Venous Thromboembolism in Children with Cancer

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Presentation Information

- This presentation was delivered at the Pediatric Pharmacy Advocacy Group (PPAG) *20th Pediatric Pharmacy Conference and 2011 Annual Meeting* in Memphis, TN, March 16-20, 2011

Disclosures

- Consultant
  - Sigma Tau Pharmaceuticals
  - Lexi-Comp, Inc
- Speakers Bureau Activities
  - Enzon Pharmaceuticals
  - Genzyme Oncology
- Fees for CPE Programs
  - Sanofi-aventis
- Advisory Boards
  - Pediatric Central IRB Initiative through NCI/NIH

Off-Label Use of Medications

- Throughout the presentation I will be discussing medications which do not have FDA approval for use in pediatric patients
- I will be referring to dosing recommendations for pediatric patients which are not FDA approved

Audience Response Question

- How many years have you been in clinical practice (not including residency and/or fellowship training)?
  - A. < 2 years
  - B. 2-4 years
  - C. 5-7 years
  - D. 8-10 years
  - E. > 10 years

Audience Response Question

- How much of your time is devoted to caring for pediatric hematology/oncology/stem cell transplant patients?
  - A. < 25%
  - B. 25-50%
  - C. 50-75%
  - D. > 75%

Objectives

- Describe the pathophysiology of venous thromboembolism (VTE) development in the setting of pediatric malignancies
- Identify risk factors for developing VTE's in children with cancer
- Summarize current preventative and treatment strategies for managing VTE's in pediatric cancer patients

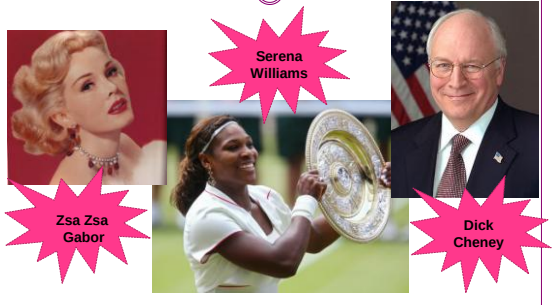
What a Timely Topic!

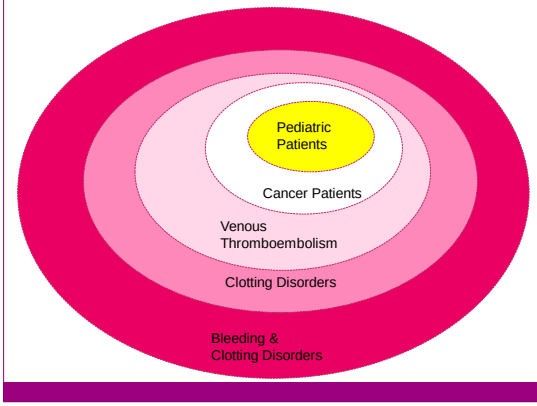
DVT Awareness Month

MARCH 2011

SUN	MON	TUES	WED	THURS	FRI	SAT
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

It Can Happen to You!





Definitions

- Deep venous thrombosis (DVT)
  - Blood clot which develops in a deep vein, typically in the leg, but can occur elsewhere such as arm or pelvis

+

- Pulmonary embolism (PE)
  - Complication resulting from the development of a DVT where blood clot breaks off from original location and moves to the lung

=

- Venous thromboembolism (VTE)
  - Collective term for DVT and PE

Definitions

- What else about VTE?
  - Superficial vein thrombosis (SVT)
    - Also called superficial thrombophlebitis
    - Clots which occur in veins near the surface of the skin
  - Catheter-related thrombosis (CRT)
    - Clot associated with a catheter
  - Cerebral vein thrombosis (CVT)
    - Sometimes called cerebral venous sinus thrombosis (CVST)
    - Rare form of stroke which occurs when a clot occurs in the dural venous sinuses
  - Post-thrombotic syndrome (PTS)
    - Chronic venous insufficiency often associated with limitations in physical activity

Venous Anatomy of the Leg

- **Inferior vena cava**
- **Common iliac**
- Internal iliac
- **External iliac**
- **Common femoral**
- **Great saphenous**
- **Deep femoral**
- **Superficial femoral**
- Popliteal
- Gastrocnemic
- Anterior tibial
- Soleus
- Peroneal
- Posterior tibial

Data Registries

Registry	Dates	Age	Events	CNS
Canadian & International – neonatal[1]	1990-1993	First month	VTE (arterial)	No
German – neonatal[2]	1992-1994	First month	VTE (arterial)	Yes
Canadian – children [3]	1990-1992	1 month – 16 years	DVT/PE	No
DPSU (Netherlands)[4]	1997-1999	Birth – 18 years	VTE[a]	Yes
BPSU (United Kingdom)[5]	2001-2003	1 month – 16 years	VTE (arterial)	No

[a] Includes a proportion of asymptomatic neonatal events

Table adapted from Reference 6

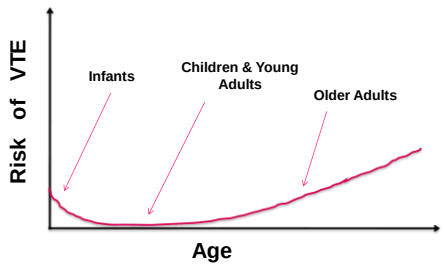
1. Andrew M, et al. *Blood* 1994;83:1251–1257. 2. Schmidt B, et al. *Pediatrics* 1995;96(5 Pt 1):939– 943. 3. Nowak-Gottl U, et al. *Arch Dis Child Fetal Neonatal Ed* 1997;76:F163– F167. 4. van Ommen CH, et al. *J Pediatr* 2001;139:676– 681. 5. Gibson BES, et al. *Thromb Haemost* 2003;1(Suppl. 1):OC422. 6. Chalmers EA. *Thromb Res* 2006;118: 3-12.

Global Incidence

- Relatively rare condition[1,2]
  - Symptomatic VTE as per the Canadian & Dutch registries[3,4]
    - 0.07-0.14 per 10,000 children in the general population
    - 0.51 per 10,000 births in neonates
    - 5.3 per 10,000 hospital admission in children
    - 24 per 10,000 neonatal intensive care unit admissions
    - Bimodal incidence
  - Incidence of PE largely unknown
    - 0.86 per 10,000 pediatric hospital admissions[3]
  - Incidence of asymptomatic VTE largely unknown

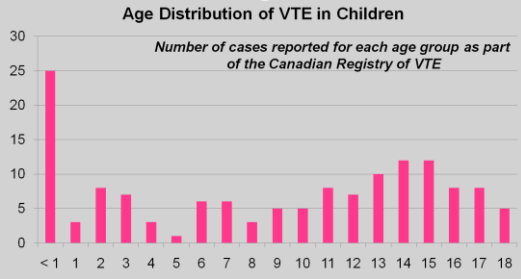
1. Tormene D, et al. *Semin Thromb Hemostasis* 2006;32:724-728. 2. van Ommen CH, et al. *Semin Thromb Hemostasis* 2003;29:391-403. 3. Andrew M, et al. *Blood* 1994;83:1251-1257. 4. van Ommen CH, et al. *J Pediatr* 2001;139:676-681.

VTE Incidence According to Age



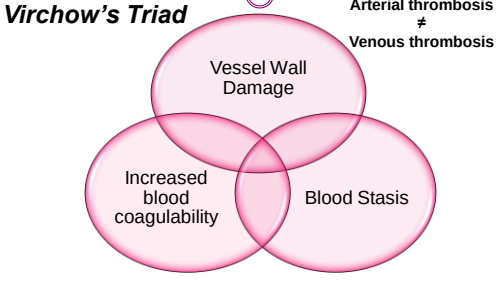
Adapted from Rosendal FR. *Lancet* 1999;353:1167-1173

VTE Incidence in Children



Adapted from Andrew M, et al. Blood 1994;83:1251-1257

Pathophysiology in 1856

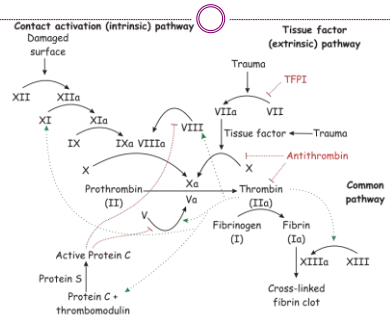


Virchow R. Phlogose und Thrombose im Gefässsystem. In: Virchow R, ed. Gesammelte Abhandlungen zur Wissenschaftlichen Medizin. Frankfurt, Germany: Von Meidinger Sohn; 1856:458–636

Arterial vs. Venous Thrombosis

Arterial	Venous
• Major factor = atherosclerosis (vessel wall changes) as is hypertension, smoking, diabetes, hyperlipidemia • Hypercoagulability has minor role • Blood stasis is not an issue as arterial blood flow rate it high	• Factors which damage vessel wall only appear to slightly increase risk • Prothrombotic and stasis abnormalities play dominate role

Pathophysiology in 2011



http://en.wikipedia.org/wiki/File:Coagulation_full.svg

Risk Factors

Patient	Medical	Hereditary
• Older age • Female sex (?) • Obesity • Smoking • Pregnancy • Minor injury • Immobilization • Prior VTE	• Surgery • Trauma • ***Catheters*** • Varicose veins • ***Cancer*** • Use of OCP • Kidney disorders • Lupus anticoagulant • PNH • IBD • DIC • Thromboangiitis obliterans	• Antithrombin III deficiency • Protein C or Protein S deficiency • Activated protein C resistance • Hypoplasminogenemia • Dysfibrinogenemia • Familial hyperhomocysteinemia

Additive

OCP, oral contraceptive pill; PNH, paroxysmal nocturnal hemoglobinuria; IBD, inflammatory bowel disease; DIC, disseminated intravascular coagulation

1. White RH. *Circulation* 2003;107:I4-I8. 2. Osinbowale O, et al. *Postgrad Med* 2010, 122:54-65. 3. Cole CH. *J Paediatrics Child Health* 2010;46:288-290. 4. Goldhaber SZ. *J Am Coll. Cardiol* 2010;56:1-7. 5. Lyman GH. *Cancer.* 2010 Nov 8. [Epub ahead of print]. 6. Caruso V, et al. *Blood* 2006;108:2216-2222.

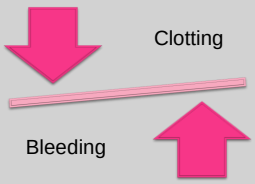
Risk Factors in Relation to Virchow's Triad

Risk Factor	Damage	Coagulation	Stasis	Fibrinolysis
Older age			√	√
Obesity			√	√
Pregnancy		√	√	√
Immobility			√	√
Prior VTE	√	√	√	√
Surgery	√	√	√	√
Trauma	√	√	√	
Varicose veins	√		√	
Cancer	√	√	√	√
Estrogens		√	√	√
Stroke			√	
Thrombophilia		√		√

Adapted from Autar R. *Br J Nurs* 2006;15:980-986

Cancer as a Risk for VTE

- Association between cancer and thrombosis first described by Armand Trousseau in 1865



Trousseau A. *Clique Medicale de l'Hotel-Dieu de Paris*. Vol 3. 2nd ed. Paris: JB Bailliere; 1865:654-712

Relationship Between Cancer & VTE

Stasis	Endothelial Damage	Increased Coaguability
• Tumor • Adenopathy • Patient immobilization	• Catheters • Cancer therapies • Tumor cytokines • Metastasis	• Tumor procoagulants • Platelets • Monocytes • Macophages

1. . Athale UH, et al. *Thromb Res* 2003;111:321-327. 2. Kolomansky A, et al. *IMAJ* 2006;8:848-852. 3. Bajzar L, et al. *Curr Opin Pediatr* 2006;18:1-9. 4. Stoffel N, et al. *Thromb Haemost* 2010;103:1228-1232.

Relationship Between Cancer & VTE

- Procoagulant molecules
  - Tissue factor
    - Also known as tissue thromboplastin and coagulation factor III
    - Over-expressed on tumor cells
    - When bound to factor VIIa, activates factor X and IX resulting in activation of the procoagulant cascade
    - May enhance tumor metastasis
  - Cancer procoagulant
    - Only known physiological substrate is coagulation factor X
    - Activates factor X independently of factor VIIa

1. . Athale UH, et al. *Thromb Res* 2003;111:321-327. 2. Kolomansky A, et al. *IMAJ* 2006;8:848-852. 3. Bajzar L, et al. *Curr Opin Pediatr* 2006;18:1-9. 4. Stoffel N, et al. *Thromb Haemost* 2010;103:1228-1232.

Relationship Between Cancer & VTE

- Cytokines
  - Tumor necrosis factor alpha (TNF-α)
    - Primary function is to regulate immune cells
    - Responsible for inflammation
  - Interleukin one beta (IL-1β)
    - Also known as catabolin

1. . Athale UH, et al. *Thromb Res* 2003;111:321-327. 2. Kolomansky A, et al. *IMAJ* 2006;8:848-852. 3. Bajzar L, et al. *Curr Opin Pediatr* 2006;18:1-9. 4. Stoffel N, et al. *Thromb Haemost* 2010;103:1228-1232.

VTE Risk Factor – Cancer

- Active diagnosis (especially if within past 6 months)
- Advanced disease/Metastatic disease
- Cancer type
  - Pancreatic
  - Lung
  - Ovarian
  - Malignant brain tumors
  - Renal cell carcinoma
  - Myeloproliferative disorders
  - Stomach
  - Colon
  - Bladder
  - Prostate
  - Testicular
  - Lymphoma

NCCN Clinical Practice Guidelines in Oncology. *Venous thromboembolic disease* (V.1.2010).

VTE Risk Factor – Pediatric Cancer

- Acute lymphoblastic leukemia (ALL)
  - Incidence widely varied in several published studies
    - BFM protocols (1.7% - 14.3%)
    - DFCI protocols (4.1% - 11.5%)
  - Inflammatory response
    - Increase in factor VIII, von Willebrand factor and fibrinogen
  - Increase in thrombin generation
  - High rate of infection

1. Athale UH, et al. *Thromb Res* 2003;111:125-131. 2. Athale UH, et al. *Thromb Res* 2003;111:199-212. 3. Athale UH, et al. *Thromb Res* 2003;111:321-327. 4. Nowal-Gotti U, et al. *Best Prac Res Clin Haematol* 2009;22:103-114. 5. Payne JH, et al. *Br J Haematol* 2007;138:430-445. 6. Athale U, et al. *Br J Haematol* 2005;129:803-810.

VTE Risk Factor – Pediatric Cancer

- Malignant brain tumors
  - Conflicting information
    - 462 patients treated at one center[1]
    - 253 patients treated at one center[2]
  - Neurosurgical interventions
  - Release of tissue factor
  - Disruption of the blood brain barrier
  - Metastatic disease
  - Compounded by placement of central venous access device

1. Tabori U et al. *Pediatr Blood* Cancer 2004;43;633-636. 2. Deitcher SR, et al. *J Pediatr* 2004;145:848-850

VTE Risk Factor – Pediatric Cancer

- Neuroblastoma[1]
  - Case series of 6 patients
  - Risk associated with involvement of the inferior vena cava
  - Related to catheters
  - Associated with procoagulant factors
    - Tissue factor (TF)
    - Vascular endothelial growth factor (VEGF)
- Sarcomas[2]

1. Schiavetti A, et al. *J Pediatr Hematol Oncol* 2010;32:93-96. 2. Athale U, et al. *Pediatr Blood Cancer* 2007;49:171-176.

VTE Risk Factor – Cancer Treatment

- Major surgery
- Placement of catheters
- Traditional chemotherapy
  - Estramustine
  - **L-asparaginase products**
- Biological therapy and other treatments
  - **Steroids** Thalidomide, Lenolidamide
  - Bevacizumab Epoetin alpha products
  - Hormonal agents (e.g., tamoxifen, raloxifene)

1. Athale UH, et al. *Thromb Res* 2003;111:199-212. 2. Athale UH, et al. *Semin Thromb Hemostat* 2007;33:416-426. 3. NCCN Clinical Practice Guidelines in Oncology. *Venous thromboembolic disease* (V.1.2010).

VTE Risk Factor – Chemotherapy

- Prothrombotic state – general mechanisms
  - Direct tumor cell damage → release of procoagulants and cytokines
  - Free radical formation, endothelial cell apoptosis, and increase in tissue factor expression/activity → direct vascular endothelial toxicity
  - Decreased synthesis of antithrombotic molecules

1. Athale UH, et al. *Thromb Res* 2003;111:199-212. 2. Athale UH, et al. *Semin Thromb Hemostat* 2007;33:416-426.

VTE Risk Factor – Chemotherapy

- L-asparaginase products
  - Consumption of coagulation factors? NO
  - Decreased synthesis of coagulation factors? YES
    - Reductions in fibrinogen, **plasminogen and antithrombin**
  - When VTE occurs, what about re-exposure?
    - UK ALL 2003 study[3]
      - Pegylated-L-asparaginase at a dose of 1000 IU/m2 used
      - 59 of 1824 patients developed VTE (3.2%)
        - 70% during induction
      - 34 patients re-challenged with the addition of a form of heparin prophylaxis without problems

1. Athale UH, et al. *Thromb Res* 2003;111:199-212. 2. Athale U, et al. *Br J Haematol* 2005;129:803-810. 3. Athale UH, et al. *Semin Thromb Hemostat* 2007;33:416-426. 4. Qureshi A, et al. *Br J Haematol* 2010;149:410-413. 5. Kieslich M, et al. *J Pediatr Hematol Oncol* 2003;25:484-487.

VTE Risk Factor – Chemotherapy

- L-asparaginase products
  - Dana Farber Cancer Institute experience
    - Rate of VTE was 8% in 548 patients (= 43 patients)
      - 27 of 501 children (5%)
      - 16 of 47 adults (34%)
      - 74% received low molecular weight heparin after VTE
        - 9% epistaxis
        - 2% bruising
        - 2 episodes of major bleeds in adults
      - 70% of patients (30 patients) went on to receive 85% of planned asparaginase doses
        - 33% recurrent VTE (17% children and 47% adults)

Grace RF, et al. *Br J Haematol* 2011;152:452-459.

VTE Risk Factor – Chemotherapy

- L-asparaginase products – PARKAA study
  - **P**rophylactic **A**ntithrombin **R**eplacement in **K**ids with **A**cute Lymphoblastic Leukemia Treated with **A**sparaginase
  - Objectives
    - Primary
      - Determine prevalence of VTE/characterize VTE
      - Trend efficacy and safety of antithrombin treatment
    - Secondary:
      - Detect any association of VTE with congenital or acquired prothrombotic disorders

1. Mitchell LG, et al. *Cancer* 2003;97:508-516. 2. Mitchell L, et al. *Thromb Haemost* 2003;90:235-244. 3. Korte W, et al. *Thromb Haemost* 2003;90:163-164. 4. Male C, et al. *Blood* 2003;101:4273-4278.

VTE Risk Factor – Chemotherapy

- L-asparaginase products – PARKAA study
  - Methods
    - Phase II 2:1 randomization (2 placebo:1 antithrombin therapy) in 10 tertiary cancer centers in the US and Canada
    - Children with ALL screened for VTE after asparaginase therapy with a variety of diagnostic methods
    - Symptomatic VTE confirmed with appropriate tests
    - Antithrombin therapy
      - Once weekly infusion x 4 weeks to increase plasma concentrations of antithrombin to ~ 3 units/mL but no more than 4 units/mL

1. Mitchell LG, et al. *Cancer* 2003;97:508-516. 2. Mitchell L, et al. *Thromb Haemost* 2003;90:235-244. 3. Korte W, et al. *Thromb Haemost* 2003;90:163-164. 4. Male C, et al. *Blood* 2003;101:4273-4278.

VTE Risk Factor – Chemotherapy

- L-asparaginase products – PARKAA study
  - Results – non-treatment group
    - 22 of 60 kids (36.7%) had a VTE
      - 19 patients had VTE located in the upper central venous system
      - None of the patients were positive for factor V Leiden or prothrombin gene 20201A
      - 4 of 8 patients with VTE had antiphospholipid antibodies

P = 0.43

  - Results – antithrombin group
    - 7 of 25 kids (28%) had a VTE
      - All in the upper central venous system
      - No major bleeding; 2 minor bleeding (in the treatment arm)
      - No patients positive for prothrombin gene 20201A; 2 patients positive for factor V Leiden

1. Mitchell LG, et al. *Cancer* 2003;97:508-516. 2. Mitchell L, et al. *Thromb* Haemost 2003;90:235-244. 3. Korte W, et al. *Thromb* Haemost 2003;90:163-164. 4. Male C, et al. *Blood* 2003;101:4273-4278.

VTE Risk Factor – Chemotherapy

- L-asparaginase products – PARKAA study[1-4]
  - Conclusions
    - Prevalence of VTE high in this patient population
    - Antithrombin therapy MAY be safe and efficacious in preventing VTE in this patient population
    - No trend between VTE and congenital prothrombotic disorders but there was an association with antiphospholipid antibodies
- L-asparaginase products – prophylaxis with fresh frozen plasma and cryoprecipitate[5]
  - Routine prophylaxis is not warranted to prevent central nervous system VTE

1. Mitchell LG, et al. *Cancer* 2003;97:508-516. 2. Mitchell L, et al. *Thromb* Haemost 2003;90:235-244. 3. Korte W, et al. *Thromb* Haemost 2003;90:163-164. 4. Male C, et al. *Blood* 2003;101:4273-4278. 5. Abbott LS, et al. *Blood* 2009;114:5146-5151

VTE Risk Factor – Chemotherapy

- Steroids
  - Known to increase platelet counts
  - Can cause a hypofibrinolytic state (increase in PAI-1 levels)

↑ **Factor VIII**
von Willebrand factor
Prothrombin
Antithrombin

↓ **Fibrinogen**
Plasminogen

  - What are the effects/risks relative to type, dose, duration?

1. Athale UH, et al. *Thromb Res* 2003;111:199-212. 2. Athale U, et al. *Br J Haematol* 2005;129:803-810. 3. Athale UH, et al. *Semin Thromb Hemostat* 2007;33:416-426. 4. Nowak-Gottl U, et al. *Best Pract Res Clin Haematol* 2009;22:103-114. 5. Nowak-Gottl U, et al. *Blood* 2003;101:2529-2533.

Risk Stratification for VTE

- Adult literature
  - Wells[1]
    - Wells Criteria or Score
  - Abdel-Razeq[2]
    - Comprehensive cancer center population model
  - Zhou[3]
    - Comprehensive cancer center lymphoma population
  - Khorana[4]
    - Multicenter cancer center population model
- Pediatric literature
  - Predictive model in acute lymphoblastic leukemia patients[5]

1. Scarvelis D, et al. CMAJ 2006;175:1087-1092. 2. Abdel-Razeq HN, et al. *J Thromb Thrombolysis* 2010;30:286-293. 3. Zhou X, et al. *Am J Med* 2010;123;935-941. 4. Khorana AA, et al. Blood 2008;111:4902-4907. 5. Mitchell L, et al. *Blood* 2010;115:4999-5004.

Quick Fact

"Only about half of the people with DVT experience symptoms. Sometimes DVT produces minimal or no symptoms"

http://www.preventdvt.org/docs/pdf/DVTAtAGlance.PDF

VTE Clinical Presentation

- Lower extremity
  - Swelling, tenderness, warmth, erythema
  - Potential organ damage: post-thrombotic syndrome
- Upper extremity
  - Facial swelling, prominent superficial veins
  - Potential organ damage: post-thrombotic syndrome
- Portal vein
  - Abdominal pain, portal hypertension
  - Potential organ damage: ascites
- Hepatic vein
  - Right upper quadrant pain, hepatomegaly
  - Potential organ damage: liver dysfunction

Young G. *Pediatr Blood Cancer* 2006;46:540-546.

VTE Clinical Presentation

- Mesenteric vein
  - Generalized abdominal pain
  - Potential end organ damage: ileus
- Renal vein
  - Lumbar tenderness, fever, hematuria, enlarged kidney
  - Potential organ damage: renal dysfunction
- Splenic vein
  - Left upper quadrant pain, splenomegaly
  - Potential organ damage: hypersplenism

Young G. *Pediatr Blood Cancer* 2006;46:540-546.

VTE Clinical Presentation

- Superior vena cava
  - Headache, neck pain, head and neck swelling
  - Potential organ damage: rare neurologic symptoms
- Pulmonary artery
  - Dyspnea, tachypnea, chest pain, cough, hemoptysis, anxiety, fever, cyanosis
  - Potential organ damage: hypoxemia, respiratory failure
- Cerebral sinus
  - Headache, neurologic deficits, seizures
  - Potential organ damage: occasional neurologic sequelae

Young G. *Pediatr Blood Cancer* 2006;46:540-546.

VTE Location in Children

Distribution of Peripheral DVT and PE in Children from Three International Registries

Site of VTE	*Canada*[1]	*Netherlands*[2]	*United Kingdom*[3]
Upper limb (UL) DVT	47 (34%)	5 (14%)	48 (30%)
Lower limb (LL) DVT	68 (50%)	21 (60%)	95 (59%)
PE alone	8 (6%)	4 (11%)	5 (3%)
UL DVT + PE	3 (2%)	2 (6%)	6 (4%)
LL DVT + PE	11 (8%)	3 (9%)	6 (4%)
Total	137	35	160

Table adapted from Reference 4

1. Nowak-Gottl U, et al. *Arch Dis Child Fetal Neonatal Ed* 1997;76:F163– F167. 2. van Ommen CH, et al. *J Pediatr* 2001;139:676– 681. 3. Gibson BES, et al. *Thromb Haemost* 2003;1(Suppl. 1):OC422. 4. Chalmers EA. *Thromb Res* 2006;118: 3-12.

VTE Diagnosis

- Obtain complete history
  - Details of event
  - Past medical history
  - Family history
  - Medication inventory
- Physical exam
- Laboratory analysis
  - Comprehensive metabolic panel
  - Complete blood count
  - PT/PTT
  - Urine analysis

Streif W, et al. *Hematol Oncol Clin N Am* 1998;12:1283-1312.

VTE Diagnosis

- Special laboratory analysis
  - Factor V Leiden
    - Mutation renders factor Va less readily susceptible to inactivation by Protein C
  - Prothrombin
    - G20210A mutation
      - Increase in messenger RNA → increase in prothrombin synthesis → increase in circulating thrombin
  - Protein C
  - Protein S
  - Antithrombin III

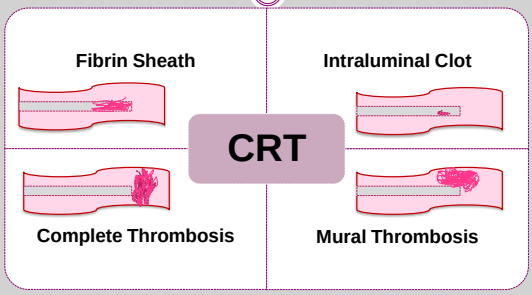
1. Streif W, et al. *Hematol Oncol Clin N Am* 1998;12:1283-1312. 2. Nowak-Gottl U, et al. *Thromb Haemost* 2001;86:464-474. 3. Gurgey A, et al. *Blood Coagul Fibrinolysis* 2004;15:657-662.

VTE Diagnosis

Test	*Advantages*	*Disadvantages*
D-Dimer	Fast, inexpensive	Variable sensitivity, in some patients specificity is poor
Doppler Ultrasound	Fairly inexpensive, easy to perform at bedside, high sensitivity for proximal DVT and internal jugular)	Operator variability, poor sensitivity for calf and pelvic DVT, not well established in children
Computed tomography venongraphy	High sensitivity and specificity for central and pelvic DVT, can be used when patient has contraindication to MRI	Expensive, need for contrast media, radiation exposure, little data on use in children
Magnetic resonance venography	High sensitivity and specificity for central and pelvic DVT (ideal for cerebral sinus thrombosis), doesn't rely on contrast media	Expensive, low availability, can't be used in patients with aneurysm clips, pacemakers or who are claustrophobic, may require sedation
Contrast venography	High sensitivity and specificity for DVT (except internal jugular), including in calf	Invasive, low availability, need for contrast media, radiation exposure, risk of complications (thrombophlebitis)

1. Somarouthu B, et al. *Postgrad Med* 2010, 122:66-73. 2. Young G. *Pediatr Blood Cancer* 2006;46:540-546.

Catheter-Related Thrombosis (CRT)



1. McCloskey DJ. *Pediatr* Nurs 2002;28:97. 2. Rosovsky RP, et al. *Hematol Oncol Clin N* Am 2005;19:183-202.

Catheter-Related Thrombosis (CRT)

- Risk factors
  - Infection
  - Underlying diagnosis
  - Catheter location/insertion technique
  - Inherited thrombophilia
- Signs and symptoms (often asymptomatic)
  - Erythema, warmth
  - Swelling in extremity, face, neck, axilla
  - Dilation of superficial veins
  - Recurrent bacteremia
  - Pain in shoulder, jaw, axilla
  - Drop in platelet counts

1. McCloskey DJ. *Pediatr* Nurs 2002;28:97. 2. Male C, et al. *Blood* 2003;101:4273-4278. 3. Fratino G, et al. *Ann Oncol* 2005;16:648-654. 4. Rosovsky RP, et al. *Hematol Oncol Clin N* Am 2005;19:183-202. 5. Pinon M, et al. *Eur J Pediatr* 2009;168:1505-1512. 6. Worth LJ, et al. *Support Care Cancer* 2009;17:811-818. 7. Journeycake JM, et al. *J Clin Oncol* 2006;24:4575-4580. 8. Shivakumar SP, et al. *J Clin Oncol* 2009;27:4858-4864. 9. Revel-Vilk S, et al. *Cancer* 2010;116:4197-4205. Ociepa T, et al. *J Pediatr Hematol Oncol* 2010;32:88-92.

Catheter-Related Thrombosis (CRT)

- Complications
  - Occlusion of catheter
  - Loss of catheter
  - Infections
  - Pulmonary embolism
  - Post-thrombotic syndrome

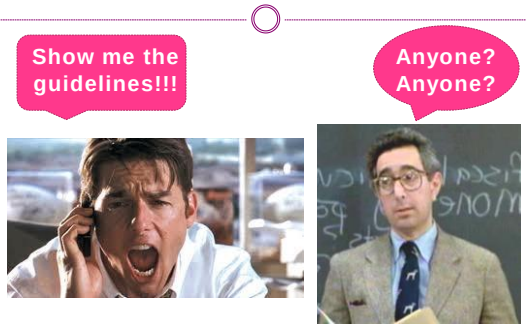
1. McCloskey DJ. *Pediatr* Nurs 2002;28:97. 2. Male C, et al. *Blood* 2003;101:4273-4278. 3. Fratino G, et al. *Ann Oncol* 2005;16:648-654. 4. Rosovsky RP, et al. *Hematol Oncol Clin N* Am 2005;19:183-202. 5. Pinon M, et al. *Eur J Pediatr* 2009;168:1505-1512. 6. Worth LJ, et al. *Support Care Cancer* 2009;17:811-818. 7. Kuhle S, et al. *J Thromb Haemost* 2008;6:589-594.

Quick Fact

"DVT-related PE is the leading cause of preventable hospital death in US hospitals"

http://www.preventdvt.org/docs/pdf/DVTAtAGlance.PDF

Treatment & Prophylaxis of VTE in Pediatric Cancer Patients



Guidelines in Cancer Patients

- American Society of Clinical Oncology (ASCO)[1]
- National Comprehensive Cancer Network (NCCN)[2]
- European Society of Medical Oncology (ESMO)[3]
- Italian Association of Medical Oncology (AIOM)[4]
- French National Federation of the League of Centers Against Cancer (FNCLCC)[5,6]
- American College of Chest Physicians (ACCP)[7]

1. Lyman GH, et al. *J Clin Oncol* 2007;25:5490-5505. 2. NCCN Clinical Practice Guidelines in Oncology. *Venous thromboembolic disease* (V.1.2010). 3. Mandala M, et al. *Ann Oncol* 2008;19(Suppl 2):ii126-127. 4. Mandala M, et al. *Crit Rev Oncol Hematol* 2006;59:194-204. 5. Debourdeau P, et al. *Ann Oncol* 2009;20:1459-1471. 6. Farge D, et al. *Crit Rev Oncol Hemtaol* 2010;73:31-46 7. Monagle P, et al. *Chest* 2008;133:887S-968S. 8. Khorana AA, et al. *J Clin Oncol* 2009;27:4919-4926.

Guidelines Caveats

- Issues
  - Under- or misdiagnosis of VTE
  - Developing hemostatic system
  - Alterations in pharmacokinetics and pharmacodynamics
  - Dietary differences
  - Lack of "pediatric friendly" anticoagulants
  - Compliance with anticoagulant regimens
  - Lack of randomized controlled trials

1. Monagle P. *Heart* 2004;90:808-812. 2.Trenor III CC. *Blood Coagul Fibrinolysis* 2010;21(Suppl 1):S11-S15.

Treatment of VTE in Pediatric Cancer Patients

- Management of DVT should follow the general recommendations of management of DVT in children (Grade = 2C)
- Suggest use of a low molecular weight heparin for a minimum of 3 months until precipitating factor has resolved (Grade = 2C)
- Presence of cancer and the need for cancer therapies or other treatments may modify the risk-benefit ratio for the treatment of DVT and these factors should be taken into consideration

Monagle P, et al. *Chest* 2008;133:887S-968S.

Treatment of VTE in Pediatric Cancer Patients

- First DVT
  - Unfractionated heparin or low molecular weight heparin (Grade = 1B)
  - Treat for at least 5-10 days (Grade = 1B)
    - If vitamin K antagonists are planned:
      - Start on Day 1 and discontinue heparin product on Day 6 (or later if INR < 2) (Grade = 1B)
        - For unfractionated heparin, goal is aPTT that corresponds to anti-Factor Xa of 0.35-0.7 U/mL
        - For low molecular weight heparin, goal is anti-Factor Xa of 0.5-1 U/mL 4 hours after an injection for BID dosing
      - After 5-10 days of treatment, if vitamin K antagonist is too challenging for the patient/family or is not maintaining therapeutic INR, change to low molecular weight heparin (Grade = 2C)

Monagle P, et al. *Chest* 2008;133:887S-968S.

Treatment of VTE in Pediatric Cancer Patients

- First DVT (catheter and non-catheter related)
  - In the setting of idiopathic VTE:
    - Treat for at least 6 months with vitamin K antagonist to achieve and INR of 2.5 (range 2-3) or alternatively with low molecular weight heparin to maintain an anti-Factor Xa level of 0.5-1 U/mL (Grade = 2C)
      - Relatively high value is placed on avoiding inconvenience and risk of bleeding and relatively low value placed on avoiding the unknown risk of recurrence in the absence of an ongoing risk factor

Monagle P, et al. *Chest* 2008;133:887S-968S.

Treatment of VTE in Pediatric Cancer Patients

- Secondary thrombosis
  - Risk factor resolved
    - Vitamin K antagonist therapy for at least 3 months, achieving an INR of 2.5 (range 2-3), or alternatively using low molecular weight heparin to maintain an anti-Factor Xa level of 0.5-1 U/mL (Grade = 2C)
  - Risk factor continues (but potentially reversible)
    - Continuing anticoagulant therapy in either therapeutic or prophylactic doses until resolution of risk factor (Grade = 2C)

Monagle P, et al. *Chest* 2008;133:887S-968S.

Treatment of VTE in Pediatric Cancer Patients

- Recurrent idiopathic VTE
  - Indefinite treatment with vitamin K antagonist to achieve and INR of 2.5 (range 2-3) (Grade = 1A)
    - Long-term use of low molecular weight heparin may be preferable, but little or no data about safety is available
- Recurrent secondary VTE (existing reversible risk factor for thrombosis)
  - Use of anticoagulant until precipitating risk factor has been removed (therapy for a minimum of 3 months (Grade = 2C)

Monagle P, et al. *Chest* 2008;133:887S-968S.

Treatment of VTE in Pediatric Cancer Patients

- Catheter-related thrombosis
  - If no longer required or malfunctioning
    - Remove catheter (Grade = 1B)
    - Anticoagulant for at least 3-5 days prior to removal (Grade = 2C)
  - If still needed and is functioning
    - Keep catheter and anticoagulate patient (Grade = 2C)
    - See next slide

Monagle P, et al. *Chest* 2008;133:887S-968S.

Treatment of VTE in Pediatric Cancer Patients

- Catheter-related thrombosis
  - 1st VTE and still need catheter
    - Vitamin K antagonist therapy for at least 3 months, achieving an INR of 2.5 (range 2-3), or alternatively using low molecular weight heparin to maintain an anti-Factor Xa level of 0.5-1 U/mL (Grade = 2C)
    - After 3 months of therapy, give prophylactic doses of vitamin K antagonist therapy to achieve INR of 1.5-1.9 or low molecular weight heparin to achieve an anti-Factor Xa level of 0.1-0.3 U/mL, continuing therapy until catheter is removed (Grade = 2C)
      - If thrombosis recurs during prophylactic therapy, continue therapeutic doses until catheter is removed but for at least 3 months (Grade = 2C)

Monagle P, et al. *Chest* 2008;133:887S-968S.

Treatment of VTE in Pediatric Cancer Patients

- Use of thrombolysis for DVT
  - Not to be used routinely (Grade = 2C)
  - If used, then supplement with plasminogen in the setting of physiologic or pathologic plasminogen deficiencies (Grade = 2C)

Monagle P, et al. *Chest* 2008;133:887S-968S.

Quick Fact

"Because DVT can occur with little or no warning, the best action to take against DVT is ***prevention***"

http://www.preventdvt.org/docs/pdf/DVTAtAGlance.PDF

Audience Response Question

- How often do you routinely provide primary VTE prophylaxis to your pediatric cancer patients?
  - A. Rarely, if ever
  - B. Only to high risk patients
  - C. Most, if not all, of the time

Audience Response Question

- If you provide primary VTE prophylaxis to your patients, how do you accomplish this?
  - A. Aspirin
  - B. Warfarin
  - C. Low molecular weight heparin
  - D. Other agent

Prophylaxis for VTE in Pediatric Cancer Patients

Evidence-Based Guidelines for Primary Prophylaxis of VTE in Children

Prophylaxis Recommended	Prophylaxis Not Recommended
Children receiving long-term home TPN (Use VKA to target INR of 2.5 (Range of 2-3) (Level of evidence = 2C)	***Children with cancer and central venous access devices (Level of evidence = 2C)***
Complex cardiac patients and associated procedures (Level of evidence = 1B (Fontan) and 2C)	Children with central venous lines (Level of evidence = 1B)
	Patients undergoing hemodialysis via central venous line or fistula (Level of evidence = 2C)

Adapted from Cole CH. *J Paediatrics Child Health* 2010;46:288-290. Monagle P, et al. *Chest* 2008;133:887S-968S.

Prophylaxis for VTE in Pediatric Cancer Patients

- Mitchell et al[1]
  - Antithrombin (25 patients) vs. placebo (60 patients)
  - VTE 37% vs. 28%
  - Study not powered to efficacy; specific to ALL
- Ruud et al[2]
  - Warfarin (29 patients) vs. control (33 patients)
  - VTE 20% vs. 24%
  - Study underpowered
- Massicotte et al[3]
  - Low molecular weight heparin (78 patients) vs. standard of care (80 patients)
  - VTE 14.1% vs. 12.5%
  - Study underpowered; not specific to cancer; only patients with catheters included

1. Mitchell L, et al. *Thromb* Haemost 2003;90:235-244. 2. Ruud E, at l. *Acta Pediatr* 2006;95:1053-1059. 3. Massicotte P, et al. *Thromb Res* 2003;109:101-108.

Unfractionated Heparin

- Unfractionated heparin
  - Agents: numerous
  - MOA: allows antithrombin to more quickly inactivate coagulation enzymes thrombin (IIa) and factor Xa
  - Goal: PTT of 1.5-2.5 times normal (age dependent?)
    - aPTT 60-85 seconds ~ anti-Factor Xa 0.35-0.7 U/mL
  - Age-dependent clearance

1. Monagle P, et al. *Chest* 2008;133:887S-968S. 2. Payne JH. *Br J* Haematol 2010;150:259-277

Unfractionated Heparin

aPTT, seconds	Bolus, U/kg	Hold, min	Rate Repeat Change, %	aPTT, hour
<50	50	0	+10	4
50-59	0	0	+10	4
60-85	0	0	0	Next day
86-95	0	0	-10	4
96-120	0	30	-10	4
>120	0	60	-15	4

1. **Loading dose = heparin 75 U/kg over 10 mins**
2. **Initial maintenance dose: 28 U/kg/hour < 1yr; 20 U/kg/hour > 1yr**
3. **Goal is aPTT 60-85 seconds**
4. **Blood draws 4 hours after loading dose and 4 hours after every change to infusion**
5. **Daily CBC and aPTT when aPTT is within therapeutic range**

Adapted from Monagle P, et al. *Chest* 2008;133:887S-968S.

Unfractionated Heparin

Advantages	Disadvantages
• Familiarity • Rapid onset of action • Short half-life • Published data in children • Antidote available	• Unpredictable dose response • Requires antithrombin • Need for frequent monitoring/inpatient use • Not effective in neutralizing clot-bound thrombin • Adverse events → heparin-induced thrombocytopenia, osteoporosis

1. Young G. *Pediatr Blood Cancer* 2006;46:540-546. 2. Payne JH. *Br J Haematol* 2010;150:259-277.

Heparin-Induced Thrombocytopenia (HIT)

The Four "T's" of Heparin-Induced Thrombocytopenia (HIT) Point System

	2	1	0
Thrombo-cytopenia	> 50% fall to nadir ≥ 20 x 10^9/L	30-50% fall (or >50% fall due to surgery) or nadir 10-19 x 10^9/L	< 30% fall or nadir < 10 x 10^9/L
Timing	Days 5-10 or ≤ Day 1 with recent heparin (past 30 days)	> Day 10 or unclear timing or < Day 1 with recent heparin (past 31-100 days)	< Day 4 (no recent heparin activity)
Thrombosis	Proven new thrombosis, skin necrosis or acute anaphylaxis after IV heparin bolus	Progressive or recurrent thrombosis, erythematous skin lesions, suspected thrombosis (not proven), asymptomatic upper limb DVT	None
oTher causes	None evident	Possible	Definite

Score 0-3 – Monitor patient; Score 4-8 – Supportive care and/or interventions

Ahmed I, et al. *Postgrad Med J* 2007;83:575-582.

Heparin-Induced Thrombocytopenia (HIT)

- Management
  - Evaluate patient
  - Discontinue heparin and vitamin K antagonists
  - Check heparin antibody
  - Change anticoagulation
    - Fondaparinux
    - Agatroban (Caution in hepatic dysfunction)
    - Lepirudin (Dose adjust in renal dysfunction)
    - Bivalirudin (Close monitoring in renal dysfunction)
    - Desirudin (Dose adjust in renal dysfunction)
  - Transition back to warfarin

Ahmed I, et al. *Postgrad Med J* 2007;83:575-582.

Low Molecular Weight Heparin

- Low molecular weight heparin
  - Agents:
    - Enoxaparin (Lovenox®)
    - Tinzaparin (Innohep®),
    - Nadroparin (Fraxiparine®)
    - Certoparin (Sandoparin®)
    - Dalteparin (Fragmin®)
    - Ardeparin (Normiflo®)
    - Reviparin (Clivarine®)
  - MOA: Specific binding to factor Xa
  - Goal: Factor Xa level 0.5-1 U/mL (4-6 hours after therapy)
    - Enoxaparin has 110 anti-Factor Xa U/mg
    - Dalteparin has 100 anti-Factor Xa U/mg
    - Reviparin has 120 anti-Factor Xa U/mg
  - Preferred agent in pediatric cancer patients
    - Ease of administration and monitoring
    - For lumbar punctures – may wish to omit 2 doses before procedure and resume 12-24 hours after procedure

1. Sutor AH, et al. *Semin Thromb Hemostasis* 2004;30 (Supp 1):31-39. 2. Ho SH, et al. *J Pediatr Hematol Oncol* 2004;26:561-566. 3. Ignjatovic V, et al. *Br J Haematol* 2010;149:734-738.

Low Molecular Weight Heparin

Agent & Use	Patient Age or Weight	Dose
Enoxaparin, mg/kg , Q 12 h initial treatment	Age > 2 months	1
Enoxaparin, mg/kg, Q 12 h initial prophylaxis	Age > 2 months	0.5
Daltaparin, U/kg, Q 24 h initial treatment	All	129 ± 43
Daltaparin, U/kg, Q 24 h initial prophylaxis	All	92 ± 52
Tinzaparin, U/kg, Q 24 h initial treatment	2-12 months	250
	1-5 yr	240
	5-10 yr	200
	10-16 yr	175
Reviparin, U/kg, Q 12 hr initial treatment	> 5 kg	100
Reviparin, U/kg, Q 12 hr initial prophylaxis	> 5 kg	30

Adapted from Monagle P, et al. *Chest* 2008;133:887S-968S.

Low Molecular Weight Heparin

Advantages

- Longer half-life and subcutaneous administration allows for outpatient use
- More predictable pharmacokinetic profile
- Less monitoring than heparin
- Less bleeding and thrombocytopenia than heparin
- Some published data in children

Disadvantages

- Subcutaneous administration not for every patient
- Still some monitoring
- Antidote is only partially effective
- Adverse effects → osteoporosis, contraindicated in patients with heparin-induced thrombocytopenia

1. Young G. *Pediatr Blood Cancer* 2006;46:540-546. 2. Payne JH. *Br J Haematol* 2010;150:259-277.

Vitamin K Antagonists (Warfarin)

- Vitamin K antagonists (warfarin)
  - Agents: Warfarin (Coumadin®)
  - MOA: Inhibits Vitamin K dependent factors II, VII, IX and X
  - Goal: INR of 2-3
  - www.warfarindosing.org
    - Barnes Jewish Hospital/University of Washington (St. Louis, MO)
    - Patient must be ≥ 20 years old
  - 6 weeks compared to 3 months
    - Evaluation of the Duration of Therapy for Thrombosis in Children (Kids-DOTT) (http://clinicaltrials.gov/ct2/show/NCT00687882)

1. Trenor III CC. *Blood Coagul Fibrinolysis* 2010;21(Suppl 1):S11-S15. 2. Payne JH. *Br J Haematol* 2010;150:259-277.

Vitamin K Antagonists (Warfarin)

Therapy	INR	Action
Day 1	If Baseline 1-1.3	Dose 0.2 mg/kg PO
Day 2-4	1.1-1.3	Repeat initial loading dose
	1.4-1.9	Repeat 50% of initial loading dose
	2-3	Repeat 50% of initial loading dose
	3.1-3.5	Repeat 25% of initial loading dose
	> 3.5	Hold until INR < 3.5; resume 50% of previous dose
Maintenance	1.1-1.4	Increase dose by 20%
	1.5-1.9	Increase dose by 10%
	2-3	No change in therapy
	3.1-3.5	Decrease dose by 10%
	> 3.5	Hold until INR < 3.5; resume 20% of previous dose

Adapted from Monagle P, et al. *Chest* 2008;133:887S-968S.

Vitamin K Antagonists (Warfarin)

Advantages	Disadvantages
• Oral administration • Longer half-life allows for ease of administration • Familiarity • Inexpensive • Available antidote • Published studies in children	• Requires "bridge" therapy before effects are seen • Unpredictable dose response (genetic polymorphisms) • Narrow therapeutic index • Numerous food- and drug-drug interactions • Requires frequent monitoring

1. Young G. *Pediatr Blood Cancer* 2006;46:540-546. 2. Ruud E. et al. *Pediatr Blood Cancer* 2006;50:710-713. 3. Bonduel. *Thromb Res* 2006;118:85-94. 4. Payne JH. *Br J Haematol* 2010;150:259-277.

Direct Thrombin Inhibitors

- Direct thrombin inhibitors
  - Agents:
    - Agatroban
    - Dabigatran (Pradaxa®)
    - Ximelagatran (Exanta)
    - Bivalirudin (Angiomax®)
    - Lepirudin (Refludan®)
    - Desirudin (Iprivask®)
  - MOA: Acts independently of antithrombin and other plasma proteins
  - Goal: Steady state aPTT 1.5-3 times baseline starting two hours after therapy (should be ≤ 100 seconds)
  - Pediatric dosing recommendations
    - www.argatroban.com

Payne JH. *Br J Haematol* 2010;150:259-277.

Direct Thrombin Inhibitors

Advantages	Disadvantages
• Predictable dose response, pharmacokinetics • Rapid onset of action, short-half-life • Inhibits clot-bound as well as free thrombin • Doesn't rely on antithrombin • No risk of heparin-induced thrombocytopenia	• Expensive • Administration by continuous infusion • No available antidote (recombinant factor VIIa?) • Little published pediatric literature

1. Young G. *Pediatr Blood Cancer* 2006;46:540-546. 2. Payne JH. *Br J Haematol* 2010;150:259-277.

Fondaparinux

- Fondaparinux (Arixtra®)
  - MOA: direct factor Xa inhibitor
  - Prospective dose finding and safety study in children
    - http://clinicaltrials.gov/ct2/show/NCT00412464

Payne JH. *Br J Haematol* 2010;150:259-277.

Fondaparinux

Advantages	Disadvantages
• Predictable dose response • Longer half-life allows for daily dosing • No cross reactivity with heparin-induced antibodies	• Subcutaneous administration not for all patients • No available antidote • Few published case reports in children

1. Young G. *Pediatr Blood Cancer* 2006;46:540-546. 2. Payne JH. *Br J Haematol* 2010;150:259-277.

Thrombolytic Therapy

- Agents
  - Tissue plasminogen activator (tPA)
    - Alteplase (Activase®)
    - Reteplase (Retavase®)
    - Tenecteplase (TNKase®)
  - Anistreplase (Eminase®)
  - Streptokinase (Kabikinase®, Streptase®)
  - Urokinase (Abbokinase®)
- MOA: Serine proteases convert plasminogen to plasmin → breaks down fibrinogen and fibrin → clot dissolution
- Which one to use?

1. Dillon PW. *J Clin Oncol* 2004;22:2718-2723. 2. Yee DL, et al. *Pediatr Blood Cancer* 2009;53:960-966. 3. Kerlin BA. *Pediatr Blood Cancer* 2009;53:920-921.

Thrombolytic Therapy

Local Instillation of Tissue Plasminogen Activator

Weight	Catheter type	Action
<10 kg	Single lumen CVL	0.5 mg diluted in 0.9% NS to volume required to fill line
	Double lumen CVL	0.5 mg diluted in 0.9% NS to volume required to fill line; treat one lumen at a time
	SC Port	0.5 mg diluted in 0.9% NS to 3 mL
> 10 kg	Single lumen CVL	1 mg diluted in 1 mL 0.9% NS use amount required to fill line, to maximum of 2 mL = 2 mg
	Double lumen CVL	1 mg diluted in 1 mL 0.9% NS use amount required to fill line, to maximum of 2 mL = 2 mg; treat one lumen at a time
	SC Port	2 mg diluted in 0.9% NS to 3 mL

CVL, central venous line; SC, subcutaneous

Adapted from Monagle P, et al. *Chest* 2008;133:887S-968S.

Thrombolytic Therapy

Advantages	Disadvantages
• Very effective • Short-half life • Hepatic metabolism	• Expensive • Short stability once compounded • Risk of hemorrhage • Several contraindications (e.g., seizure, history of bleeding)

1. Dillon PW. *J Clin Oncol* 2004;22:2718-2723. 2. Yee DL, et al. *Pediatr Blood Cancer* 2009;53:960-966. 3. Kerlin BA. *Pediatr Blood Cancer* 2009;53:920-921.

Outcomes following VTE

- Morbidity
  - Short term
    - Symptoms — Catheter malfunction
    - Prolonged hospitalization — Delays in cancer therapy
    - Risks from VTE therapies
  - Long term
    - Recurrent VTE — Venous insufficiency
    - Organ damage
- Mortality in children
  - All thrombosis = 1.5-2.2% — PE = ~ 10%

1. Goldberg NA, et al. *Blood* 2007;110:45-53. 2. Kuhle S, et al. *J Thromb Haemost* 2008;6:589-594. 3. Payne JH. *Br J Haematol* 2010;150:259-277. 4. Goldhaber SZ. *J Am Coll Cardiol* 2010;56:1-7. 5. Revel-Vilk S, et al. *Pediatr Blood Cancer* 2010;55:153-156.

Risk of Recurrent VTE

During Anticoagulant Therapy	After Discontinuing Anticoagulant Therapy
• Cancer • Immobilization • Chronic obstructive pulmonary disease	• Male gender • Overweight, Obesity • Elevations of factor VIII and D-dimer • Low high-density lipoprotein cholesterol • Presenting with symptoms of a PE (rather than DVT) • Lack of recanalization of DVT as per venous ultrasonography

1. Lin J, et al. *J Vasc Surg* 2003;37:976-983. Payne JH. *Br J* Haematol 2010;150:259-277. 2. Goldhaber SZ. *J Am Coll Cardiol* 2010;56:1-7

Resources

- www.stopvte.org
  - Conducted by ASHP Advantage
  - CPE and resources centers
    - Newsletters — Guidelines/consensus statements
    - VTE prevention resources — Useful websites
    - Standards/performance measures
- www.acforum.org
  - Anticoagulation Forum
  - Resources center for anticoagulation services and monitoring
- www.clotcare.com

Resources

- www.preventdvt.org
  - Coalition to Prevent Deep Vein Thrombosis
  - Information for patients and healthcare providers
- www.natfonline.org
  - North America Thrombosis Forum
  - Information for patients and healthcare providers
- www.thrombosisclinic.com
  - Continuing medical education
- www.venousdiseasecoalition.org
  - Promotes awareness of VTE to healthcare providers and public

Final Thoughts

- Status on research in pediatric cancer patients
- What about newer agents?
- Relationship with anticoagulation and outcomes in cancer patients

Questions

E-mail

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