Direct Thrombin Inhibitors and ECMO: What Do We Do With Our Little Ones?

Tyler Bosley, PharmD
Anasemon Aioub, PharmD
April 14, 2019

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Disclosure

- No conflicts of interest to report
- Disclosures
  - Off-label uses of direct thrombin inhibitors will be discussed during this presentation

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Objectives

- Review unique aspects of anticoagulation considerations in patients receiving extracorporeal membrane oxygenation (ECMO) support
- Examine the evidence regarding utilization of direct thrombin inhibitors (DTIs) and ECMO
- Construct an anticoagulation plan for a complex pediatric patient

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ECMO & ANTICOAGULATION

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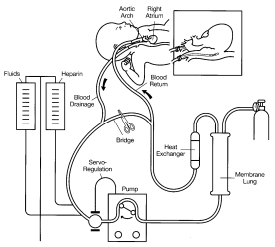
ECMO



- Temporary support for severe cardiac and/or respiratory failure
  - Venoarterial (VA) vs. venovenous (VV)
- Continuous activation of coagulation cascade
  - Hemorrhage vs. thrombosis
- 68% of patients requiring ECMO are neonates and children

Bain JC, et al. *Respir Care*. 2016;61(1):1-7.
Cho NJ, et al. *Chonnam Med J*. 2017;53(2):110-117.

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ECMO and Coagulation

Hemorrhage

- Excessive heparin
- Coagulation factor consumption
- Thrombocytopenia or platelet dysfunction
- Hyperfibrinolysis

Thrombosis

- Inadequate heparin
- Acquired antithrombin deficiency
- Heparin-induced thrombocytopenia (HIT)
- Blood stasis in cardiac chambers

Cho NJ, et al. *Chonnam Med J*. 2017;53(2):110-117.

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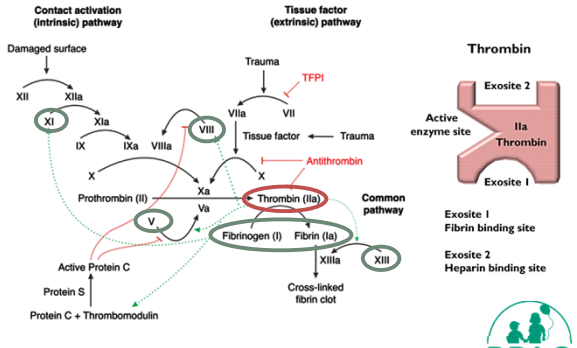
Thrombin (FIIa)



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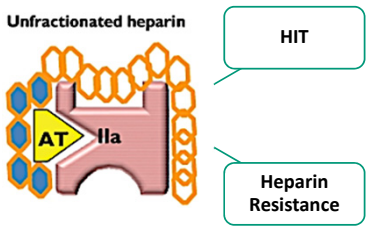
Heparin

- Historical anticoagulant of choice in ECMO
- Potentiates the inhibitory effects of antithrombin on thrombin and factor Xa



HIT

Heparin Resistance

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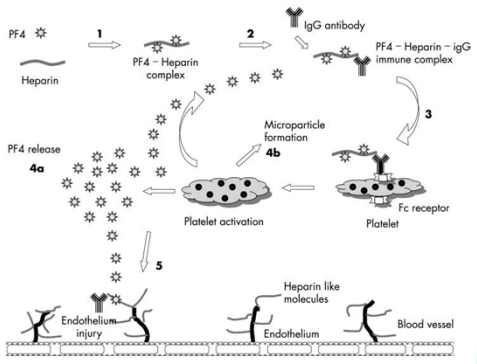
Heparin Induced Thrombocytopenia



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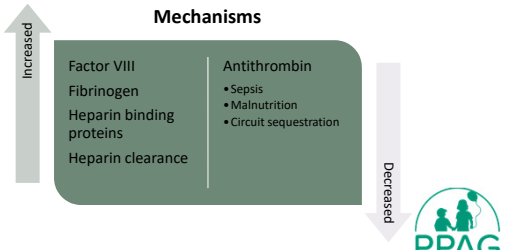
Heparin Resistance

- Unusually high doses of heparin required to achieve therapeutic levels
- Clotting persistence despite therapeutic levels



King AB, et al. *Neurohospitalist* 2016;6(3):118–121.

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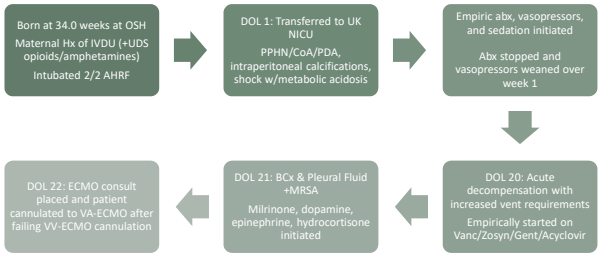
Patient Case: SH



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UK Heparin Protocol

Heparin 30 units/kg/hr initiated at 2 hours

Heparin gtt titrated to 90 units/kg/hr over 48 hours

CVVHDF Initiated

Anti-Xa (units/mL)	Dosage Adjustment	Repeat Anti-Xa
< 0.20	Give 50 units/kg bolus and increase rate by 10%	4 hours after rate change
0.20-0.29	Increase infusion rate by 10%	4 hours after rate change
0.30-0.70	**Maintain infusion rate**	**4 hours then AM labs**
0.71-0.80	Decrease infusion rate by 10%	4 hours after rate change
0.81-0.99	Hold for 30 minutes and decrease rate by 10%	4 hours after rate change
≥ 1.0	Hold for 60 minutes and decrease rate by 15%	4 hours after rate change

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ECMO and SH

- Developed right femoral DVT on DOL 24
- ECMO circuit changed on DOL 31 secondary to clotting and increased blood product administration
  - Heparin 95 units/kg/hr
- Significant bleeding noted via chest tube
- AT3 levels low throughout course despite replenishment
  - 29-76%
- Eventual discussion of transitioning to bivalirudin on DOL 36

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DIRECT THROMBIN INHIBITORS

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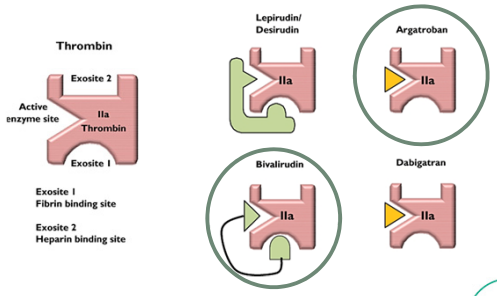
Direct Thrombin Inhibitors



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Lee CJ, Ansell JE. *Br J of Clin Pharmacol.* 2011;72(4):581–592.
Ruck ML. *J Pediatr Pharmacol Ther.* 2015;20(6):408-417.

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DTI Pros and Cons

Activity independent of antithrombin	No reversal agent
Inhibit circulating and bound thrombin	No FDA approval for use in pediatrics
No immune-mediated reactions	

Lee CJ, Ansell JE. *Br J of Clin Pharmacol.* 2011;72(4):581–592.
Buck ML. *J Pediatr Pharmacol Ther.* 2015;20(6):408-417.
Moffett BS, Teruya J. *Arch Pathol Lab Med.* 2014;138(9):1229-1232.

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Argatroban vs. Bivalirudin

	Argatroban	Bivalirudin
Structure	Univalent	Bivalent
Distribution	Extracellular fluid, ~50% protein bound	No protein binding
Metabolism	Hepatic	Renal and plasma proteolytic
$t_{1/2}$	30-45 min	25 min
Dosage Adjustment	Hepatic	Renal
Onset	Immediate	Immediate
Duration	1-2 hours	1-8 hours (dependent on duration of infusion)
Dosing	0.5-24 mcg/kg/min	0.03-1.6 mg/kg/hr
Concentration	1 mg/mL in NS, D5W, LR	0.5-5 mg/mL in D5W or NS

Lee CJ, Ansell JE. *Br J of Clin Pharmacol.* 2011;72(4):581–592.
Buck ML. *J Pediatr Pharmacol Ther.* 2015;20(6):408-417.
Hursting MJ, et al. *J Pediatr Hematol Oncol.* 2006;28(1):4–10.

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Argatroban Literature

	Hursting et al, 2006	Scott et al, 2006	Potter et al, 2007
Population	8 articles (N = 12) • Age: 1 week-6 years ECMO/VAD	17-month old boy with HIT on ECMO • Renal failure	Case series (N = 3) • Age: 3 days-1 year ECMO
Argatroban Dosing	Bolus: 0.45 mcg/kg in 1 patient, 50 mcg circuit load in 1 patient Initial: 0.1-2 mcg/kg/min Range: 1.4-24 mcg/kg/min	Bolus: none Initial: 2 mcg/kg/min Range: 1-2 mcg/kg/min	1: 50 mcg prime, 1 mcg/kg/min initial 2: 0.1 mcg/kg/min initial 3: 0.5 mcg/kg/min initial All titrated to target
Therapeutic Target Levels	ACT 160-250 (N = 8) aPTT 2x baseline (N = 4)	ACT 180-200	1: ACT 250-300 2: ACT >220 3: ACT 200-220
Results	• 5 of 12 patients died (3 due to multiorgan system failure) • 1-78 day duration range (median = 6) • No complications x 8	Transition to traditional vent and resolution of ischemia and thrombocytopenia	1: Improvement, decannulation, post-transplant 2 & 3: Deceased
Complications	• Clotting x 1 • Circuit change x 2 in one patient • DIC x 1	• None	• Clotting x 2

Abbreviations: ACT = activated clotting time; aPTT = activated partial thromboplastin time ; AT = antithrombin; BIV = Bivalirudin; CDH = congenital diaphragmatic hernia; DIC = disseminated intravascular coagulopathy; HITT = heparin-induced thrombocytopenia and thrombosis; TEG = thromboelastography; VAD = ventricular assist device

Hursting MJ, et al. *J Pediatr Hematol Oncol.* 2006;28(1):4-10.
Scott KL, et al. *Pediatr Crit Care Med.* 2006;7(5):473-475.
Potter KE, et al. *J Pediatr Hematol Oncol.* 2007;29:265-268.

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Bivalirudin Literature

	Ranucci et al, 2011	Pollak et al, 2011	Nagle et al, 2013
Population	N = 21 (10 pediatrics) Post-cardiotomy VA-ECMO	5-day old with CDH HITT while on VA-ECMO	N = 12 pediatric patients VA- or VV-ECMO
Bivalirudin Dosing	n = 8 (5 pediatric); No bolus Initial: 0.03-0.05 mg/kg/hr Range: 0.05-0.1 mg/kg/hr	Bolus: 0.4 mg/kg Initial: 0.15 mg/kg/hr Range: 0.06-1.6 mg/kg/hr	Bolus: 0.04-0.14 mg/kg Initial: 0.05-0.3 mg/kg/hr Range: 0.045-0.48 mg/kg/hr
Therapeutic Target Levels	ACT: 160-180 sec *r* time: 12-30 min aPTT: 50-80 sec AT: > 60%	ACT: 180-200 sec	ACT: 200-220 sec
Results	BIV compared to heparin • Longer ACT, aPTT, and TEG reaction times • 1 of 5 pediatric patients survived to discharge in each group	• Improvement in HITT cutaneous manifestations • ↓ need for platelet transfusion following initiation of BIV • Patient death thought to be secondary to DIC	• Median time to goal aPTT was 4 hours • Average percentage of time spent within 90-110% of goal aPTT was 70.3% • 5 patients survived to discharge
Complications	• ↓ blood loss (p = 0.015) and ↓ blood product and AT administration required with bivalirudin	• DIC	• Hemorrhage x2 • Circuit change x8

Abbreviations: ACT = activated clotting time; aPTT = activated partial thromboplastin time ; AT = antithrombin; BIV = Bivalirudin; CDH = congenital diaphragmatic hernia; DIC = disseminated intravascular coagulopathy; HITT = heparin-induced thrombocytopenia and thrombosis; TEG = thromboelastography; VAD = ventricular assist device

Ranucci M, et al. *Crit Care*. 2011;15(6):R275.
Pollak U, et al. *J Extra Corpor Technol*. 2011;43(1):5-12.
Nagle EL, et al. *Pediatr Crit Care Med*. 2013;14(4):e182-e188.

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DTI MANAGEMENT PROPOSAL

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DTI Proposal

Pediatric Literature + Adult Guidelines = Pediatric Guideline Proposal

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DTI Indications in Pediatric ECMO

- Suspected or confirmed HIT
- Previous HIT
- Heparin resistance/clot recurrence on therapeutic heparin

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DTI Initial Dosing in Pediatric ECMO

	Argatroban	Bivalirudin
Loading dose	50 mcg per 750 mL of circuit primer	0.15 mg/kg bolus
Initial	1 mcg/kg/min	0.15 mg/kg/hr
GFR 30-60 mL/min	No adjustment	0.1 mg/kg/hr
GFR <30 mL/min	No adjustment	0.08 mg/kg/hr
Child-Pugh >6	0.5 mcg/kg/min	No adjustment
Continuous renal replacement therapy	No adjustment	0.1 mg/kg/hr through CRRT circuit in addition to regular rate

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DTI Monitoring in Pediatric ECMO

- Stop heparin drip immediately after starting DTI
- Collect aPTT 2h after DTI initiation
- Obtain aPTT q2h until within goal range x2
- Space aPTT to q4h while within goal range

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DTI Dosage Adjustment in Pediatric ECMO

aPTT	Adjustment*
<1.2x control	Increase rate by 40%
1.2-1.5x control	Increase rate by 20%
1.5-2.5x control (max 80)	No change
2.5-4x control (less than 100)	Decrease rate by 20%
>4x control or aPTT >100	HOLD for 1 hour, reassess aPTT, decrease rate by 50% once aPTT <100

*Adapted from adult protocol

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PATIENT CASE

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SH and ECMO

Anticoagulation

- Heparin → Bivalirudin

Renal Function

- UOP = 0.17 mL/kg/hr
- CrCl < 30 mL/min

Dosing

- Bivalirudin Initial Dose: 0.08 mg/kg/hr
- 2.8 kg

Monitoring

- Baseline aPTT: 26 sec
- **Goal aPTT: 40-65 sec**

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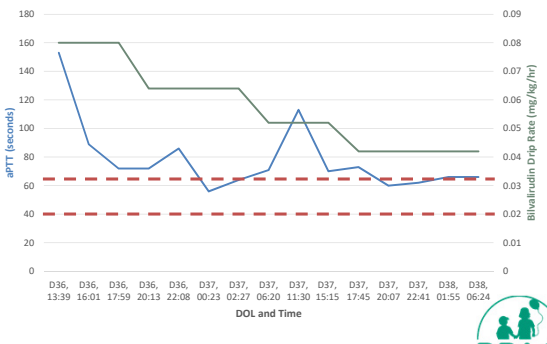
SH's Bivalirudin Adjustments



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Case: SH

Thrombosis of bilateral upper extremities with subsequent necrosis

Primary team discussed goals of care with family

Patient expired on DOL 38 at 1240

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Summary

- HIT and heparin resistance pose significant problems for anticoagulation in ECMO
- DTIs remain the primary alternative to heparin for anticoagulation in ECMO despite sparse pediatric literature
- Optimal dosing and appropriate targets remain unclear but previous patient-care experiences can help drive management
- Standardization via protocol development may be beneficial to direct care for patients

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Questions?

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