Neonatal Allo-Immune Thrombocytopenia

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SEABB

Disclosures

- No conflicts of interest or disclosures

Objectives

- Describe Neonatal Allo-Immune Thrombocytopenia (NAIT)
  - Clinical presentation
  - Pathophysiology
- Describe laboratory testing that can assist in diagnosing a patient with NAIT
- Describe management of patient affected by NAIT and implications for future pregnancies

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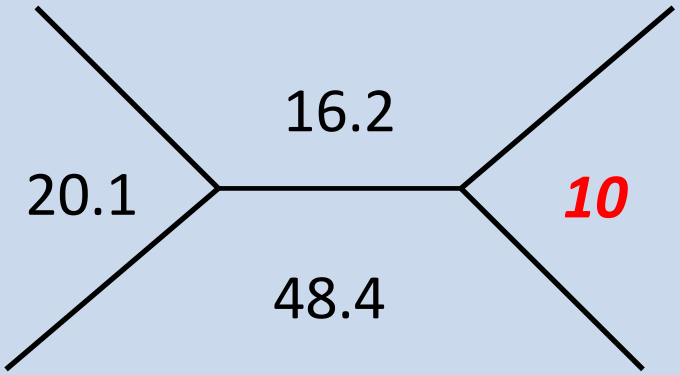
Clinical Presentation

- CC:
  - Full term infant (39-1/7 week) girl
  - Petechiae on delivery (arms and legs)
  - No other complications
- PMHx (maternal):
  - G2P1 (First pregnancy unremarkable)
  - No fever, infection, or autoimmune disorder
  - Pre-delivery labs: PLT- 325k
- 2hrs s/p delivery infant transferred to ICU for management for lethargy and R/O sepsis

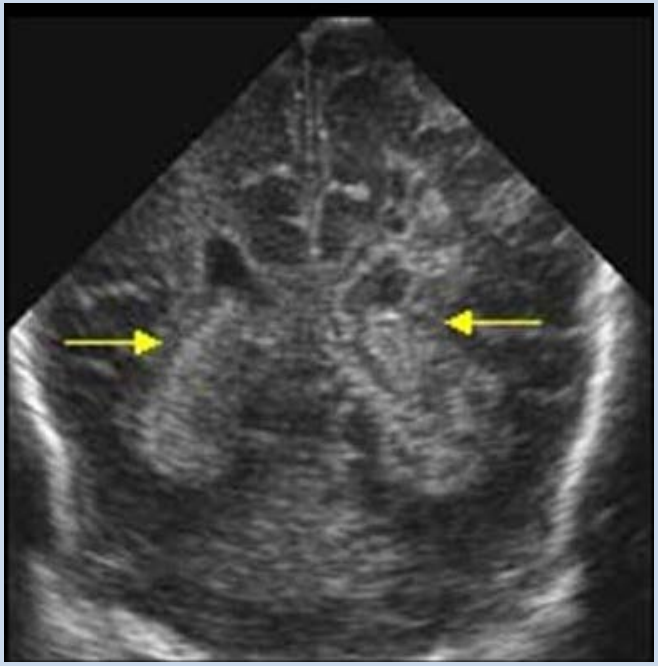
Clinical Presentation

Screening CBCD:



Additional Labs:

- PT, PTT: NL
- Fibrinogen: NL
- CRP <0.5
- Head US: IVH



Differential:

Segs: 40

Lymps: 50

Monos: 5

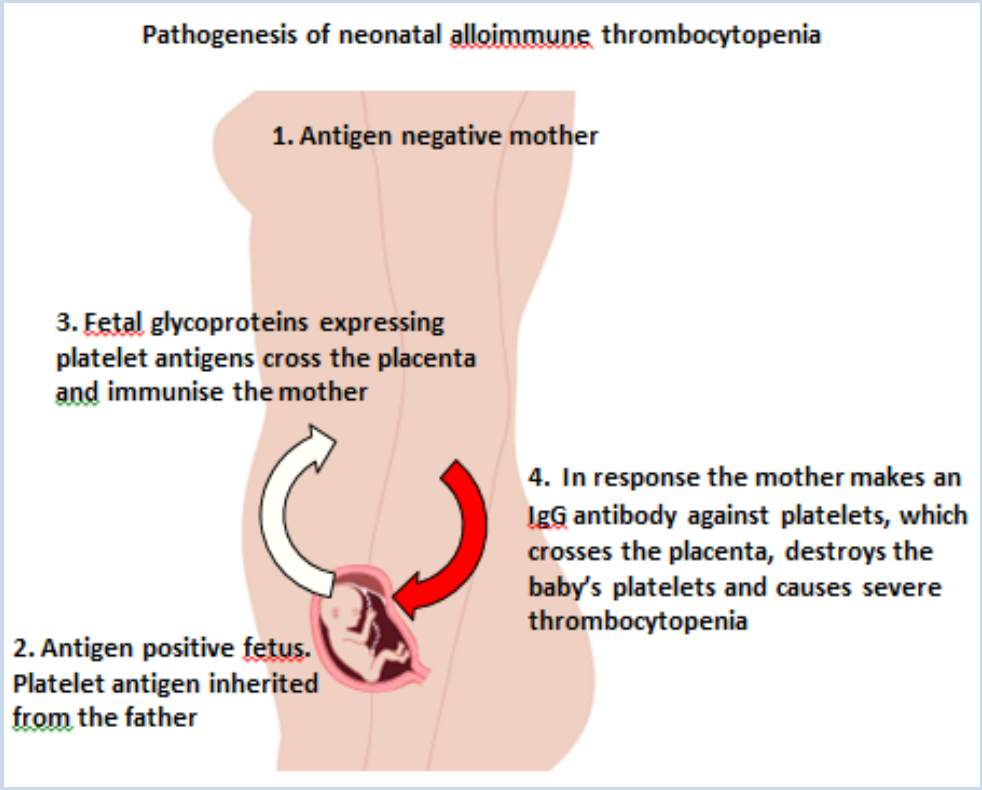
Eos: 3

Atypical Lymphs: 2

Pathophysiology

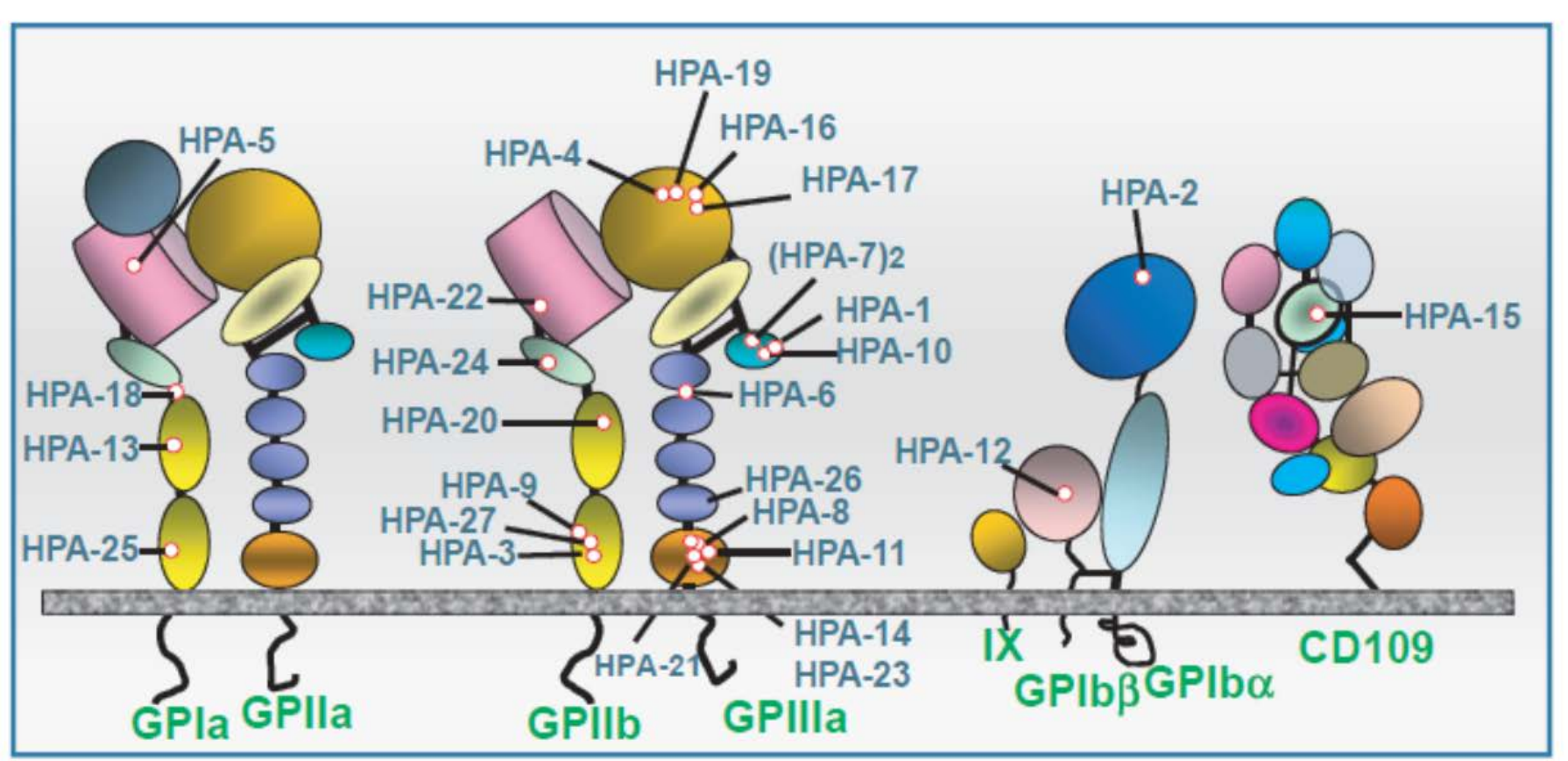
- Maternal platelet specific antibodies to paternally inherited human platelet antigens (HPA)
  - Anti-HPA1a: > 2/3rds of cases
  - Anti-HPA-5b: ~15% NAIT cases (Caucasians)
  - Anti-HPA-4a: most common in Asians
- Incidence: ~1/1000 to 1/3000 pregnancies
- Most common cause of severe thrombocytopenia in neonates
  - 10–20%→ intracranial hemorrhage (ICH)
  - 7% mortality when ICH occurs

Pathophysiology



- NAIT occurs during first pregnancy in upto 50% of cases
  - HDFN requires previous antigen exposure
- Affected fetus may develop severe thrombocytopenia (<50K/µl) as early as 20wks
  - Consistent with development of platelet antigens

Human Platelet Antigens



Peterson et al, BJH 2013

Human Platelet Antigens

- Platelet GPs are expressed in polymorphic forms
  - AA changes → changes in GP structure → HPA epitopes
  - HPA epitopes (e.g. HPA-1a) can be immunogenic to individuals having platelets *homozygous* for the opposite HPA (e.g. HPA-1b/b)
  - 37 HPAs expressed on six platelet GPs
- GP complexes have been described:
  - GPIIb/IIIa (aIIb/b3, CD41/CD61, fibrinogen receptor)
  - GPIb-V-IX (CD42a-d, von Willebrand factor receptor)
  - GPIa/IIa (a2/b1, CD49/CD29, collagen receptor)
  - CD109 (negatively regulates signalling of TGF-b)

Curtis & McFarland, 2013

Human Platelet Antigens

HPA (Specificity)	Percent of total (N = 1025)
HPA-1a HPA-1b	68.2 6.0
HPA-2a HPA-2b	0 0.2
HPA-3a HPA-3b	1.3 0.3
HPA-4a HPA-4b	0.4 0
HPA-5a HPA-5b	2.0 15.4
HPA-6bw HPA-9bw	0.1 0.1
HPA-15a HPA-15b	0.7 0.5
GPIV low frequency HPAs	2.3 0.2*
Multiple HPA	3.6

Curtis BR. Br J Haematol. 2015

- HPA antigens implicated in NAIT cases tested at BCW Platelet Laboratory (2002-2012)
- 10% of HPA-1a incompatible pregnancies result in maternal HPA-1a sensitization (Killie et al, 2007; Kjeldsen-Kragh et al, 2007)
- 99% of HPA-1b/1b women that produce HPA-1a antibodies express DRB3*01:01 (Williamson et al, 1998; Kjeldsen-Kragh et al, 2007)

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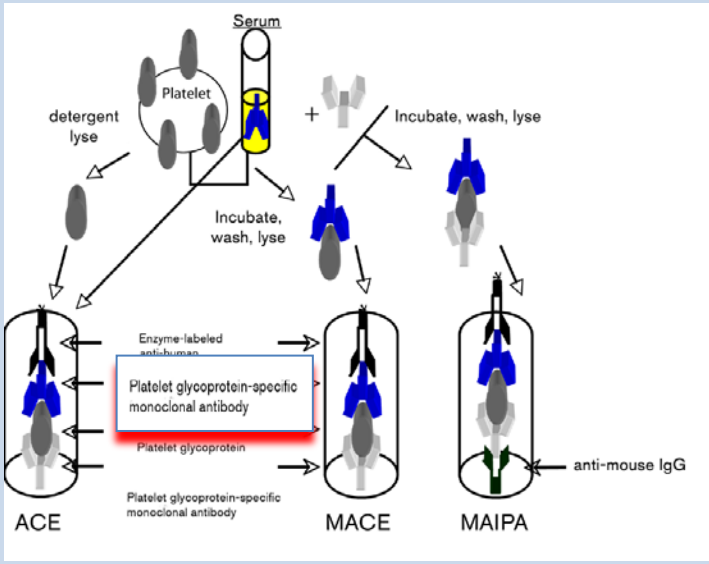
Laboratory Assays

- To confirm a diagnosis→ perform a laboratory workup that includes:
  - Testing of maternal serum for HPA antibodies
  - HPA genotyping of the parents to document HPA incompatibility
- Knowledge of the father's zygosity for the implicated HPA is useful to determine the need for prenatal genotyping and antenatal treatment in subsequent pregnancies

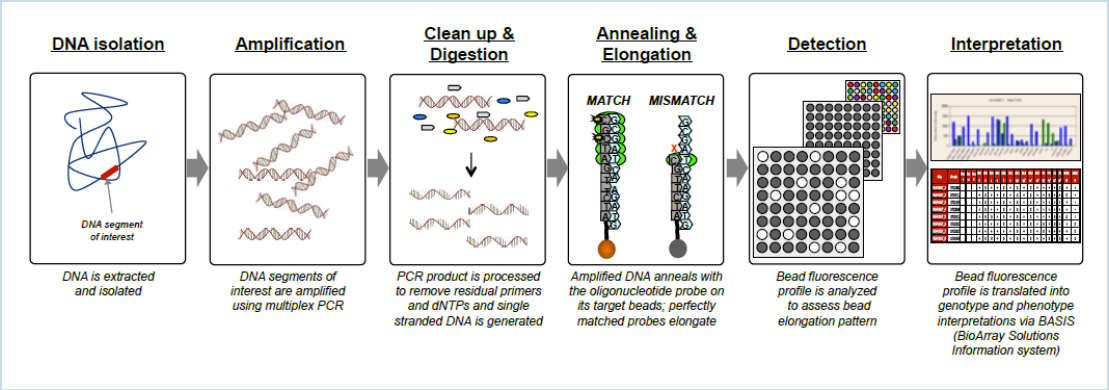
Lab Evaluation of suspected NAIT

1. Antibody Screening and Identification Assays

2. Crossmatch Using Paternal Platelets



3. HPA Typing Maternal/Paternal platelets



Laboratory Assays

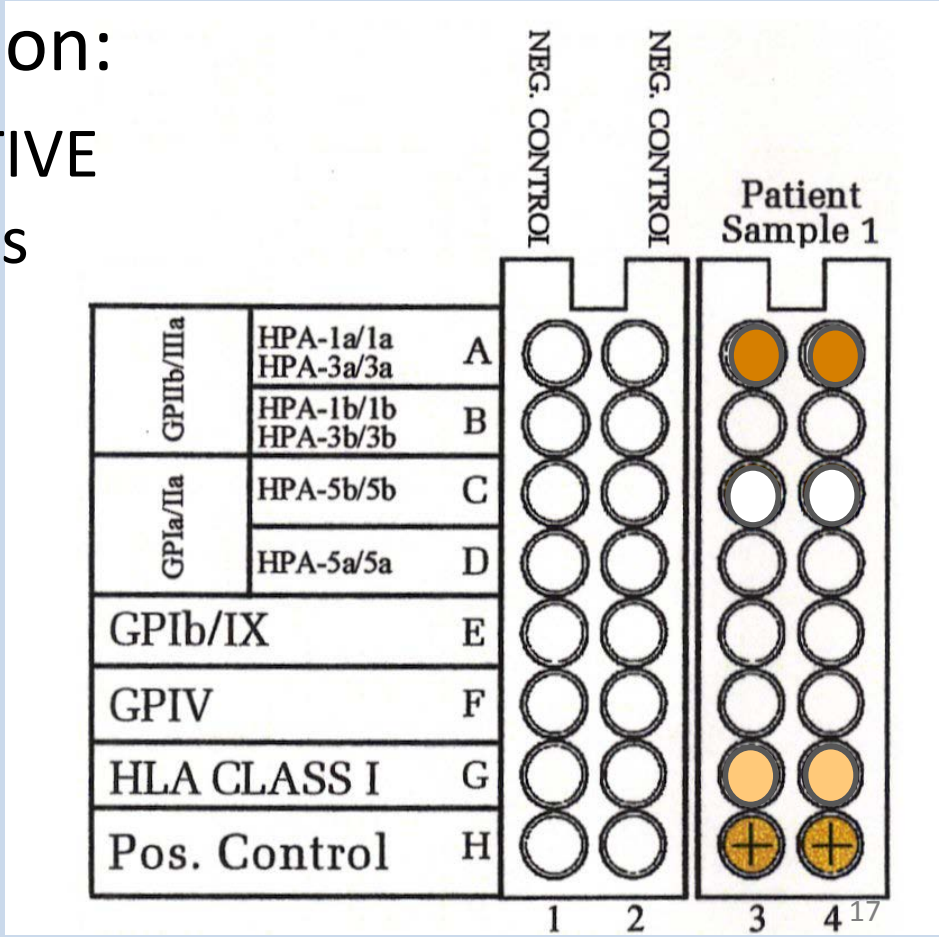
- Antibody Screening and Identification Assays
  - Solid phase red cell adherence (Capture-P® Ready-Screen)
  - ELISA (Pak-Plus)
  - Monoclonal Antibody Immobilization of Platelet Antigens (MAIPA)
  - Platelet Antibody Bead Array (PABA) or Flow Cytometry
- Crossmatch Using Paternal Platelets
  - Solid phase red cell adherence (Capture-P®)
  - MACE/MAIPA
- HPA Typing Maternal/Paternal platelets
  - SSP (eg. Thrombotype®): Usually types HPA 1-6, $^{+/-}$9, 15
  - Multiplex (beadchip) technology: Types HPA 1-9, 11, 15

Laboratory Assays: PABA Crossmatch

- BCW send-out
- Maternal serum incubated with the paternal platelets
  - Platelets are washed and lysed in detergent to release the various platelet glycoprotiens (GPs) from membrane
  - Lysate is incubated with beads that have GP-specific monoclonal antibodies attached to capture the GPs and any maternal antibodies that might be attached to the GPs.
- Antibodies detected using fluorescent anti-human IgG reagent in a Luminex flow cytometer
- Testing for antibodies against:
  - HPA-1a/b, HPA-2a/b, HPA-3a/b, HPA-4a, HPA-5a/b
  - Other specificities on GPIIb/IIIa, GPIa/IIa, GPIb/IX, GPIV and Class I HLA

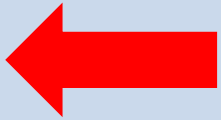
Case Serologic Results:

- Maternal serum antibody screen and identification:
  - HPA-1: Strongly POSITIVE against HPA1a platelets
  - HLA class I: weakly POSITIVE
- Crossmatch Using Paternal Platelets
  - POSITIVE



Case HPA Typing: Maternal/Paternal Platelets

Maternal HPA type	**Paternal HPA type**
HPA 1b/1b	HPA 1a/1a
HPA 2a/2a	HPA 2a/2a
HPA 3a/3a	HPA 3a/3b
HPA 4a/4a	HPA 4a/4a
HPA 5a/5a	HPA 5a/5a
HPA 6a/6a	HPA 6a/6a
HPA 9a/9a	HPA 9a/9a
HPA 15a/15a	HPA 15a/15a



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NAIT: Predictors of Severity

Clinical History	Risk
Previous fetus/newborn w/ thrombocytopenia or ICH of unknown etiology; no HPA antibodies detected	**Unknown**
Previous fetus/newborn w/ serologically confirmed FNAIT; + thrombocytopenia, - ICH	**Standard**
Previous fetus/newborn w/ serologically confirmed FNAIT; + thrombocytopenia, + ICH at ≥ 28 weeks gestation	**High**
Previous fetus/newborn w/ serologically confirmed FNAIT; + thrombocytopenia, + ICH at < 28 weeks gestation	**Very High**

Adapted from Pacheco et al, 2011

Neonatal Treatment/Management

- Intravenous immunoglobulin (IVIG) 2 mg/kg in 2-5 days
- Proposed Platelet transfusions thresholds:

<30,000	Consider transfusion for all
30,000-49,000	Do not transfuse if clinically stable Consider transfusion if: < 1000 g and < 1 wk of age Clinically unstable Previous major bleeding (GR 3-4 IVH or pulmonary hemorrhage) Current minor bleeding Concurrent coagulopathy Requires surgery or exchange transfusion
50,000-99,000	Do not transfuse
>99,000	Transfuse if bleeding

- Antigen-negative (or washed maternal) platelets
- Random-donor platelets (Kiefel V, et al Blood: 2006)

- **Antenatal treatment:** High-risk fetuses in subsequent pregnancies should be treated with high-dose IVIG during pregnancy (0.5-1 g/kg/week)

Roberts I. et al. Blood Reviews: 2008

Case Conclusion

- Infant received:
  - IVIG 2 mg/kg over 2 days on DOL 1 and 2
  - Multiple random donor platelets and HPA-1a negative platelets to maintain a plt count > 50 k/µL
- 2nd weeks of life→ platelet count was consistently > 100 k/µL
- Repeat Head US at 2 weeks demonstrated no progression of IVH

NAIT Prophylaxis: HPA Screening

- Effective prophylactic treatment
  - Antenatal IVIG for HPA-sensitized women during subsequent pregnancies
  - Antenatal IVIG has not been shown to prevent HPA sensitization in HPA-incompatible pregnancies
  - Animal and human subject evaluations of the FcRn-specific recombinant anti-HPA-1a antibody for FNAIT prophylaxis are ongoing
- Antenatal HPA screening currently not adopted as a standard of care in Europe or US

Curtis BR. Br J Haematol. 2015

Questions?