Venous thrombosis in children

BAPA annual meeting 25/04/2015

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Overview

- Introduction
- Etiology
- Risk factors
- Diagnosis
- Treatment
- Prevention
Introduction

- **Incidence** = low
  - 1/10th to 1/100th compared to adults
  - 0.07-0.14 per 10,000 and rising
  - 5.3 per 10,000 for pediatric hospital admissions

But…

- **Incidence**
  - more complex surgery, increased use of central venous catheters (CVC)
  - increased survival of children with previously fatal conditions
  - increased awareness and suspicion for VTE’s
  - changing pediatric population: oral contraceptive use, obesity, smoking
Introduction

But…

• Possible serious morbidity and mortality
  -> children survive for a long time: long term consequences = highly significant

*Mortality* 2-4%

*Morbidity*: acute and long term
Introduction

Acute Morbidity

* Prolonged hospitalization
* Cardiovascular
  - Cardiac arrest
  - Pulmonary embolism and recurrent trombosis 18.5%
  - Superior vena cava syndrome
  - Paradoxical embolic stroke (especially neonates- 60% PFO-congenital heart disease)
  - Chylothorax
* Complications from treatment: bleeding, HIT, osteoporosis
Long-term morbidity

*Postphlebitic syndrome* = a syndrome of pain, swelling and skin changes 21-70% after VTE, can occur months after the primary event

*Recurrent thrombosis 8,1%*

*Loss of venous access*

*Nidus for infection*
Etiology

• Significant differences in epidemiology and potential differences in mechanisms for VTE compared to adults

• Coagulation system different

no adult levels until 1-5 years of age
Higher levels of trombin inhibitor alpha-macroglobulin
Plasma prothrombin concentrations 10-20% lower
Peak thrombin activity reduced
Lower levels of clotting factors II, V, VII, IX, X, XII
Platelet function enhanced in neonates (VwF)
Etiology

- Adults: Virchow's triad

1. Abnormal changes in the vessel wall
2. Abnormal changes in blood flow
3. Abnormal changes in blood constituents
Risk factors

Congenital

- Congenital thrombophilia
  - Antiphospholipid antibody syndrome
  - Factor V Leiden
  - Prothrombin mutation
  - Deficiency anticoagulant: ATIII, Protein C and Protein S

- Congenital heart disease
Risk factors

Acquired

- Infections (HIV, varicella)
- Malignancy
- Drugs (L-asparaginase: chemotherapy, steroids)
- Trauma
- Surgery
- **CVC!!!!!!! Especially infants and young children**
- Lifestyle: smoking, OAC
- Vasopressor administration
- Immobilization
- Age
- Multiple medical conditions
Risk factors

• Numerous risk factors, significance of each is unknown

• Up to 90% of children with VTE have more than 1 risk factor (median of 2 risk factors)

• 80-90% of children: inciting agent can be identified (50% in adults)
Age distribution of patients with VTE at Children's Hospital of Philadelphia from 2003 to 2006 (N = 217).

Figure 2. Distribution of thrombosis risk factors identified in 707 admissions to the pediatric intensive care unit during a 6-month study period. n = raw number of admissions with each risk factor. DKA, diabetic ketoacidosis; SLE, systemic lupus erythematosus.
Figure 4. Percent of patients in study group with individual risk factors, grouped by presence of thrombus at admission (black bars, denominator = 14), acquisition of thrombus in-hospital (white bars, denominator = 18) and no evidence of thrombus (hatched box, denominator = 637). Raw numbers of patients with specific risk are expressed above each set of bars. Chi-square analysis identified significant differences between groups for the following risk factors: age 14 yrs (p = .001); exogenous estrogen (p p p p p SLE, systemic lupus erythematosus; BSA, body surface area.
CVC related VTE

Incidence: 11-50%, 85% of VTE related to CVC!!!

Etiology: ‘Virchow’s triade for CVC’

1. Abnormal changes in the vessel wall: Endothelial disruption at the insertion site, endothelial damage by the catheter or shaft tip, vascular irritation from infusion of caustic substrates

2. Abnormal changes in blood flow: stagnant venous flow past the catheter

3. Abnormal changes in blood constituents: underlying hypercoagulopathy, inherently thrombogenic catheter material itself
CVC related VTE

• 2 forms

Fibrin sheath: occludes the catheter, not the vein
Thrombus(catheter tip): adherent to catheter and vessel wall: occludes catheter and vein

• Location

Femoral>subclavian, jugular?
->avoid routine cannulation of femoral vein
CVC related VTE

• Catheter

Higher risk percutaneous and multilumen CVC? Risk increases with catheter size? Difference due to catheter material (silicone and polyurethane) negligible CVC > tunneled CVC = PICC

• Duration

risk greatest 4-5 days after catheter placement -> Remove CVC as soon as medically possible!
Diagnosis

- **Symptoms**
  - Asymptomatic!!! 1/8 symptomatic
  - Catheter associated blood stream infection
  - Acute inflammation
  - Venous congestion

- **Laboratory investigation**
  - Exclusion of systemic disorders(1C)
  - Haematology: blood count, clotting screen, renal function prior to anti-coaguation(1C)
  - D-dimers not useful (vary with age, difficult interpretation)(2C)
Diagnosis

• Imaging

* Upper extremity
  US(1B): jugular, axillary and distal subclavian veins
  Magnetic resonance venography(1C)(if not available: multi-detector CT): proximal subclavian, innominate, superior vena cava

* Lower extremity
  US (1B) and extremity surveillance
  MR venography: extension in the iliac and proximal veins (2C)
Thrombotic complications in children from short-term percutaneous central venous catheters: What can we do?
Treatment

- **Limited data** safety and efficacy of anticoagulants in children

- **Goals**

  * **Acute**: re-establishing flow

  * **Chronic**: prevent recurrence, prevent embolization of residual trombus
Treatment

Acute

1. **Heparin**: dose variability, affected by antithrombin levels

**Unfractionated heparin**
IV bolus 75-100 IU/kg
28U /kg/h(<1 year), 18-20u /kg/h >1 year

**LMWH**: risk of bleeding and of HIT, increasing use
SC: enoxaparin 2mg/kg/d, <8 weeks or 5kg: 50% larger doses

2. **Thrombolysis**: more effective than standard anti-coagulation in preventing postthrombotic syndrome
Treatment

• Indications for thrombolysis

* Limb-threatening circulatory compromise,
* Rapid thrombus extension despite anticoagulation
* Symptomatic deterioration despite anticoagulation
* First line treatment to prevent posttrombotic syndrome in patients at low risk of bleeding

Consider:
* Extensive thrombosis in the pelvic veins, SVC, IVC or intracardiac veins
* Massive PE
Treatment

- Thrombolysis should not be given...
  
  * Systematically
  * To most patients with symptoms > 21 days
  * To patients with high risk of bleeding
Treatment

Chronic

**Warfarin** (INR 2,5)

Older children with lower limb VTE+ contra-indication for systemic anticoagulation: consider removable **IVC filter** (1C)
Treatment

- Duration

3 months: secondary VTE (1C)
6 months: idiopathic VTE (1C)
**Life-long:** recurrent idiopathic VTE and antiphospholipid syndrome (1C)

- CVC related VTE
Remove CVC 3-5 days after start anticoagulant therapy especially in Neonates (paradoxical emboli), congenital heart disease, right to left shunts
Prevention

• **Children ≠ Adults**: differences in epidemiology and coagulation

• **Adolescents**: no recommendations: extrapolation from adults in some centres

• **Significant variability in thromboprophylaxis** management

• **Paucity of evidence** to guide practice
Prevention

• General preventative measures

* Good hydration

* Early mobilization

* Removal of CVC’s as soon as possible

* Postpubertal girls: Consider withholding contraceptive pill for 4 weeks prior to planned surgery (family history of thrombosis or a known thrombophilic risk factor)
Prevention

- Physical methods

  * Graduated compression stockings
  * Intermittent pneumatic compression devices
  * Venous foot pumps

  -> older children and adolescents (>40kg)

  -> effectiveness proven in studies

- Pharmacological thromboprophylaxis

  * Enoxaparin if multiple risk factors (2C): anticoagulant of choice
  * (Heparin)
  * (warfarin)

  * no evidence for aspirin (2C)
Prevention

Children and CVC

• No routine primary antithrombotic prophylaxis (grade 1B)

• Consider: multiple risk factors for VTE

• American college of chest physicians:
  Neonates: maintain CVC patency with unfractioned heparin continous infusion 0,5 unit/kg/h(grade 1A)
  Children: flushing with normal saline or heparin or intermittent recombinant urokinase as compared with no therapy (grade 2C)
  Long-term home TPN: antithrombotic prophylaxis therapy (vit K Antagonists INR 2-2,5) (grade 2C)continuously or the first three months after each CVC is inserted
Prevention

- **Heparin-bonded catheters may be beneficial**
  ex: infants with congenital heart disease: no reduction in the risk

- **Pre-existing vessel trombus = contra-indication for CVC placement?**
  1. Theoretic risk of dislodgement of the trombus
  2. Difficulty for advancing the guide wire
  3. Increased risk of new thrombus in already thrombosed or narrow vein
Prevention

• Use of ultrasound may decrease risk DVT

ASA: real time US for venous access IJ en femoral veins, static US for pre-puncture identification of anatomy and localisation

SPA endorses ASA guidelines

NICE (national institute for clinical excellence) 2002: US for CVC’s in IJ veins in adults and children electively and in most emergency situations

American society of echocardiography and the society of cardiovascular anesthesiologists: US for IJ or femoral veins

-> Use of ultrasound before removal of the catheter?

\[Vöhr M1, Berger TM. Venous access in children: state of the art. Curr Opin Anaesthesiol, 2015 Mar 30\]
Thrombotic complications in children from short-term percutaneous central venous catheters: What can we do?
Prevention

- Risk assessment tools to identify those at high risk

Reiter, Pamela; Wathen, Beth; MSN, RN; Valuck, Robert; Dobyns, Emily

DOI: 10.1097/PCC.0b013e31823893f5
Algorithm for inpatient VTE risk assessment and prophylaxis.

ALERTED MOBILITY
- Immobility refers to a permanent state of altered mobility (e.g., paralysis).
- Impaired physical mobility refers to a temporary state of altered mobility (e.g., cast, post-op activity restrictions).

VTE RISK FACTORS

ACUTE CONDITIONS
- Major lower extremity orthopedic surgery
- Spinal cord injury
- Major trauma to the lower extremities
- Lower extremity central venous catheter
- Acute infection
- Known active viral infection
- Current antibiotic treatment
- Burns
- Pregnancy

CHRONIC MEDICAL CONDITIONS
- Obesity
  - Weight > 80 kg in age 14-16
  - Weight > 85 kg over age 16
- Estrogen containing medications
- Inflammatory bowel disease
- Neoplastic syndrome
- Known acquired or inherited thrombophilia

HISTORICAL FACTORS
- Previous history of DVT/PE
- Family history of VTE in first-degree relative < 40 y

CONTRAINDICATIONS TO ANTICOAGULATION
- Intracranial hemorrhage
- Acute Stroke
- Ongoing and uncontrolled bleeding
- Uncontrolled coagulopathy
- Incomplete spinal cord injury with suspected or known paraplegic hematoma
- Allergy to pork products
- Heparin induced thrombocytopenia

PHARMACOLOGIC PROPHYLAXIS
- Enoxaparin
  - Patients > 60 kg:
    - 30 mg SQ bid (High-risk Orthopedic surgery - to be initiated 12/24 hours post-op) OR
    - 40 mg daily (Medical patients)
  - Patients < 60 kg:
    - 0.5 mg/kg SQ bid
  - uFH (Neurological patients)
    - Patients > 60 kg:
      - 5000 units SQ bid

Intervention:
- Early ambulation
- Mechanical prophylaxis
  - Pneumatic compression device (preferred) and/or
  - Graduated compression stockings

Intervention:
- MOBILITY AS TOLERATED (Active or Passive)
- AND
- MECHANICAL PROPHYLAXIS
  - Pneumatic compression device (preferred) and/or
  - Graduated compression stockings
  - AND, for strong consideration
  - PHARMACOLOGIC PROPHYLAXIS
    - Enoxaparin or uFH

Intervention:
- MOBILITY AS TOLERATED (Active or Passive)
- AND
- MECHANICAL PROPHYLAXIS
  - Pneumatic compression device (preferred), and/or
  - Graduated compression stockings
  - PHARMACOLOGIC PROPHYLAXIS
    - Enoxaparin or uFH

Intervention:
- MOBILITY AS TOLERATED (Active or Passive)
- AND
- MECHANICAL PROPHYLAXIS
  - Pneumatic compression device (preferred), and/or
  - Graduated compression stockings

Patient ≥ 14 y?

Yes
- Altered mobility?

Yes
- Other VTE Risk Factors?

Yes
- Contraindication to Anticoagulation?

Yes
- High risk

No
- Low risk

Yes
- Other VTE Risk Factors?

No
- At risk
### Paediatric Thromboprophylaxis Risk Assessment Chart

**To be followed DAILY for the following:**
- PACU patients
- HDU patients
- Patients with CVCs

**To be discontinued when child is fully mobilizing:**

<table>
<thead>
<tr>
<th>Known Risk Factors (tick):</th>
<th>Date/Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Venous Catheter</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
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<tr>
<td>Major Trauma — (Lower limb # or major organ)</td>
<td></td>
</tr>
<tr>
<td>Burns &gt;20%</td>
<td></td>
</tr>
<tr>
<td>Oral Contraceptive Pill</td>
<td></td>
</tr>
<tr>
<td>Surgery &gt; 4 hrs</td>
<td></td>
</tr>
<tr>
<td>Long term Steroids &gt; 3 months</td>
<td></td>
</tr>
<tr>
<td>Ventilated</td>
<td></td>
</tr>
<tr>
<td>Assessed by: (name)</td>
<td></td>
</tr>
<tr>
<td>Designation:</td>
<td></td>
</tr>
<tr>
<td>Signature:</td>
<td></td>
</tr>
</tbody>
</table>

**Name:**

**Date of Birth:**

**Hospital No.:**

Or attach addressograph.

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Paediatric Thromboprophylaxis Flow Chart

NB. Daily Consultant Review Decisions must be documented in the Medical Notes

Risk factors present?

No

Low risk:
- Early mobilization
- Adequate hydration

Yes

At risk:
Child must have thromboprophylaxis reviewed daily by Consultant and management plan recorded in notes.

If child has a short term CVC present, the line should be removed within 24 h unless a consultant documents that it should remain in situ.

CVC in an infant is a very high risk.

Interventions may include:
- Adequate hydration
- Early mobilization if possible
- TEDs/Flowtrons if available for size of child.
- Burns >20% consider anticoagulation
- The decision to anticoagulate must be made by a consultant.
SCH thromboprophylaxis guideline flowchart

AGE
(See APPENDIX 1)
- Neonate (<6 months) --> See "APPENDIX 1"
- Child (6 months to pre-puberty) --> 0 Points
- Adolescent (puberty onwards) --> 2 Points

Congenital diseases
(See APPENDIX 2)
- 1 point for each: Congenital heart disease
- Inherited thrombophilic conditions
- Certain metabolic diseases
- Certain malformations

Pre-existing medical problems
(See APPENDIX 3)
- 1 point for each of: Inflammatory diseases
- Connective tissue diseases
- Previous thrombosis at any site

Current medical problems
- 1 point for each of: Active Malignancy
- Active infection (Meningitis/Septicemia/Varicella/HIV)
- Major trauma and/or Burns
- Immobility
- Pregnancy
- Obesity
- HIT (not: enoxaparin contraindicated)

Medication
- 1 point for each of: Oral contraceptive pill
- Asparaginase
- Steroids
- TPN
- Smoker

Iatrogenic issues
- 1 point for each of: Shunts/Stents/PICC line
- 2 points for Central venous catheter

Total score =

## Surgery

<table>
<thead>
<tr>
<th>Risk</th>
<th>Score</th>
<th>1–2</th>
<th>3–5</th>
<th>6+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low risk</strong></td>
<td></td>
<td>Surgery of any type</td>
<td>Any surgery of duration &lt; 30 mins</td>
<td>Any surgery of duration &lt; 30 mins</td>
</tr>
<tr>
<td>• Ensure good rehydration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Early mobilisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medium risk</strong></td>
<td></td>
<td></td>
<td>Any major general surgery or minor surgery of &gt;30 min duration</td>
<td>Any minor surgery of &gt;30 min duration</td>
</tr>
<tr>
<td>• TED stockings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Flowtron boots in theatre</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Plus follow guidelines for low risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High risk</strong></td>
<td></td>
<td></td>
<td>Major orthopaedic surgery</td>
<td>Any major surgery</td>
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<tr>
<td>• ENOXAPARIN</td>
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<td></td>
<td></td>
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<tr>
<td>• Plus follow guidelines for medium and low risk groups</td>
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</tr>
<tr>
<td>Risk</td>
<td>Score</td>
<td>1–2</td>
<td>3–5</td>
<td>6+</td>
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<tr>
<td><strong>Low risk</strong></td>
<td></td>
<td>Not ventilated</td>
<td>Not ventilated</td>
<td>All 6+ patients at least medium risk</td>
</tr>
<tr>
<td>• Ensure good rehydration</td>
<td></td>
<td>Or Intubated &amp; ventilated &lt;48h</td>
<td>Or Intubated &amp; ventilated &lt;48h</td>
<td></td>
</tr>
<tr>
<td>• Early mobilisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medium risk</strong></td>
<td></td>
<td>Intubated and ventilated &gt;48h</td>
<td>ICU bed rest &gt;48h or intubated and ventilated &gt;48h</td>
<td>Not ventilated</td>
</tr>
<tr>
<td>• TED Stockings</td>
<td></td>
<td></td>
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Conclusion

• Increasing problem

• Usually a combination of several risk factors

• CVC major culprit

• Paucity of evidence to guide practice in prevention of VTE
References