

# ECMO: Basic Principles and Effects on Pharmacokinetics

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# Disclosure

Jasleen Bolina has nothing to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) mentioned in this presentation.

# Objectives

- Describe the different forms of ECMO and indications for each
- Describe typical anticoagulation monitoring in patients on ECMO
- Recognize common alterations in pharmacokinetics due to ECMO
- Formulate appropriate dosage adjustments or monitoring parameters for medications affected by ECMO

# Extra Corporeal Membrane Oxygenation (ECMO)

Overview, Indications, and General Monitoring

# Venovenous extracorporeal membrane oxygenation



④ A mixture of room air and oxygen is delivered in varying fractions to the inner core of the hollow fibers within the oxygenator.

## ⑤ Oxygenation and decarboxylation

Blood flows into the oxygenator, washing over bundles of hollow fibers where gas exchange occurs.

OXYGENATOR

CO<sub>2</sub>

O<sub>2</sub>

CO<sub>2</sub>

Exhaust gas

⑥ Oxygenated, decarboxylated blood exits under attenuated positive pressure.

③ The pump expels the blood under positive pressure and drives it to the oxygenator.

PUMP

② Deoxygenated blood is drawn into the pump by negative pressure.

## ⑦ Venous return

A cannula is placed in the right internal jugular vein. The tip is advanced into the right atrium.

Oxygenated blood is returned to the right atrium.

RIGHT ATRIUM

Blood is withdrawn from the inferior vena cava.

## ① Venous withdrawal

A cannula is placed in the right femoral vein. The tip is advanced to a point near the right atrium.

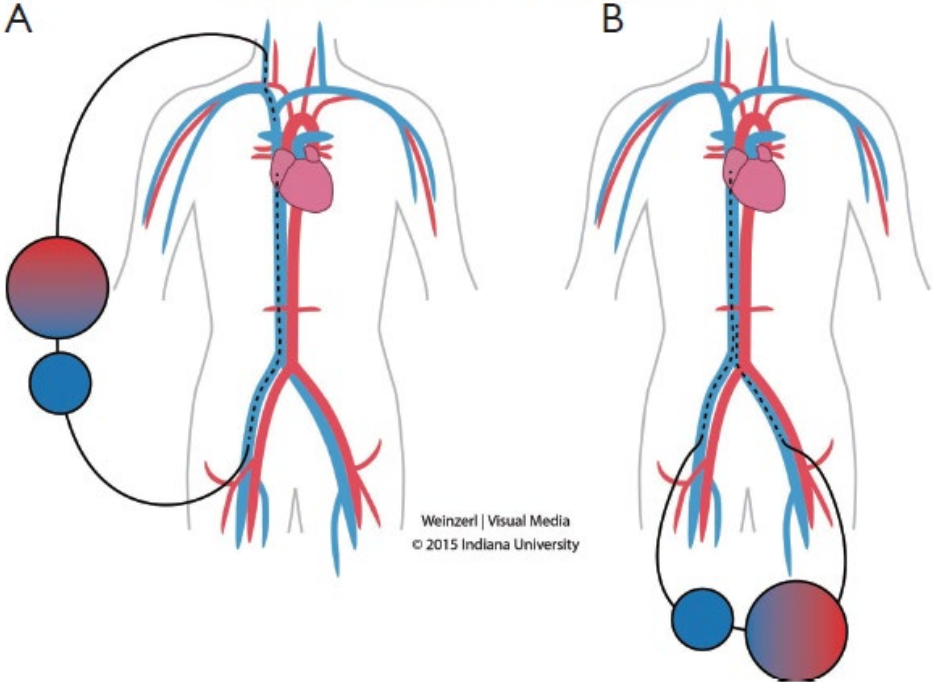
# Types of ECMO

Venovenous (VV)	Venoarterial (VA)
<ul style="list-style-type: none"><li>• Respiratory support only</li><li>• Single or double venous cannula</li><li>• Pulmonary blood flow</li><li>• Higher perfusion rate</li></ul>	<ul style="list-style-type: none"><li>• Respiratory and hemodynamic support</li><li>• Arterial and venous cannula</li><li>• Blood bypasses heart and lungs</li><li>• Reduced perfusion rate</li></ul>

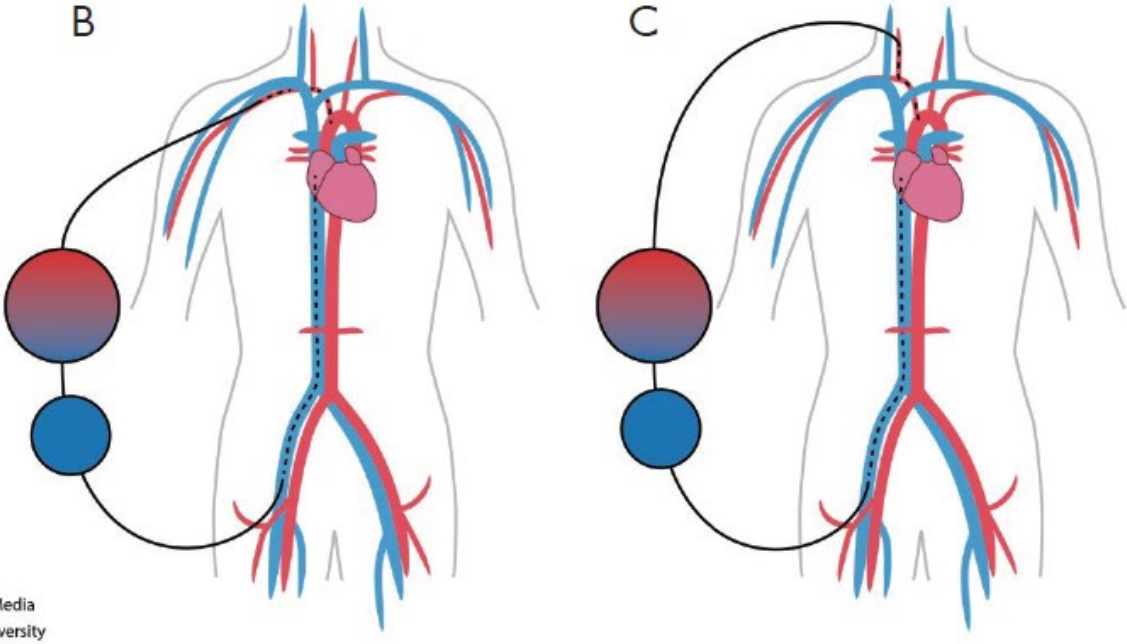
# Venovenous ECMO Cannulation

# Venoarterial ECMO Cannulation

Veno-venous ECMO: two cannulation approach



Peripheral veno-arterial ECMO cannulation approach



## Indications: VV ECMO

- Acute respiratory distress syndrome
- Bridge to lung transplant
- Primary graft dysfunction following lung transplant
- Status asthmaticus/lung hyperinflation
- Lung rest
- Acute massive pulmonary embolism or hemorrhage



## Indications: VA ECMO

- Cardiogenic shock
- Post cardiectomy
- Post heart transplant
- Bridge to transplant
- Chronic cardiomyopathy
- Periprocedural support for high-risk PCI
- Acute decompensated pulmonary hypertension

# Contraindications

Ineligible for transplant

Disseminated malignancy

Severe brain injury

Unwitnessed cardiac arrest

Prolonged CPR without adequate perfusion

Unrepaired aortic dissection

Severe aortic regurgitation

Severe chronic organ dysfunction

Compliance

# Complications of ECMO

Neurologic	<ul style="list-style-type: none"><li>• CNS hemorrhage</li><li>• CNS infarction</li><li>• Brain death</li><li>• Seizures</li></ul>
Pulmonary	<ul style="list-style-type: none"><li>• Pneumothorax</li><li>• Pulmonary hemorrhage</li></ul>
Cardiac	<ul style="list-style-type: none"><li>• Arrhythmia</li><li>• Tamponade</li></ul>
Hematologic	<ul style="list-style-type: none"><li>• Bleeding</li><li>• Hemolysis</li><li>• Clots in circuit</li></ul>
Others	<ul style="list-style-type: none"><li>• Increased SCr</li><li>• Renal replacement therapy</li><li>• Infection</li></ul>

# ECMO Monitoring

Volume  
Status

Urine  
Output

Chest x-ray

Cardiac  
output

Oxygenation

CMP

CBC

aPTT/ACT/  
anti-Xa

# Which of the following is NOT an indication for VV ECMO

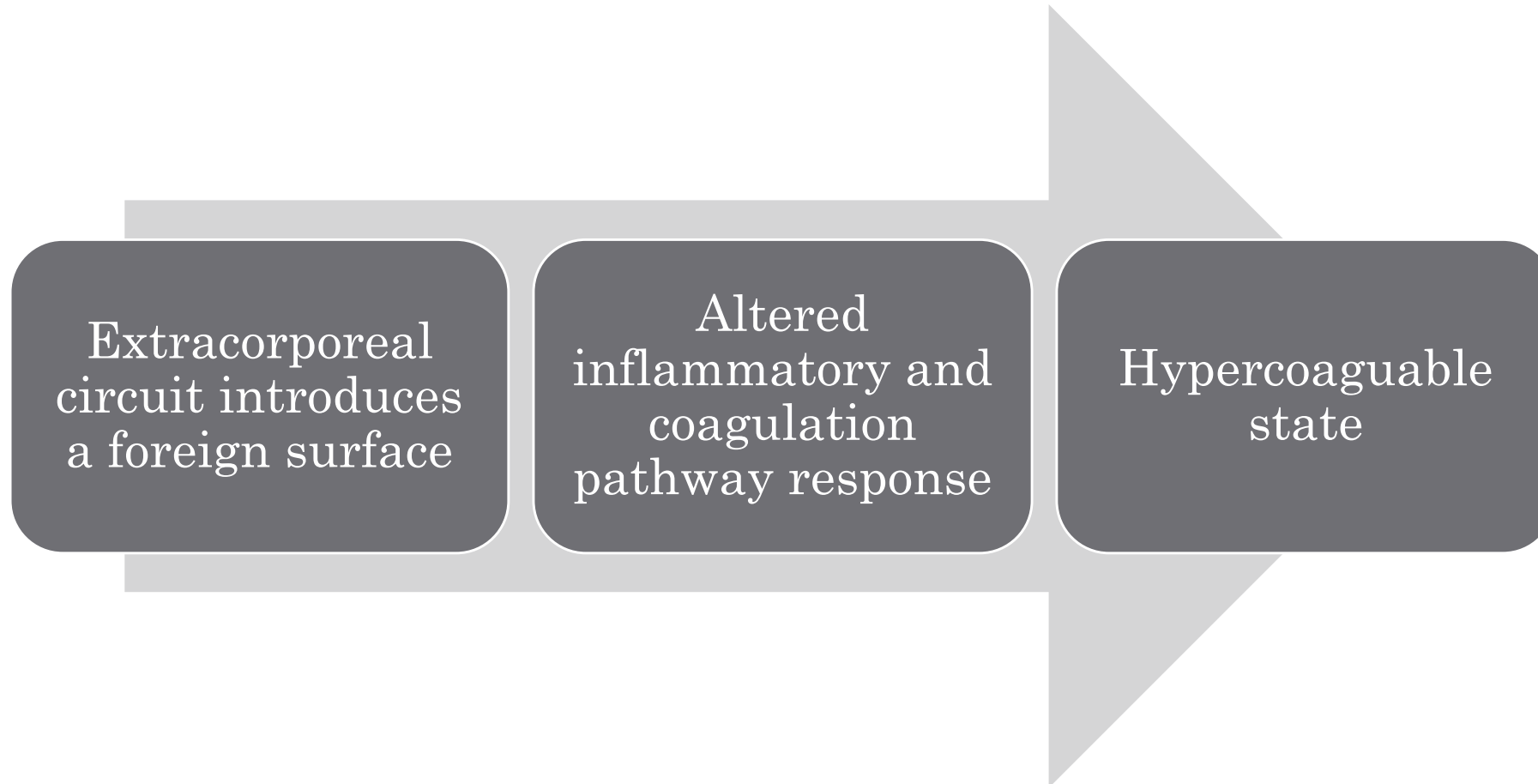
- A. Lung rest
- B. Status asthmaticus
- C. Cardiogenic Shock
- D. Acute respiratory distress syndrome
- E. All of these are indications for VV ECMO

# Which of the following is NOT an indication for VV ECMO

- A. Lung rest
- B. Status asthmaticus
- C. **Cardiogenic Shock**
- D. Acute respiratory distress syndrome
- E. All of these are indications for VV ECMO

# Anticoagulation

# Hypercoaguable State





# Anticoagulants of Choice

Drug of  
choice

- Unfractionated heparin (UFH)

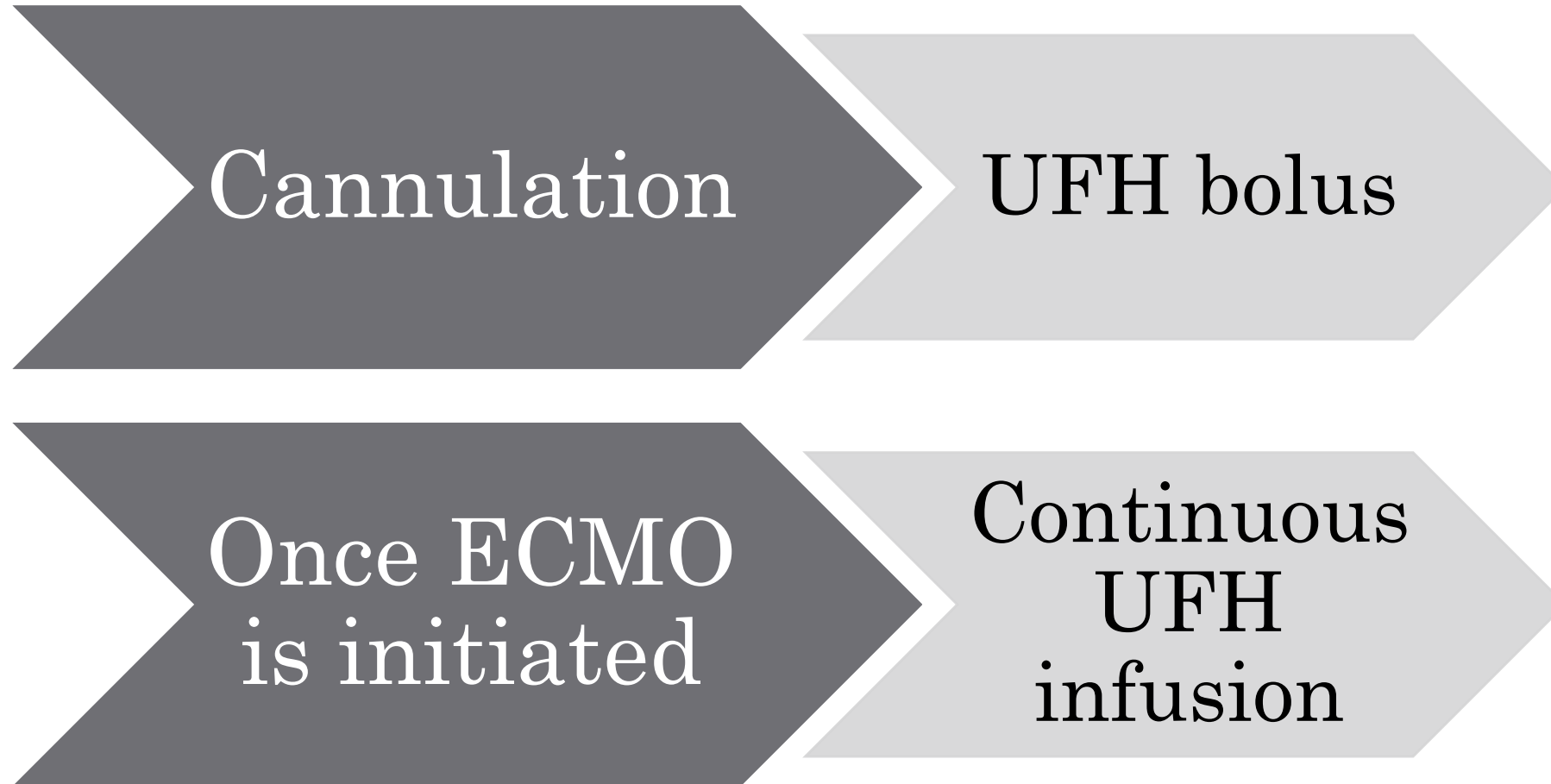
Alternative  
agents

- Bivalirudin
- Argatroban

# Anticoagulation Monitoring

	Activated Clotting Time (ACT)	Activated Partial Thromboplastin Time (aPTT)	Anti-factor Xa
<b>Availability</b>	Point of care test	Laboratory test	Laboratory test
<b>Goal Range</b>	180-220 seconds	47-79 seconds*	0.3-0.7 IU/mL
<b>Considerations</b>	Can be affected by thrombocytopenia, hypothermia, hemodilution	Measures time to fibrin formation  Not affected by platelet function	Measures effect of UFH Not affected by coagulopathy, thrombocytopenia, or hemodilution Can be affected by hyperlipidemia, hyperbilirubemia, and hemolysis

# Timing of Anticoagulation



# Pharmacokinetics

# Effects on Pharmacokinetics

Drug  
Sequestration

Altered Volume  
of Distribution  
( $V_d$ )

Altered  
Clearance (Cl)

What  
influences  
drug  
alterations?

- Molecular size
- pKa
- Ionization of drug
- Lipophilicity
- Plasma protein binding

# Potential for Toxicity

- Saturation of binding sites
- Dilution of plasma proteins
- Reintroduction of drug
- Reduced drug clearance

# Which of the following is true about drug sequestration?

- A. Sequestration is more likely to affect hydrophilic drugs
- B. Drugs that have lower protein binding may deposit on ECMO tubing
- C. Drugs may be reintroduced even after discontinuation of therapy
- D. Sequestration is due to the small surface area of the membrane oxygenator



# Which of the following is true about drug sequestration?

- A. Sequestration is more likely to affect hydrophilic drugs
- B. Drugs that have lower protein binding may deposit on ECMO tubing
- C. **Drugs may be reintroduced even after discontinuation of therapy**
- D. Sequestration is due to the small surface area of the membrane oxygenator

# Overview of drug therapy

# Therapies affected by ECMO

## Analgesia and Sedation

- Opioids
- Dexmedetomidine
- Midazolam
- Propofol

## Beta-Lactams

- Penicillins
- Cephalosporins
- Carbapenems

## Other Antimicrobials

- Aminoglycosides
- Vancomycin

# Analgesia and Sedation

	Lipophilicity (Log P)	Protein Binding (%)	Volume of Distribution (L)	Sequestration
Morphine	0.9	30-40	70-350	Minimal-moderate
Hydromorphone	1.62-1.8	8-19	280	Minimal-moderate
Dexmedetomidine	2.8	94-94	118	Significant
Propofol	3.8	95-99	4200	Significant
Midazolam	3.9	97	70-217	Significant
Fentanyl	4.1	80-85	280-420	Significant

Cheng V, et al. J Thorac Dis. 2018; 10(5): S629-S641.  
 Ha MA, et al. Pharmacotherapy. 2017; 37(2): 221-235.  
 Landolf KM, et al. Pharmacotherapy. 2020; 40(5): 389-397.

# Sedation and ECMO

- Retrospective cohort analysis
- **Population:** Adults with severe ARDS receiving a continuous infusion of at least one sedative for  $\geq 48$  hr
- **Study groups:** Patients on ECMO vs those not on ECMO
- **Primary objective:** Maximum 6-hour total sedative requirement
- **Secondary objectives:**
  - Time to maximum sedation
  - Total amount of sedation to reach maximum sedation

# Sedation and ECMO

- **Results:**

	ECMO (n=34)	Non-ECMO (n=60)	P Value
Maximum 6-hour sedative requirement	118 mg	60 mg	0.004
Time to maximum sedation	4 days	1 day	0.003
Infusion rate at time of maximum sedation	10 mg/hr	6 mg/hr	0.04

- **Conclusion:**

- Those on ECMO received almost twice the amount of sedation as those not on ECMO.
- Limitation: Age and concomitant fentanyl use may have influenced the amount of sedation used.

# Analgesia and Sedation

Fentanyl, Midazolam,  
Dexmedetomidine,  
Propofol

- More lipophilic
- Greater degree of drug sequestration
- Higher dose requirements

Morphine,  
Hydromorphone

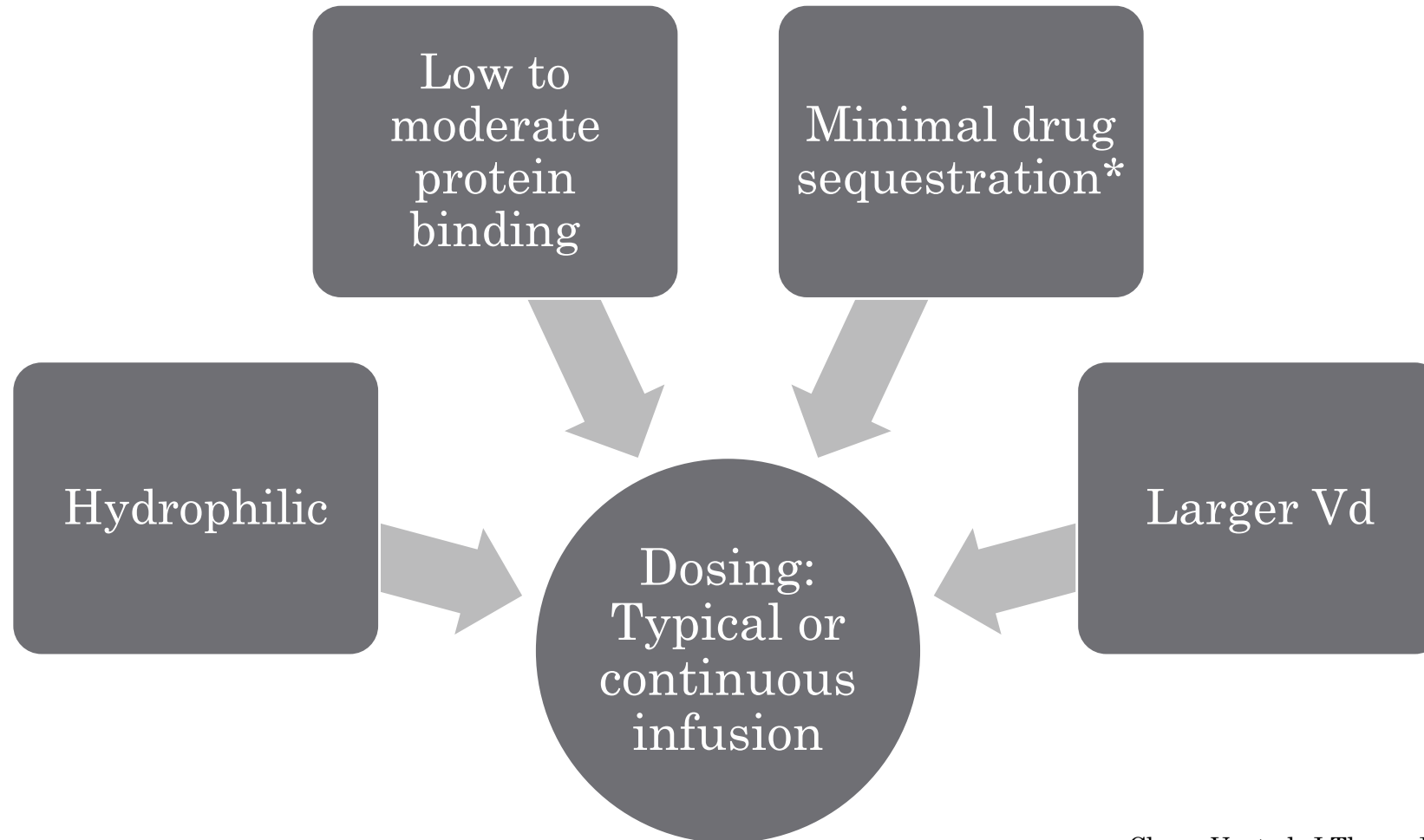
- Less lipophilic
- Lower degree of drug sequestration
- May be preferable to fentanyl

# Antimicrobials

	Lipophilicity (Log P)	Protein Binding (%)	Volume of Distribution (L)	Sequestration
Vancomycin	-3.1	50-60	28-70	Minimal
Ceftriaxone	-1.7	95	5.78-13.5	Significant
Meropenem	-0.69	2	15-20	Minimal
Aminoglycosides	<0	<30	14-21	Minimal
Piperacillin/ Tazobactam	0.67	30	16.8	Minimal
Voriconazole	1	58	322	Significant
Ampicillin	1.35	15-30	20-27	Minimal- moderate
Fluoroquinolones	<2.3	20-40	89-189	Minimal



# Beta-lactams



# Aminoglycosides

Low protein  
binding

Higher Vd

Reduced Cl

Hydrophilic

Minimal drug  
sequestration

# Vancomycin: Donadello K, et al

- Retrospective, matched cohort study of critically ill adult patients
- Study Groups: ECMO, Control
- Objective: To compare the population pharmacokinetics of vancomycin when given as a continuous infusion in critically ill patients with ECMO to patients without ECMO

**Table 1 Daily vancomycin doses according to the creatinine clearance (CrCL)**

CrCL, L/minute	Daily dose
>150	45 mg/kg
120 to 150	40 mg/kg
80 to 120	35 mg/kg
50 to 80	25 mg/kg
25 to 50	14 mg/kg
<25 or oliguria	7 mg/kg
<b>Continuous renal replacement therapy</b>	14 mg/kg

Oliguria was defined as urine output  $\leq 0.5$  mL/kg/h.

# Vancomycin: Donadello K, et al

- Results

	ECMO (n=11)	Control (n=11)
Inadequate drug levels at 12 hr	18%	0%
Inadequate drug levels at 24 hr	36%	9%
Vd	99.3 L	92.3 L
Cl	2.4 L/hr	2.3 L/hr

- Conclusion

- Vd and Cl were similar between both groups
- Fewer patients in the ECMO group attained adequate concentrations at 12 and 24 hours

# Vancomycin: Park SJ, et al

- Retrospective observational study
- **Population:** Adult patients admitted to the ICU
- **Study groups:** ECMO vs control
- **Primary objective:** To determine if conventional vancomycin dosing based on total body weight and renal function is adequate in patients on ECMO
- **Additional Outcomes:**
  - Total daily dosage
  - Dosing frequency
  - Initial trough levels prior to third dose
  - Maintenance trough levels at steady state (around 5<sup>th</sup> dose)

# Vancomycin: Park SJ, et al

	ECMO (n=20)	Control (n=60)	P Value
Subtherapeutic initial trough	95%	66.67%	0.013
Average time to therapeutic trough	84.59 hr	57.41 hr	0.013

- Dose Adjustments

- ECMO

- Following the 4<sup>th</sup> dose, the average daily dose significantly increased to 42.24 mg/kg and the frequency increased to 2.9 times/day (p=0.014)

- Control

- The frequency (2.11 to 2.37 times/day) and total daily dose (22.91 mg/kg to 31.61 mg/kg) did not significantly change prior to the 4<sup>th</sup> dose (p=0.071, p=0.350)

# Vancomycin: Park SJ, et al

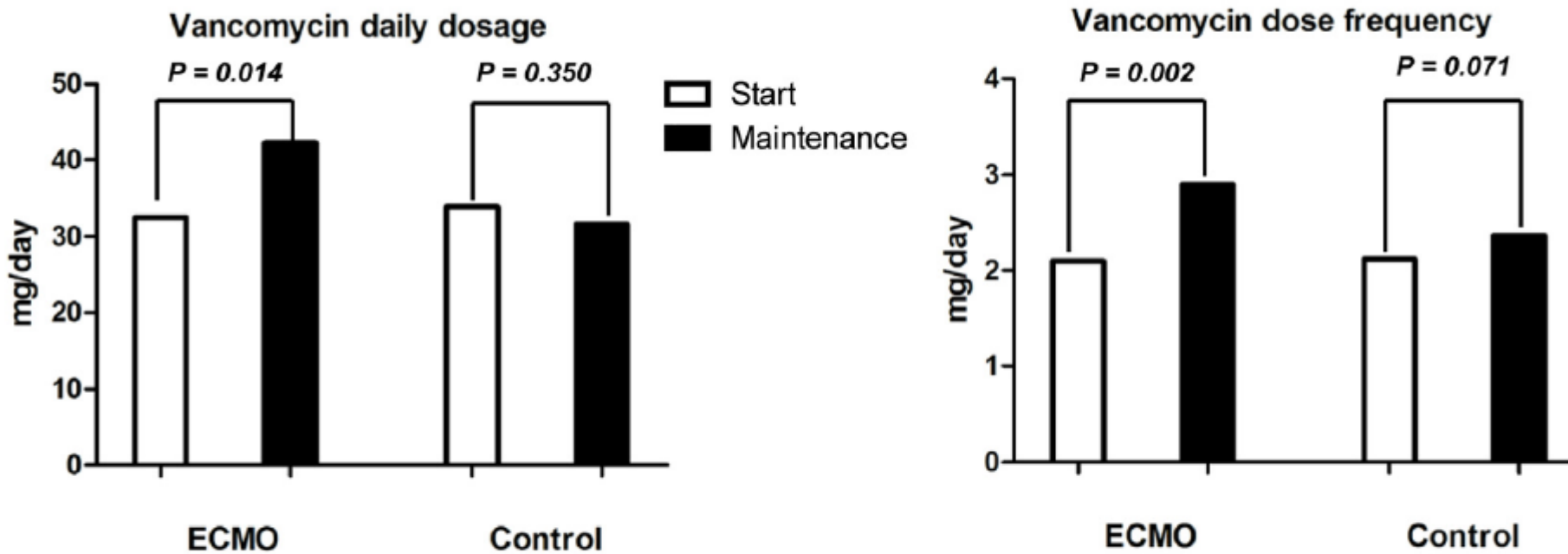
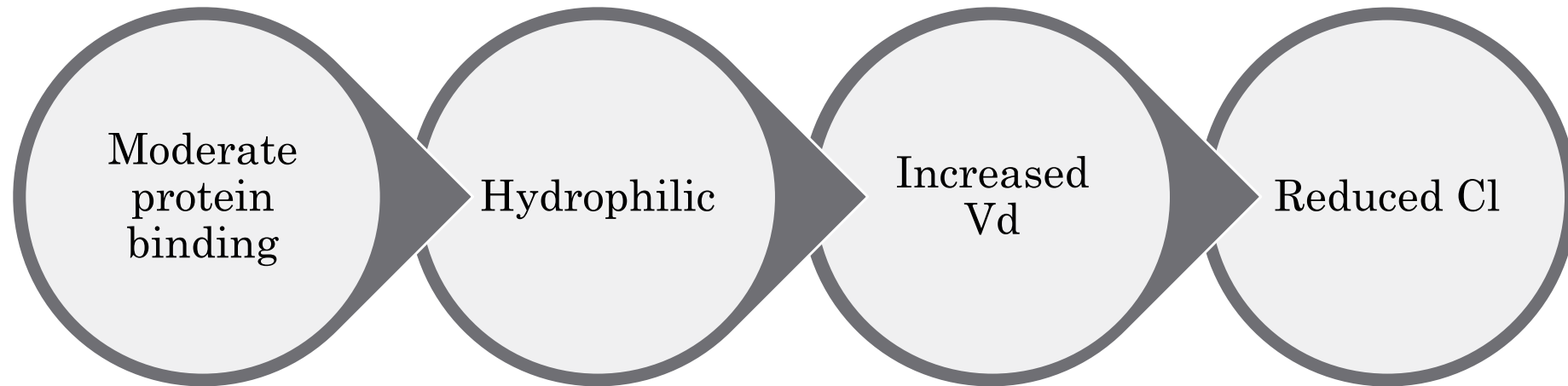


Fig 3. Differences of vancomycin daily total dosage (A) and dosing frequency (B) between initial and maintenance phase.

# Vancomycin





Doses of amikacin may need to be increased in the setting of ECMO due to:

- A. Increased  $V_d$
- B. Increased protein binding
- C. Increased Cl
- D. Increased drug sequestration

Doses of amikacin may need to be increased in the setting of ECMO due to:

- A. **Increased Vd**
- B. Increased protein binding
- C. Increased Cl
- D. Increased drug sequestration

# Conclusion

- Pulmonary or cardiopulmonary support
- Potential for coagulopathy
- Alterations in pharmacokinetics
- Adjustment in doses or therapy may be warranted

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# Questions?

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