

VTE in Children and Adolescents

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Learning Objectives

- Review incidence, presentation, characteristics
- Special situation:
 - neonate
- Treatment recommendations
- Long term outcome data
- Case studies

Case #1:

Fifteen month old girl presented to the ER with new onset seizure. She had been well until 4 days prior when she developed a temperature of 100° and vomiting. Medical history is significant for AT-III deficiency and FV Leiden but no other medical issues.

Family history is significant for her father and his brothers who have had multiple episodes of VTE beginning in their teens and were found to have AT-III deficiency and recently found to have FV Leiden. All are on warfarin.

She also has a 3 y.o. brother who at 18 mo developed a swollen, tender right leg and was found to have an extensive thrombosis of his ileo-femoral venous system.

She has a 5 year old cousin who had an IC thrombosis on day 7 of life.

Case #2:

Twelve year old male with a history of autism, hypertension and obesity was admitted for bronchoscopy after choking on a hot dog. He subsequently developed an aspiration pneumonia with increasing respiratory distress and required intubation.

Due to poor venous access, a right femoral line was placed. Three days later, his right leg became swollen and painful.

Medications: Lamictal, Klonopin, Prilosec, Captopril, Amlodipine

Family history is unremarkable for stroke, MI, DVT, PE, frequent miscarriage.

VTE in children - Statistics

VTE in children is uncommon

- 5.3 per 10,000 hospital admissions for children
- ↓ rate of thrombin generation
- ↑thrombin inhibition
- changes in plasma coagulant proteins
- ↑ α_2 macroglobulin
- antithrombotic endothelium
- platelet hyporeactivity

- >90% of VTE is a secondary event related to another illness
- clinical prothrombotic risk
- hypercoagulable state

Stein et al, J Pediatr 2004; 145:563-565 Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey

VTE in children - Statistics

Age – 2 peaks

- **neonate (first 28 days of life)**
- 24 per 10,000 NICU admissions (Ontario)
- physiologic maturation in hemostasis and illness

- **adolescent**
- 1.1 per 10,000/year (15 – 17 years old)
- use of OCP's, pregnancy

Stein et al, J Pediatr 2004; 145:563-565 Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey

Table II. Thromboembolic disease in children: 1979-2001

		Rate of diagnosis/100,000 children/year		
	Age group	All	Boys	Girls
PE	0-1	2.2 [*]	— [‡]	—
	2-14	0.4	—	—
	15-17	2.0 [*]	—	—
	All	0.9	—	—
DVT	0-1	8.7 [†]	9.3	8.0
	2-14	2.1	2.0	2.2
	15-17	9.9 [†]	6.5	13.5
	All	4.2	3.6	4.8
VTE	0-1	10.5 [†]	11.3	9.7
	2-14	2.4	2.3	2.6
	15-17	11.4 [†]	8.1	14.9
	All	4.9	4.3	5.5

**P* <.05 age 0-1 versus age 2-14, and age 15-17 versus age 2-14.
[†]*P* <.001 age 0-1 versus age 2-14, and age 15-17 versus age 2-14.
[‡]Insufficient data for interpretation according to age and sex.

Stein et al, J Pediatr 2004; 145:563-565 Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey

VTE in children - Statistics

- Abstract from ISTH – Raffini at CHOP
- 2001 – 2007 retrospective cohort study in 41 children's hospitals in U.S.
- VTE admissions: 35 → 59 per 10,000 admissions/year (68%)
Increase observed in all age groups
- Recurrent VTE with malignancy
- Use of LMWH increased from 30% to 50%
- Use of warfarin decreased

Raffini,LJ et al AS-TU-055 A significant increase in VTE in hospitalized children in the US from 2001 to 2007, ISTH July 2009

Virchow's Triad:

Blood Flow

venous stasis
impairs clearance of activated coag factors
limits accessibility of thrombin to thrombomodulin

Circulating blood coagulation factors and inhibitors

activation of coagulation - affected by blood flow
enhanced by stasis
inhibited by rapid flow

Vascular damage

gross vascular trauma
tissue injury activates endothelial cells
synthesis TF and PAI-1
decrease thrombomodulin

Virchow's triad - neonates

- Blood flow
 - affected by large bore catheters
 - increased blood viscosity
 - polycythemia
 - poor deformability of large rbc's
- Circulating blood coagulation factors
 - activation of coagulation and fibrinolytic systems
 - sepsis, shock, endothelial damage from CVL
- Vascular damage
 - CVL
 - thrombosed placental vessels
 - thrombi associated with cardiac (PDA)

VTE in neonates

- Maturation in hemostasis – prenatal, perinatal, postnatal and beyond
- Plasma proteins differ in concentration compared to adult values
- 30 – 50% lower than adult values
- Thrombosis:
 - ↓Protein C, Protein S, AT-III
 - ↓plasminogen, heparin cofactor II
- Bleeding:
 - ↓FII,VII,IX,X,XI,PK, HMWK
 - ↓reactivity endothelium, platelets
- FVIII, VWF, FXIII, FBG = adult values (sometimes ↑)
- ↑α2 macroglobulin → inhibits thrombin
- Fibrinolysis: ↑t-PA, ↓plasminogen, ↑PAI

Saracco,P et al, Thrombosis research 123 (2009) 805-809. Management and investigation of neonatal thromboembolic events: Genetic and acquired risk factors

VTE in neonates

- Maturation – prenatal, perinatal, postnatal and beyond
- Plasma proteins differ in concentration compared to adult values
- Differ in their rate of maturation to adult values
- Several mechanisms may be responsible:
 - altered synthesis and release from cells
 - accelerated clearance
 - consumption during birth
 - fetal forms of some proteins
- Neonatal physiologic balance in healthy infants which is disrupted by other risk factors and leads to thrombosis

Andrew, Monagle, Booker; Thromboembolic complications during Infancy and childhood, chapt.2 Developmental Hemostasis B.C.Decker 2000.

VTE in neonates – risk factors

Inherited:

- retrospective studies are equivocal re: inherited prothrombotic states
- vary from no association to 6 – 13% with CVL or renal vein thrombosis

Acquired:

- CVL – PICC, UVC, Hickman/Broviacs
- increasing use in critically ill infants
- >90% of thrombotic events
- damage to endothelial wall and activation of coagulation and thrombin generation
- affects IVC, right atrium, portal vein, upper venous system, ?? PE

Saracco,P et al, Thrombosis research 123 (2009) 805-809. Management and investigation of neonatal thromboembolic events: Genetic and acquired risk factors

VTE in neonate

- Acquired risk factors:
 - prematurity
 - perinatal asphyxia
 - dehydration
 - birth trauma
 - sepsis
 - congenital heart disease
 - surgery
 - extracorporeal mechanical oxygenation
- placental thrombosis and infarction:
 - maternal thrombophilia
 - maternal diabetes
 - maternal APLA
 - preeclampsia

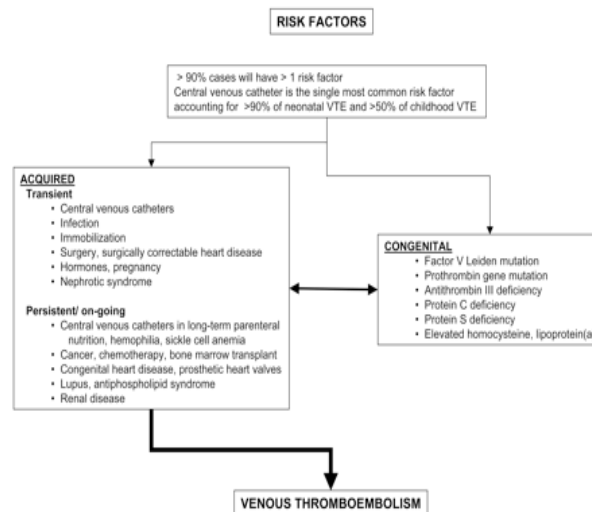
Saracco,P et al, Thrombosis research 123 (2009) 805-809. Management and investigation of neonatal thromboembolic events: Genetic and acquired risk factors

VTE in neonate- treatment

- Coagulation physiology affects treatment:
 - low AT-III and accelerated clearance → higher doses
 - ↑volume of distribution → distribution of hydrophilic drugs
- Unfractionated heparin
 - bolus and CI dosing is age and gestation dependent
 - frequent monitoring using either aPTT or anti-Xa levels
- LMWH
 - more consistent pharmacokinetics→less monitoring
 - anti-Xa level 4 hours post dose
- 1.7mg/kg/dose q 12 hrs in term infants
- 2 mg/kg/dose q 12 hrs in preterm
- SQ shots or use indwelling SQ catheter

Malowany, J et al; Thrombosis Research (2008) 122, 826-830 Enoxaparin for neonatal thrombosis: A call for a higher dose for neonates.

VTE in children – risk factors



Parasuraman, S and Goldhaber, S: **Circulation. 2006;113:e12-e16,**
Venous thromboembolism in children

VTE in children - Treatment

- Rationale: prevent further sequelae
- acute:
 - progression
 - embolization – PE 20%
 - death
- late:
 - post thrombotic syndrome – 10% – 60%
 - reoccurrence – 9% - 21%
 - occlusive thrombus
 - persistent markers of inflammation (FVIII, d-dimer)
 - multiple thrombophilic risks
- Tailor therapy
 - patient
 - thrombus

Manco-Johnson, M Blood Jan 1, 2006, 107:1, p.21-29 How I treat venous thrombosis in children

VTE in children – obstacles to treatment

- Extrapolation from adult studies difficult
- Epidemiology of VTE is different in children
- Pathophysiology of hemostasis evolves with age
- Pharmacokinetics of drugs change with age
- Illness and use of other drugs can change with age

Monagle et al, Chest 133(6)S, June 2008, 887S-968S. Antithrombotic therapy in neonates and children: American college of chest physicians evidence based clinical practice guidelines (8th edition).

VTE in children – obstacles to treatment

- Radiologic studies for dx and monitoring can be difficult to do
- Vascular access for deliver of drug and for monitoring can be limited
- Pediatric drug formulations (AC) are limited
- Dietary choices (formula, breast milk) affects AC
- Compliance – infants, parent, adolescent

Monagle et al, Chest 133(6)S, June 2008, 887S-968S. Antithrombotic therapy in neonates and children: American college of chest physicians evidence based clinical practice guidelines (8th edition).

VTE in children - Treatment

- 8th edition of the therapy guidelines:
- Since the 1st set in 1995 < 10 RCT for therapeutic intervention
- Many of the recommendations are based upon extrapolation from adult data or expert opinion, uncontrolled studies or case reports
- Separate recommendations for neonates and children reflecting the differences within these two populations
- 87 recommendations: 53 (61%) grade 2C and 27 (31%) grade 1B
- 4 (5%) grade 1A, 2 (2%) grade 2B and 1 (1%) grade 2A

Monagle et al, CHEST 133(6)S, June 2008, 887S-968S Antithrombotic Therapy in Neonates and Children: American College of chest physicians evidence based clinical practice guidelines (8th edition).

VTE in children - Treatment

- Heparin
 - unfractionated – gold standard
 - (-) sustained IV access for CI
 - (-) pharmacokinetics
 - (-) monitoring
 - (-) HIT – 1%
 - danaparoid
 - hirudin
 - argatroban
- low molecular weight heparin
 - (+/-) pharmacokinetics
 - (+/-) SQ injection (BID)
 - (-) held for ≥ 24 hours prior to procedures
 - (+/-) HIT - $\leq 1\%$

Manco-Johnson, M Blood Jan 1, 2006, 107:1, p.21-29 How I treat venous thrombosis in children

VTE in children - Treatment

Warfarin

- (+/-) oral
- tablet, no liquid preparation
- (-) food interactions
 - formula, breast milk
 - vegetarians (adolescents)
- (-) frequent monitoring
- (-) interactions with other drugs
 - antibiotics, anticonvulsants,
 - psychiatric, chemotherapy

Manco-Johnson, M Blood Jan 1, 2006, 107:1, p.21-29 How I treat venous thrombosis in children

VTE in children - Treatment

Thrombolysis

high risk thrombus
life or limb threatening thrombus
within 2 weeks of symptoms

- tPA –
- risks – active bleeding, CNS ischemia or bleeding, surgery, invasive procedures, seizures
- monitor
- imaging for clot lysis
- biochemical markers of clot lysis
- maintain adequate hemostasis to prevent bleeding
- platelet count $\geq 50,000$
- fibrinogen $\geq 100\text{mg/dl}$
- prothrombin time - within 3 seconds of normal

Manco-Johnson, M. Blood, 1 January 2006; 107/1 21-29 How I treat venous thrombosis in children

VTE in children - Treatment

- Direct thrombin inhibitors
- analogs of hirudin (in adults HIT, PCI)
- lepirudin
- bivalirudin
- argatroban

- Advantages compared to heparin
- selectively bind to and inhibit thrombin
- efficacy unaffected by AT- III levels
- adults – less bleeding
- inhibit circulating and clot bound thrombin
- do not cause HIT

Young, G. Educational sessions ASH December 2008: New Anticoagulants in Children

VTE in children - Treatment

- **Bivalirudin study** – prospective, dose finding, safety and efficacy
- Infants < 6 months - venous or arterial thrombosis
- 16 patients
- **safety** - 2 had clinical bleeding
- gross hematuria (high aPTT's)
- no IC hemorrhage, deep tissue bleeds
- no non-bleeding adverse events
- **efficacy** – imaging 48 – 72 hrs post
- 3/16 total resolution (37.5%)
- 3/16 partial resolution (37.5%)
- faster than expected with heparin
- need direct comparison studies

Young, G et al, J Thromb Hemost. 2007;5:1654-1659 Pilot dose-finding and safety study of bivalirudin in infants<6months of age with thrombosis

VTE in children - Treatment

- **Argatroban** – study included 18 children
- birth to 18 years of age
- severely ill with HIT, suspected HIT or at risk for HIT
- **safety**
- 2/18 – deaths from severe bleeding
- 4m.o. with viral myocarditis and HIT
- ECMO, cerebral infarction and bleed
- 5y.o. idiopathic dilated cardiomyopathy and HIT subarachnoid bleed
- **efficacy** (50% of HIT pts develop thrombosis untreated)
- 2/18 thrombosis while on argatroban
- 3/18 thrombosis post argatroban

Young, G and Boshkov, L. Blood. 2007;110 Abstrat#553. Prospective study of argatroban in pediatric patients requiring non-heparin anticoagulation.

VTE in children - Treatment

- **Fondaparinux** – selective Xa inhibitor
- advantages for pediatrics
- longer half life - ? daily dosing vs BID
- synthetic drug - no contamination
- HIT – lower risk
- osteoporosis – lower risk

- **Oral agents**
- ideal
- better efficacy to safety ratio
- rapid therapeutic levels
- less lab monitoring
- fewer drug and food interactions
- child friendly preparation

- **Rivaroxaban** – direct factor Xa inhibitor
planned pediatric trial

Young, G. Educational session ASH December 2008, New Anticoagulants in Children

VTE in children - Treatment

- Rationale: prevent further sequelae

- acute:
 - progression
 - embolization – PE 20%
 - death
- late:
 - post thrombotic syndrome – 10% – 60%
 - reoccurrence – 9% - 21%
 - occlusive thrombus
 - persistent markers of inflammation (FVIII, d-dimer)
 - multiple thrombophilic risks

- **Tailor therapy**
- **patient**
- **thrombus**

Manco-Johnson, M Blood Jan 1, 2006, 107:1, p.21-29 How I treat venous thrombosis in children

Table 2. Risk assessment for persistence or recurrence of venous thrombosis in children

Patient characteristics	Thrombus characteristics
Low risk Trigger resolved/removed Transient underlying medical condition	Low risk Resolved within 6 weeks
Standard risk FVIII level 150 U/dL or less D-dimer level 500 ng/mL or less Fewer than 3 trait thrombophilias*	Standard risk Atrial Nonocclusive DVT
High risk FVIII level greater than 150 U/dL D-dimer level greater than 500 ng/mL At least 3 trait thrombophilias* Persistent antiphospholipid antibody	High risk Vena cava Occlusive DVT

* Thrombophilias include genetic and acquired prothrombotic traits that can be determined in blood and are listed in Table 3

Manco-Johnson, M. Blood 2006 Jan 1, 107(1), 21 -9, How I treat venous thromboembolism.

VTE in children - Outcomes

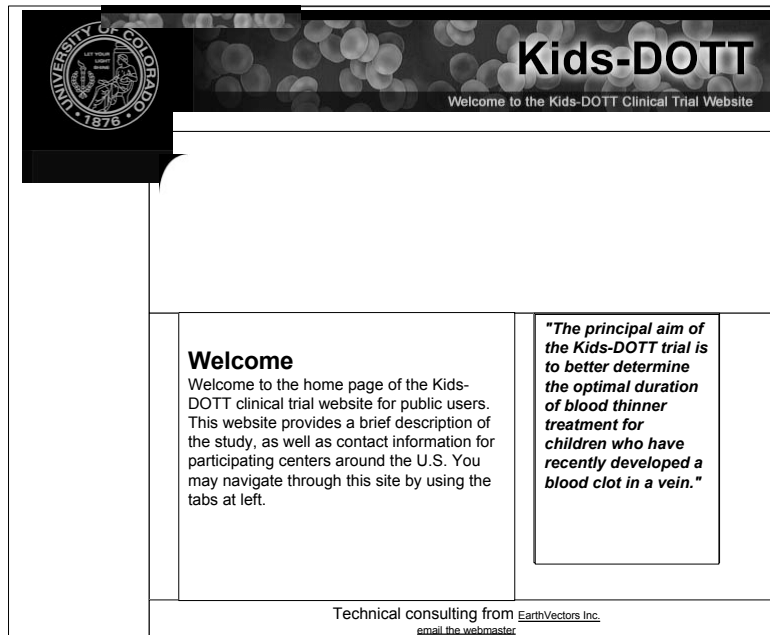
- Growth and increased activity in children demand adequate vascular flow
- Clinical risks associated with VTE affect outcome
 - acquired
 - inherited
- Poor prognostic indicators at dx and 3-6mo
 - FVIII > 150IU/dl
 - d-dimers > 500ng/ml
 - location
 - total occlusion
- Post thrombotic syndrome (PTS) – about 30% (as high as 60%) usually mild but often not followed long enough
- Mortality: overall 14% - 20%
- VTE related 1% - 2%

Goldenberg, N. Current opinion in Hematology 2005, 12:370-376, Long-term outcomes of venous thrombosis in children

VTE in children - Outcomes

- REVIVE trial - Massicotte 2003 safety and efficacy of LMWH vs UFH/oral AC over 3 months (ended early) multicenter randomized controlled trial
- 76 children - LMWH vs UF/oral AC
- Recurrent VTE – 3% vs 10% @ 3mo
- 6% vs 13% @ 6mo
- Mortality 3% vs 10% (no VTE)
- Bleeding (major) 6% vs 13%
- Bleeding (minor) 89% vs 68%
- Study limited by #'s but confirmed safety and efficacy of LMWH and
- gave more insight into outcomes

Massicotte, P et al Throm Res 2003; 109:85-92 An open labeled controlled trial of low molecular weight heparin compared to heparin and Coumadin for the treatment of venous thromboembolic events in children: the REVIVE trial.



UNIVERSITY OF COLORADO
1876

Kids-DOTT

Welcome to the Kids-DOTT Clinical Trial Website

Welcome
Welcome to the home page of the Kids-DOTT clinical trial website for public users. This website provides a brief description of the study, as well as contact information for participating centers around the U.S. You may navigate through this site by using the tabs at left.

"The principal aim of the Kids-DOTT trial is to better determine the optimal duration of blood thinner treatment for children who have recently developed a blood clot in a vein."

Technical consulting from [EarthVectors Inc.](#)
email the webmaster

<http://www.uchsc.edu/htc/kidsdott/>

VTE in children – DOTT study
University of Colorado at Denver and Health Sciences Center

- Purpose:
- The main purpose of the Kids-DOTT trial is to provide **key evidence** for the **optimal duration of anticoagulant therapy** for thrombosis in children, given that the conventional duration of such therapy in children is derived solely from evidence in adult thrombosis trials. **Study hypothesis:** Among children with first-episode acute venous thrombosis in whom thrombus resolution is evident following the initial 6 week period of anticoagulant therapy, the cumulative incidences of **recurrent venous thromboembolism (VTE) and post-thrombotic syndrome (PTS) at 2 years is not significantly different** between those receiving **6 weeks** and those receiving **3 months** total duration of anticoagulant therapy.
- **Outcomes: 5 years post treatment follow up**
 - post thrombotic syndrome
 - reoccurrence
 - QOL

<http://clinicaltrials.gov/ct2/show/NCT00687882>

Case #1:

Fifteen month old girl presents to the ER with new onset seizure. She had been well until 4 days prior when she began vomiting and Had a low grade temperature of 100°. Previous medical history was significant for anti-thrombin III deficiency and FV Leiden but no clinical problems. Family history revealed AT-III deficiency and FV Leiden on the paternal side and in her 3 y.o. brother.

Evaluation:

MRI/MRV head – superior sagittal sinus thrombosis extending into the right transverse sinus

Treatment- CI unfractionated heparin with crossover to oral warfarin and AT-III replacement.

Outcome – She is 15 y.o., no residual neurologic deficits, honor student, figure skater and on lifelong warfarin.

Case #2:

Twelve year old male with a history of autism, hypertension and obesity was admitted for bronchoscopy after choking on a hot dog. Due to poor venous access, a right sided femoral line was placed. Three days later, his right leg was noted to be swollen.

Medications: Lamictal, Klonopin, prilosec, captopril, amlodopine

Family hx: unremarkable for stroke, MI, DVT, PE, miscarriage

Evaluation: Doppler ultrasound – thrombosis right femoral vein

Labs: d-dimer 1.88ug/ml (0-0.6)
FVIII activity 320% (50-150%)

fibrinogen activity **69 mg/dl (160-420)**
fibrinogen antigen **468 mg/dl (180-400)**

Treatment: removed catheter, cryoprecipitate, LMWH continued for 12 months with resolution of thrombus, d-dimer, FVIII and no signs of PTS at 1 year out.

VTE in children - conclusions

- Rising incidence of VTE in pediatrics
- Two peaks – neonate and adolescent
- >90% VTE associated with either a clinical or inherited prothrombotic risk factor
- Overall mortality ~ 20%, VTE related mortality ~ 2%
- Morbidity:
 - PTS incidence not clearly known – 12% - 60%
 - Recurrent VTE – 9% - 21%
- Need treatment regimens better suited for children
- Need collaborative, prospective, randomized clinical trials to determine better treatment

Venous thrombosis in the elderly – conclusions sound familiar??

“There is a strong need to understand the aging/thrombosis interface. Laboratory scientists should be encouraged to examine mechanisms that increase VTE risk with age and to explore the pathophysiology of embolization and PTS. Clinical investigators should focus on developing safe and effective treatment strategies, including optimal approaches for the use of warfarin, defining the role for thrombolytics and establishing indications for vena cava filters. Furthermore, as new anticoagulants are developed, they should be tested in older patients to accurately define safe and effective dosing. Epidemiologic studies are needed to clarify and identify specific risk factors for VTE and its complications in the elderly and to determine the effectiveness of thromboprophylaxis in hospitalized elderly patients. The importance of VTE with regard to critical geriatric issues of function, independence, and QOL could be approached by a large, multicenter inception cohort study with the appropriate outcome measures.”

Silverstein et al, *Blood*, 1 November 2007, 110/9, 3097-3101 Venous thrombosis in the elderly: more questions than answers.