Drug Selection & Dosing in Patients on Extracorporeal Membrane Oxygenation

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Disclosure Statement

- I have no actual or potential conflict of interest in relation to this presentation.
- Off-label use of medication will be discussed during this presentation.
Learning Objectives

- Discuss the indications for ECMO therapy
- Explain different modalities of ECMO support
- Identify alterations in pharmacokinetics and pharmacodynamics associated with ECMO
- Implement appropriate dose modifications for medications frequently used in critically ill patients, including antimicrobials, sedatives and analgesics
ECMO

- Extracorporeal membrane oxygenation
- Type of extracorporeal life support (ECLS)
- Temporary support for respiratory and/or cardiorespiratory failure
- High-risk, complex therapy considered in patients unresponsive to optimal care

ECMO Circuit

Types of ECMO

### Cardiac Failure
- Cardiogenic shock
- Acute myocardial infarction
- Peripartum cardiomyopathy
- Decompensated heart failure
- Fulminant myocarditis
- Pulmonary hypertension and right heart failure
- Pulmonary embolus with hemodynamic compromise
- Cardiac arrest (assisted CPR)
- Medication overdose
- Non ischemic cardiomyopathy including sepsis induced cardiomyopathy
- Support post cardiac surgery

**Bridge to:**
- **Recovery**
  - Acute MI after revascularization, myocarditis, postcardiotomy
- **Transplant**
  - Unrevascularizable acute MI, chronic heart failure
- **Implantable circulatory support**
  - VAD, TAH

### Respiratory Failure
- Consider when risk of mortality ≥50%
  - PaO2/FiO2 <150 on FiO2 >90% and/or Murray score 2-3
- Indicated when risk of mortality >80%
  - PaO2/FiO2 <100 on FiO2 >90% and/or Murray score 3-4 despite optimal care for 6+ hours
- CO2 retention despite high Pplat (>30)
- Severe air leak syndromes
- Immediate cardiac/respiratory collapse
- Severe ARDS
- Status asthmaticus
- Bridge to lung transplantation
- Post lung transplantation primary graft failure
- Diffuse alveolar hemorrhage
- Pulmonary hypertensive crisis
- Pulmonary embolism
- Severe bronchopleural fistula

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**Indications**

# Contraindications

## Cardiac Failure

**Absolute:**
- Unrecoverable heart and not a candidate for transplant or VAD
- Advanced age
- Chronic organ dysfunction (emphysema, cirrhosis, renal failure)
- Compliance (financial, cognitive, psychiatric, or social limitations)
- Prolonged CPR without adequate tissue perfusion

**Relative:**
- Contraindication for anticoagulation
- Advanced age
- Obesity

## Respiratory Failure

**Absolute:**
- None, consider risks/benefits for each patient individually

**Relative:**
- MV at high settings (FiO2 >90%, Pplat >30) for 7+ days
- Major pharmacologic immunosuppression (ANC<400/mm³)
- Recent or expanding CNS hemorrhage
- Non-recoverable comorbidity (major CNS damage, terminal malignancy)
- Age

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Complications

- Bleeding
- Thrombosis
- Infection
- Acute limb ischemia, compartment syndrome
- Pulmonary edema

# ECMO for Cardiac Failure

<table>
<thead>
<tr>
<th>Design</th>
<th>Systematic review of case reports, case-series and case-control studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1494</td>
</tr>
<tr>
<td>Patients</td>
<td>Patients with cardiogenic shock or cardiac arrest</td>
</tr>
<tr>
<td></td>
<td>Cardiogenic shock: 533 patients; Cardiac arrest: 675 patients; Mixed: 286 patients</td>
</tr>
<tr>
<td>Results</td>
<td>Weaned from ECMO:</td>
</tr>
<tr>
<td></td>
<td>• All patients: Mean, 76.8 ± 4.2%; Median, 66.0% (IQR 50%, 100%)</td>
</tr>
<tr>
<td></td>
<td>Survival to discharge:</td>
</tr>
<tr>
<td></td>
<td>• All patients: Mean 47.4 ± 4.5%, Median 40.0% (IQR 20%, 75%)</td>
</tr>
<tr>
<td></td>
<td>• Cardiogenic shock: Mean 51.6 ± 6.5%, Median 38.5% (IQR 23.4%, 76.3%)</td>
</tr>
<tr>
<td></td>
<td>• Cardiac arrest: Mean 44.9 ± 6.7%; Median 42.3% (IQR 15.4%, 75%)</td>
</tr>
</tbody>
</table>

ECMO for Respiratory Failure

<table>
<thead>
<tr>
<th>Design</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>90</td>
</tr>
</tbody>
</table>
| Patients| Severe acute respiratory failure due to pneumonia, pulmonary embolism, thoracic or severe extra-thoracic trauma, sepsis, inhalation injury, fluid overload/congestive failure  
65% of patients had bacterial, viral, aspiration, or interstitial pneumonia  
7% had posttraumatic ARDS  
Average MV time before study entry: 7 vs. 9.6 days in control and ECMO groups, respectively |
| Results | ECMO group (n=42) vs. Conventional management (n=48)  
- Mortality rate: 90% vs. 92%  
- Mortality rate was 100% for posttraumatic ARDS patients  
- 7 of 8 surviving patients received no more than 7 days of MV before enrollment |

# ECMO for Respiratory Failure

**Design**
- RCT

**N**
- 180

**Patients**
- Severe but reversible respiratory failure due to pneumonia (61%), other ARDS (28%), trauma (7%), and other causes (4%)
- Excluded TBI patients and patients requiring high FiO2 ventilation for more than 7 days
- Only 76% of patients in the ECMO group actually received ECMO support

**Results**
- Consideration for ECMO (n=90) vs. Conventional management (n=90)
  - 6 month survival without disability: 63% vs. 47%
  - 6 month survival rate: 63% vs. 50%

# ECMO for Respiratory Failure

<table>
<thead>
<tr>
<th>Design</th>
<th>Retrospective cohort study</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>102</td>
</tr>
</tbody>
</table>
| Patients        | Trauma patients without an acute intracranial hemorrhage (ICH)  
65% of patients had bacterial, viral, aspiration, or interstitial pneumonia  
7% had posttraumatic ARDS  
Average MV time before study entry: 7 vs. 9.6 days in control and ECMO groups, respectively |
| Results         | ECMO group (n=26) vs. Conventional management (n=76)  
- Unadjusted survival rate: 58% vs. 55%  
- Multivariate logistic regression: ECMO independently associated with improved survival  
- Propensity scores matching for age and P/F ratio compared 2 subgroups of 17 patients  
  - 60 day survival rate post-injury: was 64.7% vs. 23.5%  
- Hemorrhagic complications were more frequent in the ECMO group  
- Pulmonary complications were higher in the conventional ventilation group |

### ECMO for Respiratory Failure

<table>
<thead>
<tr>
<th>Design</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>29</td>
</tr>
<tr>
<td>Patients</td>
<td>Trauma patients with severe ARDS refractory to maximal mechanical ventilator support. Average MV time before ECMO initiation was 7.5 days. Average time between diagnosis of severe ARDS and ECMO initiation was 1.9 days.</td>
</tr>
</tbody>
</table>
| Results | ECMO group (n=15) vs. Conventional management (n=14)  
- Mortality rate: 13.3% vs. 64% (p = 0.01)  
- No difference in ICU-free days, hospital LOS, and ventilator-free days  
- Hemorrhagic complications were more frequent in the ECMO group |

Pharmacotherapy Considerations During ECMO

- Significant PK alterations can occur during ECMO support
- Considerable implications for critically ill patients, especially those with life-threatening infections
- Balance toxicity versus the risk of therapeutic failure
<table>
<thead>
<tr>
<th>Patient Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age, weight</td>
</tr>
<tr>
<td>• Allergies</td>
</tr>
<tr>
<td>• Comorbidities</td>
</tr>
<tr>
<td>• ECMO indication</td>
</tr>
<tr>
<td>• Organ dysfunction, renal replacement therapy</td>
</tr>
<tr>
<td>• Pregnancy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pharmacology</td>
</tr>
<tr>
<td>• Drug interactions</td>
</tr>
<tr>
<td>• Toxicity profile</td>
</tr>
<tr>
<td>• Pharmacokinetics</td>
</tr>
<tr>
<td>• Vd</td>
</tr>
<tr>
<td>• Physiochemical properties</td>
</tr>
<tr>
<td>• Lipophilicity</td>
</tr>
<tr>
<td>• Protein binding</td>
</tr>
<tr>
<td>• Molecular size</td>
</tr>
<tr>
<td>• Ionization</td>
</tr>
<tr>
<td>• Chemical stability</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Circuit Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Circuit age, type</td>
</tr>
<tr>
<td>• Oxygenator</td>
</tr>
<tr>
<td>• Tubing</td>
</tr>
<tr>
<td>• Priming</td>
</tr>
</tbody>
</table>

## Mechanisms of Pharmacokinetic Changes

<table>
<thead>
<tr>
<th>ECMO-Related Change</th>
<th>PK Change</th>
<th>Drugs Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodilution</td>
<td>$\uparrow$ Vd, $\downarrow$ Cmax</td>
<td>Hydrophilic</td>
</tr>
<tr>
<td>Drug sequestration</td>
<td>$\uparrow$ Vd, $\downarrow$ Cmax</td>
<td>Lipophilic, Highly protein-bound</td>
</tr>
<tr>
<td>Drug inactivation</td>
<td>$\uparrow$ CL</td>
<td>Chemically unstable</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>$\downarrow$ CL, $\uparrow$ Vd, $\uparrow$ Vd</td>
<td>Renal/hepatic excretion</td>
</tr>
<tr>
<td>SIRS</td>
<td>$\uparrow$ CL, $\uparrow$ Vd, $\downarrow$ Cmax</td>
<td>Hydrophilic</td>
</tr>
</tbody>
</table>

Common Pharmacokinetic Alterations

Hydrophilic drugs
- Low Vd
- Renal Clearance
- Low log P

Lipophilic drugs
- High Vd
- Hepatic Clearance
- High log P

- $\uparrow$ Vd (large)
- $\downarrow$ Cmax
- $\uparrow$ or $\downarrow$ CL (dependent on renal function)

- $\uparrow$ Vd (minimal)
- $\uparrow$ Circuit sequestration
- $\uparrow$ or $\downarrow$ CL (dependent on hepatic function)

SEDATION & ANALGESIA
## PK & Physiochemical Properties

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vd (L)</th>
<th>LogP</th>
<th>Pb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>280-420</td>
<td>4.05</td>
<td>79-87</td>
</tr>
<tr>
<td>Morphine</td>
<td>70-350</td>
<td>0.89</td>
<td>20-35</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>118</td>
<td>3.39</td>
<td>94</td>
</tr>
<tr>
<td>Midazolam</td>
<td>70-217</td>
<td>3.89</td>
<td>97</td>
</tr>
<tr>
<td>Propofol</td>
<td>4200</td>
<td>3.79</td>
<td>95-99</td>
</tr>
<tr>
<td>Ketamine</td>
<td>140-210</td>
<td>2.9</td>
<td>47</td>
</tr>
</tbody>
</table>

¹Standardized to 70-kg patient

Ex vivo studies: adult ECMO circuits, composed of PVC tubing + hollow polymethylpentene fiber membrane oxygenator

- Wagner
  - Dexmedetomidine: 93% loss at 24 h

- Shekar
  - Morphine: 103% recovery at 24 h
  - Fentanyl: 70% lost in 1 h; 3% of baseline concentrations at 24 h
  - Midazolam: 50% lost in 1 h; 13% of baseline concentrations at 24 h

- Lemaitre
  - Propofol: 30% of baseline concentrations at 30 min; negligible at 24 h
  - Midazolam: 54% of baseline concentrations at 30 min; 11% at 24 h

Case report
- 30 year old male, on VV ECMO as bridge to lung transplantation
- Increased morphine and propofol requirements over 19 days of ECMO support

Single-center, retrospective study
- 29 consecutive patients requiring ECMO (13 VV, 16 VA)
- Average daily dose increase
  - Midazolam: 18 mg (p = 0.001)
  - Morphine: 29 mg (p = 0.02)
  - Fentanyl: No significant increase

Single-center, prospective cohort study
- 32 patients on VV or VA ECMO
- Median daily dose
  - Opioids: 3875 mcg
  - Benzodiazepines: 24 mg

Retrospective cohort study
- Adult patients with severe respiratory failure with or without VV ECMO support requiring at least one sedative
- ECMO (n=34) vs. no ECMO (n=60)
  - Maximum median 6-hour sedative exposure was almost twice as high in the ECMO group but no significant difference in the adjusted analyses

Ketamine for Adjunct Therapy

- Randomized trial
  - Standard sedation practices +/- low dose ketamine
  - 20 patients on VV ECMO for severe respiratory failure
  - No differences in opioid or sedative requirements

Sedation & Analgesia: Key Findings

- Fentanyl may require escalating doses; consider alternative agents
- Morphine may require dose adjustment; morphine is less lipophilic than fentanyl, thus it is a potentially superior option
- Dexmedetomidine may require an increased starting dose
- Midazolam requires an increased dose; consider alternative agents
- Propofol may require an increased dose; consider alternative agents
- Insufficient data regarding ketamine dosing

Lipophilic agents have a high propensity to be adsorbed or sequestered by the circuit

Upon ECMO initiation, anticipate requirements that exceed standard doses

Anticipate the need for significant dose reductions at the time of ECMO discontinuation

## PK & Physiochemical Properties

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vd$^1$ (L)</th>
<th>LogP</th>
<th>Pb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>20-27</td>
<td>0.67</td>
<td>15-28</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>35</td>
<td>-0.58</td>
<td>74-86</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>6-14</td>
<td>-0.01</td>
<td>85-95</td>
</tr>
<tr>
<td>Meropenem</td>
<td>15-20</td>
<td>-0.69</td>
<td>2</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>17</td>
<td>0.67</td>
<td>30</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>28-70</td>
<td>-4.4</td>
<td>50</td>
</tr>
<tr>
<td>Aminoglycosides: gentamicin, tobramycin, amikacin</td>
<td>14-21</td>
<td>&lt; 0</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>147-189</td>
<td>2.3</td>
<td>20-40</td>
</tr>
<tr>
<td>Levofloxacina</td>
<td>89</td>
<td>0.65</td>
<td>24-38</td>
</tr>
<tr>
<td>Moxifloxacina</td>
<td>119-189</td>
<td>0.01</td>
<td>50</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>8-10</td>
<td>-2.8</td>
<td>97</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>42</td>
<td>0.56</td>
<td>12</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>322</td>
<td>2.56</td>
<td>58</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>23-26</td>
<td>1.16</td>
<td>42</td>
</tr>
</tbody>
</table>

$^1$Standardized to 70-kg patient

Ampicillin

- Ex-vivo study: ECMO circuits composed of silicone membrane oxygenator
  - Blood-primed circuits
    - 15% drug loss at 24 h
  - Crystalloid-primed circuits
    - 71% drug loss at 24 h

Cefazolin

- Ex-vivo study: ECMO circuits composed of silicone membrane oxygenator
  - Blood-primed circuits
    - 22% drug loss at 24 h
  - Crystalloid-primed circuits
    - 22% drug loss at 24 h

Ceftriaxone

- Ex-vivo study: ECMO circuit composed of centrifugal pumps and polymethylpentene oxygenators
  - Average drug recovery of 80% at 24 h

Meropenem

- **Ex vivo study**: adult ECMO circuits, composed of PVC tubing + hollow polymethylpentene fiber membrane oxygenator
  - 20% of baseline concentrations at 24 h
  - Stable in the circuit and the controls in the first 120 min; 62% recovered at 6 h

- **Open-label, descriptive, matched-cohort PK study**
  - 11 patients on VV or VA ECMO; 5 patients also on RRT
  - Compared to 10 critically ill patients with sepsis not receiving ECMO (controls)
  - ECMO patients vs. Controls
    - Volume of distribution: 0.45 ± 0.17 vs. 0.41 ± 0.13 L/kg, P=0.21
    - Clearance: 7.9 ± 5.9 vs. 11.7 ± 6.5 L/h, P=0.18
  - All ECMO patients achieved trough concentrations >2 mg/L, but only 8 patients achieved a more aggressive target of >8 mg/L for less susceptible microorganisms

- **Retrospective, case-control study**
  - 26 ECMO (VA or VV) patients, 41 matched controls
  - 9 patients also received CRRT
  - 27 TDM results
    - No differences in PK parameters
    - High variability in PK parameters
    - 30% of levels were subtherapeutic

Piperacillin-Tazobactam

- Retrospective, case-control study
  - 26 ECMO (VA or VV) patients, 41 matched controls
  - 9 patients also received CRRT
  - 14 TDM results
    - No differences in PK parameters
    - High variability in PK parameters
    - 30% of levels were subtherapeutic

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Pharmacokinetic parameters for the two antibiotics.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEM (n=27)</td>
</tr>
<tr>
<td></td>
<td>ECMO</td>
</tr>
<tr>
<td>V_d (L/kg)</td>
<td>0.46 (0.26–0.92)</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>3.0 (2.1–4.8)</td>
</tr>
<tr>
<td>CL (ml/min)</td>
<td>125 (63–198)</td>
</tr>
<tr>
<td></td>
<td>TZP (n=14)</td>
</tr>
<tr>
<td></td>
<td>ECMO</td>
</tr>
<tr>
<td>V_d (L/kg)</td>
<td>0.33 (0.26–0.46)</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>2.0 (1.1–4.2)</td>
</tr>
<tr>
<td>CL (ml/min)</td>
<td>156 (91–213)</td>
</tr>
</tbody>
</table>

MEM, meropenem; TZP, piperacillin/tazobactam; ECMO, extracorporeal membrane oxygenation; V_d, volume of distribution; t_{1/2}, elimination half-life; CL, total drug clearance.

Vancomycin

- **Ex vivo studies**: adult ECMO circuits, composed of PVC tubing + hollow polymethylpentene fiber membrane oxygenator
  - Lemaitre
    - Concentration remained stable at 48 h
  - Shekar
    - 90% of baseline concentrations at 24 h

- **Retrospective matched cohort study**
  - Adult critically ill patients +/- ECMO (VA or VV) for cardiogenic shock, ARDS or sepsis; 7 patients on CRRT
  - 35 mg/kg loading dose over 4 h, followed by continuous infusion
  - ECMO (n=11) vs. Control (n=11)
    - Median AUC (mg/hr/L): 628 vs. 698
    - No significant differences in vancomycin levels during the first 24 hours

Fluoroquinolones

- Ciprofloxacin
  - Ex-vivo study: ECMO circuit composed of centrifugal pumps and polymethylpentene oxygenators
  - Average drug recovery of 96% at 24 h

PK studies largely limited to the neonatal population

Amikacin
- Observational study
  - 46 patients on VA or VV ECMO were matched with 50 critically ill patients without ECMO support (controls)
  - ECMO vs. Controls
    - Cmax (mg/l): 71.7 (58.9–79.7) vs. 68.4 (53.0–81.0)
    - Insufficient Cmax: 13/50 (26%) vs. 17/50 (34%)
    - Excessive Cmax: 12/50 (24%) vs. 15/50 (30%)
    - Cmin above toxic threshold: 28/43 (65%) vs. 30/50 (60%)
  - Comparable PK in critically ill patients with or without ECMO support

Other Antimicrobials

- **Linezolid**
  - 3 adult patients receiving ECMO
    - May not achieve therapeutic targets with standard dosing when MIC >1 mg/l
  - Ex-vivo study: ECMO circuit composed of centrifugal pumps and polymethylpentene oxygenators
    - Average drug recovery of 91% at 24 h

- **Azithromycin**
  - PK appears to be similar between ECMO patients and non-ECMO critically ill controls

- **Tigecycline**
  - Case study
  - Levels similar to expected levels based on population PK

Consider alternative agents over ampicillin

Cefazolin may require a dosage adjustment

Meropenem may require more frequent dosing or higher doses

Vancomycin does not require a dosage adjustment; dosing guided by therapeutic drug monitoring

Insufficient data for aminoglycosides; dosing guided by therapeutic drug monitoring

No dosage adjustment is necessary for ceftriaxone, piperacillin-tazobactam, or fluoroquinolones
Antifungals: Studies

- **Fluconazole**
  - Ex-vivo study: ECMO circuit composed of centrifugal pumps and polymethylpentene oxygenators
    - Average drug recovery of 91% at 24 h

- **Voriconazole**
  - Ex-vivo study: ECMO circuits composed of silicone membrane oxygenator
    - 71% drug loss at 24 h

- **Caspofungin**
  - Ex-vivo study: ECMO circuit composed of centrifugal pumps and polymethylpentene oxygenators
    - Average drug recovery of 56% at 24 h
  - Case report
    - No significant differences in peak concentrations or Vd for a patient during ECMO when compared to adult references
  - Case report
    - Low to undetectable caspofungin concentrations in a patient receiving ECMO

Antifungals: Key Findings

- Insufficient data for fluconazole; increased loading dose may be required; maintenance doses may not require adjustment.

- Voriconazole concentrations appear to be significantly affected:
  - Increased loading dose required (100% increase)
  - Daily therapeutic drug monitoring recommended to monitor for circuit saturation

- Insufficient data for caspofungin; dosage adjustment may be required.
Oseltamivir: Studies

- **PK study**
  - Intervention: oseltamivir 75 or 150 mg twice daily
  - 7 patients on VV ECMO for severe pandemic (H1N1) influenza associated with ARDS +/- CVVHDF for renal failure
  - Results: ECMO + CVVHDF (n=3) vs. ECMO (n=4)
    - Cmax (ng/mL) OC, mean (range): 4173 (3944–4551) vs. 1029 (349–1470)
    - AUC (ng•h/mL) OC, mean (range): 42,730 (39,200–49,400) vs. 9,000 (2,200–14,500)

- **Prospective, open-label, PK study**
  - Intervention: oseltamivir 150 mg twice daily
  - 12 patients on CVVHD +/- ECMO, with suspected or confirmed H1N1 influenza
  - Results: ECMO + CVVHD (n=4) vs. CVVHD (n=8)
    - Cmax (ng/ml) OC, median (IQR): 981 (553–1670) vs. 2670 (1710–3580)
    - AUC (ng•hr/ml) OC, median (IQR): 9390 (5000–17,600) vs. 29,500 (17,600–35,800)
    - No substantial differences between preoxygenator and postoxygenator serum concentrations

- **PK study**
  - Intervention: oseltamivir 75 mg twice daily
  - 14 ECMO, 4 patients also on CVVH
  - ECMO (n=14) vs. healthy adult references
    - Cmax (ng/ml) OC, median: 509 vs. 335
    - AUC (ng•hr/ml) OC, median: 4346 vs. 2976

Higher AUC of the active drug is achieved in patients receiving ECMO and therefore no dosage adjustment is necessary.

Patients with renal dysfunction may experience impaired drug clearance.

Antimicrobials: Considerations

- Select agents previously evaluated in the literature
- Consider drug properties, typically favor a high initial concentration while monitoring for potential toxicities
- Monitor drug concentrations when possible
- Individualize therapy, especially when targeting a specific microorganism

Very limited data addressing the clinical outcomes associated with observational PK changes

Must rely on surrogate endpoints (WBC, temp) to assess effectiveness in the absence of therapeutic drug monitoring

Much of the existing data is limited to simulated circuits that do not account for drug metabolism or elimination

Lack of control groups

Current studies have not fully addressed:
  - Changing blood flow rates
  - Different ECMO configurations
  - Long term circuit effects
  - Addition of renal replacement therapy
ECMO may be used as rescue therapy for respiratory and/or cardiorespiratory failure unresponsive to standard therapy.

VA ECMO provides hemodynamic and respiratory support, whereas VV ECMO provides respiratory support alone.

Significant PK alterations may occur depending on physiochemical properties of the drug & properties of the ECMO circuit.

Lipophilic drugs with high protein-binding and large volume of distribution are more susceptible to drug loss via sequestration of drug in the ECMO circuit.

Hydrophilic drugs with a small volume of distribution are greatly impacted by hemodilution.
Hemodilution has the greatest impact on drugs that are:

- (a) Lipophilic with a large Vd
- (b) Highly protein-bound
- (c) Hydrophilic with a small Vd
- (d) Lipophilic with low protein-binding
Two properties that studies have shown to affect drug sequestration to the greatest degree are:

- (a) Lipophilicity and protein binding
- (b) Lipophilicity and molecular size
- (c) Hydrophilicity and ionization
- (d) Molecular size and protein binding
Current data suggest that ECMO therapy does not significantly influence voriconazole PK and thus no dosage adjustments are required.

True or False?
Morphine is less lipophilic than fentanyl, making it a potentially superior option when managing patients on ECMO support.

True or False?
References


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References