Pharmacotherapy Management in Patients with Extracorporeal Membrane Oxygenation

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Faculty Disclosure

• I have no conflicts of interest to disclose.
• Gap = Lack of treatment guidelines and published research often leave providers with no clear way to optimally treat patients

• Need = Our learners need strategies to manage patients on extracorporeal membrane oxygenation (ECMO)
Upon completion of this educational activity, you will be able to:

1. Identify alterations in pharmacokinetics (PK) associated with ECMO

2. Review dose adjustments and monitoring of analgesics, sedatives, and antimicrobials in critically ill patients on ECMO

3. Evaluate the anticoagulation management and monitoring practices in patients on ECMO
• What is the desired change/result in practice resulting from this educational intervention?

• As a result of the information/tools provided in this activity, learners should be better able to utilize appropriate pharmacologic therapies to manage patients on ECMO
Pharmacokinetic Alterations

- Drug Factors
- Disease Factors
- Extracorporeal Factors

HealthCare
GILL HEART & VASCULAR INSTITUTE
Critical Illness

Augmented Cardiac Output

Leaky Capillaries/Volume Resuscitation

Altered Protein Binding

End-organ Dysfunction

Increased Clearance

Increased Volume of Distribution

Decreased Plasma Concentrations

Increased Plasma Concentrations

Decreased Clearance

Extracorporeal Membrane Oxygenation

- Augmented Cardiac Output
  - Increased Clearance
  - Decreased Plasma Concentrations

- Hemodilution
  - Increased Volume of Distribution

- Drug Sequestration
  - Decreased Clearance
  - Increased Plasma Concentrations

- End-organ Dysfunction
  - Decreased Clearance
Extracorporeal Membrane Oxygenation

- ECMO Circuit
  - Tubing type
  - Oxygenator membrane
  - Priming solution
  - Age of the circuit

A: Tubing/Pump
B: Oxygenator
C: Priming solution

Wildschut et al. Intensive Care Med 2010; 36(12): 2109-2116
Drug Factors - Analgesics and Sedatives

Lipophilicity (log p value) and protein-binding properties of common opioids and sedatives

Lipophilicity:
- Fentanyl: 4.1
- Midazolam: 3.9
- Propofol: 3.8
- Lorazepam: 3.0
- Ketamine: 2.9
- Dexmedetomidine: 2.8
- Hydromorphone: 1.7
- Morphine: 0.9

Protein Binding (%):
- Fentanyl: 99%
- Midazolam: 97%
- Propofol: 95%
- Dexmedetomidine: 91%
- Lorazepam: 83%
- Fentanyl: 35%
- Morphine: 27%
- Ketamine: 20%

Analgesics and Sedatives

Simulated Adult ECMO Circuit

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Morphine</th>
<th>Midazolam</th>
<th>Fentanyl</th>
<th>Propofol</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>0</td>
<td>100</td>
<td>0</td>
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<td>0</td>
</tr>
</tbody>
</table>

Lemaitre et al. Critical Care. 2015;19:40
How to Manage Pain and Sedation

Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

John W. Devlin, PharmD, FCCM (Chair)\(^1\), Yoanna Skrobik, MD, FRCP(c), MSc, FCCM (Vice-Chair)\(^1\);
Céline Gélinas, RN, PhD\(^2\); Dale M. Needham, MD, PhD\(^3\); Arjen J. C. Slooter, MD, PhD\(^4\);
Pratik P. Pandharipande, MD, MSCI, FCCM\(^5\); Paula L. Watson, MD\(^6\); Gerald L. Weinhouse, MD\(^7\);
Mark E. Nunnally, MD, FCCM\(^1,11,12,13,14\); Bram Rochwerger, MD, MSc\(^15,16\);
Michele C. Balas, RN, PhD, FCCM, FAAN\(^17,18\); Mark van den Boogaard, RN, PhD\(^19\); Karen J. Bosma, MD\(^20,21\);
Nathaniel E. Brummel, MD, MSCI\(^22,23\); Gerald Chanques, MD, PhD\(^24,25\); Linda Deney, PT, PhD\(^26\);
Xavier Drouot, MD, PhD\(^27,28\); Gilles L. Fraser, PharmD, MCCM\(^29\); Jocelyn E. Harris, OT, PhD\(^30\);
Routine assessment of pain, agitation and delirium

Pain should be treated before sedation

Target light sedation (vs deep sedation)

Propofol or dexmedetomidine preferred over benzodiazepines for sedation

Performing rehabilitation or mobilization

Key Guideline Concepts


### Application of Guidelines

<table>
<thead>
<tr>
<th></th>
<th>48-hrs post VV ECMO initiation (n=45)</th>
<th>24-hrs before VV ECMO discontinuation (n=35)</th>
<th>48-hrs post VV ECMO discontinuation (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deeply sedated, n (%)</td>
<td>43 (96)</td>
<td>8 (23)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Continuous infusion sedative, n (%)</td>
<td>43 (96)</td>
<td>16 (46)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Continuous infusion opioid, n (%)</td>
<td>44 (98)</td>
<td>24 (69)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Daily propofol dose in mg, median (IQR)</td>
<td>3,380 (1,105–4,110)</td>
<td>1,760 (960–2,960)</td>
<td>660 (540–2,220)</td>
</tr>
<tr>
<td>Daily midazolam equivalents dose in mg, median (IQR)</td>
<td>202 (103–247)</td>
<td>32 (14–81)</td>
<td>32 (10–122)</td>
</tr>
<tr>
<td>Daily fentanyl equivalents dose in mcg, median (IQR)</td>
<td>4,800 (3,000–5,820)</td>
<td>1,625 (610–3,345)</td>
<td>720 (150–1,660)</td>
</tr>
</tbody>
</table>

IQR: interquartile range
### Current Practice and Perceptions

#### Initial Preferred Opioid

<table>
<thead>
<tr>
<th></th>
<th>n=221 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>171 (77)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>36 (16)</td>
</tr>
<tr>
<td>Morphine</td>
<td>10 (5)</td>
</tr>
</tbody>
</table>

#### Second Preferred Opioid

<table>
<thead>
<tr>
<th></th>
<th>n=221 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
<td>106 (48)</td>
</tr>
<tr>
<td>Morphine</td>
<td>48 (21)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>38 (17)</td>
</tr>
</tbody>
</table>

#### Initial Preferred Sedative for Deep Sedation

<table>
<thead>
<tr>
<th></th>
<th>n=221 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>155 (70)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>54 (24)</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Ketamine</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

#### Second Preferred Sedative for Deep Sedation

<table>
<thead>
<tr>
<th></th>
<th>n=221 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>90 (41)</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>52 (23)</td>
</tr>
<tr>
<td>Propofol</td>
<td>41 (19)</td>
</tr>
<tr>
<td>Ketamine</td>
<td>27 (12)</td>
</tr>
</tbody>
</table>

#### Initial Preferred Sedative for Light Sedation

<table>
<thead>
<tr>
<th></th>
<th>n=221 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine</td>
<td>100 (45)</td>
</tr>
<tr>
<td>Propofol</td>
<td>85 (39)</td>
</tr>
<tr>
<td>Benzodiazepine infusion</td>
<td>16 (7)</td>
</tr>
<tr>
<td>Benzodiazepine prn</td>
<td>9 (4)</td>
</tr>
</tbody>
</table>

#### Second Preferred Sedative for Light Sedation

<table>
<thead>
<tr>
<th></th>
<th>n=221 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine</td>
<td>81 (37)</td>
</tr>
<tr>
<td>Benzodiazepine prn</td>
<td>49 (22)</td>
</tr>
<tr>
<td>Propofol</td>
<td>45 (20)</td>
</tr>
<tr>
<td>Ketamine</td>
<td>12 (5)</td>
</tr>
</tbody>
</table>

Perception that opioid dosing is higher with VV-ECMO = 121 (55)

Perception that sedation dosing is higher with VV-ECMO = 131 (59)
• Drug dosing recommendations are unlikely to be evidence-based
• Use published pharmacokinetic data in critically ill patients to make dosage adjustments
• Set daily sedation goals and consider daily interruption of sedatives
• Lipophilicity and protein binding appear to be important factors affecting pharmacokinetics
Antimicrobial Dosing Considerations

- Therapeutic failure
- Potential emergence of resistant microorganisms
- Toxicity
Drug Factors - Antimicrobials

Lipophilicity (log p value) and protein-binding properties of common antimicrobials

- Fluoroquinolones
  - Piperacillin/tazobactam
  - Meropenem
  - Ceftriaxone
  - Cefepime
  - Vancomycin
  - Aminoglycosides

- Ceftriaxone
  - Vancomycin
  - Fluoroquinolones
  - Piperacillin/tazobactam
  - Aminoglycosides
  - Cefepime
  - Meropenem

## Antimicrobials and ECMO

<table>
<thead>
<tr>
<th>Vancomycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td><strong>Endpoints</strong></td>
</tr>
</tbody>
</table>
| 11 ECMO 11 Controls | No difference in clearance or volume of distribution | 50 ECMO 50 Controls | No difference in $C_{\text{max}}$ and $C_{\text{min}}$
| 20 ECMO 60 Controls | $C_{\text{max}} < 60 \text{ mg/mL} = 26\%$ (ECMO) vs. $34\%$ (Controls) | 7 ECMO 50 Controls | Patients receiving ECMO had a higher $V_d$ and lower $C_l$
| 106 ECMO 11 Controls | $C_{\text{max}} < 60 \text{ mg/mL} = 39\%$ | |

$C_{\text{max}}$ = peak serum concentrations; $C_{\text{min}}$ = trough serum concentrations; $V_d$ = volume of distribution; $C_l$ = clearance

Ruiz-Ramos et al. ASAIO J. 2018;64(5):686-688
**β-Lactam Pharmacokinetics in ECMO**

- Case control cohort: Total of 41 therapeutic drug monitoring (TDM) results

<table>
<thead>
<tr>
<th></th>
<th>Meropenem (n=27)</th>
<th>Piperacillin/Tazobactam (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ECMO</td>
<td>Control</td>
</tr>
<tr>
<td>Volume of Distribution (L/kg)</td>
<td>0.46 (0.26–0.92)</td>
<td>0.60 (0.42–0.90)</td>
</tr>
<tr>
<td></td>
<td>0.33 (0.26–0.46)</td>
<td>0.31 (0.21–0.41)</td>
</tr>
<tr>
<td>Elimination half life (h)</td>
<td>3.0 (2.1–4.8)</td>
<td>2.9 (2.4–3.7)</td>
</tr>
<tr>
<td></td>
<td>2.0 (1.1–4.2)</td>
<td>1.6 (1.0–4.7)</td>
</tr>
<tr>
<td>Total drug clearance (mL/min)</td>
<td>125 (63–198)</td>
<td>144 (97–218)</td>
</tr>
<tr>
<td></td>
<td>156 (91–213)</td>
<td>134 (47–179)</td>
</tr>
</tbody>
</table>
β-Lactam Pharmacokinetics in ECMO

## Dose Adjustments for Select Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein Binding</th>
<th>Log p</th>
<th>Volume of Distribution</th>
<th>Expected Effect</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>85-90%</td>
<td>-0.01</td>
<td>5.78–13.5 L</td>
<td>Moderate sequestration</td>
<td>Not required</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>50%</td>
<td>-4.4</td>
<td>28–70 L</td>
<td>Minimal sequestration</td>
<td>Not required</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>24–38%</td>
<td>0.65</td>
<td>88.9 L</td>
<td>Minimal to moderate sequestration</td>
<td>Not required</td>
</tr>
<tr>
<td>Gentamicin/TOB/Amikacin</td>
<td>&lt; 30%</td>
<td>&lt; 0.0</td>
<td>14–21 L</td>
<td>Minimal sequestration</td>
<td>Not required</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>58%</td>
<td>2.56</td>
<td>322 L</td>
<td>Moderate to high sequestration</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Antimicrobial Dosing Considerations

- PK data in adult patients on ECMO are sparse
- Consider loading dose for drugs with moderate to high sequestration
- Dose guided by therapeutic drug monitoring when applicable
- Monitor for signs of infections
Bleeding and Thrombosis Complications

- Meta-analysis: 12 studies (1763) patients
  - Any bleeding (33%)
  - Hemolysis (18%)
  - Venous thrombosis (10%)
  - Gastrointestinal bleeding (7%)
  - Disseminated intravascular coagulation (5%)

The Clinical Challenge

Thrombosis

Bleeding

Which Anticoagulant?

Thrombosis

Guidelines

• Heparin bolus (50-100 units/kg) at time of cannulation, continuous infusion during ECLS
• Direct thrombin inhibitors
• Monitor ACT, aPTT, or anti-Xa

“These guidelines describe useful and safe practice, but these are not necessarily consensus recommendations. These guidelines are not intended as a standard of care, and are revised at regular intervals as new information, devices, medications, and techniques become available.”
**Goals**

- ACT 180-200 sec
- Median antithrombin 70%
- Anti-Xa 0.3-0.7 IU/mL

**Transfusion Triggers**

- Platelets <100k
- Fibrinogen <145mg/dL

**Monitoring Frequency**

- APTT q6-8h
- CBC q6-8h
- Fibrinogen >12h
- Free hemoglobin >12h
- Antithrombin q13-24h
- Anti-Xa q13-24h
Ideal Parenteral Anticoagulant

Pharmacokinetics (PK)
- Predictable dose response
- Stable dosing
- Quick onset

Pharmacodynamics (PD)
- Reliable monitoring
- Reversibility
- Without adverse drug reactions

Usability
- Effectively prevent thrombosis
- Minimal bleeding risk

Outcomes

**PK and PD**

**Heparin**
- Plasma Protein Binding
- ATIII Dependence

Unpredictable Onset of Action & Elimination
Nonlinear Dose Adjustments
aPTT Instability & Heparin Resistance

**Bivalirudin**
- Proteolytic Metabolism + Renal Elimination
- Direct Thrombin Binding

Predictable Onset of Action & Elimination
Predictable Dose Adjustments
aPTT Stability

Coughlin et al. ASAIO J. 2015;61(6):652-655
## Heparin vs Bivalirudin

<table>
<thead>
<tr>
<th></th>
<th>Heparin</th>
<th>Bivalirudin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monitoring</strong></td>
<td>ACT, aPTT, anti-Xa, TEG/ROTEM</td>
<td>ACT, aPTT, TT, TEG/ROTRM</td>
</tr>
<tr>
<td><strong>Reversal</strong></td>
<td>Protamine</td>
<td>No antidote</td>
</tr>
<tr>
<td></td>
<td>Half life 90 min</td>
<td>Half life 25 min</td>
</tr>
<tr>
<td><strong>ADR</strong></td>
<td>HIT, thrombocytopenia</td>
<td>Minimal</td>
</tr>
</tbody>
</table>

ACT: activated clotting time; aPTT: activated partial thromboplastin time; TEG or ROTEM, thromboelastography or rotational thromboelastometry; TT: thrombin time; ADR: adverse drug reaction

ACT: activated clotting time; aPTT: activated partial thromboplastin time; TEG or ROTEM, thromboelastography or rotational thromboelastometry; TT: thrombin time; ADR: adverse drug reaction

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Coughlin et al. ASAIO J. 2015;61(6):652-655
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Subjects</th>
<th>Bivalirudin</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranucci, 2011</td>
<td>Retrospective</td>
<td>21 (11 adults)</td>
<td>n=13 ACT 160-180 sec aPTT 50-80 sec</td>
<td>Blood product use: FFP, platelets Blood loss</td>
</tr>
<tr>
<td>Pieri, 2013</td>
<td>Retrospective</td>
<td>20 adults VA-ECMO 10</td>
<td>n=10 aPTT 45-60 sec</td>
<td>Major/Minor bleeding = ND Thrombosis = ND</td>
</tr>
<tr>
<td>Berei, 2017</td>
<td>Retrospective</td>
<td>72 adults VA-ECMO 66</td>
<td>n=44 aPTT 45-65 sec or 60-80 sec</td>
<td>Major/Minor bleeding = ND Thrombosis = ND</td>
</tr>
</tbody>
</table>

ND: No difference
Anticoagulation Considerations

- Most data in pediatric population
- Center specific protocols
- Heparin is the drug of choice???
- Variable monitoring strategies
- UK primarily uses bivalirudin and monitors aPTT
Pharmacotherapy Management in Patients with Extracorporeal Membrane Oxygenation

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University of Kentucky