An Approach to the Patient Refractory to Platelets Transfusion

Harold Alvarez, MD
Objectives

• Explain the etiology of platelet refractoriness
• Discuss the different types of platelet refractoriness
• Describe how platelet refractoriness is diagnosed
• Discuss different management approaches of platelet refractoriness
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- General Medicine: 16.6%
- ICU (Medical+Surgical): 12.4%
- Pediatrics: 4.8%
- OB/Gyn: 0.6%
- Nephrology/Dialysis: 0.4%
- Hem/Onc: 34.4%
- Transplant: 3.4%
- Trauma/ER: 4.4%
- All Surgery Departments: 17.6%
- Other: 5.4%

Mean age for WBD platelets: 3.2 days
Mean age for Apheresis platelets: 3.1 days
Refractoriness

Definition
• Failure to obtain satisfactory response to transfusion of unselected platelet components

Etiology
Approximately two-thirds are due to non-immune causes, Immune causes account for the remaining minority of cases
20% of cases have a combination of both immune and non-immune causes.
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<table>
<thead>
<tr>
<th>Non immune (2/3):</th>
<th>Immune (alloimmunization):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sepsis, fever, bleeding, splenomegaly, disseminated intravascular coagulation (DIC), hepatic sinusoidal obstruction syndrome (hepatic veno-occlusive disease), graft-versus-host disease (GVHD) and medications</td>
<td>• Development of anti-human leukocyte antigen (HLA-I) and/or human platelet antigens (HPA)</td>
</tr>
<tr>
<td></td>
<td>• Prior exposure; pregnancy, transfusion (non leukoreduced platelet products- HLA) or transplant</td>
</tr>
</tbody>
</table>

2008 Blackwell Publishing Ltd, British Journal of Haematology, 142, 348–360
Non alloimmunes

Hematopoietic cell transplant (HCT)

Graft-versus-host disease (GVHD)?

Medications?

Red cell antigens?

Splenomegaly
Non immune

Hematopoietic cell transplantation (HCT)

- Both allogeneic and autologous, is clearly associated with an impaired response to platelet transfusions. *Bone Marrow Transplant. 1996;17(6):1035*
- 310 of 484 (64 %) post-transplant platelet transfusions resulted in an inadequate response.
- Hepatic sinusoidal obstruction syndrome associated with intrahepatic thrombosis and platelet deposition in hepatic venules, (22 %) of patients undergoing HCT, contribute to platelet refractoriness.
Non immune

Graft-versus-host disease (GVHD)

Risk factor for refractoriness to platelet transfusion in the HCT patient population

• Thrombotic microangiopathy associated with GVHD Transfus Apher Sci. 2002;27(1):3

• Increased incidence of platelet autoantibodies in patients with acute or chronic GVHD, suggesting a possible immune component to increased platelet destruction in this setting Blood. 1989;73(4):1054
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**Splenomegaly:**

- Approximately one-third of an individual's platelets are sequestered in the spleen where they are in equilibrium with the circulating platelet pool. In cases of extreme splenomegaly, splenic sequestration can be increased to 90%.

Two-hour recovery in the general circulation of radioactively-labeled platelets transfused to asplenic (red), normal (green), and splenomegalic (orange) patients.

*J Clin Invest 1966; 45:645.*
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Medication

• Thrombocytopenia caused by medications is relatively common, with hundreds of drugs implicated.

• Amphotericin has been associated with a reduced corrected count increment (CCI).

• Drug-induced thrombocytopenia is usually immune-mediated.
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Sepsis

- Association with thrombocytopenia is a well known cause of refractoriness to platelet transfusion.
- The mechanisms are not completely understood. Several hypotheses have focused on immune, non-immune, sequestration, and decreased platelet production.
- In addition, consumptive processes such as disseminated intravascular coagulation (DIC) and hemophagocytosis may contribute to thrombocytopenia in some septic patients.
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Red cell antigens

Studies show that patients who have developed red blood cell (RBC) alloantibodies appear more likely to also have HLA antibodies:

- 53 surgical patients with RBC alloantibodies were compared with a control group of 69 similar patients with a history of previous transfusions but who had not developed RBC antibodies.
- HLA antibodies were found significantly more often in the group of patients who had developed RBC alloantibodies (23 versus 10 percent (23% vs 10%)).
- This may be a reflection of the degree of immunocompetency in these patients. In other words, patients who develop RBC antibodies are probably more immunocompetent and more likely to become HLA alloimmunized.

Transfusion. 2006;46(5):754
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**Allo-Immune**

Immunization to HLA antigens is a major risk factor for refractoriness to platelet transfusions

- Platelets express only HLA Class I antigens, HLA Class II antigens present on leukocytes may be essential for the development of alloimmunization to HLA Class I antigens.
- While HLA-A and HLA-B antibodies are typically implicated, antibodies to HLA-C locus antigens have also been reported as a cause for platelet refractoriness. However, for practical purposes, in the United States at the present time, lists of blood/platelet donors typed for the HLA-C locus antigen are not available.
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Human platelet antigen (HPA) system

• Alloimmune platelet refractoriness almost always results from the production of antibodies to HLA Class I antigens on the platelet surface,

• Antibodies to platelet specific antigens (HPA) have been described as a cause for refractoriness to platelet transfusion
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Definition

1 hour corrected count increment (CCI*) of less than 5x x109/L on 2 sequential occasions, using ABO identical fresh platelets

\[
*\text{CCI} = \frac{(\text{Post- transfusion platelet count} - \text{pre transfusion platelet count}) \times \text{body surface area (m}^2)}{\text{Platelets transfused (unit content= } 4.0 \times 10^{11})}
\]
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Definition cont....

- This is roughly equivalent to an absolute platelet count increment of less than 10,000/microL after administration of an apheresis unit given to an average-sized adult.

A general rule of thumb is that transfusion of six units of pooled platelets ~ one apheresis increase the platelet count by approximately 30,000/microL in an adult of average size.
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![Graph showing platelet count over time for Normal, Non-immune, and Alloimmune transfusions.](image-url)
## An Approach to the Patient Refractory to Platelets Transfusion

<table>
<thead>
<tr>
<th>NON-ALLOIMMUNE CAUSES</th>
<th>ALLOIMMUNE CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Treatment of underlying disease</td>
<td>• Crossmatched random platelets</td>
</tr>
<tr>
<td></td>
<td>• HLA platelets</td>
</tr>
<tr>
<td></td>
<td>• Antigen negative platelets</td>
</tr>
<tr>
<td></td>
<td>HLA/HPA</td>
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</tbody>
</table>

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Locus HLA-A and HLA-B.

- The value of HLA matching was first described in a study published in 1969.

It was demonstrated that administration of platelets from HLA-matched family members improved both platelet recovery and survival.

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HLA-matched donors can be found either among family members or via a registry of HLA typed unrelated individuals typically maintained by the community blood center.

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The degree of match can predict the success of post-transfusion platelet count increments

• Grade A and BU (B1U or B2U) HLA-matched platelets are associated with the best increases in platelet count.

• Selection of platelet donors with antigens in the same "cross-reactive groups" (CREGs) as the patient's antigens, has been demonstrated to be nearly as successful in supporting alloimmune platelet refractoriness as HLA-matched transfusions (Grade B1X or B2UX).

• B2X, C, and D matches give post-transfusion responses similar to that of randomly selected platelet products.

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The following tables are to be used as a reference in the matching of Platelet orders

<table>
<thead>
<tr>
<th>Match Grade</th>
<th>Description</th>
<th>Example of Donor Phenotypes for a Recipient with the HLA type of: A1, A2; B7, B8</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4-antigen match</td>
<td>A1, A2; B7, B8</td>
</tr>
<tr>
<td>B1U</td>
<td>3 antigen match, 1 antigen unknown or blank</td>
<td>A1, A-; B7, B8</td>
</tr>
<tr>
<td>B1X</td>
<td>3 antigen match, 1 cross-reactive group</td>
<td>A11, A2; B7, B8</td>
</tr>
<tr>
<td>B2UX</td>
<td>2 antigen match, 1 antigen blank and 1 cross-reactive</td>
<td>A1, A-; B27, B8</td>
</tr>
<tr>
<td>C</td>
<td>3 antigen match, 1 mismatched antigen present</td>
<td>A1, A2; B7, B49</td>
</tr>
<tr>
<td>D</td>
<td>2 antigen match, 2 mismatched antigens present</td>
<td>A1, A2; B35, B49</td>
</tr>
<tr>
<td>R</td>
<td>Random</td>
<td>A24, A33; B35, B49</td>
</tr>
</tbody>
</table>
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“HLA-Matched” Platelets

Patient: A1,2; B7,8

Matching grade
A: perfect match; A1,2; B7,8 donor
B: crossreactive (X) or unidentified (U)
   BIX, BIU; A1,3; B7,8 or A1,-; B7,8 donor
   B2X, B2U: A1,3; B7,27 or A1,-; B7,- donor
C: one MM Ag; A1,2; B7,44 donor
D: two MM Ag; A1,24; B7,44 donor
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<table>
<thead>
<tr>
<th>CREG</th>
<th>Found On:</th>
<th>8C</th>
<th>12C</th>
<th>4C</th>
<th>6C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1C</td>
<td>A1, 3, 9 (23, 24), 11, 29, 30, 31, 36, 80</td>
<td>8, 14 (64, 65), 16 (38, 39), 18, 59, 67</td>
<td>12 (44, 45), 13, 21 (49, 50), 37, 40 (60, 61), 41, 47</td>
<td>85, (51, 52, 5102, 5103), 12 (44, 45), 13, 16 (38, 39), 17 (57, 58), 27, 37, 47, 53, 59, 63, 77 and A23, 24, 25, 32</td>
<td>7, 703, 8, 18, 2708, 35, 39 (16), 3901, 3902, 4005, 41, 42, 45 (12), 46*, 48, 50 (21), 54 (22), 55 (22), 56 (22), 60 (40), 61 (40), 62 (15), 64 (14), 65 (14), 67, 71 (70), 72 (70), 73, 75 (15), 76 (15), 78, 81</td>
</tr>
<tr>
<td>10C</td>
<td>A10 (25, 26, 34, 66), 11, 28 (68, 69), 32, 33, 43, 74</td>
<td></td>
<td></td>
<td></td>
<td>*but does not react with Bw6 antisera</td>
</tr>
<tr>
<td>2C</td>
<td>2, 9 (23, 24), 28 (68, 69), B17 (57, 58)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5C</td>
<td>B5 (51, 52), 15 (62, 63, 75, 76, 77, 78), 18, 21 (49, 59), 35, 46, 53, 70 (71, 72), 73, 4005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7C</td>
<td>B7, 8, 13, 22 (54, 55, 56), 27, 40 (60, 61), 41, 42, 47, 48, 59, 67, 73, 81, 82</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
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This is a similar approach to the technique used to provide compatible RBCs for patients who have RBC antibodies. The laboratory finds units lacking only those antigens to which the patient has antibodies.

This approach was described in 29 HLA-alloimmunized patients refractory to transfusion with random-donor platelets.

- In this study, a regional blood center was able to find a mean of only six donors per patient who were a four-antigen HLA match, and 33 donors who were identical at two or three loci, while they could identify over 1400 donors who were potentially safe by the antibody specificity method.

Transfusion. 2000;40(12):1446
An alternative approach is to identify compatible units of apheresis platelets by crossmatching the units with the patient's plasma.

- The solid-phase red cell adherence test (SPRCA) and flow cytometry
- SPRCA is the most widely used method for platelet cross-matching.
Advantages of crossmatch random platelets over HLA platelets and antigen negative platelets

- Rapid and effective selection (few hours)
- Larger pool of compatible donors
- An alternative for patients with rare HLA
- Not affected by the HLA match grade
- Much more cost-effective
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- Some authors have recommended that the initial approach to managing refractory patients should be to select fresher platelet units as well as those from ABO identical donors.
- Use of ABO-identical, non-HLA compatible platelets is unlikely to be effective in patients who have true alloimmune refractoriness. However, when available, extending the match for both HLA and ABO may provide additional benefit in some patients over HLA matching alone.
• This was shown in a study of 50 pediatric patients with beta thalassemia major and platelet transfusion refractoriness following hematopoietic stem cell transplantation:

Matched at HLA and ABO compatible: 76 percent successful platelet transfusions
Matched at HLA and ABO incompatible or mismatched at HLA and ABO compatible: 67 percent successful
Mismatched at HLA and ABO incompatible: 46 percent successful

Pediatr Transplant. 2010 May;14(3):393-401. Epub 2010 Jan 07
Suspect alloimmune refractoriness

Transfuse ABO identical fresh platelets

Not refractory
Support with standard platelets

Adequate increment

Measure on 2 occasions: 10 min to 1-h Platelet increment

Inadequate increment

Search for crossmatch units

Inadequate increment

Unable to find a unit

Crossmatch compatible units found (preferably ABO-identical)

Adequate increment

HLA/HPA antibody screening

Inadequate increment

Positive
Support with HLA-A BU, BX match grade platelets (preferably ABO-identical)

Negative
Support with HLA and/or HPA antigen negative platelets (preferably ABO-identical)

Consider non-immune causes: Fever, splenomegaly, sepsis, drugs, DIC, bleeding, etc.

Continue with crossmatch compatible platelets
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Prevention of alloimmunization

The incidence of refractoriness to transfusion has been dramatically reduced given the widespread use of leukocyte-reduced blood components.

N Engl J Med 1997; 337:1861-1870
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When all else fails

<table>
<thead>
<tr>
<th>Seek out better HLA matches</th>
<th>Other treatments</th>
<th>Continuous drip platelet infusions</th>
<th>Recombinant Factor VII</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recall donors that worked in past</td>
<td>• IVIG,</td>
<td>• 1 unit q 4-6 h</td>
<td>• Doesn’t work well with counts &lt;10,000</td>
</tr>
<tr>
<td>• Try close relatives (siblings)</td>
<td>• WinRho,</td>
<td>• Of ? value; may help for short duration</td>
<td></td>
</tr>
<tr>
<td>• Try national search</td>
<td>• plasma exchange,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rituximab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Arch Pathol Lab Med—Vol 127, April 2003
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Transfusion

Follow up

Refractoriness changes over time

Keep an eye on effectiveness of transfusions

Send new specimen every 1-2 weeks

May get better
Can switch to random