Pediatric Thrombosis

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Pediatric H/O
Objectives:

• Understand which children are at greatest risk of thrombosis
• Principles of evaluation and treatment of thrombotic episodes
• Considerations for Thrombophilia evaluation
Epidemiology
Overall Thrombotic Risk Model

• Patients with low-level of baseline hyper-coagulability (no thrombophilia)
  – precipitating events

• Patients with high-level of baseline hyper-coagulability (History of thrombophilias)
  – Sub-clinical triggers
  – Appearance of “idiopathic” or “unprovoked” event
Epidemiology

- Highest incidence of thrombosis in children
  - Neonates
  - Adolescents
Neonatal Epidemiology

• Highest risk group in the pediatric population
• Thrombosis Incidence
  – 2.4/1000 NICU Admissions
• Catheters associated with:
  – 80+% of Venous Thrombi
  – 90% of Arterial Thrombotic Complications
• Renal Vein Thrombosis
  – Most common non-catheter related thrombotic complication

Older Children & Adolescents

“Other” Co-Morbid Predispositions

- Catheters
- Obesity
- Diabetic Ketoacidosis
- Sepsis
- Oral Contraceptives

- Nephrotic Syndrome
- Cystic Fibrosis
- Short Gut Syndrome
- Infections
- Pregnancy
- Autoimmune Disease
Virchow’s Triad
Neonatal Risk

• Intimal Injury:
  – Catheters
  – Polycythemia
  – Shock
  – Perinatal Asphyxia

• Abnormal Blood Flow:
  – Catheters
  – Congenital Heart Disease

• Developmentally Prothrombotic:
  – Decreased levels of Natural Anti-coagulants:
    • Protein C, Protein S, AntiThrombin III
  – Decreased levels of Fibrinolytic Proteins:
    • Esp. Plasminogen
Upper Extremity DVTs:

Prophylaxis

- **Aspirin:**
  - Most experience in Congenital Heart Disease with vascular shunt devices

- **Low-Dose Heparin:**
  - 3-5 Units/hr
  - Commonly used
  - Improves duration of catheter patency
    - Patency most likely represents absence of local thrombus

- **Heparin Capping:**
  - Broviac / Hickman CVLs
  - Implantofix / Port-a-cath CVLs

Andrew M. Developmental Hemostasis: Relevance to Newborns and Infants.
Evaluation & Management
Signs & Symptoms

• DVT:
  – Poorly Functioning Catheters
  – Edematous extremity
  – Plethoric extremity
  – Warm extremity
  – Painful extremity

• PE:
  – Cough, SOB, Hemoptysis
  – Tachycardia
Signs or symptoms of suspected DVT

- Clinical probability
  - Low clinical probability
    - D-dimer test
      - Negative
        - Exclude DVT
      - Positive
        - Venous ultrasonography
          - Positive
            - Diagnose DVT
          - Negative
            - Exclude DVT
  - Intermediate or high clinical probability
    - Venous ultrasonography
      - Positive
        - Diagnose DVT
      - Negative
        - D-dimer test
          - Negative
            - Exclude DVT
          - Positive
            - Serial venous ultrasonography
              - Negative
                - Exclude DVT
              - Positive
                - Diagnose DVT
Pearls

Consider:

• Venography as the gold standard (MRV)
• D-dimer in all cases
• CT Angio-gram for patients with Pulmonary Sx
Therapeutic Goals

• Prevent thrombus growth and/or embolization

• Restore blood flow (rapidly, when necessary)

• Minimize long-term sequelae
Thrombolysis & Thrombectomy

• Thrombolysis:
  – Reserved for patients with life-, organ-, or limb-threatening thrombi
  – Contraindicated for patients at increased risk of hemorrhage:
    • Recent surgery or trauma
    • Stroke – limited pediatric data
  – Should be administered under the supervision of an experienced Hematologist

• Surgical Thrombectomy:
  – Can be curative
  – High risk, technically difficult procedure
  – May cause further intimal damage – relapse?
  – Preferred for patients with increased risk of hemorrhage

IVC Filtration

- Overwhelming opinion in the literature is avoidance in the majority of Pediatric Patients
  - Inadequate data

- Generally reserved for:
  - Anticoagulation Contraindicated in setting of proven DVT
  - Anticoagulation Failure (PE despite adequate anticoagulation)

- When needed, temporary filters preferred
  - Inadequate long-term follow-up data

Kinney TB. Update on Inferior Vena Cava Filters. JVascIntervRadiol 2003;14:425-40.
Heparin

• Standard Heparin (vs. Low Molecular Weight)
  – Easily reversible (Protamine Sulfate)
  – Short T½
  – Dose Variability:
    • Infants have higher dose requirements than older children
      – Bolus: 75-100 Units/kg (vs. 50-75)
      – Maintenance: Mean = 28 Units/kg/hour (vs. 20)
  – Monitoring:
    • Frequent (ACT, aPTT, anti-Factor Xa)
  – IV Access required
  – Disadvantages:
    • Frequent monitoring is necessary
    • Risk of hemorrhage
    • Risk of HIT/T
      – Thrombocytopenia or Platelet Count <50% baseline

Andrew M. Developmental Hemostasis: Relevance to Newborns and Infants.
Heparin

- Standard Heparin (vs. Low Molecular Weight ~ Lovenox/Enoxaparin)
  - Irreversible (partial w/ protamine)
  - Long T½
  - Dose Variability:
    - Infants have higher dose requirements than older children
      - ~1.6 mg/kg/dose (vs. 1)
  - Monitoring:
    - Infrequent (anti-Factor Xa)
  - No IV access necessary
  - Limited SQ sites for administration?
  - Disadvantages:
    - Compliance
    - Osteoporosis?

Coumadin® (Warfarin)

- Frequent monitoring is necessary:
  - Infants are exquisitely sensitive due to relative Vitamin K deficiency
  - INR affected by:
    - Diet
      - Breast Milk is low in Vit K
      - TPN (pediatric) and Commercial Formulas are high in VK
    - Medications affecting p450 metabolism
    - Intercurrent illnesses (esp. gastroenteritis or Abx Rx)
- Should be avoided during the first year of life when possible
  - Higher risk of hemorrhage
  - Dose instability
- Less risk of osteopenia
- Oral administration

Bovill E et al. Vitamin K1 Metabolism and the Production of des-Carboxy Prothrombin and Protein C in the Term and Premature Neonate. Blood 81:77, 1993
## Anticoagulation

<table>
<thead>
<tr>
<th>Acutely</th>
<th>Convalescent</th>
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</thead>
<tbody>
<tr>
<td><strong>High Risk:</strong></td>
<td><strong>Short Courses:</strong></td>
</tr>
<tr>
<td>– Standard Heparin</td>
<td>– Enoxaparin</td>
</tr>
<tr>
<td><strong>Low Risk:</strong></td>
<td>– Warfarin</td>
</tr>
<tr>
<td>– Enoxaparin</td>
<td><strong>Chronic Anticoagulation:</strong></td>
</tr>
<tr>
<td></td>
<td>– Warfarin</td>
</tr>
<tr>
<td></td>
<td>– Enoxaparin</td>
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</tbody>
</table>
Duration of Therapy

- Highly individualized
  - Further investigation is needed
- Supportive Care or Therapy should be monitored with objective studies
  - Short courses of 2-6 weeks may be adequate
- Relapse, extension, or residual thrombus indicates need for long-term therapy (minimum of 3-6 months)
- If continued risk (CHD/catheter/protein defect) is present a longer course should be considered
- Indefinite therapy for:
  - first relapse with protein defect
  - second relapse without

Anticoagulant Duration

• “Risk Group” Stratification:
  – Ongoing Multi-institution Study
    • Low Risk:
      – Brief Inciting Events
      – 6 wks (Thrombus Resolution and no thrombophilia)
        vs.
      – 3 mos (Residual Thrombus or thrombophilia)
    • High Risk:
      – Multiple Thrombophilia or “High Risk” Lab Profile
      – Early thrombolysis followed by
      – 6 mos vs. 12 mos

• End Points:
  – Recurrent TE and/or Post-Phlebitic Syndrome

Multi-institutional studies in progress.
Ending Therapy

- Thrombus Resolved or 6 months
  - Whichever 1st
- D-dimer assay one month after end of therapy: If positive resume anticoagulation and re-evaluate after an additional 18 months.

Figure 2. Cumulative Incidence of and Hazard Ratios (HRs) for Main Outcomes. The graph compares the outcomes among patients who had a normal D-dimer level with those among patients who had an abnormal level and either resumed or stopped anticoagulation therapy.

Long-Term Follow-up

• Post-phlebitic Syndrome
  – Chronic Venous Insufficiency
    • Pain w/ walking or ADLs
    • Chronic edema
    • Venous ulceration
    • Varicosities (collateral vessels)

• Recurrent TE
  – Pulmonary Hypertension
  – Life-Threatening Embolic Disease
Thrombophilia Studies
Thrombophilia History

• Co-morbid Medical Conditions
• FMHx:
  – Deep Venous Thrombosis / Pulmonary Embolism
  – Anticoagulation – why?
  – Early Myocardial Infarction or Cerebral Vascular Accident
  – Frequent pregnancy loss, SGA, or prematurity
  – Sudden Unexplained Death
  – Autoimmune Diseases
Hemostasis

Platelet

Clotting Factors

Vessel Wall
Anti-Coagulant System

Tissue Factor

fVIIa

f IXa + Ca, PL

f IX

f Xa + Ca, PL

f X

Prothrombin

Thrombin

Fibrinogen

Slippery Pipes:
Endothelium

Trigger Guard:
Tissue Factor Pathway Inhibitor

Cleaver:
Protein C / Protein S Complex

Inhibitor:
Anti-Thrombin III

Drano:
Fibrinolytic System
Thrombophilia in Adults w/ DVT

- **Protein Deficiencies:**
  - Anti-Thrombin III ~4.8%
  - Protein C ~4.3%
  - Protein S ~4.3%

- **aPC Resistance**
  - Factor V<sub>Leiden</sub> ~40%

- **Elevated Prothrombin Levels**
  - Prothrombin G20210A ~16%

**Total**: ~69.4%
The diagnosis of an inherited thrombophilia does not change treatment recommendations

<table>
<thead>
<tr>
<th>1st episode DVT:</th>
<th>Duration of anticoagulation</th>
</tr>
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<tbody>
<tr>
<td>transient risk factor</td>
<td>3 months (1A)</td>
</tr>
<tr>
<td>idiopathic</td>
<td>6-12 months (1A) consider indefinite therapy (2A)</td>
</tr>
<tr>
<td>thrombophilia (non-LA)</td>
<td>6-12 months (1A) consider indefinite therapy (2C)</td>
</tr>
</tbody>
</table>

7th ACCP evidence based guidelines

Slide courtesy L. Michaels
Justification for Screening

Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors

Ulrike Nowak-Göttl, Ralf Junker, Wolfhart Kreuz, Arnold von Eckardstein, Andrea Kosch, Natascha Nohe, Rosemarie Schobess, and Silke Ehrenforth, for the Childhood Thrombophilia Study Group

Blood 2001;97:858-862.
Laboratory Studies at time of Acute Thrombosis ??? Or Later

- DIC Screen:
  - CBC, PT, aPTT, Thrombin Time, Fibrinogen, D-dimer
- Protein C Activity
- Protein S Activity
- Antithrombin III Activity
- Consider:
  - Mixing Studies for PT & aPTT if prolonged
  - dRVVT, StaClot, ACL Ab, β₂-GPI Ab
Antiphospholipid Antibody Syndrome

- Autoimmune Acquired Prothrombotic Disorder
- Very High Risk for recurrent thromboembolic disease
  - both venous and arterial
- Indefinite duration anticoagulation recommended +/- immunosuppression
- Strict Diagnostic Criteria
Antiphospholipid Syndrome

• Clinical criteria (≥1 must be present):
  1. Vascular thrombosis:
     - ≥ 1 clinical episode of, objectively confirmed, arterial, venous, or small vessel thrombosis
  2. Pregnancy morbidity:
     - ≥ 1 unexplained fetal death @ ≥ 10 weeks EGA
     - ≥ 1 premature birth (≤ 34th week of gestation) due to eclampsia, severe pre-eclampsia, or placental insufficiency
     - ≥ 3 unexplained consecutive spontaneous abortions @ <10 weeks EGA

Revised Sapporo/Sydney Criteria. JTH 2006;4:295-306
Antiphospholipid Syndrome

- Laboratory criteria (≥1 must be present):
  - LA (+) ≥ 2 occasions, at least 12 weeks apart, according to ISTH guidelines:
    - prolonged PL-based clotting assay, lack of correction with 1:1 mix, and correction with excess PL
  - ACLA and/or anti-β2 glycoprotein-I antibody:
    - medium or high IgG and/or IgM isotype titer ≥ 2 occasions, at least 12 weeks apart
    - Standardized ELISA assays

Revised Sapporo/Sydney Criteria. JTH 2006;4:295-306
Consider Thrombophilia Studies

- Factor V Leiden
  - and/or activated protein C resistance
- prothrombin G20210A mutation

- lipoprotein (a)
- elevated factor VIII, IX, XI
- elevated fibrinogen
- hyperhomocysteinemia and/or MTHFR C677T polymorphism
- tPA deficiency
- PAI-1 elevation
- MTHFR A1298C mutation
- euglobulin clot lysis time
- plasminogen deficiency
- high plasminogen activator inhibitor
- heparin cofactor II deficiency
- spontaneous platelet activation
- platelet receptor polymorphisms
- factor VII–activating protease (FSAP) variant Marburg I
- elevated thrombin-activatable fibrinolysis inhibitor
- thrombin-activatable fibrinolysis inhibitor AFI-438 G/A
- thrombomodulin polymorphisms
- other factor V polymorphisms
- endothelial protein C receptor mutations
- Protein Z / ZPI inhibitor
In patients with VTE, family history is a poor predictor of test results

<table>
<thead>
<tr>
<th>Family history</th>
<th>Patients with positive testing for inherited thrombophilia</th>
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<tbody>
<tr>
<td>Negative</td>
<td>32%</td>
</tr>
<tr>
<td>Positive</td>
<td>42%</td>
</tr>
</tbody>
</table>

Healthy Children w/ Family History of DVT or Thrombophilia

• Screening is rarely indicated:
  – Risk assessment limited by heterogeneity of genotype and phenotype
  – No guidelines for management
  – Potential risk of anticoagulation outweighs benefit
  – May inhibit ability to obtain life/disability insurance
  – Ethical concerns: autonomy, assent, consent
  – Appropriate age for screening unknown
  – Unnecessary anxiety
Anticipatory Guidance

• Good Hydration Habits
  – Note to School!
• Regular Exercise
• Heart Healthy Diet & Lifestyle
• Avoidance of prolonged sedentary activity:
  – Planes, Trains, & Automobiles
• Non-estrogen contraception
  – Progestins (1\textsuperscript{st} or 2\textsuperscript{nd} generation vs 3\textsuperscript{rd})?
• Family planning
  – Discuss need for prophylaxis w/ OB 1\textsuperscript{st}
Screening sometimes helpful:

Recommendations for Screening for Thrombophilic Tendencies in Teenage Females Prior to Contraceptive Initiation

Stephanie L. Savelli, MD\(^1\), Bryce A. Kerlin, MD\(^1\), Michelle A. Springer, MS, CGC\(^2\), Kay L. Monda, BSN, RN\(^1\), Jennifer D. Thornton, BSN, RN\(^1\), and Carol A. Blanchong, MD\(^1\)

Fig. 1. Decision Tree for Screening and Treatment.

HTRS: TERegistry

• Large Multi-Institutional Database
• Clinical and Demographic Data
• Thromboembolic Disease in Children and Adults
• Epidemiology
• Outcomes
• Adverse Events

PI: Bryce Kerlin – Sponsor: Hemophilia & Thrombosis Research Society (HTRS)
Summary

• Pediatric thrombosis is most common in infants and adolescents
• Co-morbid Diseases increase likelihood of thrombosis
• The upper extremity circulation is most commonly affected
• Diagnosis should be confirmed with:
  – D-dimer
  – Venous Doppler Ultrasonography
  – CT Angiogram
Summary

- Initial treatment should be standard or low molecular weight heparinization
- Short courses may be completed with heparin, longer courses may benefit from transition to Warfarin
- Duration of anticoagulant therapy is individualized based on underlying co-morbidities
- Patients should be followed closely for recurrent disease and/or post-phlebitic syndrome
Summary

• All thrombosis patients should be screened for treatable molecular thrombophilias
• Some patients may benefit from additional screening
• Asymptomatic patients and family members not at increased risk for thrombosis should not routinely be screened
Hemostasis & Thrombosis Center

• Services:
  – Acute Thromboembolic Disease
    • Consultation, Recommendations, (Co)Management
  – Outpatient Management
    • Anticoagulation therapy & monitoring
    • Long-term follow-up
    • Post-Thrombotic Syndrome management
    • Resources for Family
Hemostasis & Thrombosis Center

Call 732-235-5437 for more information