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Pathogen Reduction-Benefits and Challenges

Thomas Lightfoot MD

Medical Director

Carolinas Region

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Re/-Emerging Infections Are On The Rise

Other Sources of Blood Product Contamination

- Tissue damage with injury to underlying blood vessel walls
- Insufficient performance/maintenance of skin disinfection to VP site
- Donor presenting with an asymptomatic infection (UTI, URI)
- Apheresis technology: Amicus vs Trima

ARC study: Eder et.al. Transfusion. 2017;57:2969 – 2976.
2007 – 2014, ~2 million collections
Apheresis platform: 69% Amicus, 31% Trima

Implicated donations with septic reactions
Amicus: 25 donations rate: 17.6/ 100,000 donations
Trima: 3 donations rate: 1.8/ 100,000 donations

Contamination is ranked #3 for Transfusion Reaction Fatalities

2016 FDA reported 14 transfusion related fatalities

#1: TACO – transfusion associated circulatory overload

#2: TRALI – transfusion related acute lung injury

#3: Contamination (bacteria, parasites, viruses)

Most Common Type of Infectious Disease Contaminant in Blood Units: Bacteria

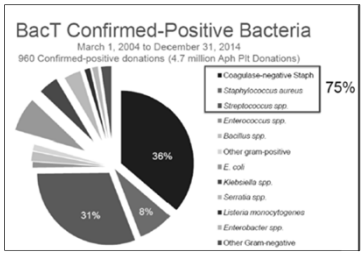
Most common blood product to be contaminated: PLATELETS

Platelets	Incidence Rate
Contaminated	1:1,000
Experience Sepsis	1:100,000
Fatal Sepsis	1:500,000

Due to overlying disease or delay in symptoms by >24 hours, the actual number of septic transfusion reactions may be as 10x higher

Hong H et.al. Transfusion Medicine. 2016;127:496-502. Ramirez-Arcos S, et.al. Transfusion. 2017;57:2174 -2181

BacT Confirmed-Positive Bacteremia



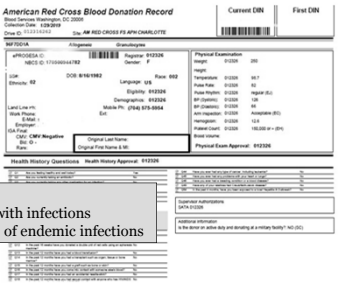
Septic Reactions

71% cases - same top three microorganisms identified

Data presented by Dr. Ross Herron, Medical Advisory Council Meeting, 5/22/2018

Eder et.al. Transfusion. 2014;54:857 – 862.

First Line of Defense: the eBDR



- Current donor health
- Exposure to persons with infections
- Travel to at-risk areas of endemic infections

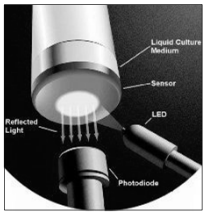
Blood Center: Preventive Measures

- **Disinfectant of VP Site:**
  - -- 2% Chlorhexidine gluconate
  - -- Isopropyl alcohol
- **Diversion Steps:** ex; initial 20-50 ml of collection to pouch

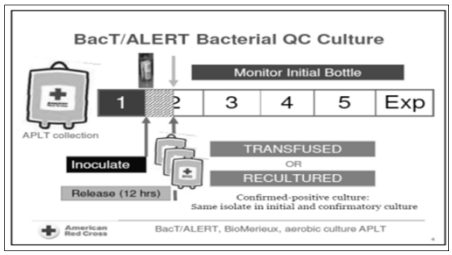
Bacterial Testing

BacT/ALERT (Biomerieux)

Sensor changes color in presence of CO_2



Blood Center: Preventive Measure



Presentation: Herron R. Initiatives for Decreasing Septic Transfusion Reactions (STRs) from Platelets. Medical Advisory Council Meeting. 2018

Summary of Bacterial Risks

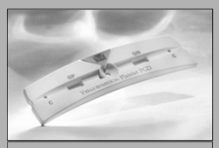
- Reliance on donor memory recall
- Collection preventive measures are not effective
- Apheresis technology (Amicus)
- Product culture testing does not have sufficient sensitivity

With current preventive measures
Contamination rate for apheresis platelets is 1:1,000 – 1:5,000
70% reduction of distributed contaminated apheresis platelet products

Under 21 Code of Federal Regulation 606.145(a)
Blood 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

Strategies Include…

Culture



Rapid Testing (Verax)

Pathogen Reduction Technology

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FDA DRAFT GUIDANCE FOR INDUSTRY
Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion

- December 2014:
  - Initial draft guidance for 5 day platelet storage
  - Include culture and rapid testing prior to transfusion
- March 2016:
  - Introduction of Pathogen Reduction technology
  - Enhancement of secondary testing to include culture as well as rapid testing
  - Testing options provided to extend platelet shelf-life to 7 days
- December 2018:
  - Refined timing for primary and secondary testing
  - Enhanced options to extend shelf-life to 7 days

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2018 FDA DRAFT GUIDANCE FOR INDUSTRY
Apheresis Platelets Bacterial Risk Control Strategies

Strategy	Performed by ARC
Primary culture:	
❑ Perform ≥ 24 hrs post collection	✓
❑ Incubate for minimum of 12 hours	✓
❑ Aerobic and anaerobic testing	✓
OR	
❑ Pathogen Reduction	✓
During 5 day platelet storage:	
❑ Secondary culture on Day 3 or 4	No
OR	
❑ Secondary testing with a rapid [Verax] test	No
OR	
❑ Pathogen Reduction	Yes

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Enhanced BacT/ALERT Testing

BacT/ALERT BPA (aerobic)	BacT/ALERT BPN (anaerobic)

▪ Aerobe: requires O2 for growth
▪ Facultative anaerobe: can use O2
	▪ Facultative anaerobe: can use O2
	  ▪ Escherichia coli, Klebsiella
	  ▪ Staphylococcus, Streptococcus

▪ Product sample 8 – 10 ml	▪ Product sample 8 – 10 ml

ADDING ANAEROBIC CULTURE

PROS
- Increased detection of strict anaerobic microbes , such as Propionibacterum acnes
- Faster growth rate of facultative anaerobes, such as Staphylococcus genus
- Increase sample volume (double)…increase detection by 30 - 35%

CON
- Product wastage due to increased positives of non-clinically significant microbes
- Loss of product potency due to expanded sample volume; impact split rates

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Presentation: Wagner S. ARC presentation 2018

Donor Eligibility Impact with Positive BacT/ALERT

INDEFINITE DEFERRAL
- Enteric (E coli, Klebsiella, Strep bovis)
- Oropharyngeal (Strep Beta hemolytic, Strep viridans)
- Staph aureus organisms
- Donor implicated in highly probable septic transfusion reaction

- Skin (non-Staph aureus)/ environmental contaminant –after second incident

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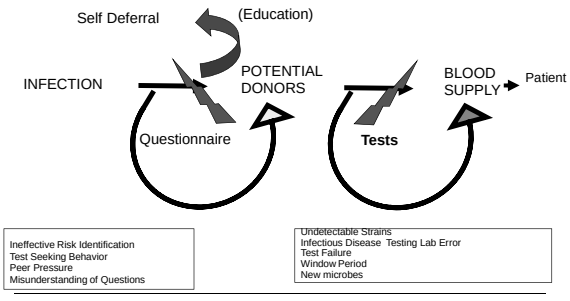
Protection of the Blood Supply



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Tests Performed on Blood Donations

Year Implemented	Disease	Test
1948	Syphilis	Antibodies
1971	Hepatitis B	Hep B Surface Ag
1985	HIV	HIV 1 antibodies
1986	Non A-Non B Hepatitis	ALT
1986	Hepatitis B	Antibodies to core antigen
1988	HTLV	HTLV 1 antibodies
1990	Hepatitis C	Antibodies to Hep C Virus
1992	HIV	HIV 2 antibodies
1995	HTLV	HTLV 2 antibodies
1996	HIV 1	HIV 1 p24 antigen
1998	HIV 1 and Hepatitis C	Nucleic Acid Testing
2003	West Nile Virus	Nucleic Acid Testing
2007	Trypanosoma cruzi	Antibodies
2008	Hepatitis B	Nucleic Acid Testing

Residual Risks for Current Infections from Blood Transfusions

Virus	Risk
HCV	1: 1,600,000
HIV	1: 1,900,000

Current and Emerging Infectious Risks of Blood Transfusions
Michael P. **Busch**, MD, PhD; Steven H. Kleinman, MD; George J. Nemo, PhDJAMA. 2003; 289(8):959-962. doi: 10.1001/jama.289.8.95 (modified)

Pathogen Reduction

Pathogen Reduction

Table 1
Degree of reduction of pathogens in log (adapted from [24] with Permission).

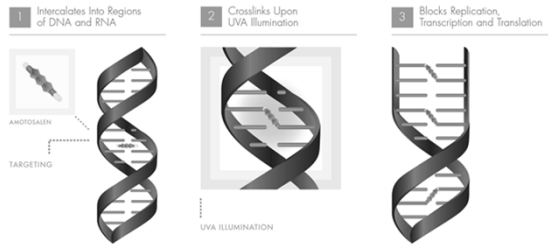
	Amotosalen/UVA	Riboflavin/UV	UVC
Enveloped virus			
HBV	>5.5	2.3	na*
HCV	>4.5	3.2	na
HIV (cell free)	>6.2	>5.9	1.4
HIV (cell-associated)	>6.1	>4.5	na
HTLV-I	4.7	na	na
CMV (cell-associated)	>5.9	na	na
West Nile virus	>6.0	>5.1	5.4
Chikungunya	>6.4	2.1	na
Influenza A virus	>5.9	>5	na
Nonenveloped virus			
HAV	0	1.8	na
Parvovirus B19	3.5 to 5.0	>5	5.46
Bacteria			
S. aureus	≥6.6	≥4	>4.8
S. epidermidis	≥6.6	4.2	4.8
P. aeruginosa	4.5	4.6	4.9
E. coli	≥6.4	4.4	>4
Spirochaete bacteria			
T. pallidum	>6.8	na	na
B. burgdorferi	>6.8	na	na
Parasite			
T. cruzi	>5.3	6	na
P. falciparum	>6	>3.2	na

* Information not available.

Blood Reviews 2014: Vol. 28 pages 235-241.

Mechanism of Action

Targeting DNA and RNA to prevent pathogen proliferation



The INTERCEPT® Blood System inactivates a broad spectrum of viruses, gram-positive and gram-negative bacteria, spirochetes, parasites and leukocytes

1. INTERCEPT Blood System for Plasma Package Insert, December 16, 2014.
2. INTERCEPT Blood System for Platelets Package Insert, December 18, 2014.

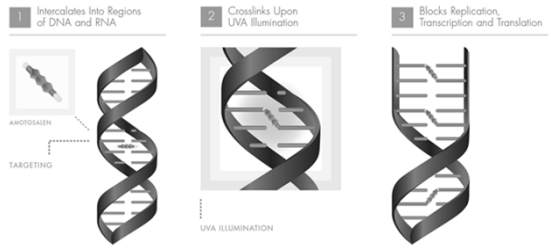
Intercept® System for Platelets

Intercept® System for Plasma

The Cerus Intercept® Pathogen Reduction System

Mechanism of Action

Targeting DNA and RNA to prevent pathogen proliferation



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Intercept® System for Platelets

The Intercept® Illumimator

How It Works

1. Transfer Apheresis platelet to the INTERCEPT® illumination bags and processing kit

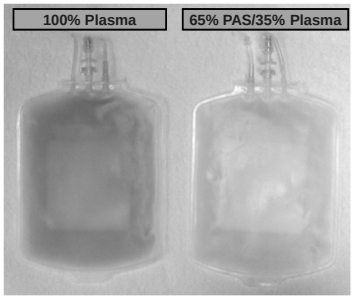
2. Add the amotosalen

3. Illuminate

4. CAD & Store

5. Labeled platelet units ready for distribution

The Cerus Intercept ® Platelets are stored in a platelet additive solution (PAS)



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PAS Composition

ACETATE	Energy source, buffer
Citrate	Anti-coagulant, energy source, buffer
Phosphate	Buffer, maintain ADP/ATP synthesis
NaCl	Isotonic osmolarity

Donor Plasma (35%) Energy source – glucose, fatty acids, dextrose (ACD-A)

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PAS Benefit #1
Expansion of Donor Plasma Inventory

- Transfusable plasma
- Plasma utilized for further manufacturing for the production of other pharmacologic treatments (albumin, IVIG, clotting factors…)

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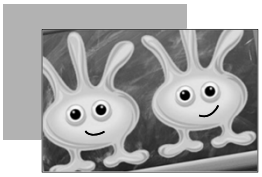
PAS Benefit #2
Improves Platelet Storage Conditions



An objective of PAS: Improve platelet storage conditions

- Keep platelets healthy, fed, and alive during storage period of 5+ days
- Decrease production of bio-waste (i.e. lactate) that maybe harmful to platelets

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PAS Benefit #3
Decrease Immune-mediated Transfusion Reactions

PAS Dilution → 36% protein loss

- Decrease anti-A and anti-B antibodies
- Decrease anti-HLA antibodies
- Decrease other proteins, biochemicals

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Surowiecka M et.al. *Transfusion*. 2012;53 suppl. 81A

Weisberg SP et.al. *Transfusion* 2018;58:891-895.

PAS Benefit #3
Decrease Immune-mediated Transfusion Reactions

- Hemolytic transfusion reactions
  - Donor Anti-A,-B antibodies passively transfused can target patient's red cells for destruction (hemolysis) – potentially causing anemia
  - Patients : transfusion of ABO incompatible platelets or transplant patients whose ABO status is mixed due to receiving a donor graft with an incompatible blood type (donor A, patient B)
- TRALI – potential benefit is currently being investigated

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Weisberg SP et.al. *Transfusion* 2018;58:891-895.

Surowiecka M et.al. *Transfusion*. 2012;53 suppl. 81A

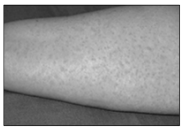
PAS Benefit #4
Reduce Allergic Type Transfusion Reactions

Allergic reactions: the most common transfusion reaction (4%)

TABLE 1. ATR incidence by type of AP transfused

APs transfused	ATRs	Transfusions	Incidence	RR (95% CI)	p value
Non-PAS	72	3884	1.85%	Referent	Referent
PAS	12	1194	1.01%	0.54 (0.30-0.99)	0.04

PAS reduces allergic reactions associated with platelet transfusions by ~ 2x



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Arm image: The Pharmaceutical Journal: https://www.pharmaceutical-journal.com

Tobian AAR et.al. *Transfusion*. 2014;54:1523 – 1529

PAS Benefit #5
Medical Cost Containment

- Pre-medication or Wash product charges
- Pre-medication side-effects, clinical management

- Reissue of blood product post-transfusion reaction
- Clinical transfusion work-ups
- Transfusion reaction may complicate patient's primary disease process
- May extend inpatient stay or if transfused in outpatient, may lead to hospitalization
- Emotional burden to patient and family

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PAS Benefit #6
Improves PR-technology Efficiency

Table 9 Platelet Collection and Processing Specifications for INTERCEPT Large Volume Processing Set

	Platelets in PAS-3	Platelets in 100% Plasma
Collection Specifications		
Platelet Source	Amicus Apheresis (PAS-3)	Trima Apheresis
Suspension Medium	PAS-3 and plasma (32-47%)	100% Plasma
Platelet Input Volume	300 – 390 mL	300 – 390 mL
Platelet Dose	$3.0 - 6.0 \times 10^{11}$	$3.0 - 5.2 \times 10^{11}$
Platelet Count	$0.8 - 2.0 \times 10^{7}$/mL	$0.9 - 1.7 \times 10^{7}$/mL
RBC Content	$< 4 \times 10^{8}$ RBC/mL	$< 4 \times 10^{8}$ RBC/mL
Processing Specifications		
Number of Storage Bags	1	1
CAD Time	6-16 Hrs	12-24 Hrs
Maximum Storage	5 Days	5 Days

CAD: Compound Adsorption Device = residual removal of psoralen

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INTERCEPT. Cerus Corporation, Concord, CA, USA. 2016

PAS/PR – Platelets: Overview of Benefits

	PAS	Pathogen Reduction
Sepsis		√
TA-GvHD		√
Allergic	√	
TRALI - theoretical	√	
Hemolytic [ABO incompatibility]	√	
Increased Plasma Inventory	√	
Maintain/ Expand Donor Base		√

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The Terumo BCT Mirasol® Pathogen Reduction System

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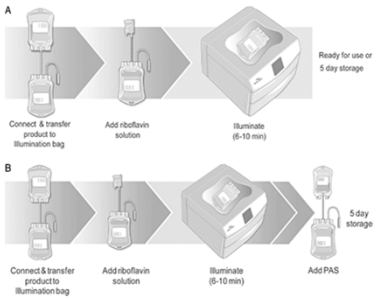
The Terumo BCT Mirasol ® System



Transfusion
pages 15-29G, 30 JUL 2009 DOI: 10.1111/j.1537-2995.2009.02279.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1537-2995.2009.02279.x/full#f1

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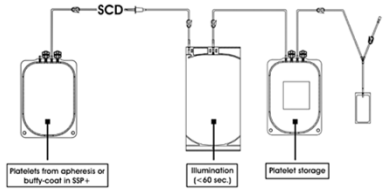
The Macopharma Theraplex ® Pathogen Reduction System

The Macopharma Theraplex ® System



Transfusion
pages 15-290, 30 JUL 2009 DOI: 10.1111/j.1537-2995.2009.02270.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1537-2995.2009.02270.x/full#f1

How Effective is PR -Technology?

	INTERCEPT
BACTERIA	
Ecoli	>6.2[1]
Serratia marsescens	>6.6[1]
Klebsiella pneumonia	5.8[1]
Enterobacter cloacae	5.5[1]
Staph epidermidis	>6.0[1]
Staph aureus	>5.3[1]
Bacillus cereus (spore)	**3.7[1]**
Priprionobacterium acnes	>6.4[1]
Yersenia enterocolitica	.5.9
PRION	-

Targeted reduction rate of ≥4 log10

	INTERCEPT
VIRUSES	
Chikungunya	>5.7[1]
CMV (cell associated)	>4.9[1]
HAV	0
HBV	>5-5
HCV	>4-5
HIV-1	>5-4[1]
WNV	>5.7[1]
Parvovirus B19	>3-5
PARASITES	
Babesia microti	>4.8[1]
Plasmodium falciparium	>5-5[1]
Trypasonosoma cruzi	>5.2[1]

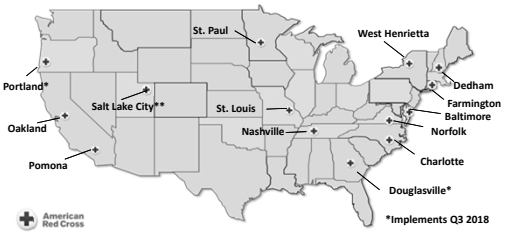
Additional Benefits of Pathogen Reduction

Transfusion Associated Graft vs Host Disease – rare but lethal (90%)

- Condition where the donor white cells see the recipient's body as foreign
- Mismatch of donor/ recipient HLA antigens
- Patients at risk: immunodeficient/ -suppressed; receiving blood from family
- Preventive measures: irradiation or Pathogen Reduction

Pathogen Reduction – disrupts white cell's DNA, preventing cellular replication

Pathogen Reduction Technology ARC Manufacturing Sites



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ARC Sales Marketing presentation, June 2018

Pathogen Reduction What's Next for Cerus?

- Cryoprecipitate
  - 10/2018: FDA approves 'Breakthrough Devise' designation
  - Expedited review and approval determination - pending
- Red Blood Cells
  - 5/2018: Cerus announces partnership with the US Dept of Health for phase 3 study in adult patients undergoing cardiac surgeries
  - 12/2018: submission of European CE Mark for approval review
- Plasma – FDA approved in 2014
- Platelets – FDA approved in 2014

The Safety of the Blood Supply — Time to Raise the Bar

Edward L. Snyder, M.D., Susan L. Stramer, Ph.D., and Richard J. Benjamin, M.D., Ph.D.

NEJM 2015; 372:1882-1885
May 14, 2015
DOI: 10.1056/NEJMp1500154

Pathogen-Reduction Technologies Approved and in Development in the United States and Europe.*

Component and Source	Manufacturer and Technology	Treatment Process	Manner of Inhibiting Replication	Regulatory Status
Platelets				
Individual volunteer donors	Cerus Intercept Blood System	Psoralen (amotosalen) and UVA light exposure	Formation of DNA and RNA monoadducts and cross-linkage	FDA approved; CE marked
	Terumo BCT Mirasol Pathogen Reduction Technology (PRT) System	Riboflavin and ultraviolet light exposure	Direct DNA and RNA damage and guanine modification	Phase 3 study planned in the United States; CE marked
	Macopharma Theraflex ultraviolet platelets	UVC light exposure	Direct DNA and RNA damage and thymine dimer formation	CE marked
Plasma				
Pools of volunteer and paid donors	Octapharma Octaplas	Plasma pools treated with solvent, tri-n-butyl phosphate and detergent (octoxynol)	Lipid membrane disruption of enveloped viruses	FDA approved; CE marked
Individual and minipools of volunteer donors	Cerus Intercept Blood System	Psoralen (amotosalen) and UVA light exposure	Formation of DNA and RNA monoadducts and cross-linkage	FDA approved; CE marked
Individual volunteer donors	Macopharma Theraflex MB Plasma System	Filtration, methylene blue treatment and visible light exposure	DNA and RNA damage by type I and type II redox reactions	CE marked
	Terumo BCT Mirasol PRT System	Riboflavin and ultraviolet light exposure	Direct DNA and RNA damage and guanine modification	CE marked
Whole blood				
Individual volunteer donors	Terumo BCT Mirasol PRT System	Riboflavin and ultraviolet light exposure	Direct DNA and RNA damage and guanine modification	Phase 3 studies planned in the United States, completed in Africa
Red cells				
Individual volunteer donors	Cerus Intercept Blood System	Frangible Anchor-Linker Effector (S303) and glutathione	Formation of DNA and RNA monoadducts and cross-linkage	U.S. phase 2 and European phase 3 studies complete

CE: European union approval

NEJM 372; 20 May 14, 2015

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NEJM 372; 20 May 14, 2015

Additional challenges

- PR reduction varies by technology
- Relative loss of component yield
- Reduced functionality
- Unknown residual infectivity of agents with pathogen loads that exceed validated inactivation efficacy
- Resistance by certain pathogens (e.g., non-enveloped viruses for certain technologies and spore forming bacteria)
- Short-term and long-term clinical adverse events have not been reproducibly documented

SPRINT Study

TRANSFUSION MEDICINE

Therapeutic efficacy and safety of platelets treated with a photochemical process for pathogen inactivation: the SPRINT Trial

Jeffrey McCullough, David H. Vesole, Richard J. Benjamin, Sherrill J. Slichter, Alvaro Pineda, Edward Snyder, Edward A. Stadtmauer, Ileana Lopez-Plaza, Steven Coutre, Ronald G. Strauss, Lawrence T. Goodnough, Joy L. Fridey, Thomas Raife, Ritchard Cable, Scott Murphy, Frank Howard IV, Kathryn Davis, Jin-Syng Lin, Peyton Metzel, Laurence Corash, Antonis Koutsoukos, Lily Lin, Donald H. Buchholz, and Maureen G. Conlan

We report a transfusion trial of platelets photochemically treated for pathogen inactivation using the synthetic psoralen amotosalen HCl. Patients with thrombocytopenia were randomly assigned to receive either photochemically treated (PCT) or conventional (control) platelets for up to 28 days. The primary end point was the proportion of patients with World Health Organization (WHO) grade 2 bleeding during the period of platelet support. A total of 645 patients (318 PCT and 327 control) were evaluated. The primary end point, the incidence of grade 2 bleeding (58.5% PCT versus 57.8% control), and the secondary end point, the incidence of grade 3 or 4 bleeding (4.1% PCT versus 6.1% control), were equivalent between the 2 groups ($P = .001$ by noninferiority). The mean 1-hour posttransfusion platelet corrected count increment (CCI) (11.1×10^3 PCT versus 16.0×10^3 control), average number of days to next platelet transfusion (1.9 PCT versus 2.4 control), and number of platelet transfusions (8.4 PCT versus 6.2 control) were different ($P < .001$). Transfusion reactions were fewer following PCT platelets (3.0% PCT versus 4.4% control; $P = .02$). The incidence of grade 2 bleeding was equivalent for PCT and conventional platelets, although posttransfusion platelet count increments and days to next transfusion were decreased for PCT compared with conventional platelets. (Blood. 2004;104:1534-1541)

Introduction

Blood. 2004; 104:1534-1541.

Table 5. Proportion of patients with grade 2 or higher bleeding

	PCT, n (%) n = 318	Control, n (%) n = 327	P
Any grade 2 bleeding	186 (58.5)	188 (57.5)	<.01[†]
Grade 2 bleeding by bleeding site			
Genitourinary	104 (32.7)	103 (31.5)	0.80
Mucocutaneous	82 (25.8)	65 (19.9)	0.08
Invasive sites	69 (21.7)	65 (19.9)	0.63
Gastrointestinal	60 (18.9)	63 (19.3)	0.92
Respiratory	35 (11.0)	28 (8.6)	0.35
Musculoskeletal	15 (4.7)	18 (5.5)	0.72
Body cavity	0 (0.0)	1 (0.3)	1.00
Neurologic	0 (0.0)	0 (0.0)	—
Any grade 3 or 4 bleeding	13 (4.1)	20 (6.1)	<.01[‡]

No difference between test and control

— indicates not applicable.
†* Fisher exact test was used to calculate the *P* value for each of the 8 potential bleeding sites
†† The *P* value for the overall proportion of patients with grade 2 bleeding was < .01, based on a noninferiority test with a noninferiority margin of 0.125 (one-sided 95% confidence interval of difference: −1, 0.07). By using this method, a *P* value of < .05 indicates that PCT was not inferior to control
‡* The *P* value for any grade 3 or 4 bleeding was < .01, based on a noninferiority test with a noninferiority margin of .07 (one-sided 95% confidence interval of difference: −1, 0.013). By using this method, a P value of < .05 indicates that PCT was not inferior to control

Table 6. Platelet and RBC transfusions during the study

	PCT, n = 318	Control, n = 327	P
Platelet transfusions			
Total number	2678	2041	—
Mean number per patient	8.4	6.2	< .001
Mean number per day of platelet support[*]	0.74	0.65	< .001
Interval between transfusions, d	1.9	2.4	< .001
Platelet dose, × 10^{11}			
Mean average dose	3.7	4.0	< .001
Percentage of platelet doses less than 3.0 × 10^{11}	20	12	< .01
Mean total dose over entire transfusion period	29.4	24.1	.01
Duration of platelet storage, d	3.4	3.6	< .05
RBC transfusions			
Mean number per patient	4.8	4.3	.13
Mean number per day of platelet support[*]	0.31	0.30	.53

Difference between test and control

•— indicates not applicable.
•†* Days of platelet support is defined as number of days from the first to the last study platelet transfusion

Table 7. Mean platelet responses following platelet transfusions

	PCT; n = 318	Control; n = 327
Before transfusion		
Platelet count, × 10^9/L	15.1	15.2
1 h after transfusion		
Platelet count, × 10^9/L	36.5[*]	49.5
Count increment, × 10^9/L	21.4[*]	34.1
Corrected count increment, × 10^3	11.1[*]	16.0
24 h after transfusion		
Platelet count, × 10^9/L	27.9[*]	36.1
Count increment, × 10^9/L	13.2[*]	21.5
Corrected count increment, × 10^3	6.7[*]	10.1

†* *P* < .001 compared with control

Table 9. Adverse events during the study

	PCT, %; n = 318	Control, %; n = 327	P
Any adverse event[*]	99.7	98.2	.12
Grade III or IV adverse event	78.9	78.6	.92
Serious adverse event[†]	27.0	24.8	.53
Treatment-related adverse event[‡]	26.4	29.4	.43
Death[§]	3.5	5.2	.34

†* Adverse events were graded I to IV using the National Cancer Institute Common Toxicity Criteria (NCI-CTC)[38] and coded to Preferred Term by using Medical Directory for Regulatory Affairs (MedDRA)[39]
†† Serious adverse events were defined by using Food and Drug Administration (FDA) criteria[40]
‡† Treatment-related adverse events were reported as possibly or probably related to the study platelet transfusions by the blinded investigator at each site
§† One patient in each group died of hemorrhage; both deaths involved pulmonary alveolar hemorrhage thought to result from toxicity of the myeloablative preparative regimen

SPRINT Study

Conclusion:

The incidence of grade 2 bleeding was equivalent for PCT and conventional platelets, although post transfusion platelet count increments and days to next transfusion were decreased for PCT compared with conventional platelets.

Discussion of Pathogen Reduction at the 11/16/2009 to 11/17/2009 meeting of the FDA Blood Product Advisory Committee

Study Designs (Phases III and IV) for Product Development of Human Platelets Using the Cerus Intercept® Blood System for Pathogen Inactivation

A summary of FDA concerns presented for the BPAC discussion

- Issue Summary — The FDA has concerns about efficacy (bleeding events) and safety (imbalance of adverse events).
- Even though the previous study (SPRINT) met the primary endpoint, secondary endpoints did not support the study conclusion that the pathogen reduction platelets were non-inferior to untreated platelets.
  - More platelets and more frequent transfusions were needed.
  - Mean days of grade 2 bleeding were higher in the treatment arm (p = 0.023).
  - Additionally, hemostatic adverse events were more frequently observed in the test arm. The data did not establish whether the reduced hemostatic efficacy was attributable to lower platelet numbers or impaired platelet function.

Study Designs (Phases III and IV) for Product Development of Human Platelets Using the Cerus Intercept® Blood System for Pathogen Inactivation

A summary of FDA concerns presented for the BPAC discussion

FDA Perspective presented by Jaro Vostal, MD, PhD:

- S59 pathogen reduction process damages platelets.
- Damage results in reduced circulation of treated platelets, which leads to lower corrected count increments, or CCIs, and more frequent platelet transfusions.
- Hemostasis appears to be impaired after S59 treatment in comparison to conventional platelets, due to either low platelet counts or loss of platelet efficacy, or both.
- S59 damaged platelets appear to be associated with ARDS, hypocalcemia, syncope and pneumonitis not otherwise specified.
- An additional phase III clinical trial is needed to resolve the hemostasis efficacy and adverse event profile of S59 treated platelets.

FDA Approves the First Systems of Pathogen Reduction for Plasma and Platelets Stored in a PAS Solution

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

FDA News Release

FDA approves pathogen reduction system to treat platelets

For Immediate Release

December 19, 2014

Release

The U.S. Food and Drug Administration yesterday approved the Intercept Blood System for platelets, the first pathogen reduction system to treat single donor apheresis platelets. The system is for use by blood establishments that collect and manufacture blood and blood components to prepare pathogen reduced platelets for transfusion to reduce the risk of transfusion-transmitted infections.

On Dec. 16, the FDA also approved the Intercept Blood System for the preparation of plasma to reduce the risk of transfusion-transmitted infections.

The Intercept System for platelets has been shown to reduce the number of a broad range of viruses, bacteria and other pathogens that may contaminate platelets. Examples of some of the pathogens that may be reduced using the Intercept Blood System include HIV, hepatitis B and C viruses, West Nile virus and gram-negative and gram-positive bacteria. The Intercept process also reduces the number of T cells (a type of white blood cell) to a level that lowers the risk of transfusion-associated graft-versus-host disease (TA-GvHD). TA-GvHD is a rare, but often fatal, complication of blood transfusion in which the donor's T cells attack the recipient's tissues.

FDA's Position on Intercept® -Treated Platelets after the Publication of the Sprint Study

Studies that lead to the approval of Intercept ® - Treated Plasma and Platelets

Package Insert for Intercept® - Treated Platelets

Post-Marketing Studies

Safety data were obtained from three hemovigilance (HV) programs in routine use without patient selection: the Cerus hemovigilance program and the regulatory surveillance programs in France and in Switzerland.(39-49)

The populations monitored in the Cerus hemovigilance studies included 4,067 patients, where 59 patients were under the age of 1 year and 185 patients were 1-18 years of age. 51% of the patients enrolled in these studies were hematology-oncology patients, of which 12% were HSCT patients. Adverse events within 24 hours and serious adverse events within 7 days of platelet transfusion were reported. The frequencies of adverse events attributed to Intercept® processed platelet transfusions were not increased compared to conventional platelet transfusions reported in European regulatory hemovigilance programs.

Package Insert for Intercept® - Treated Platelets

ANSM and Swissmedic Active HV Programs (France and Switzerland)

Since 2009, INTERCEPT ® processed platelets have been monitored in comparison to other types of platelet concentrates transfused in France and Switzerland through a national hemovigilance program.(44-49)

In Switzerland, INTERCEPT ® processed platelets were phased into routine use during 2011, accounting for approximately 80% of all platelet concentrates transfused that year, and 100% of platelets produced thereafter. No septic transfusion reactions due to bacterial contamination of platelets were observed after the introduction of Intercept® processed platelets in France or Switzerland.

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Package Insert for Intercept® - Treated Platelets

ANSM and Swissmedic Active HV Programs (France and Switzerland)

The number of TRALI reported to the HV systems during the years 2009-2013 is small, and the TRALI rates were similar in both groups. There were 6/187,142 TRALI cases per Intercept® processed platelet transfusions, for a TRALI rate of 0.33 per 10,000 platelet transfusion, compared to 37/1,109,135 TRALI cases per conventional platelet transfusions, for a rate of 0.32 per 10,000 platelet transfusions. Limitations of the hemovigilance system include data collection that was limited to only transfusion associated AEs (TRALI, TACO, TAD, etc.) as assessed by the reporter.

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While the Intercept System for platelets has been shown to be effective in reducing pathogens, there is no pathogen inactivation process that has been shown to eliminate all pathogens. Certain viruses (e.g. non-enveloped viruses, such as human parvovirus B19) and spores formed by certain bacteria are known to be resistant to the Intercept process.

Irradiation

Advancing Transfusion and Cellular Therapies Worldwide

Association Bulletin #16-05

Date: March 17, 2016

To: AABB Members

From: Donna Regan, MT(ASCP)SBB – President
Miriam A. Markowitz – Chief Executive Officer

Re: Changes to the 30th edition of *Standards for Blood Banks and Transfusion Services*

Association Bulletins, which are approved for distribution by the AABB Board of Directors, may include announcements of standards or requirements for accreditation, recommendations on emerging trends or best practices, and/or pertinent information. This bulletin describes three changes to the 30th edition of *Standards for Blood Banks and Transfusion Services (BBTS Standards)*. These changes are:

1) Revisions to Requirements for Prevention of Transfusion-Associated Graft-vs-Host Disease
2) Extended Expiration Date for Apheresis Platelets Leukocytes Reduced
3) Adjusted Effective Date for Standards Affected by FDA Final Rule (issued May 22, 2015)

1) Revisions to Requirements for Prevention of Transfusion-Associated Graft-vs-Host Disease

Summary
Standard 5.19.3 has been expanded and a new Standard 5.19.3.1 has been added. The newly renumbered Standard 5.19.3.2 (formerly 5.19.3.1) has been expanded. These changes are intended to allow for the use of certain pathogen reduction technologies to prevent transfusion-associated graft-vs-host disease.

The standards read as follows:

5.19.3 ~~Irradiation~~ Prevention of Transfusion-Associated Graft-vs-Host Disease
The BB/TS shall have a policy regarding the ~~transfusion of irradiated components~~ **prevention of transfusion-associated graft-vs-host disease**.

5.19.3.1 **Methods known to prevent transfusion-associated graft-vs-host disease shall be used, and include either irradiation or the use of a pathogen reduction technology that is known to inactivate residual leukocytes and is cleared or approved by the FDA or Competent Authority.**

5.19.3.2 At a minimum, cellular components shall be ~~irradiated when~~ **prepared by a method known to prevent transfusion-associated graft-vs-host disease when**:

AABB Symposium on Implementation of Pathogen-Reduced Blood Components
April 27 – 28, 2015

Background and Key Challenges

However, there are many barriers to adopting of Pathogen Reduction Technologies (PRT), including:

- The perception that the blood supply is already "safe enough;"
- No single PRT method can treat all blood components;
- The inability of current PRTs to inactivate all infectious agents;
- Concern over potential risks to transfusion recipients from residual chemical agents used to inactivate pathogens; and
- The high cost of PRT in the absence of favorable health economic analyses or an adequate reimbursement schema.

Perspectives on US PRT Implementation

Ed Snyder, MD, discussed Yale-New Haven Hospital's approach to implementing PR. He suggested that widespread adoption of PR may require an FDA mandate and accrediting organizations, like AABB and the College of American Pathologists (CAP), requiring PR in their standards. Dr. Snyder added that the Centers for Medicare & Medicaid (CMS) must reimburse hospitals for the additional cost of PR. Maintaining a dual inventory of PR platelets and standard issue platelets would present logistical difficulties, suggesting that moving to a 100 percent PR-platelet inventory is preferable, according to Dr. Snyder.

Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion

Draft Guidance for Industry

This guidance document is for comment purposes only.

Implications of the FDA Draft Guidance

Action	Day 4 (mandated)	Day 5 (mandated)	Day 6 (voluntary)	Day 7 (voluntary)
Need to use a secondary screening test for bacterial contamination	Yes (done the day of transfusion, valid for 24 hours)	Yes (done the day of transfusion, valid for 24 hours)	Yes (done the day of transfusion, valid for 24 hours)	Yes (done the day of transfusion, valid for 24 hours)
Need to change the label on the platelet bag (in terms of the expiration date)	No	No	**Yes**	**Yes**
Need to register with the FDA to use these platelets	No	No	**Yes**	**Yes**
Can Use Pathogen-reduced platelets as a substitute for a secondary screening test for bacterial contamination	Yes	Yes	*No*	*No*

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Benefits of PR Platelets

- Multi-log reduction of most blood borne pathogens:
- --Bacteria ⇨gram (+) and gram (-)
- --Lipid-enveloped viruses (HIV, CMV, etc…)
- Effective inactivation of lymphocytes. Protects against TA-GVHD and eliminates need for either gamma or x-ray irradiation

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Benefits of PR Platelets-continued

- Decreased generation of cytokines by PR treated leukocytes contained in the SDP platelet unit
- Decreased risk of allergic reactions for SDP stored in PAS-C

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PR Technology Constraints

- SDP collected on Amicus instrument-stored in PAS-C for 5 days at 20-24C
- SDP collected on Trima instrument- stored in autologous plasma for 5 days at 20-24C
- Storage duration, 5 days only, no 7 day approval
- Collection bags limited to single/double bags-no triple collection sets
- Guard band requirements
- Limited number of blood centers have been licensed to manufacture Pathogen Reduced platelets

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Current PR Status in American Red Cross

- American Red Cross initiated routine pathogen reduced for SDPs in July 2016
- Collected in platelet additive solution (PAS) on Amicus instrument
- 17/23 manufacturing sites have implemented INTERCEPT and are producing pathogen-reduced SDPs stored in PAS
- Distributions to 100+ hospital customers
- Additional manufacturing sites are coming on-line as well as other sites in the planning phase

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Moving forward…

- Await FDA final guidance for *Bacterial Risk Control Strategies to Enhance the Safety and Availability of Platelets…*
- Guidance will assist hospitals with plans for implementation of PR
- Guidance will assist blood centers in planning and strategy for PR platelet production
- Ongoing hospital education regarding PR

American Red Cross

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