Post-Thrombotic Syndrome: Why Anti-coagulation Matters

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Disclosures

• None
Objectives

• Understand the clinical presentation of post-thrombotic syndrome
• Explore possible risk factors for post-thrombotic syndrome in pediatric trauma patients
• Develop preventative and treatment strategies for post-thrombotic syndrome
Which of the following contributes to the highest number of deaths per year in the US?
• A) Motor Vehicle Accidents
• B) Breast Cancer
• C) HIV
• D) VTE (DVT/PE)
• E) Motor Vehicle Accident/Breast Cancer/HIV
DVT/PE

- Incidence VTE: approx 1,000,000/year
- 1:3 patients with DVT develop PE
- 20% of new VTE patients die suddenly from PE
- 20% of all VTE occurs in pts with cancer
- Up to 15% of cancer pts develop VTE
- 2\textsuperscript{nd} most frequent cause of death in patients with cancer
Hemostasis

Natural anticoagulants (protein C, protein S, AT-III)
fibrinolytic factors

Coagulation factors plateau fibrinolytic inhibitors

Hypercoagulability
Hemostasis

• Goals of Hemostasis
  – Maintain Blood in fluid state for circulation
  – Form Temporary clot at site of injury
    • Seal wall and repair endothelium when vessel is damaged
    • Break down thrombus once vessel wall is healed
Components of Hemostasis

- Blood vessel wall
- Platelets
- Clotting proteins (factors)
- Natural Anti-Coagulants
  - Protein C
  - Protein S
  - Antithrombin
- Fibrinolytic system

Together, coagulation, anticoagulation, and fibrinolysis maintain a delicate physiological balance.
Virchow’s Triad

“More than a hundred years ago Rudolf Virchow stated that there were three factors (Virchow’s Triad) involved in its causation. These were: (1) slowing of the blood stream, (2) changes in the vessel wall, and (3) changes in the blood itself. In the intervening years almost nothing of real importance has been added to our knowledge.” - Boyd 1964
VTE Risk Factors

Virchow’s Triad

- Venous Stasis
  - Post-Operative Casting/Splinting
  - Immobility
  - Leucostasis

- Endothelial Damage
  - Catheters
  - Sepsis
  - Trauma
  - Chemo
  - APA

- Hyper-coaguuble
  - Inherited/ Acquired
  - Thrombophilia

Goldenberg et al. 2008
Clinical Risk Factors (Prothrombotic Conditions)

- Central line = 60%
- Malignancy/BMT = 25%
- Congenital cardiac dis = 19%
- Surgery = 15%
- Infection = 12%
- Trauma = 10%
- OCP = 4%
- Other = 12%
- Spontaneous = 3%

Monagle et al., *Pediatr Res* 2000
VTE Risk Factors: Thrombophilia

- Any alteration in the hemostatic balance → Thrombophilia
  - Endothelial activation/damage
  - Enhanced platelet activation/aggregation
  - Increased thrombin production
  - Inhibition of fibrinolysis
VTE Risk Factors: Thrombophilia

**Inherited**
- Factor V Leiden
- PT G20210A
- MTHFR (hyperhomocysteinemia)
- Antithrombin Deficiency
- Protein C deficiency
- Protein S deficiency
- Dysfibrinogenemia

**Acquired**
- Antiphospholipid Antibody Syndrome
- Increased FVIII (infection/inflammatory conditions)
- Anticoagulant deficiencies (consumption secondary to DIC/sepsis)
- Malignancy
## VTE Risk Factors: Thrombophilia

### Population Based Risk Estimates: (Adult)

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Thrombotic Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperhomocysteinemia</td>
<td>2.5X</td>
</tr>
<tr>
<td>PT 20210 (heterozygous)</td>
<td>3X</td>
</tr>
<tr>
<td>FVL (heterozygous)</td>
<td>2-7X</td>
</tr>
<tr>
<td>FVL (homozygous)</td>
<td>80X</td>
</tr>
<tr>
<td>OCP</td>
<td>4X</td>
</tr>
<tr>
<td>FVL + OCP</td>
<td>35X</td>
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</tbody>
</table>

Goldenberg et al. 2008
VTE Incidence in Children: Bi-Modal Distribution

Neonates (<1mo)
• ~12% all pediatric clots
  – 2.4/1000 NICU admits
  – 5.1/100,000 births
  – Increased # of CSVT, RVT
• Risk Factors
  -- Immature coag system
  – Infection
  – Dehydration
  – Asphyxia
  – Central Catheters

Adolescents (>10 yrs)
• ~50% all pediatric clots (3 fold increase c/w kids)
• Risk Factors
  – Approaching adult parameters → increased thrombin generation
  – Additional acquired risk factors: APA, smoking, OCPs, injuries

Schmidt 1995; Nowak-Gottl 1997
Clinical Presentation

- DVT
  - Painful unilateral limb swelling
  - Upper extremity:
    - 80% neonatal DVT
    - 60% child DVT
    - +/- Homan’s sign
    - +/- Palpable cord
    - Possible SVC syndrome with upper extremity

Clinical Presentation

• Pulmonary Embolus
  – Unexplained shortness of breath
  – Pleuritic chest pain
  – +/- hypoxemia
  – Proximal PE/Saddle Embolus $\rightarrow$ cyanosis/sudden collapse
  – If right heart failure $\rightarrow$ hepatomegaly, peripheral edema
  – Also can be asymptomatic
## Clinical Presentation

<table>
<thead>
<tr>
<th>CSVT</th>
<th>Renal Vein Thrombosis</th>
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<tbody>
<tr>
<td>- Headache-severe/persistent</td>
<td>- Hematuria</td>
</tr>
<tr>
<td>- Blurred vision</td>
<td>- Oliguria</td>
</tr>
<tr>
<td>- Seizures</td>
<td>- Thrombocytopenia</td>
</tr>
<tr>
<td>- Cranial Nerve Palsies</td>
<td>- Possible flank mass</td>
</tr>
<tr>
<td>- Papilledema</td>
<td>- Neonates: typically with 48-72 hours</td>
</tr>
<tr>
<td>- Neonates: non-specific symptoms</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Presentation

Portal Vein Thrombosis
- Splenomegaly
- Thrombocytopenia
- Anemia
- Gastroesophageal varices/bleeding

Internal Jugular Vein
- Neck pain/swelling
- Lemierre’s syndrome
Anticoagulation: Treatment Goals

• Attenuate hypercoagulability
• Limit Thrombus Progression
• Decrease risk of thrombus embolism
• In general: intrinsic fibrinolytic mechanisms to dissolve the thrombus
• Prevent persistent thrombosis and PTS
Adapted from Balasa Ped Blood Cancer 2005
Treatment: Duration

• First-episode DVT
  – Identifiable transient risk factor (e.g. post-op): 3 months
  – Idiopathic: 6 months
  – Chronic Risk Factor: 12 months - life-long

• Recurrent DVT
  – Identifiable transient risk factor: 3-6 months
  – Idiopathic: 12 months - life-long
  – Chronic risk factor: Life-long

Monagle et al., Chest 2008
Goldenberg 2011
Acute Outcomes of VTE

- Bleeding with anticoagulation
- Early recurrent VTE-including DVT, PE
- Acute renal insufficiency
- SVC Syndrome
- Catheter related sepsis and malfunction
- Acute venous infarction with limb gangrene
- Death
Chronic Outcomes of VTE

- Chronic SVC syndrome
- Chronic Hypertension/Renal Insufficiency
- Variceal Hemorrhage in portal vein thrombosis
- Persistent Thrombosis
- Recurrent VTE
- Post-Thrombotic Syndrome
Venous thrombosis

- Recanalization
  - Venous valve damage
    - Venous valvular reflux
- Inflammatory response
- Persistent Outflow obstruction
  - Collateral venous circulation

Venous hypertension

- Telangiectasias
  - Venous ectasia
- Capillary leakage
  - Edema
  - Hyperpigmentation
  - Lipodermatosclerosis
  - Ulceration
Post-Thrombotic Syndrome

- Chronic Venous Insufficiency after VTE
- Valvular Damage
- Veno-Obstruction
- Venous Hypertension
- Capillary Leak
- Edema/Swelling
- Leg Pain/heaviness
- Physical Limitations
- Ulceration
Post-Thrombotic Syndrome

14 y/o Ileofemoral to IVC DVT with superficial collaterals

13 y/o Ileofemoral to IVC DVT with stasis dermatitis

Post-Thrombotic Syndrome

- Underappreciated, chronic complication of DVT that reduces quality of life (clinical diagnosis)
- 1/3 adult patients with DVT develop PTS
- 5-10% pts develop severe PTS -> leg ulceration
- Patients experience aching pain, heaviness, swelling, cramps, itching/tingling in affected limb
- Symptoms aggravated by standing/walking and relieved with rest, leg elevation, lying down
- Can wax and wane over time
- Use D-dimer to distinguish from recurrent DVT
Predictors of Persistent Thrombosis?

- **Occlusive thrombi** more likely to be persistent
  - Abnormal fibrinolytic function?
  - Increased coagulation activation?

- Elevated Factor VIII and D-dimer at diagnosis associated with persistent thrombosis/PTS
  - *Pro-inflammatory*, hypercoaguable state resulting in increased coagulation activation?
  - Resistance to intrinsic hypofibrinolysis?

- Presence of Thrombophilia trait in adults predictive of residual thrombosis, not PTS

Predictors of Post-Thrombotic Syndrome

• Elevated IL-6 and CRP- associated with increased venous outflow resistance (measure of residual thrombus)- and higher risk of PTS at 1 year (Roumen-Klappe)
• Elevated IL-6 and ICAM-1 four months following diagnosis associated with increased risk of PTS during a 2-year f/u period (Shbaklo)
• ?????Inflammatory state → hypofibrinolytic state

Roumen-Klappe J Thromb Haemost 2009
Shbaklo Thromb Haemost 2009
Intervention:
Elastic Compression Stocking

- Increase venous flow
- Decrease Venous Hypertension
- Decrease capillary leak (edema)
- Early intervention will re-establish flow
- Daily use to prevent PTS?
- 2 adult studies showed 50% reduction in PTS incidence
- Knee length, 30-40 mmHg, as long as patient derives benefit and able to tolerate
Treatment Options

• Systemic thrombolytic therapy and catheter directed thrombolysis does not decrease PTS and there is risk to procedures

• American College of Chest Physicians suggest it in selected patients with extensive acute proximal DVT & low bleeding risk, followed by standard anticoagulant therapy

• Venoactive medication as horse chestnut seed (aescin) PO x 1 year relieved PTS symptoms (Italian study); no added benefit when combined with compression stockings

• No evidence for use of diuretics or NSAIDS beyond anagesic effects
Acknowledgements

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