VTE in Children: Practical Issues

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Top 10 Reasons Why Pediatric VTE is Different

1. Social, ethical, and legal implications.
2. Limited studies leading in difficult direct evidence
3. Compliance issues are different in different age groups
4. Dietary differences make the use of oral VKAs difficult
5. Specific pediatric formulations of drugs are not available
6. Drug distribution, binding & clearance are age dependent
7. Diagnostic studies difficult to perform without sedation.
8. Difficult vascular access.
9. Developmental Hemostasis – dynamic and evolving
10. Epidemiology of VTE is different
Objectives:

- Epidemiology and Pathophysiology
- Complications
  - Mortality
  - Morbidity
- Principles of management
Epidemiology
Epidemiology

- **Newborn**: 5.1/100,000
- **Childhood VT**: 0.7/100,000
- **Childhood Stroke**: 2/100,000
- **Adolescent**: 10/100,000
- **Elderly**: 5-15,000/100,000

References:

Rosendaal FR: TH 1999;82(2):610-9
Physiology of hemostasis in the Newborn

- Deficiency of vitamin K-dependent factors
  - Procoagulants (II, VII, IX, X)
  - Anticoagulants (Protein C and S)
- Physiologic deficiency of hepatic synthesized factors
  - AT
  - Contact factors affect screening (↑aPTT)
- Balanced deficiency of II, VII, IX & X with AT
- Unbalanced deficiency of PC and PS with normal FVIII and FV
- Decreased levels of Fibrinolytic Proteins:
  - Plasminogen

Neonates are developmentally prothrombotic
Developmental Hemostasis

- Multiple reference ranges required because of the rapidly evolving systems
  - Diagnosis (Protein C, S, AT)
  - Treatment (AT, Plasminogen)
  - Monitoring (INR, aPTT)

- Blood sampling difficult

- True reference ranges for extremely premature infants are not available (majority with postnatal complications)
Etiology and Risk factors
What is the most common type of thrombosis in children?

a) DVT
b) Cerebral sinus venous thrombosis (CSVT)
c) Pulmonary Embolism
d) Renal Vein Thrombosis (RVT)
e) Ischemic Arterial Stroke (IAS)
DVT is the Most Common Blood Clot in Children
(n=84)

DVT, deep vein thrombosis. CSVT, cerebral sinus venous thrombosis. PE, pulmonary embolism. RVT, renal vein thrombosis. IAS, ischemic arterial stroke

What is the most common cause of DVT in Children?

a) Idiopathic
b) Cancer
c) Sepsis
d) Central lines
95% of VTEs in children are secondary to an identifiable risk factor.
Risk factors for childhood VTE.

- **RISK FACTORS**
  - > 90% cases will have > 1 risk factor
  - Central venous catheter is the single most common risk factor accounting for >90% of neonatal VTE and >50% of childhood VTE

- **ACQUIRED**
  - **Transient**
    - Central venous catheters
    - Infection
    - Immobilization
    - Surgery, surgically correctable heart disease
    - Hormones, pregnancy
    - Nephrotic syndrome
  - **Persistent/ on-going**
    - Central venous catheters in long-term parenteral nutrition, hemophilia, sickle cell anemia
    - Cancer, chemotherapy, bone marrow transplant
    - Congenital heart disease, prosthetic heart valves
    - Lupus, antiphospholipid syndrome
    - Renal disease

- **CONGENITAL**
  - Factor V Leiden mutation
  - Prothrombin gene mutation
  - Antithrombin III deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Elevated homocysteine, lipoprotein(a)

Parasuraman S, Goldhaber S Z Circulation 2006;113:e12-e16
QUIZ 3

Which is the most common site for DVT in Children?

A

B
Upper Extremity DVTs:

Complications

1. Mortality
2. Morbidity
   - Recurrence
   - Postthrombotic Syndrome (PTS)
   - Asymptomatic VTE
Mortality

- Mortality in 2.2% related to PE or cardiac VTE
Mortality Risk

- **Site**
  - Most frequent in Rt Atrial/SVC involvement (33%)
  - Stroke mortality = 6%
    - 72% residual CNS deficit
    - 22% fully recover

- **Age**
  - PFO in neonates – paradoxical emboli
  - Prematurity – increase risk of thrombosis and bleeding (IVH, NEC, BPD)

- **Weight**
  - Dose of antithrombotic therapy and bleeding risk

- **Comorbidities**

Morbidity

- Recurrence
- PTS
- Asymptomatic VTE
Recurrent VTE

- Thromboembolism recurs in 4-7% of adults.
- Recurrent VTEs occur in 7.5% of children.
- In the Canadian Registry, 19% of children developed recurrent thromboembolism.

Risk for Recurrent VTE

1) Inadequate anticoagulation
2) Persistent risk (e.g. CVC)
3) Number of underlying risk factors

Risk for Recurrent VTE

1) Number of underlying risk factors:

- None = 4.8% recurrence rate
- One = 17.6%
- 2 or more = approx. 50%

Nowak-Gottl et al. Blood 2001;97:858-862
Elevated Plasma Factor VIII and D-Dimer Levels as Predictors of Poor Outcomes of Thrombosis in Children

Neil A. Goldenberg, M.D., R. Knapp-Clevenger, M.S.N., C.P.N.P.,
and Marilyn J. Manco-Johnson, M.D.,
for the Mountain States Regional Thrombophilia Group
PTS

- Occurs in 12% to 65% of children following venous thrombosis.

- Chronic Venous Insufficiency:
  - Pain with walking
  - Chronic edema
  - Venous ulceration
  - Varicosities
  - Growth in children

- Risk Factors
  - Delay in treatment
  - Recurrent VTE

Asymptomatic VTE in Children

- Usually associated with line related sepsis
- Common source of PE in children
- Risk of paradoxical emboli in children
- Loss of venous access
- Risk of PTS (delay in treatment)
- High morbidity and mortality

Management
Practical Considerations

- Antithrombotic therapy type
- Dosing
- Monitoring
- Duration
- Complication
  - Bleeding
  - Osteoporosis
  - Compliance
Risk Stratification
(for persistence or recurrence)

- **Low Risk**
  - Thrombus post surgery, trauma, CVL
  - Resolves within 6 weeks

- **Standard Risk**
  - FVIII <150U/dL
  - D-dimer <500ng/mL
  - < 3 thrombophilic factors
  - Non-occlusive thrombus

- **High Risk**
  - FVIII >150u/dL
  - D-dimer >500ng/mL
  - >3 thrombophilic factors
  - Occlusive thrombus

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Table 3. Risk factors for thrombosis in children

<table>
<thead>
<tr>
<th>Time-limited risk factors</th>
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<tbody>
<tr>
<td>Indwelling catheters</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Postinfectious transient antiphospholipid antibodies</td>
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<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Surgically correctable congenital heart disease</td>
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<tr>
<td><strong>Ongoing risk factors</strong></td>
</tr>
<tr>
<td>Thrombophilia</td>
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<tr>
<td>Factor V Leiden, prothrombin 20210 mutation</td>
</tr>
<tr>
<td>Deficient/dysfunctional antithrombin, protein C, protein S</td>
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<tr>
<td>Elevations in lipoprotein (a), homocysteine</td>
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<tr>
<td>Other less common genetic disorders of coagulation regulation or fibrinolysis</td>
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<tr>
<td>Acquired thrombophilia (genetic contributions are variable)</td>
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<tr>
<td>Markers of inflammation (elevations in factor VIII, D-dimer, C-reactive protein)</td>
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<tr>
<td>Primary antiphospholipid antibody syndromes (lupus anticoagulant, anti-β2GPI antibody,</td>
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<tr>
<td>anticoagulant antibody)</td>
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<tr>
<td>Acquired decreases in coagulation regulatory proteins (nephrotic syndrome, protein-losing</td>
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<tr>
<td>enteropathy)</td>
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<tr>
<td>Indwelling catheters (eg, cystic fibrosis, long-term parenteral nutrition, hemophilia,</td>
</tr>
<tr>
<td>sickle cell anemia)</td>
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<tr>
<td>Leukemia, cancer, and chemotherapy (eg, L. asparaginase)</td>
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<tr>
<td>Inflammatory diseases (systemic lupus erythematosus, inflammatory bowel disease,</td>
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<td>rheumatoid arthritis)</td>
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<tr>
<td>Prosthetic cardiac valves</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Sickle cell anemia</td>
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</tbody>
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Manco-Johnson Blood 2006
Anticoagulant Duration

- Ongoing Studies: no guidelines!
  - Low/Standard Risk:
    - 6 wks (Thrombus Resolution and no thrombophilia)
    - 3 months (Residual Thrombus or thrombophilia)
  - High Risk:
    - Early thrombolysis AND
    - 6 months vs. 12 months

Manco-Johnson Blood 2006
Summary

- Pediatric thrombosis is most common in infants and adolescents
- DVT is most common form of VTE
- 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 oral VKAs
- Duration of anticoagulant therapy is individualized based on underlying co-morbidities/risk
- Patients should be followed closely for recurrent disease and/or PTS
“Neonates and children differ from adults in physiology, pharmacologic responses to drugs, epidemiology, and long-term consequences of thrombosis.”
Thanks!