Antimicrobial Considerations In ECMO Patients

UTAH SOCIETY OF
HEALTH-SYSTEM PHARMACISTS

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March 14, 2022

Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, Aaron Thibeault, PharmD:**
    - No financial conflicts of interest to disclose
  - **CE mentor, Brian Hathaway, PharmD, BCIDP:**
    - No financial conflicts of interest to disclose
  - **CE mentor, Eric Drab, PharmD, BCPS:**
    - No financial conflicts of interest to disclose
- Off-Label Uses of Medications
  - None, but doses are higher than approved for indication
  - (Refer to slide 68 for specific dosing recommendations)

Learning Objectives- Pharmacists

- Describe the various components of ECMO
- Identify the most common infections and microorganisms seen in this population
- Evaluate the pharmacokinetic factors that influence antimicrobial dosing
- Develop evidence-based antimicrobial dosing recommendations and monitoring plans

Learning Objectives- Technicians

- Describe the use of ECMO
- Memorize brand and generic names of the antimicrobials with required dosing adjustments
- Distinguish antimicrobials with modified dosing recommendations

Introduction

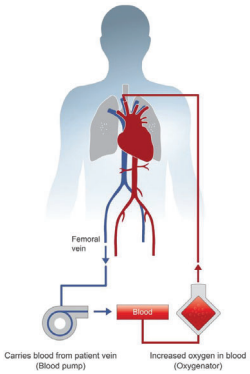
Medication dosing in ECMO patients is challenging as the ECMO machine introduces drug pharmacokinetic altering factors. There are no guidelines for antimicrobial dosing in ECMO patients, which can present challenges in determining optimal dosing.

Outline

- Introduction to ECMO
- Infection risk
- Pharmacokinetic factors that affect drug dosing
- Antimicrobial Dosing Considerations

Introduction to ECMO

Extracorporeal membrane oxygenation (ECMO)



- Heart-lung machine
  - Removes CO2 from body
  - Sends oxygen filled blood back to the body
- Supportive measure only
  - Does not cure underlying illness
  - Can provide support for days to weeks

Types of ECMO

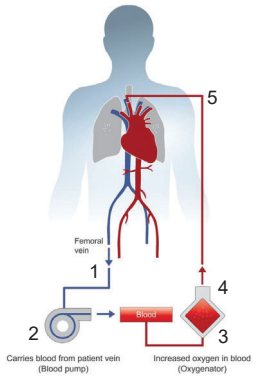
Veno-Venous (VV) ECMO

- Supports lungs
- Connected to one or more veins
  - This allows the heart to pump the blood

Veno-Arterial (VA) ECMO

- Supports lungs *and* heart
- Connected to both a vein and an artery
  - Machine oxygenates and pumps blood

The ECMO Circuit



1. Venous (drainage) cannula/catheter
2. Centrifugal pump
3. Membrane oxygenator
4. Blood warmer
5. Arterial/venous (return) cannula/catheter

Indications

Heart Conditions:

- Cardiogenic shock: +/- MI
- PE with hemodynamic compromise
- Fulminant myocarditis
- Cardiac arrest (assisted CPR)
- Support post-cardiac surgery
- Post-transplant complications
- Others

Indications

Lung Conditions:

- Acute respiratory distress syndrome (ARDS)
- Pulmonary contusion
- Severe pneumonia
- Acute lung (graft) failure following transplant
- Others

Contraindications

Absolute

- Severe brain injury
- Disseminated malignancy
- Unwitnessed cardiac arrest
- Severe aortic regurgitation
- Severe chronic organ dysfunction
- Others

Relative

- Patient specific contraindication for anticoagulation
- Obesity
- Advanced age

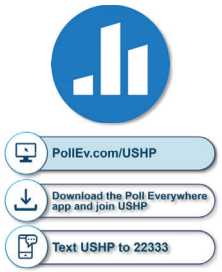
Pharmacist Role

- Pharmacokinetic issues with key medications
- Must be on therapeutic anticoagulation
  - Heparin drip → aPTT or anti-Xa monitoring
- Nearly always on some level of sedatives
  - Monitor infusion rates and level of sedation daily
- Monitor for drug complications associated with ECMO

Pharmacist Question #1

Chronic therapeutic anticoagulation is required to keep the ECMO machine from clotting

A. True
B. False



Technician Question #1

What is ECMO used for?

A. To remove carbon dioxide and oxygenate the blood
B. To remove excess water from the blood
C. To remove electrolytes from the blood
D. To remove toxins from the blood

Complications

- **Infection (10-12%)**
- Hemorrhage (30-50%)
- Clotting (DVT can be as high as 70%)
- Neurologic morbidity (~10%)

Mayo Clinic (Extracorporeal Membrane Oxygenation); Sun HY et al (*J Thorac Cardiovasc Sug.* 2010)

Infection Risk

Prevalence

- Prevalence of hospital-acquired infections in ECMO in adults is **~21%**

Infections	% of infection in all ECMO patients	% of infection only in infected ECMO patients
Lower Respiratory Tract	13.7%	42.8%
Blood Stream	11.8%	36.5%
Urinary Tract	3.2%	14.7%

- Nosocomial infections increase the risk of death by 38-63%

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Infection Risk Factors

- Increased overall number of catheters
- Increased risk of renal failure
  - Need for blood transfusions
- Homeostatic imbalance of the coagulation system

USHP

Common Pathogens

- **Most common pathogen**: Coagulase-negative staphylococci (CoNS)
- Followed by *Candida* spp. (15%), *Pseudomonas aeruginosa*, Enterobacterales, *Staphylococcus aureus*, and Enterococci
  - Overall percentage of *S. aureus* is lower than non-ECMO critically ill patients

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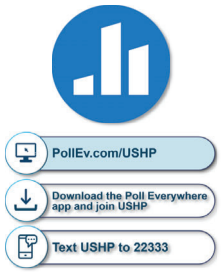
Pharmacist Question #2

Which response best describes the percentage of adult ECMO patients diagnosed with a hospital acquired infection?

A. 2%
B. 21%
C. 37%
D. 55%



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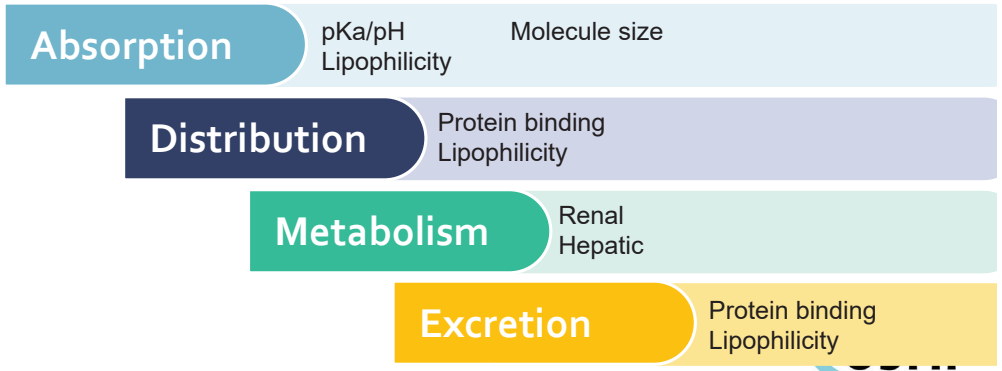
Pharmacokinetics (PK)

PK Introduction



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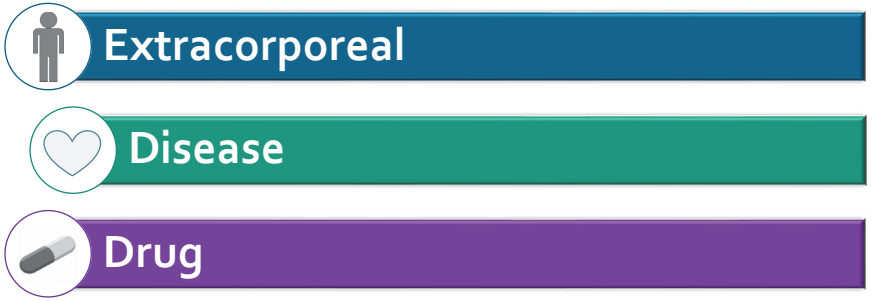
Pharmacokinetic Factors



Cheng V et al (*J Thorac Dis.* 2018)

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Extracorporeal

1. Drug sequestration by the circuit
2. Increased volume of distribution (V_d)
3. Altered drug clearance (CL)

Extracorporeal

Drug sequestration by the circuit

- Increased surface areas trap and adsorb drugs
  - ↑ V_d leads to ↓ plasma concentrations
- Sequestration interactions include:
  - Hydrophobic interactions
    - Protein binding and lipophilicity
  - Electrostatic interactions

- Adsorption phenomena should decrease over time due to saturation

Extracorporeal

Increased volume of distribution (V_d)

- Drug sequestration
- Hemodilution from priming solution
  - Increase in overall volume
- Physiological changes (i.e. blood pH)
  - Drug ionization

Extracorporeal

Altered drug clearance (CL)

- Decrease
  - Renal and hepatic hypoperfusion
  - Hypoxia
- Increase
  - Cardiac output secondary to SIRS
  - Aggressive fluid therapy
  - Inotropic support

Disease

- Leaky capillaries
  - Increased V_d → Decreased plasma concentration
- Altered protein binding
  - More free drug → Increased plasma concentration
- End-organ dysfunction
  - Decreased clearance → Increased plasma concentration

Cheng V et al (*J Thorac Dis*. 2018)

Drug

- Molecular size
- pKa and degree of ionization
- Lipophilicity and plasma protein binding
  - Increased lipophilicity → increased drug sequestration by the ECMO circuit

Cheng V et al (*J Thorac Dis*. 2018)

Pharmacist Question #3

Which of the following is an extracorporeal factor that can lead to an increased volume of distribution?

A. Leaky Capillaries
B. Sequestration
C. Lipophilicity
D. Protein Binding

Antimicrobial Dosing Considerations

Antimicrobial Dosing Considerations

- Optimal dosing is correlated with improved patient outcomes
  - Account for physiochemical characteristics of the drug and its interaction with the circuit
- Suboptimal antibiotic dosing can lead to treatment failures and bacterial resistance
- Antibiotic therapy is guided without any real-time feedback

Cheng V et al (*J Thorac Dis*. 2018)

Antimicrobials

- Beta-lactams
- Vancomycin
- Fluoroquinolones
- Aminoglycosides
- Antifungals

Beta-lactams

- First-line for most indications
- Hydrophilic in nature
- Protein binding varies
- BLA = Beta-Lactam Antibiotics

Cheng V et al (*J Thorac Dis*. 2018)

Beta-lactams

Drug	LogP	Protein Binding (%)
Oxacillin	2.38	-94% (albumin)
Piperacillin/Tazobactam (Zosyn®)	0.67	~30%
Cefotaxime	-.05	31 to 50%
Meropenem (Merrem®)	-.069	~2%
Cefepime (Maxipime®)	-0.1	~20%
Ceftazidime	-1.6	<10%
Ceftriaxone (Rocephin®)	-1.7	85 to 95%

Wishart DS (*Nucleic Acids Res*. 2006)

Beta-lactams

Ex Vivo Model to Decipher the Impact of Extracorporeal Membrane Oxygenation on Beta-lactam Degradation Kinetics

Therapeutic Drug Monitoring; April, 2017

- **Background**:
  - As a consequence of drug sequestration, increase in volume of distribution, or alteration of elimination, extracorporeal membrane oxygenation (ECMO) might lead to inadequate plasma concentrations of vital drugs

Beta-lactams

Ex Vivo Model to Decipher the Impact of Extracorporeal Membrane Oxygenation on Beta-lactam Degradation Kinetics

Therapeutic Drug Monitoring; April, 2017

- **Objective**:
  - Characterize the impact of ECMO procedure on BLA PK
- **Intervention**:
  - 5 ECMO circuits
  - Glass tubes
  - PVC tubes
- **Primary Endpoint:**
  - Concentrations after 48 hours to assess BLA PK

Beta-Lactams included:

- Cefotaxime
- Ceftazidime
- Cefepime
- Piperacillin
- Oxacillin
- Amoxicillin
- Ceftriaxone

Beta-lactams

Ex Vivo Model to Decipher the Impact of Extracorporeal Membrane Oxygenation on Beta-lactam Degradation Kinetics

Therapeutic Drug Monitoring; April, 2017

- **Results:**

Drug	ECMO circuit	Tubing Control		Inert Control	
		% Recovery	p-value	% Recovery	p-value
Ceftazidime	**73%**	69%	0.07	**66%**	**<0.05**
Cefepime	**67%**	63%	0.11	**61%**	**<0.05**
Oxacillin	46%	43%		43%	
Ceftriaxone	104%	94%		95%	
Cefotaxime	**21%**	**39%**	**<0.05**	**39%**	**<0.05**

Beta-lactams

Ex Vivo Model to Decipher the Impact of Extracorporeal Membrane Oxygenation on Beta-lactam Degradation Kinetics

Therapeutic Drug Monitoring; April, 2017

- **Analysis / Discussion:**
  - Drug loss was observed in all but one antibacterial drug (ceftriaxone)
  - Sequestration by ECMO tubing is unlikely for the other antibiotics studied
  - No significant differences were observed between controls for oxacillin
  - No difference was observed between ECMO circuits and inert controls for ceftriaxone, whereas a difference was observed for ceftazidime

Interpretation

Sequestration of beta-lactam drugs within ECMO tubing or components **does not** seem to be an issue

Beta-lactams

Prediction of Insufficient Beta-Lactam Concentrations in Extracorporeal Membranous Oxygenation Patients

Microorganisms; November 9, 2021

- **Background**:
  - Critical illness is associated with significant pathophysiological changes that limits the applicability of standard antibiotic regimens
  - ECMO may further alter drug PK and challenge appropriate antibiotic regimens

Beta-lactams

Prediction of Insufficient Beta-Lactam Concentrations in Extracorporeal Membranous Oxygenation Patients

Microorganisms; November 9, 2021

- **Objective**:
  - Report the occurrence of insufficient broad-spectrum BLA concentrations in ECMO patients
- **Intervention:**
  - Retrospective analysis
    - ceftazidime
    - cefepime
    - piperacillin/tazobactam
    - meropenem
- **Primary Endpoint**:
  - Occurrence of insufficient drug concentrations in ECMO patients

Inclusion Criteria

- >18 years of age
- Treated with study drug
- One drug level

Exclusion Criteria

- Did not receive study drug
- TDM was not performed

Beta-lactams

Prediction of Insufficient Beta-Lactam Concentrations in Extracorporeal Membranous Oxygenation Patients

Microorganisms; November 9, 2021

Antibiotic	All (n=222)	Sufficient (n=196)	Insufficient (n-26)
Cefepime-Ceftazidime	41 (19%)	41 (21%)	0 (0%)
Piperacillin/tazobactam	85 (38%)	80 (40%)	5 (19%)
Meropenem	96 (43%)	75 (38%)	21 (81%)

Beta-lactams

Prediction of Insufficient Beta-Lactam Concentrations in Extracorporeal Membranous Oxygenation Patients

Microorganisms; November 9, 2021

- **Conclusion:**
  - Insufficient concentrations were observed 12% of the time
    - Associated with a shorter time from initiation, lower single dose of antibiotic, higher CrCl, lower SOFA score, less use of CRRT

Interpretation

Higher than recommended drug regimens can be considered in very early phase of therapy in those with augmented renal clearance and less severe organ dysfunction

Beta-lactams

Key Points

- Recommend doses on the higher end of a medication's dosing range

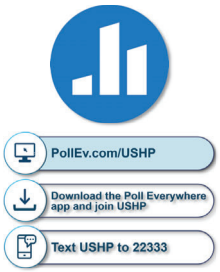
Drug	Standard Dosing	ECMO Dosing Recommendations
Ceftriaxone	1-2g q 24h or 2g q12h for meningitis	Standard dosing
Cefepime	1 g q6h or 1-2 g q8-12h	2 g over 3 hours every 8 hours
Piperacillin/ tazobactam	3.375 g q6h – 4.5 g q6-8h	4.5 g over 4 hours every 8 hours
Meropenem	500 mg q6h or 1 g q8h	2 g over 3 hours every 8 hours

Sherwin J et al (*Clin Ther.* 2017); Kois AK et al (*Open Forum Infectious Diseases.* 2021)

Technician Question #2

Question: What is the generic name of Zosyn®?

A. Ceftriaxone
B. Cefepime
C. Meropenem
D. Piperacillin/tazobactam



Vancomycin

- Drug of choice for treating beta-lactam resistant **gram-positive** bacteria
- Hydrophilic
- Moderately protein bound (55%)

Vancomycin

Trough Concentrations of Vancomycin in Patients Undergoing Extracorporeal Membrane Oxygenation

Plos One; November 6, 2015

- **Background:**
  - Appropriate drug dosing for vancomycin is not well established with ECMO
  - Many PK factors can result in delayed appropriate drug concentrations
  - Attaining appropriate vancomycin concentrations early in critically ill patients is vital

Park SJ et al (*PLos One.* 2015)

Vancomycin

Trough Concentrations of Vancomycin in Patients Undergoing Extracorporeal Membrane Oxygenation

Plos One; November 6, 2015

- **Objective**:
  - Investigate appropriateness of current vancomycin dosing strategies in adult patients with ECMO
- **Patients**:
  - Experimental: 20 ECMO patients receiving vancomycin
  - Control: 60 non-ECMO patients receiving vancomycin in medical intensive care
- **Intervention:**
  - Vancomycin dosing was 15-20 mg/kg/day every 8 to 12 hours
- **Primary Outcome:**
  - PK parameters based on vancomycin troughs
    - Troughs collected prior to third dose and prior to fifth dose

Inclusion Criteria

- >18 years of age
- Treated with vancomycin

Exclusion Criteria

- <18 years of age
- Lack of pharmacokinetic records
- End-stage renal disease
- Initial dosage not in the usual dosing range based on renal function and weight

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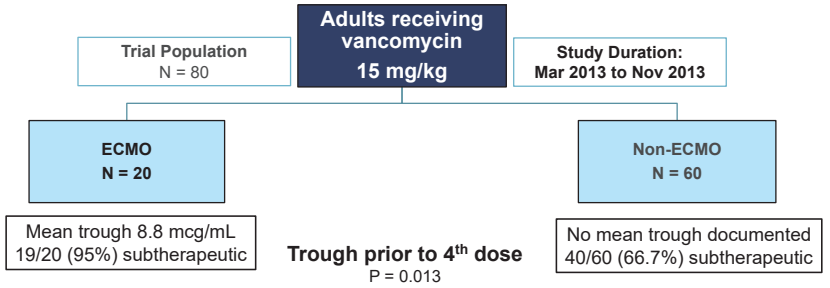
Vancomycin

Trough Concentrations of Vancomycin in Patients Undergoing Extracorporeal Membrane Oxygenation

Plos One; November 6, 2015



USHP

Vancomycin

Trough Concentrations of Vancomycin in Patients Undergoing Extracorporeal Membrane Oxygenation

Plos One; November 6, 2015

Intervention	Mean Initial dosing		Dosing Change after trough		P-value	
	Dose	Interval	Dose	Interval	Dose	Interval
ECMO	32.5 mg/kg	2.1 times/day	42.2 mg/kg	2.9 times/day	P=0.014	P=0.002
Control	33.9 mg/kg	2.1 times/day	31.7 mg/kg	2.4 times/day	P=0.350	P=0.071

	ECMO	Control	P-value
Time to target trough	84.6 hours	57.4 hours	P=0.013

USHP

Vancomycin

Trough Concentrations of Vancomycin in Patients Undergoing Extracorporeal Membrane Oxygenation

Plos One; November 6, 2015

- **Conclusion:**
  - Initial dosing strategy was not sufficient to achieve the target trough
  - Loading doses or shortened dosing interval may be needed to reach target range earlier

Interpretation

Special attention to the therapeutic trough concentration during the initial period is warranted in critically ill patients on ECMO

USHP

Vancomycin

Key Points

- Recommend loading doses closer to 30 mg/kg
- Recommend starting maintenance dosing regimen closer to 20 mg/kg/dose q8-12h
  - Could consider shortening interval instead of increasing dose
- Follow and adjust dosing regimen based on trough or AUC levels

Fluoroquinolones

- Lipophilic
- Low-moderate protein binding

Drug	LogP	Protein Binding (%)
Ciprofloxacin	2.3	20% - 40%
Levofloxacin	2.1	24% - 38%
Moxifloxacin	2.9	30% - 50%

Wishart DS (*Nucleic Acids Res.* 2006)

Aminoglycosides

- Hydrophilic
- Low protein binding

Drug	LogP	Protein Binding (%)
Gentamicin	-3.1	<30%
Tobramycin	-5.8	<30%
Amikacin	-7.4	0% - 11%

Wishart DS (*Nucleic Acids Res.* 2006)

Antifungals

- Hydrophilic
- Caspofungin, micafungin → highly protein bound
- Fluconazole → low protein binding

Drug	LogP	Protein Binding (%)
Fluconazole	0.4	11% - 12%
Caspofungin	0.1	97%
Micafungin	-1.5	>99% (albumin)

Wishart DS (*Nucleic Acids Res.* 2006)

FQ, AMG, Antifungals

Literature Review

- Fluoroquinolones:
  - Levofloxacin concentrations remained therapeutic with standard dosing
- Aminoglycosides:
  - Recommended to follow levels per protocol
- Antifungals:
  - Micafungin 100 mg failed to achieve target concentrations
  - ECMO reduced serum micafungin concentration by 23%
  - Recommend at least 200 mg daily

Sherwin J et al (*Clin Ther*. 2017); Honore PM et al (*Crit Care*. 2018)

Overview: Final Dosing Recommendations

Drug	Standard Dosing	ECMO Dosing Recommendations
Ceftriaxone	1-2g q 24h or 2g q12h for meningitis	Standard dosing
Cefepime	1 g q6h or 1-2 g q8-12h	2 g over 3 hours every 8 hours
Piperacillin/ tazobactam	3.375 g q6h – 4.5 g q6-8h	4.5 g over 4 hours every 8 hours
Meropenem	500 mg q6h or 1 g q8h	2 g over 3 hours every 8 hours
Vancomycin	25-30 mg/kg load followed 15-20 mg/kg/dose q8-12h	30 mg/kg load followed by ~20 mg/kg/dose q8-12h
Levofloxacin	500-1000mg q24h	Standard dosing
Gentamicin	Follow protocol; adjust on levels	Standard dosing and adjust based on levels
Micafungin	100-150 mg q24h	200 mg q24h

Sherwin J et al (*Clin Ther*. 2017); Kois AK et al (*Open Forum Infectious Diseases*. 2021); Honore PM et al (*Crit Care*. 2018)

Key Takeaways

- Consider loading doses for sequestered drugs
  - Highly lipophilic or protein bound
- Review primary literature on dosing change recommendations when necessary
- Use therapeutic monitoring to guide dosing when applicable
- Monitor for signs of infections
  - WBC count, tachycardia, lactate, or signs of sepsis

Pharmacist Question #4

Question: 36 y.o. male on ECMO support post-cardiac surgery. On POD3, his WBC count doubled from 8 to 16, now febrile. Started on empiric vancomycin and cefepime for a diagnosis of ventilator-associated pneumonia. What would be an appropriate starting vancomycin dose?

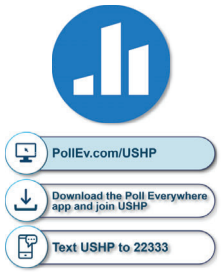
Wt 75 kg, Ht 6'2", BMI 28.2, SCr 0.8, CrCl ~180 mL/min, Albumin 3.6

A. Vancomycin 1 gm iv q 12 hours
B. Vancomycin 2 gm load, followed with 1000 mg IV q 12 hours
C. Vancomycin 2 gm load, followed with 1500 mg IV q 8 hours
D. Vancomycin 2 gm load, followed with 2000 mg IV q 8 hours

Technician Question #3

Question: Does meropenem require a higher than normal dose in ECMO patients?

A. True
B. False



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