Overview of Pharmacological Considerations in Extracorporeal Membrane Oxygenation

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Extracorporeal membrane oxygenation has become more widely used in recent years. Although this technology has proven to be lifesaving, it is not devoid of complications contributing to significant morbidity and mortality. Nurses who care for patients receiving extracorporeal membrane oxygenation should further their understanding of changes in medication profiles due to complex interactions with the extracorporeal membrane oxygenation circuitry. The aim of this comprehensive review is to give nurses a better understanding of analgesic, sedative, anti-infective, and anticoagulation medications that are frequently used to treat patients receiving extracorporeal membrane oxygenation. (Critical Care Nurse. 2019;39[2]:29-44)

Extracorporeal membrane oxygenation (ECMO) is a form of life support that provides temporizing measures for patients with refractory cardiorespiratory failure. Health care providers caring for these patients need a thorough understanding of ECMO functionality and pharmacotherapy management to optimize outcomes. The aim of this comprehensive review is to address common medication classes (analgesics, sedatives, anti-infectives, and anticoagulants) used to treat patients receiving ECMO.

CE 1.0 hour, Pharma 1.0, CERP A

This article has been designated for CE contact hour(s). The evaluation tests your knowledge of the following objectives:
1. Identify medication classes that are frequently used for patients undergoing extracorporeal membrane oxygenation (ECMO) therapy
2. Describe how the ECMO circuit can alter drug pharmacokinetic profiles
3. Evaluate individual physiochemical properties of medications to further understand how they can be influenced by the ECMO circuit

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Indications for ECMO

Guidelines describing potential indications for ECMO therapy have been established and published by the Extracorporeal Life Support Organization. These guidelines can help centers determine appropriate patient candidacy. Although individual centers may adopt more strict patient-related criteria, the use of ECMO may be considered when a greater than 50% mortality risk exists. Centers should establish indications and contraindications to identify patients who will likely benefit from therapy while avoiding controversy regarding those in whom therapy may be considered futile (Table 1).

The ECMO Circuit

The ECMO circuit consists of a blood pump, a membrane oxygenator, conduit tubing cannulas, and potentially a heat exchanger (Figures 1 and 2). Blood is pulled from the venous circulation through inflow (drainage) cannulas and pumped through an oxygenator before returning through an outflow (return) cannula. Positioning the outflow cannula into arterial circulation creates a venoarterial circuit, whereas venous return creates a venovenous circuit.

In the most fundamental sense, a venoarterial ECMO circuit provides complete cardiac and respiratory support...
and functions independently of the native heart. Cannulation strategies may vary depending on the clinical scenario but generally involve central or peripheral access (Figure 1).

Venovenous ECMO is preferred when full or partial respiratory support is required and depends on native ventricular function to help circulate blood flow. The decision between multisite or single-site cannulation depends on clinical scenario, feasibility, and operator preference (Figure 2). In an ideal scenario, only deoxygenated blood enters the drainage (inflow) cannula, allowing only oxygenated blood to be distributed to the right atrium and providing 100% oxygenated blood to enter the pulmonary arteries.

**Pharmacokinetic Implications**

Despite the wealth of information surrounding individual medication pharmacokinetic profiles in non-critically ill patients, data in patients receiving ECMO are extremely sparse. Insertion of an ECMO circuit can induce profound inflammatory responses in addition to the alterations in physiology and end-organ function caused by the criticality of individual patients. These complications are compounded by the significant distortion in medication pharmacokinetic profiles that can result from the interaction between the ECMO circuit and medications. Pharmacokinetic alterations can be caused by the type of ECMO circuit (pump design, oxygenators, tubing, etc). In an evaluation of new and used ECMO components, phenobarbital concentrations were lower in the newer circuit than in the older circuit, suggesting that the age of the circuit is another factor influencing pharmacokinetic alterations. Previous data have demonstrated how interactions among circuit, drug, and patient factors can alter the pharmacokinetic profiles of medications through changes in drug sequestration, volume of distribution (Vd), and drug clearance (Figure 3). Drug sequestration relates to abnormal changes in drug concentration due to adsorption of medications to the components of the ECMO circuit. Adsorption, or
adhesion to a surface, is thought to result from a drug’s physiochemical properties. Evidence suggests that lipophilic medications (with higher partition coefficients) and protein-bound medications tend to be at higher risk than others for drug sequestration.

Volume of distribution is affected by ECMO through alterations caused by inflammation, renal or liver dysfunction, and fluid shifts. The ECMO circuit creates an extra compartment, contributing to a larger $V_d$ because of the extra space and additional priming solution required, leading to hemodilution. Drug sequestration can also result in a perceived increase in $V_d$.

Drug clearance is also impacted by ECMO for reasons other than critical illness. Worsening renal function is often seen in adult patients receiving ECMO and can limit excretion of renally cleared medications. Glomerular filtration may also be impacted by continuous-flow devices, but this theory has not been confirmed in the literature. Additionally, the ECMO circuit may alter blood flow to the liver, which could affect the clearance of drugs with a high extraction ratio (drugs rapidly and extensively cleared by the liver).

### Analgesia and Sedation

The approach to analgesia and sedation in patients receiving ECMO is comparable to that in critically ill adults. However, given alterations to drug pharmacokinetics and pharmacodynamics and patient variability, multiple factors need to be considered when optimizing treatment for individual patients. At the time of ECMO cannulation, patients should be adequately sedated to avoid possible air embolism via spontaneous breathing, minimize the metabolic rate, and avoid movement that might complicate cannulation. Analgesia and sedation should be titrated to the individual patient’s level of anxiety and discomfort. In certain instances, deep sedation and potential paralysis might be warranted to optimize circuit flows and oxygen consumption while minimizing the risk for decannulation. Individual clinical scenarios should drive the level of analgesia and sedation provided to patients. The medical team should discuss the level of sedation a patient requires, especially because many centers are emphasizing early mobilization and early cessation of sedation. Several studies, as well as direct observation, have demonstrated that patients receiving ECMO may have higher sedative and analgesic requirements than those not receiving ECMO, further complicating the clinical picture of these patients.

### Pain and Analgesia

The Society of Critical Care Medicine guidelines for managing pain, agitation, and delirium recommend intravenous opioids as first-line medications for treatment of nonneuropathic pain. All of the available intravenous opioids are generally considered equivalent in terms of clinical efficacy when titrated to the same intensity endpoint.

Fentanyl is arguably the most commonly used intravenous opioid in the intensive care unit (ICU), given its rapid onset and lower risk for hypotension and respiratory

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**Figure 3** Factors altering drug pharmacokinetics.
depression compared with other equivalent opioids. However, fentanyl and its derivatives are lipophilic, resulting in extensive drug sequestration in the ECMO circuit. In a study assessing the degree of sequestration, fentanyl was injected into a mock circuit at therapeutic concentrations and equivalent doses were injected into whole blood. After 24 hours, the fentanyl dose was almost completely lost and sequestered in the ECMO circuit, with drug recovery of only 3%. Therefore, significantly higher doses of fentanyl may be needed to maintain adequate levels of analgesia in patients undergoing ECMO. Although this study was conducted in neonatal patients, the effects are likely the result of ECMO circuitry, and a similar response is expected in adults. Additional studies suggest that fentanyl may be best used when short-term or rapid-onset analgesia is required because concentrations may remain unchanged in the first few hours after ECMO cannulation.

Morphine’s potential accumulation in patients with renal failure and its histamine-releasing and hypotensive effects may limit its utility in clinical practice. Given its hydrophilic nature, morphine is less likely to exhibit sequestration than other drugs and, because of its pharmacokinetic profile, may be the preferred analgesic in patients receiving ECMO. Additionally, research shows that morphine provides superior analgesia and less potential for withdrawal than fentanyl. Despite these potential advantages, morphine’s use remains challenging because of the ECMO circuitry’s effect on drug clearance. Dagan and colleagues examined the pharmacokinetic effects of morphine in infants and found mean (SD) serum morphine concentrations of 87 (58) μg/mL during ECMO and 35 (17) μg/mL after ECMO. Clearance of the drug doubled when ECMO was discontinued. With much of the research being conducted in the neonatal and pediatric populations, it may not be appropriate to extrapolate or generalize these data to critically ill adult patients receiving ECMO.

Limited data regarding ketamine use within the ECMO population exist; however, ketamine has been used to decrease opioid and sedative requirements in patients in the ICU. Tellor and colleagues evaluated the effects of ketamine infusions in patients undergoing ECMO in terms of altered Richmond agitation-sedation scale scores, decreased sedative opioid use, and vasopressor requirements. The investigators found that of 26 patients, 42% had a meaningful dose decrease in vasopressors and 35% had decreased opioid and sedative requirements after receiving 2 hours of ketamine infusion. The lipophilic nature of ketamine leads to a high propensity for sequestration, necessitating potentially higher doses than those studied for general analgesia. Despite the potential benefits for both respiratory and cardiovascular status, its use must be evaluated on an individual patient basis because it can be harmful in certain subsets of patients.

With the push toward reducing opioid use to limit the development of chemical dependency, the use of alternative (nonopioid) medications has increased. We are aware of only 1 in vitro analysis evaluating intravenous acetaminophen in patients receiving ECMO. In a single-dose in vitro study, the concentration of acetaminophen did not significantly change over time, with consistent levels demonstrated in both new and old circuits. On the basis of this analysis, acetaminophen concentrations appear to remain constant over a 6-hour period and do not significantly change with circuit age.

Sedation

The Society of Critical Care Medicine guidelines for pain, agitation, and delirium management recommend using nonbenzodiazepine sedatives to improve clinical outcomes in adult ICU patients, but when deep sedation is necessary, benzodiazepines are the best option. Although midazolam is the most commonly used continuous-infusion benzodiazepine in the ICU, its lipophilic nature can lead to a high degree of sequestration within the ECMO circuit. In an ex vivo study by Shekar and colleagues, only 13% of midazolam was recovered from the ECMO circuit after 24 hours, as compared with 100% at baseline. Shekar and colleagues also conducted a retrospective analysis seeking to characterize the sedation requirements in adult patients receiving ECMO and found a statistically significant increase in required midazolam doses (18 mg/d, 10.2% increase in dose) to achieve deep sedation. Lorazepam is less lipophilic than midazolam and should undergo less absorption by the ECMO circuit. Bhatt-Meht and colleagues evaluated the clearance of single doses of morphine and lorazepam with an in vitro model that included a closed ECMO circuit. The lipophilic nature of midazolam can lead to a high degree of sequestration within the ECMO circuit.
Increased interaction, and minimal respiratory depression. However, these features may not always be attractive for patients in whom deep sedation is necessary. Despite the paucity of information, current literature suggests that the drug is extensively lost in the circuit and fails to reach adequate steady-state concentrations as compared with other lipophilic agents. Wagner and colleagues evaluated the effects of new and old ECMO membrane oxygenators on the clearance of dexmedetomidine over a 24-hour period within an in vitro configuration. Although they failed to find differences in dexmedetomidine loss between preoxygenator and post-oxygenator sampling sites and between new and old oxygenators, they noted significant drug loss in the first hour (11%-73%). These findings suggest that the loss of dexmedetomidine was due to the drug’s adsorption to the polyvinyl chloride tubing as opposed to the membrane oxygenator itself. This study used dexmedetomidine boluses, not the continuous infusions that are used in clinical practice. Nonetheless, these results still suggest that higher doses of dexmedetomidine are likely required to maintain its normal sedative effects, which can subsequently lead to a higher risk of adverse effects such as hypotension and bradycardia.

Role of Nurses in Analgesia and Sedation

Nurses play a critical role in ensuring that patients are appropriately sedated while receiving ECMO therapy. Their constant presence and keen attention to changes in patient comfort, respiratory status, and hemodynamics allow for advanced discussions regarding therapeutic plans with the medical team. They fill potentially more important roles in monitoring patients for early cessation of sedation and constantly assessing the implementation of physical therapy. Nurses can continue to push for early mobilization. Because medication is lost through saturation of the ECMO circuit over long ECMO runs, daily measurements of analgesia and sedation levels using validated pain and sedation scores are essential to ensure patients are being appropriately treated. Close monitoring of these scores puts nurses in a prime position to track potential changes in pharmacodynamics in real time by using patient-specific responses to agents. Determining analgesia and sedation goals daily can help ensure that patients are adequately sedated, limiting the risk of patient self-harm while providing the best chance for early recovery by eliminating unwarranted analgesia and sedation.

Individual drug properties can help predict how antibiotics will respond in an ECMO circuit.
Anti-infective Therapy

Although ECMO can save lives, it can also be complicated by an increased risk of nosocomial infections, with proven infections in nearly 20.5% of adult patients. Despite the noted clinical consequences in patients who develop infections, the role of prophylactic antibiotics remains unclear. In a recent review describing the prophylactic practices used in 11 studies, 2 studies directly evaluating outcomes demonstrated that infection rates were unchanged irrespective of prophylactic antibiotic use. The lack of a proven benefit coupled with the finding of heterogeneous causative organisms led the authors to recommend against universal antibiotic prophylaxis for patients receiving ECMO. The authors noted that most infections were in the bloodstream, emphasizing the importance of sterility while caring for these patients.

Current data highlight the importance of optimal antibiotic dosing in ECMO therapy to improve clinical outcomes. The high degree of variability in critically ill ECMO patients caused by frequent fluid redistribution and altered clearance should lead to use of individualized dosing approaches instead of traditional dosing strategies (Table 2). Shekar and colleagues demonstrated that meropenem administered at the traditional dose (1 g intravenously every 8 hours) reached adequate concentrations to treat *Pseudomonas* organisms with low antibiotic resistance in patients receiving ECMO, but this was not true for more resistant organisms. Meropenem dosed at 2 g intravenously every 8 hours achieved sufficient concentrations to treat more resistant *P. aeruginosa* and *Acinetobacter* isolates irrespective of patients’ renal function. Because of drug accumulation, the lower dosing regimen (1 g intravenously every 8 hours) achieved concentrations adequate to treat these more resistant isolates only in patients with kidney dysfunction.

Studies of antibiotic use in adult patients continue to be published. However, a significant portion of the current data regarding anti-infective medications in ECMO comes from studies in neonatal populations or is derived from in vitro or ex vivo circuits, making extrapolation to adult patients difficult, especially given newer ECMO technology and equipment. These complicating factors can lead to therapeutic failure or toxicity. Shekar and colleagues worked to bridge the gap between ex vivo ECMO models and in vivo scenarios by using anti-infective agents with a range of properties to better assess factors influencing drug concentrations during ECMO. Specifically, the authors evaluated drug concentrations at various time intervals and drug clearances in 7 healthy sheep, 7 healthy sheep receiving ECMO, and 6 sheep that had experienced acute lung injury from smoke inhalation and were receiving ECMO. Notable findings included increased $V_d$ values for lipophilic medications and protein-bound medications, with significantly delayed clearance in samples obtained during ECMO. These findings help clinicians better understand how alterations affect the $V_d$ and clearance of medications. Increased $V_d$ may necessitate a larger loading dose, whereas decreased clearance may necessitate a lower maintenance dose or longer time between doses to avoid drug accumulation. In a case-control study of the aminoglycoside amikacin, an increased loading dose was needed because of a large increase in $V_d$. A standard loading dose (25 mg/kg) resulted in an insufficient maximum concentration in 25% of patients receiving ECMO. In other studies, the antifungal medication voriconazole had minimal change in $V_d$, but because of significant loss of the medication (71%) within the ex vivo circuit, an increased loading dose was recommended.

Examining individual drug properties can help predict how medications will respond when subjected to an ECMO circuit. However, given the potential inconsistencies of drug properties and resultant dose adjustments and the extreme lability of patients receiving ECMO, close attention to potential drug clearance is paramount when deciding on optimal dosing. Ideally, individualized dosing strategies would be used to achieve drug concentrations targeted to specific pathogens, infection locations (skin and other soft tissues vs bloodstream), and mean inhibitory concentration if known. However, these parameters are usually available only for certain agents, such as vancomycin and aminoglycosides. When investigators monitored plasma drug concentrations in a study of $β$-lactam antibiotics, they discovered that variability within individuals led to underdosing or toxic accumulation. Individualized dosing would help limit therapeutic failure and prevent toxic effects in these patients. The Antibiotic, Sedative and Analgesic Pharmacokinetics during Extracorporeal Membrane Oxygenation study aims to develop dosing guidelines for sedatives, opioids, antibiotics, and antifungal medications on the basis of their pharmacokinetic parameters during ECMO.
### Table 2: Dosing considerations for anti-infective drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-lactams</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Large</td>
<td>Increase likely required</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Large</td>
<td>Increase likely required</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Large</td>
<td>Increase likely required</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Large</td>
<td>Increase likely required</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>Large</td>
<td>Increase likely required</td>
</tr>
<tr>
<td><strong>Glycopeptides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Large</td>
<td>Increase likely required</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Moderate</td>
<td>Potential need for increase</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Moderate</td>
<td>Potential need for increase</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Moderate</td>
<td>Potential need for increase</td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Large</td>
<td>Increase likely required</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Large</td>
<td>Increase likely required</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Large</td>
<td>Increase likely required</td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Large</td>
<td>Increase likely required</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Minimal</td>
<td>Increase likely not necessary</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Moderate</td>
<td>Potential need for increase</td>
</tr>
<tr>
<td><strong>Antivirals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>Large</td>
<td>Potential need for increase</td>
</tr>
</tbody>
</table>

**Expected effects:** increased dose and frequency likely, adjustment likely necessary, increase likely required, potential need for increase.

**Sequestration:** minimal to moderate, moderate, minimal.

**Change in Vd:** large, moderate, minimal to large (≥1 L/kg), minimal (<1 L/kg).

**Abbreviations:** AUC, area under the curve; Cmax, maximum concentration; ECMO, extracorporeal membrane oxygenation; MIC, mean inhibitory concentration; TDM, therapeutic drug monitoring; Vd, volume of distribution.

*a Vd standardized to a 70-kg patient. Vd: moderate to large (≥1 L/kg), minimal (<1 L/kg).
<table>
<thead>
<tr>
<th>Actual effects</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ex vivo</strong>: crystalloid-primed circuit: 72% loss in circuit; blood-primed circuit: 15% loss in circuit</td>
<td>Consider alternative agents because of significant drug loss in circuit</td>
</tr>
<tr>
<td><strong>Ex vivo</strong>: 22% loss in both crystalloid- and blood-primed circuits</td>
<td>Consider increased dosing</td>
</tr>
<tr>
<td><strong>Ex vivo</strong>: significant reduction between control and circuit (102% vs 80%) <strong>Ovine model</strong>: increased clearance in ECMO vs controls</td>
<td>May consider dosing increase</td>
</tr>
<tr>
<td><strong>Ex vivo</strong>: drug recovery different between control (42%) and circuit (20%) <strong>Ovine model</strong>: reduced AUC (mg/h per liter) and clearance (L/h) <strong>Matched cohort</strong>: no difference from matched controls</td>
<td>MIC &lt; 2, no adjustment necessary, MIC &gt; 8 (more resistant organisms), increased dosing likely required. Patients with preserved renal function demonstrated increased clearance.</td>
</tr>
<tr>
<td><strong>Matched cohort</strong>: no difference from matched controls</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td><strong>Ovine model</strong>: increased clearance in ECMO compared with controls <strong>Matched cohort</strong>: no difference from matched controls</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Dosing guided by TDM</td>
<td></td>
</tr>
<tr>
<td><strong>Ex vivo</strong>: no significant loss in circuit <strong>Ovine model</strong>: significant increase in volume at steady state and delayed clearance</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>Unknown; not studied</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>Unknown; not studied</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td><strong>Gentamicin</strong>: studies predominately from neonates showing increased $V_d$ with prolonged half-life elimination</td>
<td>Unknown; consider prolonged dosing intervals (every 24-36 h), TDM highly encouraged</td>
</tr>
<tr>
<td><strong>Tobramycin</strong>: studied in lambs; alterations similar to those seen with gentamicin</td>
<td></td>
</tr>
<tr>
<td><strong>Case control</strong>: ECMO does not significantly impact peak and trough amikacin levels.</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>TDM highly encouraged</td>
<td></td>
</tr>
<tr>
<td><strong>Ex vivo</strong>: no significant loss in circuit <strong>Ovine model</strong>: similar $C_{max}$ as control without significant loss in circuit</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td><strong>Ex vivo</strong>: 71% lost within circuit <strong>Case report</strong>: decreased clearance with drug accumulation over time</td>
<td>Loading dose: Increase necessary</td>
</tr>
<tr>
<td>Maintenance dose: Inconsistent findings but consider dose reduction</td>
<td></td>
</tr>
<tr>
<td>Consider TDM (however, can be inconsistent)</td>
<td></td>
</tr>
<tr>
<td><strong>Ovine model</strong>: increased clearance in sheep on ECMO compared with healthy controls <strong>Case report</strong>: undetectable caspofungin levels on 3 of 5 days <strong>Case report</strong>: caspofungin levels were maintained</td>
<td>Insufficient data with mixed reports; however, more indicate increased clearance. Consider dose adjustment</td>
</tr>
<tr>
<td><strong>Open label</strong>: increased $V_d$, $C_{max}$, and AUC compared with healthy patients</td>
<td>No dose adjustment necessary</td>
</tr>
</tbody>
</table>
Role of Nurses in Anti-infective Therapy

Because of the lack of evidence regarding anti-infective medication use in patients receiving ECMO, individualizing therapy as much as possible should be common practice. Nurses can play a large role in this individualization because of their constant assessments of patients’ clinical status. Additionally, with the development of therapeutic drug monitoring assays for more medications, nurses can be more active in deciding whether to withhold or administer doses on the basis of drug levels. Nurses also play a vital role in ensuring that drug levels are measured at the correct time, which can help optimize therapeutic drug monitoring. Nurses must use sterile technique when administering medications and cleaning patients to avoid introducing infectious organisms.

Anticoagulation

The interaction between blood and ECMO circuitry can result in significant alterations in inflammatory and coagulation pathway responses, necessitating a fine balance in antithrombotic therapy. The Extracorporeal Life Support Organization guidelines provide anticoagulation recommendations, but an individualized approach is important because patient-specific variables can drastically influence treatment principles.47 Barring any degree of patient instability, baseline laboratory tests should be obtained to help optimize hemostasis.47,48 Attempts to correct underlying coagulopathies should be made on the basis of significant derangements in these laboratory values.

Activated clotting time (ACT) has historically been the most commonly used anticoagulation marker, but it is nonspecific and has the potential to either overestimate or underestimate anticoagulation effects (Table 3).47,48 Although the Extracorporeal Life Support Organization guidelines support an ACT goal of 180 to 220 seconds in patients receiving ECMO, one case series demonstrated that a lower ACT goal of 140 to 160 seconds resulted in fewer incidences of major bleeding and bleeding-induced death, with no difference in thrombotic events.49 These results suggest that with ECMO advancements, lower anticoagulation requirements may be appropriate.

The use of activated partial thromboplastin time (aPTT) gives clinicians a marker of anticoagulation more sensitive than ACT. Although the aPTT test remains standard practice in many centers for anticoagulation monitoring, individual centers must establish their own target range based on the analyzer and reagent used.47,50 As with ACT, aPTT measurements can be vastly affected by preanalytic, analytic, and biologic factors.51

Anti–factor Xa (anti-Xa) monitoring is becoming more widespread because this parameter is more sensitive and specific than aPTT. However, discordance between these tests has been demonstrated within the mechanical circulatory support population.52 Anti-Xa activity focuses on unfractionated heparin (UFH) catalyzing antithrombin’s inhibition of factor Xa, providing a more precise measure of the anticoagulant effect of UFH while not being impacted by underlying coagulopathies.53,54

Thromboelastography evaluates multiple phases of the coagulation cascade from clot initiation to dissolution.54 Many clinicians are unfamiliar with the test and with titration of medications to appropriate levels, so

Table 3  Laboratory tests for monitoring anticoagulation47,48

<table>
<thead>
<tr>
<th></th>
<th>ACT</th>
<th>aPTT</th>
<th>Anti–factor Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Availability</strong></td>
<td>Point of care</td>
<td>Central laboratory</td>
<td>Central laboratory</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>Less sensitive</td>
<td>More sensitive</td>
<td>Sensitive and specific</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Results affected (prolonged) by thrombocytopenia, platelet</td>
<td>Not affected by platelet numbers or function</td>
<td>Not affected by platelet numbers or function</td>
</tr>
<tr>
<td></td>
<td>dysfunction, hemodilution</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Samples</strong></td>
<td>Fresh whole blood</td>
<td>Fresh or citrated blood (citrated typically more accurate)</td>
<td>Fresh citrated blood</td>
</tr>
<tr>
<td><strong>Time to laboratory result</strong></td>
<td>Rapid (minutes)</td>
<td>Dependent on laboratory (30-60 min)</td>
<td>Dependent on laboratory (30-60 min)</td>
</tr>
<tr>
<td><strong>Typical goal</strong></td>
<td>140-220 s</td>
<td>Depends on institution’s specific calibration</td>
<td>0.3-0.7 IU/mL</td>
</tr>
</tbody>
</table>

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time.
this test is infrequently used. Although thromboelastography can help identify abnormalities of hemostasis, it should not be solely relied upon to titrate medications to optimize anticoagulation.

Anticoagulation monitoring studies have demonstrated a lack of correlation between the anti-Xa test and ACT or aPTT in all patient populations. Irby and colleagues demonstrated an association between subtherapeutic anti-Xa levels and an increased need for oxygenator exchanges, suggesting potential benefits of the anti-Xa test. The relationship between ACT and aPTT has also shown inconsistencies; better correlations have been found between heparin doses and aPTT than between heparin doses and ACT. Ideally, a single test could be used to optimize anticoagulation, but previous data suggest that individual tests are not without deficiencies and that a multimodal approach to assess coagulopathies should be used. Clinicians should evaluate all available tests to help guide decision-making while patients are supported on ECMO.

### Therapeutic Agents

Unfractionated heparin exerts its effect by binding to antithrombin, accelerating the inhibitory effect of antithrombin on free and clot-bound factor Xa. Antithrombin inhibits the conversion of prothrombin to thrombin, which subsequently prevents fibrin formation during active thrombosis. Unfractionated heparin does not inhibit thrombin that has already been bound to fibrin.

At the time of cannulation, patients may receive an initial UFH bolus based on patient-specific factors (Table 4). The type of laboratory measure used to titrate the UFH infusion, target range for laboratory test results, and administration of bolus dosing are specific to each institution and patient and may also depend on the type of device used to measure these laboratory values.

Heparin-bonded circuits are used at many ECMO centers to make their circuits more biocompatible, which may attenuate activation of the coagulation cascade, limit inflammation, and limit or eliminate the need for anticoagulation during ECMO. However, the virtual half-life of heparin within these coated circuits is usually a few hours and is thus too short to be useful in patients being supported by ECMO for longer periods of time. Theoretically, UFH-bonded circuits may be beneficial when a delay in initiating systemic anticoagulation is warranted. Unfortunately, heparin-coated circuits have not demonstrated benefits with respect to mortality, length of stay, bleeding, or thrombotic events. Several reports have evaluated bleeding and thrombotic complications in heparin-bonded ECMO circuits without systemic anticoagulation. In a study of patients receiving venoarterial ECMO, transfusion requirements were similar to those reported in previous studies, but the rate of repeat sternotomy in postcardiotomy patients was reduced. Five patients developed leg ischemia; only 3 patients required oxygenator replacement. A potential confounder of this study is that all patients received heparin at time of cannulation. The authors concluded that venoarterial ECMO without systemic anticoagulation may reduce bleeding-related complications without increasing the risk of thromboembolism.

A 60-patient case series also examined patients who received only prophylactic anticoagulation during venovenous ECMO support. Patients primarily

### Table 4 Anticoagulant drug dosing

<table>
<thead>
<tr>
<th>Agent</th>
<th>Bolus</th>
<th>Starting dose</th>
<th>Monitoring</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>50-100 U/kg</td>
<td>12-18 U/kg per hour</td>
<td>aPTT = 70-95 s&lt;sup&gt;a&lt;/sup&gt; Anti-Xa = 0.3-0.7 IU/mL</td>
<td>Most common systemic agent Requires antithrombin as a substrate Reversible with protamine</td>
</tr>
<tr>
<td>Argatroban</td>
<td>0.35 mg/kg</td>
<td>0.5-1 μg/kg per minute</td>
<td>aPTT 1.5-2.5 times baseline aPTT</td>
<td>Hepatically metabolized No reversal agent available</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>0.5-1 mg/kg</td>
<td>0.05-0.15 mg/kg per hour</td>
<td>aPTT 1.5-2.5 times baseline aPTT</td>
<td>Renally cleared No reversal agent available</td>
</tr>
</tbody>
</table>

Abbreviation: aPTT, activated partial thromboplastin time.

<sup>a</sup> Per institution standard.
received enoxaparin at a dose of 40 mg subcutaneously once daily; however, doses were adjusted on the basis of body mass index. All patients also received heparin during cannulation. The median ECMO duration was 7 days. Four patients developed thrombotic events after 5 days of ECMO without any changes in oxygenator. Bleeding complications were more likely to occur after day 9 of ECMO. Overall, patients received about 30% of the blood products reported in other studies. Twenty-one patients died in this series, although mortality was not related to circuit breakdown, embolisms, or uncontrollable bleeding.

Given the risk of heparin-induced thrombocytopenia associated with long-term support, it is unclear if a heparin-bonded circuit poses any additional risk. Newer circuits with covalently bonded heparin instead of ionized heparin may have better stability, potentially preventing heparin from leaching into the blood as it flows through the circuit. A case report described a patient receiving systemic heparin and ECMO through a heparin-coated circuit. The patient developed heparin-induced thrombocytopenia. Despite transitioning to bivalirudin, thrombocytopenia and ongoing thrombus formation continued. Once the patient was decannulated, the platelet count normalized within 48 hours. Although the authors indicated multiple reasons for thrombocytopenia, the findings suggest that heparin-bonded circuits may have been the reason for the persistent thrombocytopenia and the concomitant thromboembolic event.

Direct thrombin inhibitors (DTIs) may avoid many shortcomings associated with UFH because of their ability to bind both free and clot-bound thrombin, providing a greater reduction in thrombin generation. Additionally, DTIs provide more predictable pharmacokinetics and function independently of antithrombin concentrations. Dosing remains stable even in the setting of circadian variations, which may significantly impact UFH dosing. A potential limitation of DTIs is the lack of definitive pharmacological antidotes for bleeding episodes. However, given their short half-lives, DTIs can usually be discontinued or the dose can be reduced if an acute bleeding event occurs. Three DTIs (argatroban, bivalirudin, and lepirudin) have been used in patients receiving ECMO. However, the availability of lepirudin is currently limited.

To assess the ability of argatroban to adequately prime an ECMO circuit, Young and colleagues created sham ECMO circuits and compared argatroban with heparin for the prevention of clot initiation, as assessed by thromboelastography. All agents were titrated to a goal ACT of 180 to 220 seconds. No clot initiation was detected in any circuit, but thrombin generation was reduced within the argatroban circuit. The authors concluded that argatroban may be a more efficacious anticoagulant in this setting; however, this study should be considered hypothesis generating. In another study, argatroban was demonstrated to be safe and effective for patients with suspected heparin-induced thrombocytopenia who were receiving venovenous ECMO for treatment of acute respiratory distress syndrome. Investigators found that patients had a 10-fold decrease in argatroban requirement (mean dose of 0.15 μg/kg per minute) compared with the dose recommended in the manufacturer’s labeling.

Bivalirudin, the other commonly used DTI, undergoes renal elimination, unlike the hepatic elimination of argatroban. The comparative efficacy of bivalirudin versus UFH (titrated according to ACT, aPTT, and thromboelastography reaction times) has also been assessed on the basis of thromboembolic events, blood loss, blood product usage, and costs. Investigators determined that patients in the UFH group had higher platelet, fresh frozen plasma, and antithrombin administration requirements. Those in the bivalirudin group had better overall coagulation profiles, less blood loss, and (in the pediatric population) lower costs. A case-controlled study with 10 patients in each arm evaluated the efficacy of bivalirudin and heparin (goal aPTT, 45-60 seconds). Overall, investigators found significantly more aPTT variation in the UFH treatment arm than in the bivalirudin arm. Patients receiving UFH required more titrations, although bleeding, thrombosis, ECMO duration, and rate of supratherapeutic aPTT values were not different between groups. The authors concluded that bivalirudin-based anticoagulation regimens may be safe and effective for patients receiving ECMO.

A systematic review of bivalirudin use in ECMO patients found doses ranging from 0.028 to 0.05 mg/kg per hour, likely because of patient heterogeneity and variability of drug clearance mechanisms. Patients with acute kidney injury needed less bivalirudin overall, but
continuous renal replacement therapy resulted in higher dosing requirements.\textsuperscript{67} Given the elimination mechanisms of bivalirudin, caution should be taken in the setting of low-flow states because any region of stasis in the patient (including heart chambers) or the circuit could result in augmented metabolism and thrombotic risk. In these cases, it may be beneficial to ensure that heart contractility is sufficient, even with full cardiac support, to minimize the degree of stasis.

Longer-acting agents, including oral direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), oral factor IIa inhibitors (eg, dabigatran), and the vitamin K antagonist warfarin are especially appealing in patients who are supported by ECMO for prolonged periods of time because they require less frequent monitoring and reduce the fluid volume burden associated with systemic agents. For the foreseeable future, however, their enteral administration, lack of definitive reversibility in the setting of bleeding or procedures, prolonged half-lives, and lack of data limit their use in patients receiving ECMO.\textsuperscript{1}

Case reports of anticoagulation using danaparoid and fondaparinux have also been published, demonstrating safe use of both drugs without significant episodes of bleeding or thrombosis.\textsuperscript{68,69}

Muellenbach and colleagues\textsuperscript{70} examined a UFH-free venovenous ECMO strategy in 3 patients with multiple injuries, acute respiratory distress syndrome, and traumatic brain injury. The risks of systemic UFH administration are compounded in such patients. The patients experienced no observed bleeding or thrombotic events, and all survived. Although traumatic brain injury and severe intracranial bleeding are thought to be contraindications to initiating ECMO, this case series suggests that ECMO may be a lifesaving option in this subset of patients.

### Antithrombin Deficiency

Antithrombin is naturally produced by the liver and inhibits most coagulation enzymes to various degrees. Most of its endogenous anticoagulant effects are through inhibition of thrombin and factor Xa. Heparin resistance during ECMO has been described in up to 22\% of patients, and antithrombin depletion is an identified mechanism for heparin resistance.\textsuperscript{71} However, heparin resistance can occur without antithrombin deficiency.\textsuperscript{72} Goal antithrombin activity levels vary widely (50\%-100\%), and centers have various thresholds (<30-80\%) for replacing antithrombin. Other centers measure and treat antithrombin levels only in patients with persistently subtherapeutic anticoagulation or profound heparin requirements (≥25-35 U/kg per hour). The 2 primary modalities for replacing antithrombin are antithrombin concentrate (human or recombinant) and fresh frozen plasma. If antithrombin is administered, UFH should be closely monitored because a sudden decrease in UFH dosing requirements may occur. Beyond the significant cost, no study to date has shown improved outcomes in patients receiving antithrombin replenishment while receiving ECMO. Although a study by Byrnes and colleagues\textsuperscript{73} showed a significant increase in posttreatment anti-Xa levels compared to pretreatment anti-Xa levels, administration of antithrombin did not change heparin infusion rates and was associated with an increased frequency of ECMO circuit failure compared to patients who did not receive the intervention. This scenario may represent an ideal situation for the use of DTIs such as argatroban or bivalirudin.\textsuperscript{1,47}

### Role of Nurses in Anticoagulation Therapy

Given the high degree of variability in individual patient hemostasis, nurses should continually monitor for bleeding or thrombotic developments in patients receiving ECMO therapy. Nurses should give specific attention to cannulation exit sites and should monitor cannulas for fibrin streaks (often appearing as white streaks). Nurses can play a significant role in noting coagulation changes, which may be crucial to the overall care of the patient. Nurses should continue to assess patients’ coagulation status after ECMO decannulation to ensure that bleeding and thrombotic events, which can contribute significantly to patients’ morbidity and mortality, are not developing.

### Conclusion

Although ECMO therapy continues to gain prominence as a potentially lifesaving measure, its use is complicated by significant alterations in medication pharmacokinetic profiles. With an enhanced understanding of how ECMO may influence analgesic, sedative, anti-infective, and anticoagulation therapy, nurses can be prepared to assess potential medication failures resulting from the ECMO circuit. Continued research is needed to identify the optimal medication strategies in patients with these highly complex conditions.

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None reported.
To learn more about extracorporeal membrane oxygenation, read "Recovery, Risks, and Adverse Health Outcomes in Year 1 After Extracorporeal Membrane Oxygenation" by Tramm et al in the American Journal of Critical Care, July 2017;26:311-319. Available at www.ajcconline.org.

References


Extracorporeal membrane oxygenation (ECMO) continues to gain prominence as a potentially life-saving measure; however, its use is complicated by significant alterations in medication pharmacokinetic profiles. With an enhanced understanding of how ECMO may influence analgesic, sedative, anti-infective, and anticoagulation therapies, nurses can assess potential medication failures resulting from the ECMO circuit.

Pharmacokinetic Implications
- Interactions among circuit, drug, and patient factors can alter the pharmacokinetic profiles of medications through changes in drug sequestration, volume of distribution, and drug clearance.
- Drug clearance is also affected by ECMO for reasons other than critical illness. Worsening renal function is often seen in adult patients receiving ECMO and can limit excretion of renally cleared medications.
- The ECMO circuit may alter blood flow to the liver, which could affect the clearance of drugs with a high extraction ratio.

Analgesia and Sedation
- At the time of ECMO cannulation, patients should be adequately sedated to avoid possible air embolism via spontaneous breathing, minimize the metabolic rate, and avoid movement that might complicate cannulation.
- Nurses’ keen attention to changes in patient comfort, respiratory status, and hemodynamics allow for advanced discussions regarding therapeutic plans with the medical team.
- Nurses have important roles in monitoring patients for early cessation of sedation and constantly assessing the implementation of physical therapy. Nurses can continue to push for early mobilization.
- Daily measurements of analgesia and sedation levels are essential to ensure patients are being appropriately treated. Nurses are in a prime position to track potential changes in pharmacodynamics in real time by using patient-specific responses to agents.

Anti-infective Therapy
- Because of the lack of evidence regarding anti-infective medication use in patients receiving ECMO, individualizing therapy as much as possible is important.
- Nurses can be more active in deciding whether to withhold or administer doses on the basis of drug levels. Nurses also play a vital role in ensuring that drug levels are measured at the correct time, which can help optimize therapeutic drug monitoring.
- Nurses must use sterile technique when administering medications and cleaning patients to avoid introducing infectious organisms.

Anticoagulation Therapy
- Given the high degree of variability in individual patient hemostasis, nurses should continually monitor for bleeding or thrombotic developments in patients receiving ECMO therapy.
- Nurses should give specific attention to cannulation exit sites and should monitor cannulas for fibrin streaks (often appearing as white streaks).
- Nurses should continue to assess patients’ coagulation status after ECMO decannulation to ensure that bleeding and thrombotic events, which can contribute significantly to patients’ morbidity and mortality, are not developing. CCN