Pediatric Coagulation Case Studies for Blood Bankers

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Overview

- Introduction to pediatric hemostasis

- Congenital bleeding disorders & therapy
  - Factor VIII deficiency (Hemophilia A)
  - Von Willebrand Disease

- Acquired bleeding disorder
  - Trauma-induced massive transfusion

- Blood bank and transfusion medicine roles in therapy
Primary Hemostasis

*Interaction of platelet and endothelium that lead to formation of the platelet plug*
Blood vessel smooth muscle, fibroblasts, extracellular matrix contribute to vessel constriction.
Endothelial Cells and Hemostasis

- **Vasconstriction**
  - renin $\rightarrow$ bradykinin
  - platelet activating factor (PAF) $\rightarrow$ WBC adhesion

- **Vasodilatation**: Nitric Oxide (NO), PGI$_2$

- **Anticoagulation**: heparin/ dermatan sulfate
  - accelerates ATIII/HCII
  - activates thrombomodulin (TM)

- **Coagulation**: TF release

- **Fibrinolytic**: TPA, PAI-1 release

- **Vascular repair**: smooth muscle/ fibroblast proliferation
Secondary Hemostasis

Formation of Fibrin Clot
The Clotting Cascade: The old paradigm

**Intrinsic Pathway**
- Endotoxin
- PLT Aggregation
- Endothelial Damage
- Immune Complexes

**Extrinsic Pathway**
- Tissue Thromboplastin

**Clotting Cascade Diagram**

- XII → XI → IX → VIII → II → Thrombin → Fibrinogen → Fibrin
A New Way to View Coagulation

Adapted from Hoffman M, Monroe DM, III, Roberts HR. Blood Coag Fibrinol 1998;9:561-564; Used by Permission
Blood Flow

Endothelial Cell

Platelet

Monroe DM. Presented at: World Federation of Hemophilia Congress; May 19-24, 2002; Seville, Spain.
Blood Flow

Platelet

Endothelial Cell

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Platelet

Endothelial Cell

Monroe DM. Presented at: World Federation of Hemophilia Congress; May 19-24, 2002; Seville, Spain.
Role of Thrombin

- Activation of Fibrinogen, FV, VIII, XI, XIII
- Platelet activation
- TPA release from endothelial cell
- Complex with thrombomodulin: Protein C
- Thrombin activatable fibrinolysis inhibitor (TAFI)
Inhibitors to Coagulation

ATIII: Inactivates serine proteases

: Inhibitors in bold
Unique coagulation qualities in children

- Liver immaturity contributes to low hemostatic factors (vit k dependent) in infants compared to children and adults.

- Hemostatic factor activity decreases with degree of prematurity.

- 30 - 38 weeks gestation: coag factors range from 12% - 50% of adult levels.

- Full term 30% - 95% of adult levels.

- Hemostatic factors progress rapidly to 80% - 90% of adult ranges within 6 months to 1 year.
Developmental changes in the hemostasis system

- Normal platelet count, fibrinogen levels, FV (adult levels)
- Slightly prolonged INR (low Vit K factors)
- Elevated aPTT (low contact factors)
- Elevated vWF, FVIII
- Decreased ATIII, Pro C, Pro S, plasminogen
- Normal levels by age 6 months except Protein C (by adolescents)
- Elevated TPA, Plasminogen activator Inhibitor (PAI-1)
- Normal $\alpha_2$ anti-plasmin
## General Treatment Considerations

### Plasma Derived Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Dose</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet concentrate</td>
<td>10cc/kg</td>
<td>- Low plt; plt dysfunction</td>
</tr>
<tr>
<td>Apheresis platelets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>10-20 cc/kg</td>
<td>- Multi-factor coag</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- FII, V, X (XI, XIII) def</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>1- 2 units/5 -10kg</td>
<td>- Low fibrinogen, FXIII</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Platelet dysfunction</td>
</tr>
<tr>
<td>Prothrombin concentrate</td>
<td>75-100 U/kg</td>
<td>- Multiple Factor (Vitamin K ) def</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Liver Disease (?)</td>
</tr>
</tbody>
</table>
## General Treatment Considerations

### Plasma and Non-Plasma Derived Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Dose</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminocaproic Acid</td>
<td>100 mg/ kg (max 6 gm) Q6H</td>
<td>Excessive fibrinolysis</td>
</tr>
<tr>
<td>Tranexamic Acid</td>
<td>25mg/kg Q8hrs</td>
<td></td>
</tr>
<tr>
<td>DDAVP</td>
<td>0.3 mcg/ kg</td>
<td>Platelet dysfunction, VWD</td>
</tr>
<tr>
<td>Stimate</td>
<td>1-2 sprays (150 mcg/spray)</td>
<td></td>
</tr>
<tr>
<td>Factor concentrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- rFVIIa</td>
<td>20-30 mcg/ kg</td>
<td>FVII deficiency</td>
</tr>
<tr>
<td>- FVIII</td>
<td>40-50 U/ kg</td>
<td>FVIII deficiency</td>
</tr>
<tr>
<td>- FIX</td>
<td>80-100 U/ kg</td>
<td>FIX deficiency</td>
</tr>
<tr>
<td>- Humate-P</td>
<td>dose on risto cof units</td>
<td>VWD non-responsive to DDAVP/Stimate</td>
</tr>
</tbody>
</table>
Case 1

- 8 year old male severe factor VIII deficiency presents with neck pain and tingling in arms after diving through a hoop in the pool and hitting his head on the bottom of the pool. Parents delayed treatment by 2 days.

- Patient taken to ER by parents

- Patient usually receives Kogenate FS (second generation FVIII recombinant protein)
Case 1

What should be done first for the patient?
A factor VIII containing product should be administered immediately.
The does should be for a 100% factor correction (50 U/kg).

What should be done second for the patient?
Patient should have STAT CT scan of cervical spine after factor administration.

What laboratory tests should be done if any?
Unless an inhibitor is suspected or the patient and family aren’t able to give a good history of the type of hemophilia the patient has no laboratory testing needs. Eventually FVIII levels may be necessary for monitoring purposes.

How long should the patient be treated?
This is dependent upon the CT and neurologic findings.
Definitions: Hemophilia A and B

- Congenital bleeding disorder
  - X-linked

- Deficiency of factor VIII or IX
  - 80-85% VIII deficiency
  - Severe hemophilia (60%)
    - 15% moderate
    - 25% mild

- Prolongation of aPTT
Factor Replacement: FVIII and FIX Deficiencies

- 1u/kg raises FVIII levels by 2%
  - 1/2 life: 8 to 12 hrs

- 1u/kg raises FIX levels by 1%
  - 1/2 life: 20 to 24 hrs

- Dosing may be higher in pediatric patients
  - rFIX dosing = 1.4 x pFIX
## Classification of Hemophilia

<table>
<thead>
<tr>
<th>Type</th>
<th>FVIII/IX</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>&lt;1%</td>
<td>Spontaneous bleeds</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 to 5%</td>
<td>Trauma/surgery bleeds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occasional joint bleeds</td>
</tr>
<tr>
<td>Mild</td>
<td>6 to 40%</td>
<td>Major trauma/surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rare joint bleeds</td>
</tr>
</tbody>
</table>
Diagnosis at Birth

- Take a family history prior to delivery
  - Always order FVIII/IX levels-not just aPTT
  - Send cord blood

- 20 to 30% hemophilia pts have neg FH
  - High index of suspicion
  - Know patterns of bleeding
Diagnosis Patterns of Bleeding

- **Neonatal**: circumcision, umbilical cord, cephalohematoma

- **Infant**: tongue/teeth/frenulum, soft tissue (forehead, bruising, immunization)

- **Children**: hemarthrosis, muscle, soft tissue
Right Knee
Hemarthrosis
Bleeding in Hemophilia

- Spontaneous hemarthroses the hallmark
- Triggers: trauma and surgery
- Other bleeding manifestations
  - Muscle
  - CNS
  - Kidney
  - GI tract
Left-sided Iliopsoas Bleed
Subdural Hemorrhage
Retropharyngeal Bleed
Duration of Treatment

High Risk Hemorrhage

- Consider continuous infusion FVIII
- Maintain factor levels > 70% for two weeks
- Consider prophylaxis (40% to 50% correction q.o.d.) until problem resolved
  - Consider long-term prophylaxis for CNS bleed
- Surgery: Initial 100% correction
  > 50% levels: week 1
  > 30% levels: week 2
Case 2
13-year-old girl with active, severe menorrhagia with first period. History of recurrent epistaxis and easy bruising.

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>11.5 g/dL</td>
</tr>
<tr>
<td>Platelet count</td>
<td>110,000/μL</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>12 Minutes</td>
</tr>
<tr>
<td>VWF:RCo</td>
<td>15 (63-185)</td>
</tr>
<tr>
<td>VWF:Ag</td>
<td>40 (62-236)</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>50 (50-150)</td>
</tr>
<tr>
<td>Blood type</td>
<td>B pos</td>
</tr>
<tr>
<td>PT, PTT, Fibrinogen</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Next Steps and Results

- vWF multimer—decreased large molecular weight forms
- Family studies—mother c/w VWD
- Gene analysis—not done
- Platelet aggregation: Response to ristocetin at both “standard-dose” and “low-dose”
Von Willebrand Disease

**Type 2B**

- Abnormal platelet adhesion due to “gain-of-function”
- Increased affinity of vWF for platelet
- Loss of highest MW multimers due to adsorption from plasma
- Normal or mildly decreased VWF:Ag with decreased ristocetin cofactor
- Thrombocytopenia exacerbated by stress, age, pregnancy, DDAVP
Types of von Willebrand Disease

Quantitative Defects

Type 1: Hypoproteinemia (low amount of protein)
Type 3: Aproteinemia (no protein)

Qualitative Defects

Type 2: Dysproteinemia (dysfunctional protein)
Pathophysiologic Classification of vWD

Primary
Quantitative defect: type 1, type 3
Qualitative defect: type 2

Secondary
Platelet adhesion defect:
  – Loss-of-function
    Absent high MW multimers: type 2A
    Normal multimers: type 2M
  – Gain-of-function: type 2B
Factor VIII binding defect: type 2N
vWD versus Hemophilia: Making the distinction

Patient History

<table>
<thead>
<tr>
<th>VWD</th>
<th>Hemophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy bruisability</td>
<td>Hematomas</td>
</tr>
<tr>
<td>Hematomas</td>
<td>Hemarthrosis</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Muscle hemorrhage</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>Bleeding with tooth extraction &amp; surgery</td>
<td>Bleeding with tooth extraction &amp; surgery</td>
</tr>
</tbody>
</table>

Family History

vWD: usually autosomal dominant; rarely autosomal recessive homozygous or double heterozygous

Hemophilia: X-linked recessive
vWD by Sex and Race

- Affects men and women equally
- Affects all racial groups but varied levels
  - Higher levels of VWF:Ag in African-American (AA)
  - Decreased VWF:RCo/VWF:Ag in AA compared to Caucasians (0.79 vs 0.97)

Prevalence of vWD

- VWD is characterized for low penetrance and variable expressivity

- Estimated prevalence in epidemiological studies 1%

- More than 2/3 of the patients are asymptomatic (or mildly symptomatic)

- Prevalence of symptomatic disease is 1/10,000

Diagnosing vWD: Initial Evaluation

- Detailed personal and family history is key
- Screening laboratory values are often normal
  - Platelet count
  - Prothrombin time (PT)
  - Activated partial thromboplastin time (aPTT)
- Bleeding time (BT) is an insensitive screening tool for type 1 disease
- PFA: Platelet function analyzer; used more often

Standard Diagnostic Testing for vWD

- VWF antigen assay (VWF:Ag)
  - Protein quantification
  - Typically done by enzyme-linked immunosorbent assay (ELISA)
- FVIII clotting activity (FVIII:C)
  - Activity often parallels VWF levels

Standard Diagnostic Testing for VWD

- Ristocetin cofactor activity (VWF:RCo)
  - Functional assay using patient’s plasma and normal fixed platelets
  - Ristocetin induces platelet agglutination via VWF interaction with platelet receptor Ib/IX

- VWF multimer analysis
  - VWF protein displayed on agarose gel
  - VWF multimers are separated by size

Plasma vWF Multimers
vWF Levels Can Be Modified by Co-existing Conditions

- Conditions associated with higher vWF levels
  - Age
  - Acute and chronic inflammation
  - Diabetes
  - Malignancy
  - Pregnancy or oral contraceptive use
  - Stress; exercise
  - Hyperthyroidism

- Conditions associated with reduced vWF levels
  - Hypothyroidism
  - Blood type O

# VWF Levels: Influence of Blood Type

<table>
<thead>
<tr>
<th>Blood Type</th>
<th>Lower VWF:Ag Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type O</td>
<td>35.6 U/dL (mean 74.8 U/dL)</td>
</tr>
<tr>
<td>Type A</td>
<td>48.0 U/dL (mean 105.9 U/dL)</td>
</tr>
<tr>
<td>Type B</td>
<td>56.8 U/dL (mean 116.9 U/dL)</td>
</tr>
<tr>
<td>Type AB</td>
<td>63.8 U/dL (mean 123.3 U/dL)</td>
</tr>
</tbody>
</table>

VWF Levels and VWD

VWF levels:
- Normal
- VWD

<10 40 50 60
Mild VWD Type 1: Influence of Blood Type

- Mild bleeding appears to be common in the general population.
- By definition 14% of individuals type O will have VWF levels < 50u/dL.
- The overlap may trigger diagnosis of mild VWD type 1.
VWF-Containing Concentrates

- All currently available are plasma-derived and pathogen-inactivated (heat or solvent detergent treated, Nucleic acid testing)
  - Humate-P®
  - Alphanate®
  - Koate®-DVI

- Cryoprecipitate is not recommended as it is not pathogen-inactivated

Humate-P

Plasma based VWD product dosing

1 unit/kg VWF:RCo Units=1.5% rise in plasma levels

desired VWF:RCo%-baseline WWF:RCo % x wt in kg

\[ \frac{\text{Ratio of VWF:RCo to FVIII:C}}{2} \approx 2.5:1 \]
# Humate-P Severe Type 1 and 3

<table>
<thead>
<tr>
<th>Stressor</th>
<th>Dose IU/kg</th>
<th>Frequency</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major surgery</td>
<td>50</td>
<td>Daily</td>
<td>Trough F:VIII &gt;50% until healing complete</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>40</td>
<td>Daily or every other day</td>
<td>Trough F:VIII &gt;30% until healing complete</td>
</tr>
<tr>
<td>Dental extraction</td>
<td>30</td>
<td>Single dose</td>
<td>Factor VIII &gt;50% for 12 hours</td>
</tr>
<tr>
<td>Spontaneous bleeds</td>
<td>25</td>
<td>daily</td>
<td>Factor VIII &gt;50% for 3-4 days</td>
</tr>
</tbody>
</table>

Humate-P Study Group

- Pre-operative dose of 60-80 IU VWF:RCo/kg
- Maintenance dosing of 40-60 IU VWF:RCo/kg every 8-12 hours for 3 days
- If needed 40-60 IU VWF:RCo/kg daily for up to 7 days
- Goal nadir of VWF:RCo activity >50%

Humate-P and Type 2 VWD

- **Major surgery**
  - Loading dose 60-80 U/kg VWF:RCo
  - 30-40 U/Kg VWF:RCo every 12 hours for 7 days

- **Minor surgery**
  - loading dose 40-60 U/kg VWF:RCo
  - repeat 40 U/kg VWF:RCo in 24 hours

- **Dental extractions/Mucocutaneous bleeds**
  - 40-60 U/kg VWF:RCo
Cryoprecipitate

MASAC: cryoprecipitate should not be used except in an emergency situation where DDAVP or VWF containing plasma derived products are not available and delay of treatment would be life or limb-threatening.

MASAC #112, March 2001
9 year old female in a MVC
Pt weight estimated at 25 kg
TBV: 1400 – 2100 ml (~ 4 – 6 pRBC units)
Patient received 25 units of pRBCs within first 3 hours. (3 – 4 blood volumes)
7 (250 cc) doses of FFP given in total
No cryoprecipitate or platelets ordered or given

Initial labs at start of Trauma: Fibrinogen not ordered, PT- 46 sec, PTT – 156 sec, plt ct – 94k
Labs: approx 3 – 3.5 hours into resuscitation
Fibrinogen: 55 mg/dl, PT – 27 secs, PTT 78.5 secs, plt ct 76K

patient expired
## Total Blood Volume Estimation in Children

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Total Blood Volume (ml)</th>
<th>Units of red blood cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 3</td>
<td>10</td>
<td>700</td>
<td>2 – 3</td>
</tr>
<tr>
<td>4 - 5</td>
<td>20</td>
<td>1400</td>
<td>4 – 5</td>
</tr>
<tr>
<td>6 - 7</td>
<td>30</td>
<td>2100</td>
<td>6 – 7</td>
</tr>
<tr>
<td>8 - 9</td>
<td>40</td>
<td>2800</td>
<td>8 – 9</td>
</tr>
<tr>
<td>10 - 12</td>
<td>50</td>
<td>3500</td>
<td>10 – 11</td>
</tr>
<tr>
<td>Teen</td>
<td>60</td>
<td>4200</td>
<td>12 - 13</td>
</tr>
</tbody>
</table>
Dilutional Coagulopathy resulting from Massive Transfusion

FIGURE 26-1 Decreases in platelet count and fibrinogen as increasing blood volumes are replaced with packed red cells and crystalloid solutions. Each patient is represented by a solid continuous line. (Used with permission from Murray DJ et al: Anesthesiology 69:839, 1988.)
Trauma Blood Bank Procedures

- Emergency Release Blood: O negative (2 – 5 minutes)
  - trying to send a specimen prior to transfusion
- Type specific blood: (5 – 10 minutes) no crossmatch
- Type and crossmatched blood (10 – 20 minutes)
- Thawing AB negative plasma products (FFP and cryo)
- 1 platelet pheresis set aside
- Blood bank technologists notifying –
  - pathology residents, transfusion medicine fellows, transfusion medicine attendings
- Calling ER or OR for laboratory tests to stay ahead with plasma products
Laboratory Monitoring

Suggested schema for monitoring in bleeding patient during massive transfusion

1. PT, aPTT, fibrinogen, platelet count
2. Repeat after each plasma product cycle administered.

NO SUBSTRATE  NO CLOT
Transfusion Triggers for Blood Product Replacement in Massive Transfusion

- Platelet Count < 100,000 --- transfuse plts (10-15 ml/kg)
- Fibrinogen < 100 mg/dl --- transfuse cryo (1-2u/10kg) and/or FFP (10-15 cc/kg)
- PT and/or aPTT > 1.5 x control --- transfuse FFP (10-15 cc/kg)
Collaboration between Trauma Teams and Blood Bank to Optimize Transfusion Support for Trauma Patients

- Notifying blood bank prior to Trauma patient arrival (enroute)

- Blood Bank proactively support all trauma staff during massive transfusion episodes.

- Set up algorithm for reflexive testing with regard to **STAT PT, Fibrinogen, and platelet testing** to better guide plasma and platelet replacement therapy in an attempt to return patient to hemostatic equilibrium
Just Remember:

All bleeding... eventually stops

Confucius  505 BC
Any Questions?