Venous Thromboembolism in Children with Cancer

Susannah E. Koontz, Pharm.D., BCOP
Principal & Consultant
Pediatric Hematology/Oncology & HSCT
Koontz Oncology Consulting LLC
Houston, TX

Presentation Information

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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**

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</tbody>
</table>

It Can Happen to You!

Serena Williams

Zsa Zsa Gabor

Dick Cheney

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

- 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

<table>
<thead>
<tr>
<th>Registry</th>
<th>Dates</th>
<th>Age</th>
<th>Events</th>
<th>CNS</th>
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<tr>
<td>Canadian &amp; International</td>
<td>1990-1993</td>
<td>First month</td>
<td>VTE (arterial)</td>
<td>No</td>
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<tr>
<td>German – neonatal</td>
<td>1990-1994</td>
<td>First month</td>
<td>VTE (arterial)</td>
<td>Yes</td>
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<tr>
<td>Canadian – children</td>
<td>1990-1992</td>
<td>1 month – 16 years</td>
<td>DVT/PE</td>
<td>No</td>
</tr>
<tr>
<td>DPSU (Netherlands)</td>
<td>1997-1999</td>
<td>Birth – 18 years</td>
<td>VTE (arterial)</td>
<td>Yes</td>
</tr>
<tr>
<td>BPSU (United Kingdom)</td>
<td>2001-2003</td>
<td>1 month – 16 years</td>
<td>VTE (arterial)</td>
<td>No</td>
</tr>
</tbody>
</table>

*Includes a proportion of asymptomatic neonatal events
Table adapted from Reference 6

4. van Ommen CH, et al.
5. Gibson BES, et al.
6. Chalmers EA.

Global Incidence

- Relatively rare condition
  - Symptomatic VTE as per the Canadian & Dutch registries
  - 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
  - Incidence of asymptomatic VTE largely unknown

VTE Incidence in Children


Pathophysiology in 1856

Virchow’s Triad

Arterial thrombosis
Venous thrombosis
Vessel Wall Damage
Blood Stasis
Increased blood coagulability

Arterial vs. Venous Thrombosis

**Arterial**
- Major factor = atherosclerosis (vessel wall changes) as is hypertension, smoking, diabetes, hyperlipidemia
- Hypercoaguability has minor role
- Blood stasis is not an issue as arterial blood flow rate it high

**Venous**
- Factors which damage vessel wall only appear to slightly increase risk
- Prothrombotic and stasis abnormalities play dominate role

Pathophysiology in 2011

Risk Factors

**Patient**
- Older age
- Female sex (?)
- Obesity
- Smoking
- Pregnancy
- Minor injury
- Immobilization
- Prior VTE

**Medical**
- Surgery
- Trauma
- **Catheters**
- Varicose veins
- **Cancer**
- Use of OCP
- Kidney disorders
- Lupus anticoagulant
- PNH
- IBD
- DIC
- Thrombocytopenia

**Hereditary**
- Antithrombin III deficiency
- Protein C or Protein S deficiency
- Activated protein C resistance
- Dysfibrinogenemia
- Familial hyperhomocysteinemia

Risk Factors in Relation to Virchow’s Triad

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Damage</th>
<th>Coagulation</th>
<th>Stasis</th>
<th>Fibrinolysis</th>
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<td>Older age</td>
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<tr>
<td>Obesity</td>
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<td>Pregnancy</td>
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<td>Immobility</td>
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<tr>
<td>Prior VTE</td>
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<td>Surgery</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Varicose veins</td>
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<tr>
<td><strong>Cancer</strong></td>
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<tr>
<td>Estrogens</td>
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<tr>
<td>Stroke</td>
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<td>Thrombophilia</td>
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</tbody>
</table>

Cancer as a Risk for VTE

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

**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

**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
  - Myleoproliferative disorders

**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
- Malignant brain tumors
  - 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

VTE Risk Factor – Cancer Treatment

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

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

VTE Risk Factor – 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: 59 of 1824 patients developed VTE (3.2%)
  - 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)

VTE Risk Factor – L-asparaginase products – PARKAA study

- Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase
- 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

References:
**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
  - **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

**Published References**

**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**
- Routine prophylaxis is not warranted to prevent central nervous system VTE

**Published References**

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**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

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**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

**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
- **Spleenic vein**
  - Left upper quadrant pain, splenomegaly
  - Potential organ damage: hypersplenism


- **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

**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

**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**


**VTE Location in Children**

<table>
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<tr>
<th>Site of VTE</th>
<th>Canada</th>
<th>Netherlands</th>
<th>United Kingdom</th>
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<tr>
<td>Upper limb (UL) DVT</td>
<td>47 (34%)</td>
<td>5 (14%)</td>
<td>48 (30%)</td>
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<tr>
<td>Lower limb (LL) DVT</td>
<td>68 (50%)</td>
<td>21 (60%)</td>
<td>95 (59%)</td>
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<td>PE alone</td>
<td>8 (6%)</td>
<td>4 (11%)</td>
<td>5 (3%)</td>
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<tr>
<td>UL DVT + PE</td>
<td>3 (2%)</td>
<td>2 (6%)</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>LL DVT + PE</td>
<td>11 (8%)</td>
<td>3 (9%)</td>
<td>6 (4%)</td>
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<tr>
<td>Total</td>
<td>137</td>
<td>35</td>
<td>160</td>
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Distribution of Peripheral DVT and PE in Children from Three International Registries

Table adapted from Reference 4


**VTE Diagnosis**

- **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
- **Computed tomography venography**
  - High sensitivity and specificity for central and pelvic DVT, can be used when patient has contraindication to MRI
- **Magnetic resonance venography**
  - High sensitivity and specificity for central and pelvic DVT (ideal for cerebral sinus thrombosis), doesn’t rely on contrast media
- **Contrast venography**
  - High sensitivity and specificity for DVT (except internal jugular), including in calf


Catheter-Related Thrombosis (CRT)

- Risk factors
  - Infection
  - Underlying diagnosis
  - Inherited thrombophilia
  - Catheter location/insertion technique

- Signs and symptoms (often asymptomatic)
  - Erythema, warmth
  - Swelling in extremity, face, neck, axilla
  - Dilation of superficial veins
  - Drop in platelet counts
  - Recurrent bacteremia

Risk factors
- Infection
- Underlying diagnosis
- Inherited thrombophilia
- Catheter location/insertion technique

Signs and symptoms (often asymptomatic)
- Erythema, warmth
- Swelling in extremity, face, neck, axilla
- Dilation of superficial veins
- Drop in platelet counts
- Recurrent bacteremia


Quick Fact

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

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

Guidelines in Cancer Patients
- American Society of Clinical Oncology (ASCO)
- National Comprehensive Cancer Network (NCCN)
- European Society of Medical Oncology (ESMO)
- Italian Association of Medical Oncology (AIOM)
- French National Federation of the League of Centers Against Cancer (FNCLCC)
- American College of Chest Physicians (ACCP)

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


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


- 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)


- 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)


- 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)

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


- 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)


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**
- Children receiving long-term home TPN (Use VKA to target INR of 2.5 (Range of 2-3) (Level of evidence = 2C)
- Complex cardiac patients and associated procedures (Level of evidence = 1B (Fontan) and 2C)

**Prophylaxis Not Recommended**
- Children with cancer and central venous access devices (Level of evidence = 2C)
- Patients undergoing hemodialysis via central venous line or fistula (Level of evidence = 2C)


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**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**

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**Unfractionated Heparin**

**Advantages**
- Familiarity
- Rapid onset of action
- Short half-life
- Published data in children
- Antidote available

**Disadvantages**
- Unpredictable dose response
- Requires antithrombin
- Need for frequent monitoring/patient use
- Not effective in neutralizing clot-bound thrombin
- Adverse events → heparin-induced thrombocytopenia, osteoporosis


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**Heparin-Induced Thrombocytopenia (HIT)**

**The Four "T"s" of Heparin-Induced Thrombocytopenia (HIT) Point System**

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<tr>
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<th>2</th>
<th>1</th>
<th>0</th>
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<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>&gt; 50% fall to nadir ≥ 20 x 10⁹/L</td>
<td>30-50% fall (or &gt;50% fall due to surgery) or nadir 10-19 x 10⁹/L</td>
<td>&lt; 30% fall or nadir &lt; 10 x 10⁹/L</td>
</tr>
<tr>
<td>Timing</td>
<td>Days 5-10 or Day 1 with recent heparin (past 30 days)</td>
<td>&gt; Day 10 or unclear timing</td>
<td>&lt; Day 4 (no recent heparin activity)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Progressive or recurrent thrombosis, erythematous skin lesions, suspected thrombosis (not proven), asymptomatic upper limb DVT</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Other causes</td>
<td>None or evident</td>
<td>Possible</td>
<td></td>
</tr>
</tbody>
</table>

Score 0-3 – Monitor patient; Score 4-6 – Supportive care and/or interventions

Heparin-Induced Thrombocytopenia (HIT)

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


Low Molecular Weight Heparin

- Low molecular weight heparin
  - Agents:
    - Enoxaparin (Lovenox®)
    - Dalteparin (Fragmin®)
    - Tinzaparin (Innohep®), Ardeparin (Normiflo®)
    - Nadroparin (Fraxiparine®)
    - Certoparin (Sandoparin®)
  - 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


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/NCT00687685)


Low Molecular Weight Heparin

<table>
<thead>
<tr>
<th>Agent &amp; Use</th>
<th>Patient Age or Weight</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin, mg/kg, Q 12 h initial treatment</td>
<td>Age &gt; 2 months</td>
<td>1</td>
</tr>
<tr>
<td>Enoxaparin, mg/kg, Q 12 h initial prophylaxis</td>
<td>Age &gt; 2 months</td>
<td>0.5</td>
</tr>
<tr>
<td>Dalteparin, U/kg, Q 24 h initial treatment</td>
<td>All</td>
<td>129 ± 43</td>
</tr>
<tr>
<td>Dalteparin, U/kg, Q 24 h initial prophylaxis</td>
<td>All</td>
<td>92 ± 52</td>
</tr>
<tr>
<td>Tinzaparin, U/kg, Q 24 h initial treatment</td>
<td>2-12 months</td>
<td>250</td>
</tr>
<tr>
<td>Tinzaparin, U/kg, Q 24 h initial prophylaxis</td>
<td>1-5 yr</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td>5-10 yr</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>10-16 yr</td>
<td>175</td>
</tr>
<tr>
<td>Reviparin, U/kg, Q 12 h initial treatment</td>
<td>&gt; 5 kg</td>
<td>100</td>
</tr>
<tr>
<td>Reviparin, U/kg, Q 12 h initial prophylaxis</td>
<td>&gt; 5 kg</td>
<td>30</td>
</tr>
</tbody>
</table>


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


Vitamin K Antagonists (Warfarin)

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

### Vitamin K Antagonists (Warfarin)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oral administration</td>
<td>• Requires “bridge” therapy before effects are seen</td>
</tr>
<tr>
<td>• Longer half-life allows for ease of administration</td>
<td>• Unpredictable dose response (genetic polymorphisms)</td>
</tr>
<tr>
<td>• Familiarity</td>
<td>• Narrow therapeutic index</td>
</tr>
<tr>
<td>• Inexpensive</td>
<td>• Numerous food- and drug-drug interactions</td>
</tr>
<tr>
<td>• Available antidote</td>
<td>• Requires frequent monitoring</td>
</tr>
<tr>
<td>• Published studies in children</td>
<td></td>
</tr>
</tbody>
</table>


### Direct Thrombin Inhibitors

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Direct thrombin inhibitors</td>
<td>• Agents:</td>
</tr>
<tr>
<td>• Agents</td>
<td>o Agrotrapin</td>
</tr>
<tr>
<td>• Fondaparinux (Arixtra®)</td>
<td>o Bivalirudin (Angiomax®)</td>
</tr>
<tr>
<td>• MOA</td>
<td>o Dabigatran (Pradaxa®)</td>
</tr>
<tr>
<td>• Acts independently of antithrombin and other plasma proteins</td>
<td>o Lepirudin (Refludan®)</td>
</tr>
<tr>
<td>• Goal: Steady state aPTT 1.5-3 times baseline starting two hours after</td>
<td>o Ximelagatran (Exanta)</td>
</tr>
<tr>
<td>therapy (should be &lt; 100 seconds)</td>
<td>o Desirudin (Iprivask®)</td>
</tr>
<tr>
<td>• Pediatric dosing recommendations</td>
<td></td>
</tr>
<tr>
<td>• <a href="http://www.argatroban.com">www.argatroban.com</a></td>
<td></td>
</tr>
</tbody>
</table>


### Fondaparinux

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Predictable dose response, pharmacokinetics</td>
<td>• Expensive</td>
</tr>
<tr>
<td>• Rapid onset of action, short-half-life</td>
<td>• Administration by continuous infusion</td>
</tr>
<tr>
<td>• Inhibits clot-bound as well as free thrombin</td>
<td>• No available antidote (recombinant factor VIIa?)</td>
</tr>
<tr>
<td>• Doesn’t rely on antithrombin</td>
<td>• Little published pediatric literature</td>
</tr>
</tbody>
</table>


### Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tissue plasminogen activator (tPA)</td>
<td>• Agents:</td>
</tr>
<tr>
<td>• Alleplase (Activase®)</td>
<td>o Alteplase (Activase®)</td>
</tr>
<tr>
<td>• Replase (Retavase®)</td>
<td>o Tenecteplase (TNKase®)</td>
</tr>
<tr>
<td>• Anistreplase (Eminase®)</td>
<td>o Anistreplase (Eminase®)</td>
</tr>
<tr>
<td>• Streptokinase (Kabikinase®, Streptase®)</td>
<td>o Streptokinase (Kabikinase®, Streptase®)</td>
</tr>
<tr>
<td>• Urokinase (Abbokinase®)</td>
<td>o Urokinase (Abbokinase®)</td>
</tr>
<tr>
<td>• Serine proteases convert plasminogen to plasmin → breaks down fibrinogen</td>
<td>o MOA: Serine proteases convert plasminogen to plasmin → breaks down fibrinogen</td>
</tr>
<tr>
<td>• clot dissolution</td>
<td>o Which one to use?</td>
</tr>
</tbody>
</table>

Thrombolytic Therapy

Local Instillation of Tissue Plasminogen Activator

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

CVL, central venous line; SC, subcutaneous


Advantages
- Very effective
- Short-half life
- Hepatic metabolism

Disadvantages
- Expensive
- Short stability once compounded
- Risk of hemorrhage
- Several contraindications (e.g., seizure, history of bleeding)

Outcomes following VTE

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

Risk of Recurrent VTE

During Anticoagulant Therapy
- Cancer
- Immobilization
- Chronic obstructive pulmonary disease

After Discontinuing Anticoagulant Therapy
- 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

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

- www.preventdvt.org
  - Coalition to Prevent Deep Vein Thrombosis
  - Information for patients and healthcare providers
- www.nationline.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**

Susannah.Koontz@koontzoncology.com