Thrombosis occurs in children of all ages.

The peak incidence is in the neonatal period and during adolescence.
The incidence of pediatric thrombosis is increasing.

Raffini evaluated the incidence of deep vein thrombosis over a six year period from 2001 to 2007 using a discharge database. During this time, the incidence increased across all age group from 34 cases to 58 cases per 10,000 pediatric hospital admissions.

Thrombosis in Children

- **Abnormalities in the vessel wall**
  - Intravascular catheters damaging endothelium

- **Aberration of blood flow**
  - Large bore catheters in small veins
  - Anatomy
  - Surgery

- **Alterations in the constituents of the blood**
  - Malignancy, infection
  - Antiphospholipid antibodies
  - Acquired or physiologic deficiency of natural anticoagulants and fibrinolytics
  - Inherited prothrombotic disorders
Types of Thrombotic Events

- Deep vein thrombosis (upper and lower extremity)
- Catheter-related deep vein thrombosis
- Pulmonary embolus
- Cerebral sinovenous thrombosis
- Renal vein thrombosis
- Portal vein thrombosis
Types of Thrombotic Events

- Arterial stroke/TIA
- Arterial thrombosis (central and peripheral)
- Blalock-Taussig shunt thrombosis
- Kawasaki disease
Types of Patients

- General pediatric patients
- Infants in neonatal intensive care unit
- Children and adolescents in pediatric intensive care unit
Types of Patients

- Pediatric oncology patients
- Pediatric cardiology patient/children with congenital heart disease
- Children s/p liver or renal transplant
- Children with renal failure on hemodialysis
- Children with feeding intolerance on TPN
Types of Patients

- Children with antiphospholipid antibody syndrome
- Children with obesity
- Children with congenital or acquired antithrombin deficiency
- Children with heparin induced thrombocytopenia
Age Groups

- Less than 1 year (<2 mo v. 2-12 mo)
- 1-5 years
- 6-10 years
- 11-16 years
- 17-18 years
Anticoagulants

- Unfractionated heparin
- Low molecular weight heparins
- Warfarin
- New anticoagulants
  - Direct thrombin inhibitors
  - Anti-Xa inhibitors
Drugs Used for Pediatric Thrombosis

- Thrombolytics
  - Tissue plasminogen activator (t-PA)
Drugs Used for Pediatric Thrombosis

- Antiplatelet agents
  - Aspirin
  - Clopidogrel
The CHEST guidelines provide pediatric specific recommendations for evaluation and management of pediatric thrombosis.

Many of the recommendations are derived from adult data.

Children are Not Small Adults
Heparin


Children are Not Small Adults
Low Molecular Weight Heparins

- **Dosing**
  - Sanchez de Toledo J, et al. Do neonates, infants and young children need a higher dose of enoxaparin in the cardiac intensive care unit? Cardiol Young 2010;20:138-43.
  - Dosing in renal insufficiency

- **Twice v. once daily dosing**

- **Need for monitoring**

- **Duration of therapy; approved for 7-10 days of treatment in adults**

- **Administration via Insuflon**

- **IV administration**
Children are Not Small Adults

Warfarin

- No pediatric formulation, need for frequent monitoring, susceptibility to changes in diet, and the impact of intercurrent infection.

- Dose response?
  - Biss et al. VKORC1 and CYP2C9 genotype and patient characteristics explain a large proportion of the variability in warfarin dose requirement among children. Blood 2011.

- Reliability of point of care testing?
Safety Concerns

- Bleeding
- Bone density
  - Aluminum loading

Efficacy Concerns

- Need to optimize efficacy given the long-term consequences of recurrent thrombosis and post-thrombotic syndrome
  - A recent pediatric study showed no correlation between duration of anticoagulation or time within therapeutic range and risk of recurrence

Efficacy Concerns

- **t-PA**
  - Dosing recommendations for t-PA vary widely.
  - Can this drug be used in children in the critical hours after stroke?
  - Can this drug be used in children with congenital heart defects with deep vein thrombosis?
  - Is the risk worth the benefit?
Although guidelines exist, they are not necessarily adhered to.

Recent review of treatment practices in PICUs documented barriers to implementation.
- e.g. only 28% of cases had anti-FXa level titrated to appropriate goal

Gaps in Knowledge

- Epidemiology/Pathophysiology
- Outcomes
  - Clinical
  - Laboratory
- Long-term Safety
- Drug Dosing
  - Off patent drugs
  - t-PA
Research Questions

- Epidemiology/Prevalence/Pathophysiology of Thrombosis in Children
- Outcomes in Therapy
  - Outcome Measures
  - Determining Therapeutic Ranges
- Safety Monitoring of Long-term Therapies
- Drug Dosing Studies
  - Off-patent drugs and t-PA
Working Group Questions in Determining Priorities

- Consideration of evidence already available on the recommendation
- Potential effect on children, families, communities, and the delivery of care
- Consideration of the different populations that may benefit from research
Working Group Questions in Determining Priorities

- **Evidence**
  - Does this recommendation address an unmet need in research?
  - Are there gaps in the available evidence?

- **Population**
  - Does the recommendation address the following:
    » Diverse and broad range of populations
    » Needs of most vulnerable
    » Health disparities
    » Patients outside of the United States

- **Impact**
  - Is the recommendation targeting a disease/condition with high prevalence, severity, and/or cost?
  - What is the frequency of use of the nominated drug?
  - Does the recommendation have potential for multiplicative effect across diseases?
  - Are alternative treatments available?
  - What is the likely time to realize the benefit of the nominated research?
## Proposed Priorities

<table>
<thead>
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<td>Drug dosing</td>
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<td>7 (4-9)</td>
<td>6.5 (4-8)</td>
<td>21 (16-25)</td>
</tr>
</tbody>
</table>

N=4
Reported as median (range)
Priority #1

- Evaluate epidemiology/pathophysiology of thrombosis in children
  - Large and expanding vulnerable groups
    » Oncology, cardiology, nephrology, NICU, PICU
  - Need these data to guide drug dosing studies and clinical trials
NCT01435473 (The Hospital for Sick Kids)

- Prospective, observational study of thromboembolic complications and risk factors in children who have undergone cardiac surgery.
Priority #2

- Drug dosing studies
  - t-PA
  - Off patent drugs

Ongoing Clinical Trials

- **NCT00687882 (University of Colorado)**
  - Phase III study of the duration of therapy for children with thrombosis (Kids-DOTT); Fragmin in subset of children

- **NCT00952380 (Eisai, Inc.)**
  - Phase II study of Fragmin for the treatment of thrombosis in children with cancer.

- **NCT00182104 (McMaster University)**
  - International Multi Centre Randomized Clinical Trial Of Anticoagulation In Children Following Fontan Procedures

- Warfarin Pharmacogenetics Studies
Step 1:
- Adult pharmacokinetic studies need to be performed to determine the target therapeutic concentration achieved with current dosing. This can be performed in patients who are receiving the drug as standard of care for treatment of stroke. Approximately 15 – 20 adults would be required.

Step 2:
- Pediatric PK/safety studies need to be performed. A dose escalation study should be performed based on adult dosing and pharmacokinetics.

Step 3:
- Randomized controlled trial of optimal dose vs. placebo to determine safety and efficacy.
Proposed Studies

- Performing PK and dose-ranging studies in the largest patient populations (heme/onc or children with long-term indwelling IV catheters, pediatric cardiology patients), and then...

- PK/PD studies in unique populations known to be at risk for under-treatment (neonates, obese children).

- Need to study reversal agents particularly in new anticoagulants
Priority #3

Outcomes

- Laboratory
  » Need to establish pediatric therapeutic ranges/index

- Clinical
  » What outcomes should be used as clinical endpoints for clinical trials?

- Need to establish quantitative relationship between degree of anticoagulation as measure by laboratory measures and outcomes
Clinical Outcomes

- Resolution
- Recurrence
- Post-thrombotic syndrome
- Death
- Quality of life
- Neurocognitive outcomes
- Pulmonary hypertension
Laboratory Outcomes

- What is the best assay?
  - e.g., aPTT v. heparin level v. thrombin generation

- What is the optimal therapeutic range?
Priority #4

- Long-term safety
  - What is the bleeding risk associated with anticoagulants in different groups of children with thrombosis?
  - What is impact of heparins on bone density?
Types of Studies

- Epidemiology/surveillance
- Outcome studies to determine assay and assay range associated with best outcome in terms of efficacy and minimal risk
- Drug dosing studies
- Randomized controlled trials
  - Treatment
  - Prevention
Barriers

- Smaller populations than for adult studies
- Diverse population
- Most children are critically ill
  - Exclusion criteria
  - Ability to obtain consent
- Venous access for blood samples
Collaborators

- Pediatric Trials Network
- BPCA Renal Working Group
- American Thrombosis and Hemostasis Network
- Neonatal Research Network
- Pediatric Heart Network
- Pediatric Critical Care Research Network
- Children’s Oncology Group
Summary

- Need further study of venous thrombosis epidemiology and tailored treatment in high risk and unique pediatric populations

- As part of the research we need to define ideal assays and therapeutic ranges which result in optimal safety and clinical outcomes