Challenges of Drug Dosing During Extracorporeal Membrane Oxygenation

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Disclosures

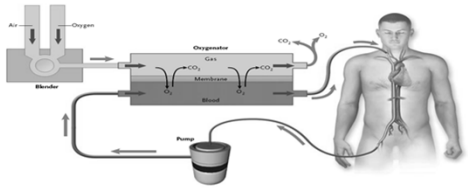
- None

Objectives

- Evaluate the use of extracorporeal membrane oxygenation (ECMO) for patients with respiratory failure
- Describe the effects of altered pharmacokinetics and pharmacodynamics of drugs commonly used during ECMO
- Formulate recommendations on dosing strategies based on current literature

What is ECMO?

Blood is drained from venous circulation
Pumped through a membrane
Returned to the patient



N Engl J Med 2011;365:1905-14

ECMO Configurations

Veno-venous (V-V)
Respiratory

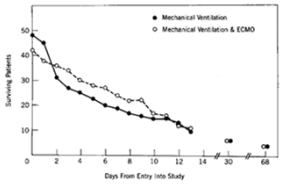
Veno-Arterial (VA)
Respiratory and hemodynamic

Respiratory Indications for ECMO

- Severe acute respiratory distress syndrome
  - Bacterial / viral / aspiration pneumonia
  - Shock
  - Trauma
  - Pancreatitis
  - Asthma
- Bridge to lung transplantation
- Asthma
- Pulmonary hypertension
- Pulmonary embolism

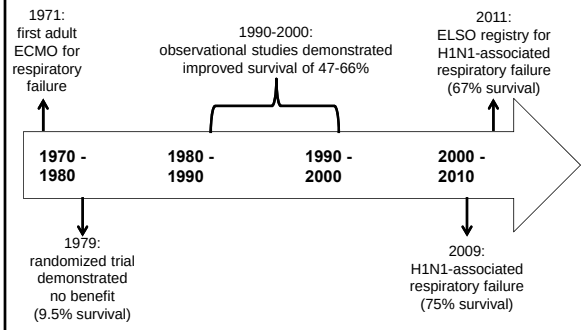
ECMO for Severe ARDS

- 90 patients with acute respiratory failure
- Randomized to conventional MV vs. ECMO with MV



JAMA 1979;242:2193-6

Improved Survival Over Time



Advances in Critical Care
Improvements in Outcomes

- Ventilator management
- Fluid management
- Prevention of infection (CLABSIs, VAPs, CAUTIs)
- Trauma management
- Sedation protocols
- Physical & occupational therapy

Does ECMO Improve Clinical Outcomes in Severe ARDS?

CESAR study

Conventional ventilation or ECMO for Severe Adult Respiratory failure

- Randomized controlled trial
- 180 adults enrolled with severe respiratory failure
- Primary Outcome: survival without severe disability at 6 months
  - ECMO: 57/90 patients (63%)
  - Conventional ventilation: 41/87 patients (47%)

Lancet 2009;374:1351-63

CESAR Trial: Results

- Relative risk reduction in favor of ECMO
  0.69 (0.05–0.97; p = 0.03)

Reasonable Conclusion

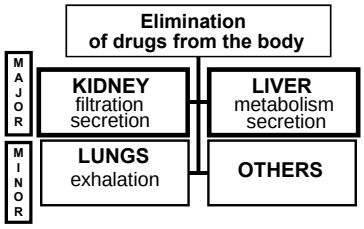
Supports a strategy of transferring patients with severe cases of ARDS to a specialized center capable of conducting ECMO as part of a standardized management protocol

Lancet 2009;374:1351-63

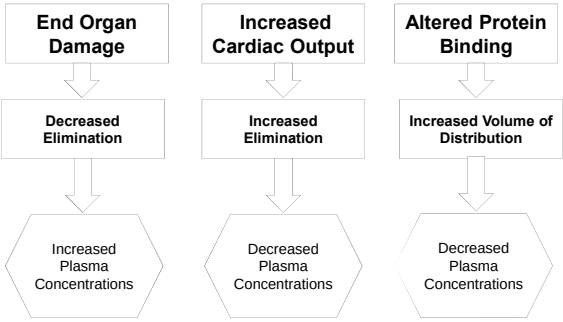
Pharmacotherapy for Patients on ECMO

Basic Principals of Drug Elimination

- Elimination of drugs depends on:
  - Clearance and volume of distribution

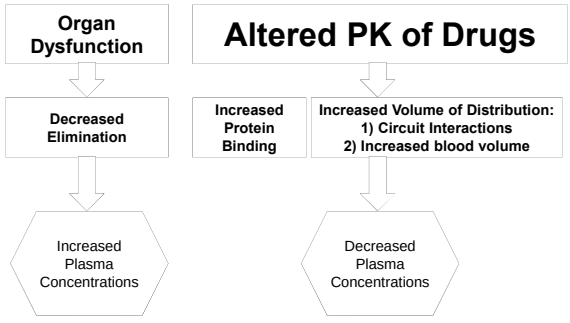


Drug Alterations in the Critically Ill



Crit Care Med 2009;37:840-51
Clin Pharmacokinet 1998;34:25-56

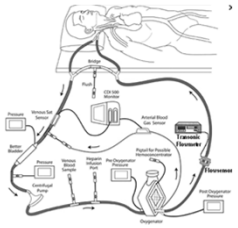
Drug Alterations With ECMO



Intensive Care Med 2007;33:1018-1024
Perfusion 2005;20:309-15

Factors Influencing Drug Disposition

- Volume and type of priming solution
- Site of drug administration
- Membrane oxygenator
- PVC tubing
- Better Bladder®
- Heat exchangers
- Flow rates



ELSO Specialist Training Manual 3rd edition

Predicting Drug Alterations

	Hydrophilic Drugs	Lipophilic Drugs
General PK	Low Vd CL dependent on renal function	High Vd CL dependent on hepatic function
ICU PK	Increased Vd CL dependent on renal function	Unchanged Vd CL dependent on renal function
ECMO PK	Increased Vd (hemodilution) CL unchanged	Increased Vd and CL (circuit-related factors)
	B-lactam antibiotics Aminoglycosides Glycopeptides Linezolid Morphine	Fluoroquinolones Tigecycline Propofol Midazolam Fentanyl

Analgesia and Sedation Management

Analgesia and Sedation During ECMO

Patient comfort and ventilatory optimization
Minimize catheter malposition or dislodgement
Optimize ECMO flows and decrease oxygen consumption

GOAL

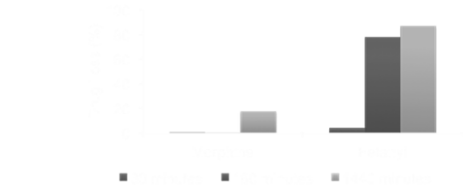
OVERSEDATION

UNDERSEDATION

Crit Care Med. 2002;30:119-141

Analgesic Loss With ECMO

Simulated neonatal ECMO circuit:
PVC tubing
Silicone membrane oxygenator



Intensive Care Med 2007;33:1018-24

Sedative Loss With ECMO

Simulated neonatal ECMO circuit:
PVC tubing
Silicone membrane oxygenator
Bladder reservoir
Heat exchanger

Perfusion 2000;15:21-6

Dexmedetomidine Loss With ECMO

Simulated adult ECMO circuit:

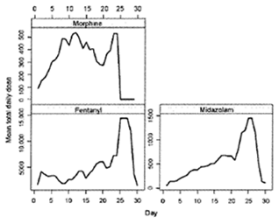
PVC tubing
Quadrox-D® oxygenator
Heat exchanger

24-hour Dexmedetomidine Loss			
New Circuit		Old Circuit	
Pre-oxygenator	Post-oxygenator	Pre-oxygenator	Post-oxygenator
76-89%	67-93%	67-88%	77-82%

Perfusion 2012; [Epub ahead of print]

Increased Sedation Requirements

Retrospective analysis of 29 patients receiving ECMO
Local protocol = heavy sedation at ECMO initiation

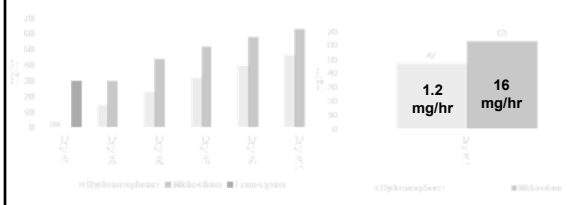


- Daily dose of midazolam increased 18 mg (95%CI 8-29); p=0.001
- Daily dose of morphine increased 29 mg (95%CI 4-53); p=0.02
- No difference in fentanyl daily dose

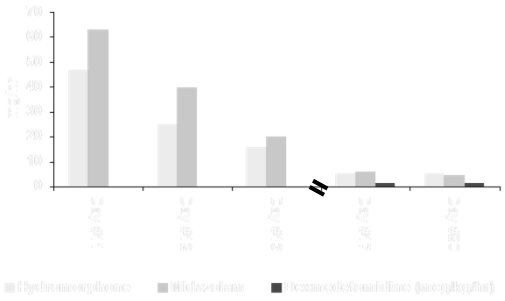
Anaesth Intensive Care 2012;40:648-55

Patient Experience

40 year old man initiated on ECMO for severe respiratory failure due to pneumonia



Patient Experience



Limitations of Studies

- Simulated circuit does not account for metabolism or elimination of the drugs
- Early circuit studies use neonatal ECMO circuit
- Lack of standardized ECMO configuration
- Variable priming solutions
- Changing blood flow rates
- Unknown implications of aged circuits
- Lack of clinical outcomes associated with observational experiences
- Absence of control subjects

Recommendations: Sedation

- Consider minimal exposure to sedatives

Recommendations: Sedation

- Use continuous infusions for analgesia (fentanyl / hydromorphone) and sedation (midazolam) in patients with severe ARDS at ECMO initiation
- Requirements usually exceed standard doses
- Establish daily sedative goals with potential sedative interruption
- Anticipate significant dose reduction at ECMO discontinuation
- Monitor for signs of delirium / withdrawal

Antimicrobial Dosing

Neonatal Studies With ECMO

Drug	Volume of Distribution	Elimination Half Life	Recommendations
Gentamicin[1]	Increased	Decreased	Extend dosing interval and monitor drug concentrations
Vancomycin[2]	Increase to no change	Decreased	Extend dosing interval and monitor drug concentrations
Cefotaxime[3]	Increased	No change	Standard dosing regimens

[1]*Clin Pharmacokinet* 2003;42:403-17
[2]*Pharmacother* 1998;18:1082-6
[3]*Antimicrob Agents Chemother* 2010;54:1734-41

Vancomycin With ECMO

- 45 neonates, children, and adults receiving V-V and V-A ECMO
- Results
  - Increased volume of distribution
  - Decreased elimination half-life
- Limitations
  - Fluctuating renal function
  - Variable vancomycin trough goals
  - Older ECMO equipment

Br J Clin Pharmacol 2005;60:265-75

Adult Case Reports With ECMO

Drug	Configuration	Drug Concentrations
Caspofungin[1]	V-V	No effect
Voriconazole[1]	V-V	Decreased
Caspofungin / voriconazole / liposomal amphotericin B[2]	V-A	Caspofungin and voriconazole levels low to undetectable. No effect on liposomal amphotericin B.
Tigecycline[3]	V-V	No effect

[1]*J Antimicrob Chemother* 2009;63:767-70
[2]*Intensive Care Med* 2009;35:183-4
[3]*J Antimicrob Chemother* 2012;67:1047-8

Limitations of Studies

- Very few drugs studied in adult patients
- Simulated circuit does not account for metabolism or elimination of the drugs
- Early circuit studies use neonatal ECMO circuit
- Lack of standardized ECMO configuration
- Variable priming solutions
- Changing blood flow rates
- Unknown implications of aged circuits
- Lack of clinical outcomes associated with observational experiences
- Absence of control subjects

Implications of Inappropriate Antimicrobial Dosing

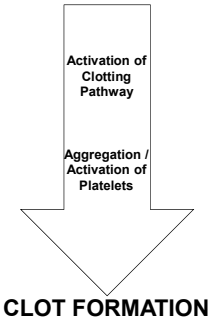
- Therapeutic failures
- Toxicity
- Development of resistance

Recommendations: Antimicrobials

- Use published PK data in the critically ill to make dosage adjustments
- Therapeutic drug monitoring is critical for dose adjustments
- Monitor the clinical status of the patient

Management of Anticoagulation During ECMO

Effect of ECMO on Coagulation



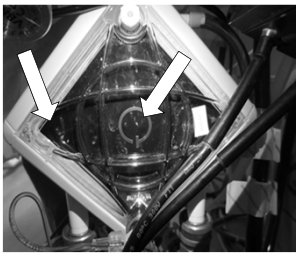
CLOT FORMATION

BLEEDING

Clotting Factor Consumption

Thrombo-cytopenia

Need for Anticoagulation



Qudrox-D® Oxygenator

- Anticoagulation is necessary to prevent clotting
- An ideal drug would inhibit platelet and coagulation activation without causing bleeding

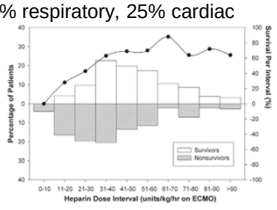
Unfractionated Heparin

- Accelerates the action of endogenous antithrombin (AT) and inhibits the formation of clotting factors
- Rapid acting
- Inexpensive
- Reversible

Heparin and Survival

- Retrospective review of 604 pediatric patients on V-A ECMO
- Conducted over a 20 year period
- Indication for ECMO: 75% respiratory, 25% cardiac
- Goal ACT 180-220 sec
- 58% overall survival

Higher doses of heparin (not ACT) was predictive of survival (p<0.0001)



Ann Thorac Surg 2007;83:912-20

Heparin Management

- Loading dose at the time of cannulation
  - 50-100 units/kg
- Maintenance infusion
  - 7.5-10 units/kg/hr
- Depending on bleeding risk at ECMO initiation, heparin may be delayed

Heparin Monitoring

- Activated clotting time (ACT)
- Activated partial thromboplastin time (aPTT):
  - Higher aPTT levels for lower extracorporeal blood flow
  - Lower aPTT levels have been used successfully (40-60 sec)
- Anti-Xa level
- Antithrombin
- Thromboelastogram (TEG)

Direct Thrombin Inhibitors

- Binds to thrombin independently of AT
- Alternative anticoagulant for patients that cannot receive heparin or in the treatment of heparin-induced thrombocytopenia
- Argatroban
  - Use limited to case series and case reports
  - Higher bleeding rates in ICU patients (11%)
- Bivalirudin
  - When compared to heparin, no difference in platelet count or thrombotic complications

Pharmacother 2009;29:1073-81
Crit Care 2011;15:R275

Limitations of Current Studies

- Lack of adult studies
- No clear consensus on optimal heparin dose and level of anticoagulation

Recommendations: Anticoagulation

- Anticoagulation should be initiated at the commencement of ECMO to prevent thromboembolic complications
- Heparin remains the primary agent for ECMO anticoagulation
- Maintaining low levels of anticoagulation with routine monitoring reduces the risk of bleeding complications

Summary

- Dose adjustments during adult ECMO are not well defined
- Experience limited to case reports/series
- More thorough pharmacokinetic studies needed with modern technology
- Drug regimens need to be individualized
- Additional extracorporeal devices add to complexity of drug regimens