Treatment of Coagulopathy in Neonates

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Disclosures

• Octapharma – consultant
• Biomet – medical advisory board
• Immucor - consultant
Learning Objectives

• Review the clotting cascade and hemostasis in the newborn

• Examine specific coagulopathic situations in the neonate that result in bleeding
  a. Hemorrhagic Disease of the Newborn due to vitamin K deficiency
  b. Hypoxic-Ischemic Encephalopathy (HIE) Bleeding and hypothermic treatment

• Describe different treatment choices for bleeding in the newborn
Overview of Hemostasis

A “New” Way to View Procoagulant Coagulation

http://trialx.com/curetalk/wp-content/blogs.dir/7/files/2011/05/diseases/Platelet_Aggregation-3.jpg
Primary Hemostasis

*Interaction of platelet and endothelium that lead to formation of the platelet plug*
Platelet-Vessel Interaction

Blood vessel smooth muscle, fibroblasts, extracellular matrix contribute to vessel constriction
Endothelial Cells and Hemostasis

- Vasconstriction
  - renin → bradykinin
  - platelet activating factor (PAF) → WBC adhesion
- Vasodilation: Nitric Oxide (NO), PGI₂
- Anticoagulation: heparin/dermatan sulfate
  - accelerates ATIII/HCIІ
  - 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

**Extrinsic Pathway**

1. **Endotoxin**
2. **PLT Aggregation**
3. **Endothelial Damage**
4. **Immune Complexes**
5. **XII**
6. **XI**
7. **IX**
8. **VIII**
9. **VII**
10. **X**
11. **v**
12. **Thrombin**
13. **Fibrinogen**
14. **Fibrin**

**Intrinsic Pathway**
New Way to View Coagulation

Cell Based Model of Hemostasis

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

TF-Bearing Cell

VIIa

TF

Platelet

Platelet

Xa

VIII/vWF → VIIIa + Free vWF

Amplification begins here

TF-Bearing Cell

VIIa

TF

Priming Dose of Thrombin

VIIa

TF

Activated Platelet

vWF = von Willebrand Factor.

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

Now enough thrombin burst to propagate additional platelet activation and more FIIa and subsequent fibrin formation.
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

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

**Inhibitors in bold**

- APC + PS
- TFPI
- ATIII + Heparin Sulfate
- Plasmin

**Protein C**
- Thrombin
- C4b BP

**ATIII** : Inactivates serine proteases

**Inhibitors in bold**
TISSUE FACTOR PATHWAY
(Extrinsic Pathway)
"Tissue Damage"

Protein Concentrations

<table>
<thead>
<tr>
<th>Component</th>
<th>Molecular Weight</th>
<th>Plasma Half Life</th>
<th>Plasma Concentration μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (I)</td>
<td>330,000</td>
<td>120 hr</td>
<td>9.09</td>
</tr>
<tr>
<td>Prothrombin (II)</td>
<td>72,000</td>
<td>100 hr</td>
<td>1.388</td>
</tr>
<tr>
<td>Factor V</td>
<td>330,000</td>
<td>25 hr</td>
<td>0.03</td>
</tr>
<tr>
<td>Factor VII</td>
<td>50,000</td>
<td>5 hr</td>
<td>0.01</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>330,000</td>
<td>10 hr</td>
<td>0.0003</td>
</tr>
<tr>
<td>Factor IX</td>
<td>56,000</td>
<td>20 hr</td>
<td>0.08928</td>
</tr>
<tr>
<td>Factor X</td>
<td>58,800</td>
<td>65 hr</td>
<td>0.13605</td>
</tr>
<tr>
<td>Factor XI</td>
<td>160,000</td>
<td>65 hr</td>
<td>0.031</td>
</tr>
<tr>
<td>Factor XII</td>
<td>80,000</td>
<td>60 hr</td>
<td>0.375</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>320,000</td>
<td>150 hr</td>
<td>0.03125</td>
</tr>
<tr>
<td>Protein C</td>
<td>62,000</td>
<td>6 hr</td>
<td>0.0645</td>
</tr>
<tr>
<td>Protein S</td>
<td>69,000</td>
<td>60 hr</td>
<td>0.1449</td>
</tr>
<tr>
<td>Protein Z</td>
<td>62,000</td>
<td>ND</td>
<td>0.0355</td>
</tr>
<tr>
<td>Prekallikrein</td>
<td>86,000</td>
<td>ND</td>
<td>0.5814</td>
</tr>
<tr>
<td>HK</td>
<td>110,000</td>
<td>170 hr</td>
<td>0.6363</td>
</tr>
<tr>
<td>Fibrinectin</td>
<td>450,000</td>
<td>60 hr</td>
<td>0.6667</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>58,000</td>
<td>72 hr</td>
<td>5</td>
</tr>
<tr>
<td>Plasminogen</td>
<td>90,000</td>
<td>Glu 60 hr, Lys 18 hr</td>
<td>2.4</td>
</tr>
<tr>
<td>Urokinase</td>
<td>53,000</td>
<td>10 min</td>
<td>0.001887</td>
</tr>
<tr>
<td>Heparin Cofactor II</td>
<td>66,000</td>
<td>60 hr</td>
<td>1.3636</td>
</tr>
<tr>
<td>Alpha 2 Antiplasmin</td>
<td>63,000</td>
<td>60 hr</td>
<td>0.9524</td>
</tr>
<tr>
<td>Protein C Inhibitor</td>
<td>57,000</td>
<td>18 min</td>
<td>0.0702</td>
</tr>
<tr>
<td>Alpha 2 Macroglobulin</td>
<td>725,000</td>
<td>ND</td>
<td>2.8966</td>
</tr>
</tbody>
</table>

Inhibitors in black
*Thrombophilia gene mutation
ND-Not Determined
## Characteristics of Clotting Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Incidence</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (I)</td>
<td>rare</td>
<td>afibrinogen-recessive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hypofibrinogen-dominant</td>
</tr>
<tr>
<td>Prothrombin (II)</td>
<td>rare</td>
<td>recessive</td>
</tr>
<tr>
<td>V</td>
<td>1/1 million</td>
<td>recessive</td>
</tr>
<tr>
<td>VII</td>
<td>1/500,000</td>
<td>recessive</td>
</tr>
<tr>
<td>VIII</td>
<td>1/5,000</td>
<td>x-linked</td>
</tr>
<tr>
<td>IX</td>
<td>1/30,000</td>
<td>x-linked</td>
</tr>
<tr>
<td>X</td>
<td>1/500,000</td>
<td>recessive</td>
</tr>
<tr>
<td>XI</td>
<td>rare</td>
<td>recessive</td>
</tr>
<tr>
<td>XII</td>
<td>1/50 (heterozygous)</td>
<td>recessive</td>
</tr>
<tr>
<td>XIII</td>
<td>rare</td>
<td>recessive</td>
</tr>
<tr>
<td>VWF</td>
<td>1/100</td>
<td>Type 1 dominant</td>
</tr>
<tr>
<td></td>
<td>1/500,000</td>
<td>Type 3 recessive</td>
</tr>
</tbody>
</table>
## Characteristics of Clotting Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Invivo $T^{1/2}$</th>
<th>Synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (I)</td>
<td>4 days</td>
<td>liver/megakaryocyte</td>
</tr>
<tr>
<td>Prothrombin (II)</td>
<td>3 days</td>
<td>liver</td>
</tr>
<tr>
<td>V</td>
<td>36 hrs</td>
<td>liver/mega/EC</td>
</tr>
<tr>
<td>VII</td>
<td>5 hrs</td>
<td>liver</td>
</tr>
<tr>
<td>VIII</td>
<td>12 hrs</td>
<td>liver/RE system</td>
</tr>
<tr>
<td>IX</td>
<td>22 hrs</td>
<td>liver</td>
</tr>
<tr>
<td>X</td>
<td>40 hrs</td>
<td>liver</td>
</tr>
<tr>
<td>XI</td>
<td>80 hrs</td>
<td>liver/mega</td>
</tr>
<tr>
<td>XII</td>
<td>60 hrs</td>
<td>liver</td>
</tr>
<tr>
<td>XIII</td>
<td>10 days</td>
<td>liver/mega</td>
</tr>
<tr>
<td>VWF</td>
<td>12 hrs</td>
<td>endothelial cells/mega</td>
</tr>
</tbody>
</table>
Unique Coagulation Qualities in Pediatrics

- Liver immaturity contributes to low hemostatic vitamin K dependent factors II, VII, IX, X, PC, PS 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 Hemostatic System

- Normal platelet count, fibrinogen levels, FV (adult levels)
- Slightly prolonged INR (low Vit K factors)
- Prolonged 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 alpha2 anti-plasmin

Jaffray J and Young G. Pediatr Clin N Am 60;2013: 1407-1417
Maturation of the Coagulation Proteins
Birth to Adulthood

<table>
<thead>
<tr>
<th>Procoagulants</th>
<th>Birth</th>
<th>1 mo</th>
<th>6 mo</th>
<th>1–5 y</th>
<th>11–16 y</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>FII</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>FV</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Adult</td>
</tr>
<tr>
<td>FVII</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Adult</td>
</tr>
<tr>
<td>FVIII</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
</tr>
<tr>
<td>FIX</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Adult</td>
</tr>
<tr>
<td>FX</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Adult</td>
</tr>
<tr>
<td>FXI</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Adult</td>
<td>Decreased</td>
<td>Adult</td>
</tr>
<tr>
<td>FXII</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Adult</td>
<td>Decreased</td>
<td>Adult</td>
</tr>
<tr>
<td>FXIII</td>
<td>Decreased</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
</tr>
<tr>
<td>PK</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
</tr>
<tr>
<td>HMWK</td>
<td>Decreased</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticoagulants</th>
<th>Birth</th>
<th>1 mo</th>
<th>6 mo</th>
<th>1–5 y</th>
<th>11–16 y</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
</tr>
<tr>
<td>α2M</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Adult</td>
</tr>
<tr>
<td>HCII</td>
<td>Decreased</td>
<td>Increased</td>
<td>Increased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Adult</td>
</tr>
<tr>
<td>Protein C</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Adult</td>
</tr>
<tr>
<td>Protein S</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
</tr>
</tbody>
</table>

**Abbreviations:** HMWK, high-molecular-weight-kininogen; PK, prekallikrein.
All values are compared with adult means and ranges.

- Denotes values that are within the adult lower range but less than the adult mean.
- Denotes values that are within the adult mean, but 15% of the values are less than the adult low range.

Data from Refs. 6-8

Jaffrey J and Young G. *Pediatr Clin N Am* 60;2013: 1407-1417
Coagulation Testing Comparison Birth to Adulthood

Table 2
Comparison of coagulation testing between the normal term infant or child and the adult

<table>
<thead>
<tr>
<th>Coagulation Tests</th>
<th>Birth</th>
<th>1 mo</th>
<th>6 mo</th>
<th>1-5 y</th>
<th>11-16 y</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>1.15</td>
<td>0.95</td>
<td>0.99</td>
<td>0.97</td>
<td>0.99</td>
<td>1.0</td>
</tr>
<tr>
<td>aPTT</td>
<td>1.2</td>
<td>1.27</td>
<td>1.11</td>
<td>1.10</td>
<td>1.14</td>
<td>1.0</td>
</tr>
<tr>
<td>INR</td>
<td>1.2</td>
<td>0.95</td>
<td>0.95</td>
<td>0.96</td>
<td>0.97</td>
<td>1.0</td>
</tr>
<tr>
<td>TCT</td>
<td>1.12</td>
<td>1.17</td>
<td>1.22</td>
<td>0.84</td>
<td>0.81</td>
<td>1.0</td>
</tr>
<tr>
<td>D-dimer</td>
<td>8.17</td>
<td>1.22</td>
<td>1.22</td>
<td>1.39</td>
<td>1.50</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Values represent the ratio between infant and child means compared with adult means. A ratio greater than 1 reflects a higher mean value in the infant/child compared with the adult mean.

Data from Refs. 6–8,13

Jaffrey J and Young G. Pediatr Clin N Am 60;2013: 1407-1417
Platelet Facts in Newborns

• Platelet structure similar to adults

• ~ Half the number of alpha$_2$ adrenergic receptors are on neonatal platelets accounting for poor response to epi stimuli (Corby et al. Dev Pharmacol Ther 1981; Davidson et al. Am J Dis Child. 1991)

• At 2 months alpha$_2$ adrenergic receptors reach adult levels (Davidson et al. Am J Dis Child. 1991)

• Granule release from neonatal platelets is reduced (Israels et al. Pediatr Res. 1987)
Platelet Facts in Newborns

• Agonist-induced secretion of platelet granule content is reduced in term and preterm neonates due to immature signal transduction pathways not granule content. (Israels et al. Pediatr Res. 1987)

• Reduced response to collagen due to impairment of calcium mobilization. (Israels et al. Pediatr Res. 1990)

Platelet Facts in Newborns

• Relative deficiency of platelet function.  

• No difference plt cts adults versus full term infants  
  (mean MPV same).  (Beverly et al. Early Human Develop. 1984; Andrew et al.  

• Preterm infants mean plt cts lower but still within nl range  

• Increased number cirrculating mega progenitors and  
  mature megas in newborns & preterm infants.  
Platelet Facts in Newborns


Functional Differences Between Neonatal and Adult Platelets

- Decreased aggregation responses to agonists (including: epi, collagen, ADP, thrombin, thromboxane A₂ analogues)
- Decreased agonist-induced exposure of the fibrinogen binding site on the GPIIb-IIIa complex
- Decreased agonist-induced granule secretion
- Decreased agonist-induced calcium mobilization
- Increased vWF-mediated platelet adhesion and agglutination
- Shorter bleeding times and PFA closure times

# Neonatal Platelet Function

## Table 1. Summary of selected neonatal platelet function literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cord blood</th>
<th>Peripheral blood</th>
<th>Mode of assessment</th>
<th>Agonist(s) tested</th>
<th>Platelet function—as compared with adult</th>
<th>Authors’ conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>X</td>
<td></td>
<td>Platelet aggregation, thromboelastography, bleeding time</td>
<td>Thrombin</td>
<td>Platelet aggregation: ↓</td>
<td>The hyporesponsiveness observed for platelet aggregation may balance the hypercoaguability observed in the TEG testing.</td>
</tr>
<tr>
<td>7</td>
<td>X</td>
<td></td>
<td>Measurement of $^{14}$C arachidonic acid release and thromboxane generation through thin-layer chromatography</td>
<td>Thrombin</td>
<td>AA uptake: ↑</td>
<td>Increased AA uptake may signify that neonatal platelet membranes may be less stable. Decreased thromboxane generation may be balanced by increased AA uptake.</td>
</tr>
<tr>
<td>8</td>
<td>X</td>
<td></td>
<td>Radioimmunoassay of thromboxane B$_2$ production</td>
<td>Thrombin</td>
<td>TXB$_2$ production in response to collagen: =</td>
<td>There are subtle differences in arachidonic acid metabolism between adult and neonatal platelets, but these do not account for the differences in aggregation.</td>
</tr>
<tr>
<td>9</td>
<td>X</td>
<td></td>
<td>Aggregation, serotonin secretion, protein phosphorylation, flow cytometry for GP IIb/IIIa, platelet adhesion, inositol phosphorylation, AA release, and TXB$_2$ formation</td>
<td>Thrombin</td>
<td>All tests in response to collagen: ↓↓</td>
<td>Decreased response to collagen is due to impaired signal transduction.</td>
</tr>
<tr>
<td>10</td>
<td>X</td>
<td>X</td>
<td>Flow cytometry: GP Ib, GP IIb/IIIa</td>
<td>Thrombin</td>
<td>GPIb, GP IIb/IIIa expression for all agonists: ↓</td>
<td>Neonatal platelets have decreased function.</td>
</tr>
</tbody>
</table>

# Neonatal Platelet Function

<table>
<thead>
<tr>
<th>X</th>
<th>Calcium mobilization</th>
<th>Collagen</th>
<th>Thrombin</th>
<th>All agonists: </th>
<th>Impaired calcium release causes the different neonatal platelet response.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>PLC (beta) activation, GTPase activity, calcium mobilization</td>
<td>U46619</td>
<td>Thrombin</td>
<td>All agonists: </td>
<td>Signal transduction is impaired. At rest, the receptor quantity is equivalent.</td>
</tr>
<tr>
<td>X</td>
<td>PFA-100</td>
<td>Collagen/ADP</td>
<td>Coll/ADP: ↑(shorter closure time)</td>
<td>Shorter closure times in neonates are associated with increased hematocrit and increased von Willebrand factor.</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>Flow cytometry of mepacrine fluorescent staining</td>
<td>Thrombin</td>
<td>Number of dense granules: </td>
<td>Neonatal platelets have deficient platelet dense granule secretion when compared with adults.</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>Flow cytometry: CD41, CD42, CD61, CD62, and PAC-1</td>
<td>TRAP</td>
<td>GP IIb/IIIa, GP Ib, P sel expression: ↓</td>
<td>Neonatal platelets have decreased function that lasts at least 12 d from birth.</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>PFA-100</td>
<td>Collagen/ADP</td>
<td>Coll/ADP: ↑(shorter closure time)</td>
<td>Peripheral blood and cord blood platelets are not equivalent.</td>
<td></td>
</tr>
<tr>
<td>17,18</td>
<td>Clotting times, annexin V, phospholipid content</td>
<td>Thrombin</td>
<td>Clotting times were shorter</td>
<td>No difference in PL content or PS exposure between adult and neonatal platelets.</td>
<td></td>
</tr>
</tbody>
</table>

Publications are listed by first author and year of publication. Type of blood used for neonatal samples is listed as either cord blood or peripheral blood. The results of the platelet function testing with regard to neonatal vs. adult platelet function is noted: ↑ denotes that neonatal platelet responsiveness exceeds adult platelet responsiveness, ↓ denotes that neonatal platelet responsiveness is less than adult platelet responsiveness, and  denotes that neonatal and adult platelet responsiveness are equivalent. ADP, adenosine diphosphate; PL, phospholipid; PLC, phospholipase C; PS, phosphatidylyserine; TEG, thromboelastography; TRAP, thrombin receptor agonist peptide.
Although infants have lower levels of coagulation proteins than adults the typical healthy infant has a much lower incidence of thrombosis without an increased risk of bleeding.

Table 3
Vitamin K deficiency classification

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Classic</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>First 24 h</td>
<td>2–7 d</td>
<td>1–6 mo (even later)</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Maternal use of drugs that interfere with vitamin K metabolism (warfarin, anticonvulsants)</td>
<td>None (all newborns are prone)</td>
<td>Disorders that interfere with vitamin K intake (cystic fibrosis, other GI fat malabsorption disorders, chronic antibiotic use, liver disease)</td>
</tr>
<tr>
<td>Bleeding sites</td>
<td>ICH, GI, umbilical stump, bruising</td>
<td>ICH, GI, umbilical stump, bruising</td>
<td>ICH, GI, mucocutaneous</td>
</tr>
<tr>
<td>Treatment</td>
<td>Recognition of drugs that can cause this and eliminating them from maternal use</td>
<td>Prevention with neonatal vitamin K administration</td>
<td>Parenteral vitamin K</td>
</tr>
</tbody>
</table>

Abbreviation: GI, gastrointestinal; ICH, intracranial hemorrhage.

Jaffrey J and Young G. Pediatr Clin N Am 60;2013: 1407-1417
Prevalence of Initial Coagulopathy and Associated Outcomes in Neonates with Moderate-to-Severe Hypoxic-Ischemic Encephalopathy (HIE)

- Hypoxic-ischemic encephalopathy (HIE) is a significant cause of neonatal morbidity and mortality.

- Hemostasis is often disrupted, with disseminated intravascular coagulation seen in up to 20% of patients in clinical trials.

- The prevalence of initial coagulopathy among infants with HIE and the association with bleeding events has not been fully described.

- Therapeutic Hypothermia likely plays a role in the coagulopathy associated with HIE.

Pakvasa M et al. PAS Poster 2015
Dilutional Coagulopathy Coagulation Factors

Plasma proteins reduced to 30-40% after 1-2 blood volumes replaced
Dilution of Coagulation Factors

- Fibrinogen < 100 mg/dl after 1.5 blood volumes replaced

- Coagulation factors < 25% after 2 blood volumes replaced

- Platelets < 50,000 after 2 blood volumes replaced
Hypothermia Decreases Coagulation Factor Activity

<table>
<thead>
<tr>
<th>Temp °C</th>
<th>Percent of Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II</td>
</tr>
<tr>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td>35</td>
<td>82</td>
</tr>
<tr>
<td>37</td>
<td>100</td>
</tr>
</tbody>
</table>

Effect of Body Temperature on Coagulation Studies (PTT)

Other Consequences of Hypothermia

• Decreased $O_2$ delivery to tissues due to increase $O_2$ affinity for hemoglobin
• Decreased tissue perfusion secondary to vasoconstriction
• Impaired platelet function
• Decreased drug metabolism (ie. citrate) caused by liver cooling and resulting in hypocalcemia
• Cold blood transfused through central line with tip near sinoatrial node can cause fatal arrhythmias

pH Effect on Coagulation Factors

• Acidosis can have profound effect on procoagulant function and should be considered a contributor to coagulopathic bleeding

• Example: prothrombinase complex (V,X,II) shows a 50% reduction in activity as a patient’s plasma pH drops from 7.4 to 7.2.
Objectives: HIE and Coagulopathy

- To evaluate the prevalence of initial coagulopathy upon admission in neonates with moderate-to-severe HIE.
- To determine the association between severity of coagulopathy and abnormal bleeding events.

Pakvasa M et al. PAS Poster 2015
Methods: HIE and Coagulopathy

- Retrospective observational cohort study at a single academically-affiliated hospital in Atlanta, GA from 1/2008 to 12/2013.
- Inclusion criteria: 1) Birth weight > 1800g; 2) Moderate-to-severe HIE.
- Of 63 infants in cohort, 50 had coagulation testing.
- Definitions:
  - Coagulopathy defined as a PT > 18 seconds.
  - Moderate-to-severe HIE determined using criteria from Neonatal Research Network trials.
  - Bleeding events ascertained by a diagnosis or notation of abnormal bleeding in physician, nursing or respiratory therapist documentation.
Methods: HIE and Coagulopathy

- Statistical Analysis
  - Patient characteristics compared between infants with and without bleeding events.
  - Frequency of abnormal bleeding events compared by severity of initial PT prolongation.
  - Multivariable logistic regression used to determine if the level of PT prolongation was independently associated with bleeding events, after controlling for the severity of HIE.

Pakvasa M et al. PAS Poster 2015
Results: Maternal and Neonatal Characteristics

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>No bleeding (n=42)</th>
<th>Bleeding (n=21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (yr)</td>
<td>28 ± 8</td>
<td>30 ± 5</td>
<td>0.25</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12 (29%)</td>
<td>8 (38%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>25 (60%)</td>
<td>9 (43%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (10%)</td>
<td>3 (14%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Delivery by cesarean</td>
<td>31 (74%)</td>
<td>15 (71%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Severe trauma</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>7 (17%)</td>
<td>10 (48%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Uterine rupture</td>
<td>4 (10%)</td>
<td>4 (19%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>1 (2%)</td>
<td>1 (5%)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neonatal characteristics</th>
<th>No bleeding (n=42)</th>
<th>Bleeding (n=21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>3302 ± 712</td>
<td>3373 ± 699</td>
<td>0.71</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>39 ± 1</td>
<td>39 ± 2</td>
<td>0.68</td>
</tr>
<tr>
<td>Female gender</td>
<td>20 (48%)</td>
<td>7 (33%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Inborn</td>
<td>27 (64%)</td>
<td>13 (62%)</td>
<td>0.85</td>
</tr>
<tr>
<td>1 min Apgar, median (IQR)</td>
<td>1 (1-2)</td>
<td>1 (0-2)</td>
<td>0.56</td>
</tr>
<tr>
<td>5 min Apgar, median (IQR)</td>
<td>3 (2-5)</td>
<td>3 (1-4)</td>
<td>0.99</td>
</tr>
<tr>
<td>Delivery room care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>37 (88%)</td>
<td>17 (81%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Chest compressions</td>
<td>17 (41%)</td>
<td>7 (33%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>12 (29%)</td>
<td>8 (38%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Saline administration</td>
<td>7 (17%)</td>
<td>6 (29%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Severity of HIE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>29 (69%)</td>
<td>15 (71%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Severe</td>
<td>13 (31%)</td>
<td>6 (29%)</td>
<td></td>
</tr>
<tr>
<td>Therapeutic hypothermia</td>
<td>42 (100%)</td>
<td>20 (95%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Death (in hospital)</td>
<td>7 (17%)</td>
<td>3 (14%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Death from hemorrhage</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Number of blood product transfusions, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed Red Blood Cell</td>
<td>0 (0-0)</td>
<td>0 (0-1)</td>
<td>0.14</td>
</tr>
<tr>
<td>Platelet</td>
<td>0 (0-0)</td>
<td>0 (0-2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>1 (0-2)</td>
<td>2 (1-4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>0 (0-0)</td>
<td>0 (0-1)</td>
<td>0.007</td>
</tr>
<tr>
<td>Any product transfusion</td>
<td>24 (57%)</td>
<td>17 (81%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
### Results: Coagulation Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>No bleeding</th>
<th>Bleeding</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT &gt; 18sec</td>
<td>50</td>
<td>20/32 (63%)</td>
<td>16/18 (89%)</td>
<td>0.046</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>50</td>
<td>19 (17-29)</td>
<td>30 (21-46)</td>
<td>0.008</td>
</tr>
<tr>
<td>PTT (sec)</td>
<td>44</td>
<td>54 (49-63)</td>
<td>71 (59-135)</td>
<td>0.005</td>
</tr>
<tr>
<td>INR (sec)</td>
<td>49</td>
<td>2 (1-3)</td>
<td>3 (2-4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>44</td>
<td>160 (104-196)</td>
<td>70 (62-158)</td>
<td>0.10</td>
</tr>
<tr>
<td>Fibrinogen &lt;100</td>
<td>44</td>
<td>7/29 (24%)</td>
<td>9/15 (60%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Pakvasa M et al.  *PAS Poster 2015*
Results: Association between severity of coagulopathy and abnormal bleeding events

<table>
<thead>
<tr>
<th>Factor (univariable)</th>
<th>Odds ratio for bleeding (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (per 10 sec increase)</td>
<td>1.60 (1.06-2.41)</td>
<td>0.02</td>
</tr>
<tr>
<td>PT (categorized)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18 sec</td>
<td>1 (reference)</td>
<td>-</td>
</tr>
<tr>
<td>18-30 sec</td>
<td>2.77 (0.47-16.5)</td>
<td>0.26</td>
</tr>
<tr>
<td>30 or greater sec</td>
<td>8.57 (1.44-50.9)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

| Factor (multivariable)               |                                 |      |
| PT (per 10 sec increase)             | 1.90 (1.11-3.25)                | 0.02 |
| HIE severity (severe vs. moderate)   | 0.27 (0.05-1.59)                | 0.15 |
Results: Site of abnormal bleeding events

- Subgaleal or subdural: 16%
- Upper GI: 20%
- Pulmonary: 28%
- Lower GI: 4%
- Intracranial: 8%
- Intraabdominal: 4%
- Bleeding around umbilicus: 8%
- Other bleeding site: 12%

Pakvasa M et al.  PAS Poster 2015
Results: Risk of any abnormal bleeding by initial level of PT prolongation

Pakvasa M et al. PAS Poster 2015
Conclusions: HIE and Coagulopathy

- Initial coagulopathy was highly prevalent among infants with moderate-to-severe HIE.
- Estimated prevalence of 72% (95% CI 58-84%)
- The severity of coagulopathy was associated with an increased risk of any abnormal bleeding, independent of the severity of HIE.
- Although blood product transfusion and bleeding was common among this population, fatal hemorrhage was very uncommon.
- Further studies are needed to evaluate transfusion practices and its effects on bleeding and other outcomes among infants with moderate-to-severe HIE.

Pakvasa M et al. PAS Poster 2015
## Treatment Choices for Bleeding in Neonates: Blood Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Dose</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet concentrate</td>
<td>10-15 ml/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 ml/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>
</tbody>
</table>
## Treatment Choices for Bleeding in Neonates: Drug and Factor 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>25 mg/kg Q8hrs</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>
Off-label Use of NovoSeven RT (rFVIIa) in Neonates

- Examined off-label use rFVIIa in US tertiary care pediatric hospitals
- Multicenter, retrospective looking at Pediatric Health Information System administrative dataset from 2000-2007
- 4942 rFVIIa admissions investigated, 3764 patients and 74% (3655) were off-label

Off-label Use of NovoSeven RT (rFVIIa) in Neonates

Off-Label Recombinant Factor VIIa Use and Thrombosis in Children: A Multi-Center Cohort Study
Char M. Witmer, MD, Yuan-Shung Huang, MS, Kevin Lynch, PhD, Leslie J. Raffini, MD, MSCE, and Samir S. Shah, MD, MSCE

Table I. Subject demographics by admission

<table>
<thead>
<tr>
<th>Age at admission (n, %)</th>
<th>Total rFVII admissions n = 4942</th>
<th>Off-label admissions n = 3685</th>
<th>Label admissions n = 1297</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 year</td>
<td>1555 (31.5)</td>
<td>1455 (39.8)</td>
<td>100 (7.8)</td>
</tr>
<tr>
<td>1-5 years</td>
<td>1292 (26.1)</td>
<td>778 (21.3)</td>
<td>514 (39.9)</td>
</tr>
<tr>
<td>6-11 years</td>
<td>897 (18.2)</td>
<td>588 (16.1)</td>
<td>309 (24)</td>
</tr>
<tr>
<td>12-18 years</td>
<td>1196 (24.2)</td>
<td>834 (22.8)</td>
<td>384 (28.3)</td>
</tr>
<tr>
<td>Sex (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3329 (67.4)</td>
<td>2100 (57.5)</td>
<td>1229 (95.5)</td>
</tr>
<tr>
<td>Female</td>
<td>1612 (32.6)</td>
<td>1554 (42.5)</td>
<td>58 (4.5)</td>
</tr>
<tr>
<td>Race (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3204 (64.8)</td>
<td>2460 (67.3)</td>
<td>744 (57.8)</td>
</tr>
<tr>
<td>Black</td>
<td>961 (19.4)</td>
<td>586 (16)</td>
<td>375 (29.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>158 (3.2)</td>
<td>133 (3.6)</td>
<td>25 (1.9)</td>
</tr>
<tr>
<td>Native American</td>
<td>37 (0.7)</td>
<td>20 (0.6)</td>
<td>17 (1.3)</td>
</tr>
<tr>
<td>Other</td>
<td>438 (8.9)</td>
<td>331 (9.1)</td>
<td>107 (8.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>144 (2.9)</td>
<td>125 (3.4)</td>
<td>19 (1.5)</td>
</tr>
<tr>
<td>Disposition (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>3116 (63.1)</td>
<td>1932 (52.9)</td>
<td>1184 (92)</td>
</tr>
<tr>
<td>Died</td>
<td>1279 (25.9)</td>
<td>1258 (34.4)</td>
<td>21 (1.6)</td>
</tr>
<tr>
<td>Home health service</td>
<td>303 (6.1)</td>
<td>241 (6.6)</td>
<td>62 (4.6)</td>
</tr>
<tr>
<td>Other</td>
<td>244 (4.9)</td>
<td>224 (6.1)</td>
<td>20 (1.6)</td>
</tr>
</tbody>
</table>

**Admitting service does not indicate the prescriber for rFVIIa.

Figure 1. Admitting service specialty for off-label admissions.

Off-label Use of NovoSeven RT (rFVIIa) in Neonates

- Mortality rate in the off-label group was 34% (1258/3655)
- Thrombotic events occurred in 10.9% (399/3655) of the off-label admissions
- 10 fold increase in annual rate of off label admits (2 to 20.8 per 10,000 hospital admits, P< 0.001)

Off-label Use of NovoSeven RT (rFVIIa) in Neonates

Conclusions

• Off-label use of rFVIIa in hospitalized children is increasing rapidly despite the absence of adequate clinical trials demonstrating safety and efficacy.

• Thrombotic events are common and mortality is high among pediatric patients receiving off-label rFVIIa.

• Further studies are needed to determine if adverse events due to rFVIIa.

Bleeding Treatments

- NovoSeven RT FVIIa Package Insert

- In January 2010 the BLACKBOX warning for thrombosis was issued by the FDA
Summary

- Neonatal hemostasis is different than adult hemostasis. Platelet function, hyporesponsiveness, and decreases in both procoagulant and anticoagulant proteins characterize the differences.

- Classic hemorrhagic disease of the newborn is caused by immature liver functioning resulting in lower functioning vitamin K dependent factors produced by the neonate.

- There is increased bleeding in infants with HIE who initially have moderate to severe coagulopathy and are treated with therapeutic hypothermia.

- Treating bleeding in infants requires careful thought and off-label FVIIa use has become less indicated due to increased risk of thrombosis and no improvement in mortality.
Just Remember:

All bleeding... eventually stops

Confucius 505 BC
Thank you for your attention!!
Any Questions?