Risk Factor Evaluation for Thrombosis and Bleeding in Pediatric Patients with Heart Disease

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Why Does it Matter?

- Pediatric congenital heart disease and acquired heart failure are associated with higher risk of prothrombotic tendencies as compared to similar age-matched peers.
- Cardiac surgery further increases both bleeding and clotting abnormalities due to platelet dysfunction and activation, coagulation abnormalities and inflammation.
- Young infants have an immature coagulation system that exhibits a low capacity to inhibit clot formation and a high resistance to anticoagulation.
- Blood flow for many types of congenital heart lesions is dependent on shunts that are prone to thrombotic and/or stenotic occlusions.
- Vascular access is frequent and may be prolonged.
- Diuresis is frequently necessary.
Incidence, Management and Outcomes

• Largely unknown-heterogenous review
• Lack of standardized evaluation (imaging and laboratory)
• Institutional practice variability
• Reporting bias-most critical patients get reported
• No level of evidence A recs
• Mostly retrospective reviews
• Need to evaluate multiple factors
  – CLABSI data, ultrasound vessel size
Background

- Retrospective institutional review
- 15/124 (12.1%) patients with heart disease were identified to have symptomatic VTE
- 9/15 (60%) had single ventricle anatomy at time of thrombus formation:
  - 3 with Stage I Norwood or Damus-Kaye Stansel
  - 3 with Glenn shunts
  - 2 with Blalock-Taussig (BT) shunts
  - 1 with a pulmonary artery band
Background

- 53% were male
- Patients ranged in age from 4 days to 18 months (mean age 5.3 months)
- 93% patients had at least 1 VTE associated with a central venous line (CVL) detected by ultrasound
Background

- 46.7% had >1 location with VTE
- 78.6% had percutaneous CVLs, with line tip not within vena cava in 63.6%
- Mean number of days from central line insertion to thrombus discovery was 8.6 days
- 33% of patients were on heparin at time of thrombus discovery to maintain shunt/conduit patency, but none had systemic levels of heparin
- TEG R times <5 in all patients with thrombosis
- Fibrinogen >350 in 60% of patients with thrombosis
Background

• General inflammatory state, line association, and surgery ≤ 7 days were identified risk factors

• All patients with active infection or with excessive protein loss (chest tube output > 200 ml/day) developed VTE

• Only 2 patients were found to have a genetic prothrombotic predisposition
Manlhiot C et al. Table 2: Factors Associated With Increased Odds of Thrombosis in Multivariable Logistic Regression Model Adjusted for Repeated Measures (n=1542)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Reliability, %</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger age at surgery</td>
<td>78</td>
<td>2.0 (1.3–3.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>0–31 d</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>&gt;31 d–&lt;1 y</td>
<td></td>
<td>0.4 (0.2–0.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>1–9 y</td>
<td></td>
<td>0.5 (0.2–1.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>≥10 y</td>
<td></td>
<td>2.0 (1.3–3.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Oxygen saturation &lt;85%</td>
<td>53</td>
<td>2.6 (1.6–4.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous thrombosis</td>
<td>89</td>
<td>4.1 (2.1–7.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart transplantation</td>
<td>67</td>
<td>1.9 (1.2–3.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Use of deep hypothermic circulatory arrest</td>
<td>50</td>
<td>1.2 (1.1–1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Longer cumulative time with central lines (⁄5 d)</td>
<td>87</td>
<td>5.2 (2.8–9.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

• Distilled down from Supplemental Table 2 (RFs prior to multivariate analysis)
• NOT associated: previous cardiac surgery, preop hemostasis (?), cardiac diagnosis; increased surgical complexity & periop pRBCs associated with increased thrombosis but highly correlated with age at surgery
Goal

• Identify patients at risk and strategies for preventing or minimizing thrombus formation
Hypothesis

- Pediatric patients with heart disease have identifiable risk factors for thrombus formation, many of which may be mitigated by standardized evaluation and therapy to prevent thrombotic and bleeding complications
Proposed Methods

• Retrospective review
• Survey of practice patterns
Proposed Methods

- Prospective data collection with standardized evaluation
- All patients <=18 yrs old with a primary diagnosis of cardiac disease in the admission being evaluated
  - Surgical-CPB vs non-CPB
  - Procedural-cardiac cath
  - Medical-heart failure, myocarditis, CM, post-surgical pt admitted for medical reason (after initial admission)
Surgical

- **CPB**
  - CPB, XC, DHCA times (cannulation sites)
  - MUF
  - Perfusion strategy
  - Type of repair (RACHS/STAT score)
  - Post-op TEE/TTE-documentation of function, intracardiac, SVC/IVC thrombus
  - Chest open v not
  - Reoperation
  - Central venous and arterial line size and location
  - Steroid use
  - Thyroid hormone use
  - Antifibrinolytic use
  - Antithrombin use
  - Factor VII use

- **Non-CPB**
  - Type of repair
  - Post-op TEE/TTE-documentation of function, thrombus
  - Central venous and arterial line size and location
Procedural

- Cardiac cath
- Diagnostic
- Therapeutic - procedure completed
- Cannulation sites
- Central venous and arterial line size and location
Medical

• Cardiac diagnosis
• ECHO-function, intracardiac thrombus, SVC/IVC views?
• Central venous and arterial line size and location
Patient Demographics

- Date of admit to PICU
- Age, sex
- BMI
- Primary and secondary diagnoses
- Prior cardiac surgeries, prior cath procedures
- Previous thrombus-location, treatment, outcome
- Prior hypercoagulability work-up
  - Family hx
- Pre-op use of anticoagulant
- Pre-op use of PGE
- Pre-op use of steroids
- ICU LOS
- Hospital LOS
Unit Demographics

- Separate cardiac ICU
- Policies in place-CVL, anticoagulation
Data Collection

- CVL and art line specifics:
- Location of line and tip location
- Line attempts
- Line size-Fr, lumens
- Vessel size (by ultrasound)
- Heparin concentration/rate
- Antibiotic impregnated
- Heparin coated
- Days of use
- Use of central line evaluation policy- Y or N
Data Collection

- Imaging
- ECHO
- Ultrasound of line tip
Data Collection

- Blood product administration
  - Intra-op
  - 1st 24 hrs of ICU stay

- Type
- Volume
- Date
Data Collection-Laboratory

- Inflammatory
- CBC with diff
- CRP
- Fibrinogen
Data Collection-Laboratory

- Cardiac output
- BNP
- Lactate
- MV sats
Data Collection-Laboratory

- End organ
- BUN/Cr
- AST/ALT/TB
Data Collection-Laboratory

- Coagulation
- Hgb/Hct
- Plt
- PT/INR
- PTT
- D dimer
- Fibrinogen
- Antithrombin
- TEG R, angle, MA
- Thrombin generation/potential
Data Collection-Monitoring

- Arterial oxygen saturations
- MV sats
- NIRS-somatic/cerebral
- Vasoactive infusion score
- UOP/Fluid balance/weight
  - Diuretic use
- Chest tube output
- Temperature-core v extremity (including extremity where CVL or arterial line is located)
  - Fever or hypothermia
- Infection-use of antibiotics?
Anticoagulation

- **Indication**
  - Systemic
  - Line patency
- **Planned vs unplanned**
  - If delayed, reason
- **Type**
  - UFH, LMWH, DTI, warfarin
- **AT replacement**
- **Concentration/rate**
- **Labs:** anti-Xa, PTT, AT, TEG, thrombin generation, INR
Timing of Collection

- Pre-op visit or at induction of anesthesia
- Admit to ICU
- 6 hrs
- 12 hrs
- 24 hrs
- 48 hrs
- 5-7 days
Symptomatic v Non-symptomatic Thrombi-Standardized Evaluation

• Imaging at ICU admit to document line tip, presence/absence of thrombus and at line day 5-7
• Symptomatic
  – Complete lab evaluation at time of suspicion and chart review 24-48 hrs prior
  – May include additional imaging locations and modalities
• Non-symptomatic
  – Complete lab evaluation at time of documentation and chart review 24-48 hrs prior
• Both-hypercoag work-up
• Repeat imaging if thrombus found-2-3 days if no treatment; 5-7 days if treatment
Symptomatic Definition

- tPA use for line
- Swelling, edema
- Erythema
- Abdominal distention
- Cool extremity
- Hemodynamic parameters-hypotension, low UOP
Thromboembolic Events

- Cerebral stroke-ischemic v embolic
- Renal
- Hepatic
- Splanchnic
- Coronary
- SVC
- Pulmonary
- Cardiac shunt
Bleeding Events

- Hemothorax
- Intracerebral bleed
- Subgroup eval: vWF def, platelet antibodies (post-CPB to protamine)
Imaging Documentation

• Thrombi
• Location
  – Line presence? (tip location)
• Mobility
• Occlusive, partially occlusive, non-occlusive
Intervention: Treatment if Asymptomatic Thrombi Discovered

- Discretion of ICU and surgeon
- Disclosure to family—potential risks vs benefits of therapy
Co-morbidities

- CPR-reason (rhythm), duration, outcome
- Renal failure-use of RRT
- Hepatic insufficiency
- Chylothorax
- CLABSI
- ECMO
- VAD
Outcomes

• Treatment
  – Therapy, duration
    • Heparin, DTI, warfarin
    • tPA
  – Mechanical or surgical removal

• Morbidity
  – End organ dysfunction, Collaterals
  – Need for re-operation, re-intervention

• Mortality
Cost Analysis

- Screening (asymptomatic)
- Symptomatic
- Comparison to previously reported incidence
- Cost of treating vs not treating with possible extension
Proposed Patients

• Single institution first?
• Multi-center
  – 30-50 consecutive patients per institution?
• 4-6 months
• Provide preliminary data to apply for AHA or other grants
Study Cost

- Ultrasounds
- ECHOs
- Labs
- Data collection

- What JHU provides:
  - All checklists (to identify symptomatic patients and standardized evaluation)
  - Survey to identify institutional practice