Antithrombosis Management for Pediatric VAD and Beyond

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Disclosures

I have no financial disclosure.

I do need to disclose the source of information:

- 0% Randomized trials specifically addressing anticoagulation in pediatric MCS population
- 1% basic pharmacology and hematology
- 2% Pediatric VAD trials and registry data
- 97% trial and error, clinical experience and tears
Tale of Sisyphus:
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Sophia’s Story

- 18 month old with dilated cardiomyopathy with 25 cc Berlin Heart EXCOR as bridge to transplant
- Started heparin at 12 hrs, bled, stopped it at 18 hrs, and restarted at 21 hrs
- Finally achieved consistent therapeutic heparin levels (anti-Xa) after 5 days, due to interruption of heparin for minor bleeding, chest tube removal and error
  - Error related to stopping heparin for falsely elevated heparin level from sampling off a contaminated line
Sophia’s Story Continued

• On day 6 routine echo demonstrated mobile thrombus (size of a pea) at LV apical inflow cannula
• UFH level was 0.72, and was on ASA

What do you do?

1. Do nothing, continue to maintain therapeutic heparin with daily echos? *(Wait and watch)*

2. Systemic TPA? *(Do something medically)*

3. Go to OR and try to remove clot? *(Do something surgically)*
Sophia’s Story Continued

• After 16 hours of deliberation, decision to go back to OR, but on repeat echo, clot was gone
• She was sedated but with “wake up test” noted right hemiplegia
• CT head demonstrated left MCA territory infarct
“Nothing ever goes away until it teaches us what we need to know.”

– Pema Chodron
Objectives

• Understand the unique challenges of hemostasis and thrombosis in pediatric VAD support

• Review antithrombosis agents and regimes applicable to different types of VAD support
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Goals of Hemostasis and Antithrombosis

Hemostasis with controlled antithrombosis

Stop all post operative bleeding, and at exactly the right moment start anticoagulation to prevent the body's natural response of developing fibrin and clot to artificial material and endothelial disruption.

WE WANT IT ALL.
The Delicate Balance of Bleeding and Clotting
Reality of Anticoagulation

Platelets
Fibrinogen
Factors
Fibrin
Thrombin
AT III

WBC
CRP
ESR
Plastic

US

Bleeding
Clotting
VAD
Why can’t we successfully accomplish our goal: *Hemostasis and Antithrombosis*?

1. We don’t completely understand hemostasis—especially in children (developmental hemostasis)
2. We can’t predict who will bleed or clot with accuracy
3. We don’t know how **best** to monitor antithrombosis (aPTT?, anti-Xa level?, INR?, fibrinogen?)
4. We don’t know what should be our **ideal** target range of antithrombosis treatment: same for all ages? Same for all devices?
## Developmental Hemostasis

- Age-related physiological changes in coagulation system as it develops over time from fetal life to adulthood
- Both quantitative and qualitative changes in plasma proteins impacting both coagulation and fibrinolysis

<table>
<thead>
<tr>
<th>Coagulation</th>
<th>Fibrinolysis</th>
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<tbody>
<tr>
<td>↓ FII, FVII, FIX, FX&lt; FXI, FXII, protein C, protein S, antithrombin</td>
<td>↓ tPA, plasminogen</td>
</tr>
<tr>
<td>↑ α^2^ macroglobulin</td>
<td>↑ plasminogen activator inhibitor type 1</td>
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Why does developmental hemostasis exist?

• Changes in coagulation plasma proteins may be a by-product of widespread changes in broad-acting proteins “serpin”, that have multiple actions in inflammation, wound repair and angiogenesis

• For example: **antithrombin (AT)**
  • AT reduced <50% of levels observed in adulthood
  • AT in addition to anticoagulant effect, has potent anti-angiogenic properties
  • Early life is time of prolific angiogenesis, therefore lower levels of AT may be beneficial for healthy development
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3 stages of antithrombosis therapy

1. Immediate post-op (24-72 hours)
2. Early post-op (3-10 days)
3. Maintenance (weeks-months)
Stages of Antithrombosis Management

1. **Immediate post op**: Induce Coagulation
   - Stop surgical and coagulopathic bleeding
   - *Surgical bleeding*: good CV surgeon
   - *Coagulopathic bleeding*: normalize coags
     - INR/PT aim for <1.3 (or similar to pre-op)
     - aPTT aim for 30 (or similar to pre-op)
     - Platelet aim for >100,000
     - Fibrinogen >200 and <450

**Factors**
- **FFP**
- **PLT**
- **Cryo**
2. **Early post-op: Induce Anticoagulation**

   – Goal is *prudent* but *effective* anticoagulation

   – What defines “effective”?
     - Based on lab values (aPTT, ACT, antiXa level/heparin activity level)
     - Based on clinical effect: no clot formation, no excessive bleeding
     - First line agents: unfractionated heparin, direct thrombin inhibitors (bivalirudin, argatroban)
Stages of Antithrombosis Management

3. Maintenance Antithrombosis

- Goal is stable anticoagulation
- Common agents: low molecular weight heparin (LMWH), Vitamin K antagonists (Warfarin), direct thrombin inhibitors (bivalirudin, argatroban)
- Addition of antiplatelet agent (aspirin ± clopidogrel ± dipyridamole)
- Weight based dosing or titration based on platelet responsiveness tests (TEG with platelet mapping, VerifyNow®)
Anticoagulation Options for Children

1. Unfractionated Heparin (UFH)
2. Low molecular weight heparin (LMWH)
   • Lovonox® (enoxaparin), fondaparinux
3. Vitamin K antagonists (VKA): Warfarin (Coumadin®)

What else?

• Direct thrombin inhibitors (intravenous medication)
  • Bivalirudin, argatroban
• Novel oral anticoagulant medications (apixaban, rivaroxaban, etc.)
Challenges with Heparin

- Every vial of UFH ~1/3 of 18 saccharide unit required to bind AT for thrombin inhibition
  - Variable size= variable activity against AT and aFXa
- Dependent on AT to potentiate its activity 100x fold-which is physiologically low in infants
- Non-linear dose response curve
- Sticks to anything positively charged (proteins and plastic
- Causes HIT and osteopenia
Looking to alternative agents

Direct Thrombin inhibitors: Bivalirudin, argatroban

- Proteolytic degradation with renal excretion
- Fast onset (2 min) short half life (19 min with normal renal function)
- Half life up to 4 hrs if severe renal failure
- Linear dose response curve
- No dependence on AT III
- *No commercially available reversal agent (plasma, blood products at this time)
- COST ~ $ 800USD per day, but cost may be offset in no need to AT, and decrease in pump exchanges
Device Specific Antithrombosis Strategies

Paracorporeal devices (Berlin Heart/Rotaflow)
Intracorporeal devices (HeartWare/HM II/III)
Paracorporeal Devices: EXCOR and CF pumps

- Generally start anticoagulation 12-24 hours
- Start UFH or DTI as primary anticoagulant agent
  - For UFH: use anti-Xa level (0.35-0.7 target range)
  - For DTI: use 1.5-3 x baseline aPTT as target range
- Start antiplatelet regime day 2-4
Intracorporeal Devices: HeartWare and HMII

- Start heparin once all bleeding stops and coags normalized – can delay ~ 1-4 days
- Target anti-Xa 0.35-0.7 (~aPTT 70-90)
- Transition to warfarin once enteral feeding
- Target INR 2-3
- Start antiplatelet (ASA) once therapeutic on warfarin
  - Can use TEG with platelet mapping AA inhibition <70%
Take Home Message:

• No one size fits all anticoagulation algorithm for all patients and all device

• Avoid common anticoagulation mistakes:
  – Too many cooks in the kitchen
    • Limit anticoagulation management to a individual or singular team
    • Protocolization is not enough- need continuity
  – Line contamination- making decisions on bad data
Dedicated to all those who trust us with their lives and loved ones while we continue to learn.
Thank you