Captured in a Circuit: Pharmacologic Considerations in Extracorporeal Membrane Oxygenation

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Disclosures

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Learning Objectives

1. Recall appropriate indications for extracorporeal membrane oxygenation (ECMO) in critically ill patients

2. Identify potential effects on medication pharmacokinetics in the presence of the ECMO circuit

3. Recognize appropriate drug regimens for sedatives, analgesics, and antimicrobials based on available literature for patients receiving ECMO

Introduction to ECMO

Extracorporeal Membrane Oxygenation (ECMO)

ECMO is a form of advanced mechanical circulatory support utilized in patients with acute refractory cardiopulmonary failure

Type of ECMO	Venovenous (VV) ECMO	Venoarterial (VA) ECMO
Organ Support	Pulmonary	Cardiopulmonary
Indications	• Acute severe pulmonary failure with high mortality risk • Pulmonary support during periods of temporary malfunction (extensive bronchoalveolar lavage, trachea procedure) • Bridge to transplant	• Acute severe cardiac and/or pulmonary failure with high mortality risk • Cardiac or cardiopulmonary support during periods of temporary malfunction (mediastinum procedure, coronary artery occlusion) • Bridge to transplant or long-term support modality (i.e. left-ventricular assist device) • Inability to wean from cardiopulmonary bypass post-operatively

Source: Extracorporeal Life Support Organization. *ELSO*. 2017;1.4:1-26.

ECMO Circuit

Tubing types

- Modified vs un-modified polyvinyl chloride (PVC)

Pump

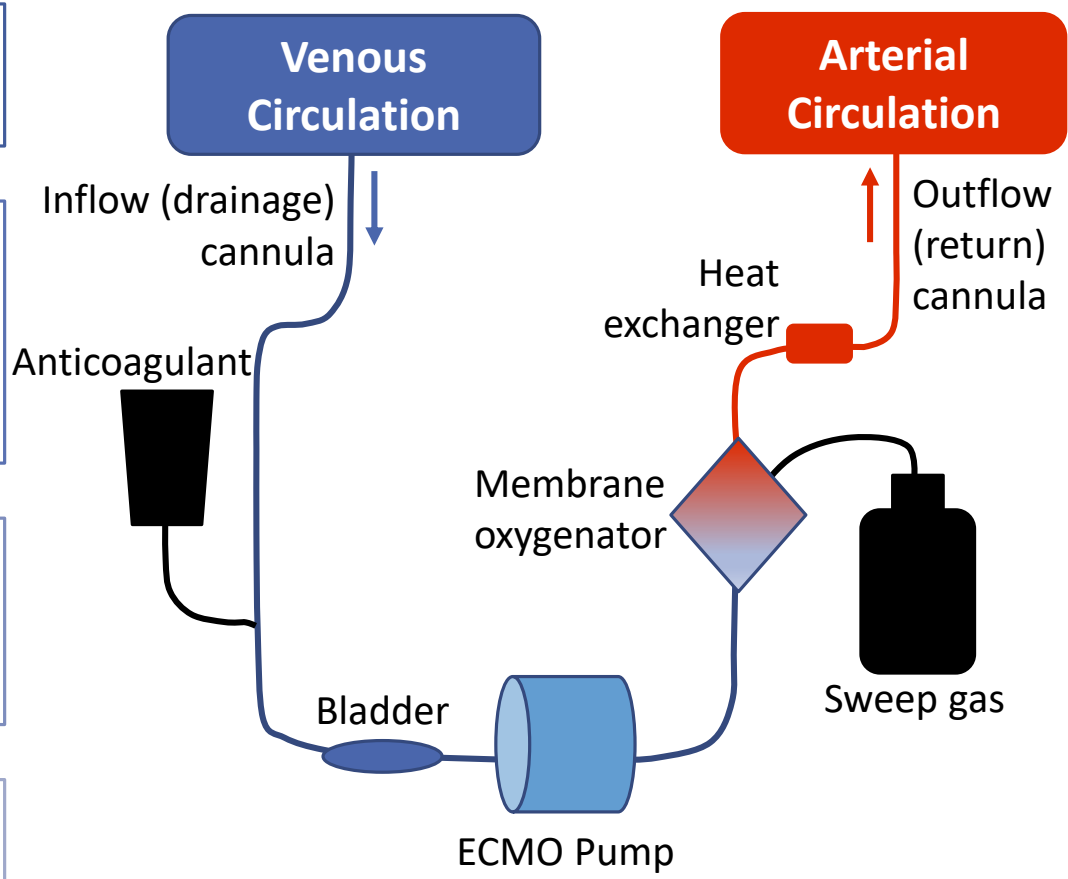
- Circulates the blood determining flow rate and degree of support
- Bladder ensures adequate blood flow and pressure

Oxygenator

- Oxygenates blood and removes carbon dioxide
- Sweep gas provides 100% O_2 or O_2/CO_2 mixture

Heat exchanger

- Warms blood prior to return to patient



Sources: Sieg A, et al. *Crit Care Nurse*. 2019;39(2):29-43.
Ha MA, et al. *Pharmacotherapy*. 2017;37(2):221–35.
Extracorporeal Life Support Organization. *ELSO*. 2017;1.4:1-26.

Effect of ECMO on Medications

Medication alterations may develop in patients receiving ECMO support due to both the ECMO circuit as well as the pharmacokinetics principles of the medication

Circuit Factors	Patient Factors	Medication Factors
• Drug sequestration within circuit • Hemodilution and increased volume of distribution • Circuit tubing, age, and priming solution	• Renal and/or hepatic function • Fluid status • Serum protein levels	• Volume of distribution • Lipophilicity • Protein binding

Sources: Sieg A, et al. *Crit Care Nurse*. 2019;39(2):29-43.
Shah AG, et al. College of Pharmacy Faculty Papers. 2017. Paper 31. https://jdc.jefferson.edu/pharmacyfp/31

Volume of Distribution

- Volume of distribution (Vd) is related to the amount of drug that remains in the plasma as compared to the dose of medication given
  - ↑ Vd = ↓ plasma concentration
  - ↓ Vd = ↑ plasma concentration
- Vd is increased in the setting of ECMO due to multiple mechanisms
  - Presence of an extra compartment
  - Drug sequestration in the ECMO circuit
  - Hemodilution secondary to circuit priming agents

$$Vd = \frac{Dose(mg)}{Plasma\ concentration\ (\frac{mg}{L})}$$

Sources: Dzierba AL, et al. *Crit Care*. 2017;21(1):66.
Sieg A, et al. *Crit Care Nurse*. 2019;39(2):29-43.
Shah AG, et al. College of Pharmacy Faculty Papers. 2017. Paper 31. https://jdc.jefferson.edu/pharmacyfp/31

Lipophilicity

- Lipophilicity describes a medication's affinity for an aqueous (hydrophilic) vs lipid (lipophilic) environment
- Octanol-water partition coefficients, denoted as logP, numerically measure a drug's lipophilicity
- Highly lipophilic medications tend to have decreased concentrations in the setting of ECMO
  - Adherence to ECMO circuit
  - Hemodilution secondary to circuit priming agents

Drug Property	Hydrophilic	Lipophilic
Vd	Low	High
Primary clearance	Renal	Hepatic
LogP	Low	High
Effect with ECMO	No change in clearance	Increased clearance

Sources: Poole SK, et al. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2003;797(1-2):3-19.
Dzierba AL, et al. *Crit Care*. 2017;21(1):66.
Sieg A, et al. *Crit Care Nurse*. 2019;39(2):29-43.

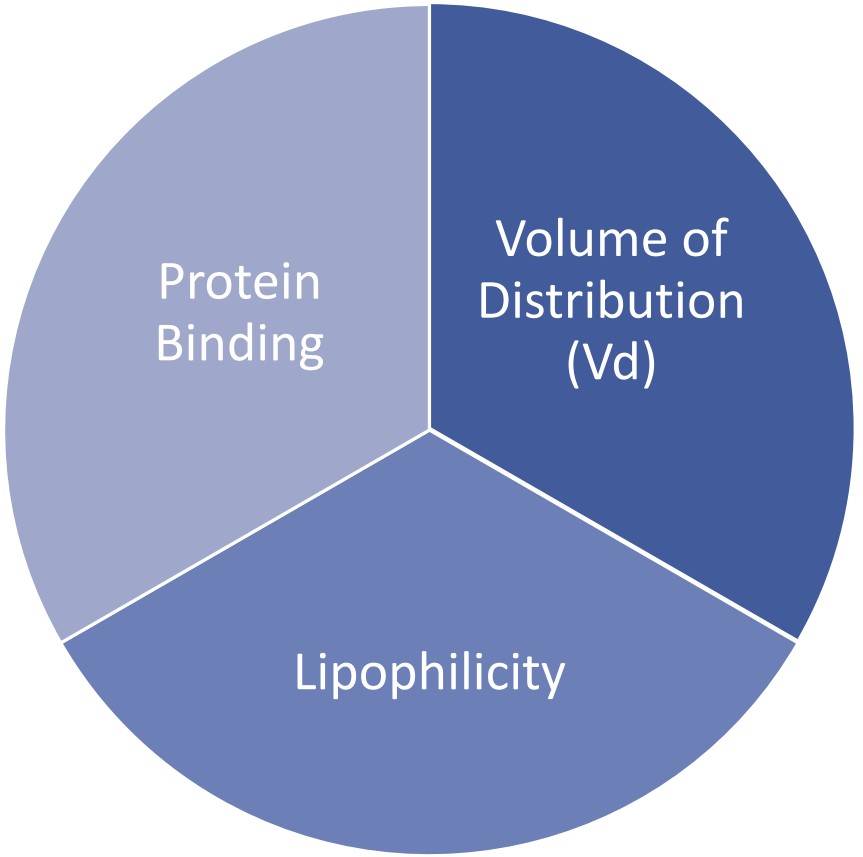
Protein Binding

- Protein binding (PB), dictated as a percentage, describes the amount of drug bound to plasma protein
  - ↑ protein binding = ↓ plasma concentration
  - ↓ protein binding = ↑ plasma concentration
- Highly protein bound drugs have been associated with decreased drug concentrations in the setting of ECMO
  - Reduced protein concentrations due to critical illness as well as loss to ECMO circuit
  - Deposition of protein within ECMO circuit leading to further drug sequestration of highly protein-bound medications

Sources: Dzierba AL, et al. *Crit Care*. 2017;21(1):66.
Shekar K, et al. *Crit Care*. 2015;19(1):164.
Zeitlinger MA, et al. Antimicrob Agents Chemother. 2011;55(7):3067-74.

Drug Considerations in ECMO

- Due to pharmacokinetic (PK) principles, some agents may require dose adjustment in the setting of ECMO
- The effects of the ECMO circuit must be considered in conjunction with drug PK parameters to understand expected drug concentrations and efficacy
- Favorable medication PK parameters in ECMO
  - ↓ lipophilicity
  - ↓ protein binding



Sources: Dzierba AL, et al. *Crit Care*. 2017;21(1):66.
Sieg A, et al. *Crit Care Nurse*. 2019;39(2):29-43.
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PK Effects and Drug Dosing in ECMO

PK Changes

Vd	Expected Vd change	Loading Dose Adjustment
≤ 1 L/kg (≤ 70 L)	Moderate to large increase	Increase likely necessary
> 1 L/kg (> 70 L)	Minimal increase	Adjustment likely not necessary

Drug Sequestration

	Protein Binding		
LogP	**< 30%**	**30 – 70%**	**> 70%**
< 1	Minimal	Minimal to moderate	Moderate
1 – 2	Minimal to moderate	Moderate	Moderate to high
> 2	Moderate	Moderate to high	High

Drug sequestration	Dose adjustment
Minimal	Adjustment likely not required
Moderate	Increased dose, frequency, or rate may be necessary
High	Increased dose, frequency, or rate likely necessary

Source: Ha MA, et al. *Pharmacotherapy*. 2017;37(2):221–35.

Analgesics

Analgesics

- Critically ill patients may experience various painful procedures throughout their admission
- Based on the available literature, the Society of Critical Care Medicine (SCCM) recommends multimodal pain management in the care of critically ill patients
  - Opioids remain the mainstay of analgesia management, but other non-opioids may be utilized in conjunction
- Extracorporeal Life Support Organization (ELSO) does not delineate specific agents recommended for analgesia management in ECMO patients

Sources: Devlin JW, et al *Crit Care Med*. 2018;46(9):e825-73.
Extracorporeal Life Support Organization. *ELSO*. 2017;1.4:1-26.

Analgesic Options

Analgesic	Mechanism of Action	Typical Dosing	Considerations
Fentanyl	Mu-opioid agonist	Infusion: 25 – 300 mcg/hr Bolus: 25 – 100 mcg	Accumulation with hepatic impairment
Morphine		Infusion: 1 – 10 mg/hr	Accumulation with hepatic impairment; active metabolite accumulation with renal impairment; hypotension; bradycardia
Hydromorphone		Infusion: 0.5 – 4 mg/hr	Accumulation with hepatic impairment
Ketamine	Non-competitive NMDA receptor antagonist	Infusion: 0.04 – 2.5 mg/kg/hr	Emergence reactions; hypertension

Sources: Devlin JW, et al *Crit Care Med*. 2018;46(9):e825-73.
Lexi-Drugs Online [database on the Internet]. Hudson (OH): Lexi-Comp, Inc; 2022 [cited 2022 April]. Available from: http://online.lexi.com.

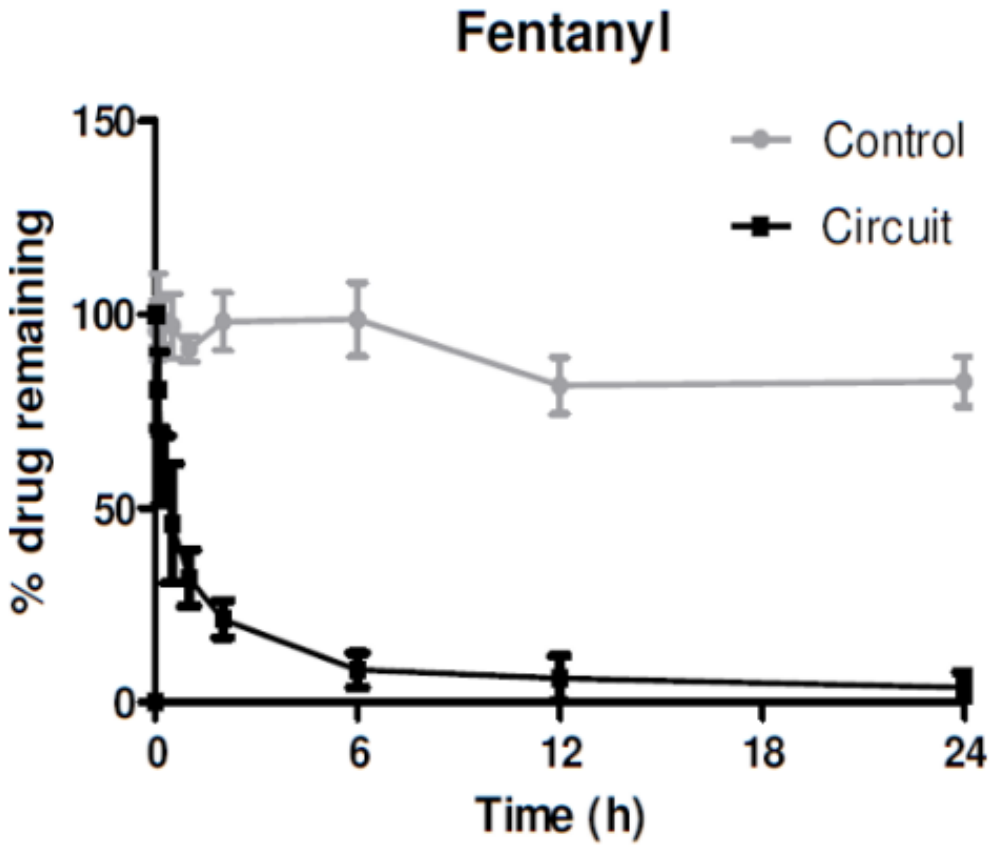
Analgesics Effects in ECMO

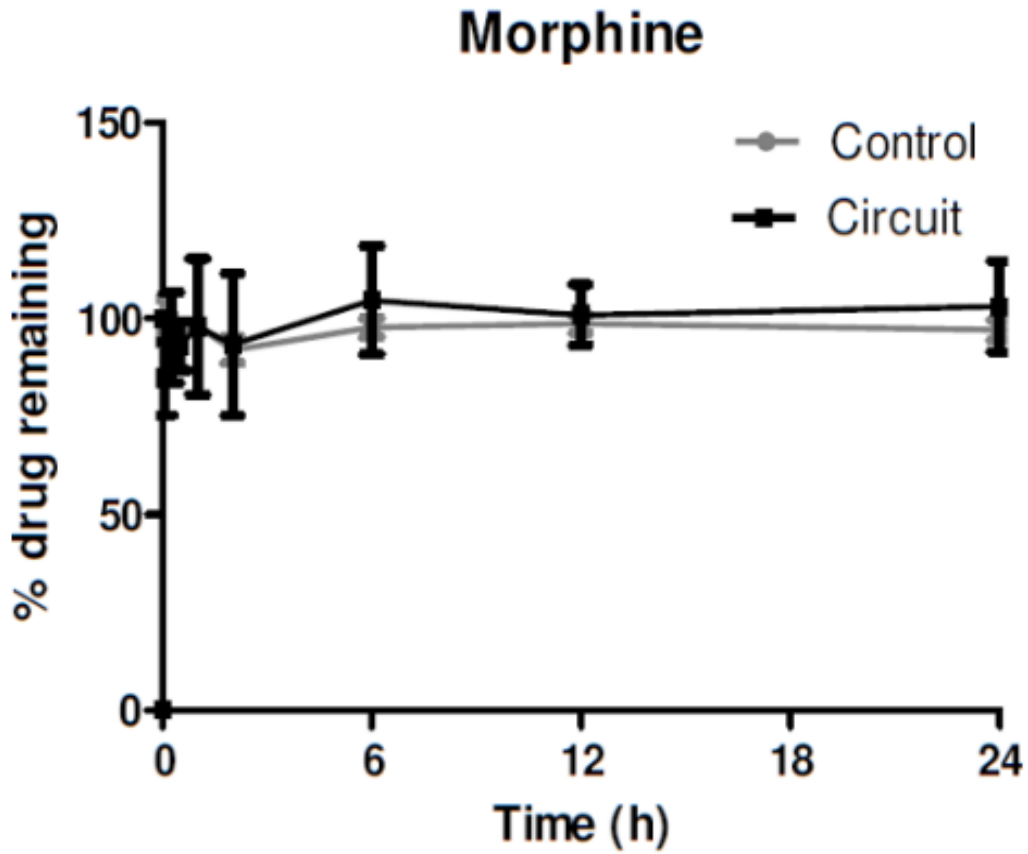
Drug	PK Parameters*	Expected Effects	Actual Effects	Dosage Adjustments
Fentanyl	Vd 280 – 420 L (↑) PB 79 – 87% (↑) LogP 4 (↑)	Minimal change in Vd; High drug sequestration	Significant drug loss (~80 – 100% loss in circuit)	Consider increased doses or alternative agents
Morphine	Vd 70 – 420 L (↑) PB 20 – 35% LogP 0.8 (↓)	Minimal to moderate change in Vd; Limited drug sequestration	Minimal drug loss and/or sequestration (~6 – 8% loss in circuit)	Typical dosing regimens in non-ECMO patients may be appropriate

*Vd standardized for 70 kg patient

Sources: Shekar K, et al. *Crit Care*. 2015;19(1):164.
Mehta NM, et al. *Intensive Care Med*. 2007;33(6):1018-24.
Wildschut ED, et al. *Intensive Care Med*. 2010;36:2109-16.
Lexi-Drugs Online [database on the Internet]. Hudson (OH): Lexi-Comp, Inc; 2022 [cited 2022 April]. Available from: http://online.lexi.com.
National Library of Medicine [database on the Internet]. Bethesda (MD): PubChem; 2022 [cited 2022 April]. Available from: https://pubchem.ncbi.nlm.nih.gov/.
Dagan O, et al. *Crit Care Med*. 1994;22(7):1099-101.

Fentanyl & Morphine in ECMO





Source: Shekar K, et al. *Crit Care*. 2012; 16(5): R194.

Analgesics Effects in ECMO

Drug	PK Parameters*	Expected Effects	Actual Effects	Dosage Adjustments
Hydromorphone	Vd 280 L (↑) PB 8 – 19% (↓) LogP 1.8 (↓)	Minimal change in Vd; Minimal drug sequestration	Minimal drug loss (~20 – 25% loss in circuit)	No dosage adjustments likely needed
Ketamine	Vd 168 L (↑) PB 27% (↓) LogP 2.2 (↑)	Minimal to moderate change in Vd; Moderate drug sequestration	No data available regarding drug loss	Limited data to support need for dose adjustment

*Vd standardized for 70 kg patient

Sources: Tellor B, et al. F1000Res. 2015;4:16.
Heith CS, et al. *J Pediatr Pharmacol Ther*. 2019;24(4):290-5.
Lexi-Drugs Online [database on the Internet]. Hudson (OH): Lexi-Comp, Inc; 2022 [cited 2022 April]. Available from: http://online.lexi.com.
National Library of Medicine [database on the Internet]. Bethesda (MD): PubChem; 2022 [cited 2022 April]. Available from: https://pubchem.ncbi.nlm.nih.gov/.

Comparison of Hydromorphone versus Fentanyl-based Sedation in Extracorporeal Membrane Oxygenation

LANDOLF KM, ET AL. *PHARMACOTHERAPY*. 2020;40(5):389-97.

Methods

Study Design

- Single-center retrospective observational study at a large academic tertiary medical center between 2016 and 2018

Objective

- Evaluate the number of days alive delirium-free and coma-free (DFCF), and narcotic and sedative exposure in patients on ECMO receiving fentanyl or hydromorphone

Intervention

- Analgesia (continuous infusion narcotic) ± sedation titrated to a goal Sedation-Agitation Scale (SAS) score of 3 to 4

Source: Landolf KM, et al. *Pharmacotherapy*. 2020;40(5):389-97.

Patient Population

Inclusion Criteria

Age 18 years or older

ECMO for > 48 consecutive hours

Continuous infusion fentanyl or hydromorphone for at least 6 hours (required to respective drug for at least 75% of time on sedation)

Exclusion Criteria

Cannulated > 24 hours prior to transfer to study hospital

Administration of continuous infusion paralytics

Source: Landolf KM, et al. *Pharmacotherapy*. 2020;40(5):389-97.

Outcomes

Primary Efficacy Outcome

- Days alive DFCF between fentanyl and hydromorphone group at days 7 and 14
  - Scales utilized:
    - Sedation: Riker Sedation-Agitation Scale (SAS)
    - Delirium: Intensive Care Delirium Screening Checklist (ICDSC)

Drug Utilization Outcomes

- Median narcotic, benzodiazepine, and antipsychotic use through day 14

Propensity Matching:
Type of ECMO (VA vs VV), open chest, SOFA score, age, hepatic failure, and weight

Source: Landolf KM, et al. *Pharmacotherapy*. 2020;40(5):389-97.

Baseline Characteristics

Characteristic	Hydromorphone (n = 54)	Fentanyl (n = 54)	P-value
Age, yrs – median (IQR)	55 (40 – 64)	51 (41 – 64)	0.0002
Female sex – n (%)	22 (40.7)	16 (29.6)	0.22
Weight, kg – median (IQR)	91.2 (78 – 113)	88 (68 – 98.5)	0.006
SOFA score – median (IQR)	11 (8 – 12)	10 (7 – 13)	0.01
ICU length of stay, days – median (IQR)	17.4 (10.6 – 33)	20 (9.9 – 44.1)	0.002
Hepatic failure – n (%)	6 (11.1)	11 (20.4)	0.1
CRRT – n (%)	24 (44.4)	22 (40.7)	0.02
ECMO indication – n (%) Acute respiratory failure Cardiac	 35 (64.8) 11 (20.4)	 27 (50) 16 (29.6)	0.32
ECMO duration, days – median (IQR)	7.2 (4 – 10.6)	5.7 (3.9 – 9.8)	0.009
VV ECMO – n (%)	33 (61.1)	31 (57.4)	0.26

Source: Landolf KM, et al. *Pharmacotherapy*. 2020;40(5):389-97.

Results

Endpoint	Hydromorphone (n = 54)	Fentanyl (n = 54)	P-value
Primary outcome – Delirium-free coma-free days			
Day 7, n (%)	125 (53.2)	85 (42.1)	0.006
Day 14, n (%)	163 (54.1)	113 (45.7)	0.059
Coma-free days (%)	71.5	62.1	< 0.005
Delirium-free days (%)	64.8	58.9	0.14
Drug utilization outcomes – opioid, benzodiazepine, and antipsychotic requirements			
Fentanyl equivalents, mcg – median (IQR)	554.8 (286.7 – 905.1)	2291.1 (1052.5 – 4022.7)	< 0.005
Midazolam equivalents, mg – median (IQR)	1.1 (0.5 – 2.5)	1.4 (0.7 – 3.7)	0.35
Chlorpromazine equivalents, mg – median (IQR)	91.4 (40.3 – 243)	134.9 (36.8 – 231.8)	0.80

Source: Landolf KM, et al. *Pharmacotherapy*. 2020;40(5):389-97.

Conclusions

- Hydromorphone, as compared to fentanyl, use in patients receiving ECMO support was associated with more delirium-free and coma-free days
- Significantly less narcotic exposure was noted in patients receiving hydromorphone
- Based on the results of this retrospective review in conjunction with pharmacokinetics of hydromorphone, a hydromorphone-based analgosedation approach may be more suitable for patients on ECMO

Source: Landolf KM, et al. *Pharmacotherapy*. 2020;40(5):389-97.

Sedatives

Sedatives

- Upon cannulation and the first 12 to 24 hours of ECMO, patients should be adequately sedated to achieve a level of light anesthesia in intubated patients
  - Target levels of sedation may differ based on patient characteristics (i.e. intubated vs non-intubated, paralysis)
- Beyond the above time period, sedation should then be minimal, but adequate to avoid removal of cannulas or occlusion of perfusion lines
- Appropriate dosing of sedatives is essential to ensure avoidance of oversedation, which may increase time to extubation and increase tracheostomy rates

Sources: Devlin JW, et al *Crit Care Med*. 2018;46(9):e825-73.
Extracorporeal Life Support Organization. *ELSO*. 2017;1.4:1-26.

Sedation Options

Sedative	Mechanism of Action	Typical Dosing	Considerations
Propofol	GABA agonist	Infusion: 5 – 50 mcg/kg/min	Caution with renal and hepatic impairment; hypotension; hypertriglyceridemia; propofol related infusion syndrome
Midazolam	Benzodiazepine; GABA-A agonist	Infusion: 1 – 8 mg/hr	Caution with renal and hepatic impairment; delirium
Dexmedetomidine	Selective alpha2-adrenoreceptor agonist	Infusion: 0.2 – 1.5 mcg/kg/hr	Caution with hepatic impairment; hypotension; bradycardia; hyperthermia

Sources: Devlin JW, et al *Crit Care Med*. 2018;46(9):e825-73.
Lexi-Drugs Online [database on the Internet]. Hudson (OH): Lexi-Comp, Inc; 2022 [cited 2022 April]. Available from: http://online.lexi.com.

Sedatives Effects in ECMO

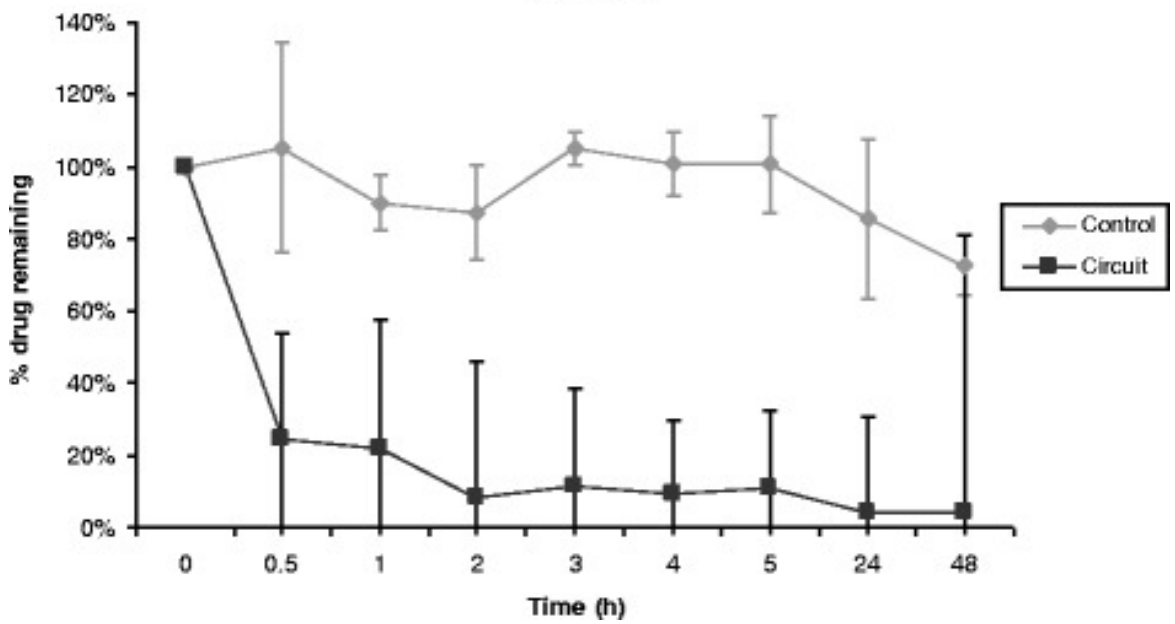
Drug	PK Parameters*	Expected Effects	Actual Effects	Dosage Adjustments
Propofol	Vd 140 – 700 L (↑) PB 97 – 99% (↑) LogP 3.8 (↑)	Minimal change in Vd; High drug sequestration	Significant drug loss (~40 – 90% loss in circuit)	Consider higher doses or alternative agents
Midazolam	Vd 70 – 217 L (↑) PB 97% (↑) LogP 3.9 (↑)	Minimal change in Vd; High drug sequestration	Significant drug loss (~90% loss in circuit)	Consider higher doses or alternative agents

*Vd standardized for 70 kg patient

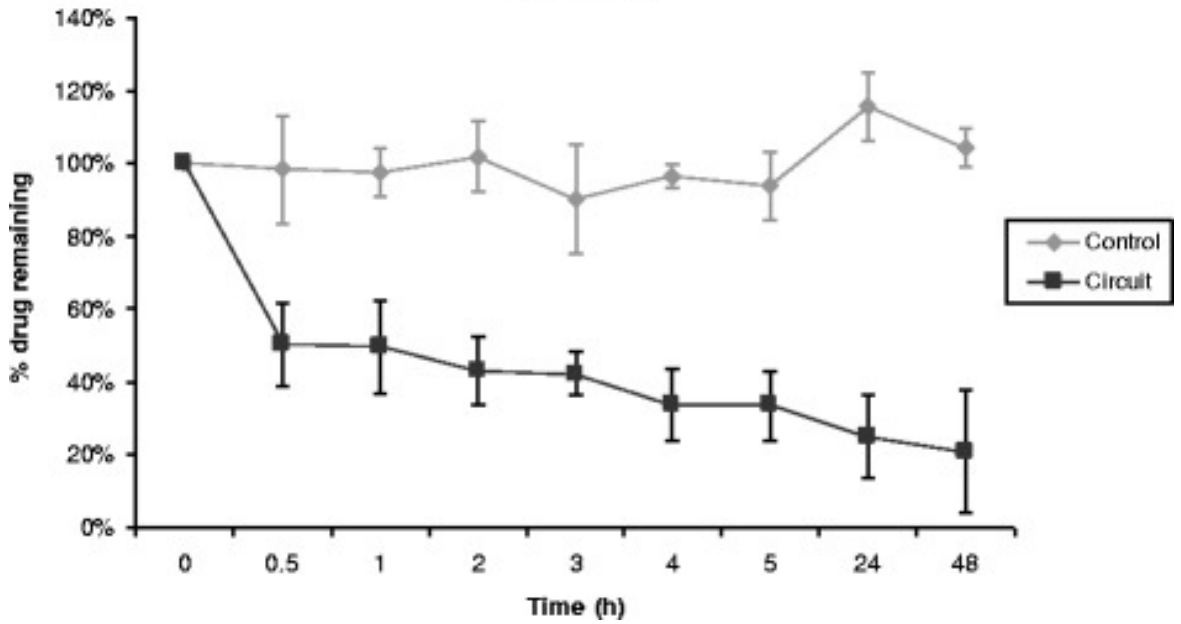
Sources: Lemaitre F, et al. *Crit Care*. 2015; 19(1): 40.
Hynynen M, et al. *Can J Anaesth*. 1994;41(7):583-8.
Shekar K, et al. *Crit Care*. 2015;19(1):164.
Lexi-Drugs Online [database on the Internet]. Hudson (OH): Lexi-Comp, Inc; 2022 [cited 2022 April]. Available from: http://online.lexi.com.
National Library of Medicine [database on the Internet]. Bethesda (MD): PubChem; 2022 [cited 2022 April]. Available from: https://pubchem.ncbi.nlm.nih.gov/.

Propofol & Midazolam in ECMO

Propofol



Midazolam



Source: Shekar K, et al. *Crit Care*. 2015;19(1):164.

Sedatives Effects in ECMO

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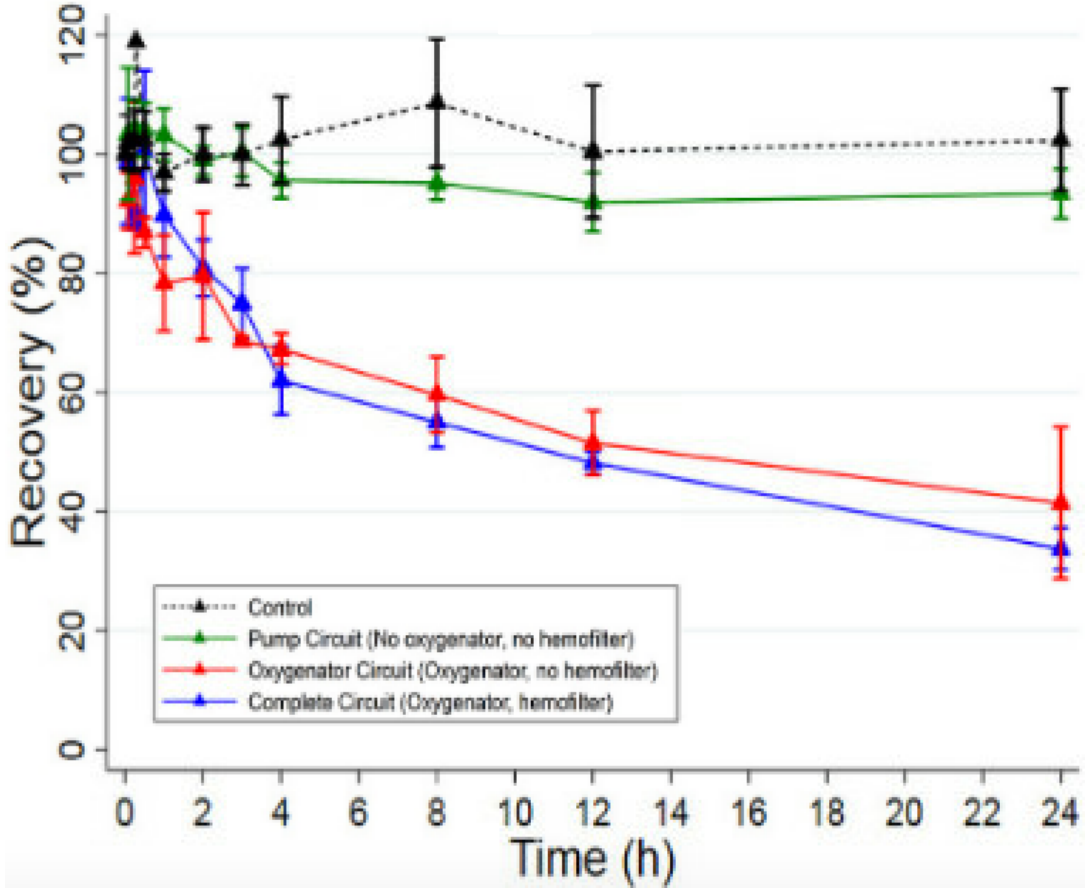
Midazolam	Vd 70 – 217 L (↑) PB 97% (↑) LogP 3.9 (↑)	Minimal change in Vd; High drug sequestration	Significant drug loss (~90% loss in circuit)	Consider higher doses or alternative agents
Dexmedetomidine	Vd 118 L (↑) PB 94% (↑) LogP 3.1 (↑)	Minimal change in Vd; High drug sequestration	Significant drug loss (~80 – 85% loss in circuit)	Consider higher doses or alternative agents

*Vd standardized for 70 kg patient

Sources: Dallefeld SH, et al. *Perfusion*. 2020;35(3):209-16. Lexi-Drugs Online [database on the Internet]. Hudson (OH): Lexi-Comp, Inc; 2022 [cited 2022 April]. Available from: http://online.lexi.com. Shekar K, et al. *Crit Care*. 2015;19(1):164. Lemaitre F, et al. *Crit Care*. 2015; 19(1): 40.
Hynynen M, et al. *Can J Anaesth*. 1994;41(7):583-8. Wagner D, et al. *Perfusion*. 2013;28(1):40-6.
Wildschut ED, et al. *Intensive Care Med*. 2010;36:2109-16. National Library of Medicine [database on the Internet]. Bethesda (MD): PubChem; 2022 [cited 2022 April]. Available from: https://pubchem.ncbi.nlm.nih.gov/.

Dexmedetomidine in ECMO



Source: Dallefeld SH, et al. *Perfusion*. 2020;35(3):209-16.

Analgesics & Sedatives PK

Sedative	Vd*	Protein Binding	LogP
Hydromorphone	280 L	8 – 19 %	1.8
Morphine	70 – 420 L	20 – 35%	0.8
Ketamine	168 L	27%	2.2
Fentanyl	280 – 420 L	79 – 87%	4.0
Dexmedetomidine	118 L	94%	3.1
Midazolam	70 – 217 L	97%	3.9
Propofol	140 – 700 L	97 – 99%	3.8

*Vd standardized for 70 kg patient

Sources: Lexi-Drugs Online [database on the Internet]. Hudson (OH): Lexi-Comp, Inc; 2022 [cited 2022 April]. Available from: http://online.lexi.com.
National Library of Medicine [database on the Internet]. Bethesda (MD): PubChem; 2022 [cited 2022 April]. Available from: https://pubchem.ncbi.nlm.nih.gov/.
Welliver M, et al. *Curr Rev Nurs Anesth*. 2019;42(14):161-76.

Analgesics and Sedatives Considerations

Therapeutic considerations

- Analgesics and sedatives may be initiated as continuous infusions in patients receiving ECMO therapy with titration parameters
- Hydrophilic medications are anticipated to have less of an effect when administered in the setting of ECMO

Evaluation and adjustments

- Response to these agents should be evaluated utilizing a validated tool
- Adjustments to dosing should be made as necessary for the specific patient to achieve the desired effect with the minimal amount of drug necessary
- Daily sedation vacations should be incorporated to assess neurologic status
- Higher than anticipated doses may be required given drug PK

Antimicrobials

Antimicrobials

- Patients requiring ECMO therapy may require antimicrobials for a variety of reasons
  - Acute respiratory distress syndrome (ARDS) has been shown to be precipitated by pneumonia in a large percentage of patients, which may require pulmonary support via VV-ECMO
  - The implantation of multiple invasive devices with ECMO, patients may also be at increased risk of nosocomial infections
- Prophylactic antibiotics are not recommended solely for the presence of ECMO, but may be considered if other indications exist
- Dependent on the indication, various antibiotics may be considered, and their PK parameters must be acknowledged when dosing them appropriately

Sources: Hines MH, et al. *ELSO Infectious Disease Task Force*. Available from: https://www.elso.org/Portals/0/Files/Infection-Control-and-Extracorporeal-Life-Support.pdf
Gomez F, et al. *Antibiotics (Basel)*. 2022;11(3):338.
Combes A, et al. *Intensive Care Med*. 2020;46(11):2048-57.

Beta-lactams Effects in ECMO

Drug	PK Parameters*	Expected Effects	Actual Effects	Dosage Adjustments
Cefazolin	Vd 13.5 L (↓) PB 80% (↑) LogP -0.4 (↓)	Large increase in Vd; Moderate drug sequestration	Moderate drug loss (~20% loss in circuit)	No dosage adjustment necessary
Cefepime	Vd 18 L (↓) PB 20% (↓) LogP -0.1 (↓)	Large increase in Vd; Minimal drug sequestration	Appropriate efficacy with minimal toxicity concentrations (~40 – 90% efficacy and ~1 – 44% toxicity)	No dosage adjustment necessary

*Vd standardized for 70 kg patient

Sources: Booke H, et al. *Sci Rep*. 2021;11(1):16981. Mehta NM, et al. *Intensive Care Med*. 2007;33(6):1018-24. Wildschut ED, et al. *Intensive Care Med*. 2010;36:2109-16. Cheng V, et al. *Int J Antimicrob Agents*. 2021;58(6):106466. Lexi-Drugs Online [database on the Internet]. Hudson (OH): Lexi-Comp, Inc; 2022 [cited 2022 April]. Available from: http://online.lexi.com. National Library of Medicine [database on the Internet]. Bethesda (MD): PubChem; 2022 [cited 2022 April]. Available from: https://pubchem.ncbi.nlm.nih.gov/.

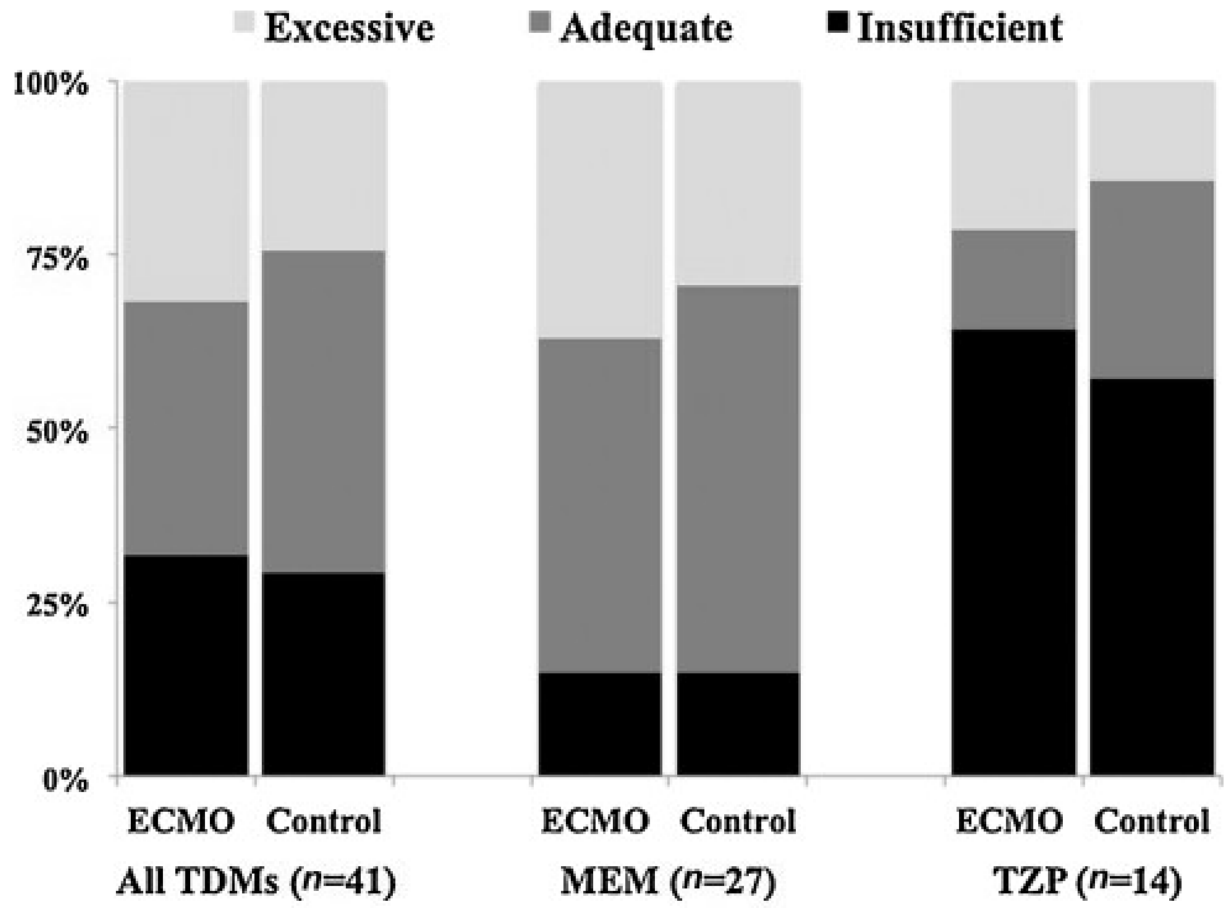
Beta-lactams Effects in ECMO

Drug	PK Parameters*	Expected Effects	Actual Effects	Dosage Adjustments
Piperacillin-tazobactam	Vd 17 L (↓) PB_P 26 – 33% (↓) PB_T 31 – 32% (↓) $LogP_P$ 0.5 (↓) $LogP_T$ -2 (↓)	Large increase in Vd; Minimal drug sequestration	No significant changes in PK parameters (Vd, clearance, $t_{1/2}$)	No dosage adjustment necessary; Consider dose optimization/ extended infusion
Meropenem	Vd 15 – 20 L (↓) PB 2% (↓) LogP -2.4 (↓)	Large increase in Vd; Minimal drug sequestration	Minimal drug loss (~20% loss in circuit)	No dosage adjustment necessary

*Vd standardized for 70 kg patient

Sources: Shekar K, et al. *Crit Care*. 2012; 16(5): R194. Donadello K, et al. *Int J Antimicrob Agents*. 2015;45(3):278-82. Hahn J, et al. 2021. doi: 10.21203/rs.3.rs-498132/v1. Wildschut ED, et al. *Intensive Care Med*. 2010;36:2109-16. Lexi-Drugs Online [database on the Internet]. Hudson (OH): Lexi-Comp, Inc; 2022 [cited 2022 April]. Available from: http://online.lexi.com. National Library of Medicine [database on the Internet]. Bethesda (MD): PubChem; 2022 [cited 2022 April]. Available from: https://pubchem.ncbi.nlm.nih.gov/.

Beta-lactams in ECMO



MEM: meropenem
TZP: piperacillin-tazobactam

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

Vancomycin Effects in ECMO

Drug	PK Parameters*	Expected Effects	Actual Effects	Dosage Adjustments
Vancomycin	Vd 21 – 70 L (↓) PB 55% LogP -2.6 (↓)	Large increase in Vd; Moderate drug sequestration	No significant drug loss (~1 – 9% loss in circuit)	No dosage adjustment necessary; Utilize therapeutic drug monitoring

*Vd standardized for 70 kg patient

Sources: Mehta NM, et al. *Intensive Care Med*. 2007;33(6):1018-24.
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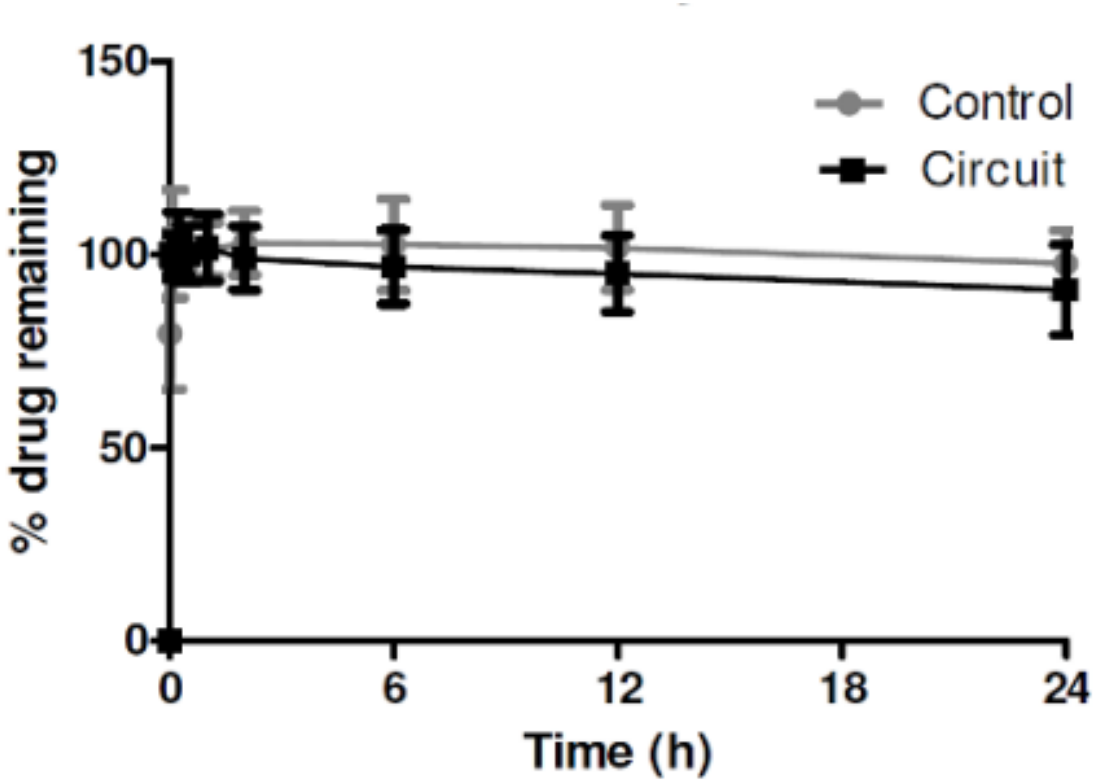
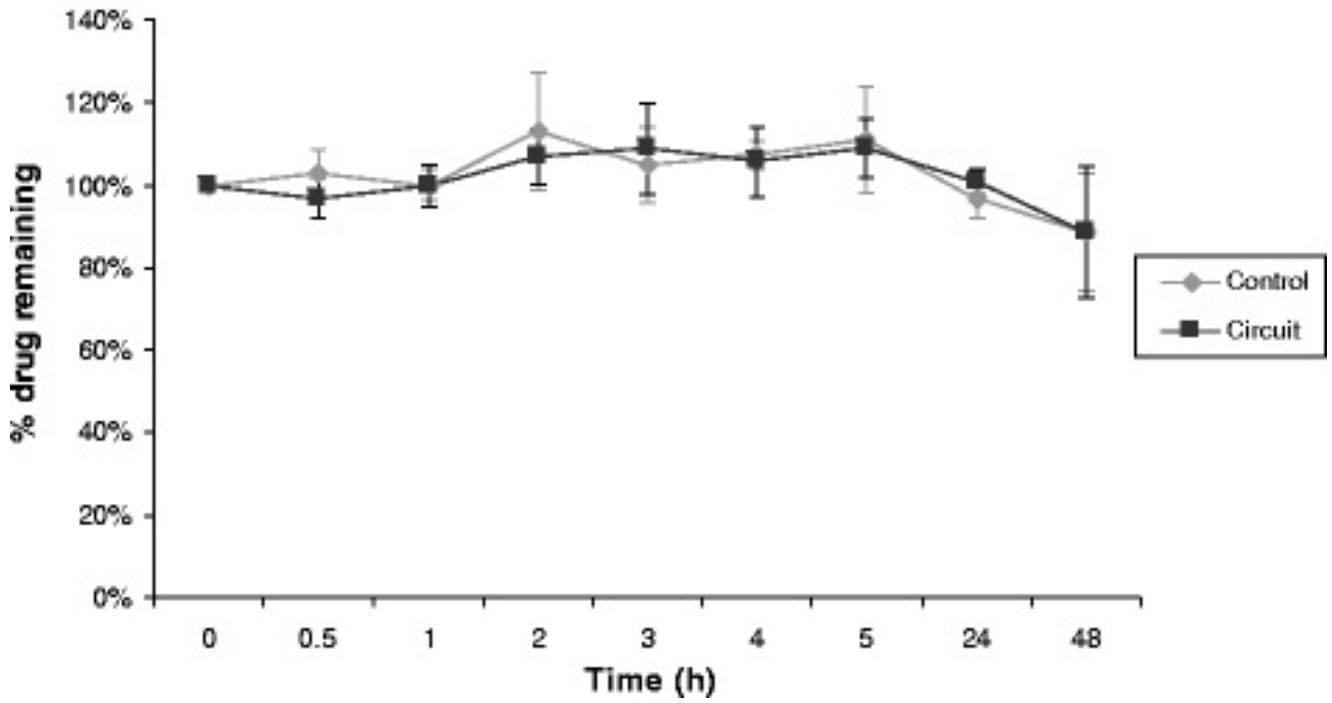
Vancomycin in ECMO





Sources: Shekar K, et al. *Crit Care*. 2012; 16(5): R194.
Lemaitre F, et al. *Crit Care*. 2015; 19(1): 40.

Aminoglycosides Effects in ECMO

Drug	PK Parameters*	Expected Effects	Actual Effects	Dosage Adjustments
Amikacin	Vd 17.5 L (↓) PB 0 – 11% (↓) LogP -7.9 (↓)	Large increase in Vd; Minimal drug sequestration	No significant drug loss or accumulation (C_{max} and adequate/ excessive peak concentrations similar)	No dosage adjustment necessary; Utilize therapeutic drug monitoring
Gentamicin	Vd 14 – 21 L (↓) PB < 30% (↓) LogP -4.1 (↓)	Large increase in Vd; Minimal drug sequestration	No data available in adult population; Neonatal data difficult to extrapolate to adults given patient PK/PD	
Tobramycin	Vd 14 – 21 L (↓) PB < 30% (↓) LogP -6.2 (↓)	Large increase in Vd; Minimal drug sequestration		

*Vd standardized for 70 kg patient

Sources: Gélisse E, et al. *Intensive Care Med*. 2016;42:946-8. Lexi-Drugs Online [database on the Internet]. Hudson (OH): Lexi-Comp, Inc; 2022 [cited 2022 April]. Available from: http://online.lexi.com.
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Fluoroquinolones Effects in ECMO

Drug	PK Parameters*	Expected Effects	Actual Effects	Dosage Adjustments
Ciprofloxacin	Vd 147 – 189 L (↑) PB 20 – 40% LogP -1.1 (↓)	Minimal increase in Vd; Minimal drug sequestration	No significant drug loss (~20% lost in circuit ex-vivo)	No dosage adjustment necessary
Levofloxacin	Vd 89 L PB 24 – 38% LogP -0.4 (↓)	Moderate increase in Vd; Minimal drug sequestration	No data available yet	No dosage adjustment likely necessary

*Vd standardized for 70 kg patient

Sources: Shekar K, et al. *Crit Care*. 2015;19(1):164.
Lexi-Drugs Online [database on the Internet]. Hudson (OH): Lexi-Comp, Inc; 2022 [cited 2022 April]. Available from: http://online.lexi.com.
National Library of Medicine [database on the Internet]. Bethesda (MD): PubChem; 2022 [cited 2022 April]. Available from: https://pubchem.ncbi.nlm.nih.gov/.

Antifungals

Drug	PK Parameters*	Expected Effects	Actual Effects	Dosage Adjustments
Fluconazole	Vd 42 L (↓) PB 11 – 12% (↓) LogP 0.4 (↓)	Moderate increase in Vd; Minimal drug sequestration	No significant drug loss (~2-5% loss in circuit)	No dosage adjustment necessary
Voriconazole	Vd 322 L (↑) PB 58% LogP 1.5	Minimal increase in Vd; Moderate drug sequestration	Significant drug loss (~70% loss in circuit; saturation of circuit over time may increase levels)	Initial dose may require adjustment; Utilize therapeutic drug monitoring
Micafungin	Vd 27.3 L (↓) PB > 99% (↑) LogP -1.6 (↓)	Large increase in Vd; Moderate to high drug sequestration	Significant drug loss in complete circuit (~75% loss in as compared to ~2-10% loss in circuit without hemofilter)	Increased dosages may be necessary

*Vd standardized for 70 kg patient

Sources: Watt KM, et al. *J Extra Corpor Technol*. 2017;49(3):150-9.
Mehta NM, et al. *Intensive Care Med*. 2007;33(6):1018-24.
Spriet I, et al. *J Antimicrob Chemother*. 2009;63(4):767-70.
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Antimicrobials Considerations

- Antimicrobial use should be reserved for patients with an indication for therapy
- In addition to the expected effects based on PK parameters and actual effects seen within clinical studies, antimicrobial therapy should be guided by multiple factors
  - Patient clinical status
  - Patient response to therapy
  - Therapeutic drug monitoring levels, if available

Conclusions

Summary

- ECMO is an invasive mechanical circulatory support device that may be utilized in patients with severe cardiopulmonary failure despite other therapies
- The presence of ECMO, alongside drug PK parameters, may affect medication efficacy due to increased Vd and drug sequestration within the ECMO circuit
- Data is very limited assessing medications in the presence of ECMO and dosing remains a challenge due to the paucity in specific guideline recommendations
- Medications administered in ECMO should be analyzed for their PK parameters and considered for necessary dose adjustments based on the available literature

Assessment Questions

Question One

What is the difference in indication between VV-ECMO and VA-ECMO?

A. VV-ECMO provides cardiopulmonary support whereas VA-ECMO provides pulmonary support
B. VA-ECMO provides cardiopulmonary support whereas VV-ECMO provides pulmonary support
C. VV-ECMO provides cardiac support whereas VA-ECMO provides cardiopulmonary support
D. VA-ECMO provides cardiac support whereas VV-ECMO provides cardiopulmonary support

Question One: Response

What is the difference in indication between VV-ECMO and VA-ECMO?

A. VV-ECMO provides cardiopulmonary support whereas VA-ECMO provides pulmonary support

B. VA-ECMO provides cardiopulmonary support whereas VV-ECMO provides pulmonary support

C. VV-ECMO provides cardiac support whereas VA-ECMO provides cardiopulmonary support

D. VA-ECMO provides cardiac support whereas VV-ECMO provides cardiopulmonary support

Question Two

Which of the following are drug factors that may be affected by the presence of ECMO?

A. Volume of distribution
B. Protein binding
C. Lipophilicity
D. All of the above

Question Two: Response

Which of the following are drug factors that may be affected by the presence of ECMO?

A. Volume of distribution
B. Protein binding
C. Lipophilicity
D. **All of the above**

Question Three

Which of the following intravenous medication's pharmacokinetics is most likely to be affected by ECMO?

A. Cefazolin
B. Meropenem
C. Midazolam
D. Ciprofloxacin

Question Three: Response

Which of the following intravenous medication's pharmacokinetics is most likely to be affected by ECMO?

A. Cefazolin
B. Meropenem
C. **Midazolam**
D. Ciprofloxacin

Question Four

Since propofol is a lipophilic and highly protein bound medication, what may be expected when used in the setting of ECMO?

A. Sequestration of the drug in the ECMO circuit leading to lower levels in the patient
B. Accumulation of the drug in the patient leading to oversedation
C. The pharmacokinetics of highly protein bound drugs are not affected by ECMO

Question Four: Response

Since propofol is a lipophilic and highly protein bound medication, what may be expected when used in the setting of ECMO?

A. **Sequestration of the drug in the ECMO circuit leading to lower levels in the patient**
B. Accumulation of the drug in the patient leading to oversedation
C. The pharmacokinetics of highly protein bound drugs are not affected by ECMO

Question Five

A 56-year-old male with acute renal failure is being initiated on VA-ECMO for acute refractory cardiopulmonary failure. He has been hypotensive requiring vasopressor support since cannulation. Which of the following analgesics would be most appropriate to initiate based on each medication's pharmacokinetic profile in the presence of ECMO as well as this patient's current clinical status?

A. Ketamine
B. Morphine
C. Hydromorphone
D. Fentanyl

Question Five: Response

A 56-year-old male with acute renal failure is being initiated on VA-ECMO for acute refractory cardiopulmonary failure. He has been hypotensive requiring vasopressor support since cannulation. Which of the following analgesics would be most appropriate to initiate based on each medication's pharmacokinetic profile in the presence of ECMO as well as this patient's current clinical status?

A. Ketamine
B. Morphine
C. **Hydromorphone**
D. Fentanyl

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Thank you!

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