BPCA Hematology Working Group

Courtney Thornburg, MD, MS
Associate Professor of Pediatrics
Duke University Medical Center

Pediatric Thrombosis-Age Distribution

- **Thrombosis occurs in children of all ages.**
- **The peak incidence is in the neonatal period and during adolescence.**

Andrew. Thromboembolic Complications of Infancy and Childhood.

Pediatric Thrombosis-Incidence

- **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.**

Raffini et al. Pediatrics 2009. 124: 1001-1008.

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

NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

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**

NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Types of Thrombotic Events

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

NATIONAL INSTITUTES OF HEALTH

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Types of Patients

- **General pediatric patients**
- **Infants in neonatal intensive care unit**
- **Children and adolescents in pediatric intensive care unit**

NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

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**

NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Age Groups

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

Drugs Used for Pediatric Thrombosis

- **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

CHEST guidelines

- **The CHEST guidelines provide pediatric specific recommendations for evaluation and management of pediatric thrombosis.**

- **Many of the recommendations are derived from adult data.**

Monagle et al. Chest 2008. 133: 877- 968.

NATIONAL INSTITUTES OF HEALTH

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Children are Not Small Adults Heparin

- **Andrew et al. Heparin therapy in pediatric patients: a prospective cohort study. Pediatr Res 1994;35:78-83.**

- **Newall et al. Age is a determining factor for measures of concentration and effect in children requiring unfractionated heparin. Thrombosis and Haemostasis 2010. 103:1085-1090.**

- **Newall et al. In vivo age dependency of unfractionated heparin in infants and children. Thrombosis Research 123:710-714, 2009.**

NATIONAL INSTITUTES OF HEALTH

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Children are Not Small Adults
Low Molecular Weight Heparins

- **?Dosing**
  - Bauman et al. Evaluation of enoxaparin dosing requirements in infants and children. Better dosing to achieve therapeutic levels. Thromb Res 2009. 101(1): 86-92.
  - 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.
  - Lewis et al. Increased enoxaparin dosing is required for obese children. Pediatrics 2011;127:e787-e90.
  - ?Dosing in renal insufficiency
- **?Twice v. once daily dosing**
  - Schobess R, During C, Bidlingmaier C et al. Long-term safety and efficacy data on childhood venous thrombosis treated with a low molecular weight heparin: an open label pilot study of once-daily versus twice daily enoxaparin administration. Haematologica 2006. 91:1701-1704.
- **?Need for monitoring**
- **?Duration of therapy; approved for 7-10 days of treatment in adults**
- **?Administration via Insuflon**
- **?IV administration**

NATIONAL INSTITUTES OF HEALTH

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

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?
  - Andrew et al. Oral anticoagulation therapy in pediatric patients: a prospective study. Thromb Haemost 1994;71:265-269.
  - Massicotte et al. Enhanced thrombin regulation during warfarin therapy in children compared to adults. Thrombosis and Haemostasis 1998. 80: 570-574.
  - 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?

NATIONAL INSTITUTES OF HEALTH

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Safety Concerns

- **Bleeding**
- **Bone density**
  - Aluminum loading

Lefkou et al. Lupus 2010. 19(1): 3-12.

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

Estepp et al. Pediatr Blood Cancer 2011. doi: 10.1002/pbc.23396.

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?

Implementation Concerns

- **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

Hanson et al. Pediatric Anesthesia 2011. 21: 1052-57.

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**

NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

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?

NATIONAL INSTITUTES OF HEALTH

Eunice Kennedy Shriver NICHD National Institute of Child Health & Human Development

Proposed Priorities

	Evidence	Population	Impact	Overall
Epidemiology/ pathophysiology	6.5 (6-7)	7.5 (6-9)	8 (6-9)	22 (19-24)
Outcomes	7 (7-9)	6.5 (5-9)	7 (5-8)	20.5 (17-26)
Safety	7 (5-8)	6 (5-8)	7.5 (5-8)	19 (18-24)
Drug dosing	8 (7-8)	7 (4-9)	6.5 (4-8)	21 (16-25)

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

Ongoing 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

Recently Published Studies New Anticoagulants

- **Young et al. Pilot dose-finding safety study of bivalirudin in infants <6 months of age with thrombosis. J Thromb Haemost 2007.5(8):1654-9.**

- **Young et al. Argatroban therapy in pediatric patients requiring nonheparin anticoagulation: an open-label, safety, efficacy and pharmacokinetic study. Pediatr Blood and Cancer 2011. 56(7): 1103-9.**

NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

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

Proposed 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.

NATIONAL INSTITUTES OF HEALTH

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

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

NATIONAL INSTITUTES OF HEALTH

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

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**

NATIONAL INSTITUTES OF HEALTH

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

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**

NATIONAL INSTITUTES OF HEALTH

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development