Management of Acquired Bleeding Disorders

W Beau Mitchell, MD
Mount Sinai School of Medicine
Case Presentation

5 year old male

- Wet Purpura
- Bruises Trunk/Extremities
Diagnosis:

Immune Thrombocytopenia
Clinical History

- Ecchymoses
- Purpura
- Petechiae
- Epistaxis
- GI Bleeding
- Intracranial Hemorrhage
Immune Thrombocytopenia

- Acquired Immune Mediated Disorder
- Platelet Count < 100,000 /μL
- Absence of initiating/underlying cause

Rodeghiero et al, Blood (2009)
ITP Classification

• Newly Diagnosed

• Persistent (3 – 12 months)

• Chronic ( > 12 months duration)

Rodeghiero et al, Blood (2009)
Pathophysiology of ITP

- Thrombopoietin
- Peripheral blood
- Bone marrow
- Megakaryocyte
- Platelet
- Macrophage
ITP Presentation

**Pediatric**
- Incidence: 2 - 6 per 100,000
- Abrupt Onset
- M = F
- < 20% Chronic

**Adults**
- Incidence: 3.3 per 100,000
- Insidious Onset
- F > M
- > 50% Chronic Course

Adapted Nathan and Oski 7th Edition (2009)
Pediatric ITP Treatment

• Observation
• Intravenous Anti-D Immunoglobulin
• Intravenous Immunoglobulin
• Corticosteroids

• Role of Platelet Transfusion
Intravenous Immunoglobulin

Autoantibody-dependent immune thrombocytopenia

IVIG

IgG glycovariant rich in terminal sialic acid residues

SIGNR1

Macrophage

Lymph node?

Anti-inflammatory effects of IVIG independent of IL-4, IL-33 and basophils

FcyRIIB

Effector macrophage

↑ Inhibitory FcRs
↓ Activating FcRs
↓ Platelet phagocytosis

Blood and tissues

Autoantibody
Platelet

Immune complex

# Intravenous Immunoglobulin

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>0.8 -1 g/kg IV</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>~ 80 % Response</td>
</tr>
<tr>
<td></td>
<td>(dose dependent)</td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td>1- 2 days</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>Headache [ Severe]</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
</tr>
</tbody>
</table>

# Corticosteroids

| Dose                        | 1-2 mg/kg x 14 days  
<table>
<thead>
<tr>
<th></th>
<th>4 mg/kg x 3-4 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>~ 75% Response (dose dependent)</td>
</tr>
<tr>
<td>Time</td>
<td>2 - 7 days</td>
</tr>
</tbody>
</table>
| Toxicity                    | Mood Swings  
|                            | Gastritis  
|                            | Weight Gain  
|                            | Infectious Risk  |

Intravenous Anti-D

## Intravenous Anti-D

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>50 - 75 mcg/kg IV</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>50 - 77% Response (dose dependent)</td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td>&gt; 50% Respond w/in 24 hr</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>Headache, Fever / Chill (less common), Hemolysis, Renal Failure (Rare)</td>
</tr>
</tbody>
</table>

Emergency Treatment

Life Threatening Bleeding Event

Platelet Transfusion

– IV Corticosteroids
– IVIG or IV Anti-D

– Consideration:
  • Anti-Fibrinolytics
  • Vincristine
  • Emergency Splenectomy

Goal: ↑ Platelet Count & Minimize Bleeding
Pediatric ITP

• Persistent ITP Treatment
  – Steroids
  – Infusions of IVIG or IV Anti-D
  – Anti-CD 20
  – Immunosuppressants (MMF/ CSA/ Azathioprine)
  – Thrombopoietic Agents
Anti-CD 20

Kaplan-Meier response duration curves after month 6 in patients who achieved sustained response (SR) after dexamethasone monotherapy, dexamethasone plus rituximab, and dexamethasone plus rituximab salvage therapy.

Rituximab + Standard of Care.

Thrombopoietin-Receptor Agonists

Imbach and Crowther, NEJM 2011
Eltrombopag

- Promacta / Revolade
- Small Molecule
- Binds to transmembrane TPO-Receptor
- Oral Administration
  - Dietary Restraints
  - East Asian Clearance Rate
Eltrombopag

• Phase II – Day 15
  70% Response (50mg)
  80% Response (75mg)
  59% Response (50mg) → 1/3 responded at 75mg

• Phase III (RAISE)
  79% Responses (50mg → 75 mg escalation)
  59% Reduce/ Discontinue concurrent ITP therapy
Additional Data

• RAISE - 6 month treatment

• REPEAT - Intermittent treatment

• EXTEND - Open Label Extension Trial

• PETIT - Pediatrics
Romiplostim

- Nplate / AMG-531
- Peptibody
- Dimerized C-MPL Receptor
- Weekly SQ injections
Romiplostim

• Phase III
  – Splenectomized
    79% Response/ 38% Durable Response
  – Non-Splenectomized Patient
    87% Response / 61% Durable response
  – Randomization vs Standard of Care
    • 3 ug/kg/dose → 10 ug/kg/dose escalation
    • 234 unsplenectomized patients
      ↑ incidence of a sustained platelet response
      ↓ bleeding / transfusions
      ↓ Other treatments (including splenectomy)
      ↑ greater improvement in quality of life
Thrombopoietin-Receptor Agonists

Considerations

• Headache
• Nausea/ Emesis / Diarrhea / Fatigue/ Arthralgia
• Abnormal LFTs
• Thrombosis
• Rebound thrombocytopenia
• Bone marrow Fibrosis (reticulin)
• Hematological malignancy
• Cataracts
Adult ITP

- Aggressive approach

- Avoid development of chronic ITP
Adult Treatment

First Line
- Corticosteroids
  - Dexamethasone
  - Prednisone
- IVIG
- IV Anti-D

Second Line
- Azathioprine
- Cyclosporine
- Danzol
- Anti-CD 20
- Dapsone
- MMF
- VCR
- Thrombopoietic Agents
- Splenectomy
ITP requiring treatment

First-line therapies
Corticosteroids/IVig/Anti-D

No response, requires high dose or relapse after Corticosteroids

Choose a second-line treatment based on the following factors

Restrictions on use of TPO-RA/rituximab by health funding authorities.

1- Contraindication to splenectomy, e.g. comorbidity.
2- No restrictions on use of TPO-RA/rituximab.

Other factors:
1- Old age (>60-70y depending upon physical condition).
2- Mixed or hepatic platelet sequestration on radioisotope study.
3- Newly diagnosed (0-3 mo) or persistent (3-12 mo) ITP.
4- Exposure to malaria, babesia or other infections cleared by the spleen.

Other factors:
1- Chronic ITP (>1 year).
2- Patient prefers Rx with high cure rate and/or no maintenance therapy.
3- Wish to become pregnant.

1- Patient refuses splenectomy but prefers Rx with curative intent.
2- High risk of art. or ven. thrombosis.
3- Anticipated poor compliance.
4- Reliability/cannot cope with dietary restrictions (eltrombopag).

Splenectomy

Rituximab

TPO-RA

Ghanima et al. Blood 2012
Splenectomy

Pros:

• Splenectomy is “Curative”
• Laparoscopic Technique
• Well Characterized Safety
• Cost Reduction
• Pregnancy

Cons:

• Unpredictable Response
• Invasive Procedure
• Overall Mortality
• Risk of Infection /Sepsis
• Vascular Complications

Ghanima et al. Blood 2012
Medical Therapy

Rituximab

Pro
- Curative Potential
- Relative Safety Profile
- CR ~ 44%
  (↑ with Steroids / Maintence)

Con
- Infusion Reactions
- Rare PML / Hep B
- Altered T/B/ Immunoglobulin
- ↓ Durable Remission

TPO Agents

Pro
- RCT Data
- SQ / PO options
- Response rate 59-88%

Con
- Indefinite duration of tx
- Healthcare / Dietary Constraints
- Long Term Safety Data

Ghanima et al. Blood 2012
Secondary ITP

- NAIT
- HIT
- Drug Induced
- Autoimmune Disease
- Infection
- Lymphoproliferative Disorders
## Acquired Platelet Defects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Platelet effect</th>
<th>Approximate duration of increased bleeding risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Irreversible</td>
<td>5 days</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Reversible</td>
<td>24 hours</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Reversible</td>
<td>Up to 4 days†</td>
</tr>
<tr>
<td>Thienopyridines</td>
<td>Irreversible</td>
<td>7 days</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Reversible</td>
<td>Minimal to no risk with procedures</td>
</tr>
<tr>
<td>Long-acting dipyridamole/aspirin</td>
<td>Reversible/irreversible</td>
<td>5 days</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>Reversible</td>
<td>Minimal to no risk with procedures</td>
</tr>
</tbody>
</table>

*Individual patient risks and circumstance should be considered.
†Based on minimal data; no time points between 2 hours and 4 days.
Case Presentation

3 month old ♀

Fibrinogen: 88 mg/dL
D-Dimer: > 200 mg/L
Diagnosis:

Kasabach-Merrit Syndrome with DIC
Disseminated Intravascular Coagulation

Clinical Diagnosis

- Thrombocytopenia
- Elevated D-Dimer
- Low Fibrinogen
- Elevated PT/PTT
DIC

• Infection
• Malignancy
• Trauma / Burns
• Obstetric Conditions
• Purpura Fulminans
• Giant Hemangioma
Contact activation (intrinsic) pathway

Damaged surface

XII \rightarrow XIIa

\rightarrow XI \rightarrow Xla \rightarrow IX \rightarrow IXa \rightarrow VIIIa \rightarrow VIII

Prothrombin (II) \rightarrow Xa

Thrombin (IIa) \rightarrow Va

Active Protein C

Protein S

Protein C + Thrombomodulin

Tissue factor (extrinsic) pathway

Trauma

VIIa \rightarrow VII

Tissue factor

TFPI

Antithrombin

Thrombin (IIa) \rightarrow Fibrinogen (I) \rightarrow Fibrin (Ia) \rightarrow XIIIla \rightarrow XIII

Cross-linked fibrin clot

Common pathway

Icahn School of Medicine at Mount Sinai

http://en.wikipedia.org/wiki/Coagulation
DIC

Cytokines  Thrombin  Plasmin

Activation Coagulation
Impaired Fibrinolysis
Suppression of Anticoagulants

Anticoagulant
Underlying Disease

Intravascular Activation of Coagulation

Platelets

Clotting Factors

Bleeding

Fibrin Deposition and Fibrinolysis

Microvascular Thrombosis

Anticoagulants
DIC

Bleeding

Thrombosis
DIC Treatment

TREAT THE UNDERLYING DISEASE

Supportive Care
  Circulatory Volume
  Gas Exchange
  Electrolyte Balance
  Acid/Base Balance
DIC Treatment

Blood Product Support

- Active Bleeding?
- Invasive Procedure?
- Risk for Bleeding Complications?

PRBC  Plts  FFP  Cryo
Alternative Treatments

• Heparin
• Antithrombin
• Protein C Concentrate
The withdrawal of Activated Protein C from the use in patients with severe sepsis and DIC [Amendment to the BCSH guideline on disseminated intravascular coagulation]

PROWESS-SHOCK Trial
Withdrawal of Activated Protein C
(Eli Lily October 2011)
Systemic Disease

- DIC
- Vitamin K Deficiency
- Liver Disease
- Renal Disease

Antihemostatic drivers
- Thrombocytopenia
- Abnormal platelet function
- Decreased production of thrombopoietin
- Increased production of nitric oxide and prostacyclin
- Low levels of factors II, V, VII, IX, X, and XI
- Vitamin K deficiency
- Dysfibrinogenemia
- Low levels of α2-antiplasmin, factor XIII, and TAFI
- Elevated level of t-PA

Coagulation

Fibrinolysis

Hemostasis in patients with chronic liver disease
Case Presentation

• 8 year old with SLE
  – History of Trauma
  – Right thigh hematoma

Mixing Study

| 13 | 80 | 53.9 |

Factor VIII: < 1%

Inhibitor Titer: 9.6 BU
Diagnosis:

Acquired Hemophilia A
Acquired Hemophilia A (AHA)

- Autoimmune Disease
- Auto-antibody to Factor VIII
- Rare Bleeding Disorder
- Incidence < 1 cases per million people/year
- Increased Incidence with Age
- Morbidity/Mortality
Clinical Presentation of AHA
Bleeding, negative personal and family history of bleeding disorder, prolonged APTT with normal PT

Mixing study
(APTT on a 1:1 mixture of patient and normal plasma. Incubation 2 hr at 37 °C)

APTT mix normal

Specific deficiency of one or more clotting factor(s) of the intrinsic pathway

Exclude Lupus Anticoagulant*

Reduction of multiple factors

Dilution tests

Reduction of FVIII activity

Specific inhibitor quantification (Bethesda or Nijmegen assay)

DIAGNOSIS OF ACQUIRED HEMOPHILIA A
Diagnosis

- Prolonged PTT
- Normal PT
- Mixing Study
  - Not corrected with incubation
- Inhibitor Study (Bethesda Units)

Clotting times remain prolonged = Inhibitor

vs

Clotting times normalize or decrease to near-normal = Factor deficiency

www.labmed.yale.edu
Acquired Hemophilia

![Pie chart showing various causes of acquired hemophilia.]

- Dermatological
- MGUS
- Medication
- Infection
- Pregnancy
- Autoimmune disease
- Malignancy
- Idiopathic

Sobrov and Rodgers, BHJ (2013)
AHA Treatment Goals

- Hemostasis
- Treatment of Underlying Disorder
- Inhibitor Eradication
- Avoidance of trauma/intervention
AHA Treatment

- Hemostatic Treatment
- Diagnosis of AHA
- Inhibitor eradication (IST)
- No bleeding
- Identification and treatment of underlying conditions

Coppola et al, Seminars in Thrombosis & Hemostasis (2012)
AHA Treatment

Bleeding Control:
Factor VIII Bypassing

rFVIIA - Recombinant Factor VIIa
70- 90 mcg/kg q 2-3 hours

APCC (FEIBA)
50 -100 units/kg q 6 -12 hours

DDAVP

Anti-Fibrinolytics

Factor VIII (Human/ Porcine)

Collins PW, Journal of Thrombosis and Hemostasis (2011)
AHA Treatment

Inhibitor Eradication

– Steroids
– Cyclophosphamide

– Rituximab
– Cyclosporin A

Additional Strategies

○ IVIG
○ Immunoadsorption
○ Plasmapheresis
○ Immune Tolerance Induction
Acquired VWD

- Von Willebrand Disease
  - Multimeric Glycoprotein
  - Primary Hemostasis
  - Binds:
    - Platelets
    - Collagen
    - Factor VIII Carrier
Acquired VWD

• Rare Disease
• Underestimated
• Multifactorial Etiology
  – Autoantibody Neutralization
  – Adsorption onto malignant cell clones
  – Shear Stress with accelerated clearance
  – Decreased Synthesis

Shetty et al. European Journal of Hematology (2011)/
Federici et al. Seminars in Thrombosis & Hemostasis (20130
Acquired VWD

![Graph showing the frequency of underlying conditions associated with acquired von Willebrand syndrome in 186 patients identified in an ISTH registry. Miscellaneous conditions include infectious diseases, other systemic diseases, drug-induced and idiopathic diseases. ISTH, International Society on Thrombosis and Haemostasis.]

Acquired VWD

• Lymphoproliferative Disease
• Myeloproliferative Disorders
• Cardiovascular Disease
• Autoimmune Disease
• Hypothyroidism
• Malignancy
• Drug Induced
## Diagnosis

<table>
<thead>
<tr>
<th>Normal</th>
<th>Type 1</th>
<th>Type 2A</th>
<th>Type 2B</th>
<th>Type 2M</th>
<th>Type 2N</th>
<th>Type 3</th>
<th>PLT-VWD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>VWF:Ag</td>
<td>N</td>
<td>L, ↓ or ↓↓↓</td>
<td>↓ or L</td>
<td>↓ or L</td>
<td>N or L</td>
<td>absent</td>
<td>↓ or L</td>
</tr>
<tr>
<td>VWF:RCo</td>
<td>N</td>
<td>L, ↓ or ↓↓</td>
<td>↓↓↓ or ↓↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>N or L</td>
<td>absent</td>
</tr>
<tr>
<td>FVIII</td>
<td>N</td>
<td>N or ↓</td>
<td>N or ↓</td>
<td>N or ↓</td>
<td>N or ↓</td>
<td>↓↓</td>
<td>1-9 IU/dL</td>
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<tr>
<td>RIPPA</td>
<td>N</td>
<td>often N</td>
<td>↓</td>
<td>often N</td>
<td>↓</td>
<td>N</td>
<td>absent</td>
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<tr>
<td>LD-RIPA</td>
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<td>absent</td>
<td>absent</td>
<td>↑↑↑↑</td>
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<td>absent</td>
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<tr>
<td>PFA-100® CT</td>
<td>N</td>
<td>N or ↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>↑↑↑↑</td>
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<td>BT</td>
<td>N</td>
<td>N or ↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>↑↑↑↑</td>
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<tr>
<td>Platelet count</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>↓ or N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<tr>
<td>VWF multimer pattern</td>
<td>N</td>
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<td>abnormal</td>
<td>abnormal</td>
<td>N</td>
<td>N</td>
<td>absent</td>
</tr>
</tbody>
</table>

Treatment AVWS

• Treat Underlying Disorder
• Acute Bleeding Treatment:
  – DDAVP
  – Purified Plasma Derived VWF
  – Recombinant VWF
  – Recombinant Factor VIIa
  – IVIG / Plasmapheresis

Franchini /Lippi, Am J of Hem (2007)
Management of Acquired Bleeding Disorders

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