Bleeding disorders in Pediatrics: From Birth and Beyond

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Conflicts of Interest

- No conflicts of interest to disclose
Objectives

- Explain diagnostic and treatment approach to a pediatric patient with a possible bleeding disorder
- Describe hemophilia presentation and treatment
- Describe Von Willebrand disease presentation and treatment
- Characterize rare bleeding disorders
Overview

- **Introduction**
  - Symptoms
  - Approach to a bleeding patient

- **Discussion & learning through real life case scenarios**
  - Hemophilia and Von Willebrand Disease
  - Rare bleeding disorders
Introduction

- **Diagnosis of bleeding disorders**
  - Clinical personal history
  - Family history
  - Laboratory testing

*All of the above and sometimes ONLY one of the above*
Introduction: Symptoms

- Variable depending on
  - Underlying bleeding disorder
  - Levels of the blood clotting protein
  - Genetic mutation
  - Age of the patient
  - Sex

*Despite all this, no better diagnostic tool than a good history*
Introduction: Symptoms

- Common bleeding symptoms
  - Muco-cutaneous
  - Musculoskeletal
  - Post injury or surgery

Recent emergence of several bleeding score questionnaires* to assist healthcare practitioners to distinguish normal from unusual bleeding

Several of these:
Clearly Abnormal

SUBGALEAL

INTRACRANIAL
Introduction: Symptoms

What is abnormal when it is “not so obvious”

- Epistaxis: More than 10 minutes, requiring packing or cauterization, causing iron deficiency or anemia, requiring PRBC transfusion
- Bruising: > 1 cm with hematomas, without associated injury, in unexposed areas
- Bleeding from cuts/minor wounds: > 5 minutes or > 5 episodes, or requiring consultation, intervention, or surgery
- Menorrhagia: Soaking through super size pads once every 2-3 hours lasting for 3-4 days, low iron stores, anemia, requiring PRBC transfusion

## Introduction:

**Symptoms by Age Span & Diagnoses**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Birth</th>
<th>Toddler</th>
<th>Child</th>
<th>Adol/Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe Hemophilia</strong></td>
<td>Bleeding with heel-sticks, circumcision, ICH</td>
<td>Joint, muscle &amp; soft tissue spontaneous/ activity, post vaccination</td>
<td>Joint, muscle &amp; soft tissue spontaneous/ activity associated</td>
<td>Joint, muscle and soft tissue spontaneous</td>
</tr>
<tr>
<td><strong>Moderate Hemophilia</strong></td>
<td>Circumcision bleeding +/-; other invasive procedures</td>
<td>Injury related, post procedure</td>
<td>Injury related, post procedure</td>
<td>Injury related, post procedure</td>
</tr>
<tr>
<td><strong>Mild Hemophilia</strong></td>
<td>Bleeding unusual in neonatal period unless invasive procedures performed</td>
<td>Post surgical and injury related</td>
<td>Post surgical and injury related</td>
<td>Post surgical and injury related</td>
</tr>
<tr>
<td><strong>VWD</strong></td>
<td>Severe -circumcision bleeding, rest--uncommon</td>
<td>Epistaxis, easy bruising</td>
<td>Post procedure T&amp;A, dental extraction</td>
<td>Menorrhagia, post procedure</td>
</tr>
<tr>
<td><strong>Rare Bleeding Disorders</strong></td>
<td>FXIII ICH &amp; umbilical stump bleeding</td>
<td>Hematomas epistaxis</td>
<td>Post procedure, GI bleeds</td>
<td>Post surgical, PPH, menorrhagia</td>
</tr>
</tbody>
</table>
INTRODUCTION: APPROACH TO DIAGNOSIS

SCREENING STUDIES
CBC, Blood smear, PT, APTT
Bleeding time/PFA

PT, APTT ABNORMAL

APTT ONLY PROLONGED
• Hemophilia: FVIII, FIX, FXI

PT ONLY PROLONGED
• FVII

PT & APTT PROLONGED
• FV, FX, prothrombin fibrinogen

ABNORMAL CBC, BLOOD FILM
BLEEDING TIME/PFA

VWD

PLATELET DISORDERS:
CONGENITAL OR ACQUIRED

VWF ANTIGEN
VWF:RCo
FVIII
VWF MULTIMERS
RIPA

Platelet count
Morphology
Aggregometry
Electron microscopy
Review medications
Evaluate for other systemic disorders

FXIII ASSAY
Consider rare Fibrinolytic Disorders: PAI-1 or alpha 2 antiplasmin deficiency

EVALUATE FOR:
• Connective tissue disorder, HHT, child abuse

CASE 1

- Newborn with excessive bleeding post circumcision with normal PT, fibrinogen and CBC BUT prolonged APTT of 80 seconds,
Hemophilia

- Basic Science
- Prevalence
- Inheritance
- Presentation
- Diagnosis
- Treatment
- What’s new?
Hemophilia: Basic Science

**Intrinsic Pathway**

Contact factors (HMWK, Kalikrein, FXII) → FXI → FXIa

FXIa → FIX → FIXa

FXa → FVIIa/TF

Platelet activation

**Tissue Factor Pathway**

Tissue injury → Tissue factor release → FVII → FXIIa/TF

FXIII

Prothrombin → Thrombin → Fibrinogen → Fibrin

Plasminogen → Plasmin → Cross-linked fibrin → Fibrin polymer

Phospholipids

Ca++

FXa
Hemophilia: Prevalence

- **Factor VIII deficiency: Hemophilia A**
  - 1 in 5000 live male births

- **Factor IX deficiency: Hemophilia B or Christmas disease**
  - 1 in 30,000 males

- **Factor XI deficiency: Hemophilia C/Rosenthal syndrome**
  - 1 to 3/1000 Ashkenazi Jews

- **Prevalence comparison**

<table>
<thead>
<tr>
<th>Factor VIII</th>
<th>&gt;</th>
<th>Factor IX</th>
<th>&gt;</th>
<th>Factor XI</th>
<th>&gt;</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>→</td>
<td>1</td>
<td>→</td>
<td>?</td>
<td>→</td>
<td>?</td>
</tr>
</tbody>
</table>

Hemophilia A & B Inheritance: X linked XI deficiency: Autosomal Recessive

## Hemophilia: Presentation

<table>
<thead>
<tr>
<th>Classification</th>
<th>Factor Level</th>
<th>Bleeding Pattern</th>
<th>Estimated Annualized Bleed Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>&lt;1%</td>
<td>Spontaneous hemorrhage</td>
<td>~ 1 / week</td>
</tr>
<tr>
<td>Moderate</td>
<td>1-5%</td>
<td>Hemorrhage with incidental injury</td>
<td>~ 4 – 6 / year</td>
</tr>
<tr>
<td>Mild</td>
<td>&gt;5%</td>
<td>Hemorrhage with injury or surgery</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

Hemophilia: Presentation

- **Soft tissue**
  - Bruising
    - Superficial bleeding into soft tissues
    - Symptoms include cutaneous discoloration and swelling
    - May or may not require treatment depending on extent and discomfort
  - Hematomas
    - Bleeding into soft tissues resulting in a collection of blood which is often palpable

**Hemophilia: Presentation**

**Muscle: 30%**

- Acute: Often confused with a pulled muscle
  - Symptoms may include pain, swelling, inability to use
- Chronic: Atrophy and limb dysfunction
- Bleeding into the calf, forearm, and groin can create pressure on nerves resulting in numbness, pain and inability to move
  - Neurovascular compression can lead to a compartment syndrome

Hemophilia: Presentation

- **Joint: 60%**
  - Acute: Pain, swelling, interference with normal activities
  - Chronic: Synovial hypertrophy and synovitis leading to hemophilic arthropathy, disability

**COMMON BLEEDING SITES:**
- Elbows
- Knees
- Ankles

Hemophilia: Acute Hemarthrosis Presentation

- Swelling
- Warmth
- Acute pain
- Limited movement
Hemophilia Target Joint Presentation: Knee

Boggy

Swollen
Hemophilia: Diagnosis

- Of course – HISTORY!
- Prolonged APTT

**Exceptions**
- Mild FIX due to insensitivity of assay
- Mild FVIII due to elevated level with stress

Always perform FVIII, FIX activity assays.
Repeat if high index of clinical suspicion even if previously normal.
Hemophilia: Treatment

- **On-demand**
  - A treatment method which provides replacement therapy for bleeding episodes once they have occurred

- **Prophylaxis**
  - Treatment methods that provide replacement therapy in the absence of bleeding episodes
  - Usually started after age 1 year or after 1\textsuperscript{st} joint bleed

## Hemophilia: Treatment Products

<table>
<thead>
<tr>
<th>FVIII</th>
<th>NAME</th>
<th>GENERATION</th>
<th>FVIII LENGTH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Advate</td>
<td>3rd</td>
<td>Full length</td>
</tr>
<tr>
<td></td>
<td>Xyntha</td>
<td>3rd</td>
<td>B Domain deleted</td>
</tr>
<tr>
<td></td>
<td>Helixate-FS / Kogenate-FS</td>
<td>2nd</td>
<td>Full length</td>
</tr>
<tr>
<td></td>
<td>Recombinate</td>
<td>1st</td>
<td>Full length</td>
</tr>
<tr>
<td></td>
<td>Eloctate*</td>
<td>4th</td>
<td>BDD; fusion to IgG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FIX</th>
<th>NAME</th>
<th>GENERATION</th>
<th>FIX LENGTH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BeneFIX</td>
<td>3rd</td>
<td>Full length</td>
</tr>
<tr>
<td></td>
<td>RIXUBIS</td>
<td>3rd</td>
<td>Full length</td>
</tr>
<tr>
<td></td>
<td>Alprolix*</td>
<td>4th</td>
<td>Full length; fusion to IgG</td>
</tr>
</tbody>
</table>

* New generation long lasting fusion products

Hemophilia: Treatment
New Product Development Strategies

**STRATEGIES**

1. Strategies to increase production e.g. intracellular processing
2. Use of transgenic animals

**GOALS**

1. Increase available product(s)
2. Lower cost
3. Increase availability worldwide
4. Alternate delivery route

**STRATEGIES**

1. **Extended half-life**
2. Bioengineered proteins: degradation resistant, ↑ specific activity, proteins with ↓ immunogenicity
3. Use of human cell lines

**GOALS**

1. Decrease infusions
2. Longer protective period
3. Impact inhibitor rates

**Impact hemostasis through alternative pathways e.g. TFPI, protein C, AT3, aptamers (mimetics & inhibitors)**

1. Prolonged protection with infusion
2. Treatment without “factor” exposure
3. Alternate delivery route

**Cure : Gene Therapy**

1. Convert to moderate-mild state
2. Achieve prolonged expression without vector related AEs
3. Achieve without invasive procedure

Hemophilia: Treatment Dosing

- For minor bleeds such as muscle, early joint etc. desired factor level 40-50%; achievable with
  - Factor VIII concentrate: 20-25 international units/kg
  - Recombinant factor IX concentrate: 50-60 international units/kg

- For major bleeding such as ICH, advanced joint, iliopsoas or surgical, desired factor level 80-100%; achievable with
  - Factor VIII concentrate: 40-50 international units/kg
  - Recombinant factor IX concentrate: 100-120 international units/kg

Hemophilia Treatment: Avoiding Errors

ADVATE
Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method (rAHF-PFM)

Contents: One bottle 5 mL dried Antihemophilic Factor (Recombiant), 5 mL Sterile Water for Injection; a double-ended needle; a filter needle; infusion/blood collection set; 10 mL sterile syringe, alcohol swabs; bandages; one full prescribing physician insert; one patient package insert.

Stabilizing agents present in the following maximum amounts when reconstituted:
Mannitol (3.8%), Trehalose (1.0%), Histidine (12 mM), Tris (12 mM), Calcium (1.9 mM), Polysorbate 80 (0.017%), Glutathione (0.1 mg/mL), Sodium (108 mEq/L).

Sterile – Nonpyrogenic – No preservative

ADVATE is a trademark of Baxter International Inc.

Lot No: LE01C027AB
Exp. Date: MAR-13-2005
FW VIII IU/Bottle: 1020
Hemophilia Treatment: Avoiding Errors

- Always infuse the entire contents of each vial opened
  - Entire vial was charged to patient, do not waste it

- Check patients deficiency and product use before mixing product
  - Have two people sign off on product

- Product only compatible with normal saline
  - Do not use Dextrose solutions
  - Do not piggyback in other drugs or solutions
  - Only use diluents packaged with product
Newborn with excessive bleeding post circumcision and prolonged APTT of 80 seconds
- FVIII activity <1%
- VWF:Ag 150%
- Diagnosis: Severe hemophilia A

Required one dose with a 100% correction of rFVIII concentrate and close follow up
CASE 2

- 7 year old with post tonsillectomy bleeding on day 7 with pre- and post-operative coagulation screen
Case 3

- 14 year old female with Hgb 10 and low ferritin of 7
- Reports normal menstrual flow
VWD

- Basic science
- Prevalence
- Inheritance
- Presentation
- Diagnosis
- Treatment
- What’s new?
VWF: Basic Science

Slide courtesy: Dr. Robert Montgomery, MD
VWD: Prevalence

- Most common inherited bleeding disorder
- Estimated to occur in 1-3% of population
- Affects equally
  - Males and females
  - All racial groups
    - No consistent data regarding frequency differences among racial and ethnic groups

Mainly autosomal dominant inheritance

- Males and females equally affected
- Risk: 50% to each child

Type 2N and Type 3 are Autosomal Recessive

VWD: Autosomal Dominant Inheritance

Slide courtesy: Dr. Robert Montgomery, MD
VWD: Presentation

- **Mucosal-type bleeding**
  - Epistaxis
  - Easy bruising
  - Prolonged bleeding from wounds
  - Menorrhagia and post-partum hemorrhage

- **Excessive bleeding with injury**
  - Postoperative bleeding
  - Bleeding following dental extraction

- **Severe deficiency**
  - Gastrointestinal and joint bleeding

VWD: Diagnosis

- APTT
- Factor VIII activity
- VWF antigen: VWF:Ag
- **VWF Ristocetin cofactor: VWF:RCo**
- Multimer analysis
- Ristocetin Induced Platelet Aggregation: RIPA

VWD: Subtypes

- Divided into subtypes based upon VWF structure
  - **Type 1:**
    - Most common
    - Decrease in amount of VWF with normal protein structure
  - **Type 2:**
    - Less common *except* in Indiana!
    - Abnormal structure of VWF protein
  - **Type 3:**
    - Least common
    - Most severe
    - Absence of VWF protein
## VWD: Subtypes

<table>
<thead>
<tr>
<th>Type</th>
<th>FVIII</th>
<th>VWF:Ag</th>
<th>VWF:RCo</th>
<th>RIPA</th>
<th>Multimeric Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>All sizes present</td>
</tr>
<tr>
<td>2A</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>Absence of large and med forms</td>
</tr>
<tr>
<td>2B</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>Normal Absence of large forms</td>
</tr>
<tr>
<td>2M</td>
<td>Normal</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>All sizes present</td>
</tr>
<tr>
<td>2N</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>All sizes present</td>
</tr>
</tbody>
</table>

3 Absent Absent Absent Absent Absent

VWD: Treatment

- **DDAVP** ≡ Desmopressin acetate, testing is required to document response before use
  - Synthetic derivative of vasopressin
  - Parenteral administration: IV or SQ
  - Intranasal administration: Stimate®
    - Concentration 1.5 mg/ml vs. 1mg/ml used for Diabetes Insipidus

- Plasma-derived FVIII products containing high concentrations of intact VWF

VWD: Adjunctive Treatment

- **Antifibrinolytics** *
  - Aminocaproic Acid; Amicar®
  - Tranexamic acid; Lysteda®
  - Used to treat mucous membrane bleeding

- **Oral or parenteral estrogen** *

- **Fibrin glue** *

- **Local measures**
  - Example epistaxis: Amicar nasal spray, local moisture, pressure, Urgent QR, Hemcon, etc.

VWD: Treatment

**DDAVP**

- Increases plasma VWF concentrations by stimulating release from intracellular stores in endothelial cells
- Treatment of choice for type 1
- Variable response in types 2A and 2M
- Ineffective in type 3, not recommended in type 2B

VWD: Treatment

**VWF-Containing Concentrates**

- Currently available are plasma-derived, NAT* tested, and pathogen-inactivated → heat or solvent detergent treated
  - Humate-P®
  - Alphanate®
  - Wilate®
- Cryoprecipitate not recommended as it is not pathogen-inactivated

*NAT*: Nucleic acid amplification testing

VWD: What’s New

- Recombinant VWF concentrate
  - The PK of rVWF Ristocetin cofactor activity, VWF antigen, and collagen-binding activity were similar to those of the comparator plasma-derived (pd) VWF-pdFVIII

- Screening assays
  - Collagen-binding assay
  - VWF pro-peptide assay
  - GPIIb binding assay

- Diagnostic, subclassification assays
  - DNA analysis

Case 2: Outcome

- 7 year old with post tonsillectomy bleeding on day 7 and normal coagulation screen pre- and post-operatively

- Diagnosis: Type 1 VWD
  - VWF RCo: 30%; VWF Antigen: 35%; FVIII 40%; Multimers all bands present with decreased intensity

- Treated with Stimate and Amicar
Case 3: Outcome

- 14 year old with Hgb 10 and low ferritin of 7, thinks she has normal menstrual flow

- Diagnosis Type 1 VWD
  - VWF RCo 40%; VWF Ag 45%; FVIII 60%; Multimers all bands present with decreased intensity

- OCP’s, Iron supplements
Rare bleeding disorders

- Prevalence
- Common features
*More than 600 registered patients in database.
European Network of Rare Bleeding Disorders. [http://www.rbdd.eu/patient.htm](http://www.rbdd.eu/patient.htm); Slide courtesy ASPHO 2013.
Common Features of RBDs

- Generally autosomal recessive inheritance
- Severe manifestations in homozygotes or compound heterozygotes
- More common in racial groups practicing endogamous/consanguineous marriage
- Severe bleeding diatheses evident in some RBDs including intracranial (ICH) and umbilical stump hemorrhage


Slide courtesy ASPHO 2013
Common features of RBDs (cont)

- Common symptoms in women include
  - Menorrhagia
  - Excessive bleeding during childbirth
  - Hemoperitoneum during ovulation

- Typical symptom is excessive bleeding during invasive procedures

- Bleeding in mucosal tracts is frequent, unexplained feature

- Some deficiencies associated with uncommon manifestations
  - Afibrinogenemia: Intraosseous hemorrhage, splenic rupture, thrombosis

Slide courtesy ASPHO 2013
Common Features of RBDs (cont)

- Broad spectrum of clinical phenotypes
  - Ranges from asymptomatic to fatal hemorrhagic disorder

- RBDs include deficiencies of FI, FII, FV, FV/FVIII, FVII, FX, FXI, FXIII, PAI-1, Alpha -2 antiplasmin, factors II/VII/IX/X complex; rare inherited platelet disorders include Glanzmann thrombasthenia, Bernard-Soulier syndrome

- RBDs appear to be less severe than hemophilia A or B, with life- and limb-threatening symptoms definitely less frequent
  - Exceptions include factors X and XIII deficiencies and afibrinogenemia

Slide courtesy ASPHO 2013
11 year old male with melena and Hgb 5g/dl, PT 86 seconds, APTT 34 seconds, Fibrinogen 300 gm/dL
**FVII deficiency**

- Autosomal recessive disorder: 1 in 300,000-500,000

- Symptoms: Epistaxis, hematomas, menorrhagia, GI, CNS bleeding

- Treat for acute bleeds or prophylaxis: Replacement product → NovoSeven
  - 15-30 mcg/kg for acute bleeds
  - 90 mcg/kg/week prophylaxis usually as a divided dose

Case 5

- 6 week old female infant presents with lethargy and bulging fontanelle
- On examination extensive bruising and bleeding from the mouth
Laboratory Evaluation

- WBC: 10.9 K/cumm
- Hgb: 7.8 gm/dL
- Platelets: 417,000 K/cumm
- Fibrinogen: 360 mg/dL
- APTT/PT: APTT >100 seconds; PT >65 seconds

\[ \text{FII, VII, IX, X : all low at <5%} \]
**Vitamin K Deficiency**

- **VKDB**: vitamin K deficiency of the newborn

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>INCIDENCE</th>
<th>CLINICAL</th>
<th>ETIOLOGY/RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (1-7 days)</td>
<td>0.25-1.7%</td>
<td>ICH, GI &amp; umbilical bleeding</td>
<td>Idiopathic, maternal meds</td>
</tr>
<tr>
<td>Late (2-24 weeks)</td>
<td>0.04-0.07%</td>
<td>ICH, GI</td>
<td>Fat malabsorption, liver disease and breast feeding</td>
</tr>
</tbody>
</table>

Prophylaxis
- 0.5 mg IM or PO Vit K protects against early VKDB
- PO Vit K does not fully protect against late VKDB

Treatment response
- PO, SQ Vit K: Factor activities correct in 24-48 hours
- IV Vit K: Factor activities correct in 4-6 hours
- FFP: Acutely may help with some improvement in factor activities

“Take home” points for bleeding disorders

- Major diagnostic tool is a good history supplemented with a thorough physical examination
- Bleeding disorders are underdiagnosed due to a low index of clinical suspicion
- When in doubt – best to refer
- Hemophilia is most commonly seen in males
  - Manifests as deep tissue bleeding
  - Mild cases can be missed if not thoroughly investigated
- VWD is seen in both genders
  - Manifests as muco-cutaneous bleeding
  - Most common inherited bleeding disorder
“Take home” points for bleeding disorders

When to refer

- Abnormal coagulation laboratory evaluation
- Unusual bleeding symptom/symptoms even in the face of a normal laboratory evaluation
- Family history of a bleeding disorder or significant bleeding symptoms

Call 24-7:
317-871-0000 or 1-877-256-8837
Thank you