CONTINUING CONTROVERSIES IN PLATELET TRANSFUSION THERAPY

Paul M. Ness, M.D.
Professor
Pathology, Medicine, and Oncology
The Johns Hopkins Medical Institutions
Baltimore, Maryland, USA
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 Garratty

• 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
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 &quot;expert&quot; opinion.</td>
</tr>
</tbody>
</table>
Seven Alternatives to Evidence-Based Medicine
David Isaacs and Dominic Fitzgerald
Oncologist 2001;6:390-391
DOI: 10.1634/theoncologist.6-4-390
<table>
<thead>
<tr>
<th>Basis for clinical decisions</th>
<th>Marker</th>
<th>Measuring device</th>
<th>Unit of measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence</td>
<td>Randomized controlled trial</td>
<td>Meta-analysis</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Eminence</td>
<td>Radiance of white hair</td>
<td>Luminometer</td>
<td>Optical density</td>
</tr>
<tr>
<td>Vehemence</td>
<td>Level of stridency</td>
<td>Audiometer</td>
<td>Decibels</td>
</tr>
<tr>
<td>Eloquence (or elegance)</td>
<td>Smoothness of tongue or nap of suit</td>
<td>Tefliometer</td>
<td>Adhesin score</td>
</tr>
<tr>
<td>Providence</td>
<td>Level of religious fervor</td>
<td>Sextant to measure angle of genuflection</td>
<td>International units of piety</td>
</tr>
<tr>
<td>Diffidence</td>
<td>Level of gloom</td>
<td>Nihilometer</td>
<td>Sighs</td>
</tr>
<tr>
<td>Nervousness</td>
<td>Litigation phobia level</td>
<td>Every conceivable test</td>
<td>Bank balance</td>
</tr>
<tr>
<td>Confidence*</td>
<td>Bravado</td>
<td>Sweat test</td>
<td>No sweat</td>
</tr>
</tbody>
</table>

*Applies only to surgeons*
Relationship of Thrombocytopenia to Hemorrhage

Blood Loss in Stool (mL/day)

Platelet Count (x10^3/µL)

# 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></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15.6%</td>
<td>15.0%</td>
</tr>
<tr>
<td>2-4</td>
<td>5.9%</td>
<td>5.0%</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>1¶</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

¶ Occuring when platelet count = 32,000/µL

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/m$^2$ 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
### Table 3. Primary and Key Secondary End Points, According to Treatment Group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Platelet Dose&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P Value, Low vs. Medium Dose</th>
<th>P Value, Medium vs. High Dose</th>
<th>P Value, High vs. Low Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Dose (N=417)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 Episode of bleeding of grade 2 or higher — % of patients</td>
<td>71</td>
<td>0.60</td>
<td>69</td>
<td>0.71</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest grade of bleeding during study — % of patients</td>
<td></td>
<td>0.30</td>
<td>0.65</td>
<td>0.54</td>
</tr>
<tr>
<td>No bleeding or grade 1</td>
<td>30</td>
<td>32</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>58</td>
<td>59</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>9</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Death from hemorrhage — no. of patients</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
<td>1</td>
</tr>
<tr>
<td>No. of days with bleeding of grade 2 or higher</td>
<td></td>
<td>0.90</td>
<td>0.91</td>
<td>0.99</td>
</tr>
<tr>
<td>Median</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0–4</td>
<td>0–4</td>
<td>0–4</td>
<td></td>
</tr>
<tr>
<td>Days from randomization to onset of bleeding of grade 2 or higher</td>
<td></td>
<td>0.85</td>
<td>0.66</td>
<td>0.55</td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>3–18</td>
<td>3–19</td>
<td>3–19</td>
<td></td>
</tr>
</tbody>
</table>
Time to the Primary Outcome.

No prophylaxis

Prophylaxis

Hazard ratio, 1.30 (95% CI, 1.04-1.64)
P=0.02

No. at Risk

Prophylaxis 298 188 170 165
No prophylaxis 300 152 140 139

PLATELET TRANSFUSION GUIDELINES

- Platelet count <10,000/ul in presence of marrow failure with no bleeding
- Platelet count < 50,000/ul in patients who are bleeding or with invasive procedures
- Platelets with qualitative platelet abnormalities for bleeding or prophylaxis
- Platelet dosage appropriate for body mass;
  one unit/10 kg (6 WBDP units for most adults or 1 apheresis split unit)
Good Old Boys Sitting Around Talking
Pump by-pass

- Platelet consumption/dysfunction
- Factor consumption
- Heparin effect
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
FIGURE 17.2. Autologous reinfusion studies in healthy volunteers of radiolabeled (chromium 51) platelets stored as PRP for 18 hours at various temperatures. The graph on the left shows the survival of platelets stored at 22°C is nearly equivalent to that of fresh platelets, whereas the survival of platelets stored at 4°C is very short. The initial recovery of 50% to 60% of the platelets infused results from physiologic pooling in the spleen (26) rather than from platelet injury. The half-life of fresh platelets is 3 to 5 days. The graph on the right shows that the half-life is normal after storage at 22°C but is reduced after storage at lower temperatures. (Data are redrawn from Murphy S, Gardner FH. Platelet preservation. Effect of storage temperature on maintenance of platelet viability-deleterious effect of refrigerated storage. N Engl J Med 1969; 280:1094–1098; and Murphy S. Platelet transfusion. Prog Hemost Thromb 1976;3:289–310, with permission.)
HEMOSTATIC FUNCTION OF APHERESIS PLATELETS STORED AT 4°C AND 22°C

Kristin M. Reddoch,* Heather F. Pidcoke,† Robbie K. Montgomery,† Chriselda G. Fedyk,† James K. Aden,† Anand K. Ramasubramanian,* and Andrew P. Cap†

*Department of Biomedical Engineering, The University of Texas at San Antonio, San Antonio, Texas; and †US Army Institute of Surgical Research, Fort Sam Houston, Texas

Shock. 2014 May;41 Suppl 1:54-61.
A = TEG R Time
B = TEG K Time
C = Alpha Angle
D = MA
E = Clot Strength
F = TTG

- - - = CON 22; - - - = CON 4; - - - - = PRT 22; - - - - - = PRT 4.
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
TRAP study: results

Slichter, 1997
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
Total amount: 50ml
WBC: 10^6/ml
Transfusion groups

| Treated Platelets with leukocytes ($10^6$) | Untreated platelets with leukocytes | Saline |

① ② ③ ④ ⑤ ⑥ ⑦ ⑧

CsA 5mg/kg 3 times/week

0 10w 1week 2week 3week
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.
Septic Platelet Reactions

Outcome

Fatal
Survived

<table>
<thead>
<tr>
<th>Year</th>
<th>Fatal</th>
<th>Survived</th>
</tr>
</thead>
<tbody>
<tr>
<td>87-88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>89-90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>91-92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>93-94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95-96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>97-98</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
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
**Allergic Reactions**

**Pathogenesis**
- Immune-Mediated
  - Release of Histamines

**Management**
- Antihistamines
- Steroids (Severe)
- Epinephrine (Severe)
- Washed Red Cells (Anti-IgA)

**Urticaria**
Incidence of ATRs

Hemovigilance data: Percent of total reported adverse reactions by product transfused.

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

- ATRs to APs (n=179)
  - Significant or multiple ATRs
    - Concentrated APs (n=135)
      - Decreased number of ATRs
        - Remained on concentrated APs (n=91)
      - Continued ATRs
        - Washed APs (n=44)
  - Severe or life threatening ATRs
    - Washed APs (n=44)

Tobian et al. TRANSFUSION, 2011
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 = 0.04</td>
</tr>
</tbody>
</table>
Platelet Transfusion Reactions

- Febrile reactions due to white cells or cytokines produced during storage
- TRALI
- Allergic transfusion reactions
- Bacterial sepsis
- TA-Graft vs Host Disease
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
Process For Platelet Decontamination

Platelets and Plasma → Ultraviolet Light → Treated Platelets and Plasma

S-59
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?