NEONATAL PK/PD APPLICATIONS IN UNIQUE SCENARIOS

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Disclosures

- I consult for Wolters Kluwer Clinical Drug Information, Inc. for Lexi-drug™ as a member of the Neonatal Advisory Panel.
- I will be discussing off-label use of medications.

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LEARNING OBJECTIVES

- Review basic pharmacokinetic (PK) and pharmacodynamic (PD) properties and how they apply to neonates.
- Analyze how PK/PD are altered in unique settings, including:
  - Extracorporeal life support (ECLS)
  - Therapeutic hypothermia (TH)
  - Acute kidney injury (AKI)
  - Renal replacement therapies (RRT)

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PK/PD REVIEW

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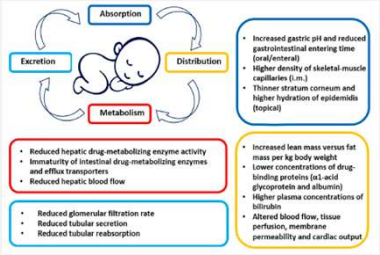
PK/PD REVIEW

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**limination/**E**xcretion



Mork ML, et al. Frotiers Pharmacol. 2022.

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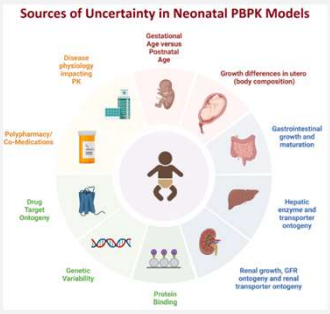
PK/PD REVIEW

- Neonatal PK-PD is complex
- Changes occur across the neonatal spectrum



Dinh J, et al. Pharmaceutics. 2023.

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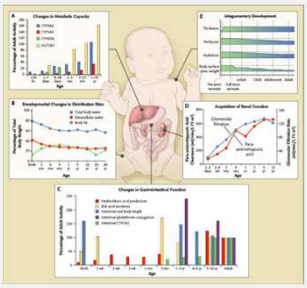
PK/PD REVIEW



Kearns GL, et al. *N Eng J Med.* 2003.

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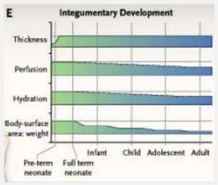
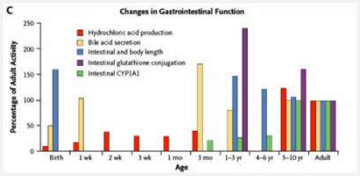
PK/PD REVIEW

- Absorption





Kearns GL, et al. *N Eng J Med.* 2003.

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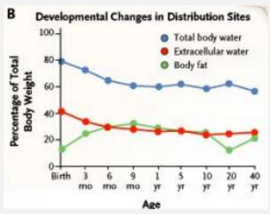
PK/PD REVIEW

- Distribution



Kearns GL, et al. *N Eng J Med.* 2003.

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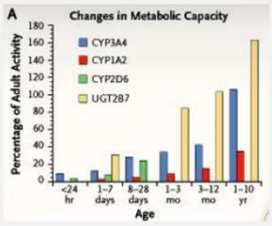
PK/PD REVIEW

- Metabolism



Kearns GL, et al. *N Eng J Med.* 2003.

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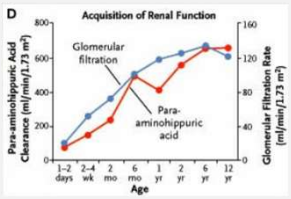
PK/PD REVIEW

- Elimination



Kearns GL, et al. *N Eng J Med.* 2003.

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EXTRACORPOREAL LIFE SUPPORT (ECLS)

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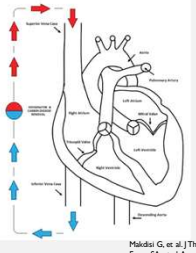
TYPES OF ECMO

Venovenous (VV) ECMO

Venous circulation (via right atrium or internal jugular vein) → Deoxygenated blood → Oxygenator (via right atrium or femoral vein) → Oxygenated blood → Provides only pulmonary support



Makdisi G, et al. J Thorac Dis. 2015.
Esper SA, et al. Anesth Analg . 2014

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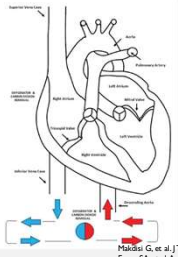
TYPES OF ECMO

Venoarterial (VA) ECMO

Arterial circulation (via ascending aorta or common femoral artery) → Deoxygenated blood → Oxygenator (via right atrium, femoral vein, or internal jugular vein) → Oxygenated blood → Provides cardiac and respiratory support



Makdisi G, et al. J Thorac Dis. 2015.
Esper SA, et al. Anesth Analg . 2014

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FACTORS AFFECTING ABSORPTION ON ECMO

- Gastric pH
- Gut edema
- Mucosal injury
- Perfusion to GI tract

POTENTIAL FOR REDUCED ABSORPTION

Castro, et al. Clin Pharmacokinet. 2023.

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FACTORS AFFECTING DISTRIBUTION ON ECMO

- Volume of distribution (Vd) increased
  - Hemodilution from circuit priming
  - Hemodilution from frequent need for transfusions
  - Drug sequestration
  - Systemic inflammation
  - Hydrophilicity of drugs

Volume of Distribution and Loading Doses

Vd	Expected Change in Volume of Distribution	Loading Dose Adjustment
≤ 1 L/kg	Moderate to large increase	Dose increase likely required
> 1 L/kg	Minimal increase	Dose adjustment likely not required

Ha MA, et al. Pharmacotherapy. 2017.
Shekar K, et al. J. Crit Care. 2012.

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FACTORS AFFECTING DISTRIBUTION ON ECMO

- Drug sequestration = drug absorption to ECMO components

Circuit Factors	Drug Factors
• Tubing	• Lipophilicity
• Oxygenator	• Protein binding
	• Molecule size
	• Degree of ionization

Ha MA, et al. Pharmacotherapy. 2017.
Shekar K, et al. Crit Care. 2012.
Shekar K, et al. Crit Care. 2015.

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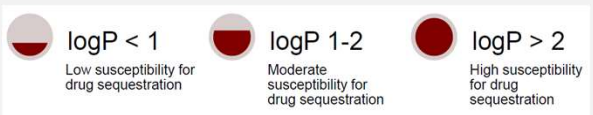
FACTORS AFFECTING DISTRIBUTION ON ECMO

- Drug sequestration is affected by drug lipophilicity
  - Octanol/water partition coefficient (logP) = measure of lipophilicity



- Higher logP = may require higher doses

Patel JS, et al. Ann Pharmacother . 2022.

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FACTORS AFFECTING DISTRIBUTION ON ECMO

- Drug sequestration is affected by protein binding
  - % of protein binding correlates with likelihood of drug sequestration

  - Higher % protein binding may require higher doses

Patel JS, et al. Ann Pharmacother . 2022.

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FACTORS AFFECTING DISTRIBUTION ON ECMO

- Drug sequestration may be affected by molecule size and ionization
  - Tendency for inverse relationship with likelihood of sequestration (e.g., large ionized molecules will ↓ likelihood of drug sequestration)
  - Insufficient data to characterize specific effects

Maintenance Dose Adjustment Based on Drug Sequestration	
Drug Sequestration	Dose Adjustment
Minimal	Dose adjustment likely not required
Moderate	Increased dose, frequency, or infusion rate may be required
High	Increased dose, frequency, or infusion rate likely required

Ha MA, et al. Pharmacotherapy. 2017.
Shekar K, et al. J Crit Care. 2012.

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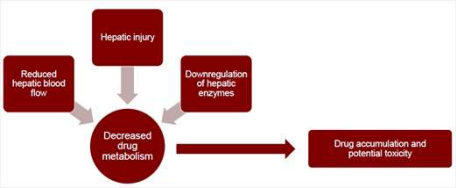
FACTORS AFFECTING METABOLISM ON ECMO

- Reduced hepatic function



Ha MA, et al. Pharmacotherapy. 2017.
Shekar K, et al. Crit Care. 2012.

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FACTORS AFFECTING ELIMINATION ON ECMO

- Reduced drug clearance → accumulation of drug
- VA ECMO: continuous blood flow
  - Altered tissue perfusion
  - Decreased glomerular filtration
  - Upregulated renin-angiotensin system

Ha MA, et al. Pharmacotherapy. 2017.
Shekar K, et al. Crit Care. 2012.

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FACTORS AFFECTING ELIMINATION ON ECMO

- Renal replacement therapy (RRT) required in some ECMO patients
  - Renal hypoperfusion (non-pulsatile blood flow)
  - Microemboli within renal vasculature
  - Nephrotoxic medications
  - Nephropathy
- Will discuss further in RRT section on dose adjustments!

Ha MA, et al. Pharmacotherapy. 2017.
Shekar K, et al. Crit Care. 2012.

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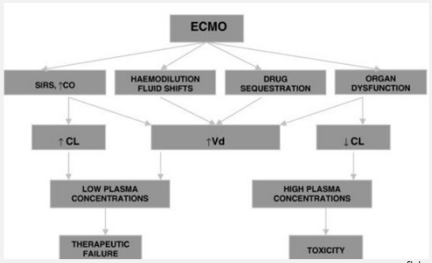
OVERALL PK/PD IMPACTS OF ECLS



Shekar K, et al. Crit Care. 2012.

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COMMON ECMO MEDICATION ALTERATIONS

Medication	Expected PK/PD Alterations on ECLS	Dose Adjustments
Heparin	• ↓ antithrombin • ↑Vd • ↑ clearance rate	• May need higher doses • Consider supplementation of antithrombin or FFP • May need to switch to alternative (e.g., bivalirudin) if heparin resistance
Gentamicin	• ↑↑Vd • ↑ drug sequestration • ↓ clearance	• May need a larger dose given less frequently (should assess through drug level monitoring)
Beta-lactams (e.g., ampicillin, ceftazidime)	• ↑Vd • May have ↓ clearance • Drug sequestration varies	• Drug-specific information may indicate that larger doses are need to ensure adequate levels (refer to primary literature) • May consider drug level monitoring in severe infections
Vancomycin	• ↑Vd • ↑ drug sequestration • ↓ clearance	• Need frequent drug level monitoring and will likely need less frequent dosing as renal function worsens over time

McMichael ABV, et al. ASAIO Journal. 2022. Esper SA, et al. Anesth Analg . 2014. Raffaeli G, et al. Front Pediatr. 2019.
Chlebowski MM, et al. Crit Care. 2020. Patel JS, et al. Ann Pharmacother 2022. Yalcin N, et al. BMJ Paediatr Open. 2022.

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COMMON ECMO MEDICATION ALTERATIONS

Medication	Expected PK/PD Alterations on ECLS	Dose Adjustments
Fentanyl	• ↑Vd • ↑↑ drug sequestration	• Likely will need larger doses of sedation on ECLS than for non-ECLS patients • Consider initial larger boluses (or even priming with sedation) at initiation of ECLS • Some centers avoid fentanyl due to concern for significant drug sequestration (my center just primes with fentanyl and have tolerated staying on fentanyl for most patients)
Morphine	• ↑Vd • ↑ drug sequestration	
Hydromorphone	• ↑Vd • ↑ drug sequestration	
Midazolam	• ↑↑Vd • ↑↑ drug sequestration	
Dexmedetomidine	• ↑Vd • ↑↑ drug sequestration	

Buscher H, et al. ASAIO Journal. 2013.
Cheng V, et al. J Thorac Dis. 2018.
Patel JS, et al. Ann Pharmacother . 2022.
Raffaeli G, et al. Front Pediatr. 2019.
Yalcin N, et al. BMJ Paediatr Open. 2022.

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COMMON ECMO MEDICATION ALTERATIONS

Medication	Expected PK/PD Alterations on ECLS	Dose Adjustments
Phenobarbital	• ↑Vd • ↑ drug sequestration	• Consider regular drug level monitoring with dose adjustments as indicated
Phenytoin	• ↑↑Vd • ↑↑ drug sequestration	• Consider regular drug level monitoring with dose adjustments as indicated
Levetiracetam	• Possibly negligible or slight ↑Vd and/or drug sequestration	• No empiric changes
Lacosamide	• Unknown	• No empiric changes

Patel JS, et al. Crit Care. 2022.
Raffaeli G, et al. Front Pediatr. 2019.
Yalcin N, et al. BMJ Paediatr Open. 2022.

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THERAPEUTIC HYPOTHERMIA

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THERAPEUTIC HYPOTHERMIA (TH)

- Provides neuroprotection and ↓ extent of brain injury in neonates with hypoxic ischemic encephalopathy (HIE)
- AAP guidelines for use:
  - History of acute perinatal event
  - Profound metabolic/mixed acidemia (pH < 7 or base deficit ≥16) from umbilical artery
  - Apgar score < 5 or assisted ventilation at 10 minutes of life
  - Neurologic abnormalities demonstrating moderate-severe HIE (seizures, hypotonia, Sarnat scoring)
  - Use at < 35 weeks' gestation should be done in a research setting with parental consent

Committee on Fetus and Newborn, et al. *Pediatrics*. 2014.

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