VTE in Children and Adolescents: Epidemiology and Special Considerations for Therapy

Ellis J. Neufeld MD, PhD
Associate Chief,
Division of Hematology/Oncology
Boston Children’s Hospital and Dana Farber Cancer Institute

Egan Family Foundation Chair in Transitional Medicine
Harvard Medical School

September, 2012
Virchow’s Triad (as a conceptual base) applies reasonably well to pediatric VTE.

Vascular damage
e.g. inflammation, trauma, Pelvic surgery

Central venous lines

Impaired flow
e.g. catheters, compression, immobility, CHF, venous valve damage, immobility

TTP and related states

“Hypercoagulability”

So the differences in pediatric (from adult) VTE are related to the different prevalence and quality of the risk factors.
How do we know anything about pediatric thrombosis

- Rare genetic disorders of childhood onset
  - (e.g. homozygous protein C deficiency/ purpura fulminans)
- By learning from adult studies
  - Pulmonary embolism is a leading cause of death in hospitalized adults
  - Millions of people take warfarin
  - By comparison, relatively rare problem in pediatrics
- Anecdotes predominate
  - (we are all prisoners of our own anecdotes).
Population Risk of clots by age:

Relative risk of thrombosis is high in neonates, drops rapidly until puberty, then rises throughout life.
Thrombosis as a “life course event” of summed genetic and environmental risk

Risk for individuals varies rapidly (even daily) with time, depending on baseline and transient risk factors.

Not all transient risks cross threshold for thrombus

Same concept in pediatrics

(after Miletich, J)
“Hypercoagulable states”

• Primary = “thrombophilia”
  – Decreased antithrombotic proteins
    • Antithrombin deficiency
    • Protein C deficiency
    • Protein S deficiency
  – Increased prothrombotic proteins
    • Factor V Leiden (activated protein C resistance)
    • Prothrombin gene mutation G20210A
    • Increased levels of factors VII, VIII

To be distinguished from
• Secondary (acquired)
  – e.g. Nephrotic syndrome (loss of plasma volume and anticoagulants)
Acquired hypercoagulable states

• Medical
  – Viscosity and low flow states
    • Nephrotic syndrome
    • CHF
  – Obesity and sedentariness
  – Inflammatory
    • Sepsis
    • Vasculitis **
    • Inflammatory bowel disease
    • Lupus and related disorders
  – Oncologic
    • Adenocarcinoma (adults >> peds)
    • Acute Lymphoblastic leukemia with asparaginase Rx**
    • Paroxysmal nocturnal hemoglobinuria
  – Parenteral nutrition (CVCs)
  – Disorders specific to neonates:
    • RDS
    • Infants of diabetic mothers (e.g. renal vein thrombosis)
    • Necrotizing enterocolitis
    • Congenital nephrotic syndrome
    • polycythemia

• Mechanical
  – Stasis
    • Braces/casts
  – Central Venous Catheters (CVCs)**
  – ECMO

• Postoperative states
  – Immobility
  – Very high risk:
    • Knee or hip replacement
    • Neurosurgery (adults)

• Drugs
  – L-asparaginase**
  – Coagulation factor concentrates**
  – Heparin
  – Antifibrinolytic agents
  – Oral contraceptives**

• Vascular malformations!
Inherited Prothrombotic Risk Factors

- **Common**
  - Factor V G1691A gene mutation (Factor V Leiden/APC Resistance)
  - Prothrombin 20210A gene mutation
  - Increased concentrations of Apolipoprotein (a)
  - Methylenetetrahydrofolate reductase (MTHFR) gene → hyperhomocysteinemia

- **Rare**
  - Protein C deficiency
  - Protein S deficiency
  - Antithrombin deficiency
  - Heparin cofactor II deficiency
  - Increased homocysteine concentrations > 10 mol/L

- **Very rare**
  - Dysfibrinogenemia
  - Plasminogenemia
  - Homozygous homocystinuria

- **Probably inherited**
  - Increased levels of factor VIII, IX, or fibrinogen
  - Decreased levels of factor XII
## Risk factors for 12 consecutive PEs at BCH

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Surgery?</th>
<th>Underlying Dx</th>
<th>? Hypercoag</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 y.o. – M</td>
<td>NO</td>
<td>LE DVT r/t trauma</td>
<td>(+)ALL antiphos testing, lipo(a) 81</td>
</tr>
<tr>
<td>4 y.o.-M</td>
<td>YES - debulk VM</td>
<td>KT</td>
<td>post-op line/KT</td>
</tr>
<tr>
<td>19 y.o.-M</td>
<td>NO</td>
<td>pontine glioma</td>
<td>bedbound/onc</td>
</tr>
<tr>
<td>19 y.o.-M</td>
<td>YES-fontan surg</td>
<td>none</td>
<td>CHF</td>
</tr>
<tr>
<td>22 y.o.-F</td>
<td>YES - spine surgery</td>
<td>KT</td>
<td>hx of PE in 2005/KT</td>
</tr>
<tr>
<td>17 y.o.-F</td>
<td>YES- Ladd proc.</td>
<td>none</td>
<td>obesity, OCPs</td>
</tr>
<tr>
<td>17 y.o. –F</td>
<td>YES – debulk calf VM</td>
<td>KT</td>
<td>PE on ppx Lovenox/KT</td>
</tr>
<tr>
<td>16 y.o. -F</td>
<td>NO</td>
<td>none</td>
<td>OCPs x3wks prior, Obese</td>
</tr>
<tr>
<td>19 y.o. –F</td>
<td>NO</td>
<td>Wilms Tumor</td>
<td>Onc</td>
</tr>
<tr>
<td>16 y.o. –M</td>
<td>NO</td>
<td>myelodysplastic syndrome</td>
<td>Onc, + anticardiolipin, family hx,</td>
</tr>
<tr>
<td>18 y.o. –M</td>
<td>NO</td>
<td>Crohn's</td>
<td>thalidomide, +anticardiolipin,</td>
</tr>
<tr>
<td>17 y.o. –M</td>
<td>NO</td>
<td>none</td>
<td>OCPs, obesity, + anticardiolipin, lipo(a) elevated, + LA,</td>
</tr>
</tbody>
</table>
Risk factors for poor outcome in pediatric DVT

1. Positive D Dimer,
2. persistence of occlusive thrombus, and/or
3. elevated factor VIII levels >150% controls predict higher risk of postphlebitic syndrome after DVT

- Either elevated at diagnosis: 6-fold relative risk
- Either elevated at 3-6 months 4 fold relative risk
- Both blood tests elevated: 91% specific for post phlebitic syndrome

- Suggests a population for more aggressive initial therapy, e.g. thrombolysis. Basis for interventional trial:
  - Goldenberg et al, Blood, 2007
Catheters and clots
Clots from BCH Anticoagulation Service
First 150 clots

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line-related DVT</td>
<td>57</td>
</tr>
<tr>
<td>DVT (excludes CVC*)</td>
<td>42</td>
</tr>
<tr>
<td>DVT and PE</td>
<td>11</td>
</tr>
<tr>
<td>PE alone</td>
<td>13</td>
</tr>
<tr>
<td>Dural sinus thrombosis</td>
<td>20</td>
</tr>
<tr>
<td>Stroke</td>
<td>19</td>
</tr>
<tr>
<td>Cardiac thrombus</td>
<td>3</td>
</tr>
<tr>
<td>Retinal infarct</td>
<td>2</td>
</tr>
</tbody>
</table>

CVC: Central venous catheter
Central Venous Catheters are the leading cause of pediatric venous thrombosis.

- 30-60% of pediatric thrombi attributable to central venous lines (highest in NICU, probably due to relative caliber of small lines in extremely small veins)
- Mechanism for thromboses: foreign body, obstruction of venous flow, trauma, and endothelial irritation
- Distinguish three kinds of CVC clot:
  - Fibrin sheath at tip (no flow impairment)
  - Clotted catheter tip (Rx alteplase)
  - Line-associated DVT – consider as a real DVT
- Significant PE with upper system CVC clots are rare
- By the time the arm is swollen from a CVC, the clot has usually extended outward from the catheter past axillary collaterals
Venograms to evaluate upper venous system

Five TPN-dependent patients with history of worsening recurrent CVC problems.
Andrew et al, J. Peds, 1995
Cancer and clots

- Adults with adenocarcinoma have high DVT risk. (so high as to warrant specific cancer screening for idiopathic DVT after some age)
  - But adenoCA is rare in childhood.
- Cancer patients in pediatrics are much more likely to have central venous catheters
- Asparaginase to treat childhood ALL is a particularly high risk: acquired ATIII (and many other factors) deficient.
  - Dural sinus thrombosis
  - DVTs
  - Catheter-related or not.
Who needs a “hypercoagulable workup”

• Severe family history***
  – Virtually mandatory
  – Access to the affected individuals is best.
  – If the grandparents and others were studied before mid 1990s, they should go back for modern genetic workup if possible

• Recurrent thrombosis (especially on anticoagulation)

• “Unexplained thrombosis,” unusually severe, unusual locations
What’s a “severe family history?”

- Asked to provide prenatal counseling for a woman early in gestation, who has married into a family with thrombosis.
- She had been found to have fVLeiden after marrying a man whose two children from a prior marriage had perinatal strokes. The husband’s brother had a prior DVT.
- The husband’s family was found to have had the bad luck to have developed an AT3 mutation on a factor V Leiden chromosome (the two genes are very closely linked on 1q23.3).
- Therefore, every offspring of affected individuals in father’s family had a 50% chance of inheriting both disorders.
- For this couple, 25% chance in this mating of homozygous FVLeiden and heterozygous AT3 deficiency. Extremely high risk to fetus.
Are any pediatric hypercoagulability evaluations urgent?

- **Thrombosis on heparin/enoxaparin**
  - Consider heparin-induced thrombocytopenia in the appropriate clinical setting (e.g. 4T score >4), especially in patients previously exposed to heparin. But true HIT with thrombosis is extremely rare in childhood.

- **Perinatal stroke if acutely ill or evidence of consumption coagulopathy**
  - Placental pathology if at all possible
  - Parental protein C/S (unless at least one parent is heterozygous, the infant cannot be homozygous)

- **Purpura fulminans**
  - Give plasma (FFP) awaiting results

- (By exclusion, the rest are NOT urgent)
Oral contraceptives and hypercoagulable states
“Why can’t we get straightforward guidelines for testing prior to starting birth control?”

• “What is wrong with you hematologists?”
• If we just test everyone, surely we’ll save some blood clots, right?
• Problems
  – Number needed to test among OCP users:
    • Per DVT (hundreds), Per PE (thousands), to prevent one death (at least tens of thousands) @ $$$/test
  – Pregnancy/post-partum states have high thrombosis risk; would every positive test require alternative contraception?
• Compromise:
  – Counsel about risk; cite firm risk numbers; establish family history; discourage smoking. Follow published guidelines (ACOG, WHO, CDC)

Trenor et al Pediatrics, 2011
Firm risk numbers OCP and DVT

• Leiden thrombophilia study, first DVT:
  – Risk in normals: 8/100,000 woman-years
  – OCP: 4X ↑ 30/100,000 woman yrs
  – FV Leiden: 5-7X ↑ ~ 60/100,000 woman-yr
  – FVL and OCP 35X ↑ ~ 240/100,000 woman-yr

Absolute magnitude of risk. 0.24% per year, 2.4% in 10 yrs

Millions of women take OCP. Low absolute risk can add up to a lot of blood clots.
Mechanical risk factors play a role in some young patients:

- For recurrent line-related VTE, evaluate upper venous system in detail
- For upper extremity clots in athletes, check for thoracic outlet obstruction
  - Pitchers, swimmers, rowers: Paget-Schroetter syndrome
- For large, proximal left leg DVT, consider May-Thurner syndrome (iliac vein compression by iliac artery)
Vascular malformations

• Large venous and veno-lymphatic malformations (e.g. Klippel-Trenauny-Weber) fulfill Virchow’s triad every day:
  – Stasis and abnormal flow in lesions; large-caliber draining veins; frequent sclerosis procedures.
  – Abnormal endothelial surfaces.
  – constant thrombin generation (reflected as chronic + D-dimers and often low fibrinogen). Not “DIC” but “LIC.” Intrinsically “hypercoagulable.”

• Extremely large draining veins in large lesions
• Preoperative anticoagulation can quiet the thrombin generation. Postoperative anticoagulation very important.
Data from the Thrombosis/Anticoagulation Service at Children’s Hospital Boston
Hypercoagulable states among thrombosis service clot patients in our first five years. Not tested in every case (tested if unprovoked and/or family history), n=37 (35%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden heterozygous</td>
<td>12</td>
</tr>
<tr>
<td>Factor V Leiden homozygous</td>
<td>2</td>
</tr>
<tr>
<td>Prothrombin gene mutation 20210A</td>
<td>6</td>
</tr>
<tr>
<td>Elevated Lipoprotein (a)</td>
<td>3</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>2</td>
</tr>
<tr>
<td>Prot S deficiency</td>
<td>4</td>
</tr>
<tr>
<td>Prot C deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Paget-Schroetter syndrome</td>
<td>4</td>
</tr>
<tr>
<td>May-Thurner</td>
<td>3</td>
</tr>
</tbody>
</table>
Acquired risk factors (often in combination with primary hypercoag states)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCPs only</td>
<td>12</td>
</tr>
<tr>
<td>Malignancy OR asparaginase</td>
<td>22</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome/lupus anticoagulant</td>
<td>18</td>
</tr>
<tr>
<td>Lupus alone</td>
<td>6</td>
</tr>
<tr>
<td>Obesity alone</td>
<td>4</td>
</tr>
<tr>
<td>Infection</td>
<td>7</td>
</tr>
<tr>
<td>High dose estrogen</td>
<td>1</td>
</tr>
<tr>
<td>Vascular malformation</td>
<td>4</td>
</tr>
<tr>
<td>Postoperative</td>
<td>7</td>
</tr>
</tbody>
</table>
Do all pediatric clots warrant a hypercoagulable workup?

- Canadian Registry (13% of all VTE with identifiable “hypercoagulable” disorder): “Because the majority of risk factors for VTEs in children are CVCs and/or other medical conditions, registry results do not justify screening all children with VTEs.”

- German Registry (57% of VTE patients have identifiable hypercoagulable disorders): higher proportion of spontaneous VTEs, higher prevalence of thrombophilic traits; “results justify screening all children with VTEs.”

- Boston Children’s data fall between these extremes. CVCs are the largest cause of clots but not the majority. 33% with identified hypercoagulable disorders (without extensive workups in most).

- Our conclusion: individualize the evaluation based on family history, provoking factors, patient age, gender, and clinical circumstances.
VTE event-free survival dependent on Inherited Thrombophilia. Freedom from VTE over time is shown for relatives of pediatric index patients stratified for different types of IT.

Authors advocate testing even though: “prepubertal events are very rare,” and teens are like young adults.

Holzhauer S et al. Blood 2012;120:1510-1515
Thrombosis Consultation and Anticoagulation Service: Joint effort of Nursing, Hematology, Pharmacy

• Original rationale: sentinel event
• Three main roles for service:
  • Inpatient monitoring
    – Low molecular weight heparin (enoxaparin) use
  • Discharge planning
    – Goal – 100% of patients discharged on anticoagulation to have a monitoring plan.
      • Indication, target drug level/INR, clinician in charge
  • Consultation
    – Hypercoagulability evaluation, treatment strategies,
    – Planning for invasive procedures/Bridging warfarin
• Staff:
  – Kathy Harney, NP; Juliann McSweeney, RN, four physicians (Michelson, Neufeld, Grace, Saxena)
Treatment Considerations (1)

- Testing of drugs in pediatrics lags WAY BEHIND adult testing.
  - Enoxaparin label accessed 9/1/12: “Safety and effectiveness of Lovenox in pediatric patients has not been established.”
  - For DTIs, your speaker didn’t need to look
- Little kids hate needles (enoxaparin problem)
- Some kids and teens don’t have diets optimal for warfarin (like some adults)
- “Lifelong” anticoagulation is a long time for school age kids.
- In growing children, IVC filters are a terrible long-term liability (use retrievable filters if one is absolutely required)
Treatment considerations (2)

- Many pediatric and teenage patients with clots are otherwise healthy, especially true athletes with provoked clots. Pulmonary reserve tends to be excellent.
- Mortality from all causes is very low, (clots, co-morbidities and bleeding (but we’ve had two deaths from PE in last 10+ years, no deaths from anticoagulation bleeding).
- The relative good health of patients affects some evidence-based decision making (when there is any evidence):
  - Example: Sub-massive PE and thrombolytic Rx
    - “In selected high-risk patients without hypotension who are judged to have a low risk of bleeding, we suggest administration of thrombolytic therapy (Grade 2B). (Chest adult guidelines, 2008)”
• Yes, there are Pediatric “Chest Guidelines” but nearly all the evidence is low-grade (Monagle et al, 2012)

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Paul Monagle, MBBS, MD, FCCP; Anthony K. C. Chan, MBBS; Neil A. Goldenberg, MD, PhD; Rebecca N. Ichorod, MD; Janna M. Journeyake, MD, MSCS; Ulrike Nowak-Göttli, MD; and Sara K. Vesely, PhD
DOES FINDING A HYPERCOAGULABLE STATE CHANGE SUGGESTED THERAPY IN PEDIATRIC PATIENTS?

• No firm data, we tend to rely on summary in adult Chest Guidelines (and its pediatric cousin)
• Factor V Leiden and first episode DVT:
  – NO
• Homozygous state for fVL, or genetic protein C or S deficiency with severe thrombosis:
  – YES: recommend lifelong therapy
• Hyperhomocysteinemia:
  – give folate? (Rule out B12 disorders)
  – Efficacy of folate is unproven on population basis, however!
• Elevated factor VIII:
  • consider longer term therapy. Consider thrombolysis?
Thank you!

Acknowledgments: Kathy Harney, PNP
and the Boston Children’s
Thrombosis/anticoagulation service
“I just found out my patient scheduled for _____ has fVLeiden!”

• Practical approach
  – 5% of all your Caucasian patients have this trait. Why do you know the answer for this one?
    • Family history?
    • Other?
  – Does this procedure cause risk of DVT or prolonged immobility?
  – Does the patient already have other known risk factors?
  – Consider prophylactic post-procedure anticoagulation if the answers are yes.
How do we know *anything* about pediatric thrombosis? From rare genetic disorders of childhood onset (e.g. homozygous protein C deficiency), and by learning from adult studies;

**“Hypercoagulable states”**
- Primary = “thrombophilia”
  - Decreased antithrombotic proteins: Antithrombin, Protein C, Protein S deficiency
  - Increased prothrombotic activities/proteins: Factor V Leiden (activated protein C resistance); Prothrombin gene mutation G20210A; elevated fVIII(?)

To be distinguished from
- Secondary (acquired)
  - e.g. Nephrotic syndrome (loss of plasma volume and anticoagulant proteins)
  - many medical, mechanical states

**Acquired hypercoagulable states** (**denote very common findings in pediatric VTE inpatients**)

**Medical disorders**
- Viscosity, protein loss, and low flow states
- Nephrotic syndrome, CHF
- Obesity and sedentariness
- Inflammatory: Sepsis, vasculitis, IBD,** Lupus and related disorders
- Oncologic
  - Adenocarcinoma (adults >> peds); Acute Lymphoblastic leukemia with asparaginase Rx**; PNH (rare in adults, very rare in kids)
- Parenteral nutrition (CVCs)
- Disorders specific to neonates: Respiratory Distress Syndrome, Infants of diabetic mothers (e.g. renal vein thrombosis from polycythemia); NEC; Congenital nephrotic syndrome
- Vascular malformations constitute a unique and severe risk (peds and adult)

**Mechanical issues**, e.g. stasis from braces/casts; Central Venous Catheters (CVCs), ** ECMO circuits**

**Postoperative states** due to immobility

**Drugs** including L-asparaginase,** Coagulation factor concentrates,** Heparin, Antifibrinolytics; OCPs

**Risk factors for poor outcome in pediatric DVT**
1. Positive D Dimer,
2. persistence of occlusive thrombus, and/or
3. elevated factor VIII levels >150% controls predict higher risk of postphlebitic syndr. after DVT
  - Either elevated at diagnosis: 6-fold relative risk; Either elevated at 3-6 months 4 fold relative risk; Both blood tests elevated: 91% specific for post phlebitic syndrome (Goldenberg NA et al, NEJM 351:1081 (2004))
  - Suggests a population for more aggressive initial therapy, e.g. thrombolysis. Basis for interventional trial: Goldenberg et al, Blood, 2007

**Catheters and Thrombotic risk:**
- Central Venous Catheters are the *leading cause of pediatric venous thrombosis* at all pediatric tertiary hospitals and constitute About 1/3 of DVT and PE at Boston Children’s.
• Literature reports: 30-60% of pediatric thrombi attributable to central venous lines (highest in NICU, probably due to relative caliber of small lines in extremely small veins)
• Mechanism for thromboses: foreign body, obstruction of flow, trauma, and endothelial irritation
  – Distinguish three kinds of CVC clot: Fibrin sheath at tip (no flow impairment); Clotted catheter tip (Rx alteplase); true line-associated DVT.
• Significant PE with upper system CVC clots are rare
• By the time the arm is swollen from a CVC, the clot has usually extended outward from the catheter past axillary collaterals
• Venograms (bilateral standard venography or CT-venograms) are the best way to evaluate the upper venous system in detail. MRV has less radiation but slower.

Cancer and clots
• Adults with adenocarcinoma have high DVT risk. (so high as to warrant specific cancer screening for idiopathic DVT after some age), but adenocarcinoma is rare in childhood.
• Cancer patients in pediatrics are much more likely (than other kids) to have central venous catheters, and this is part of the risk, but L-asparaginase to treat childhood ALL is a particularly high risk: acquired ATIII (and many other factors) are low for many days after each cycle. Clots with L-asparaginase include both dural sinus thrombosis and DVTs, +/- catheter related

Who needs a “hypercoagulable workup” in pediatrics? Evaluation is mandatory if severe family history is present. Access to the affected family members is best. Other indications for evaluation include recurrent thrombosis (especially on anticoagulation) and “Unexplained thrombosis,” unusually severe, unusual locations

Are any pediatric hypercoagulability evaluations urgent? Only three circumstances (Neufeld opinion):
  • Thrombosis on heparin/enoxaparin
    – Consider HIT in the appropriate clinical setting (e.g. 4T score >4), especially in patients previously exposed to heparin. But true HIT with thrombosis is very rare in childhood.
  • Perinatal stroke if acutely ill or evidence of consumption coagulopathy
    – Placental pathology if at all possible
    – Parental protein C/S (unless at least one parent is heterozygous, the infant cannot be homozygous)
  • Purpura fulminans (Give plasma (FFP) awaiting results and while ruling out sepsis/DIC

Oral contraceptives and hypercoagulable states
• Millions of women take OCP. Low absolute risk can add up to a lot of blood clots, but doesn’t necessarily justify broad screening for risk factors. See Trenor et al, 2011, Pediatrics.

Mechanical risk factors play a role in some young patients: Paget Schroetter syndrome (thoracic outlet obstruction) and May-Thurner syndrome should be considered in the appropriate clinical settings.

Large Venous and Veno-lymphatic Vascular malformations are a very severe risk factor for VTE due to localized thrombin activation on abnormal endothelium, stasis, and huge draining veins (caliber can be several centimeters)

Data from the Thrombosis/Anticoagulation Service at Children’s Hospital Boston will be reviewed.

Do all pediatric clots warrant a hypercoagulable workup? Reasonable experts disagree:
• **Canadian Registry (13% of all VTE with identifiable “hypercoagulable” disorder):** “Because the majority of risk factors for VTEs in children are CVCs and/or other medical conditions, registry results do not justify screening all children with VTEs.”

• **German Registry (57% of VTE patients have identifiable hypercoagulable disorders):** higher proportion of spontaneous VTEs, higher prevalence of thrombophilic traits; “results justify screening all children with VTEs.”

• **Boston Children’s data fall between these extremes. Our conclusion: individualized evaluation** based on family Hx, provoking factors, age, gender, clinical circumstances.

Thrombosis Consultation and Anticoagulation Service: Joint effort of Nursing, Hematology, Pharmacy: The service was started because of a sentinel event (a subdural hematoma at home in an anticoagulated patient. The service has three main goals: (1) Inpatient monitoring of all enoxaparin use; (2) Discharge planning: Our goal is that 100% of patients discharged on anticoagulation will have a monitoring plan including Indication, drug, target drug level/INR, and identification of the clinician in charge after discharge. (3) We consultation for hypercoagulability evaluation, treatment strategy, planning for invasive procedures/bridging warfarin, in addition to home warfarin monitoring.

**Treatment Considerations**

- Testing of drugs in pediatrics lags behind adult testing so that approved drugs are few to none.
  - Enoxaparin label accessed 9/1/12: “Safety and effectiveness of Lovenox in pediatric patients has not been established.”
- DTIs: barely studied in pediatrics, certainly not approved yet.
- Little kids hate needles (enoxaparin problem)
- Some kids and teens don’t have diets optimal for warfarin (like some adults)
- “Lifelong” anticoagulation is a long time for school age kids.
- In growing children, IVC filters are a terrible long-term liability (use retrievable filters if one is absolutely required)
- Many pediatric and teenage patients with clots are otherwise healthy, especially true athletes with provoked clots. Pulmonary reserve tends to be excellent.
- Mortality from all causes is very low, (clots, co-morbidities and bleeding (but we’ve had two deaths from PE in last 10+ years, no deaths from anticoagulation bleeding).
- The relative good health of patients affects some evidence-based decision making (when there is any evidence). Example: Sub-massive PE and thrombolytic Rx
  - “In selected high-risk patients without hypotension who are judged to have a low risk of bleeding, we suggest administration of thrombolytic therapy (Grade 2B). (Chest adult guidelines, 2008)”

**Does finding a hypercoagulable state change suggested therapy in pediatric patients?** Absent firm data, we tend to rely on summary in adult and pediatric Chest Guidelines:

- Factor V Leiden and first episode DVT: NO
- Homozygous state for fVL, or genetic protein C or S deficiency with severe thrombosis: YES
- Hyperhomocysteinemia: give folate? (Rule out B12 disorders) Efficacy of folate is unproven
- Elevated factor VIII: consider longer term therapy. Consider thrombolysis?
REFERENCES


