Objectives

- To review platelet refractoriness and fetal and neonatal alloimmune thrombocytopenia
- To describe how serologic testing can aid clinical management and selection of blood products
- To describe how HPA genotyping can be helpful in differential diagnosis of FNAIT
- To describe how the platelet donors are screened to identify those whose platelet products may be useful for HPA alloimmunized patients
- To use cases to illustrate these points
Platelet Refractoriness

- Thrombocytopenia – deficiency of platelets in the blood causing bleeding into the tissues, bruising and blood clotting after injury.
- Refractoriness is the repeated failure to achieve the desired level of platelets following transfusion.
  - 20 – 70% of multi-transfused patients with thrombocytopenia experience a less-than-expected increase in platelet count.
  - Patients treated for non-malignant hematopoietic disorders (anemia, hemophilia, etc.) are most likely to become refractory to platelet transfusions.
- Cause of platelet refractoriness may be immune or non-immune.

Immune Causes of Refractoriness

- HLA sensitization
  - Presence of significant levels of antibodies to HLA Class I antigens in a refractory patient’s serum.
  - The most common immune cause of platelet refractoriness.
- Antibodies to HPA antigens
- ABO Incompatibility
- Antibodies in the sera of patients with congenital platelet glycoprotein deficiencies
  - Ex - Glanzmann’s thrombasthenia – abnormality in genes for GPIIb/IIIa.

Non-Immune Causes of Refractoriness

- Massive bleeding
- Fever
- Sepsis
- Splenomegaly
- Disseminated intravascular coagulation (DIC)
- Allogeneic transplantation
- Poor storage of platelets prior to transfusion
- Drugs
- Intravenous amphotericin B (suspected toxic effect on platelet function)
- Thrombotic thrombocytopenic purpura (TTP)
- Treatment regimen (such as chemotherapy)
- Liver dysfunction
Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT)

- A clinical condition caused by immune destruction of fetal platelets by maternal platelet antibody
- IgG antibody crosses the placenta, causing thrombocytopenia in the fetus or neonate
- Mother becomes sensitized to an incompatible fetal platelet antigen that the fetus inherited from the father
- 40-60% of FNAIT occurs in first pregnancy

Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT): Symptoms

- Symptoms include petechiae, hematoma, severe bleeding, intracranial hemorrhage and death
- FNAIT is the leading cause of severe thrombocytopenia in the fetus and the leading cause of intracranial hemorrhage (ICH) full-term infants
- Incidence is 0.3 to 1 in 1000
- If untreated, 10-20% develop ICH (75% antenatally)
- 15% fatality in FNAIT with ICH

Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT): Causes

Antibodies to HPA Antigens
- HPA-1a incompatibility between mother and fetus is the most commonly reported finding
  - Antibodies to other HPAs have also been implicated [eg., HPA-2b, 3b, 5b, 15b]
- Only ~12% of HPA-1a negative mothers make anti-HPA-1a
- 90% of mothers with anti-HPA-1a carry HLA DRB3*01:01
- While only 27% of general population carries this allele

Antibodies to ABO Antigens
- For example, Group O patients have large amounts of anti-A and anti-B IgG

Antibodies to HLA Antigens
- Platelets carry class I HLA antigens
Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT)

- Serologic diagnosis of FNAIT is determined by:
  - testing maternal serum for platelet antibodies using assays that can differentiate platelet-specific from non-platelet-specific reactivity
  - performing platelet genotyping on parental DNA
- Diagnosis is confirmed if HPA antibody is demonstrating in the maternal serum and there is incompatibility for the antigen on the paternal platelet
- Treatment for newborns includes administration of IVIG with or without antigen-compatible platelet transfusions
  - HPA negative platelets or washed maternal platelets
- Once a diagnosis of FNAIT has been made in a family, all future fetuses may be at risk
  - antenatal treatment with IVIG is an effective means of reducing fetal thrombocytopenia and reducing intracranial hemorrhage

FNAIT Diagnosis Algorithm, part I

The results of these tests can inform the risk and guide the clinical management of future pregnancy

FNAIT Diagnosis Algorithm, part II
Other Causes of Thrombocytopenia in Neonates

- Infection
- Hypertension
- Autoimmune disorders
- Chronic hypoxia
- Necrotizing enterocolitis
- Thrombosis
- Congenital defect in platelet production

Part 1

Fetal and neonatal alloimmune thrombocytopenia (FNAIT)

for Recommendations FNAIT interventions

If a platelet transfusion is indicated, HPA-selected platelets should be used if immediately available.

If HPA-selected platelets are not immediately available, HPA-unselected platelets should be transfused.

Platelets should be transfused immediately if life-threatening bleeding is present.

Part 2

In the presence of life-threatening bleeding in a neonate such as intracranial or gastrointestinal bleeding, platelets should be transfused to maintain platelet counts initially above 50,000/µL and then above 50,000/µL for at least 7 days.

In the absence of life-threatening bleeding in a neonate such as intracranial or gastrointestinal bleeding, platelets should be transfused to maintain a platelet count above 30,000/µL.

Antenatal IVIG administration to the mother commencing at 22-36 weeks’ gestation should be offered to all women in a subsequent pregnancy with maternal fetal incompatibility who have had a previous FNAIT-related ICH.

For other pregnancies with a previous neonate with FNAIT (without ICH), administering antenatal IVIG to the mother should be discussed prior to a subsequent pregnancy or when pregnancy with maternal fetal incompatibility is confirmed.

a. If antenatal interventions is required, IVIG administration to the mother should be started between 20 to 22 weeks (and not later than 24 weeks) gestation.

If the fetal platelet count is unknown, assisted delivery and invasive procedures on the fetus during delivery should be avoided including forceps, vacuum-assisted delivery, scalp blood sampling and scalp electrodes.
International Collaboration of Transfusion Medicine Guidelines (ICTMG) for FNAIT

- International team was comprised of adult and pediatric hematologists, maternal fetal medicine specialists, methodologists and transfusion medicine physicians
- Goal of developing a guideline for the management of FNAIT using a systematic approach and standardized method to optimize transfusion care
- Examined antenatal care, diagnostic tests including HLA genotyping and HPA alloantibody testing, postnatal interventions

3 Recent Systematic Reviews by ICTMG

- Systematic review of 4 randomized controlled trials (RCT) and 22 non-RCT were used to assess antenatal treatment strategies for FNAIT
  - Fetal blood sampling and intrauterine PLT transfusion had high (11%) complication rate including preterm delivery and fetal loss
  - Noninvasive management of pregnant mother with history of FNAIT using weekly IVIg (typically 1g/kg) was effective with 98.7% success for preventing intracranial hemorrhage
    - In cases with sibling with FNAIT (high risk), start IVIg between 12 and 20 weeks gestation
    - In cases without sibling with FNAIT (standard risk), start IVIg between 20 and 24 weeks
  - No consistent evidence for value of adding steroids to maternal IVIg
  - Paternal genotyping is recommended in suspected FNAIT (index case)
Systematic review of postnatal management of FNAIT
- Variables: HPA selected vs unselected platelets and/or IVIg
- Outcomes: platelet increments, hemorrhage and mortality

Findings
- HPA-selected platelets resulted in higher platelet increments and longer response times than unselected platelets
- Unselected platelets generally led to sufficient platelet increments to achieve clinical goals
- Platelet increments were not improved with IVIg

Summary of ICTMG Findings
- Non-invasive management of pregnant mothers with prior history of NAIT using IVIG is effective; no evidence that steroids add benefit; paternal genotyping in index case
- HPA selected platelet transfusions were more effective than HPA-unselected platelets but unselected platelets were often effective to achieve clinical goals
- Maternal titers of anti-HPA-1a measured during the third trimester may be useful predictor of disease severity
ICTMG: FNAIT Antenatal Algorithm

ICTMG: FNAIT Postnatal Algorithm

Red Cross Standard Protocol for FNAIT
Objectives

- To review platelet refractoriness and fetal and neonatal alloimmune thrombocytopenia
- To describe how serologic testing can aid clinical management and selection of blood products
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- To use cases to illustrate these points

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**Solid Phase Red Cell Adherence (SPRCA)**

Platelet Monolayer

![Image of SPRCA](image)

- Reactive / Incompatible
- Non-Reactive / Compatible

Anti-Platelet Ab

Indicator Red Cell Coated with Anti-Human IgG

Used for Ab detection, typing and platelet crossmatching

---

**Luminex-Based Antibody Detection**

- Patient serum with HPA-specific Ab
- PE-conjugated anti-human IgG
- Wash beads

HPA-1, -2, -3, -4, -5, GP IV and GPs 1, 11a, 12b, 2b

---

American Red Cross
Platelet Suspension Immunofluorescence Test (PSIFT)

Objectives

- To review platelet refractoriness and fetal and neonatal alloimmune thrombocytopenia
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Human Platelet Antigens

### Antigens, Glycoproteins and Genes

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Glyco-</th>
<th>HGNC</th>
<th>Chromosome</th>
<th>Nucleotide</th>
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</table>

https://www.ebi.ac.uk/ipd/hpa/freqs_1.html

### HPA Genotyping

- Is used to assess incompatibility between partners
  - if woman has anti-HPA antibody or history of FNAIT
  - if platelet count is low and FNAIT is suspected in current fetus/newborn
- Typically performed on maternal and paternal samples and evaluated for incompatibility
- Can be performed on DNA from the fetus or newborn
  - standard sampling by fetal blood sampling (but with risk)
  - non-invasive prenatal testing (NIPT) via circulating cell-free fetal DNA from maternal plasma (ccffDNA)*

*not widely available

### HPA Genotyping Assays

All “Research Use Only” (RUO)
- HPA-1a/1b SSP-PCR (LDT)
- HPA BeadChip (Immucor)
- Fluogene HPA (Inno-train)
- IDCore HPA (Grifols)
- HemoID HPA/HNA (Agena)
- HPA-1,2,3,4,6,15

Reaction for allele “a”

Reaction for allele “b”

https://www.ebi.ac.uk/ipd/hpa/freqs_1.html
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- To use cases to illustrate these points

Supplying HPA Negative Platelets

- There is a need to have platelets available that lack specific HPA
- Most commonly requested HPA-negative platelet product is HPA-1a negative
- Serologic antigen typing or HPA-1a/b genotyping can be used to screen donors
- Platelets found to be lacking HPA-1a are genotyped to determine their status of other clinically significant HPA antigens

HPA Genotype Frequencies

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Genotype Frequency (%)</th>
<th>Whites</th>
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<td>HPA-1a/2b</td>
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</tr>
<tr>
<td>HPA-1b/2b</td>
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<tr>
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<tr>
<td>HPA-2b/2b</td>
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<td>HPA-2a/5b</td>
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<td></td>
<td>0</td>
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</tbody>
</table>

* Genotyping was performed on DNA from 100 unrelated individuals in each group.

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Case Study #1

Clinical Presentation:

- Suspected NAIT
- 21 y/o Hispanic female, platelet count of 250 K/μL, not transfused in the previous three months
- Infant platelet count at birth was 25 K/μL
  - transfused with platelets – 15mL/kg

Testing to be Completed

- SPRCA – for antibody detection, compatibility testing and platelet antigen typing (HPA-1a), if requested
- Bead Immunoassay – to detect platelet and HLA Class I antibodies
- PSIFT – to verify platelet antigen typing and to detect serum and cell-bound antibodies directed against platelet surface markers
- ABO/Rh typing of maternal and paternal sample; antibody screen on maternal sample
- HPA genotyping panel
Results

<table>
<thead>
<tr>
<th>SPRCA</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody Screen</td>
<td>HLA typed platelets + maternal serum</td>
</tr>
<tr>
<td>Crossmatch</td>
<td>Maternal serum + paternal platelets</td>
</tr>
<tr>
<td>Serological HPA-1a typing</td>
<td>Paternal sample</td>
</tr>
<tr>
<td>Serological HPA-1a typing</td>
<td>Maternal sample</td>
</tr>
</tbody>
</table>

Results

<table>
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<th>PSIFT</th>
<th>Result</th>
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<tbody>
<tr>
<td>Antibody Panel</td>
<td>Maternal serum + HPA typed platelets</td>
</tr>
<tr>
<td></td>
<td>Maternal serum + chloroquine treated platelets</td>
</tr>
<tr>
<td>Crossmatch</td>
<td>Maternal serum + paternal platelets</td>
</tr>
<tr>
<td></td>
<td>Maternal serum + chloroquine treated paternal platelets</td>
</tr>
<tr>
<td>Bead Immunoassay</td>
<td>Maternal serum</td>
</tr>
</tbody>
</table>

Results

- ABO testing
  - Probable ABO incompatibility – maternal sample is group O, antibody screen negative. Paternal sample is group A.
**Conclusion, Case 1**

- Multiple HPA incompatibilities including HPA-1a
  - HPA-1a negative mother and HPA-1a positive father
  - 100% chance of his children being HPA-1a positive
- Maternal HPA-1a antibody detected
- HPA-1a negative platelet products available if needed
- All future pregnancies have potential for NAIT with this father

**Case Study #2**

Clinical Presentation:
- Suspected NAIT
- 38 y/o Hispanic female, not transfused in the previous three months
- Six prior pregnancies with previously affected infants
- Infant platelet count at birth was 107K/μL

**Results**

<table>
<thead>
<tr>
<th>SPRCA</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody Screen</td>
<td>HLA typed platelets + maternal serum</td>
</tr>
<tr>
<td>Crossmatch</td>
<td>Maternal serum + paternal platelets</td>
</tr>
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</table>
### Results

<table>
<thead>
<tr>
<th>PSIFT</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td><strong>Antibody Panel</strong></td>
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<tr>
<td>Maternal serum + HPA typed</td>
<td>3/3 positive</td>
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<tr>
<td>platelets</td>
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<tr>
<td>Maternal serum + chloroquine</td>
<td>3/3 Positive</td>
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<tr>
<td>treated platelets</td>
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<tr>
<td><strong>Crossmatch</strong></td>
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<tr>
<td>Maternal serum + paternal</td>
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<td>platelets</td>
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<td><strong>Dried Immunosorbent</strong></td>
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<tr>
<td>Maternal serum</td>
<td>Antibody to HPA-5b and HLA Class I antigens detected</td>
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</tbody>
</table>

### Results

- ABO testing
  - maternal sample is Group A Positive
  - paternal sample is Group B Positive

### HPA-1a/1b Genotyping

### Conclusion, Case 2

- Antibody to HLA Class I antigens detected
  - recommend further testing to determine HLA specificity
- HPA-1b incompatibility noted, no antibody detected
- Antibody to HPA-5b detected
  - Panel of HPA-5b negative HLA compatible platelets recommended for crossmatching
  - HPA-5b negative platelets also offered for emergency
- Suspected ABO incompatibility
  - maternal ABO/Rh is A Positive (with anti-B)
  - paternal ABO/Rh is B Positive
Case Study #3

Clinical Presentation:
- Suspected NAIT
- 33 y/o Caucasian female, not transfused in the previous three months
- Infant platelet count at birth was 64K/uL

Results

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<td>HLA typed platelets + maternal serum</td>
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<tr>
<td>Maternal serum + paternal platelets</td>
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<table>
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<tr>
<td>Maternal serum</td>
<td>Antibody to HLA Class I antigens detected</td>
</tr>
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</table>
Results

- ABO testing
  - maternal sample is group A
  - paternal sample is group O

HPA Genotyping Panel

Conclusion, Case 3

- Maternal and paternal sample both type HPA-1a positive; incompatibility for HPA-15b
- No ABO incompatibility
- Antibody to HLA Class I antigens detected
  - recommended further testing to determine specificity of HLA reactivity
  - HPA-15b negative platelets could be used for crossmatching

Case Study #4

Clinical Presentation:
- Suspected NAIT
- 25 y/o Caucasian female, transfused with one unit of RBC in the previous three months
- Infant platelet count at birth was 37K/uL
## Results

<table>
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<tr>
<td>Crossmatch</td>
<td></td>
</tr>
<tr>
<td>Maternal serum + paternal platelets</td>
<td>Positive</td>
</tr>
</tbody>
</table>

## Results

<table>
<thead>
<tr>
<th>PSIFT</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody Panel</td>
<td></td>
</tr>
<tr>
<td>Maternal serum + HPA typed platelets</td>
<td>3/3 negative</td>
</tr>
<tr>
<td>Maternal serum + chloroquine treated platelets</td>
<td>3/3 negative</td>
</tr>
<tr>
<td>Crossmatch</td>
<td></td>
</tr>
<tr>
<td>Maternal serum + paternal platelets</td>
<td>Positive</td>
</tr>
<tr>
<td>Maternal serum + chloroquine-treated paternal platelets</td>
<td>Positive</td>
</tr>
</tbody>
</table>

### Bead Immunoassay

<table>
<thead>
<tr>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal serum</td>
</tr>
<tr>
<td>No HLA or platelet antibodies detected</td>
</tr>
</tbody>
</table>

## Results – Additional Testing

<table>
<thead>
<tr>
<th>SPRCA</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO Typed Platelets</td>
<td></td>
</tr>
<tr>
<td>Maternal Serum + Group B platelets</td>
<td>5/5 positive</td>
</tr>
<tr>
<td>Maternal Serum + Group O platelets</td>
<td>5/5 negative</td>
</tr>
</tbody>
</table>

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Results

- ABO testing
  - maternal ABO/Rh is A Positive
  - paternal ABO/Rh is B Positive

HPA Genotyping Panel

<table>
<thead>
<tr>
<th></th>
<th>H</th>
<th>P</th>
<th>A</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mom</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Dad</td>
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<td>0</td>
<td>+</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

Conclusion, Case 4

- Maternal and paternal sample both type HPA-1a positive
  - Incompatibility for HPA-3b, -5b
- No platelet or HLA antibodies detected
- Reactivity observed is consistent with the presence of platelet-reactive ABO antibody (anti-B)

Review of 4 years of FNAIT Testing in NRLST

Serologic Findings in 126 NAIT Cases

27% anti-HPA
61% non-HPA, ABO non-ELISA
4% HLA antibodies
3% rHD
3% Non-specific
6% No antibodies detected
Summary

- Platelet serologic testing can aid in differentiating immune from non-immune platelet refractoriness.
- Platelet serologic testing and HPA genotyping can aid in ruling in/out FNAIT.
- FNAIT testing can detect antibodies to HLA, ABO or HPA antigens with the most commonly reported incompatibility being anti-HPA-1a.
- Platelet product selection can be personalized based on the laboratory findings.
- For FNAIT, these findings also inform physicians for testing and treatment of future pregnancies.

Thank you for your attention!

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Margaret.Keller@redcross.org