Platelet Alloimmunization

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Johns Hopkins Hospital
DISCLOSURES

Off-Label Usage
  • None

Interests
  • None
Topics

• Alloimmune Thrombocytopenias
• Important Alloantigen Systems
• Clinical and Laboratory Issues
• Platelet Transfusion Therapy in Alloimmune Disorders
• Platelet Transfusion Therapy
• Alternatives to Transfusion
## Immune Cytopenias

<table>
<thead>
<tr>
<th>RED CELLS</th>
<th>PLATELETS</th>
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<tbody>
<tr>
<td>AUTOIMMUNE HEMOLOYTIC ANEMIA</td>
<td>AUTOIMMUNE THROMBOCYTOPENIA</td>
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<td>HEMOLYTIC DISEASE OF THE NEWBORN</td>
<td>FETAL ALLOIMMUNE THROMBOCYTOPENIA</td>
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<tr>
<td>TRANSFUSION ALLOIMMUNIZATION</td>
<td>TRANSFUSION REFRACTORINESS</td>
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<tr>
<td>DRUG INDUCED AIHA</td>
<td>DRUG PURPURA</td>
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<tr>
<td>DELAYED HEMOLYTIC TRANSFUSION REACTION</td>
<td>POST TRANSFUSION PURPURA</td>
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</table>
PLATELET ALLOANTIGENS

- HLA CLASS I ANTIGENS – Transfusion Refractoriness
- HUMAN PLATELET ALLOANTIGENS - cause Post Transfusion Purpura, Neonatal Alloimmune Thrombocytopenia, Link to platelet hyper-reactivity??
- ABO BLOOD GROUPS
Platelets – Adhere, Secrete, Aggregate, Catalyze
PLT-GP IIB-IIIa

or $\alpha_{\text{IIB} \beta_{\text{IIIa}}}$ – fibrinogen receptor

More variants than other PLT Glycoproteins
These variants give rise to diallelic platelet antigen systems
PLT-GP IB/IX/V – von Willebrand receptor

1 known polymorphism of Ib alpha

Ab block function
Human Platelet Alloantigens (HPA)

- Human Platelet Antigens, formerly called platelet specific antigens represent variations of platelet glycoprotein integrins.
- These integrins are present on platelets, endothelial cells.
- Conformational immunogens.
- Give rise to alloimmune mediated thrombocytopenic disorders of:
ANTIBODIES TO HPA LEAD TO:

• POST TRANSFUSION PURPURA

• FETAL/NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

• PLATELET TRANSFUSION REFRACTORYNESS
### Human Platelet Alloantigens (HPA)

<table>
<thead>
<tr>
<th>HPA System</th>
<th>Original names</th>
<th>Plt Glycoprotein</th>
<th>Amino Acid Substitution</th>
<th>DNA substitution</th>
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<tbody>
<tr>
<td>1a</td>
<td>Pl(A1)</td>
<td>IIIa</td>
<td>Leu33</td>
<td>T196</td>
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<td>1b</td>
<td>Pl(A2)</td>
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<td>Pro33</td>
<td>C196</td>
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<td>2a</td>
<td>Ko(b)</td>
<td>Ib</td>
<td>Thr145</td>
<td>C524</td>
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<tr>
<td>2b</td>
<td>Ko(a)</td>
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<td>Met145</td>
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<td>3a</td>
<td>Bak(a)</td>
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<td>Bak(b)</td>
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<td>Pen(a)</td>
<td>IIIa</td>
<td>Arg143</td>
<td>G526</td>
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<td>Ia</td>
<td>Glu505</td>
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<td>5b</td>
<td>Br(a)</td>
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<td>Lys505</td>
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+ 10 other less common
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<th>Antigen System</th>
<th>*Caucasian</th>
<th>African American</th>
<th>**Asian</th>
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<td>HPA-1a</td>
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<td>0.92</td>
<td>0.95</td>
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<td>HPA-2b</td>
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<td>HPA-3a</td>
<td>0.67</td>
<td>0.63</td>
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<td>HPA-3b</td>
<td>0.33</td>
<td>0.37</td>
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<td>HPA-4a</td>
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<td>0.99</td>
<td>0.99</td>
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<tr>
<td>HPA-4b</td>
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<td>0.01</td>
<td>0.01∗</td>
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<tr>
<td>HPA-5a</td>
<td>0.89∗</td>
<td>0.79</td>
<td>0.97</td>
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<tr>
<td>HPA-5b</td>
<td>0.11</td>
<td>0.21</td>
<td>0.03</td>
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IMMUNOREACTIONS INVOLVING PLATELETS. V. POST-TRANSFUSION PURPURA DUE TO A COMPLEMENT-FIXING ANTIBODY AGAINST A GENETICALLY CONTROLLED PLATELET ANTIGEN. A PROPOSED MECHANISM FOR THROMBOCYTOPENIA AND ITS RELEVANCE IN “AUTOIMMUNITY

Note: important ground work for characterization of first important integrin- fibrinogen receptor, relevancy to Autoimmunity – target of autoAB
Post Transfusion Purpura (PTP)

- Characterized by sudden onset of severe thrombocytopenia 7-10 days after transfusion after blood or plasma.
- The Enigma of PTP, at the time of thrombocytopenia an alloantibody to HPA develops and persists despite the resolution of the thrombocytopenia.
- Seen in females previously transfused or pregnant – Only 1 male reported!
Clinical Presentation in PTP

- Petechiae
- Wet Purpura
- Bleeding from multiple operative sites
Platelet counts < 5,000/ul
Development of Thrombocytopenia is abrupt – 24 hours!!
Persist for mean duration of 7 days with range of up to 35 days; suggests possibility of different mechanisms
Anti-HPA-1a > 90% of cases - never anti HPA-1b
In our series no African Americans, Asians
Associated with severe, acute febrile reactions transfusions
Unmatched Platelet Transfusions Ineffective
Of 8 patients transfused with platelets developed thrombosis, both arterial and venous; no thrombosis in non transfused patients

Antibody Testing for HPA Testing
(uses monoclonal captured platelet glycoprotein variants)

<table>
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<tr>
<th>Platelet Phenotypes</th>
<th>Patient Sample 1</th>
<th>Patient Sample 2</th>
<th>Patient Sample 3</th>
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<tr>
<td>HPA-1a/1a (Pl^A1/A1)</td>
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<td>HPA-3a/3a (Bak^a/a)</td>
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<td>HPA-4a/ Pen^a)</td>
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<tr>
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<td>POS.CONTROL</td>
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</tbody>
</table>

Kickler, Herman, Kunicki, Aster. Blood v. 73
PTP Treatment

• Steroids – no effect on platelet count but wet purpura, petechiae improve
• Plasma exchange – in use at JHH until 1987
• IV-IgG** Treatment of Choice
• Platelets transfusions if necessary HPA matched, and HLA compatible?
IV-IgG Treatment

35 yr old female post Cardiac surgery

Rothko, Kickler  Role of IVGG in Immune Thrombocytopenia. Blood v :75
Prevention- future elective operations

• Use autologous blood
• Antigen negative if available – Red Cross has several HPA-1b donors, the result of readily available HPA genotyping of donors
• Any woman who has child with neonatal alloimmune thrombocytopenia should be cautioned of risk of post transfusion purpura in future with transfusion
Pathogenesis of PTP- Why Enigmatic Destruction of Autologous Platelets By an Alloantibody?

Anamnestic immune response to make anti HPA + Soluble PLA 1 Ag from stored unit of blood

Mechanism One – Quick Recovery
- Hapten Like Mechanism: Incubating Ultracentrifuged plasma from (+) unit of stored blood permits binding of PLA 1 Ab to PLA 1 (-) Platelets
- Patient’s plasma has PLA 1 antigen and it disappears with platelet recovery

Mechanism Two – Delayed Recovery
- Autoimmune Process: Display phage cloning shows autoreactive clones
- also serologic data
- HPA1a inhibits thrombopoiesis in culture

Kickler. Et al. Blood v. 75
Fetal/Neonatal Alloimmune Thrombocytopenia Due to Fetal-Maternal Incompatibility

HPA1a antigen

Fetus
HPA1a/1a

Thrombocytopenia

Trans placental transfer of Anti HPA 1a

Mother
HPA 1b/1b
Immune Response To make Anti HPA1a

PLACENTA

To make Anti HPA 1a

Trans placental transfer of Anti HPA 1a
Fetal/Neonatal Alloimmune Thrombocytopenia

- Antibody formation by mother, cross placenta
- Occurs in first pregnancy—early contrast to Rh Disease
- Antigen stimulus—shed, circulating syncytiophoblast that express $\alpha_{III\beta_{IIIA}}$ PRO 33—detect in maternal blood by 9 weeks

Twins at 9 weeks gestational age in separate amniotic cavities. Placental villi extend from chorionic plate into maternal decidua (not present).
Fetal/Neonatal Alloimmune Thrombocytopenia

- Caused by alloantibodies to HPA
- Most cases are diagnosed at birth (NAIT)
- In contrast to Rhesus Hemolytic Disease Newborn frequently seen in first pregnancy
- HPA1a (Caucasians) alloimmunization most frequent, followed by HPA-3a or b or HPA-5a or b in African Americans, Asians
- Occurs in 1 of 1000 – 2000 pregnancies
Clinical Characteristics

- Serious fetal consequences are common
  Intra Cranial Hemorrhage occurs in ~20% (10% fatal)
- Risk of ICH in subsequent fetal-antigen + pregnancies is virtually 100%
- A cause of recurrent pregnancy loss
- Fetus small, with small placenta – gives rise to Intrauterine growth retardation
CNS Bleeding In Utero

- Intracranial bleeds, which led to porencephaly

### Genotype Frequency for HPA-1 - Caucasians

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<th>Gene Frequency</th>
<th>Homozygous</th>
<th>Heterozygous</th>
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<tr>
<td>HPA-1a (PLA 1)</td>
<td>.83</td>
<td>.69</td>
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<tr>
<td>HPA-1b</td>
<td>.17</td>
<td>.03</td>
<td>.28</td>
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</table>

- With 3% population being 1b/1b- expect about 3% of population being at risk for alloimmunization to 1a.
- With 69% being 1a/1a expect about 69% at risk for alloimmunization to 1b.
FMAIT, contd

- There is a strong association with HLADRw 52a (HLADR3*0101)
- HLADRw 52a (HLADR3*0101) is present in 1 in 3 Caucasians
- The negative predictive value of making anti HPA1a in the absence of HLADRw 52a (HLADR3*0101) is >99%
- Positive predictive value of HLADRw 52a (HLADR3*0101) is < 30%
- Kickler TS, Tissue Antigen: 45
FMAIT Testing - How to Workup suspected case of NAIT

- First choice to genotype both parents for HPA-1
- Screen maternal serum against a panel of phenotyped glycoproteins, much like a RBC panel
- Where father is heterozygous genotype the fetus for prenatal management
- Do not utilize newborn sample for antibody testing, antibody frequently undetectable

- Ante Natal Screening – no proven cost effectiveness, unlike Rh
**Screening Multiply Transfused Patients by ELISA Testing**

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<thead>
<tr>
<th></th>
<th>NEG. CONTROL</th>
<th>Patient Sample 1</th>
<th>NEG. CONTROL</th>
<th>Patient Sample 2</th>
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<td>GPIb/IIa</td>
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Provision of Platelet Support

- Historically, washed maternal platelets
- Platelets need to be available soon after delivery or at time of delivery since severe bleeding occurs in first 48 hours
- Centers developing typed donor pools of HPA-1a and HPA-5b donors; if none matched random platelets may be used
- Absence of HPA, HLA antibodies, incompatible isoagglutinins, CMV negative + other donor requirements and testing
Treatment and platelet count response

TP – unmatched Plt TRX

TPθ – HPA matched Plt TRX
A Polymorphism of a Platelet Glycoprotein Receptor as an Inherited Risk Factor for Coronary Thrombosis

• To investigate the relation between the \( Pl^{A2} \) polymorphism and acute coronary syndromes, we conducted a case–control study of 71 case patients with myocardial infarction or unstable angina and 68 inpatient controls without known heart disease. The groups were matched for age, race, and sex. PLA genotyping was done by allele specific restriction digestion.
GENOTYPES OF THE CASE PATIENTS AND CONTROLS
ACCORDING TO AGE

<table>
<thead>
<tr>
<th>GENOTYPE</th>
<th>CASE PATIENTS</th>
<th>CONTROLS</th>
<th>P VALUE</th>
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<tbody>
<tr>
<td></td>
<td>N (% )</td>
<td>N (%)</td>
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<tr>
<td>ALL AGES</td>
<td></td>
<td></td>
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<tr>
<td>PLA1 / PLA1</td>
<td>43 (60.6)</td>
<td>55 (80.9)</td>
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<tr>
<td>PLA1 / PLA2 +</td>
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<tr>
<td>PLA2 / PLA2</td>
<td>23 +5 (39.4)</td>
<td>12+1 (19.1)</td>
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<tr>
<td>TOTAL</td>
<td>71 (100)</td>
<td>68</td>
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<tr>
<td>AGE &lt; 60</td>
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<tr>
<td>PLA1 / PLA1</td>
<td>21 (50)</td>
<td>31 (86.1)</td>
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<tr>
<td>PLA1 / PLA2 +</td>
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</tr>
<tr>
<td>PLA2 / PLA2</td>
<td>19 +2 (50)</td>
<td>5 + 0 (13.9)</td>
<td>.002</td>
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<tr>
<td>TOTAL</td>
<td>42 (100)</td>
<td>36 (100)</td>
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</table>

Chi square test was used to compare prevalence of PLA2 in case patients and controls.
### ODDS RATIO FOR SELECTED RISK FACTORS ACCORDING TO AGE

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>CLASS</th>
<th>ALL AGES ODDS RATIO (CI)</th>
<th>LESS THAN 60 ODDS RATIO (CI)</th>
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<tr>
<td>PLA GENOTYPE</td>
<td>PLA2 POSITIVE PLA2 NEGATIVE</td>
<td>2.8 (1.2-6.4)</td>
<td>6.3 (1.8-22.4)</td>
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<tr>
<td>SMOKING</td>
<td>CURRENT OR + HX. NEVER</td>
<td>2.2 (1.0-4.8)</td>
<td>3.5 (1.2-12.0)</td>
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<tr>
<td>SYSTOLIC BP</td>
<td>&lt; 140</td>
<td>1.9 (0.9-3.9)</td>
<td>2.1 (0.7-5.9)</td>
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<td></td>
<td>&gt; 140</td>
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<tr>
<td>TOTAL CHOLESTEROL</td>
<td>&lt;200</td>
<td>1.3 (0.4-3.0)</td>
<td>3.7 (0.8-18.7)</td>
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<tr>
<td></td>
<td>&gt;200</td>
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</table>

*NEJM 334;1090-1094*
The Grinkov Factor

Pascal Goldschmidt, et al., Lancet July 1995
Meta Analysis  HPA-1b (PLA2) as Risk Factor
Is there an increased risk for carrying at least one copy of PLA2 Allele, 7, 197 patients, 11, 665 controls

<table>
<thead>
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“Genotype does not always equal phenotype”

Victor McKusick M.D.
Guidelines For Platelet Transfusions

- Bone marrow failure
- Threshold of 10,000/ul if no other risk factors
- Sepsis, coagulopathy
- Threshold of 20,000/ul of other risk factors present

continued
Guidelines for PLT Transfusion

- Invasive Procedures
- A count of 50,000/ul for LP, indwelling lines, epidural anesthesia, gastroscopy and Biopsy, transbronchial biopsy, laparotomy or liver biopsy
- A count of 100,000 for brain and eye surgery

continued
Guideline for PLT Transfusion

- DIC
- Massive Transfusion
- Cardiac Surgery

- Aim for count > 50,000/ul
- Keep count > 50,000
- Reserve PLTs for those with severe bleed and surgical cause ruled out

continued
Guideline for PLT Transfusion

- Qualitative PLT Disorder
- DDAVP
- Correct HCT to >30%
- Consider PLT Transfusion when other measures failed
- IF Glanzmann’s consider rVIIa
Dose of Platelets

- Depends on therapeutic goal
- If prophylaxis in myelosuppressed, keep above trough of 10,000/ul
- Factors affecting dose, size, bleeding, splenomegaly, DIC, antibodies, microvascular damage
- Single donor platelets have at least $3 \times \log_{10}$ platelets-increase count by 20-30,000/ul
- If lower dose may still decrease bleeding, but more transfusion episodes needed!
Platelet Refractoriness

- Immune Refractory - Alloimmunization to HLA major cause
- Non Immune refractory
  - DIC, Sepsis, fever, splenomegaly
  - No identifiable cause
  - Poorly preserved platelet transfusion
Alloimmune Platelet Transfusion Refractoriness

- HLA Abs account for the majority of immune mediated PLT transfusion refractoriness
- 15-25% of Patients become HLA alloimmunized, maybe more if in patient group non alloimmunized
- 8-35% of HLA matched platelet transfusions have poor increments not related to clinical factors
- 3-8% caused by antibodies to HPA
- Rarely caused by ABO antibodies
OTHER CAUSES OF IMMUNE MEDIATED REFRACCTORINESS

• AUTOANTIBODIES
• DRUG INDUCED ANTIBODIES
• ANTIBODIES TO PLATELET GLYCOPROTEINS, IN GLANZMAN’S OR BERNARD SOULIER DISEASE ***
Screen weekly during extended transfusion, antibodies develop after 1-2 weeks in induction chemo of leukemic patients, may disappear—good news.
Prevention of Alloimmunization

- Limit transfusion exposure - no dose response
- Only use pheresis platelets not those prepared from units of whole blood - not effective
- Leukocyte depletion - removing WBCs, the immunizing agent in blood or platelets, works!
PREVENTION OF ALLOIMMUNIZATION

TRAP STUDY
NEJM:337:1861, 1998
HLA Matching of Platelets

• Ideal situation would be to give HLA identical platelets to everyone
• Genetic polymorphisms of this complex antigen system makes this impossible
• Strategy is to prevent alloimmunization if cannot do this
• Circumvent the antibodies by HLA matching or selective mismatches
HLA Transfusion Strategy

- Platelets have HLA-A, and HLA-B antigens on them.
- It is not necessary to match for HLA-C antigens since these are weakly expressed.
- Try to give HLA A and B antigens that are identical or cross-reactive with the recipient, once the recipient has HLA antibody.
- This will allow successful transfusions > 60-70% of the time.
When HLA Matched Platelets are not Available

- Laboratory can do platelet crossmatching of the donor pool available
- This approach is not only practical but highly successful in > 78-80% of difficult to match transfusion recipients
- Alternatively HLA serologic identification of the antibodies may permit finding donors who lack the Antigens that the patient has antibodies to. I.e. give “antigen negative platelets”
Alternative Management Strategies

- Reticuloendothelial Blockage—High Dose IgG- only transiently helpful
- Immunosuppressive Therapy – not helpful
- Growth Factors – if no megakaryocytes, no benefit
- Repeated Platelet Transfusions – benefit?
- Amicar- no control trials showing benefit
Recombinant VIIa in Congenital Platelet Disorders

- 28 patients with Glanzmann’s thrombasthenia treated, 2 with Bernard Soulier and 2 with pseudo vWD
- rVIIa used in 3 major and 10 minor surgical procedures, and for 57 bleeding episodes
- Red cells needed in 24 and Amicar used in 54 cases
rVIIa, continued

- For 13 invasive procedures, results good in 11, not evaluable in 2
- 9 GI bleeds, 1 had recurrence after 36 hours
- Of 42 others, 11 were failures
- For 34 non GI bleeds total doses received 1-14
rVIIa Continued

- Dose recommended 85 mcg/kg given every 2 hours
- Effective in covering invasive procedures and stopping bleeding episodes
SUMMARY

• Alloimmune Thrombocytopenias

• Important Alloantigen Systems

• Clinical and Laboratory Issues

• Platelet Transfusion Therapy in Alloimmune Disorders

• Alternatives to Transfusion