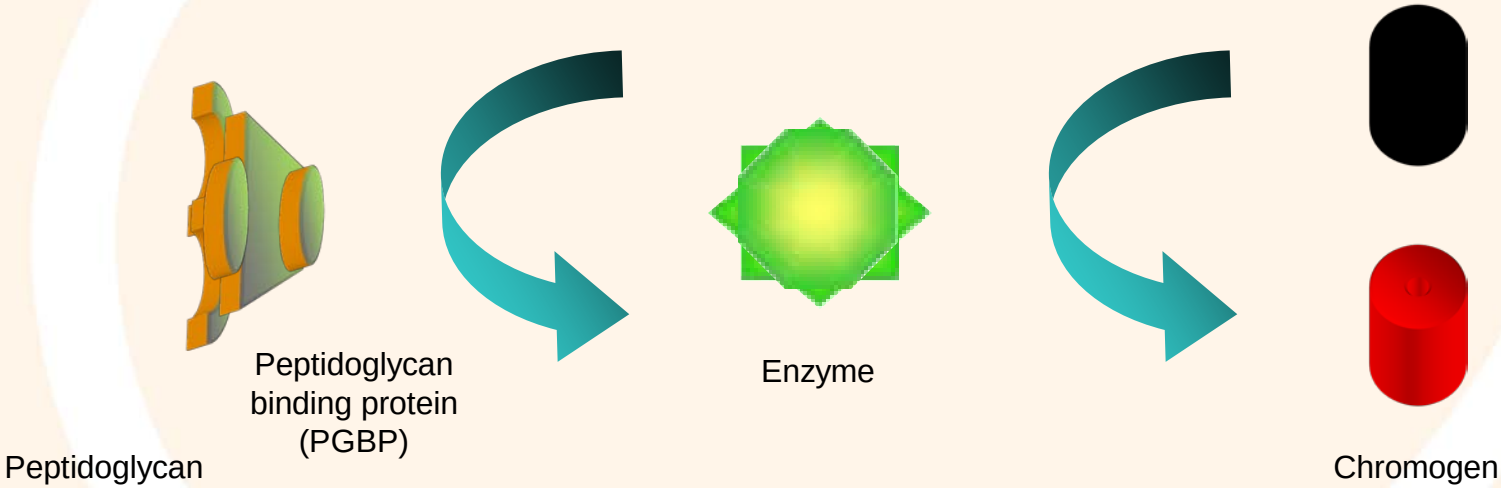
- **7 – day 3 (47%)**
- **3 – day 4 (20%)**
- **5 – day 5 (33%)**

- 1:3,000 culture negative apheresis PLTs are contaminated
- Translates to ~550 contaminated apheresis PLT units transfused a year
- What is clinical significance?
  - Observed rate of septic reaction reported in studies and by surveillance data is much lower (possibly underreported/underrecognized).

Another Point of Issue Test

- New Kid on the Block: Immunetics BacTx
  - 510(k) approved in June, 2012
    - QC testing of LR WB derived platelets pooled within 4 hours prior to transfusion
  - Clinical trials with LR apheresis platelets are under way.
  - Detects both gram positives and gram negatives
  - 10^3 – 10^4 CFU/ml assay sensitivity

BacTx™ Assay Technology



Binding of PGBP to peptidoglycan triggers enzymatic conversion of chromogenic substrate to visible product

Should Hospitals Implement ”Issue” Test?

Clinical effectiveness decision = Need vs. Benefit vs. Cost

- Benefit: Perceived vs. theoretical vs. estimated ROI based on operations
- What is the blood provider doing to detect and/or limit bacterial contamination?
- ROI: given the number of platelets transfused, residual risk, and cost of testing, staffing issues how long to interdict x number of contaminated units? At what cost?
- Implications of false positives

Pathogen Reduction

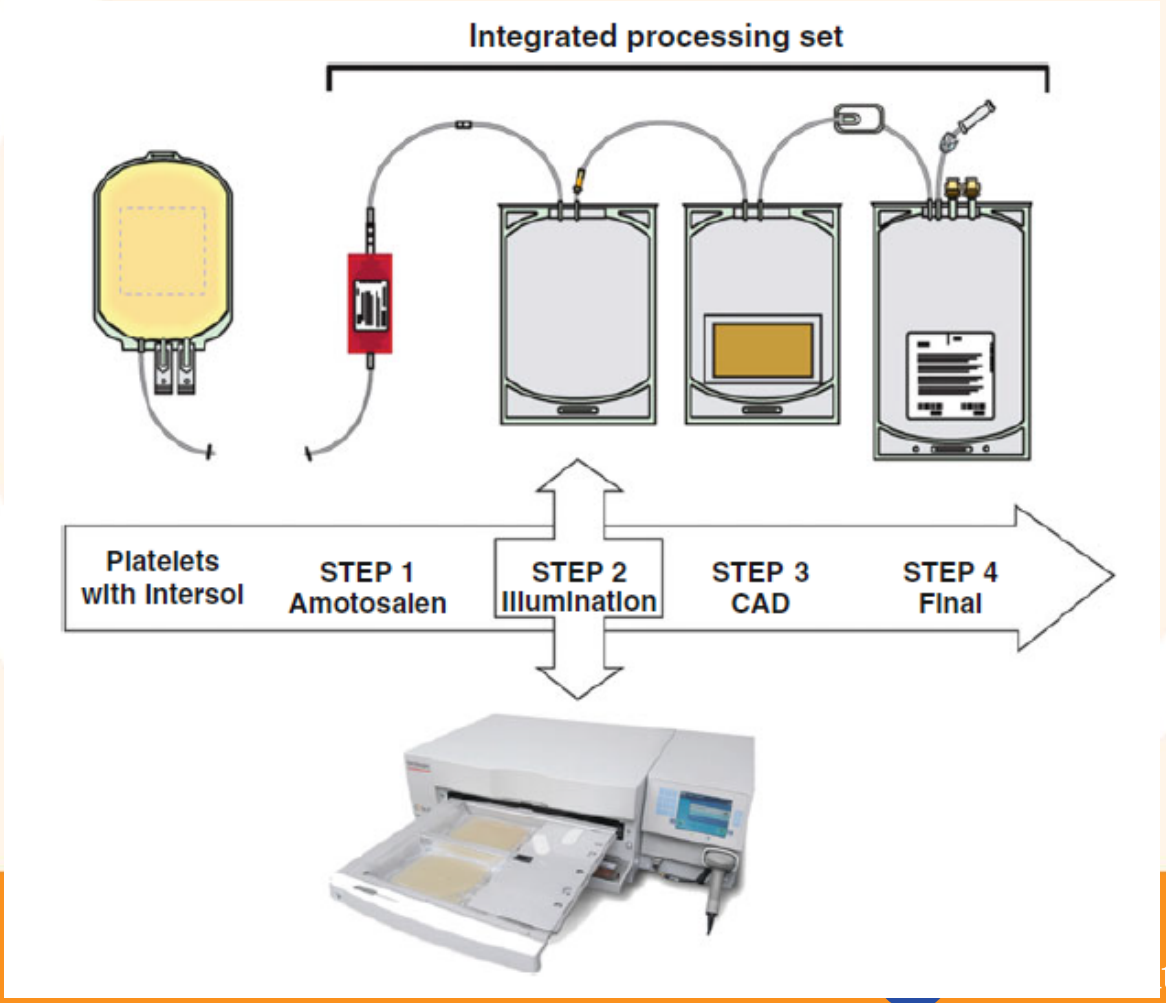
Rationale for pathogen reduction

- Viruses, bacteria, protozoa pathogenesis is dependent on reproduction (nucleic acid replication)
- Preventing replication prevents pathogenesis
- Universal safety measure – not specific to one organism
- Can be cost effective by replacing need for detection

Cerus INTERCEPT Technology

- Amotosalen intercalates into DNA and RNA
- UVA light causes crosslinking at pyrimidine bases
- Interferes with replication and transcription

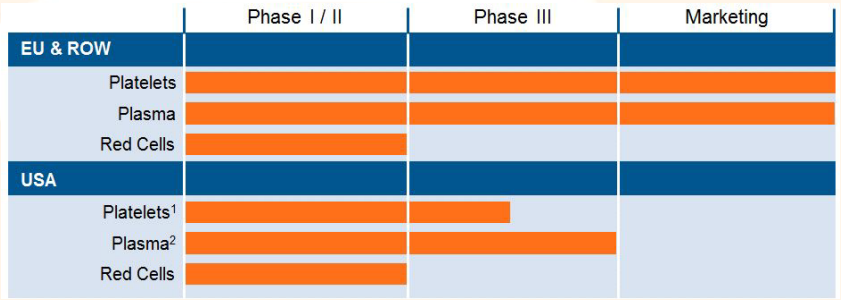
INTERCEPT Pathogen Reduction System - Platelets



Summary of INTERCEPT Studies

- INTERCEPT technology effectively reduces infectious risk
- INTERCEPT platelets appear to achieve a lower CCI than untreated platelets
- Dose-per-dose, INTERCEPT platelets appear to be slightly less effective at stopping bleeding; larger dose may be needed

INTERCEPT Status



- European CE Mark approval for platelets and plasma
- In use
  - Europe: Belgium, France, Norway, Slovenia, Spain, Sweden, Switzerland, Russia
  - Middle East: Saudi Arabia, Israel, Turkey
- USA
  - One Phase III platelet trial completed; additional data required

TerumoBCT Mirasol System

- Riboflavin (vitamin B2) intercalates into DNA and RNA. UV light causes modifies guanine → interferes with replication and transcription
- MIRACLE Trial (Mirasol PLTs vs untreated PLTs)
  - Slightly lower CCIs
  - No significant differences in bleeding events (WHO scale)
  - No ↑ platelet or RBC transfusions needed

Cazenave et al. Transfusion 2010 50:2362

Cost effectiveness

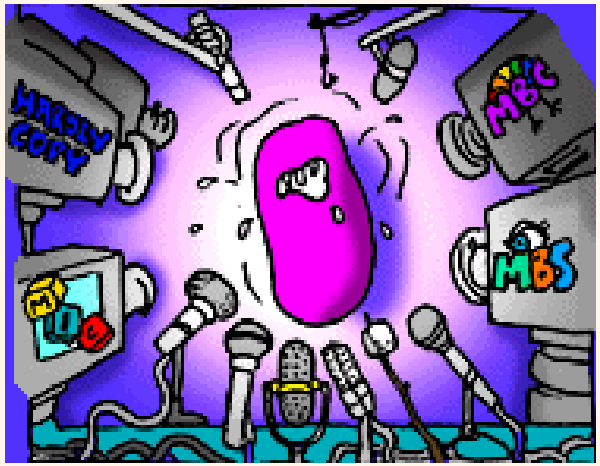
- The cost-effectiveness of PI via Intercept system is comparable to that of other accepted blood safety intervention (NAT testing)

Bell et al. Clinical Therapeutics. 2003

Summary

- Culture ↓ risk of platelet bacterial contamination/septic reaction
- Due to variable bacterial growth rates and small inoculum size, residual risk remains
- Options for enhanced detection measures include point-of-issue assays, ↑ sampling volume, and repeat/later sampling.
- Pathogen reduction technologies are in clinical trials and used worldwide but not yet available in US
- Need to balance Safety – Cost – Availability

Questions



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