What’s New In Pediatric Thrombosis? (everything you wanted to know but were afraid to ask)

Melissa Frei-Jones, MD MSCI
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Disclosure

• I have no relationships with commercial companies to disclose.
• I will be discussing off-label use of medications in children.
  – FDA
  • “There are no adequate and well controlled studies on heparin or coumadin in pediatric patients.”
  • “Safety and effectiveness of lovenox in pediatric patients has not been established.”

Learning Objectives

• Understand the most common causes of venous thrombosis in children
• Plan the evaluation of a child with new onset venous thrombosis
• Choose the most appropriate anticoagulation therapy in a child with venous thrombosis

First, A Review of the Coagulation Cascade

Basic of Hemostasis

Procoagulant proteins
Adhesive proteins
Platelets
Tissue factor
Vessel wall

Anticoagulant proteins
Prostacyclin
NO
Endothelium
Blood flow

Clot
No clot
Yeah….

Thrombosis – When the brakes don’t work

Venous Thrombosis
- Deep Vein Thrombosis (DVT)
- Sinus Venous Thrombosis of Cerebral Sinuses (CSVT)
- Pulmonary Embolism (PE)
- Renal Vein Thrombosis

Arterial Thrombosis
- Acute ischemic stroke (cerebrovascular event)
- Myocardial infarction
- Arterial thrombosis of an extremity

How many clots happen in kids?
- 1994 Andrews et al.
  - DVT/PE incidence 5.3 per 10,000 pediatric hospital admissions
- 2006, Setty et al. KIDS inpatient database
  - 18.8 VTE per 10,000 discharges
- 2009, PHIS
  - 58 VTE per 10,000 discharges
- 3 to 10 fold increase in VTE in hospitalized children in past 15 years

Why do kids get clots?
- Canadian Registry
  - Cancer most common condition associated with pediatric VTE
- KID and PHIS databases
  - Cardiovascular disease most common condition associated with pediatric VTE

Risk Factors for Thrombosis
- 95% of VTE in children is associated with acquired risk factors.
- 2/3 of pediatric VTE have 2 or more risk factors.
- Idiopathic VTE is rare.
- Inherited risk factors are found in 10-78% of pediatric VTE.

Acquired Risk Factors for Thrombosis
- Indwelling catheters
- Surgery
- Immobility
- Infection/Inflammation
- Pregnancy
- Oral Contraceptives
- Vasculitis
- Inflammatory Bowel Disease
- Malignancy
- Paroxysmal Nocturnal Hemoglobinuria (PNH)
- Myeloproliferative syndrome
- Anti-phospholipid Antibody Syndrome
- Nephrotic Syndrome
Inherited Risk Factors for Thrombosis

- **Anti-Thrombin III**
  - Homozygous mutations lethal in utero
  - Heterozygous carriers
    - RR VTE 17.5
- **Protein C**
  - Heterozygous carriers
  - Great clinical variability
  - RR VTE 11.3
  - Homozygous/Compound Heterozygous Mutations
    - Presents with purpura fulminans in neonatal period
- **Protein S**
  - Heterozygous carriers
  - Diagnosis difficult
  - Transient deficiencies
  - Homozygous/Compound Heterozygous Mutations
    - Presents with purpura fulminans in neonatal period
- **Factor V leiden**
  - Heterozygous
    - 10 fold increase risk of thrombosis
  - Homozygous
    - 50-100 fold
  - Prevalence
    - 5% of Caucasian population
    - 15-65% of thrombosis patients
- **Prothrombin 20210**
  - Increased FII levels
  - RR VTE 1.9
- **Combined FV Leiden and Prothrombin**
  - RR VTE 3.2
- **Homocysteine levels (MTHFR)**
  - RR VTE 2.5

Anatomic Risk Factors

- **May-Thurner**
  - Iliac vein compression syndrome
- **Paget-Schroetter**
  - “effort induced thrombosis”
  - Clavicle impingement

When to evaluate for clots?

- Signs and symptoms vary based on location.
  - Extremity (VTE)
    - Painful swelling in limb affected
  - PE
    - Shortness of breath, chest pain, hypoxia
  - CSVT
    - Early morning headache, dizziness, blurry vision

Imaging

- Ultrasound
  - Best for lower extremity clots
  - May miss upper extremity clots in subclavian due to clavicle
- CT Venogram
  - Abdominal or CNS clots
- MR Venogram
  - Abdominal or CNS clots
- CT pulmonary angiogram or V/Q scan
  - PE

Laboratory Testing

**Acute Testing**

- Mechanism
  - Anti-phospholipid antibodies
    - Anti Beta2 GPI
    - Lupus Anticoagulant
    - Anti-Cardiolipin
- Prognosis
  - D-dimer
  - Factor VIII level
- Therapeutic
  - ATIII
  - Anticoagulant dependent

**Long-term Testing**

- Inherited risk factors
  - Protein C/S activity
  - ATIII
  - FVL
  - Prothrombin 20210
  - Fasting Homocysteine
- Prognosis
  - D-dimer
  - Factor VIII level
Prognostic Value of Testing

TREATMENT - THE OLD AND THE NEW

“Old” Anticoagulants in Children

Heparin-UFH/LMWH
- UFH
  - IV, Bolus + continuous infusion
  - ½ life 30 minutes
  - ATIII dependent
  - Protamine reversal
- LMWH (Lovenox/enoxaparin)
  - Subcu, dosed q12
    - Infants need higher dose
    - Older teens q day
  - ½ life 6 hours
  - ATIII dependent
  - Partial Protamine reversal

Coumadin/Warfarin
- Oral
  - ½ life 36-40 hours
  - Not ATIII dependent
  - Reversal – Prothrombin complex concentrates

Heparin Induced Thrombocytopenia
- Antibodies to UFH bound to platelets (PF4)
- Risk of Thrombosis
- Testing
  - ELISA >95% sen/50% spec
  - Functional >90% sen/spec
  - serotonin release assay, SRA
- 5-10 fold lower risk of HIT with LMWH

Avoid Heparin Initiative
- LMWH first choice over UFH
- New DTI if need drip
- 2016, McGowan et al.
  - Annual rate of HIT decreased by 42%
  - Reduced 85 to 49 per 10,000 admissions

“New” Anticoagulants in Children

Direct Thrombin Inhibitors
- Bivalirudin
  - IV, bolus + continuous infusion
  - ½ life 25 min
  - Not ATIII dependent
  - No reversal
- Argatroban
  - IV continuous
  - ½ life 40 min
  - Not ATIII dependent
  - No reversal

VLMWH
- Fondaparinux
  - Subcu
  - Once daily
  - ½ life 17 hours
  - ATIII dependent
  - No reversal
  - No risk of HIT

New Oral Anticoagulants

Factor Xa Inhibitors
- Apixaban
  - Initial pedi study terminated early
  - 4 active trials
- Rivaroxaban
  - 4 completed PD/PK pediatric studies

Direct Thrombin Inhibitors
- Dabigatran
  - 2 safety studies completed
  - 2 active safety/therapeutic trials
**Systemic Anticoagulants**

- **Thrombolysis**: Systemic thrombolysis (TPA) should be considered in patients with high risk clots within 2 weeks of onset.
  - Life or limb threatening thrombosis
- **Contraindications**
  - Active bleeding; CNS bleeding in past 10 days; surgery in past 7 days; seizures in past 48 hrs

- **Catheter directed thrombolysis (IR)**
  - 83% resolution of DVT
  - Limit systemic effects of TPA
  - Older age children/adolescents
- **Contraindications**
  - Catheter size in small children

**Interventional Radiology**

- **Thrombectomy**
  - Percutaneous Mechanical or Pharmaco-mechanical
    - TPA or Heparin
  - ClotBuster, Angiojet
  - Limitation of catheter cannulation

- **Vena Caval Filters**
  - For patients >10 kg with lower extremity DVT and contraindication to systemic anticoagulation.
  - Initiate anticoagulation as soon as possible.
  - Remove filter as soon as possible

**Duration of Therapy**

- **Drug Levels**
  - LMWH q month
  - Anti XA 0.5-1
  - Coumadin
    - INR 2 - 3
- **Imaging**
  - Q 3 months
  - Earlier in neonates
  - Any change in symptoms

**Sequelae of Thrombosis**

- **Acute Sequelae**
  - PE develops in 16-20% of VTE
  - Large vessel thrombosis mortality of 1-4%
  - Limb ischemia
  - Renal insufficiency
- **Chronic Sequelae**
  - Post-thrombotic syndrome (PTS)
    - Venous obstruction and valvar reflux
    - Limb pain, edema, stasis dermalin, ulceration, limitation of activity
    - 26% of pediatric VTE
  - Recurrent thrombosis
    - 6-11% over 2 years

**Summary**

- Prevalence of VTE is increasing in children.
- Most patients have multiple risk factors for VTE.
- Extensive coagulation testing at the time of acute thrombosis results in false positive results.
- Newer anticoagulants are under active investigation.
- Thrombolysis/Thrombectomy should be considered in limb or life threatening thrombosis
Questions

Off-Label Use of Medications in Children

• 20% of FDA approved medication have a pediatric label.
  – Pediatric Research Equity Act (PREA) 1998
    • New drugs must have plan to include children or explain why not included.
    • Drug companies get an extra 6 months of exclusive marketing if they also include children in their studies.