CONTINUING CONTROVERSIES IN PLATELET TRANSFUSION THERAPY

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Petteway-Shepherd Award Recipients
NCABB 1989 - Present

- Christine Lomas-Francis
- Joanne Kurtzburg
- Marilyn Telen
- Mark Brecher
- Steve Bredehoeft
- Marion Reid
- Delores Mallory
- James AuBuchon
- Edward Snyder
- W. John Judd
- Harold Meryman
- George Garraty
- Jerry Squires
- Kathleen Sazama
- Marcus Simpson
- Rebecca Haley
- James Laningham
- Robert Langdell
- Francis Jones
- Kenneth Brinkhous
- Ronald Strauss
- Wendell Rosse
- Peter Issitt
- Francis Widmann
- Patrick Mollison

Platelet Components

Produced
-- from whole blood
- platelet-rich plasma (PRP)
- buffy coat (in Europe and Canada)
-- Platelet apheresis

APHERESIS PLATELETS
POTENTIAL ADVANTAGES

- Reduction in infectious complications
- Reduction in transfusion reactions
- Ease of leukodepletion
- Reduction in transfusion frequency
- Treatment of alloimmunized recipients
- Prevention of alloimmunization (UNPROVEN)
- Platelet quality
- No need to pool PC in blood bank

Indications for Platelet Transfusions

To treat or prevent bleeding associated with thrombocytopenia and/or platelet dysfunction, for example:
- Bone marrow failure
- Massive transfusion
- Acute DIC
- Inherited or acquired platelet function disorders
- Neonatal alloimmune thrombocytopenia
- ITP or TTP (only if significant hemorrhage)
Platelet Transfusion Progress 2015

- Platelets now widely available
- Platelets can be stored for 5 days, perhaps longer in the future
- Platelet alloimmunization has been reduced by LR and can be managed by platelet matching
- Bacterial sepsis and other adverse reactions have been reduced
- Platelet triggers (and platelet dosage) are evidence based

Evidence Based Medicine

TABLE 1. Levels of scientific evidence that can be used to evaluate the efficacy of various transfusion medicine interventions (modified from Sackett3)

<table>
<thead>
<tr>
<th>Level</th>
<th>Scientific evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Data from RCTs that are sufficiently large to give clear-cut results, with only a small risk of an error. This level of evidence includes meta-analyses from such RCTs.</td>
</tr>
<tr>
<td>2</td>
<td>Data from small RCTs that give uncertain results and that may have a moderate to high risk of error. This level of evidence includes meta-analyses from such RCTs.</td>
</tr>
<tr>
<td>3</td>
<td>Nonrandomized cohort observational studies that use concurrent control data.</td>
</tr>
<tr>
<td>4</td>
<td>Nonrandomized cohort observational studies that use historical control data.</td>
</tr>
<tr>
<td>5</td>
<td>Case series that use data from uncontrolled observations, or that represent unsubstantiated “expert” opinion.</td>
</tr>
</tbody>
</table>

Prophylactic Platelet Transfusion Trigger

Randomized, Controlled Trial in AML Induction

<table>
<thead>
<tr>
<th>Threshold:</th>
<th>10,000/µL</th>
<th>20,000/µL</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>135</td>
<td>120</td>
</tr>
<tr>
<td>Major bleeding episodes</td>
<td>21.5%</td>
<td>20%</td>
</tr>
<tr>
<td>1-2</td>
<td>15.6%</td>
<td>15.0%</td>
</tr>
<tr>
<td>&gt;4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Days with major bleeding</td>
<td>3.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Hemorrhagic deaths (cerebral)</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

21.5% fewer transfusions

*or 10-20,000/µL and temp ≥ 38.0°C, active bleeding or invasive procedure

¶ Occurring when platelet count = 32,000/µL

Rebuffo et al. NEJM 1997;337:1870-5.
PLADO Trial: Study Design

- Subjects randomly assigned to low, medium, high dose platelets
  - $1.1 \times 10^{11}$, $2.2 \times 10^{11}$, or $4.4 \times 10^{11}$ plt/m² per transfusion
- Used morning platelet count 10,000 as transfusion trigger
- 1300 patients enrolled
- Enrollment into 4 strata: allo-BMT, auto-BMT, heme malignancy, solid tumor

Surprising Result: Everyone Bled!

![Graph showing time to primary outcome]

Table 1: Primary and Key Secondary End Points, According to Treatment Group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>Platelet Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>55</td>
<td>58</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Karnofsky</td>
<td>70</td>
<td>75</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>750</td>
<td>250</td>
<td>175</td>
<td>200</td>
</tr>
<tr>
<td>Platelet count</td>
<td>5000</td>
<td>10000</td>
<td>15000</td>
<td>20000</td>
</tr>
</tbody>
</table>

GOBSAT

Good Old Boys Sitting Around Talking
CARDIAC SURGERY

Platelets in Cardiac Surgery

• Prophylactic transfusions have not been shown to be efficacious
• A subset of patients develop persistent platelet dysfunction and do not respond quickly to current transfusion therapy

Massive injury leads to the rapid consumption of platelets

• You only have 15 ml of platelets in your body.
• You have enough capillaries in your lung to cover a football field.
• You have enough platelets in your body to cover 82 sq ft.
• Massive tissue injury creates millions of endothelial microtears exposing collagen and tissue factor.
• 5% of trauma patient present with a platelet count less than 100K, 2% with less than 50K.

Breaking the “Bloody Vicious Cycle”

• Control hemorrhage
• Use best possible resuscitation products
• Prevent hypothermia
• Prevent hemodilution
• Treat coagulopathy
Data on Platelet Storage Temperature

4C Platelets May Improve Hemostasis

- Response to aggregation, a marker of platelet function, was higher in 4C-stored platelets compared to conventional RT, consistent with better preservation of platelet function.
- Conversely, the 4C response to inhibition was similar to fresh, suggesting that 4C platelets remain under physiologic controls and are unlikely to cause DIC in vivo.

PLATELET ALLOIMMUNIZATION

- Most important long term complication of platelet transfusion therapy
- Incidence depends upon patients under study, previous transfusions or pregnancies, and intensity of therapy
- About 1/3 of patients with AML become alloimmunized and refractory to random platelets

Persistent Alloimmunization in Platelet Recipients – 2014

- 57/224 (25.4%) patients at JHH receiving treatment/transfusions for leukemia in 2009 have positive HLA antibody screen
- 26/85 (30.6%) patients requiring platelets at JHH for hematologic malignancies required some degree of matched platelet support
Riboflavin binds to DNA by intercalation. Photolysis of the complex induces guanine oxidation, single strand breaks and the formation of covalent adducts.

Ennever et al., Pediatric Res. 1983, 17, 234
Ito et al., J. Biol Chem 1993, 268, 13221

Transplantation, 2007
Asano and Baldwin, JHH

Collaborative Research with Dr. William Baldwin, Johns Hopkins University

<table>
<thead>
<tr>
<th>Transfused Platelet Product</th>
<th>IgM Production</th>
<th>IgG Production</th>
<th>Transplant Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6/6</td>
<td>6/6</td>
<td>5/6</td>
</tr>
<tr>
<td>Mirasol PRT</td>
<td>1/6</td>
<td>1/6</td>
<td>0/6</td>
</tr>
</tbody>
</table>

Septic Platelet Transfusion Reactions (circa 2003)

- Septic platelet transfusion reactions (SPTR) are the most common, serious infectious risk of transfusion in the United States.
- Although the risks of viral transmission now are less than 1:1,000,000, the risks of SPTR are approximately 1:5000
- SPTR occur from donor skin contaminants or asymptomatic bacteremia in the donor.
**SPTR - Conclusions**

- Single donor platelets substantially reduce but do not eliminate SPTR.
- Prospective evaluations of all suspect platelet transfusion reactions are required to identify the true incidence of SPTR.
- Other measures such as pathogen reduction or pretransfusion screening will be required to eliminate all SPTR.
- These data provided useful information for regulatory policy decisions.

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**SPTR at Johns Hopkins Hospital**

Rates per 100,000 transfusions

- **Persistent Problems with Bacterial Sepsis**
  - Current bacterial testing delays product release and lessens platelet availability.
  - Point of release testing is costly, has false positives and negatives, and may be difficult for hospitals and blood centers to use.
  - Pathogen inactivation for platelets recently approved in the US.

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**Incidence of ATRs**

Matthew Karafin, MD
No Effect of Diphenhydramine Premedication

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Product</th>
<th>Patients</th>
<th>Transfusions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang 2002</td>
<td>Randomized, Placebo controlled</td>
<td>PLT</td>
<td>51</td>
<td>98</td>
<td>NS</td>
</tr>
<tr>
<td>Kennedy 2008</td>
<td>Randomized, Placebo controlled</td>
<td>PLT, RBC</td>
<td>323</td>
<td>323</td>
<td>NS</td>
</tr>
<tr>
<td>Patterson 2000</td>
<td>Prospective</td>
<td>PLT</td>
<td>716</td>
<td>3,472</td>
<td>NS</td>
</tr>
<tr>
<td>Sanders 2005</td>
<td>Retrospective</td>
<td>PLT, RBC</td>
<td>385</td>
<td>7,900</td>
<td>NS</td>
</tr>
<tr>
<td>Szelei-Stevens 2006</td>
<td>Retrospective</td>
<td>PLT, RBC, FFP</td>
<td>31,665</td>
<td>301,210</td>
<td>NS</td>
</tr>
</tbody>
</table>

Adapted from Tobian, King, and Ness. Transfusion. 2007

Removing Plasma Reduces ATRs

Platelet Additive Solutions

- Used extensively in Europe to save plasma for transfusion or fractionation
- Platelet storage is not affected by PAS
- By diluting plasma, PAS may decrease risk of allergic reactions
- PAS is now available in US to reduce transfusion reactions (allergic and hemolytic reactions to ABO antibodies in platelets)

Allergic Transfusion Reactions

Johns Hopkins 2013

<table>
<thead>
<tr>
<th></th>
<th>ATRs</th>
<th>TX</th>
<th>Incidence</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>72</td>
<td>3884</td>
<td>1.85%</td>
<td></td>
</tr>
<tr>
<td>PAS</td>
<td>12</td>
<td>1194</td>
<td>1.01%</td>
<td>p&lt;0.04</td>
</tr>
</tbody>
</table>

Transfusion-associated GVHD

- Classic GVHD symptoms: diarrhea, skin rash, hepatitis
- Bone marrow failure - aplastic anemia common with TA-GVHD
- Death (infection) 2 to 3 weeks post transfusion
PATIENTS AT RISK

• In-utero transfusions
• SCID children
• Any recipient of related donor blood
• Patients with acquired immunosuppression
• Anyone unfortunate to receive unintentional HLA matched blood

IRRADIATED BLOOD

• Indicated to eliminate risk of transfusion-associated graft versus host disease
• Indicated for patients with congenital immunodeficiency, bone marrow and solid organ transplants, neonates, etc.
• Pathogen inactivation can eliminate TA-GVHD without irradiation
• No need for physicians to select high risk patients to receive irradiated blood to prevent TA-GVHD if PI is available

Pathogen Inactivation Current Status

• Pathogen inactivation is available for plasma and platelets in Europe and the US, and in earlier stages for red cells. Two companies, Cerus and Terumo BCT, are developing procedures for PI
• Platelets are the most compelling issue now but screening has diminished the urgency. Emerging infections could change this picture at any time.
• Reducing immune complications may emerge as the most important clinical effect
• Issues of toxicity, mutagenicity, and adverse effects on infused cells must be addressed.
• If implemented, component preparation and delivery systems will undergo major change.
• Cost effective issues will need to be resolved.

Why is Pathogen Reduction Potentially Important?

• Reduced risk of bacterially contaminated platelet transfusion
• Further closing of window period for screened viruses
• Added protection against untested pathogens (e.g. Chagas disease, Malaria)
• Proactive protection against emerging pathogens (e.g. Chikungunya, West Nile virus)
• Possible reduction in adverse transfusion events caused by residual white cells
• Potential to extend Platelet shelf-life to 7 days
• Potential to replace or revisit existing blood safety measures (e.g. bacterial testing, gamma-irradiation)
• Public expectation of “zero risk”

Platelet Issues - 2015

• Platelet triggers and dosage for blood intensive procedures and trauma
• New (maybe old) formulations of platelets to enhance hemostatic efficacy
• Cold stored platelets under study
• Alloimmunization and adverse reactions such as bacterial sepsis and allergic reactions need to be further reduced
• Will PI reduce/eliminate these persistent problems?