Managing the platelet-refractory patient

Patricia A. R. Brunker, MD, MHS, DPhil
Division of Transfusion Medicine
Department of Pathology
The Johns Hopkins University School of Medicine

Disclosures

• None

Overview

• Defining platelet refractoriness
• Causes & Epidemiology
• Integrating tiered laboratory data for patient management
• Describe the Hopkins Transfusion Coordinator Service (a.k.a. the PLT service)
• Current challenges
**Definition**

- Insufficient post-transfusion platelet increment
- Generally need at least 2 consecutive transfusions to be ineffective before patient considered refractory
- Some also require that the platelets be fresh and ABO-compatible

**Definition**

- Ballpark expected increment:
  - 5-10,000/mm³ for each random donor PLT
  - 30-60,000/mm³ for each apheresis PLT
- Over 24 hours:
  - < 5 x 10⁹ platelets/L falls short
  - 7 x 10⁹ platelets/L are consumed daily
  - 24 hours is a LONG TIME for a sick patient, so...

**Formulas**

- Post-transfusion platelet increment (PPI) = Post-transfusion platelet count - pretransfusion platelet count
- Corrected count increment (CCI) = PPI / body surface area (m²)
- Percentage platelet recovery (PPR) = PPI / (final blood volume x 100%)
- Percentage platelet increment = PPR x 0.67 (0.67 accounts for splenic pooling)

- CCI less than 5,000-7,500 or PPR less than 20% at 1 hour
- CCI requires platelet count of the infused product as well as body surface area
- Can use estimate of 3 x 10¹¹ platelets for an apheresis unit
Overview

• Defining platelet refractoriness
• Causes & Epidemiology
• Integrating tiered laboratory data for patient management
• Describe the Hopkins Transfusion Coordinator Service (a.k.a. the PLT service)
• Current challenges

Causes

<table>
<thead>
<tr>
<th>Non-immune causes</th>
<th>Immune causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>HLA antibodies</td>
</tr>
<tr>
<td>Infection/sepsis</td>
<td>HPA antibodies</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>ABO incompatibility</td>
</tr>
<tr>
<td>Sequestration (e.g., splenomegaly)</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td></td>
</tr>
<tr>
<td>Graft versus host disease</td>
<td></td>
</tr>
</tbody>
</table>

Non-immune causes much more common than immune causes (non-immune factors present in 72-88% of cases and HLA antibodies present in 25-39%)

Patterns of platelet refractoriness

• Two patterns of refractoriness:
  • Shortened platelet survival: Sepsis, BMT, DIC, meds
  • No increment: Alloimmunization

www.uptodate.com
Epidemiology

- 5-15% of patients receiving multiple platelet transfusions
- Clinical refractoriness is NOT correlated with quantity of HLA and HPA alloantibodies

Immune causes

- Platelets express multiple antigens that can serve as targets for antibody formation/alloimmunization
  - HLA class I antigens (predominantly HLA-A and HLA-B, HLA-C not well-expressed)
  - Human platelet antigen (HPA) system antigens – polymorphisms in 5 of them can lead to alloimmunization, including GPIa, GPIb, GPIIb, GPIIIa, and CD200
- Antibodies directed against class I HLA molecules are responsible for most cases of immune-mediated platelet refractoriness
  - HPA antibodies less frequent (2-11% incidence) and unclear whether they cause a significant reduction in the CCI

Immune causes, cont.

- The primary alloimmunization event against the class I HLA antigens on platelets requires the presence of contaminating leukocytes in platelet products
  - The leukocytes have class II HLA on their surface and act as APCs, stimulating recipient T cells to induce an antibody response to class I HLA
- Leukoreduction is a preventative measure which decreases alloimmunization – TRAP study:
  - Leukoreduction reduced rate of HLA immunization from 45% to 17-21%
**The TRAP Trial**

![Graph showing cumulative alloimmunization rates over weeks for control, UVB irradiated, and filtered platelet concentrate (RDP) conditions.]


**Blood bank factors affecting response to platelets**

- ABO-incompatible platelets associated with worse post-transfusion CCI
  - Platelets express ABH antigens (both intrinsic to platelet membrane and passively adsorbed from plasma)
- Platelet age affects CCI
- Therefore, best to give fresh (stored for <48 hrs), ABO-compatible platelets to reduce number of variables when trying to determine cause for poor response to platelets

**Risk factors for alloimmunization**

- History of multiple transfusions
  - Donor leukocytes in transfused products
- Female with history of pregnancy
- History of transplantation
Overview

• Defining platelet refractoriness
• Causes & Epidemiology
• Integrating tiered laboratory data for patient management
• Describe the Hopkins Transfusion Coordinator Service (a.k.a. the PLT service)
• Current challenges

Testing for HLA antibodies

• Cell-based method
  • Complement-dependent cytotoxicity (CDC)/Lymphotoxicity test (LCT)
• Solid-phase methods
  • ELISA
  • Flow cytometry

Sensitivity for detecting anti-HLA antibodies:
Flow cytometry > ELISA > cytotoxicity

Lymphocytotoxicity test (LCT)

• Examines ability of antibodies to bring about complement-mediated lysis of a panel of lymphocytes

• Method:
  • Add patient serum, antibodies, complement, and complement to a panel of lymphocyte sensitized with anti-HLA antibodies
  • Fix antibody binding using anti-CD; add cell to cell-binding antibody (s) panel for a day
• Limitations:
  • Does not detect HLA antibodies
  • Only detects cytotoxic antibodies
  • Using a panel representing most of the given HLA antigens, a panel-negative antibody (PNA) score can be calculated (Wolff positive tests)
  • PNA score suggests probable HLA antibodies
**Solid-phase methods**

- HLA and HPAs bound to a solid matrix such as polystyrene beads or microtiter plates
- Patient serum added to the plates and then washed
- Detection of bound antibody by AHG conjugated to a chemical or enzyme
- More sensitive
- Limitations:
  - May have false-positive or false-negative reactions because the antigens on the beads or in the microtiter wells don’t exist in their native forms

---

**ELISA**

![ELISA Diagram]

- Enzyme labeled AHG
- Antigen
- Microtiter well

---

**Bead Assay**

![Bead Assay Diagram]

- Fluorochrome labeled AHG
- Purified antigen
- Microsphere

---


• HLA & HPA
• Used by some when HLA testing is in process
Management of alloimmunized patients

- Once presence of alloantibodies known or suspected, there are 3 options for identifying compatible units:

  1) Antigen-negative platelets

  2) HLA-matched platelets—takes additional time because both patient and donors must be HLA-typed (either by cytotoxicity method or molecular testing)

  3) Cross-matched platelets—can be done even before knowing results of HLA antibody testing

Pros/Cons of each option

- Cross-matched platelets
  - Advantages—less, doesn’t require HLA antibody testing or HLA typing, identifies compatible donors from standpoint of both HLA and HPA antigens
  - Disadvantages—low probability of finding compatible unit in highly sensitized patients

- HLA-matched platelets
  - Advantages—may be only way to find compatible unit for highly sensitized patients
  - Disadvantages—delay involved in typing recipient, time required to identify or recruit well-matched donor

- Antigen-negative platelets
  - Advantages—once patient has been tested for HLA antibodies, finding compatible units can happen quickly, most compatible donors relative to matched platelets
  - Disadvantages—time required for HLA antibody testing

A management algorithm


- Defining platelet refractoriness
- Causes & Epidemiology
- Integrating tiered laboratory data for patient management
- Describe the Hopkins Transfusion Coordinator Service (a.k.a. the PLT service)
- Current challenges


**A management algorithm**

**Overview**

- Team of PAs & MTs with extensive clinical training
- Advise oncology inpatient service on daily rounds
- Educate clinicians in all departments
- Real-time updates to patient assessment
- Proactive
  - Pts anticipated to require multiple PLTs are HLA types and screened on admission
- IT: Custom-built "Patient Transfusion History" card
- 2-way relationship with supplier

IT designed for PLTs

Hopkins Transfusion (PLT) Coordinators

• Only 1% wastage over 10-year period
  • Outdated (one major incident around a weather event)
  • Loss in pneumatic tube system
  • Nursing error (didn’t call for a product that was ordered)
  • Broken bags during storage or manipulation

  • Sharing with other hospitals
    • Returns not accepted by blood supplier, but requests received by supplier are forward to PLT coordinators

  • Commitment to supplier
    • Contracted to purchase 95% of PLTs from that supplier

Overview

• Defining platelet refractoriness
• Causes & Epidemiology
• Integrating tiered laboratory data for patient management
• Describe the Hopkins Transfusion Coordinator Service (a.k.a. the PLT service)
• Current challenges
Current Challenges

- Rituximab, TPE, IVIG?

- Logistics:
  - Reducing wastage and improving workflow to get HLA-matched products requires substantial financial investment in the form of highly-trained, proactive, specialist staff.
  - What is achievable for a community hospital setting?

References


Thanks

- Alice Fuller
- Karen King
- Sue Shirey
- Elise Gelwan
- Paul Ness