Central Venous Line Related Deep Vein Thrombosis in Pediatric Patients

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Pediatric Venous Thrombosis
- Epidemiology
- Risk factors
- CVL related DVT
  - Background
  - Literature
  - WCHOB
- Thrombosis
  - Diagnosis/management
  - Complications/Outcomes

Venous Thrombosis
- Balance exists between prothrombotic and antithrombotic factors within blood
- Endothelium generally has antithrombotic properties
- Certain factors can overcome antithrombotic characteristics of the blood/endothelium
- Various congenital and acquired factors can contribute to a shift in the balance leading to a prothrombotic state

Clotting Cascade

Venous Thrombosis
- Occurs in 2-5% of adult population
- Rates of venous thrombosis lower in pediatrics
  - Decreased thrombin generation
  - Increased antithrombotic effect of vessel wall
- Pediatric thrombosis has bimodal distribution
  - Highest frequency in neonatal period
  - Highest in any age group
  - Second peak in adolescence
- Adolescent females secondary to OCP use and pregnancy
- Increasing frequency/awareness
- Lack of consistent treatment methods and low overall frequency make large studies difficult
Frequency of Pediatric Thrombosis

- With increased awareness/frequency several registry studies attempted to determine overall rate
- General pediatric population
  - van Ommen et al - Netherlands
    - 0.14 per 10,000 children
  - Monagle et al from Canadian registry
    - 0.07 per 10,000 children
- Hospitalized Patients
  - Increased risk in hospitalized patients
    - Canadian registry
      - 5.3 per 10,000 hospitalizations
    - Stein et al US National Hospital Discharge Survey
      - 4.9 per 10,000 childhood years
  - Highest risk noted in NICU patients
    - Up to 24 per 10,000 NICU admissions
    - van Ommen et al – Netherlands
      - 14.9 per 10,000
- Most hospitalized children with VTE have at least one and often multiple identifiable risk factors

Risk Factors for Thrombosis

- Congenital
  - Factor V mutations
  - Prothrombin gene mutation
  - Deficiency of protein C, protein S or antithrombin
  - Elevations of lipoprotein a, homocysteine, factor VII/VIII/IX/XI may also increase risk
- Acquired
  - CVL
    - Most common risk
    - 60-90% of DVTs associated with CVL
  - Malignancy, trauma, surgery, hormone therapy, nephrotic syndrome/renal disease, antiphospholipid syndrome, medications, hemoglobinopathies, PNH

Central Venous Lines

- Most common risk factor associated with development of DVT
- Overall are the cause of majority of DVTs
  - Massicotte et al from Canadian registry
    - 244 cases of VTE
    - 60% associated with CVL
  - Schmidt et al
    - Neonates with non-renal vein thrombosis
      - 89% associated with CVL
- With improved overall survival of critically and chronically ill children use of CVLs has become more frequent
- Leads to increasing rate of DVT in pediatric patients

Literature

- Overall rate of DVT formation in the presence of a CVL varies from institution to institution and by diagnostic methodology/criteria
**General Pediatric Population**
- Dubois et al
  - Review of 214 pediatric patients with PICC lines placed in their radiology dept
  - 9.3% of patients developed thrombus detected on screening at time line pulled
  - Only 1 symptomatic
- Male et al
  - Prospective cohort study in general pediatric population including 158 children
  - Overall 13% developed thrombus on U/S or venogram
  - Femoral or subclavian lines were found to have statistically higher rate than brachial or jugular (32%/27% vs 12%/8%)
  - No statistically significant difference for type of line (PICC vs tunneled vs non-tunneled), size of line or duration of placement

**Pediatric ICU Patients**
- DeAngelis et al
  - 76 PICU patients screened with U/S
  - 4% with thrombus
  - All in femoral lines
- Shefler et al
  - 56 PICU patients with femoral lines screened with U/S of IVC
  - 11% with thrombus
  - One symptomatic

**Pediatric ICU Patients**
- Hanslik et al
  - Review of 90 pediatric patients with congenital heart disease with short term venous catheters
  - Predominantly jugular lines
  - Using combination of venography, U/S and Echo detected thrombus in 28% of patients
- Sheridan et al
  - Review of 289 children in a burn ICU with 1056 venous lines
  - Protocol includes rotating CVL sites weekly
  - Symptomatic DVT developed at site of previous cannulation in 0.6%

**Neonatal ICU**
- Butler-O'Hara et al
  - Review of 210 neonates with umbilical vein catheters
  - 20% of SGA neonates developed thrombus
  - 9% of AGA/LGA developed thrombus

**Oncology Patients**
- Male et al
  - Prospective cohort study of 85 children with ALL
  - 34% with thrombosis
  - Left sided, subclavian and percutaneously inserted catheters were independently associated with increased risk of thrombosis
- Journeycake et al
  - 287 pediatric oncology patients
  - Thrombosis associated with line-related infections, repeated occlusions, need for multiple catheters

**CVL Related DVT**
- Many series report high rate of thrombus formation when screening using various methods to screen
  - When screening a group of pediatric patients with CVL regardless of symptoms >30% may have evidence of a thrombus
CVL Related DVT

- Significantly smaller percentage of clots identified on screening are clinically symptomatic
- Despite some even being occlusive clots
- Long term outcome of the asymptomatic DVTs related to CVLs is unknown at this time

Outcomes with CVL Related DVT

- Outcomes often poorer
  - Likely related to seriousness of underlying disorders
- Massicotte et al
  - Review of data from Canadian registry
  - All-cause mortality 23%
  - VTE-related mortality 4%
  - Recurrence in 6.5%
  - Post-thrombotic syndrome in 10%

Prophylaxis with CVLs

- Data thus far does not support prophylactic anticoagulation in children with CVLs
- PROTEKT study
  - Multicenter, randomized trial of prophylactic riviparin vs routine heparin flushes
  - Closed early with low enrollment
  - No major bleeding events
  - 14% developed a thrombus
    - Though only screened with venography

QA/QI Analysis

- Retrospective review of all patients admitted to the PICU at WCHOB from July 2008 to June 2009 requiring placement of a CVL
- Goals:
  - Determine rate of thrombotic complications of CVL placement
  - Identify risk factors for development of thrombosis
  - Review outcomes of patients with CVL related DVT

Risk Factors

- Based on historical data and theoretical risks will compare several groups of hypothetical risk factors
  - Patient age/weight
  - Admission diagnosis
    - Infectious, surgical, traumatic
    - Sepsis, malignancy
  - CVL duration
  - CVL size
  - CVL location
  - Evidence of low flow state
    - Hypotension requiring volume or pressor support
    - Immobility related to intubation and/or paralytics

Subjects

- Reviewed all available records for patients from January 2009 to June 2009
  - 637 total PICU admissions
  - 150 with CVL
  - 106 with available medical records/data
    - 2/106 (2%) dialysis catheters
    - 95/106 (90%) non-tunneled catheters
      - 91/106 (8%) tunneled catheters
        - 2 Broviac
        - 7 Mediport
### Characteristics
- Evaluating individuals with non-tunneled, temporary CVLs
  - Femoral, jugular, subclavian lines
- Mean age of 3.9 years
- Diagnosis
  - 52/71 (73%) Infectious
  - 11/71 (15%) Other Medical
  - 4/71 (6%) Trauma
  - 6/71 (8%) Surgical

### Thrombosis
- Only 1/71 (1.5%) with symptomatic CVL related thrombus
  - Femoral line related clot in infant septic with meningococcemia
  - 2 other non-CVL-related DVTs
    - One related to local infection with osteomyelitis
    - One spontaneous DVT

### WCHOB PICU
- Rate of thrombotic complications of CVLs comparable to reported data
  - Relatively low overall
- Current numbers very small so at this point unable to assess other factors/risks

### Pediatric Venous Thrombosis
- Presentation
- Diagnosis
- Management
- Long term
  - Complications
  - Prophylaxis?

### Presentation
- Clinical presentation depends on site and extent of thrombus
  - Many are asymptomatic
  - Most commonly located in extremities
  - Swelling, pain, discoloration
  - SVC syndrome
  - Chylothorax/chylopericardium
  - CVL related clots often present with catheter dysfunction or catheter related sepsis
  - May present with thrombocytopenia from platelet consumption

### Diagnosis
- Most commonly diagnosed with doppler ultrasound with compression
  - Non invasive
  - Sensitive and specific for diagnosing most lower extremity and many upper extremity DVTs
- CT with contrast can be used for upper extremity, abdominal or pelvic clots
- Venography not generally necessary but can be helpful in select situations
Acute Treatment

- Anticoagulation
  - Initially with one form of heparin
    - Unfractionated (UFH)
    - Short half-life so can be turned off quickly
  - Low molecular weight
  - Decreased incidence of HIT
  - Requires adequate levels of antithrombin III which is normally low in neonates/infants
  - FFP prior to initiating therapy
- Therapeutic monitoring
  - aPTT frequently does not correlate well with anti-FXa levels in pediatrics (particularly infants)

Thrombolytics

- Not generally used with few exceptions
  - Significant IVC thrombus or pulmonary embolism
  - Most DVTs related to CVLs are well organized by diagnosis

Treatment

- Beyond immediate acute treatment - two options
  - Warfarin
    - Oral
    - Affected by diet, absorption, other medications
    - Sensitivity to drug varies at different developmental stages
    - May require freq. INR monitoring to maintain therapeutic range
  - LMWH
    - Daily subcutaneous injection
    - More predictable pharmacokinetics - less frequent monitoring
- REVIVE trial
  - Randomized comparison of LMWH vs UFH/oral anticoagulant
  - Closed early due to poor accrual
  - Recurrence: 6% rivaparin vs 13% UFH/oral anticoag
    - Not significant though likely due to low power

Evaluation of Initial Thrombus

- Identify risk factors for recurrent thrombosis
- Most pediatric cases have transient risk factors such as underlying disease state, CVL
- Identify congenital, non-modifiable risk factors that may impact future treatment or counseling

Risk Factors for Thrombosis

- Congenital
  - Factor V mutations
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  - Deficiency of protein C, protein S or antithrombin
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- Acquired
  - CVL
    - Most common risk
    - 60-90% of DVTs associated with CVL
  - Malignancy, trauma, surgery, hormone therapy, nephrotic syndrome/renal disease, antiphospholipid syndrome, medications, hemoglobinopathies, PNH

Risk Factors for Thrombosis

- Idiopathic venous thrombosis is rare in pediatrics
- Almost always an underlying risk factor/disease
- Andrew et al
  - Canadian registry
  - 50% with 3-4 identified risk factors
  - <10% with congenital disorder
  - FVL screening not available, Prot C and S only screened in 1/3
- Hagstrom et al
  - Close to 40% with either congenital risk factor or antiphospholipid antibody
    - Most common congenital risk factor was FVL
Initial Evaluation
- Generally includes
  - Protein C Activity
  - Protein S Levels (Total/Free)
  - Antithrombin III
  - LUPAC panel (Anticardiolipin Ab, dRVVT) 
  - Activated protein C (APC) resistance
  - Potentially screen for factor V Leiden and other mutations
  - Homocysteine
  - Potentially screen for MTHFR mutations
  - Prothrombin 20210A mutation
  - Factor VIII
  - D-dimer
  - PT/PTT/Fibrinogen
  - ESR

Congenital Risk Factors
- Factor V Leiden
  - Mutation at cleavage site for activated protein C (APC)
  - Results in decreased sensitivity to natural anticoagulation effect of protein C and increased thrombin generation
  - Risk increased 7-fold for heterozygous and 80-fold for homozygous
  - Around 5% of US population are carriers

Congenital Risk Factors
- Antithrombin deficiency
  - Leads to excess thrombin formation
  - Heterozygotes with 5-fold increased risk
  - Homozygous rare, likely not compatible with life

- Protein C and Protein S deficiencies
  - Controls activity of factors Va and VIIIa
  - Heterozygotes with 5-10-fold risk
  - Homozygous generally present with purpura fulminans in infancy

- Prothrombin 20210A mutation
  - Increased prothrombin levels
  - Heterozygotes with 3-fold increased risk

- Hyperhomocysteinemia
  - Approximately 2.5-fold increased risk
  - Increases risk when associated with other known risk factors particularly factor V Leiden
  - Unknown mechanism
  - Related to mutation in MTHFR gene

Acquired Risk Factors
- Central venous line
  - Significant risk factor for venous thrombosis
  - Likely related to
    - Venous stasis
    - Turbulent blood flow around line
    - Endothelial cell damage
    - Thrombogenicity of catheter surface

- Antiphospholipid Antibodies (Lupus anticoagulant)
  - Anticardiolipin, Antiphosphatidylserine, β2 glycoprotein Ab
  - Present in 6-8% of general population
  - Often associated with collagen vascular diseases or some medications
  - Mechanism not clear but may be related to impaired regulation of thrombin, acquired abnormalities in protein C-protein S system
  - Persistent presence increases risk around 20-fold i.e. antiphospholipid syndrome

Acquired Risk Factors
- Trauma
  - Significant risk factor for thrombosis in adult patients, but not in pediatrics
  - Azu et al
    - Retrospective review at Level 1 Trauma center
    - No thrombotic events in 2,320 patients under 13yo
    - Two PEs in 1,025 patients from 13-17yo
    - Both with high trauma scores
    - Most received prophylaxis in this group
Malignancy

- Most common associated medical condition in CVL related VTE in Canadian Registry
- Cancer itself induces hypercoagulable state
- Some therapies have thrombotic risks
- Highest rates in ALL
  - Reported rates from 1%-32%
  - Average rate about 3%
  - Higher risk related to frequent use of Asparaginase
    - Halts protein synthesis including those in the Protein C-Protein S system
- Additional risks related to
  - Frequent long-term use of CVLs
  - Tumor compression of vessels

Therapy Duration

- No well established recommendations in pediatrics
  - Mostly extrapolated from adult data
- Most uncomplicated clots treated 3-6 months
- Individuals with clot progression, occlusive clots, persistently elevated inflammatory markers may be at increased risk of treatment failure
  - May benefit from longer period
  - Persistent elevation of Factor VIII or D-dimer may predict recurrence risk

Complications

- Thromboembolic events
  - Deep Vein Thrombosis
  - Pulmonary embolism
    - Estimated to occur in 30-60% of patients w/document DVT
- Cerebrovascular events
- Other (usually specific situations)
  - Portal Vein Thrombosis
  - Renal Vein Thrombosis
  - Superior Mesenteric Artery Syndrome
- Treatment related complications
  - Bleeding though generally rare

Long Term Clot Resolution

- Up to 50% of clots fail to completely resolve following therapy
- Recurrent Thrombosis
  - Nowak-Gottl et al Childhood Thrombophilia Study Group registry
    - Registry of 301 neonates/children treated w/6m anticoag
      - 21% recurrence w/mean f/u 7 years
  - Increasing data supporting importance of factor VIII and D-dimer in risk for recurrence
    - Goldenberg, NA et al
      - Elevated levels of either or both at diagnosis and at 3-6 months highly predictive of poor outcomes defined as incomplete clot resolution, recurrent thrombosis or post-thrombotic syndrome
    - Cosmi et al
      - D-dimer and factor VIII elevation 1 month following withdrawal of therapy are independent risk factors for recurrent VTE

Post-Thrombotic Syndrome

- Destruction of venous valves by thrombus or persistent thrombus
  - Venous hypertension
    - Increased hydrostatic pressure to soft tissue and skin
  - Most commonly in lower extremities
  - Pain, swelling, skin pigmentation, ulceration
  - Reported to affect up to 60% of patients
    - Less frequently in pediatrics
  - Monagle et al from Canadian pediatric registry
    - Over 12% diagnosed w/PTS at mean f/u of 3y
    - No comment on severity of symptoms
  - Generally mild in children
    - Increased limb circumference, swelling, varicose veins, pain
    - Rarely ulcerations

Mortality

- Neonates
  - Schmidt et al from Canadian registry
    - All cause mortality 18%
    - Did not report VTE-specific mortality
  - Beyond Neonatal period
    - Monagle et al report from Canadian registry
      - Median f/u of 3 years in 356 patients
      - 2% VTE-related mortality
      - All deaths in CVL-related clots
      - Several other series with similar rates of 1-4%
Prophylaxis

- Having genetic prothrombotic disorder does not necessarily require anticoagulation
  - Risks of long term anticoagulation often outweigh the benefit
- Most asymptomatic individuals (no VTE history) with known prothrombotic disorder do not require prophylaxis
  - Screening asymptomatic individuals for prothrombotic disorders also generally not necessary

Symptomatic Prophylaxis

- Individuals with significant congenital risk factor or antiphospholipid syndrome may be considered for long term anticoagulation
  - Initial thrombotic event - often anticoagulated up to 6 months
  - After initial therapy need to decide on long term prophylaxis
  - Many would save long-term prophylaxis for individuals with recurrent thrombosis
  - Depends on age, presentation and severity of underlying disorder
  - Long-term prophylaxis difficult when a diagnosis of thrombosis occurs in young age
  - Significant内外-threatening clot

Summary

- Thrombosis is rare in kids
  - Most often seen with acquired risk factor
  - Most common risk is presence of a CVL
  - Overall still rare in patients with CVLs and prophylaxis likely not indicated
- Underlying predisposition/thrombophilia adds to risk
  - May help guide therapeutic decisions
  - Despite added risk, screening in asymptomatic patients not necessary

References


More References