Platelets- To Transfuse or Not

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SECTION ONE

Evidenced-Based Platelet Transfusion Thresholds
Introduction

• All platelets and cryoprecipitate, most plasma, and rarely RBCs given for coagulation management.

• 5.9 million non RBC products US/year
  – Plasma – 2.7 million units
  – Platelets – 2.0 million doses
    • 10% given as 4-6 U pools
  – Cryo – 1.2 million units

2017 NBCUS
Benefit, Risk, and Cost

- Benefit – varies clinical situation
- Risk – at least 50,000 transfusion reactions year including small number deaths
- Cost – at least $2.5 billion just for products, more for handling ...

JAMA 2016; 316: 2025-2035
Why do we believe we need to treat low platelets and long clotting times?
How did low platelet counts and long clotting times become a surrogate for bleeding risk?

J Hess – AABB Webinar 10/09/14
Risk of New-Onset Bleeding is the Same with Platelet Counts Between 5-80x10^9/L

Blood Use

- About half of all components given in coagulation management are given prophylactically
- Prophylactic platelets in thrombocytopenic patients
- Prophylactic platelets and/or plasma before invasive procedures
Patient Blood Management

• Blood is expensive and not without risk
• Many patients receive blood in situations where evidence of benefit is poor
• Mounting evidence suggests that conservative use is associated with equivalent outcome

Transfusion 2010; 50: 753-65
How do Platelets Function?

Platelets adhere, activate, secrete and aggregate.

Adherence and activation are coupled by vWF pulling on GPIb-IX. Activation, secretion, and aggregation are coupled by Ca++ signaling.
Where Do Transfusion Thresholds Come From?

• Randomized trials
  – 10,000/uL platelet transfusion threshold in cancer patients

• Expert opinion
  – Platelets- 50,000/uL platelet transfusion threshold for major surgery, 100,000/uL for optho & neuro
  – Plasma - > 2.0 INR
  – Cryoprecipitate-100 mg/dL fibrinogen threshold
Relationship Between Platelet Count and Hemorrhage

[Graph showing the relationship between platelet count and days with gross hemorrhage, with different lines for all bleeding, skin & epistaxis excluded, and gross hemorrhage.]

RCTs comparing prophylactic platelet transfusion at 10K/uL vs. 20K/uL

<table>
<thead>
<tr>
<th>First Author</th>
<th>≤10,000/µL transfusion trigger</th>
<th>≤20,000/µL transfusion trigger</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of patients</td>
<td>% major bleeding</td>
</tr>
<tr>
<td>Gil-Fernandez, 1996</td>
<td>103</td>
<td>12</td>
</tr>
<tr>
<td>Rebulla, 1997</td>
<td>53</td>
<td>22</td>
</tr>
<tr>
<td>Heckman, 1997</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Wandt, 1998</td>
<td>58</td>
<td>18</td>
</tr>
<tr>
<td>Navarro, 1998</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>Lawrence, 2001</td>
<td>77</td>
<td>15</td>
</tr>
<tr>
<td>Zumberg, 2002</td>
<td>78</td>
<td>14</td>
</tr>
</tbody>
</table>

Major bleeding generally indicated bleeding that led to transfusion.

J Hess AABB Webinar 10/09/14
Are prophylactic transfusions needed?

- Randomized, open-label, noninferiority trial
- 14 centers in UK and Australia
- Randomly assigned receive, or not to receive, prophylactic platelet transfusions when morning platelet counts were < 10,000/uL
- Time to first bleeding episode significantly shorter no-prophylaxis group vs. prophylaxis group
TOPPs Conclusion

• Results of study support need for continued use of prophylaxis with platelet transfusion
• Showed benefit of such prophylaxis for reducing bleeding, as compared with no prophylaxis

Platelet Transfusions AABB Clinical Practice Guidelines

• Literature search from 1900 to September 2014
• An expert panel reviewed data
• Developed recommendations using Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework

Ann Intern Med. 2015;162:205-213
Recommendation 1

• Prophylactically count 10,000/uL or less
• Reduce the risk for spontaneous bleeding
• Hospitalized adult patients
• Hypoproliferative thrombocytopenia
• *Grade: strong recommendation; moderate-quality evidence*

Ann Intern Med. 2015;162:205-213
Recommendation 2

• Prophylactic platelet transfusion for elective central venous catheter placement with platelet count less than 20,000/uL

• Grade: weak recommendation; low-quality evidence

[Image of a medical diagram]

www.medical-dictionary.thefreedictionary.com 07/19
Ann Intern Med. 2015;162:205-213
Recommendation 3

- Prophylactic platelet transfusion for patients having elective diagnostic lumbar puncture with platelet count less than 50,000/uL

- *Grade: weak recommendation; very low-quality evidence*  
  
  www.enwikipedia.org 07/19

Ann Intern Med. 2015;162:205-213
Recommendation 4

• Prophylactic platelet transfusion for patients having major elective nonneuraxial surgery with a platelet count less than 50,000/uL

• Grade: weak recommendation; very low-quality evidence

Ann Intern Med. 2015;162:205-213
Recommendation 5

- Cardiopulmonary bypass (CPB)
- Perioperative bleeding with thrombocytopenia and/or evidence of platelet dysfunction

- Grade: weak recommendation; very low-quality evidence

Ann Intern Med. 2015;162:205-213
Recommendation 6

• The AABB cannot recommend for or against platelet transfusion for patients receiving antiplatelet therapy who have intracranial hemorrhage (traumatic or spontaneous)

• Grade: uncertain recommendation; very low-quality evidence

Ann Intern Med. 2015;162:205-213
Active Bleeding
No High-Quality Evidence for Guidance

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Platelet Count (/uL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenic Bleeding Patients</td>
<td>Often recommended maintain count above 50,000/uL</td>
</tr>
</tbody>
</table>

Some facilities use 100,000/UL for ophthalmologic, neurologic and pulmonary hemorrhage

Thrombocytopenia

- Causes
  - Congenital (e.g., Glanzmann thrombasthenia)
  - Acquired as the result of disease (e.g., myelodysplasia)
  - Drug treatment (e.g., with aspirin or glycoprotein IIb/IIIa antagonists)

- Transfusion Decisions
  - Acceptable even at normal counts
  - Based upon patient’s clinical status
  - Test platelet function

Platelets-Pre and Post Counts

- Platelet count should be obtained
  - Before
  - 10 to 60 minutes after transfusion
- Platelet count should increase by 30,000 to 60,000/uL
- Assess adequacy of response to transfusion

Platelet Products Available

- Pooled platelets (Acrodose)- average 4-6 platelets per pool
- Apheresis Platelets 100% plasma
- Apheresis Platelets in PAS (platelet additive solution 65%, 35% plasma)
- Pathogen Reduced Apheresis Platelets (collected in PAS)

AABB Standards for Blood Banks/Transfusion Services 31st ed. 2018
Apheresis Platelets in PAS (platelet additive solution 65%, 35% plasma)

- Standard apheresis platelet collected and upon finalization of collection
- 65% percent of plasma is removed
- Replaced with additive solution
- Solution added is InterSol Solution, Platelet Additive Solution 3 (also called PAS 3)

Apheresis Platelets in PAS

• Study conducted at six sites 14,005 transfusions
  – Allergic transfusion reactions - 1.37% vs. 0.55%
  – Febrile nonhemolytic transfusion reactions - 0.66% to 0.40%
  – Removal of plasma, anti-A and anti-B titers may be decreased potentially reducing risk of hemolytic transfusion reactions that can occur with high-titer donors
  – Platelet viability and function is not affected

• Decrease in AB titer allows for products to be used interchangeably with patients with different ABO

  Transfusion 2014; 54: 1927-1934
  J Clin Apheresis 2012; 27: 93-98
  Transfusion 2012; 52: 1237-1244
**Pathogen Reduction Technology (PRT) Mechanism of Action**

- INTERCEPT® Blood System for Platelets uses amotosalen and UVA light to irreversibly cross-link nucleic acids
- Blocks replication of viruses, bacteria, parasites and T-cells; rendering them ‘inactive’
- After processing, residual amotosalen is negligible
Efficacy

- November 2010 - April 2016
- 469 hematology-oncology patients with chemotherapy-induced thrombocytopenia
- Randomized to 567 transfusion treatment periods
  - 283 control arm – platelets in plasma (PP)
  - 284 intervention arm (PRT)

Blood 2018; 132: 223-231
Efficacy

- 3% absolute difference (51% PP vs. 54% PRT) significant (WHO classification - grade ≥ 2 bleeding) P=.012

- Transfusion increment parameters were lower and transfusion interval shorter- PRT arm

- There was no difference in proportion of patients developing HLA class I alloantibodies

Blood 2018; 132: 223-231
Efficacy

• Other studies
  – Small losses in platelet function
• Effective eliminating transfusion-associated graft vs. host disease and the need for irradiation

ISBT Science Series. 2014; 9:44-50
Vox Sanguinis 2017; 112; 606-613

Conventional (left) and Psoralen-Treated (right) Apheresis Platelets
# Platelet Components

Equivalent to 4-6 Whole-Blood Derived Platelets

<table>
<thead>
<tr>
<th></th>
<th>Apheresis Platelets- Includes Plasma, PAS and PRT</th>
<th>Prestorage Pooled Platelets (Acrodose)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>• Single donor exposure</td>
<td>• Closed system</td>
</tr>
<tr>
<td></td>
<td>• HLA matching possible</td>
<td>• Allows pooling 4-6 ABO identical units</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>• Limited availability</td>
<td>• Matching impractical</td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
<td>• $\geq 3.0 \times 10^{11}$ ((\geq 90%))</td>
<td>• $\geq 5.5 \times 10^{10}$ ((\geq 75%))/each unit</td>
</tr>
</tbody>
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Transfusion Therapy. 3rd ed. 2011  
AABB Standards for Blood Banks/Transfusion Services 31st ed. 2018
# Platelet Components

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<th>Prestorage Pooled Platelets (Acrodose)</th>
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</thead>
<tbody>
<tr>
<td><strong>Leukocyte Reduction</strong></td>
<td>• Prestorage</td>
<td></td>
</tr>
<tr>
<td><strong>Bacterial Detection</strong></td>
<td>• Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Shelf Life</strong></td>
<td>• 5 days (7 days with point of release testing*)</td>
<td>• 5 days</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>• 20-24 C continuous gentle agitation</td>
<td></td>
</tr>
<tr>
<td><strong>Transport</strong></td>
<td>• As close to 20-24 C-maximum time without agitation: 30 hours</td>
<td></td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>• ≥ 6.2 end of allowable storage period (&gt;90%)</td>
<td></td>
</tr>
</tbody>
</table>

*Does not include PRT

Transfusion Therapy. 3rd ed. 2011

AABB Standards for Blood Banks/Transfusion Services 31st ed. 2018
Fiscal Years 2013-2017

- TACO - 32%
- TRALI and Possible TRALI - 30%
- Microbial contamination - 12%
- HTR due to non-ABO incompatibilities - 11%
- Remainder - <10% each

Fatalities Reported to FDA Following Blood Collection and Transfusion Annual Summary for FY2017
Transfusion Related Acute Lung Injury (TRALI)

FDA Fatalities Report FY2017
SECTION TWO
Platelet Refractoriness and Patient Response
Corrected Count Increment (CCI)

\[
CCI = \frac{\text{Platelet increment} \times \text{BSA (m}^2\text{)}}{\text{Platelets transfused} \times 10^{11}}
\]

Example: A patient with a BSA of 2.0 \(\text{m}^2\) and a platelet count of 5000/\(\mu\text{L}\) receives a unit of apheresis platelets containing \(4 \times 10^{11}\) platelets, and the posttransfusion platelet count is 25,000/\(\mu\text{L}\). The CCI may be calculated as follows:

\[
CCI = \frac{20 \times 2.0}{4.0} = 10
\]

**Successful transfusion:** \(\geq 7.5\)

**Refractory patient:** Two or more transfusions with CCI <5.0
Refractory Patient

- Poor increments $\leq 10,000/\mu\text{L}$ on at least two posttransfusion counts
Corrected platelet count increments after apheresis platelet units - PLADO study

- Mean absolute increment 28,000/uL
- 95% CI 0-60,000/uL

Alloimmune Platelet Refractoriness

<table>
<thead>
<tr>
<th>Nonimmune</th>
<th>Immune</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>HLA antibodies</td>
</tr>
<tr>
<td>Medications (eg, amphotericin, vancomycin)</td>
<td>ABO incompatibility</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Human platelet antigen (HPA) antibodies</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Drug-dependent autoantibodies</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td></td>
</tr>
<tr>
<td>Graft-vs-host disease</td>
<td></td>
</tr>
<tr>
<td>Prolonged platelet storage</td>
<td></td>
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</tbody>
</table>

Patterns of response to platelet transfusion

UpToDate Graphic 82283 Version 2.0
ABO Compatible

• Some patients may be refractory from ABO
• Provide one or more transfusions of donor PLTs ABO compatible
• Monitor post-transfusion increments
HLA antibody screening test
Panel-reactive antibody (PRA)

• Percent of HLA targets to which patient has made antibodies
• Different assays
  – Lymphocytotoxic assay (with or without antiglobulin enhancement)
  – Enzyme-linked immunoassay, or fluorescence-based assay
• Choice of assay not critical although serial assays are best done by the same method for ease of comparison

Transfusion 2007;47:374-378
Undetectable PRA (0 percent sensitization)

- HLA matching will not be beneficial
- Other strategies should be tried (discussed later)
- For patients with positive PRA result, an algorithm can be used
Positive PRA - Decision algorithm for HLA-selected platelets used at Massachusetts General Hospital

Monitor posttransfusion platelet count obtained 15 to 60 min after transfusion. If a strategy fails, consider the strategy described in the box to the right of current strategy.
Strategies for HLA-selected Platelets

- HLA antigen avoidance
- PLT crossmatching
- HLA-matching

Transfusion 2007;47:374-378
HLA-Antigen Avoidance

- Identify HLA specificity that accounts for majority of PRA
- Most straightforward approach

Transfusion 2007;47:374-378
HLA lab is unable to identify specificity

• Donor selection can proceed along two fronts

Transfusion 2007;47:374-378
Platelet Crossmatching - Fastest

- Transfusable units with higher survival rate \textit{in vivo} can be located without need for HLA typed donors
- Patient HLA typing and/or HLA antibody identification is not required

Transfusion 2007;47:374-378
Platelet Crossmatching

- Strong HLA antibodies directed against antigens not found on PLTs will not be detected
- Lower costs to support mildly refractory patients or those with short to medium term matched platelet support
- Wide availability of some crossmatch methodologies

Transfusion 2007;47:374-378
Disadvantages of Platelet Crossmatching

• Sensitivity to mediating antibodies varies depending upon which crossmatch methodology is utilized
• Highly alloimmunized patients may require numerous (e.g. ≥ 20) crossmatches to identify a compatible unit
• Logistical challenges posed by managing inventory of platelet units used in crossmatch testing

Transfusion 2007;47:374-378
High-PRA Patients

- While crossmatch–compatible PLTs are being tried
- Explore HLA matched platelets based on HLA-A and HLA-B types of recipient
Degree of Matching (Duquesnoy Grades) for HLA Antigens HLA Class I A and B Loci

- “Standard” approach is to identify a donor whose four HLA-A and HLA-B antigens match those of the recipient (grade A match) - may be difficult to find
- Alternatives - grade A, B1u, B1x, or B2u matches,
- Most hospitals do not want to accept B2x matches or lower grades - much less likely to be successful

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4 antigens match</td>
</tr>
<tr>
<td>B1U</td>
<td>3 antigens detected in the donor, all match</td>
</tr>
<tr>
<td>B1X</td>
<td>3 donor antigens match, 1 cross-reactive</td>
</tr>
<tr>
<td>B2U</td>
<td>2 antigens detected in the donor, both match</td>
</tr>
<tr>
<td>B2UX</td>
<td>3 antigens detected in the donor, 2 match and 1 cross-reactive</td>
</tr>
<tr>
<td>B2X</td>
<td>2 donor antigens match, 2 cross-reactive</td>
</tr>
<tr>
<td>C</td>
<td>1 antigen in donor not present in recipient and not cross-reactive</td>
</tr>
<tr>
<td>D</td>
<td>2 antigens in donor not present in recipient and not cross-reactive</td>
</tr>
</tbody>
</table>

Transfusion Medicine Self-Assessment and Review. 3rd ed. 2017

Transfusion 2007;47:374-378
HLA Public Antigens

• Consider not only the public groups of patient (public antigens to match)
• Public groups of target antigens that reacted in PRA (public antigens to avoid)

Transfusion 2007;47:374-378
HLA Public Antigens

- Public matching can often identify donor who gives good increment much more quickly than private antigen matching.
- Strategy of matching for public antigens generally results in greater number of suitable donors.

Transfusion 2007;47:374-378
Platelet Antigens

- Alloimmunization to platelet-specific antigens should be considered.
- Sensitization to platelet-specific antigens may be a cause of refractoriness when a donor product that is well matched for HLA fails to give an increment.
- Identify antibodies to platelet antigens, test patient’s serum with a commercially available enzyme assay.

Transfusion 2007;47:374-378
Vox Sang 1998; 74(Suppl 2):359-63
Non-HLA

- Current era of leukoreduction, immune causes of refractoriness often reflecting a secondary immune response is particular problem with multiparous females
- Outside of this group nonimmune causes of PLT refractoriness are more common than immune-mediated causes and so refractory patients with a low PRA are often commonplace

Transfusion 2007;47:374-378
N Engl J Med 1997; 337: 1861-9
Drug-related thrombocytopenia

- Degree of thrombocytopenia is considered clinically unacceptable
- Serious paring down of medications, especially antibiotics, may be tried

Transfusion 2007;47:374-378
Curr Hematol Rep 2003; 2:158-64
What Does not Work-Shock and Awe

• Massive doses of platelets is rarely effective and for most patients
• Little more than an invitation to serious transfusion reactions
• Exception
  – Patient splenomegaly for whom double dose of platelets may be needed to achieve typical platelet increment

Transfusion 2007;47:374-378
What Does not Work- Treatments for Another Problem

- Platelet refractoriness not the same as autoimmune thrombocytopenia
- Treatments such as intravenous anti-D or high-dose intravenous immunoglobulin G fail to improve platelet increments among refractory patients

Transfusion 2007;47:374-378
What Does not Work- Voodoo drips

• Notion of a continuous drip of ineffective platelets has never made any sense largely “bad theater”
• Equally theatrical is arranging for infusion of platelets to be simultaneous to performance of a bedside invasive procedure
• We simply do not do this!

Transfusion 2007;47:374-378
Local Bleeding–Local Treatment

• Appropriate hemostatic treatment for nonimmune refractory patient is local treatment
• For example, clinical team may be frustrated by continued oozing at site of insertion of central line despite repeated attempts to stop this with platelet transfusions
• This situation is better approached through use of topical agents at site of bleeding
• Topical fibrin glue or extra suture or two may be all that is needed

Transfusion 2007;47:374-378
Hemostatic Defects

• Hypofibrinogenemia, coagulation factor defects, or depressed von Willebrand’s factor

• Addressed with transfusion/pharmaceuticals

Transfusion 2007;47:374-378
Conclusions

• Prophylactic platelet transfusions remain standard of care
• Laboratory testing and donor selection are necessary steps in support of platelet transfusion refractory patient
• Many patients continue to require additional transfusion approaches and/or adjunctive therapy to treat and prevent bleeding

Transfusion 2007;47:374-378
200th anniversary year of the first successful attempts at human-to-human transfusion
The End...Questions

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Florida Society of Pathologists
July 14, 2019