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# Pharmacotherapy Management in Patients with Extracorporeal Membrane Oxygenation

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# Faculty Disclosure

- I have no conflicts of interest to disclose.

# Educational Need/Practice Gap

- Gap =  Lack of treatment guidelines and published research often leave providers with no clear way to optimally treat patients
- Need = Our learners need strategies to manage patients on extracorporeal membrane oxygenation (ECMO)

# Objectives

Upon completion of this educational activity, you will be able to:

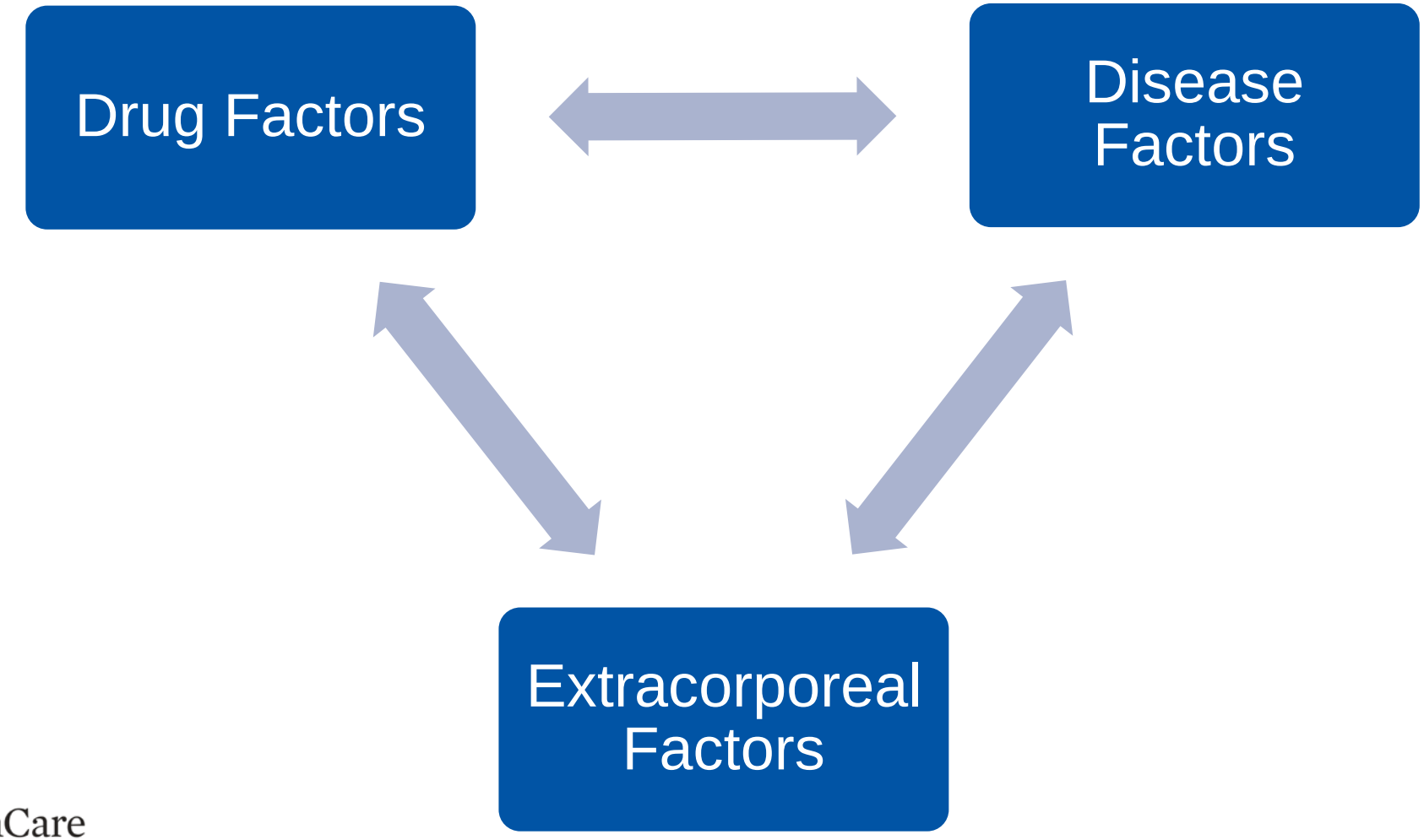
1. Identify alterations in pharmacokinetics (PK) associated with ECMO

2. Review dose adjustments and monitoring for common medications in critically ill patients on ECMO, including antimicrobials, sedatives, analgesics, and anticoagulation

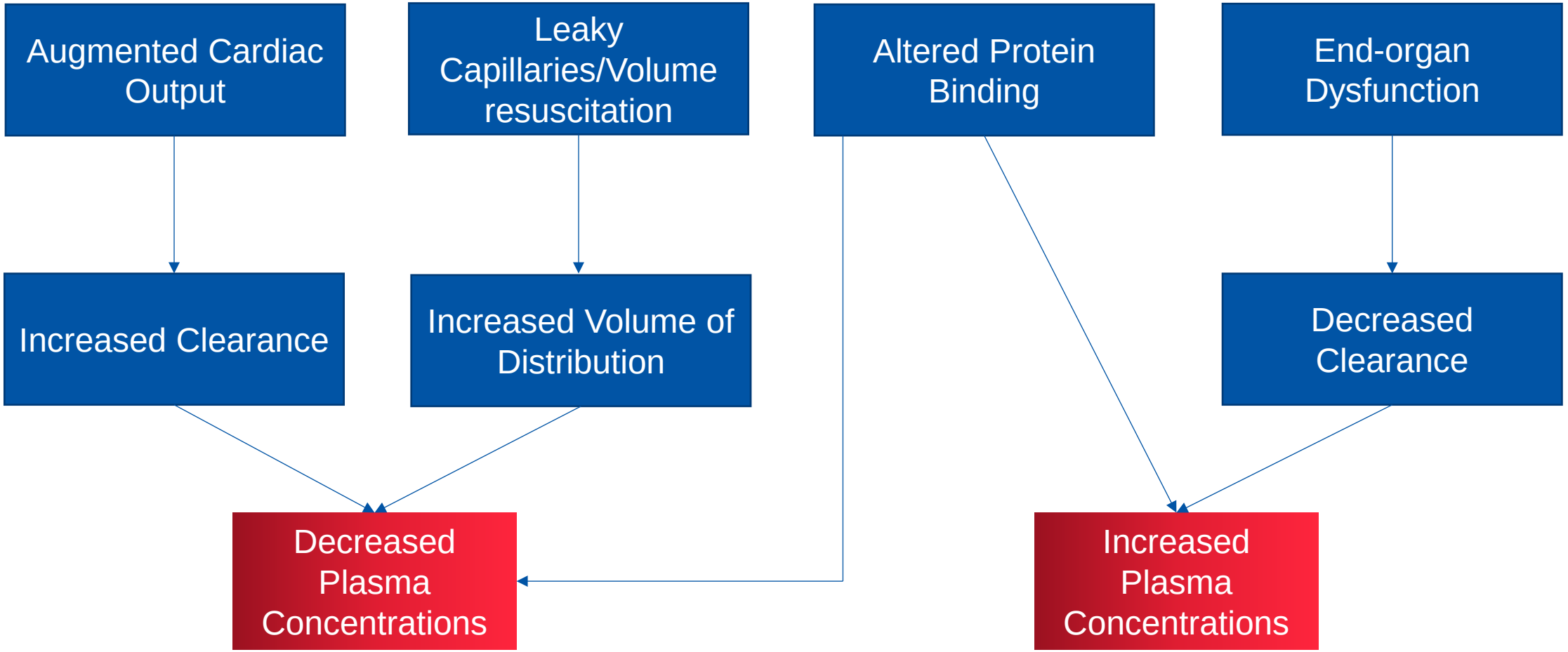
# Expected Outcome

- What is the desired change/result in practice resulting from this educational intervention?
  - As a result of the information/tools provided in this activity, learners should be better able to utilize appropriate pharmacologic therapies to manage patients on ECMO

# Pharmacokinetic Alterations



# Critical Illness

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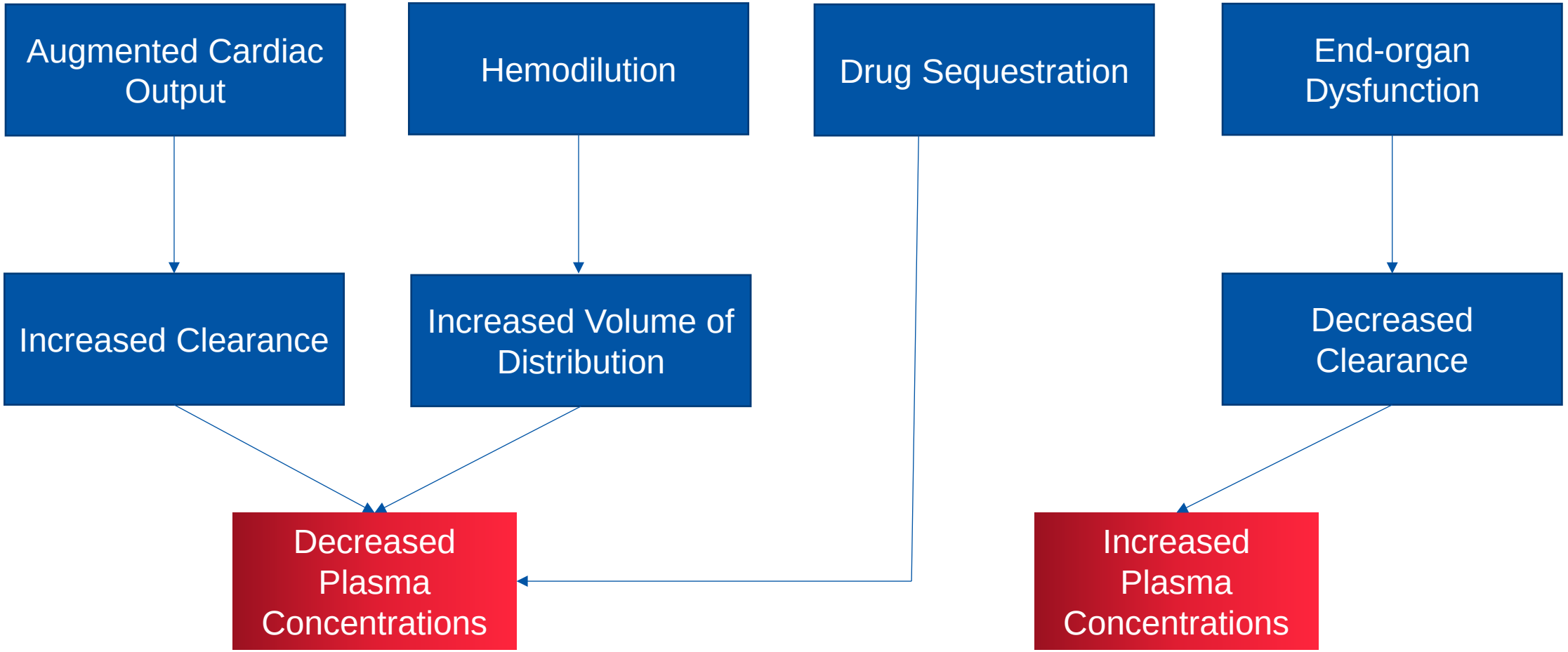
Dzierba et al. Crit Care. 2017:21;21(1):66

# Extracorporeal Membrane Oxygenation

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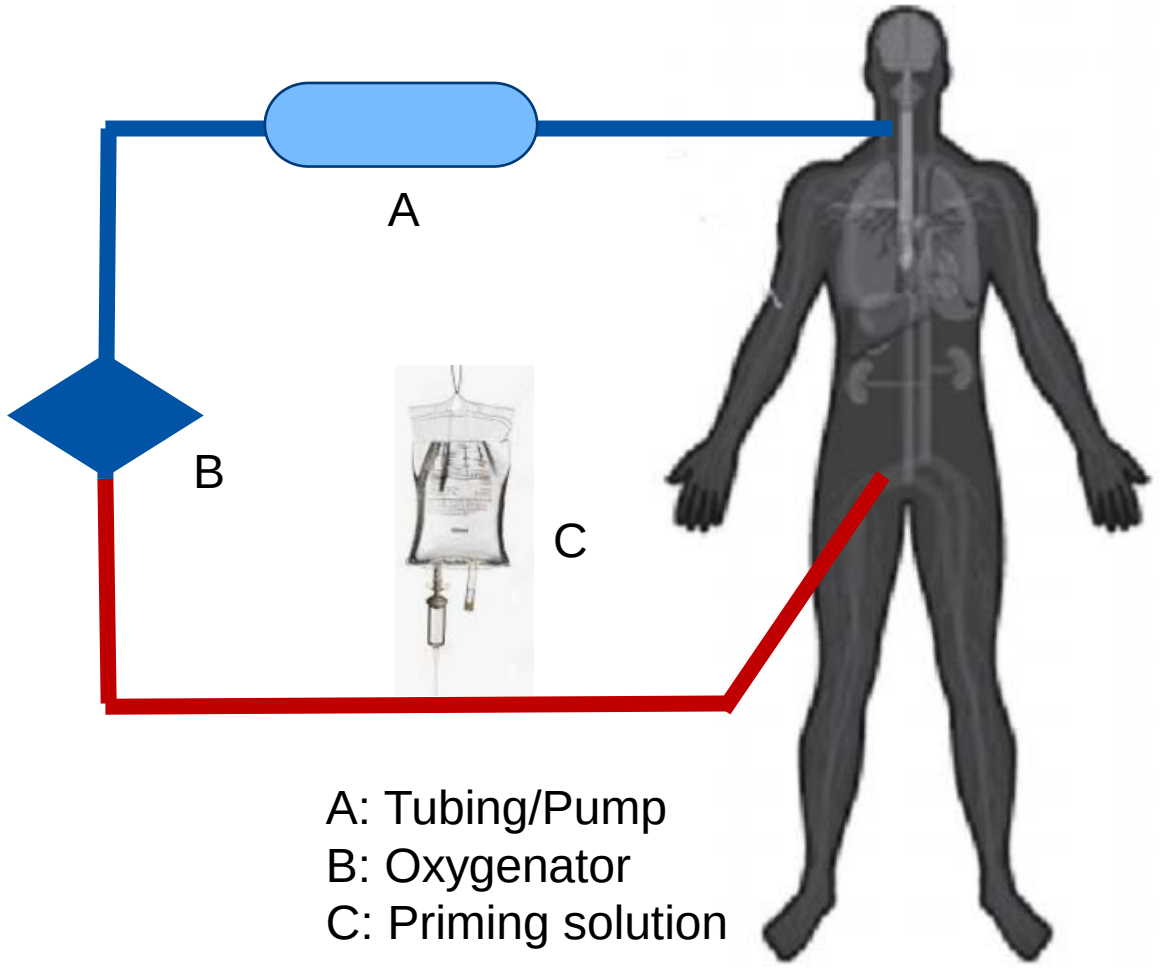
# Extracorporeal membrane oxygenation

- **ECMO Circuit**
  - Tubing type
  - Oxygenator membrane
  - Priming solution
  - Age of the circuit

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Preston et al. J Extra Corpor Technol 2010 S;42(3):199-202
Shekar et al. J Crit Care 2012; 27(6): 741.e9-18
Wildschut et al. Intensive Care Med 2010; 36(12): 2109-2116

# Drug Factors

**Protein Binding**

**Lipophilicity**

| Drug | Protein Binding | Octanol/Water Partition (log p) |
|---|---|---|
| Propofol | 95-99% | 4.0 |
| Fentanyl | 79-87% | 3.9 |
| Lorazepam | 85-91% | 3.5 |
| Midazolam | 97% | 3.3 |
| Dexmedetomidine | 94% | 3.3 |
| Hydromorphone | 8-19% | 0.9 |
| Morphine | 20-35% | 0.8 |


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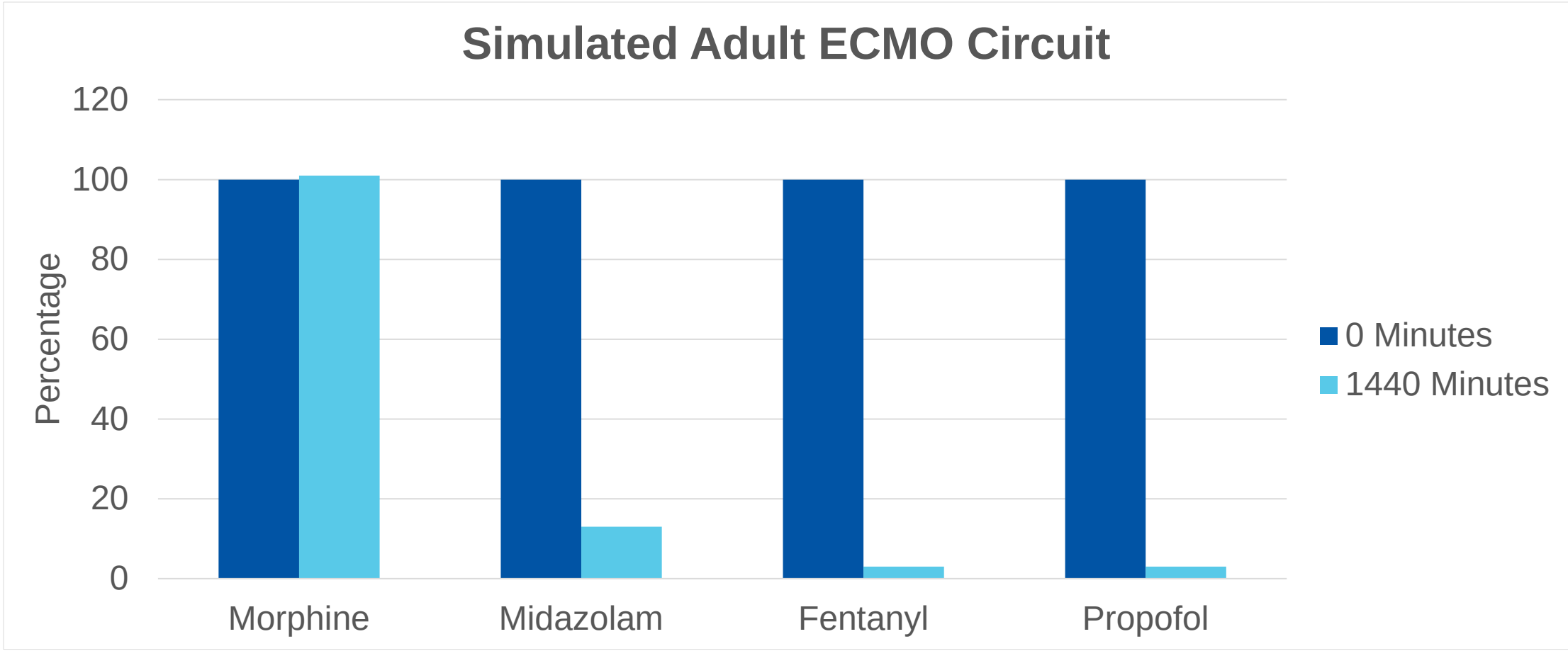
HA et al. Pharmacotherapy. 2017;37(2):221-235
Nucleic Acids Res. 2008 Jan;36(Database issue):D901-906

# Analgesics and Sedatives

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Shekar et al. Crit Care. 2012;16(5):R194
Lemaitre et al. Critical Care. 2015;19:40

# Analgesics and Sedatives

- Retrospective study of 29 patients on VA or VV ECMO

| Drug | Average Daily Dose | Population Consideration |
|---|---|---|
| Midazolam | Increased by 18 mg (95% CI 8-29; p=0.001) | All |
| Morphine | Increased by 29 mg (95% CI 4-53; p=0.021) | Conserved renal function |
| Fentanyl | No difference (p= 0.94) | Renal dysfunction or renal replacement therapy |

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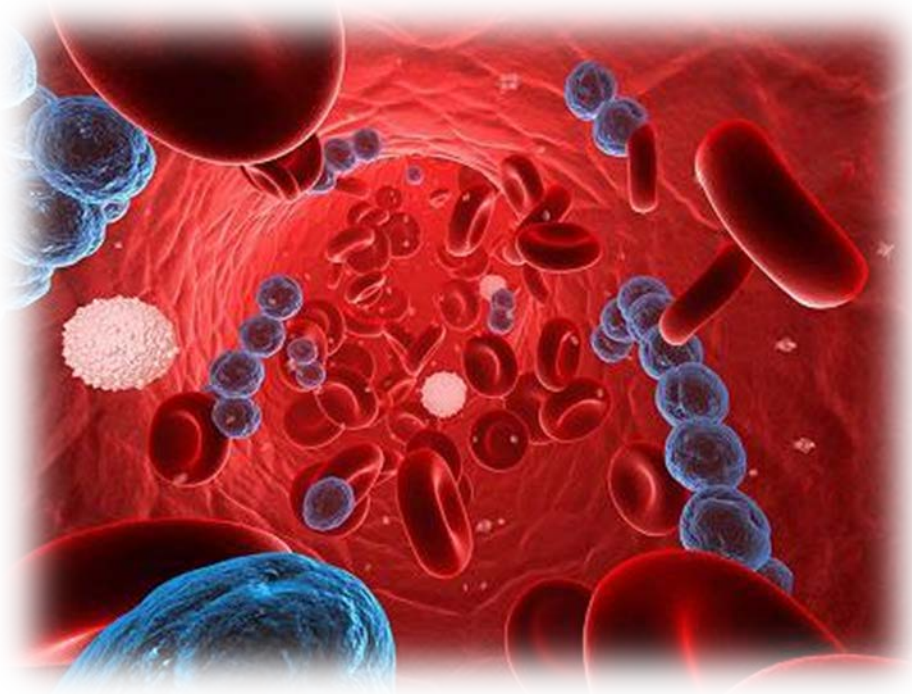
Shekar et al. Anaesth Intensive Care. 2012;40(4):648-55

# Analgesics and Sedation Considerations

- At ECMO initiation, use continuous infusions
- Set daily sedation goals and consider daily interruption of sedative
- After ECMO decannulation, re-evaluate doses of analgesics and sedatives
- Monitor for delirium or signs of withdrawal

# Antimicrobial Dosing Considerations

- Therapeutic failure
- Potential emergence of resistant microorganisms
- Toxicity



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# β-Lactam Pharmacokinetics in ECMO

- Case control cohort: Total of 41 therapeutic drug monitoring (TDM) results

| | Meropenem (n=27) | | Piperacillin/tazobactam (n=14) | |
|---|---|---|---|---|
| | ECMO | Control | ECMO | Control |
| **Volume of Distribution *(L/kg)*** | 0.46 (0.26–0.92) | 0.60 (0.42–0.90) | 0.33 (0.26–0.46) | 0.31 (0.21–0.41) |
| **Elimination half life *(h)*** | 3.0 (2.1–4.8) | 2.9 (2.4–3.7) | 2.0 (1.1–4.2) | 1.6 (1.0–4.7) |
| **Total drug clearance (mL/min)** | 125 (63–198) | 144 (97–218) | 156 (91–213) | 134 (47–179) |

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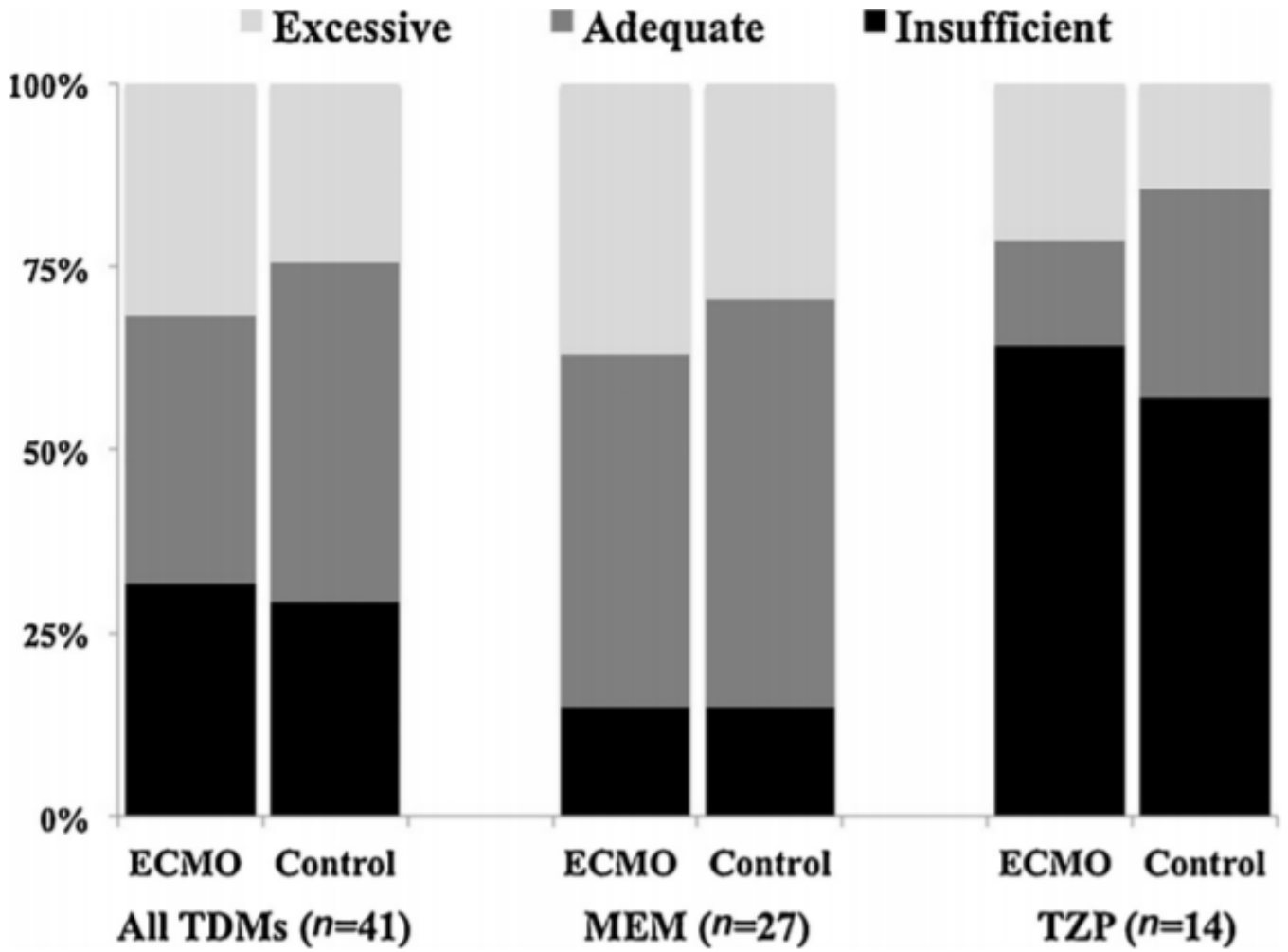
Donadello et al. Int J Antimicrob Agents. 2015;45(3):278-82

# β-Lactam Pharmacokinetics in ECMO

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# Dose Adjustments for Select Antibiotics

| Drug | Protein Binding | Log p | Volume of Distribution | Expected Effect | Dose Adjustment |
|---|---|---|---|---|---|
| **Ceftriaxone** | 85-90% | -0.01 | 5.78–13.5 L | Moderate sequestration | Not required |
| **Vancomycin** | 50% | -4.4 | 28–70 L | Minimal sequestration | Not required |
| **Levofloxacin** | 24–38% | 0.65 | 88.9 L | Minimal to moderate sequestration | Not required |
| **Gentamicin/ Tobramycin/ Amikacin** | < 30% | < 0.0 | 14–21 L | Minimal sequestration | Not required |
| **Voriconazole** | 58% | 2.56 | 322 L | Moderate to high sequestration | Yes |

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# Antimicrobial Dosing Considerations

- PK data in adult patients on ECMO are sparse
- Consider loading dose for drugs with moderate to high sequestration
- Dose guided by therapeutic drug monitoring when applicable
- Monitor for signs of infections

# Bleeding and Thrombosis Complication

- Meta-analysis: 12 studies (1763) patients
  - Any bleeding (33%)
  - Hemolysis (18%)
  - Venous thrombosis (10%)
  - Gastrointestinal bleeding (7%)
  - Disseminated intravascular coagulation (5%)

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Zangrillo et al. Crit Care Resusc. 2013;15(3):172-178

# Hemostasis Alterations During ECMO


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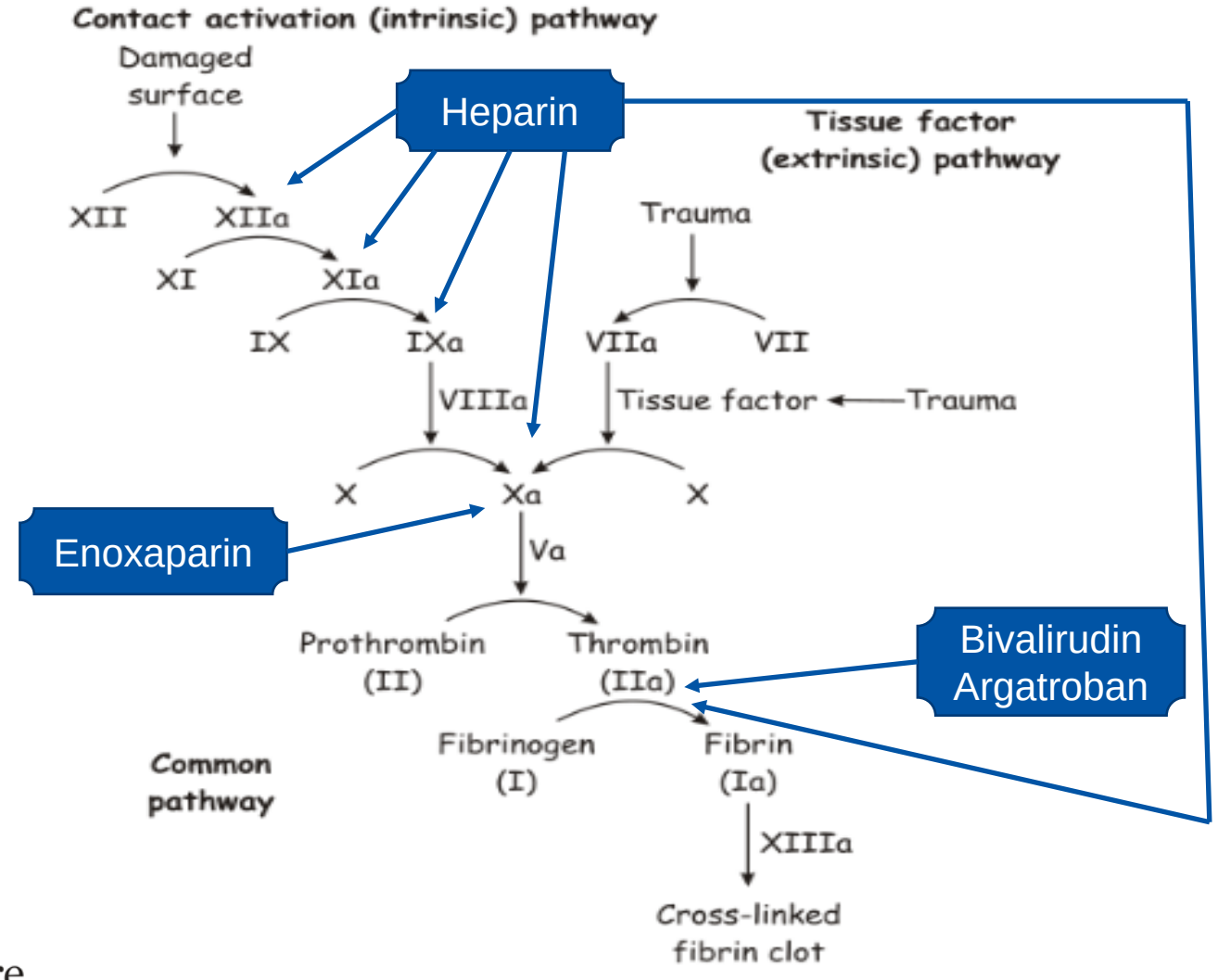
Kamdar et al. Semin Perinatol. 2018;42(2):122-128

# Coagulation Cascade




http://mrcpandme.blogspot.com/2010/09/mrcp-revision-battle-142-clotting.html

# Anticoagulation Management

| Drug | Advantages | Disadvantages |
|---|---|---|
| **Unfractionated heparin** | • Well known<br>• Easy to antagonize (protamine)<br>• Easy to monitor (aPTT/ACT) | • Non-linear, variable effect<br>• Dependent on AT activity<br>• Possible HIT induction |
| **Low-molecular weight heparin** | • Easy to administer<br>• Lower risk of HIT induction | • Accumulation in renal impairment<br>• Can only be partially antagonized<br>• Not easy to monitor (anti-Xa levels) |
| **Direct thrombin inhibitors** | • Independent of AT activity<br>• Quick onset<br>• No HIT induction<br>• **Bivalirudin**: cleared renally<br>• **Argatroban**: cleared hepatically | • No antagonist<br>• Interference with INR<br>• aPTT and coagulopathy |

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# Guidelines


- Heparin bolus (50-100 units/kg) at time of cannulation, continuous infusion during ECLS
- Monitor ACT, aPTT, or anti-Xa

*"These guidelines describe useful and safe practice, but these are not necessarily consensus recommendations. These guidelines are not intended as a standard of care, and are revised at regular intervals as new information, devices, medications, and techniques become available."*

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# Practice Survey of 121 ECMO Centers

**Goals**

ACT 180-200 sec

Median antithrombin 70%

Anti-Xa 0.3-0.7 IU/mL

**Transfusion Triggers**

Platelets <100k

Fibrinogen <145mg/dL

**Monitoring Frequency**

APTT q6-8h

CBC q6-8h

Fibrinogen >12h

Free hemoglobin >12h

Antithrombin q13-24h

Anti-Xa q13-24h

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Bembea et al. Pediatr Crit Care Med 2013;14(2): e77

# Unfractionated Heparin Monitoring

| Key Factors | ACT | aPTT | Anti-Xa |
|---|---|---|---|
| **Availability** | Point of care | Central Lab | Central Lab |
| **Results** | Results may be affected (prolonged) by:<br>•**Thrombocytopenia**<br>•**Platelet dysfunction**<br>•**Hemodilution** | Not affected by platelet numbers or function<br>**Hepatic congestion** | Least affected by physiologic alterations<br>Direct assessment of anticoagulant effect of heparin |
| **Turn around** | Rapid (minutes) | Dependent on lab (30 min to hours) | Dependent on lab (30 min to hours) |
| **Typical goal** | 160 – 200 for ECMO | 1.5 – 3 x baseline<br>(typically 40-70 range) | 0.3 – 0.7 IU/mL<br>0.25 – 0.5 IU/mL |

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# Anticoagulation for ECMO at UK HealthCare

- MCS Heparin Protocol
  - Full-Dose ➔ Higher therapeutic targets
  - Low-Dose ➔ Lower therapeutic targets
  - Utilizes both anti-Xa and aPTT concurrently
- ACT protocol
- Fixed dose heparin protocol

# Bleeding Complications

- Contributing Factors
  - Systemic anticoagulation
  - Thrombocytopenia
  - Platelet dysfunction
  - Coagulopathy secondary to primary disease and/or liver dysfunction

- Prevention
  - Optimize anticoagulation (avoid over anticoagulation)
  - Maintain platelets
  - Caution with suctioning and placement of lines and catheters
  - Prepare for invasive procedures if necessary

# Therapeutic Options

- Administer antidotes/reversal agents when appropriate

- Blood products
  - Red blood cells (RBCs)
  - Platelets Fresh frozen plasma (FFP)
  - Cryoprecipitate

- Pharmacologic agents
  - Local hemostatic agents/sealants
  - Vitamin K
  - Antifibrinolytics
  - Protamine
  - Desmopressin (DDAVP)
  - Recombinant activated factor VII (rFVIIa)
  - Prothrombin Complex Concentrates (PCCs)

# Anticoagulation Considerations

- Most data in pediatric population
- Center specific protocols
- Heparin drug of choice for now
- Variable monitoring strategies
- UK primarily uses heparin; aPTT and Anti-Xa

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