Bacterial Contamination of Platelets, Detection versus Pathogen Reduction, Our Current Conundrum.

Hospitals

Bacterial Contamination of Platelets

Detection versus Pathogen Reduction

Our Current Conundrum.

Brecher –

possible conflicts:

Research grants
Advisory boards
Consultant
Honorarium

Abbot
Amgen
Baxter/Fenwal/Caridian
Becton Dickinson
Blood Cell Storage Inc
Corda
Cutter/Biologics
CTC Caridian BCT
Cutter/Spyer/Weck/Medley/Pal
Fireside
Geis/Prodi
Hoechst Marion Roussel
Hospira
Immucor
Milacron
Neregéa Biotech
Olympus
DBS Bioresearch
PathoVue and Advanced Diagnostics
Texas
Venix

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Platelet bacterial contamination

1/58,000-1/149,000
1/872,000-1/1,700,000
1/1,400,000-1/2,400,000


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Gram negative risk of death = 45%, Gram positive risk of death = 10%


“Thank you for puncturing your skin with your fingernail…”
Platelet transfusions in the United States

4 million platelet bags transfused/year
1:1000 - 1:2000 bacterially contaminated
(N = 2000 - 4000 bags)
1/10 to 2/5 result in clinical sepsis
(N = 200 - 1600 cases)
Perhaps 1/5 to 1/3 result in fatalities
(N = 40 - 533 deaths)
or
(1:7,500 to 1:100,000 fatalities/unit)

Summary comments - Dr. E. Snyder.

Bacterial contamination of platelets workshop September 24, 1999
U.S. Dept of Health and Human Services, CBER

The imperative is to act so you can explain on Night Line.
Regulation is necessary to achieve the goal.
"Nothing says I care like a page of 483s"
When all else fails do something,
give us a mandate and we will do the rest.

5.1.5.1 The blood bank or transfusion service shall have methods to limit and detect bacterial contamination in all platelet components. Standard 5.6.2 applies. [Arm Prep]

TRM.4955 Phase I

Does the laboratory have a system to detect the presence of bacteria in Platelet components?

5.1.5.1.1 Detection methods shall either be approved by the FDA or validated to provide sensitivity equivalent to FDA-approved.

This standard took effect Jan. 31, 2011

Single donor apheresis versus pooled platelets

Percent utilization

1986 - 51.7%  1998 - 99.4%  1986 - 1,4818 transfusions
1986 - 48.3%  1998 - 0.6%  1998 - 1,15,068 transfusions

Reaction rate

1986 - 1:4,818 transfusions
1998 - 1:15,098 transfusions


A contaminated collection detection rate of 1 in 5157.

...this new procedure has been effective in identifying and preventing the transfusion of many, although not all, bacterially contaminated PLT units.


Septic reaction case reports

From March 2003 through December 2003, before screening, 15 septic reactions involving apheresis PLTs were reported. Twelve were assessed as high probability, 2 of which were fatal. In the same period following screening, 8 septic reactions involving apheresis PLTs were investigated and 3 were assessed as high probability.


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Modified from Richard Benjamin, MD, PhD

Reports from hospitals during this 24-month time interval did not reveal any infections transmitted by Bact/ALERT screened PLTs. This contrasts with three known instances of transfusion of bacterially infected PLT apheresis components documented by BSI in the 24 months before implementation of bacterial detection testing.


Results for culturing 122,971 apheresis PLTs


Fuller AK, Uglik KM, Savage WJ, Ness PM, King KE. Bacterial culture reduces but does not eliminate the risk of septic transfusion reactions to single-donor platelets. Transfusion. 2009;49:2588-2593.
A study of 27,620 apheresis platelet doses with the Verax PGD Test on day of issue identified 9 contaminated platelets. (31) All apheresis platelets had been previously released as culture negative by collection centers. All 9 of the identified organisms were Gram-Positive (Coagulase-negative staphylococci, N=6; Bacillus species, N=2; and Enterococcus faecalis, N=1). An additional 3 Gram-Positive cases were found to be non-reactive by PGD, but were subsequently identified (Streptococcus oralis, a Coagulase-negative Staphylococcus and a Streptococcus sanguinis).

1. The current practice of early screening by culture is effective in preventing Gram-Negative post transfusion sepsis.

2. If their data is extrapolated to the entire US apheresis platelet supply, it would be expected that approximately 550 contaminated units per year are being transfused per year and that the use of the PGD Test has the potential to prevent over 300 transfusion reactions/fatalities per year.

Residual Risk for Sepsis

<table>
<thead>
<tr>
<th>Method A</th>
<th>Method B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured Rate</td>
<td>1.93/100-160,000</td>
</tr>
<tr>
<td>Correction Factor for Platelet Reporting</td>
<td>19</td>
</tr>
<tr>
<td>Patient Risk (per unit)</td>
<td>1.83 - 1.33</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>99%</td>
</tr>
<tr>
<td>Patient Risk</td>
<td>1.707</td>
</tr>
<tr>
<td>True positive</td>
<td>129/173</td>
</tr>
<tr>
<td>False negative</td>
<td>50/173</td>
</tr>
<tr>
<td>True negative</td>
<td>110/209</td>
</tr>
<tr>
<td>False positive</td>
<td>2/209</td>
</tr>
</tbody>
</table>

Vox Sang 2007;93:260-277. Total = 1/5977
October 5, 2005 - Pall Corporation
FDA clearance for the new Pall Acrodose™ PL System.

“Bacterial contamination of PSPs was assessed at 5.8-fold our current rate for apheresis PLTs utilizing comparable culture protocols.”


Collateral Donor Benefit of Bacterial Detection
Colonic Adenocarcinoma


In addition, deviation from culture methods that meet manufacturer's recommendations (e.g., decreased blood volume) can result in reduced sensitivity and produce false negatives. For patient B, the volume of the platelet sample was less than the manufacturer's recommended volume for platelet screening.

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Platelet Pathogen Reduction Platforms

- Intercept, Cerus: Amotosalen + UV
- Mirasol, Terumo: Riboflavin + UV
- Theraflex, Macropharma: UV-C light

**Parameter** | **Small Volume Set** | **Large Volume Set** | **Dual Storage Set**
--- | --- | --- | ---
Storage Medium | PAS + Plasma | PAS + Plasma | PAS + Plasma
Platelet ratio | 32% - 47% | 32% - 47% | 32% - 47%
Platelet Count | 2.5-5.0 x 10^11 | 3.0-6.0 x 10^11 | 6.0-8.0 x 10^11
Platelet Count | 6.0-8.0 x 10^11 | 6.0-8.0 x 10^11 | 6.0-8.0 x 10^11
Volume | 255-325 mL | 300-390 mL | 375-420 mL
RBC | < 6 x 10^10/mL | < 6 x 10^10/mL | < 6 x 10^10/mL
CAD Time | 4-16 hours | 6-16 hours | 6-16 hours
Maximize Platelet Shelf-life | 5 days | 5 days | 5 days

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Platelet Pathogen Reduction Platforms

**Fig. 1. Module Plasma Thesauri 3% for plasma.**

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**The INTERCEPT Blood System for Platelets and Plasma**

- Routine Line is One
- Center: 100
- Customer Experience of One
- Ten Years in Routine Line

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**Platelet Pathogen Reduction Performance in Platelets Stored in 65% InterSol/35% Plasma**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Log Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1</td>
<td>-2.8</td>
</tr>
<tr>
<td>HIV-2</td>
<td>-2.8</td>
</tr>
<tr>
<td>HBV</td>
<td>-2.8</td>
</tr>
<tr>
<td>HCV</td>
<td>-2.8</td>
</tr>
<tr>
<td>VDRL</td>
<td>-2.8</td>
</tr>
<tr>
<td>FV</td>
<td>-2.8</td>
</tr>
<tr>
<td>HEV</td>
<td>-2.8</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>-2.8</td>
</tr>
<tr>
<td>Poliovirus</td>
<td>-2.8</td>
</tr>
</tbody>
</table>

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**IBS Bacterial Reduction Performance in Platelets in 65% InterSol/35% plasma**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Log Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial spores</td>
<td>-2.8</td>
</tr>
<tr>
<td>Other bacterial spores</td>
<td>-2.8</td>
</tr>
</tbody>
</table>

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**TABLE 1. Log reduction of bacteria and viruses in platelets**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Log Reduction</th>
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<tbody>
<tr>
<td>E. coli</td>
<td>-2.8</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>-2.8</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>-2.8</td>
</tr>
<tr>
<td>Salmonella enteritidis</td>
<td>-2.8</td>
</tr>
<tr>
<td>Shigella flexneri</td>
<td>-2.8</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>-2.8</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>-2.8</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>-2.8</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>-2.8</td>
</tr>
</tbody>
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IBS Bacterial Reduction Performance in Platelets in 65% InterSol/35% plasma

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Log&lt;sub&gt;2&lt;/sub&gt; Reduction (pH 6 or pH 7.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmodium falciparum</td>
<td>≥ 6</td>
</tr>
<tr>
<td>Rhodotorula mucilaginosa</td>
<td>≥ 3</td>
</tr>
<tr>
<td>Propionobacterium acnes</td>
<td>≥ 3</td>
</tr>
<tr>
<td>Leishmania mexicana</td>
<td>≥ 0</td>
</tr>
</tbody>
</table>

Tables from IBS Package Insert

Bacterial spores are resistant to inactivation by IBS

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IBS Bacterial Reduction Performance in Platelets in 65% InterSol/35% plasma

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Tables from IBS Package Insert

Bacterial spores are resistant to inactivation by IBS

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Planned post-transfusion transmission of Hepatitis E


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Hepatitis E transmission by transfusion of Intercept


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Platelet recovery and survival

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Corash et al ASH 1997

Platelet recovery and survival

<table>
<thead>
<tr>
<th>Control</th>
<th>Treated</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>50.3%</td>
<td>42.5%</td>
</tr>
<tr>
<td>Survival</td>
<td>6.0 days</td>
<td>4.8 days</td>
</tr>
</tbody>
</table>


Hospitals

Platelet recovery and survival (Intercept)

<table>
<thead>
<tr>
<th>Control</th>
<th>Treated</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>66.5%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Survival</td>
<td>66.5 hours</td>
<td>104 hours</td>
</tr>
</tbody>
</table>


Hospitals

Platelet recovery and survival (Mirasol)

<table>
<thead>
<tr>
<th>Control</th>
<th>Treated</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>66.5%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Survival</td>
<td>66.5 hours</td>
<td>104 hours</td>
</tr>
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Pulmonary Adverse Events

| TABLE 6. Confirmed treatment-emergent clinically serious pulmonary AEs (C-SPAE) using EFP version: number of events and rate of occurrence in original study population*
<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Reference arm</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevented C-SPAE</td>
<td>C-SPAE no EFP</td>
<td>169 (22.9)</td>
<td>121 (16.6)</td>
</tr>
<tr>
<td>CRCPA, no EFP</td>
<td>169 (15.0)</td>
<td>121 (10.8)</td>
<td>0.029</td>
</tr>
<tr>
<td>No test arm or no CRCPA, no EFP</td>
<td>169 (19.6)</td>
<td>121 (16.6)</td>
<td>0.490</td>
</tr>
<tr>
<td>ALG only</td>
<td>169 (2.2)</td>
<td>121 (3.4)</td>
<td>0.470</td>
</tr>
<tr>
<td>ALG+CENTRIS</td>
<td>169 (3.8)</td>
<td>121 (4.9)</td>
<td>0.866</td>
</tr>
</tbody>
</table>

* Prevented C-SPAE: Administer EFP protocol within 1 h of treatment.

- There were 100 patients in the treatment arm and 97 patients in the reference arm for a total of 197 patients.
- The mortality rate for patients with ALG or CRCPA in the treatment and reference arms did not differ (p = 0.002).
- In 2011, the treatment arm had 169 events, and the reference arm had 121 events (p = 0.002).

In 2013, there were 2 million units of red cells, and 312,000 units of platelets issued in the UK

Transfusion-transmitted infections in platelets in the UK Through 2013

Bacteria
- 35 confirmed cases 1995-2009 (13 apheresis, 22 pooled)
- 3 deaths
- Preventive measures:
  - 2003: diversion pouch for first 30mL of whole blood and platelet donations
  - 2007: improved method for donor arm cleansing
  - 2011: routine bacterial screening (BacT/Alert)
- No cases since 2009

In 2013, there were 2 million units of red cells, and 312,000 units of platelets issued in the UK
The committee concluded that "the driver for pathogen inactivation for platelets, in the absence of systems for red cells/whole blood added that "clear evidence of overall clinical benefit, however, is not available at this time."

The committee noted that there have been no proven bacteria transmissions through platelets and only a single "near-miss" in more than 600,000 units distributed. The NHS Blood and Transplant’s current model of continuous culture to outdate adds a potential layer of protection and has allowed the blood service to extend its platelet shelf-life to seven days.

In terms of the cost to implement the three systems, estimates ranged between £8.14.6million ($13.4 - 24.5million) per year, compared with the current irradiation and bacterial screening costs of about £3.8 million ($6.4 million) per year. "In all combinations of these, the cost per quality adjusted life year (QALY) saved is over £1 million for all three PI systems, significantly above the usual requirement of £25 thousand per Quality Adjusted Life Year (QALY)."

Additional concerns noted included the need for an estimated 5% additional platelets due to production loss and in vivo recovery.

The Irish Blood Transfusion Service wishes to tender for one or more systems of pathogen inactivation for Platelet concentrate for Transfusion, in either plasma or plasma/additive solution. The IBTS intends to use the system or systems on one or more production sites for up to 24,500 platelet therapeutic doses divided between Apheresis and Whole Blood derived buffy coat (BC) polled platelet units.
In simple terms, the treatment of platelets with pathogen reduction technology has been estimated to increase production costs 71.7% to 85.5% (with the Intercept Platelet System [Cerus Corp., Concord, CA]).

However, cost-effectiveness models must balance multiple variables in deriving any potential savings or loss. Such variables include the potential elimination or reduction of the need for leukocyte reduction, gamma irradiation, and bacteria testing.


A recent patient-oriented risk/benefit analysis of pathogen-reduced apheresis platelets in the United States concluded that the “evidence indicates a favorable risk-benefit profile for the implementation of PLT PI [platelet pathogen inactivation] and argues for a path forward toward US regulatory approval.”


Based on data from 1422 patients from 10 trials, the authors concluded that there was no evidence for a difference in mortality, “clinically significant” or “severe bleeding”, and transfusion reactions or adverse events between pathogen-reduced and standard platelets. However, for a range of laboratory outcomes, the results indicated evidence of some benefits for standard platelets (eg, a need for 7% more platelet transfusions and more frequent transfusions in those patients receiving multiple transfusions) over pathogen-reduced platelets.


IBS approved only for LR apheresis platelets collected by AMICUS and stored in nominal volume ratio of 65% InterSol/35% plasma

• CERUS SPRINT clinical hemostasis study was conducted using AMICUS LR apheresis platelets stored in 65% InterSol/35% plasma out to 5 days

• IBS not approved for whole blood-derived platelets

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IBS for Platelets

- Warnings and Precautions
  - Pulmonary events: ARDS
  - Package insert prompts user to monitor patients for signs and symptoms of ARDS
  - Pivotal study: higher incidence of ARDS in the IBS arm vs. control; difference was statistically significant
  - Reanalysis of subset of patients with clinically serious pulmonary AEs: difference in ARDS no longer statistically significant, however
  - Trend persisted against IBS arm
  - Subset was of small size, low power
  - Post-marketing study will monitor patients for clinically significant pulmonary injury

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2007 Canadian Consensus Conference on Pathogen Inactivation Processes for Blood Components

PI should be implemented when a feasible and safe method to inactivate a broad spectrum of infectious agents is available.

Absence of an integrated system does not imply that PI of any one component should be delayed until a method is proven satisfactory for all components

The treated product should be used universally

Increased bacterial safety Potential to: eliminate irradiation eliminate CMV testing eliminate leukocyte reduction reduce known infectious risk reduce unknown infectious risk

Increased cost Need for 5-7% more platelets Only available on Amicus PLTs Not considered cost effective

Only 1 source Blood Shield law risk

HHS Advisory Committee on Blood Safety and Availability
January 2008, Recommendations

a) Adopt as a high priority the urgent development of safe and effective pathogen reduction technologies for all blood transfusion products and implement as they become available

b) Provide resources to overcome current barriers to development and validation of pathogen reduction technologies
c) Ensure adequate safety monitoring of pathogen reduced blood products post-marketing using an active national hemovigilance system
d) Ensure that other efforts to improve blood safety and availability are not compromised by these efforts.

Increased bacterial safety Increased cost
Potential to: Need for 5-7% more platelets
eliminate irradiation Only available on Amicus PLTs
eliminate CMV testing Not considered cost effective
eliminate leukocyte reduction Blood Shield law risk

So, have we missed the boat?
Do we know where we are going?