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Neonatal Thromboembolism: Management Challenges and Potential Solutions

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Speakers: Jennifer L. Meldau, MSN CPNP CPHON RN-BC and Yaser Diab, MBBS
Children's National Health System
Disclosures

• Yaser Diab: no disclosures
• Jennifer Meldau: no disclosures
Objectives

• Review important aspects of the neonatal hemostatic system and their impact on the pathophysiology, diagnosis and treatment of neonatal thromboembolic events

• Discuss diagnosis and management of common neonatal thromboembolic events

• Explore the role of pediatric multi-disciplinary anticoagulation consult services with focus on Advanced Practice Nurse Practitioner-managed service model
Physiology of Hemostasis in Neonates

- Coagulation factors cannot cross the placenta
- 5 weeks gestation: FVII, FVIII, FIX, FX, AT, PC
- 20 weeks gestation: All procoagulants & anticoagulants in plasma
- At birth:

<table>
<thead>
<tr>
<th>Decreased Hemostasis</th>
<th>Increased Hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyporeactive platelets</td>
<td>↑VWF (UHMW multimers)</td>
</tr>
<tr>
<td>↓FII, FVII, FIX, FX, FXI and FXII</td>
<td>↓AT, PC, PS</td>
</tr>
<tr>
<td>Fetal Fibrinogen</td>
<td>↓Overall fibrinolytic capacity</td>
</tr>
<tr>
<td></td>
<td>NL FV, FVIII, FXIII</td>
</tr>
</tbody>
</table>
Neonatal hemostatic system

- Neonatal hemostatic system remains physiologically intact but lacks adequate reserve under stress conditions.
  → The risk of bleeding/thrombosis is increased in the sick neonates, and is further increased in premature infants.

Thrombosis

Bleeding
Epidemiology of Neonatal Thrombosis

- Neonates have the highest risk for thromboembolism among pediatric patients
- 45–55% occur in preterm population
- M=F

<table>
<thead>
<tr>
<th>Data source</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian registry</td>
<td>2.4 per 1000 NICU admissions</td>
</tr>
<tr>
<td>German registry</td>
<td>5.1 per 100,000 live births</td>
</tr>
<tr>
<td>Dutch registry</td>
<td>0.7 per 100,000 live births</td>
</tr>
<tr>
<td>PHIS database</td>
<td>44-75 per 10,000 admissions</td>
</tr>
</tbody>
</table>

Rates of VTE diagnosis according to age group, from 2001 to 2007.

- <28 d
- 1 mo to <1 y
- 1 to <6 y
- 6 to <13 y
- 13 to 18 y
- All age groups

*p < .001 for all groups*
Common neonatal TE events

Neonatal TE

Venous TE
- Non-CNS
  - CVC-related extremity DVT
  - UVC-related IVC thrombosis
  - UVC-related portal vein thrombosis
  - Renal vein thrombosis
- Purpura fulminans
- CNS
  - CSVT

Arterial TE
- Non-CNS
  - UAC-related aortic thrombosis
  - Catheter-related peripheral arterial thrombosis
  - Non-catheter related arterial thrombosis
- CNS
  - Perinatal AIS

CNS

Renal vein thrombosis

CSVT

Purpura fulminans
Risk factors for thromboembolism

- Neonatal: Infection, CHD, prematurity/LBW, NEC, dehydration, polycythemia, thrombophilia
- Perinatal: Meconium aspiration, low Apgars
- Maternal: Chorioamnionitis, diabetes, hypertension, thrombophilia
- Iatrogenic: Catheters, ECMO, surgery
CVC-related thrombosis

- CVC=UVC, PICC, others
- Thrombosis
- 89% of neonatal venous thrombosis is CVC-related
- Overall incidence 9.2% (1.1–66.7%)
- No significant difference in incidence with different CVCs
## Sites of CVC-related thrombosis

<table>
<thead>
<tr>
<th>Site of thrombus</th>
<th>UVC-related (n)</th>
<th>Surgically inserted CVC (n)</th>
<th>Unspecified type of CVC (n)</th>
<th>Overall (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrium</td>
<td>12</td>
<td>0</td>
<td>23</td>
<td>35</td>
</tr>
<tr>
<td>Left atrium</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Unspecified location in the heart</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Ductus venosus</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Right atrium—inferior vena cava junction</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Inferior vena cava</td>
<td>23</td>
<td>1</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>Hepatic vein (± intrahepatic portal vein)</td>
<td>43</td>
<td>0</td>
<td>14</td>
<td>57</td>
</tr>
<tr>
<td>Superior vena cava</td>
<td>0</td>
<td>1</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Subclavian vein</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>101</td>
<td>2</td>
<td>59</td>
<td>162</td>
</tr>
</tbody>
</table>

Clinical Presentation

- Catheter dysfunction
- Limb or face swelling, discoloration of the skin, distention of the superficial veins
- **Persistent unexplained thrombocytopenia**
- Persistent chylous effusion (Cardiac patients)
- SVC syndrome
- Asymptomatic identified incidentally on radiologic studies
Diagnosis

- Compression Doppler ultrasound.
- Echocardiography
- Venography (MR, CT, conventional): proximal central venous system
Portal Vein Thrombosis

- Likely under-recognized
- UVC related in almost all cases
- Incidence: variable → 3.6 per 1000 admissions

Presentation

- Nonspecific or absent clinical and laboratory signs

<table>
<thead>
<tr>
<th>Indication for US</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal evaluation of hypertension</td>
<td>6</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>26</td>
</tr>
<tr>
<td>Inappropriate UVC placement</td>
<td>6</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>9</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>5</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>46</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>22</td>
</tr>
<tr>
<td>Sepsis</td>
<td>6</td>
</tr>
</tbody>
</table>

* Diagnosis: Doppler US

Renal vein thrombosis

• The most prevalent non-catheter-related thromboembolism during the neonatal period
• Accounts for up to 20% of all neonatal TEs
• Males 67%
• Unilateral 70% (Left 64%), IVC involved (40%)
• Incidence:
  • Germany: 2.2 per 100 000 live births
  • Canada: 2.3 cases per year over a 10-year period in Montreal
  • International: 0.5 per 1000 NICU admissions
Presentation and diagnosis

- Hematuria (56%)
- Palpable flank mass (45%)
- Thrombocytopenia (48%)
- Full triad (22%)
- Renal insufficiency (56%)
- Hypertension (Rare)

Diagnosis: Doppler US
CSVT

- 40% of pediatric CSVT occurs in neonates
- Incidence: at least 2.6 per 100,000
- Venous infarcts in > 50%

Presentation and diagnosis

- Subtle and non-specific
  - Seizures
  - Lethargy
  - IVH: CSVT is the most frequently recognized cause of symptomatic IVH, and is associated with basal ganglia and thalamic hemorrhage in term neonates
  - Focal CNS deficits are rare

- Diagnosis: CTV or MRV

Peripheral arterial thrombosis

• Catheter-related thrombosis
  • Indwelling catheter
    • UAC → aortic thrombosis
    • PAL → LE or UE arterial thrombosis
  • Cardiac catheterization: → LE (femoral) artery thrombosis

• Non-catheter-related thrombosis: rare
  • Spontaneous neonatal aortic thrombosis (SNAT)

• Incidence:
  • Indwelling UAC: up to 32% (symptomatic in 3%)
  • Indwelling PAL 3% (55% neonates)
  • Cardiac catheterization: 11% (57% neonates)
Presentation and diagnosis

- Absent pulses
- BP difference of >10 mmHg in legs
- Decreased skin temperature
- Skin discoloration
- Prolonged capillary refill
- Hypertension
- UAC-related aortic thrombosis: asymptomatic identified incidentally on radiologic studies
- SNAT: just like critical aortic coarctation

- Diagnosis: Doppler US
Perinatal AIS

• Arterial stroke that occurs between 20 weeks of fetal life through the 28th postnatal day, confirmed by neuroimaging or neuropathologic studies

• 2 types:
  • Symptomatic neonatal AIS
  • Presumed Perinatal Ischemic Stroke

• Incidence: 1 in 2300 live births

Presentation and diagnosis

- Symptomatic neonatal AIS: seizures within a day after birth and without focal deficits or encephalopathy
- Presumed Perinatal Ischemic Stroke: seizures or emerging hemiparesis in infancy/childhood

Diagnosis: diffusion weighted MRI and MRA
Purpura fulminans

• A rare hematological emergency
• Few hours or days after birth:
  • Skin lesions: macules → skin necrosis
  • DIC
  • Large vessel thrombosis
• Severe protein S/C deficiency due to homozygous or compound heterozygous mutations
• FFP (10–20 ml/kg every 8–12 h)

Management of neonatal TEs

• Published guidelines:
  • ACCP-2012
  • AHA 2008
  • AHA 2011
  • AHA 2013
  • BCSH 2011
  • ISTH 2015

  ❖ Chest. 2012 Feb;141(2 Suppl):e737S-e801S.
Management outline

• **No antithrombotic therapy**
  → monitor clinically/radiologically
  • Bleeding risk outweighs benefit
  • Clinically asymptomatic thrombosis
    • Small/non-occlusive
    • Non-critical site
    • Chronic
    • Trigger removed
  • AIS

• **Antithrombotic therapy**
  • Anticoagulation:
    • UFH
    • LMWH
    • ?Fondaparinux
    • ?DTIs (Argatroban and Bivalirudin)
  • Thrombolysis:
    • Systemic: life/organ/limb threatening thrombosis
    • ?CDT
Symptomatic catheter-related thrombosis

• Venous thrombosis → can keep catheter
  • Remove catheter after 48-72 hours of anticoagulation if:
    • Not needed
    • Not working
    • Thrombosis progression during anticoagulation

• Arterial thrombosis → remove catheter
Duration of anticoagulation

- Venous thrombosis
  - Treat x 6 weeks
  - Resolution → D/C therapy
  - No resolution → Continue x 3 months total
  - Continue (prophylactic doses) after completion of therapy if trigger still present

- Arterial thrombosis:
  - Treat until resolution for up to 3 months
  - Assess response at 2 weeks, 6 weeks and 3 months
Thrombophilia testing

• ISTH 2002: all pediatric patients with thrombosis should to be tested!
• Challenges in neonates:
  • Required sample volume for comprehensive thrombophilia testing is prohibitive
  • Interpretation of borderline results is difficult
• Testing is not helpful:
  • AIS: [Blood. 2017 Jul 20;130(3):382]
• Testing could be helpful:
  • Unprovoked thrombosis
  • Recurrent thrombosis
  • ?Non-catheter related thrombosis
Long-term follow-up

- Extremity DVT: monitor for PTS for at least 2 years
- Portal vein thrombosis: monitor for portal HTN for at least 5 years
- Renal vein thrombosis: monitor for HTN, renal dysfunction for at least 5 years
- Peripheral arterial thrombosis: monitor for limb-length discrepancy and chronic arterial insufficiency
- CSVT/AIS: f/u with neurology

NP Service Model

• How it works
  • Daily rounding by NP
  • Provides consistency at teaching hospital
  • Teaching for families, nursing, residents, fellows, etc
  • Increased availability
  • Guideline/protocol driven
  • Reminders for labs, imaging, d/c and f/u needs
Our experience with NP managed anticoagulation service

• Less:
  • Improperly administered medication (Insuflon™, incorrect sites, etc.)
  • Inconsistent or incomplete therapy
  • Loss to f/u
  • Varied management from each attending
Our experience with NP managed anticoagulation service (continued)

• More
  • IV enoxaparin in critical care units
  • More quickly therapeutic (appropriate dose recommendations)
  • Subcutaneous injection teaching on floors in preparation for discharge
  • Educational material provided to each family
  • Safer discharges with appropriate dose ordered
IV Enoxaparin


**TABLE 2. Comparison of Therapeutic Enoxaparin (Target Antifactor Xa Level, 0.5–1 U/mL) According to Administration Route in Infants and Children More than 3 Months Old**

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV Enoxaparin (n = 30 Courses Given to 17 Patients)</th>
<th>Subcutaneous Enoxaparin (n = 26 Courses Given to 39 Patients)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>8 (4–56)</td>
<td>29 (7–85)</td>
<td>0.34</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>14 (4–56)</td>
<td>12 (7–14.9)</td>
<td>0.21</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>11 (65)</td>
<td>19 (60)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiac disease, n (%)</td>
<td>12 (71%)</td>
<td>21 (72%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Duration enoxaparin given (d)</td>
<td>8 (5–28)</td>
<td>12 (7–27)</td>
<td>0.37</td>
</tr>
<tr>
<td>Baseline platelet count (x10^3)</td>
<td>293 (165–480)</td>
<td>275 (205–370)</td>
<td>0.75</td>
</tr>
<tr>
<td>Baseline partial thromboplastin time (s)</td>
<td>33 (29–41)</td>
<td>33 (31–40)</td>
<td>0.69</td>
</tr>
<tr>
<td>Baseline international normalized ratio</td>
<td>1.19 (1.07–1.31)</td>
<td>1.21 (1.07–1.40)</td>
<td>0.70</td>
</tr>
<tr>
<td>Baseline anhrobin (%)</td>
<td>60 (44–88)</td>
<td>76 (69–102)</td>
<td>0.05</td>
</tr>
<tr>
<td>Baseline creatinine (mg/dL)</td>
<td>0.80 (0.40–0.60)</td>
<td>0.40 (0.20–0.60)</td>
<td>0.16</td>
</tr>
<tr>
<td>Time required to achieve target anticoagulation levels (d)</td>
<td>4 (2–23)</td>
<td>9 (4–19)</td>
<td>0.30</td>
</tr>
<tr>
<td>Proportion of patients who achieved target levels on initial dosing, n (%)</td>
<td>8 (40%)</td>
<td>14 (39)</td>
<td>1.00</td>
</tr>
<tr>
<td>No of dose adjustments</td>
<td>3 (1–6)</td>
<td>2 (0–3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Dose adjustments per day of therapy</td>
<td>2 (0–3)</td>
<td>1 (0–2)</td>
<td>0.89</td>
</tr>
<tr>
<td>Time in target range (d)</td>
<td>4 (2–23)</td>
<td>9 (5–19)</td>
<td>0.23</td>
</tr>
<tr>
<td>Percent time in the target range</td>
<td>70 (45–94)</td>
<td>75 (60–90)</td>
<td>0.71</td>
</tr>
<tr>
<td>Major or clinically relevant hemorrhage, n (%)</td>
<td>1 (5)</td>
<td>2 (9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Radiologic response, n (%)</td>
<td>Complete: 7 (34%)</td>
<td>14 (50)</td>
<td>1.00</td>
</tr>
<tr>
<td>Partial</td>
<td>1 (6)</td>
<td>6 (21.5)</td>
<td>0.72</td>
</tr>
<tr>
<td>No resolution</td>
<td>2 (11%)</td>
<td>2 (7)</td>
<td>0.36</td>
</tr>
<tr>
<td>No follow-up studies available</td>
<td>3 (12%)</td>
<td>6 (21.2)</td>
<td>0.72</td>
</tr>
<tr>
<td>Anticoagulation failure, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Data are reported as median (interquartile range or frequency, n) and analyzed using Mann-Whitney U test or Fisher exact test, as appropriate.
Development of inpatient pediatric anticoagulation management service: the advanced practice nurse practitioner service model 2015 ISTH 13 (Suppl2) p400
Questions?

• Thank you!
• ydiab@childrensnational.org
• JMeldau@childrensnational.org
Questions?

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