Thrombosis In The Pediatric Patient: Unique Risk Factors, Diagnosis & Management Issues. Surgeon General's Workshop on DVT May 8-9, 2006 Bethesda, Maryland

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## **DVT is the Most Common Blood Clot in Children** (n=84)



DVT=63%
CSVT=18%
Isol PE=5%
RVT=6%
IAS=10%

Goldenberg et al. NEJM 2004;351:1081-8. Although Rare, DVT is a Health Risk During Childhood, Especially for Newborn Infants & Adolescents

 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

Nowak-Göttl U, et al. Arch Dis Child Fetal Neonatal Ed. 1998;78:F163 Andrew M, et al Blood 1994;83:1251-7 Rosendaal FR: TH 1999;82(2):610-9

#### DVT is an Important Cause of Death in Children



**2.2%** (9/405) Monagle et al. *Pediatr Res* 2000;47:763-6

**3.8%** (3/79) Nowak-Göttl et al. *Arch Dis Child* 1997;76:F163-7

**1%** (1/100) Van Ommen et al. *J Thromb Haemost* 2003;1:2516-23

2.2% (13/584) Composite

DVT Has a High Risk of Pulmonary Embolism in Children



18% (11/61) Nuss et al. Pediatrics 1995;96:291-4.
17% (69/405) Monagle et al. Pediatri Res 2000;47:763-6.

17% (80/466) Composite

## DVT in Children Can Be Recurrent



- Monagle P, et al Pediatr Res 2000;47:763-6
  8.1% (33/405) median 2.8 yrs
- Van Ommen, *et al* J Thromb Haemost 2003;1:2516-22
  8% (8/100) after 1 year
  18% (18/100) after 7yrs

10% (51/505) Composite

## Children with DVT are More Likely to Have Multiple Thrombophilia Traits

Mountain States Regional Hemophilia &	Thrombosis Center
Number of Children Seen 2001-2003	293
Thrombosis	131
Family Study	162

#### Thrombophilia testing:

- No abnormality: 19%
- Single trait: 27%
- Two traits:
  - 27% Multiple traits in 54% evaluated 5%
- Three traits:
- Four traits: 22%

DVT recurrence is more likely with multiple thrombophilia traits!

## LMWH Dosing Is More Variable in Children & Requires More Monitoring

Theraputic Dose of Enoxaparin (mg/kg Q12h by age cohort)	1.00	1.25	1.375	1.5	1.625	1.75-2.0
<b>Birth to &lt; 1 month</b> N=11	0%	9%	9 %	36%	28%	18%
<b>1 month to &lt; 1 year</b> N=12	8%	8%	0%	<b>59%</b>	8%	17%
<b>1 year to &lt; 6 years</b> N=16	0%	31%	25%	44%	0%	7%
<b>6 years to &lt; 12 years</b> N=12	0%	75%	17%	8%	0%	0%
<b>12 years to &lt; 21</b> <b>years</b> N=43	5%	88%	5%	0%	2%	0%

N=94

Manco-Johnson et al., "Low Molecular Weight Heparin dose requirements are Age-Related Through Childhood," Pediatric Research 2003;53:284a.

#### Post Thrombotic Syndrome (PTS) Causes Disability in Children & Adolescents



Stage1: Swelling: DVT age 16 years; FVL, OCP Stage 2: Visible Collaterals

*DVT* age 14 yrs; *APA*, prolonged bus ride







Stage 4: Stasis ulcers; DVT age 10 yrs; PC, tibial fracture

Stage 3: Induration, hyperpigmentation DVT age 13 years; FVL, APA

12.4% 59% 63% 70% 29%

(50/405) median 2.8 yrs Monagle P, et al Pediatr Res 2000;47:763-6
(10/17) pain 41% (7/17) abn PE IVC Hausler M, Arch Dis Child 2001;85:228-33.
(96/153) Kuhle S, et al. Thromb Res 2003;111:227-33.
(23/33) Van Ommen, et al J Thromb Haemost 2003;1:2516-22
(179/608) Composite

DVT Therapy is Frequently Delayed in Children Due to Under-Recognition.

Treatment Delay Results in Poor DVT Resolution and Long-Term Pain.



Results of 81 DVT in Children treated with Anticoagulation Manco-Johnson et al, Pediatr Res 2003; 53:284a.

## Teen Age is a Risk Factor for PTS

Physical Exam (CEAP) Score following DVT in Children



Manco-Johnson, et al Blood 2003; 102:553a.

### Overweight Predisposes to PTS in Children & Teens





88% rate of overweight in children with PTS

#### Stage 3: Skin induration, venous eczema





Overweight children have RR of 7 for PTS

#### January, 2004

October, 2004

**MSRHTC**, 2006



Goldenberg, et al NEJM 2004;351:1081-8.

 (Inflammatory Markers\* at Diagnosis Predicts a Poor Outcome of Thrombosis in Children

Probability of a Poor DVT Outcome: Positive Likelihood Ratio 6.1



\* ( FVIII, DD, Goldenberg, et al NEJM, 2004;351:1081-8

## The Newborn Infant Has a Unique Hemostatic Balance:

**Thrombin Generation** 

**BLEEDING** 

**Fibrin Tensile Strength** 

Platelet Aggregation

Rate of Thrombin Generation & Thrombin Regulation

**THROMBOSIS** 

[TF Expression, Whole Blood Clotting & Hematocrit

Platelet Adhesion

# Thrombosis May Be Devastating in Neonates



## Children Have an Excellent Chance for Recovery From Severe DVT





Now 18 years old, this "Gifted & Talented" HS Senior with severe protein C deficiency (compound heterozygous, <1%) is going to college.

Outcome of *In Utero* Thrombosis with Severe Thrombophilia is Good with Treatment

CXR on Infant with Respiratory Infection

PMH: normal pregnancy, labor and delivery; well until acute respiratory illness

FH: negative for bleeding, thrombosis





Left: Organized IVC clot, left adrenal hemorrhage
Right: Organized right atrial clot
Thrombophilia eval: Homozygous Factor V Leiden,
Heterozygous Protein C Deficiency;
D-dimer, F 1+2, TAT persistently elevated



## Critical Issues in DVT in Children

- DVT is an important and increasing problem in infancy, childhood and adolescence.
- Health and cost burdens of DVT and its longterm complications are disproportionately higher in children:
  - Children will live 60 80 years following DVT.
  - PTS limits aerobic activities that are necessary for normal childhood development.
- DVT trials specific for children are urgently needed.

## **DVT is the Most Common Blood Clot in Children** (n=84)

Time-Limited Risk Factors: Trauma, surgery, immobility Indwelling Catheters Infection, Post infectious APA Surgically Correctible Congenital Heart Disease Leukemia, Cancer, Chemotherap Steroids



DVT=63%
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On-Going Risk Factors: Genetic Thrombophilia Primary or Secondary APAS Inflammatory Diseases Prosthetic Cardiac Valves Sickle Cell Anemia

Goldenberg et al. NEJM 2004;351:1081-8.

#### **Clot Formation is Accelerated in the Newborn**



**CloFAL Assay** Goldenberg et al. Thromb Res 2005; 116:345-56.



Newborn

Adult

Thromboelastogram (TEG) Markarian M et al Biol Neonate, 1971; 17(1): 84-97