Chapter e26: Critical Care: Considerations in Medication Selection, Dosing, Monitoring, and Safety

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Appendix 3, Critical Care: Patient Assessment and Pharmacotherapy.

KEY CONCEPTS

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1. Intensive care units (ICU) are designed to support the complex needs of critically ill patients with acute organ dysfunction in need of a higher level of monitoring and treatment.
2. The four phases of critical illness include rescue, optimization, stabilization, and de-escalation, each of which can affect medication selection, dosing, and monitoring.
3. Ideal medications for use in the ICU have predictable bioavailability, fast onset, rapid titratability, and a wide therapeutic window.
4. Critically ill patients exhibit a uniquely complex pharmacokinetic profile and response to therapies that needs to be considered when individualizing drug regimens.
5. Acute changes to end-organ function occur more commonly in the ICU and dynamically affect drugs.
6. Perfusion deficits and iatrogenic exposures can decrease enteral, subcutaneous, and intramuscular drug bioavailability which makes the intravenous route preferred in acutely ill unstable patients in the ICU.
7. The use of advanced organ support devices is common in the ICU and each device differentially affects the pharmacokinetics and pharmacodynamics of medications.
8. Key properties of drugs susceptible to sequestration in the extracorporeal membrane oxygenation (ECMO) circuit include high percentage of protein binding and high degree of lipophilicity.
9. Highly protein-bound medications are readily cleared by molecular adsorbent recirculating system (MARS) and therapeutic plasma exchange (TPE), but not efficiently cleared by renal replacement therapies.
10. Many patient, provider, and environmental factors increase an ICU patient's vulnerability to medical errors, adverse medication reactions, and their related consequences, relative to their noncritically ill counterparts.

BEYOND THE BOOK

BEYOND THE BOOK

Watch the first 12 minutes of the video "Right dose, right now: customizing drug dosing for the critically ill patient" available at https://youtu.be/mG9BdYFocQk. This video briefly overviews some of the key pharmacokinetic and pharmacodynamic changes present in critically ill patients and the potential impact on anti-infective effectiveness and safety in the ICU.

INTRODUCTION

Epidemiology of Critical Illness

Since the poliomyelitis epidemic of the 1950s when mechanical ventilation was first introduced, significant advancements have been made in our understanding of the pathophysiology of syndromes of critical illness and the interventions needed to improve patient outcomes.[1] Only recently, however, have we begun to quantify the true global burden of critical illness. In the United States, 27% of all hospitalizations or 4.6 million stays annually include an intensive care unit (ICU) admission.[2] Short-term mortality for ICU patients is 8% to 22%, but can be much higher in patients with sepsis, acute respiratory distress syndrome, shock, or those in the developing world, where mortality may reach 50% to 60%.[3] Although surviving critical illness is a short-term goal, survivors can experience long-term physical, psychological, and cognitive consequences, collectively termed "post-intensive care syndrome." When considering these sequelae, care of critically ill patients is estimated to cost $121 to $263 billion annually in the United States, on par with the financial burden of cancer care or cardiovascular disease.[4] Clinicians and scientists seek new ways to more effectively prevent and treat critical illness to improve patient outcomes and limit the global health burden.

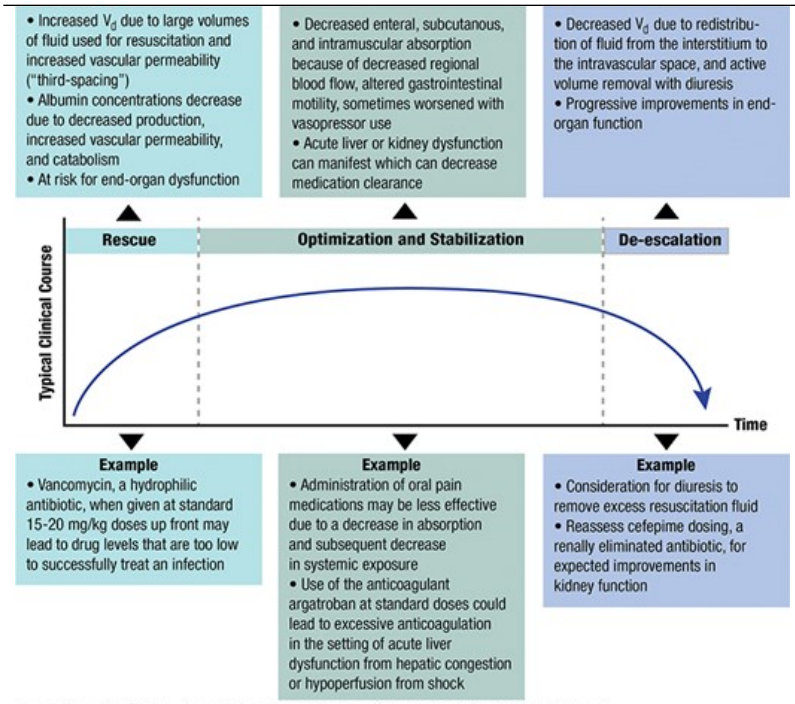
The Dynamic Trajectory of Critical Illness

1 Critical care medicine is a diverse discipline that integrates aspects of medicine, surgery, and anesthesia. Broadly, contemporary ICU patients include those with acute organ dysfunction in need of resuscitation or organ support and those in need of monitoring after a major event or intervention who are at high risk for complications (eg, surgical procedure, trauma, bleed).[5]

2 Generally, patients pass through four phases of critical illness on their path to recovery: rescue, optimization, stabilization, and de-escalation (Fig. e26-1). Movement through the phases of critical illness is dynamic and bidirectional. Upon presentation, ICU patients often exhibit a mismatch between systemic oxygen supply and demand, which can result in tissue hypoxia and end-organ dysfunction. Early interventions during the "rescue" phase often include fluid resuscitation, vasoactive medications, and the application of targeted organ support devices. After resuscitation during the "optimization" and "stabilization" phases, persistently increased capillary permeability from inflammation may perpetuate fluid leakage into the interstitium and an expanded volume of distribution. Continued use of vasoactive therapy may be necessary to preserve organ and tissue perfusion. After the point at which patients have stabilized and begin to experience clinical improvement, they pass into the "de-escalation" phase of care delivery, which includes active weaning of advanced medical support and efforts to restore them to their pre-illness health state.

FIGURE e26-1

Key pharmacokinetic and pharmacodynamic changes in the critically ill. There are four distinct phases of critical illness that patients may pass through in a dynamic and bidirectional manner: rescue, optimization, stabilization, and de-escalation. The rescue phase often includes fluid resuscitation, vasoactive medications, and the application of targeted organ support devices in the setting of hemodynamic instability and associated end-organ dysfunction. Optimization and stabilization phases may include continuation of therapies to achieve physiologic end points and preserve organ and tissue perfusion. The de-escalation phase includes active weaning of advanced medical support and efforts to restore patients to their pre-illness health state.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Checklists, protocols, and bundles are often used to optimize care during the dynamic course of critical illness. Patient care should still be individualized, but these tools provide a reasonable standard of care to support clinicians in this complex environment. Checklists increase adherence to best practices and improve clinical outcomes including length of stay and mortality.[6] One mnemonic proposed for a checklist to standardize patient assessment is FAST HUG. The component items include assessment of **F**eeding, **A**nalgesia, **S**edation, **T**hromboembolism prevention, **H**ead of the bed elevation, stress **U**lcer prophylaxis, **G**lucose control.[7] Others have expanded this to include **S**pontaneous breathing trial, **B**owel function evaluation, removal of **I**ndwelling catheters, and **D**e-escalation of antimicrobial, and other pharmacotherapies (FAST HUGS BID).[8] Each item may not apply to every patient every day, nor are these the only factors to evaluate in a critically ill individual. Rather, intentional evaluation with a streamlined, easily recalled mnemonic limits the potential to overlook essential components of standard care which are broadly applicable.

After critical illness, survivors may experience either complete or partial recovery or instead sustain permanent organ dysfunction.[9] Post-intensive care syndrome (PICS) is increasingly recognized as a complication of ICU survivorship. By one year after hospitalization, approximately half of patients experience impairments in physical, psychological, and/or cognitive function.[10] Standardized assessment for limitations in each of these domains is recommended within 2 to 4 weeks of discharge.[11] Some centers have developed "PICS Clinics" to comprehensively care for patients recovering from critical illness. Medication reconciliation, typically performed by a pharmacist, is a core component of post-dismissal evaluation for ICU survivors.[12] Other activities performed include adverse medication reaction identification and prevention/management, vaccination, and patient education.[13]

OVERVIEW OF MEDICATION USE PRINCIPLES IN THE ICU

3 Because of the dynamic nature of critical illness, ideal medication characteristics in the ICU setting include a predictable bioavailability, fast onset, rapid titratability, and a wide therapeutic window. In critical care, the intravenous route of drug administration is more common and often more desirable than the enteral route. Intravenous drug delivery assures 100% bioavailability even when tissue or organ perfusion is compromised. Intravenous medication use is also reliable when mentation is altered or advanced organ support devices (ie, invasive mechanical ventilation) limit access to the enteral route of drug delivery.

Rapid onset, titratable medications are preferred in the ICU. It is not uncommon for critically ill patients to receive multiple continuous intravenous infusions including vasoactive drugs, analgesics, sedatives, antithrombotics, and insulin. These medications may be used to treat acute conditions or chronic comorbidities. As an example, a critically ill patient with a new submassive pulmonary embolism will initially receive intravenous

unfractionated heparin rather than warfarin or a direct oral anticoagulant via the enteral route. This assures rapid, predictable anticoagulation, but provides flexibility should the patient decompensate and require alternative interventions such as thrombolysis. With clinical improvement, more invasive therapies will be transitioned to suitable long-term options for home-going care. Titratable parenteral therapies may also be used to replace long-acting chronic medications. For instance, a patient with a history of type 2 diabetes mellitus managed with insulin glargine prior to admission who is admitted to the ICU after cardiovascular surgery may initially be converted postoperatively to an intravenous infusion of regular insulin for 24 to 48 hours until they clinically recover.

Under- and over-treatment are risks associated with medication use in ICU, so clinicians prioritize essential medications and prefer agents with wide therapeutic indices. A high severity of illness with decreased physiologic reserve warrants aggressive dosing to maximize therapeutic success. In sepsis, loading doses of wide therapeutic window antibiotics are used to optimize early treatment of the infection. While aggressive dosing is often warranted in the ICU, clinicians must also be attentive to ICU patients' heightened susceptibility for adverse medication reactions, due to underlying disease state(s), altered end-organ function, polypharmacy, and medication interactions.[14] Medications for chronic conditions may be adjusted or temporarily held to limit toxicity, interactions, or minimize confounding of the complex clinical picture. As an example, chronic oxybutynin for overactive bladder may be held due to the risk for anticholinergic side effects such as delirium and the presence of an indwelling urinary catheter which obviates the clinical need. Chronic gabapentin for neuropathic pain may be dose reduced or temporarily held due to acute kidney injury or altered mentation, with careful monitoring of pain control.

Patients in the ICU are closely followed for response to therapy and changes in clinical status, vital signs, and laboratory or imaging findings. Preferably, an objective tool would be used to monitor medication therapy, such as continuous blood pressure monitoring for titration of vasopressors. Plasma concentrations of medications may also help guide therapy, but to date drug concentrations are available for relatively few medications (eg, vancomycin, aminoglycosides) and the relationship between concentration and clinical effect is often unclear. In the absence of these objective monitoring tools, surrogate markers are often used to assess progress toward therapeutic endpoints. For anti-infectives, defervescence, white blood cell (WBC) count trajectory, and resolution of radiographic findings may be used to guide medication discontinuation, although no one of these tests definitively indicates that an infection has been eradicated. Just as the critically ill patient's course is dynamic, so too should be their pharmacotherapy plan. Clinicians must continuously evaluate medication regimens in the ICU and iteratively revise the program to achieve the therapeutic goals.

PHARMACOKINETIC AND PHARMACODYNAMIC CHANGES IN THE CRITICALLY ILL

4 Critically ill patients suffer from physiologic changes throughout their illness that alter the relationship between a medication's dose and its corresponding disposition (pharmacokinetics) and/or the response (pharmacodynamics).[15,16] Acute, or in many cases, acute-on-chronic organ dysfunction influences the dose-response relationship. Whereas chronic comorbidities that impact medication disposition are routinely evaluated in pharmacokinetic studies and early-phase clinical trials, acute organ dysfunction is difficult to detect, dynamic, and its impact on systemic drug exposure is challenging to quantify.[17,18] Extrapolation of dosing regimens derived from noncritically ill subjects to the critically ill patient may result in therapeutic failures or unintended toxicities from altered bioavailability, volume of distribution, and elimination. Creating an individualized therapeutic plan for critically ill patients through an applied understanding of their altered pharmacokinetic and pharmacodynamic profile is essential for maximizing therapeutic benefit while minimizing potential toxicity. Pharmacokinetic changes in critical illness and selected medications affected are presented in Table e26-1.

TABLE e26-1

Pharmacokinetic Changes in Critical Illness

PK Parameter	Changes in the Critically Ill	Etiologies	Example Medications Affected
Absorption	↓ Absorption	• Perfusion abnormalities	Enteral, intramuscular, or subcutaneous medications *eg, itraconazole (capsules need an acidic medium for absorption), phenytoin (significant*

		• Decreased GI motility • Altered gastric pH • Bowel wall edema • Drug-nutrient interactions	*drug-nutrient interactions), subcutaneous enoxaparin (incompletely absorbed in the setting of vasopressors and edema)*
Distribution	↑ Vd	• Large-volume resuscitation • Capillary leak syndrome • Ascites • Mechanical ventilation	Hydrophilic medications *eg, aminoglycosides, beta-lactams, daptomycin, hydromorphone, morphine, vancomycin*
		• Hypoalbuminemia	Albumin-bound medications *eg, amiodarone, ceftriaxone, midazolam, morphine, phenytoin, propofol, valproic acid, warfarin*
		• Extracorporeal circuits with expansive surface area (ECMO)	Lipophilic medications *eg, diazepam, fentanyl, fluoroquinolones, macrolides, midazolam, propofol*
	↓ Vd	• Decreased α1-acid glycoprotein	Medications bound to α1-acid glycoprotein *eg, azithromycin, carvedilol, fentanyl, lidocaine, olanzapine, phenobarbital*
Metabolism	↑ Metabolism	• Hepatic enzyme induction • Augmented hepatic blood flow	Flow dependent medications (hepatic extraction ratio >0.7) *eg, propofol, midazolam, morphine, metoprolol*
	↓ Metabolism	• Hepatic enzyme inhibition • Decreased hepatic blood flow	Flow-independent medications (hepatic extraction ratio <0.3) *eg, warfarin, diazepam, phenytoin*
Excretion	↑ Clearance	• Augmented renal clearance • Extracorporeal removal	Renally eliminated medications *eg, beta-lactam antibiotics, vancomycin, enoxaparin, gabapentin, levetiracetam*
	↓ Clearance	• Acute kidney injury	Nephrotoxic medications *eg, aminoglycosides, NSAIDs, antivirals, contrast*

ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; PK, pharmacokinetic; Vd, volume of distribution.

Absorption

Pharmacokinetics is the study of medication movement through the body and includes drug absorption, distribution, metabolism, and excretion, each of which can be affected by critical illness (see Chapter e6).[15,16] Bioavailability refers to the fraction of administered medication that reaches the systemic circulation. The extent of drug absorption is the main factor that influences a medication's bioavailability. Intravenous administration of medication therapy results in 100% bioavailability, whereas intramuscular, subcutaneous, transdermal, sublingual, and enteral formulations typically have lower bioavailability. Medication-specific factors affecting the rate and extent of absorption include the drug size, water solubility, lipophilicity, ionization, dissociation rate constant, first-pass metabolism, and presence of a binder or chelator. Patient factors that affect absorption in the critically ill include gastric pH, gastrointestinal motility, regional blood flow, and peripheral or gut edema.[16] The time to maximum concentration (T_{max}) is used to describe rate of absorption, whereas maximum concentration (C_{max}) and area under the plasma concentration-time curve (AUC) reflect the extent of absorption and overall bioavailability.

Enteral Absorption in Critical Illness

Numerous factors alter the rate and extent of absorption of an enterally administered medication in the critically ill. Perfusion deficits, delayed gastric emptying or dysmotility, loss of bowel integrity (ie, perforations), surgical alterations in anatomy, and altered pH can lead to unpredictable enteral absorption of medications.[16] Additionally, medications can adhere to the gastrointestinal and small bowel tubes used for enteral feeding and medication administration in the ICU, which decreases the delivered dose.

In shock, blood flow is shunted to vital organs (eg, brain, heart) at the expense of other nonvital tissues such as the gastrointestinal tract.[16,19] While vasopressors tend to restore macrocirculation as evidenced by indicators like mean arterial pressure, microcirculatory failure may persist.[20] Absorption deficits in shock states have been described, but for many medications, these pharmacokinetic changes do not universally translate into an altered clinical response.[21,22] For example, in 50 critically ill patients prescribed acetaminophen, 25% of whom had septic shock, enterally administered medication was associated with a longer time to maximum concentration and a slight decrease in overall drug exposure compared to intravenously administered medication, but pain scores and core temperatures were similar between groups.[21]

Delayed gastric emptying and gastrointestinal dysmotility affect more than half of ICU patients.[23] The etiologies are multifactorial and include acute and chronic diseases, electrolyte abnormalities, surgery, and circulating cytokines, among other factors. Medications can lead to or worsen these symptoms. Vasopressors override vagal tone and reduce gastric emptying.[23] Opioids diminish motility by activating peripheral mu receptors in the gastrointestinal tract.[24] Medications with anticholinergic properties such as first-generation histamine-1 receptor antagonists (eg, diphenhydramine) or calcium channel blockers (eg, diltiazem) reduce gastric emptying.[23] These gastrointestinal changes can increase the T_{max}, or slow the rate of absorption, which may delay the onset of medication effect. Systemic drug exposure evidenced by C_{max} or AUC may be comparable or slightly reduced. This has been demonstrated in pharmacokinetic studies of fluoroquinolones in the critically ill.[25] Therefore, parenteral medication administration may be preferred to the enteral route, especially early in critical illness, when time to onset and extent of drug exposure is essential.

Medications can adhere to the lumen of gastric or small bowel tubes thereby decreasing systemic drug exposure. Several possible drug-nutrient interactions exist as a function of medication complexation or altered gastrointestinal motility and osmolarity. Enteral feeding and acid-suppressive therapies alter the gastrointestinal pH. Depending on the degree of drug ionization (pKa), absorption can be affected. Reduced absorption of amiodarone, carbamazepine, ciprofloxacin, phenytoin, fluconazole, minocycline, digoxin, and warfarin has been observed in the presence of enteral feeds.[26,27] Stress ulcer prophylaxis with proton pump inhibitors or histamine-2 receptor antagonists increases the gastric pH and decreases absorption of antifungals, antivirals, and tyrosine kinase inhibitors, to name a few.[28] To mitigate the impact of these interactions, it may be appropriate to pause tube feedings 1 to 2 hours before and after medication administration with appropriate flushing of the enteral tube. In this situation, adjustments in the tube feeding rates when running should be made to account for these pauses and ensure adequate caloric provision. Acid-suppressive therapy should be re-evaluated to determine clinical indication. Also, certain medications such as extended-release products are not

suitable for administration via enteric tubes. Often these products are converted to an alternate medication formulation such as an equivalent immediate release product that can be crushed. This change adds benefit as the duration of action of immediate release preparations is typically shorter, which facilitates more rapid titration in the ICU.

Subcutaneous or Intramuscular Absorption

Reduced peripheral perfusion from the use of vasopressors and increased peripheral edema from large-volume fluid resuscitation may impair systemic absorption of medications given subcutaneously or intramuscularly. As an example, absorption of subcutaneously administered heparin for venous thromboembolism prophylaxis is reduced in the presence of vasopressors, which then can increase the risk of clot formation.[29] Less than one-third of ICU patients on standard doses of chemical prophylaxis achieved the target peak anti-factor Xa levels, a surrogate marker for reduced effectiveness. Use of vasopressors was a risk factor for undetectable peak anti-factor Xa levels.[30] Similarly so, edematous individuals exhibit reduced heparin absorption compared to non-edematous patients, although the findings have been less consistent.[31,32]

In summary, intravenous administration may be preferable in acutely ill, hemodynamically unstable patients. However, once stabilized, a transition to enteral medication delivery should be pursued to limit costs, avoid excess fluid administration, and decrease the need for sustained intravenous access.[33]

Distribution

Volume of distribution refers to the theoretical volume (L) of fluid in which a given dose (mg) of medication distributes to yield the observed plasma concentrations (Chapter e6). Medication distribution is highly dependent on the patient's physiology (eg, blood flow, body composition, protein concentrations) and the physicochemical properties of drugs (eg, affinity for protein binding, solubility, molecular weight, degree of ionization at a given physiologic pH).[15,16] Major contributors to changes in volume of distribution in the critically ill patient include fluid shifts, tissue perfusion, and changes in plasma protein binding. In general, hydrophilic (water-soluble) medications exhibit a smaller volume of distribution and are dependent on tissue perfusion and blood volume. Reduced tissue perfusion decreases distribution of hydrophilic medications from the central compartment to the extravascular space. This phenomenon can decrease drug exposure at the target site of action. In contrast, lipophilic (lipid-soluble) medications penetrate well into tissues independent of blood flow, which increases the apparent volume of distribution.

In critical illness, fluid shifts may result from resuscitation, cirrhosis, heart failure, thermal injury, mechanical ventilation, or kidney failure. Endothelial glycocalyx, a carbohydrate-rich layer, maintains the osmotic gradient between the vessel wall and the bloodstream. Degradation of the glycocalyx in inflammatory states such as in sepsis, trauma, and ischemia-reperfusion injury can lead to increased capillary permeability.[34] This increased capillary permeability coupled with large volume resuscitation leads to redistribution of fluid from the intravascular compartment to the interstitium. Accumulation of excessive fluids in the interstitium, also referred to as "third-spacing," results in hypotension, decreased cardiac output, and manifests as pulmonary and peripheral edema, pleural effusions, ascites.[16,19] Patients are often grossly net volume positive, but intravascularly deplete. These changes lead to an expanded volume of distribution of hydrophilic medications, such as aminoglycosides, with corresponding reductions in plasma concentrations and potentially decreased effectiveness.[35,36] For example, amikacin volume of distribution may be increased from the normal range of 0.25 to 0.35 L/kg to as high as 0.65 L/kg in some critically ill patients.[35] To achieve desired therapeutic concentrations for a hydrophilic medication, larger doses may be required. In contrast, lipophilic medications (eg, fluoroquinolones, macrolides) remain largely unaffected by fluid shifts.[16]

In critical illness, serum concentrations of plasma proteins are altered, which modifies the unbound fraction of a drug and the overall distribution. Plasma albumin concentrations decrease as a consequence of increased vascular permeability, decreased production, and increased catabolism. Additionally, most patients with liver dysfunction will be hypoalbuminemic due to synthetic dysfunction. In contrast, alpha 1-glycoprotein concentrations increase in response to an increase in physiologic stress. In general, acidic medications bind to albumin (eg, valproic acid, phenytoin, propofol) and basic medications bind to alpha 1-glycoprotein (eg, fentanyl, carvedilol).[16] These physiologic changes lead to an increase in free plasma concentrations of highly protein-bound (>90%) acidic medications and a decrease in free plasma concentrations of basic medications (Table e26-1). Uremia, metabolic derangements, and medication interactions may also lead to alterations in plasma protein binding.

Metabolism

Overview of Hepatic Drug Clearance

The liver serves as the primary site for medication metabolism. To a lesser extent medications are metabolized in the gastrointestinal tract, kidneys, lung, and brain.[16] Hepatic clearance (CL_H) is a function of blood flow (Q) and the hepatic extraction ratio (E) and is calculated as $CL_H = Q \times E$ (see Chapter e6). Hepatic medication elimination is altered during critical illness due to changes in blood flow (ie, with high-extraction ratio medications) and intrinsic enzyme activity (ie, with low-extraction ratio medications).

Perfusion

The liver is a highly perfused organ, receiving approximately 20% to 30% of the cardiac output. When cardiac output and thus hepatic perfusion are altered in critical illness, medication clearance and systemic exposure may be dramatically impacted. Reductions in hepatic blood flow as with cardiogenic or hypovolemic shock, mechanical ventilation, vasopressor use, or hypothermia decreases the clearance of high-extraction ratio medications (>0.7; eg, propofol, midazolam, morphine, metoprolol).[37] Moreover, increased bioavailability of enterally administered medications with a high-extraction ratio will be observed due to lower first-pass metabolism. In these cases, dose reductions or use of an intravenous formulation should be considered. An opposite phenomenon can occur in the early phases of distributive shock. Cardiac output acutely increases to compensate for end-organ perfusion deficits. This hyperdynamic state temporarily augments hepatic perfusion and could increase clearance of high-extraction ratio medications.[38]

Enzyme Activity

The bioavailability of low-extraction ratio medications (<0.3; eg, warfarin, diazepam, phenytoin) is primarily affected by intrinsic metabolic activity of the liver. Medications that undergo phase I metabolism mediated by cytochrome P450 (CYP) isoenzymes will have lower metabolism in the setting of systematic inflammatory response and burns.[39] Temporary induction of therapeutic hypothermia (32-34°C for 24-hours) has been used to improve neurologic prognosis after cardiac arrest. Therapeutic hypothermia to this threshold leads to decreased CYP activity and a corresponding decrease in clearance of low-extraction ratio medications.[37] Elimination of sedatives, analgesics, and neuromuscular blocking agents have been relatively well studied in this context.[37] As an example, both fentanyl and midazolam are hepatically cleared via CYP3A4, and during therapeutic hypothermia, their clearance is decreased by 20% to 45%.[37] This could lead to increased systemic exposure and prolonged sedation which, in the case of cardiac arrest patients, may preclude effective neurologic prognostication. When using these medications in the setting of therapeutic hypothermia, consider starting at lower dosing ranges with more judicious titration increments, to use the lowest dose possible to achieve the desired effect.

Acute Alterations in Liver Function

Assessment of Liver Function

The Food and Drug Administration recommends that the pharmacokinetics of drugs with >20% hepatic elimination be evaluated across the spectrum of liver disease as stratified by Child-Pugh classification (mild, moderate, and severe).[18] The Child-Pugh score includes parameters of liver synthetic function (ie, bilirubin, albumin, international normalized ratio) and clinical status (ie, degree of ascites and hepatic encephalopathy).[40] It is important to recognize that generalizing recommendations that extrapolate these pharmacokinetic and medication dosing data from stable patients with chronic conditions to complex ICU patients with acute organ dysfunction or multiorgan failure is problematic.

Numerous acute factors can interfere with the components of the Child-Pugh classification leading to a misclassification of hepatic function. As mentioned previously, albumin is a negative acute-phase reactant with suppressed plasma concentrations in critical illness, independent of hepatic function.[16] The international normalized ratio may be affected by malnutrition, disseminated intravascular coagulation, or antibiotics. Encephalopathy may be attributable to sepsis, delirium, metabolic disturbances, and medications. In each of these cases, calculation of the Child-Pugh score from acute variables could indicate a greater degree of hepatic impairment than truly exists. This could result in recommendations for medication doses that are too low to effectively treat the underlying disease state.

Conditions of Acute Liver Dysfunction

Acute liver dysfunction exhibits a very different natural course than chronic liver disease. Whereas chronic liver disease is a relatively stable, irreversible, reduction in hepatic function, acute conditions such as congestive hepatopathy or hypoxic hepatitis are dynamic and responsive to interventions.

Congestive hepatopathy. Hepatic congestion is common in patients with acute decompensated heart failure (ie, cardiac index < 1.5 L/min/m^2 [0.025 L/s/m^2]) or valvular disease (ie, severe tricuspid regurgitation). This can result in modest elevations in hepatic enzymes and total bilirubin without clinically apparent hepatic disease.[41] With adequate diuresis, this syndrome can be transient and resolve in a matter of days. A minority of patients with heart failure can progress to congestive liver fibrosis and cardiac cirrhosis over time, which is more akin to other sources of chronic liver disease.

Hypoxic hepatitis. Hypoxic hepatitis, also referred to as "ischemic hepatitis" or "shock liver" occurs when either arterial blood volume or oxygen delivery is insufficient for hepatocyte survival.[42] Endogenous compensation for oxygen extraction leads to relative sparing of the liver and a low overall incidence of hypoxic hepatitis (1%-2% in ICU patients).[42] Profound or persistent hypotension can result in hypoxic hepatitis, which has an associated mortality of 50% at 1 month. The general diagnostic criteria for hypoxic hepatitis includes 1) acute cardiopulmonary failure, 2) a substantial, but transient increase in serum aspartate or alanine aminotransferase activity [AST or ALT >1000 international units/L [16.7 μkat/L] occurs in 57% of patients[42]], and 3) exclusion of other etiologies such as viral hepatitis or toxin-induced liver disease.[43] Increases in hepatic enzymes 10- to 20-fold higher than normal typically peak 1 to 3 days after the acute event and normalize by 5 to 10 days if the triggering physiologic disturbance is addressed.

Impact of Acute Liver Dysfunction on Medication Management

The degree to which acute liver dysfunction affects medication selection, dosing, and monitoring involves the complex interplay between the underlying etiology and pattern of the condition, the therapeutic window of the medication, the available alternative agents, the medication hepatic extraction ratio, and the enzymatic pathways involved in the medication's metabolism. Congestion in the liver improves rapidly with diuresis, operative intervention, or mechanical circulatory support. Decreased medication clearance in this setting is transient and typically reversible in a matter of days. This has been demonstrated with warfarin after valvular surgery where transient reductions in doses are necessary in the postoperative period, but doses normalize as cardiac output and volume status improve.[44] In hypoxic hepatitis, improved perfusion and oxygen delivery typically lead to resolution of liver dysfunction within several days of the insult.

Dosing of hepatically cleared medications in critically ill patients is distinct from stable chronic liver disease. For instance, caspofungin is an intravenous antifungal that undergoes primary hepatic elimination. The package insert recommends a 30% dose reduction (50-35 mg/day) for individuals with moderate hepatic impairment (Child-Pugh scores 7-9) and drug avoidance in patients with severe hepatic impairment (Child-Pugh scores 10 or greater).[45] In a patient with septic shock with an albumin of 2.5 mg/dL (25 g/L) without cirrhosis, the Child-Pugh score would still be 7, indicative of a recommended dose reduction. Misapplying this score to acute liver dysfunction or laboratory abnormalities common in critical illness risks an inappropriate dose reduction and treatment failure. Caspofungin has a wide therapeutic window and mortality in this population is high, so doses of at least 50 mg/day are warranted.

Excretion

The kidneys serve as the primary organ responsible for medication elimination, followed by the biliary tract, feces, and lungs.[16] Approximately 60% of medications are eliminated extensively by the kidneys; therefore, it is important to have an accurate assessment of kidney function for medication dosing in the ICU.[46]

Assessment of Kidney Function

Classically, either the estimated creatinine clearance (eCrCl) or estimated glomerular filtration rate (eGFR) based upon the serum creatinine has been used to quantify kidney function for medication dose adjustments.[47] Serum creatinine concentration and urine output are used to diagnose acute kidney injury (Chapter 61) and chronic kidney disease (Chapter 62).[48] Creatine from dietary protein is primarily stored in skeletal muscle and eventually metabolized by the liver to form creatinine. Creatinine then undergoes passive elimination via glomerular filtration and, to a lesser degree, active tubular secretion, thus the observed concentration is generally inversely related to GFR.[49]

When these tools are applied to renal dose adjustment of medications in the critical care setting, numerous potential sources of error are introduced.

In ICU patients with altered dietary intake, deconditioning, inflammation, or cachexia, creatinine production may be reduced. Large-volume fluid resuscitation can also dilute the observed serum concentration of creatinine. An adjustment factor for diluted creatinine has been proposed for research purposes, but it is rarely used by bedside care providers as fluid balance is often inaccurate and the calculation is cumbersome.[50]

Conditions Associated with Acute Alterations in Kidney Function

Acute Kidney Injury (AKI)

Creatinine lags by as much as 48 hours from the onset of kidney damage and as much as 50% of kidney function is lost before detectable changes in serum creatinine occur.[49] This is significant as 20% to 50% of critically ill patients experience AKI, an independent predictor of increased risk of morbidity, mortality, and resource utilization.[51,52] During this so-called "creatinine blind" period, patients are at risk for undetected medication accumulation and avoidable nephrotoxin exposure. Similarly, during renal recovery, failure to incrementally increase doses or reintroduce held therapies could lead to undertreatment of acute and chronic conditions.

Augmented Renal Clearance (ARC)

Although AKI is typically the focus of acute care nephrology, ARC, defined variably as a measured or estimated CrCl >120 to 160 mL/min/1.73 m^2 (1.16-1.54 mL/s/m^2), is an important consideration in the ICU and contributes to *underdosing* of medications.[53] Hyperdynamic cardiac function, increased renal blood flow, and systemic inflammation are just some of the mechanistic explanations proposed for ARC, yet much still remains to be understood about this condition. Predictors of ARC include younger age, surgical rather than medical patients, trauma, burns, and brain injury. Maximal solute clearance is observed 5 to 7 days after the injury/event. Serum creatinine is somewhat insensitive to these extreme values and dosing algorithms rarely stratify recommendations among patients with GFR > 90 mL/min (1.5 mL/s) into those with and without ARC. Critically ill patients with ARC who receive renally eliminated antibiotics may have a twofold increased risk of therapeutic failure compared to patients without ARC.[54]

Future Directions for Kidney Assessment

Given the known limitations of creatinine and urine output, in the last decade new technologies (real-time GFR monitoring using fluorescent tracers) and alternate serum and urine biomarkers (eg, serum cystatin C, urinary TIMP2•IGFBP7) have emerged to more accurately and precisely estimate GFR and identify patients at risk for or with early evidence of AKI.[55] Application of these new tools to medication selection and dosing is in its infancy, but preliminary evidence is promising.[56–58]

ADVANCED ORGAN SUPPORT

Significant advancements have been made in organ support technology concurrent with advancements in our understanding of critical illness syndromes. Modern devices include mechanical ventilation, extracorporeal membrane oxygenation (ECMO), therapeutic plasma exchange (TPE), and extracorporeal liver support systems (ELSS). Key features of these devices are presented in Table e26-2. Operational considerations of these methodologies and a detailed overview of renal replacement therapy are described in Chapter 61.

TABLE e26-2

Key Features of Advanced Organ Support Devices

Device	Basic Circuit Components	Adjunctive Solution(s)	Anticoagulation	Frequency	Features of Medications Likely to Be Impacted
Therapeutic plasma exchange (TPE)	• Tubing • Centrifugal pump • Cell separator • Plasma waste bag	• Crystalloid prime • Albumin or fresh frozen plasma replacement	• ACD-A citrate	Intermittent (1-4 hours/day); every 48-hours or as per the indication	• Low Vd • High protein binding • Administered at TPE initiation
Continuous renal replacement therapy (CRRT)	• Tubing • Roller pump • Filter • Effluent bag	• Crystalloid prime • Commercially available replacement fluids for convective clearance CRRT modalities (eg, Prismasol®, Phoxillum®)	• None • UFH • ACD-A citrate	Continuous	• Small molecule • Low Vd • Low protein binding
Extracorporeal membrane oxygenation (ECMO)	• Tubing • Centrifugal pump • Membrane oxygenator	• Crystalloid prime	• UFH • Direct thrombin inhibitor	Continuous	• High protein binding • Lipophilic (log P >2)
Extracorporeal liver support systems (ELSS)	• Tubing • Roller pump • High-flux polysulphone membrane (MARS® Flux) • Components of dialysis	• Crystalloid prime • Replacement fluid analogous to CRRT	• UFH	Intermittent (typically 6-8 hours/day)	• Both low and high protein binding • Low Vd

ACD-A, anticoagulant citrate dextrose solution A; TPE, therapeutic plasma exchange; UFH, unfractionated heparin; Vd, volume of distribution.

Mechanical Ventilation and Aerosolized Medication Delivery

The primary routes of medication administration in ICU patients are enteral and intravenous, but aerosolized medication delivery is a promising adjunct or alternative. Inhaled medications offer several advantages: rapid onset of action, ability to achieve high lung tissue drug concentrations for a sustained period of time, limited systemic toxicity, and no requirement for intravenous access. For these reasons, nearly one in four critically ill patients is administered at least one aerosolized therapy during their ICU stay, most commonly, bronchodilators, corticosteroids, and anti-infectives.[59]

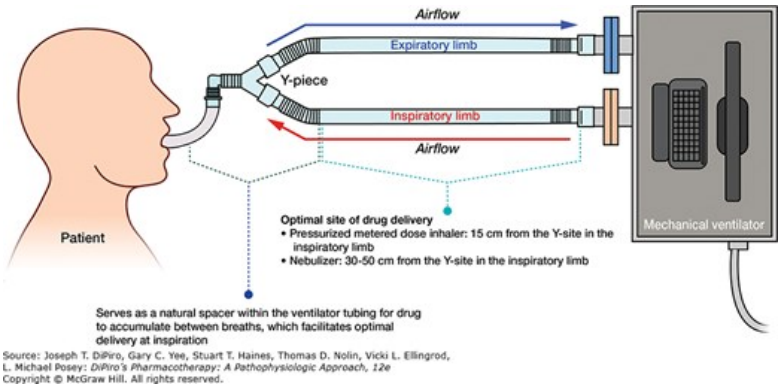
Factors That Influence Adequacy of Aerosolized Medication Delivery

Several patient, medication, and delivery-factors affect successful administration of aerosolized therapies to critically ill patients. Patient factors include bronchoconstriction, inflammation, mucous quality or quantity, and chronic lung diseases. Particle size is one drug factor that impacts the effectiveness of aerosolized medications. In order to adequately deliver medications to the terminal bronchioles and alveoli, drug particles must be aerosolized to a mass median aerodynamic diameter (MMAD) less than 5 µm. MMADs greater than 5 µm will deposit in the ventilator circuit or central airways rather than the more distal site of action.[60,61] Particle size is a function of medication formulation and delivery device (eg, metered dose inhaler vs nebulizer – jet, ultrasonic, or vibrating mesh). Other medication factors that impact effectiveness and tolerability include solubility, pH, and osmolarity. Highly soluble medications have heightened systemic absorption from the lungs and decreased overall contact time at the site of action. Medications with an altered pH or high osmolarity can induce bronchospasm, which jeopardizes deposition at the site of action and compromises patient tolerance. Concurrent nebulization of multiple medications can lead to incompatibilities and decreased effectiveness.[62] Finally, use of a pressurized metered dose inhaler must be coordinated with inspiratory effort to maximize medication delivery. Nebulized medications can be delivered independent of the respiratory cycle, but are associated with medication waste during continuous administration and longer administration time.

During mechanical ventilation, circuit set-up impacts the ability of a medication to reach the site of action and its corresponding effectiveness. Even with in-line chamber spacers, nebulizers that coordinate with the inspiratory cycle, and use of ventilator settings to optimize medication delivery, only 10% to 15% of the medication delivered reaches the lung parenchyma with the remainder lost to deposition on the artificial airway. To optimize aerosolized medication delivery during mechanical ventilation, it is recommended to synchronize administration with the respiratory cycle and place the inhaler adapter/chamber or the nebulizer about 15 cm and 30 to 50 cm, respectively, from the patient Y-piece in the inspiratory limb of the circuit (Figure e26-2). If the patient has a passive heat and moisture exchange (HME) in circuit, the HME should be removed before medication administration or the drug should be delivered between the HME and the patient.[63] Optimal settings for medication delivery during invasive mechanical ventilation include a tidal volume of at least 500 mL, a lengthened inspiratory flow time, and an inspiratory flow rate of 30 to 50 L/min. If ventilator settings are adjusted for medication administration, then they must be restored thereafter.[64]

FIGURE e26-2

Aerosolized medication delivery during mechanical ventilation. Optimization of aerosolized medication delivery during mechanical ventilation includes synchronized administration with the respiratory cycle and placement of the inhaler adapter/chamber or nebulizer about 15 cm and 30 to 50 cm, respectively, from the patient Y-piece in the inspiratory limb of the circuit.



Aerosolized Antibiotics for Pneumonia

Outside of anti-inflammatories and bronchodilators, gram-negative antibiotics are the next most common aerosolized agents used in the ICU. Inhaled colistin (75-150 mg colistimethate nebulized twice daily) and inhaled tobramycin (300 mg nebulized twice daily) have the greatest degree of evidence in support of their use as an adjunct for treatment of multidrug-resistant gram-negative pneumonia. Updated guidelines recommend the use of inhaled colistin along with systemic polymyxin therapy for hospital-acquired pneumonia from *Acinetobacter* spp. or other gram-negative species sensitive only to polymyxins.[65] For ventilator-associated pneumonia (VAP) caused by gram-negative organisms with susceptibility only to aminoglycosides or

polymyxins, systemic and inhaled therapy should be administered concurrently to optimize pulmonary concentrations of medication and limit development of resistance. Patients with VAP unresponsive to systemic therapy are suitable candidates for salvage use of adjunctive inhaled agents given the high mortality rate of the disease and the relatively low risk of toxicity from the inhaled medication.[65]

Extracorporeal Medication Disposition and Clearance

7 Extracorporeal organ support devices including renal replacement therapy, ECMO, TPE and ELSS can be used as temporizing measures while a patient's underlying condition improves and/or other interventions take effect. These devices markedly influence medication disposition and must be considered when developing patient-specific pharmacotherapy regimens.

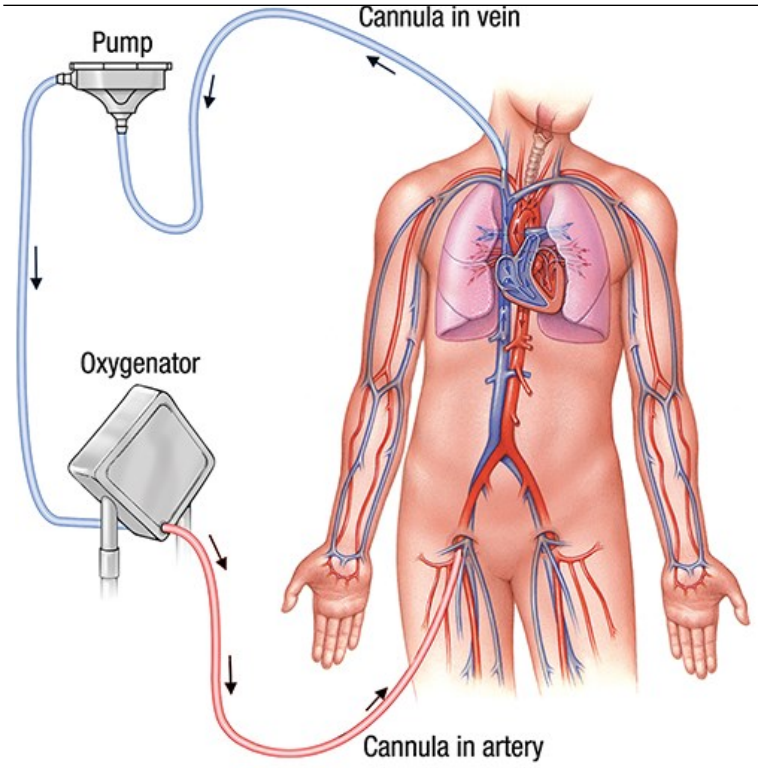
Continuous renal replacement therapy (CRRT) and ECMO are around-the-clock therapies, which establishes a new "steady state" for the patient. In contrast, hemodialysis, TPE, and ELSS are intermittent (2-12 hours/day), which changes medication disposition and elimination when the patient is "on support" versus "off support." Unfortunately, there is a dearth of pharmacokinetic trials that characterize drug disposition during TPE, ECMO, and ELSS. Furthermore, while *in vitro* studies are useful for assessing the effect of a closed-loop extracorporeal circuit on medication clearance, they are somewhat limited as they do not integrate underlying pathophysiologic changes in critical illness that occur in parallel. Pharmacokinetic changes during extracorporeal support depend on the circuit, priming solution, and physicochemical properties of the medication (Table e26-2). This leaves clinicians with the difficult task of selecting medications and dosage regimens for patients that are based on extrapolation from low-quality evidence and patient response to therapy.

Extracorporeal Membrane Oxygenation (ECMO)

ECMO provides gas exchange and hemodynamic support to individuals with respiratory or cardiac failure. Blood is drained through large-bore cannulas, pumped through an oxygenator (usually by means of a centrifugal, non-pulsatile pump), and actively returned as oxygenated blood back into the body (Figure e26-3). Venovenous (VV) cannulation is primarily for respiratory failure as deoxygenated blood from the vena cava or right atria is removed and returned as oxygenated blood near the right atrium. VV ECMO relies on native heart function to circulate blood to maintain end-organ perfusion. Peripheral or central venoarterial (VA) cannulation can be used to address both cardiac and respiratory failure. Peripheral cannulation removes blood from the vena cava via an internal jugular or femoral vein and returns oxygenated blood to a femoral artery (or descending aorta with axillary cannulation). Central cannulation removes blood from the right atrium and returns the blood oxygenated into the ascending aorta.

FIGURE e26-3

Extracorporeal membrane oxygenation (ECMO) circuit. Schematic representation of a patient cannulated for venoarterial extracorporeal membrane oxygenation (ECMO). Deoxygenated blood is drained from the patient and pumped through an oxygenator (carbon dioxide from the blood diffuses out and oxygen saturates the hemoglobin) and actively returned as oxygenated blood back into the patient.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Pharmacokinetic Changes During ECMO

The primary pharmacokinetic change observed in ECMO patients is an increased volume of distribution.[66] Variability in medication adsorption to the circuit is dependent on the age of the circuit, the type of membrane oxygenator, and composition of the tubing. Medication clearance changes have also been observed, but the directional impact varies and it is less consistent. When designing pharmacotherapy regimens drug properties along with the potential interactions with the ECMO circuit should be considered.

Increases in medication volume of distribution have been attributed to hemodilution or sequestration of medications within the circuit.[66] At the initiation of ECMO, hydrophilic medications may have an increase in volume of distribution either from the initial bolus of prime solution or an inflammatory response with capillary leak. The fluid bolus can also cause a dilution of plasma proteins and an increase in free fraction of protein-bound medications. 8 Throughout therapy, lipophilic and highly protein-bound medications can become sequestered in the ECMO circuit. Circuit components including the membrane oxygenator and polyvinyl chloride (PVC) tubing provide a large surface area for lipophilic medication sequestration. The octanol-water partition coefficient or log P is used to characterize lipophilicity. High log P (>2.0) drugs are very soluble in organic materials such as the PVC tubing used in the ECMO circuit.[66] For example, the antifungal voriconazole (log P 1.8) exhibits considerable circuit sequestration, and significant variability in concentrations may be associated with each membrane oxygenator change.[67] Currently, the absorptive capacity of the ECMO circuit and the release of drug from the ECMO circuit after medication discontinuation are not clear.

Medication Management During ECMO

Several adjunctive medical therapies are typically necessary during ECMO including analgesia, sedation, antibiotics, and anticoagulation. Treatment of pain, agitation, and delirium in patients receiving ECMO should be similar to other critically ill patients (Chapter e27). Analgosedation is preferred, benzodiazepines should be minimized, and light sedation is desirable.[24] Opioid analgesics such as fentanyl, hydromorphone, or morphine may be used to treat pain. Fentanyl will be sequestered in the ECMO circuit to a greater extent than hydromorphone or morphine (Table e26-3). Sedatives such as propofol, midazolam, and dexmedetomidine are prone to significant sequestration within the circuit and may require higher doses to achieve the

desired level of sedation.[66,68,69]

TABLE e26-3

Analgesic and Sedative Properties and Pharmacokinetic Considerations During Extracorporeal Membrane Oxygenation

Drug	Log P	Protein Binding (%)	PK Considerations
Opioids			
Fentanyl	4.1	80-85	Increased dose required; titrate to pain control
Hydromorphone	1.7	8-19	No PK studies in ECMO; minimal sequestration expected
Morphine	0.9	30-40	Minimal-to-moderate sequestration; use limited because of accumulation and hypotension
Sedatives			
Dexmedetomidine	2.8	94-97	Increased dose required; titrate to goal sedation
Midazolam	3.9	97	Increased dose required; titrate to goal sedation
Lorazepam	3.0	91	No PK studies in ECMO; minimal sequestration expected; dose used may be limited by propylene glycol toxicity
Propofol	3.8	95-99	Increased dose required; titrate to goal sedation
Ketamine	2.9	27	No PK studies in ECMO; moderate sequestration expected

ECMO, extracorporeal membrane oxygenation; PK, pharmacokinetics.

Infections are common in ECMO patients and antibiotics are used routinely as either prophylaxis or treatment. There is a paucity of pharmacokinetic data for antibiotics in patients on ECMO. Hydrophilic, beta-lactam antibiotics are highly susceptible to changes in volume of distribution. Expanded volume of distribution can lead to subtherapeutic concentrations at the site of infection. Yet, this is not exclusive to the ECMO subpopulation. In patients treated with piperacillin/tazobactam or meropenem on or off ECMO, up to 30% of patients may fail to achieve their pharmacodynamic targets regardless of ECMO use.[70] Given the majority of anti-infectives exhibit a wide therapeutic window, it is appropriate to select a dose at the higher end of the range and closely monitor the patient's trajectory toward therapeutic goals (eg, WBC improvement, fever curve). ECMO use is a compelling indication for antibiotic therapeutic drug monitoring if available.[71,72]

Anticoagulation is needed during ECMO to maintain circuit patency, prevent clot formation, and treat underlying conditions that precipitated ECMO cannulation (eg, massive pulmonary embolism, cardiothoracic surgery). ECMO patients are at high risk for both clotting and bleeding due to continuous exposure of blood to foreign material in the circuit, activation of platelets and clotting factors, and fibrinolysis. Intravenous unfractionated heparin is the standard anticoagulant for ECMO patients. Heparin is easy to monitor, titratable, and reversible with protamine.[73] Direct thrombin inhibitors such as bivalirudin and argatroban are preferred in patients with suspected or confirmed heparin-induced thrombocytopenia. Direct thrombin inhibitors have been considered for use as primary anticoagulants during ECMO, but little supporting evidence exists currently compared to heparin and they lack a direct antidote. Intravenous heparin is typically initiated with a bolus of 50 to 100 units/kg at ECMO initiation, with a continuous infusion thereafter titrated to a specified target.[73] The most common tests/targets for monitoring degree of anticoagulation during ECMO include the activated clotting time and activated partial thromboplastin time.[74]

Therapeutic Plasma Exchange (TPE)

TPE or plasmapheresis is a closed-circuit blood purification system that removes large molecules (pathogenic auto antibodies, immune complexes, cryoglobulins, myeloma light chains, endotoxins, and cholesterol-containing lipoproteins). Blood is removed from the body via standard vascular access, passed through a centrifuge that splits plasma from blood by a cell separator, and then blood cells are returned while the plasma is discarded.[75] In order to maintain normal plasma volume, replacement solutions, typically human albumin solution or fresh frozen plasma, are then administered back to the patient. Typical TPE sessions last 1 to 3 hours depending on the indication, goals, and patient tolerance. In the ICU, TPE may be used to treat patients suffering from a wide range of neurologic, renal, immunologic, or hematologic diseases. Examples include thrombotic thrombocytopenic purpura (TTP), myasthenia gravis, Guillain-Barré syndrome, demyelinating polyneuropathy, anti-glomerular basement membrane disease, rapidly progressive glomerulonephritis, systemic vasculitis, hemolytic uremic syndrome, and acute antibody-mediated renal allograft rejection.[76]

Pharmacokinetic Changes During TPE

TPE can alter the volume of distribution, protein binding, and clearance of a medication. First, approximately one-third of replacement fluids used during TPE remain in the patient at the end of the session. This may increase the volume of distribution of hydrophilic medications. Second, when human albumin solution is used for replacement, the fraction of protein-bound medication may increase. Finally, and most consequentially, TPE removes drugs present in the plasma, which can lead to subtherapeutic concentrations and therapeutic failure. Key properties of removed medications include low volume of distribution (eg, <0.2 L/kg), high protein binding (ie, >80%), and timing of administration close to TPE initiation. For example, cefepime (volume of distribution 0.2-0.3 L/kg) would typically be susceptible to removal, but when administered at least 2 hours before TPE, only 4% of the drug was cleared.[77] This highlights that half-life and time to tissue distribution influence whether a medication will be removed by TPE. When ceftazidime (volume of distribution 0.23 L/kg), was administered either 15 or 35 minutes before TPE, closer administration to TPE nearly doubled medication removal.[78] Other factors that may influence medication elimination include the duration and frequency of TPE sessions.

Medication Management During TPE

While these traditional characteristics of highly cleared medications can be helpful, drug-specific literature should be reviewed as real-world observations can deviate from the expected pattern. Unfortunately, existing studies are often limited to case reports, single-dose studies, and medically stable patients. Rarely does the evidence reflect critically ill patients, particularly those with multiorgan failure or numerous extracorporeal therapies used concurrently. The impact of TPE on select drugs is presented in Table e26-4.[75,79] Although TPE may increase elimination of susceptible medications, this may not necessarily translate to a jeopardized biological effect.[75] For example, in patients with TTP being treated with rituximab, medication concentrations declined by 65% after TPE, yet pharmacodynamic markers including a decline in peripheral B cell count and improved TTP markers indicated a favorable medication response.[80] Whenever possible, medications should be administered after TPE or, when prior to TPE, administered with ample lead time to allow for distribution and minimize medication loss. If a medication cannot be delayed or retimed, supplemental doses of medications susceptible to removal may be necessary to achieve therapeutic concentrations.

TABLE e26-4

Effect of Therapeutic Plasma Exchange on Select Medications and Dosing Considerations

Drug	Vd (L/kg)[a]	Protein Bound (%)	Medication Removal	Dosing and Timing
Amiodarone	66	>98	Not removed	No adjustments
Acyclovir	0.8	9-33	<10% removed	Administer ≥3 hours before TPE
Ceftriaxone	0.1-0.2	85-95	Up to 25% removed when administered <3 hours from TPE initiation	Administer after TPE or at least 15 hours before; consider supplemental dose if administered <3 hours before
Cefepime	0.2-0.3	20	<10% removed	Administer after TPE or at least 3 hours before
Digoxin	5-8	25	Not removed	No adjustments
Gentamicin/Tobramycin	0.25-0.35	10	25-50% removed	Administer after TPE; consider supplemental dose if administered before
Phenytoin	0.6-0.7	90-95	Not removed	No adjustments
Valproic acid	0.3-0.7	80-90	Not removed	No adjustments
Vancomycin	0.4	55	Up to 50% reduction in concentration	Administer after TPE; consider supplemental dose if administered before
Voriconazole	4.6	58	Not removed	No dose adjustments necessary

TPE, therapeutic plasma exchange; Vd, volume of distribution.

[a]Values are for non-critically ill adult patients.

Extracorporeal Liver Support System (ELSS)

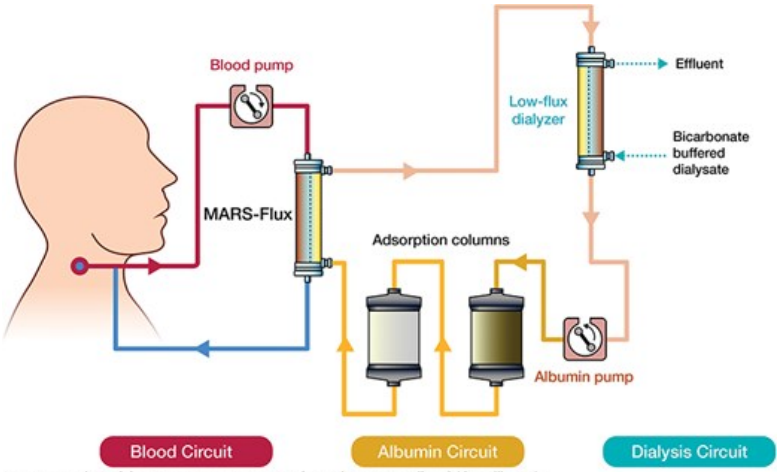
In acute or acute-on-chronic liver failure, effective clearance of water-soluble and albumin-bound toxins is diminished. ELSS is used to support the functions of the failing liver, maintain hemostasis, clear toxins, and allow hepatocytes to recover or temporize until liver transplantation.[81] The two major categories of ELSS used clinically include artificial and bioartificial devices. Artificial ELSS consists of nonbiological or cell-free devices and includes high-volume plasma exchange, albumin dialysis systems (eg, Molecular Adsorbent Recirculating System [MARS®]), single-pass albumin dialysis, and devices that combine both fractional plasma separation and adsorption (eg, Prometheus®). Bioartificial ELSS, such as the extracorporeal liver assist device (ELAD®) and the bioartificial liver support system (BLSS®), combine hepatocytes with or without the artificial systems, which provides both blood purification and several synthetic and regulatory functions to compensate for the failing liver. Hepatocytes used in these extracorporeal devices may come from humans (not commercially available), porcine, or cancer-derived cell lines.[82]

MARS®, a form of artificial ELSS, is the only FDA-approved device that integrates several mechanisms for clearing small, middle, and large molecules (Figure e26-4). Blood is removed from the patient using a conventional hemodialysis circuit and passes through the high-flux polysulphone

membrane, which removes protein-bound and water-soluble toxins up to a size of 50 kDa against an albumin dialysate. The albumin dialysate is then regenerated by passing countercurrent to a standard dialysate fluid through a low-flux filter to clear water-soluble toxins and provide electrolyte/acid-base balance. Next, successive passage of the albumin dialysate through two adsorbers containing activated charcoal and anion-exchange resin provides removal of albumin-bound toxins, but not albumin. In addition, a conventional dialysis circuit is integrated into the albumin circuit to remove water-soluble toxins. The regenerated albumin solution is free to bind new toxins from the blood.[83]

FIGURE e26-4

Molecular adsorbent recirculating system (MARS®) circuit. Schematic representation of the MARS® circuit in which blood is removed from the patient and dialyzed across an albumin-impregnated high-flux polysulphone membrane. The albumin dialysate then passes through a column countercurrent to a standard dialysate fluid through a low-flux filter to clear water-soluble toxins and provide electrolyte/acid-base balance. It is then perfused successively over an activated charcoal and an anion exchange resin column to remove the albumin-bound toxins and ultimately returned to the patient.



Medication Management During ELSS

Little objective evidence exists to guide medication dosing during ELSS. The evidence base is limited to single case reports that describe few medications.[84–87] Optimal medication dosing in patients receiving MARS® must account for removal of protein-bound and larger molecules (via the MARS® Flux dialyzer), and smaller water-soluble molecules (via the traditional dialysis circuit). A logical approach would be to use dialysis clearance as a starting point and account also for additional clearance via the MARS® Flux dialyzer. Highly protein-bound medications could be administered after the albumin dialysis portion to limit adsorption. Importantly, this is typically an intermittent therapy (6-8 hours/day) so the patient has both an "on circuit" steady state and an "off circuit" steady state. When on circuit, clearance would be expected to increase, relative to off circuit clearance based on native organ function. Where possible, therapeutic drug monitoring should be used, because of the difficulty with predicting drug elimination in this complex system. In certain circumstances with high-risk medications, for example, phenytoin, clinicians may be left to make difficult decisions about intradialytic medication supplementation. Little guidance exists to assist with this decision, but if possible, such medications should be substituted for more predictable therapies with wider therapeutic indices.

OVERVIEW OF PATIENT SAFETY IN THE ICU

Considerable advances have been made in our understanding of the pathophysiology of critical illness, acute and chronic organ dysfunction, and patient response to discrete therapeutic interventions. This enhanced sophistication and growing evidence-base for management of critically ill patients however does not obviate patient exposure to risk.[10] The ICU environment is dynamic and unpredictable, which leads to a heightened risk for medical errors and threats to patient safety. As part of daily work, critical care clinicians are expected to triage, multitask and emergently address decompensating patients and interruptions.[88] Complex clinical decisions must be made rapidly and integrate and interpret a vast array of disparate

data. This high-risk milieu leads to avoidable iatrogenic harm and errors, either of commission (unintentionally doing the wrong thing) or omission (unintentionally not doing the right thing).[89] Unintended sentinel events occur commonly in the ICU. For instance, in the Sentinel Event Evaluation (SEE) 1 study, unintended events pertaining to the artificial airway (eg, unplanned extubation), equipment failure (eg, infusion devices), indwelling devices (eg, dislodgement), mishandling of alarms, and medication errors occurred at an incidence rate of 38.8 events per 100 patient days in the ICU.[90] Increasingly the factors that influence safe and effective care delivery in the ICU are gaining attention. In 2000, the Institute of Medicine published the landmark report, "To err is human: building a safer healthcare system."[91] This report exposed the considerable room for advancement that remains in improving the processes of health care delivery (see Chapter e4). In 2009, these principles were reinforced by the critical care community in the Declaration of Vienna, which sought to draw attention to the unique challenges of promoting patient safety in intensive care.[89]

An essential component of optimal care delivery in the ICU is an intensivist-led multidisciplinary care team that utilizes open, goal-directed, and closed-loop communication.[88,92] Historically, key members of the ICU care team included physicians, advanced practitioners, nurses, pharmacists, and respiratory care specialists. More recently, practice guidelines and international initiatives have promoted early mobilization of critically ill patients with physical therapist support and compassionate patient and family engagement as part of the critical care team.[24] Multidisciplinary teams in the ICU not only improve patient and provider satisfaction, but enhance adherence to standardized protocols and optimal processes of care, and decrease duration of organ support, length of stay, cost, and mortality.[92,93]

A joint task force representing the Society of Critical Care Medicine, American College of Clinical Pharmacy Critical Care Practice and Research Network, and the American Society of Health-Systems Pharmacists recently published a joint position paper describing critical care pharmacist activities.[94] There were 82 statement recommendations on pharmacist activities categorized as patient care, quality improvement, research and scholarship, training and education, and professional development. Each activity is rated as either foundational or desirable based on the level of critical care services provided at a particular institution. Characterization of critical care pharmacist activities provided according to this position paper was recently described in a survey including 493 ICUs across the United States.[95] Seventy-one percent of ICUs reported direct clinical pharmacy services with most pharmacists attending rounds 5 days/week. Pharmacist activities in a typical workweek consisted predominantly of direct patient care followed by other non-direct patient care activities such as teaching and scholarship. Comparing results from a similar survey conducted in 2004, pharmacist roles have become more diverse in regard to provision of clinical, educational, research and scholarship, and administrative activities.[96]

Effective use of health information technology has become a central tenet of safe care delivery in the ICU. It has revolutionized access to information and the ability to translate complex protocols and algorithms into simple bedside care solutions. Yet, technology alone will not improve patient outcomes. If inaccurate data are presented to the clinician or delivered in a context insensitive way, it can paradoxically expose patients to new or different errors attributed to workflow disruptions, decreased efficiency, and increased cognitive burden for the care team.[88] Specific steps must be taken to ensure that the clinician has the right information, at the right time, for the right patient to make effective and safe medical decisions.

Medication Safety in the ICU

Safe medication use is a particular focus in the ICU, given the numerous errors that can be introduced during prescribing, dispensing, administering, and monitoring. A medication error (ME) is any error in the medication use process, regardless of whether it is associated with adverse consequences (Chapter e4). An adverse drug event (ADE) is any injury or harm related to use of a drug.[97] The harm that results from MEs or ADEs in ICU patients is greater than in non-ICU patients.[97] In the multinational SEE 2 study, ME associated with parenteral therapies including the wrong drug, dose, route, time, or a missed medication altogether occurred at a rate of 74.5 events per 100 ICU patient days, 1% of which contributed to permanent harm or death.[98] Outside of MEs, several additional factors compound the difficulty of achieving safe medication use in the ICU including the rapidly changing pharmacokinetic/pharmacodynamic profile of patients, high severity of illness with decreased physiologic reserve, increased susceptibility to adverse medication reactions, polypharmacy, and use of off-label therapies in nearly half of all ICU patients.[14]

As recommended by ICU-specific guidelines on medication safety, computerized prescriber order entry and clinical decision support systems (CDSS) are two key components of improving safe medication use.[97] CDSS can include electronic surveillance tools and triggers to send an alert or a "pop-up" to the clinician to provide a warning or additional information to inform decision making. However, in the ICU, the considerable volume of alerts generated from CDSS contributes to alert fatigue and desensitization. Suggested strategies to reduce alert fatigue and improve "alert value" are outlined in Table e26-5.[99]

TABLE e26-5

Strategies to Improve Alert Value in the Intensive Care Unit

- End-user engagement in alert design
- Local customization of commercially available alert packages
- Alert prioritization based on severity and clinical relevance
- Preserved alert sensitivity with enhanced specificity through integration of patient-level data
- A focus on atypical or rare prescribing events
- Iterative review of alert metrics to learn from overrides

Other elements of a comprehensive effort to reduce MEs and ADEs in the ICU include promotion of a non-punitive culture of safety, audit and feedback with clinician education, use of protocols/bundles, use of automated medication packaging and dispensing, bar-code medication administration systems, smart intravenous infusion pumps, medication reconciliation at transitions of care, standardized medication concentrations, and use of validated assessment tools to monitor patient response to therapy (see Chapter e4).[97]

Pharmacists are equipped with the knowledge to establish and maintain a culture of safety within the ICU through prevention of ADEs and MEs with pharmacist participation on the multidisciplinary team.[100,101] A landmark study in 1999 demonstrated a 66% reduction in preventable adverse drug events with the addition of a pharmacist to ICU patient care rounds.[102] This has since been reproduced in a contemporary large multicenter cohort.[103] Higher impact interventions were made by a pharmacy specialist as compared with less-experienced pharmacy team members.[104] Recently, the impact of pharmacist interventions in the care of patients presenting to the emergency room have also been demonstrated.[105] Significant avoidance of healthcare costs were noted in ADE prevention and hands-on care. Pharmacists also play a role in the accurate medication reconciliation at key transitions of care for an ICU patient. A decrease in the number of medication error transfers and reduction in potential harm is possible when medication reconciliation is conducted at the time of ICU admission and discharge.[106]

CONCLUSIONS

Critically ill patients are a heterogeneous group of individuals with a high severity of illness, rapidly changing organ function and clinical status, and frequent exposure to advanced technologies and organ support modalities. Collectively, these factors alter pharmacokinetics and pharmacodynamics and the predictability of the dose-response relationship for medications. Individualized pharmacotherapy plans specific to the ICU should be developed rather than broad extrapolation of therapeutic strategies from noncritically ill patients as these can bidirectionally increase patient risk, both for therapeutic failure as well as toxicity. In patients with dynamic end-organ function or on advanced organ support devices, pharmacotherapy plans should be adapted to expected pharmacokinetic/pharmacodynamic changes and patient response to therapy should be closely monitored. Finally, given the high potential for MEs and ADEs in the ICU, systems-based interventions for optimizing medication safety should be implemented in accordance with practice guidelines tailored to this environment.

ABBREVIATIONS

ADE	adverse drug event
AKI	acute kidney injury
ALT	alanine aminotransferase
ARC	augmented renal clearance
AST	aspartate aminotransferase

AUC	area under the concentration time curve
BLSS	bioartificial liver support system
CDSS	clinical decision support systems
C_{max}	maximum concentration
CRRT	continuous renal replacement therapy
CYP	cytochrome P450
ECMO	extracorporeal membrane oxygenation
eCrCl	estimated creatinine clearance
ED	emergency department
eGFR	estimated glomerular filtration rate
ELAD	extracorporeal liver assist device
ELSS	extracorporeal liver support system
HME	heat and moisture exchange
ICU	intensive care unit
INR	international normalized ratio
MARS	molecular adsorbent recirculating system
ME	medication error
MMAD	mass median aerodynamic diameter
NGT	nasogastric tube
PD	pharmacodynamic
PK	pharmacokinetic
PVC	polyvinyl chloride (tubing)
SEE	Sentinel Event Evaluation (study)
T_{max}	time to maximum concentration
TPE	therapeutic plasma exchange
VA	venoarterial

VV	venovenous
WBC	white blood cell count

REFERENCES

1. Grenvik A, Pinsky MR. Evolution of the intensive care unit as a clinical center and critical care medicine as a discipline. *Crit Care Clin.* 2009;25(1):239–250. [PubMed: 19268805]

2. Barrett M, Smith M, Elixhauser A, Honigman L, Pines J. Utilization of Intensive Care Services, 2011. HCUP Statistical Brief #185. December 2014. Agency for Healthcare Research and Quality, Rockville, MD. Available at http://www.hcup-us.ahrq.gov/reports/statbriefs/sb185-Hospital-Intensive-Care-Units-2011.pdf.

3. Vincent J-L, Marshall JC, Namendys-Silva SA, et al. Assessment of the worldwide burden of critical illness: The intensive care over nations (ICON) audit. *Lancet Respir Med.* 2014;2(5):380–386. [PubMed: 24740011]

4. Coopersmith CM, Wunsch H, Fink MP, et al. A comparison of critical care research funding and the financial burden of critical illness in the United States. *Crit Care Med.* 2012;40(4):1072–1079. [PubMed: 22202712]

5. Adhikari NKJ, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. *Lancet.* 2010;376(9749):1339–1346. [PubMed: 20934212]

6. Vukoja M, Dong Y, Adhikari NKJ, et al. Checklist for Early Recognition and Treatment of Acute Illness and Injury: An Exploratory Multicenter International Quality-Improvement Study in the ICUs With Variable Resources. *Crit Care Med.* 2021;49(6):e598–e612. [PubMed: 33729718]

7. Vincent JL. Give your patient a fast hug (at least) once a day. *Crit Care Med.* 2005;33(6):1225–1229. [PubMed: 15942334]

8. Vincent WR, Hatton KW. Critically ill patients need "FAST HUGS BID" (an updated mnemonic). *Crit Care Med.* 2009;37(7):2326–2327. [PubMed: 19535943]

9. Gajic O, Ahmad SR, Wilson ME, Kaufman DA. Outcomes of critical illness. *Curr Opin Crit Care*. 2018;24(5):1. [PubMed: 29176329]

10. Marra A, Pandharipande PP, Girard TD, et al. Co-occurrence of post-intensive care syndrome problems among 406 survivors of critical illness. *Crit Care Med.* 2018;46(9):1393–1401. [PubMed: 29787415]

11. Mikkelsen ME, Still M, Anderson BJ, et al. Society of Critical Care Medicine's International Consensus Conference on prediction and identification of long-term impairments after critical illness. *Crit Care Med.* 2020;48(11):1670–1679. [PubMed: 32947467]

12. Sevin CM, Bloom SL, Jackson JC, Wang L, Wesley Ely E, Stollings JL. Comprehensive care of ICU survivors: Development and implementation of an ICU recovery center. *J Crit Care*. 2018;46:141–148. [PubMed: 29929705]

13. Stollings JL, Bloom SL, Wang L, Ely EW, Jackson JC, Sevin CM. Critical care pharmacists and medication management in an ICU recovery center. *Ann Pharmacother.* 2018;52(8):713–723. [PubMed: 29457491]

14. Smithburger PL, Buckley MS, Culver MA, et al. A multicenter evaluation of off-label medication use and associated adverse drug reactions in adult medical ICUs. *Crit Care Med.* 2015;43(8):1612–1621. [PubMed: 25855897]

15. Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. *Chest*.

2012;141(5):1327–1336. [PubMed: 22553267]

16. Roberts DJ, Hall RI. Drug absorption, distribution, metabolism and excretion considerations in critically ill adults. *Expert Opin Drug Metab Toxicol.* 2013;9(9):1067–1084. [PubMed: 23682923]

17. U.S. Food and Drug Administration. Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling, draft guidance. Sept 2020. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing-and.

18. U.S. Food and Drug Administration. Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. May 2003. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-hepatic-function-study-design-data-analysis-and-impact-dosing-and.

19. Vincent J-L, De Backer D. Circulatory shock. *N Engl J Med.* 2013;369(18):1726–1734. [PubMed: 24171518]

20. Saugel B, Trepte CJ, Heckel K, Wagner JY, Reuter DA. Hemodynamic management of septic shock: Is it time for "individualized goal-directed hemodynamic therapy" and for specifically targeting the microcirculation? *Shock*. 2015;43(6):522–529. [PubMed: 25643016]

21. Kelly SJ, Moran JL, Williams PJ, et al. Haemodynamic effects of parenteral vs. enteral paracetamol in critically ill patients: A randomised controlled trial. *Anaesthesia*. 2016;71(10):1153–1162. [PubMed: 27611038]

22. Ariano RE, Sitar DS, Zelenitsky SA, et al. Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. *CMAJ.* 2010;182(4):357–363. [PubMed: 20159892]

23. Chapman MJ, Nguyen NQ, Fraser RJL. Gastrointestinal motility and prokinetics in the critically ill. *Curr Opin Crit Care*. 2007;13(2):187–194. [PubMed: 17327741]

24. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med.* 2018;46(9):e825–e873. [PubMed: 30113379]

25. Kees MG, Schaeftlein A, Haeberle HA, Kees F, Kloft C, Heininger A. Population pharmacokinetics and pharmacodynamic evaluation of intravenous and enteral moxifloxacin in surgical intensive care unit patients. *J Antimicrob Chemother.* 2013;68(6):1331–1337. [PubMed: 23463212]

26. Zhu L-L, Zhou Q. Therapeutic concerns when oral medications are administered nasogastrically. *J Clin Pharm Ther.* 2013;38(4):272–276. [PubMed: 23600913]

27. Lourenço R. Enteral feeding: Drug/nutrient interaction. *Clin Nutr.* 2001;20(2):187–193. [PubMed: 11327750]

28. Lahner E, Annibale B, Delle Fave G. Systematic review: Impaired drug absorption related to the co-administration of antisecretory therapy. *Aliment Pharmacol Ther.* 2009;29(12):1219–1229. [PubMed: 19302263]

29. Lim W, Meade M, Lauzier F, et al. Failure of anticoagulant thromboprophylaxis: Risk factors in medical-surgical critically ill patients. *Crit Care Med.* 2015;43(2):401–410. [PubMed: 25474533]

30. Jochberger S, Mayr V, Luckner G, et al. Antifactor Xa activity in critically ill patients receiving antithrombotic prophylaxis with standard dosages of certoparin: A prospective, clinical study. *Crit Care*. 2005;9(5):R541–R548. [PubMed: 16277716]

31. Haas CE, Nelsen JL, Raghavendran K, et al. Pharmacokinetics and pharmacodynamics of enoxaparin in multiple trauma patients. *J Trauma*. 2005;59(6):1336–1343. [PubMed: 16394906]

32. Rommers MK, Van der Lely N, Egberts TCG, van den Bemt PMLA. Anti-Xa activity after subcutaneous administration of dalteparin in ICU patients

with and without subcutaneous oedema: A pilot study. *Crit Care*. 2006;10(3):R93. [PubMed: 16790078]

33. Magee CA, Bastin MLT, Laine ME, et al. Insidious harm of medication diluents as a contributor to cumulative volume and hyperchloremia: A prospective, open-label, sequential period pilot study. *Crit Care Med.* 2018;46(8):1217–1223. [PubMed: 29727367]

34. Schött U, Solomon C, Fries D, Bentzer P. The endothelial glycocalyx and its disruption, protection and regeneration: A narrative review. *Scand J Trauma Resusc Emerg Med.* 2016;24(1):1–8. [PubMed: 26733395]

35. Mahmoudi L, Mohammadpour AH, Ahmadi A, Niknam R, Mojtahedzadeh M. Influence of sepsis on higher daily dose of amikacin pharmacokinetics in critically ill patients. *Eur Rev Med Pharmacol Sci.* 2013;17(3):285–291. [PubMed: 23426530]

36. Roger C, Nucci B, Molinari N, et al. Standard dosing of amikacin and gentamicin in critically ill patients results in variable and subtherapeutic concentrations. *Int J Antimicrob Agents*. 2015;46(1):21–27. [PubMed: 25857948]

37. Anderson KB, Poloyac SM, Kochanek PM, Empey PE. Effect of hypothermia and targeted temperature management on drug disposition and response following cardiac arrest: A comprehensive review of preclinical and clinical investigations. *Ther Hypothermia Temp Manag.* 2016;6(4):169–179. [PubMed: 27622966]

38. Prin M, Bakker J, Wagener G. Hepatosplanchnic circulation in cirrhosis and sepsis. *World J Gastroenterol.* 2015;21(9):2582–2592. [PubMed: 25759525]

39. Blanchet B, Jullien V, Vinsonneau C, Tod M. Influence of burns on pharmacokinetics and pharmacodynamics of drugs used in the care of burn patients. *Clin Pharmacokinet.* 2008;47(10):635–654. [PubMed: 18783295]

40. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg.* 1973;60(8):646–9. [PubMed: 4541913]

41. Laribi S, Mebazaa A. Cardiohepatic syndrome: liver injury in decompensated heart failure. *Curr Heart Fail Rep.* 2014;11(3):236–240. [PubMed: 24890902]

42. Tapper EB, Sengupta N, Bonder A. The incidence and outcomes of ischemic hepatitis: A systematic review with meta-analysis. *Am J Med.* 2015;128(12):1314–1321. [PubMed: 26299319]

43. Henrion J, Schapira M, Luwaert R, Colin L, Delannoy A, Heller FR. Hypoxic hepatitis: Clinical and hemodynamic study in 142 consecutive cases. *Medicine (Baltimore)*. 2003;82(6):392–406. [PubMed: 14663289]

44. Rahman M, BinEsmael TM, Payne N, Butchart EG. Increased sensitivity to warfarin after heart valve replacement. *Ann Pharmacother.* 2006;40(3):397–401. [PubMed: 16507614]

45. Inc M&C. Caspofungin package insert. 2018;1–23.

46. Seyffart G. *Seyffart's Directory of Drug Dosage in Kidney Disease*. 1st ed. Oberhaching, Germany: Dustri-Verlag Dr. Karl Feistle; 2011.

47. Hudson JQ, Nolin TD. Pragmatic use of kidney function estimates for drug dosing: The tide is turning. *Adv Chronic Kidney Dis.* 2018;25(1):14–20. [PubMed: 29499882]

48. Kellum J a, Lameire N, Aspelin P, et al. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl.* 2012;2(1):1–138.

49. Levey AS, Inker LA. Assessment of glomerular filtration rate in health and disease: A state of the art review. *Clin Pharmacol Ther.* 2017;102(3):405–419. [PubMed: 28474735]

50. Bouchard J, Macedo E, Soroko S, et al. Comparison of methods for estimating glomerular filtration rate in critically ill patients with acute kidney injury. *Nephrol Dial Transplant.* 2010;25(1):102–107. [PubMed: 19679558]

51. Bellomo R, Kellum JA, Ronco C, et al. Acute kidney injury in sepsis. *Intensive Care Med.* 2017;43(6):816–828. [PubMed: 28364303]

52. Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, et al. Cost and mortality associated with postoperative acute kidney injury. *Ann Surg.* 2015;261(6):1207–1214. [PubMed: 24887982]

53. Udy AA, Lipman J, Jarrett P, et al. Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance? *Crit Care*. 2015;19(1):1–9. [PubMed: 25560635]

54. Claus BOM, Hoste EA, Colpaert K, Robays H, Decruyenaere J, De Waele JJ. Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. *J Crit Care*. 2013;28(5):695–700. [PubMed: 23683557]

55. Barreto EF, Rule AD, Voils SA, Kane-Gill SL. Innovative use of novel biomarkers to improve the safety of renally eliminated and nephrotoxic medications. *Pharmacotherapy*. 2018;38(8):794–803. [PubMed: 29883532]

56. Frazee E, Rule AD, Lieske JC, et al. Cystatin C-guided vancomycin dosing in critically ill patients: A quality improvement project. *Am J Kidney Dis.* 2017;69(5):658–666. [PubMed: 28131530]

57. Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: The PrevAKI randomized controlled trial. *Intensive Care Med.* 2017;43(11):1551–1561. [PubMed: 28110412]

58. Göcze I, Jauch D, Götz M, et al. Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery: The Prospective Randomized BigpAK Study. *Ann Surg.* 2018;267(6):1013–1020. [PubMed: 28857811]

59. Ehrmann S, Roche-Campo F, Bodet-Contentin L, et al. Aerosol therapy in intensive and intermediate care units: Prospective observation of 2808 critically ill patients. *Intensive Care Med.* 2016;42(2):192–201. [PubMed: 26602786]

60. Labiris NR, Dolovich MB. Pulmonary drug delivery. Part I: Physiological factors affecting therapeutic effectiveness of aerosolized medications. *Br J Clin Pharmacol.* 2003;56(6):588–599. [PubMed: 14616418]

61. Labiris NR, Dolovich MB. Pulmonary drug delivery. Part II: The role of inhalant delivery devices and drug formulations in therapeutic effectiveness of aerosolized medications. *Br J Clin Pharmacol.* 2003;56(6):600–612. [PubMed: 14616419]

62. Burchett DK, Darko W, Zahra J, Noviasky J, Probst L, Smith A. Mixing and compatibility guide for commonly used aerosolized medications. *Am J Heal Pharm.* 2010;67(3):227–230.

63. Dhand R, Guntur VP. How best to deliver aerosol medications to mechanically ventilated patients. *Clin Chest Med.* 2008;29(2):277–296. [PubMed: 18440437]

64. Guerin C, Fassier T, Bayle F, Lemasson S, Richard J-C. Inhaled bronchodilator administration during mechanical ventilation: How to optimize it, and for which clinical benefit? *J Aerosol Med Pulm Drug Deliv.* 2008;21(1):85–96. [PubMed: 18518835]

65. Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis.* 2016;63(5):e61–e111. [PubMed: 27418577]

66. Shekar K, Fraser JF, Smith MT, Roberts JA. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. *J Crit Care*. 2012;27(6):741.e9–e18. [PubMed: 22520488]

67. Winiszewski H, Rougny A, Lagoutte-Renosi J, et al. The pharmacokinetic challenge of treating invasive aspergillosis complicating severe influenzae assisted by extracorporeal membrane oxygenation. *Crit Care*. 2018;22(1):355. [PubMed: 30577863]

68. Cheng V, Abdul-Aziz MH, Roberts JA, Shekar K. Optimising drug dosing in patients receiving extracorporeal membrane oxygenation. *J Thorac Dis.* 2018;10(Suppl 5):S629–S641. [PubMed: 29732181]

69. Dzierba AL, Abrams D, Brodie D. Medicating patients during extracorporeal membrane oxygenation: The evidence is building. *Crit Care*. 2017;21(1).

70. Donadello K, Antonucci E, Cristallini S, et al. β-Lactam pharmacokinetics during extracorporeal membrane oxygenation therapy: A case-control study. *Int J Antimicrob Agents*. 2015;45(3):278–282. [PubMed: 25542059]

71. Bouglé A, Dujardin O, Lepère V, et al. PHARMECMO: Therapeutic drug monitoring and adequacy of current dosing regimens of antibiotics in patients on Extracorporeal Life Support. *Anaesth Crit* Care Pain Med. 2019;38(5):493–497. [PubMed: 30831307]

72. Guilhaumou R, Benaboud S, Bennis Y, et al. Optimization of the treatment with beta-lactam antibiotics in critically ill patients - Guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique - SFPT) and the French Society of Anaesthesia. *Crit Care*. 2019;23(1):1–20. [PubMed: 30606235]

73. Lequier L, Annich G, Al-Ibrahim O, et al. *Extracorporeal Life Support Organization: Anticoagulation Guideline*. Ann Arbor, MI: 2014.

74. Esper SA, Welsby IJ, Subramaniam K, et al. Adult extracorporeal membrane oxygenation: An international survey of transfusion and anticoagulation techniques. *Vox Sang.* 2017;112(5):443–452. [PubMed: 28466601]

75. Cheng CW, Hendrickson JE, Tormey CA, Sidhu D. Therapeutic plasma exchange and its impact on drug levels: An ACLPS Critical Review. *Am J Clin Pathol.* 2017;148(3):190–198. [PubMed: 28821193]

76. Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. *J Clin Apher.* 2016;31(3):149–162. [PubMed: 27322218]

77. Ibrahim RB, Liu CY, Cronin SM, et al. Influence of plasma exchange on the disposition of the fourth generation cephalosporin cefepime. *J Oncol Pharm Pract.* 2009;15(4):217–222. [PubMed: 19304881]

78. Bozkurt F, Schollmeyer P, Keller E. Kinetics of ceftazidime during plasmapheresis. *Eur J Clin Pharmacol.* 1987;33(2):197–201. [PubMed: 3319644]

79. Ibrahim RB, Balogun RA. Medications in patients treated with therapeutic plasma exchange: Prescription dosage, timing, and drug overdose. *Semin Dial*. 2012;25(2):176–189. [PubMed: 22321259]

80. McDonald V, Manns K, Mackie IJ, Machin SJ, Scully MA. Rituximab pharmacokinetics during the management of acute idiopathic thrombotic thrombocytopenic purpura. *J Thromb Haemost.* 2010;8(6):1201–1208. [PubMed: 20175870]

81. Bernal W, Wendon J. Acute liver failure. *N Engl J Med.* 2013;369(26):2525–2534. [PubMed: 24369077]

82. Bunchorntavakul C, Reddy KR. Acute liver failure. *Clin Liver Dis.* 2017;21(4):769–792. [PubMed: 28987262]

83. Mitzner SR, Stange J, Klammt S, Peszynski P, Schmidt R, Noldge-Schomburg G. Extracorporeal detoxification using the molecular adsorbent recirculating system for critically ill patients with liver failure. *J Am Soc Nephrol.* 2001;12 Suppl 1(28):S75–S82.

84. Personett HA, Larson SL, Frazee EN, Nyberg SL, Leung N, El-Zoghby ZM. Impact of molecular adsorbent recirculating system therapy on tacrolimus elimination: A case report. *Transplant Proc.* 2014;46(7).

85. Personett HA, Larson SL, Frazee EN, Nyberg SL, El-Zoghby ZM. Extracorporeal elimination of piperacillin/tazobactam during molecular adsorbent recirculating system therapy. *Pharmacotherapy*. 2015;35(8):e136–e139. [PubMed: 26289310]

86. Weiler S, Falkensammer G, Seger C, Joannidis M, Bellmann R. Teicoplanin pharmacokinetics during albumin dialysis. *Artif Organs*. 2011;35(10):969–971. [PubMed: 21501193]

87. Ruggero MA, Argento AC, Heavner MS, Topal JE. Molecular Adsorbent Recirculating System (MARS(®)) removal of piperacillin/tazobactam in a patient with acetaminophen-induced acute liver failure. *Transpl Infect Dis.* 2013;15(2):214–218. [PubMed: 23279615]

88. Pickering BW, Litell JM, Herasevich V, Gajic O. Clinical review: The hospital of the future - building intelligent environments to facilitate safe and effective acute care delivery. *Crit Care*. 2012;16(2):220. [PubMed: 22546172]

89. Moreno RP, Rhodes A, Donchin Y. Patient safety in intensive care medicine: The declaration of Vienna. *Intensive Care Med.* 2009;35(10):1667–1672. [PubMed: 19697007]

90. Valentin A, Capuzzo M, Guidet B, et al. Patient safety in intensive care: Results from the multinational Sentinel Events Evaluation (SEE) study. *Intensive Care Med.* 2006;32(10):1591–1598. [PubMed: 16874492]

91. Kohn LT, Corrigan JM, Donaldson MS. *To Err is Human: Building a Safer Healthcare System*. Washington, DC: National Acadamies Press; 2000.

92. Weled BJ, Adzhigirey LA, Hodgman TM, et al. Critical care delivery: The importance of process of care and ICU structure to improved outcomes: An update from the American college of critical care medicine task force on models of critical care. *Crit Care Med.* 2015;43(7):1520–1525. [PubMed: 25803647]

93. Leguelinel-Blache G, Nguyen T-LL, Louart B, et al. Impact of quality bundle enforcement by a critical care pharmacist on patient outcome and costs. *Crit Care Med.* 2018;46(2):199–207. [PubMed: 29189346]

94. Lat I, Paciullo C, Daley MJ, et al. Position paper on critical care pharmacy services: 2020 Update. *Crit Care Med.* 2020;48(9):e813–e834. [PubMed: 32826496]

95. MacLaren R, Roberts RJ, Dzierba AL, Buckley M, Lat I, Lam SW. Characterizing critical care pharmacy services across the United States. *Crit care Explor.* 2021;3(1):e0323. [PubMed: 33458690]

96. Maclaren R, Devlin JW, Martin SJ, Dasta JF, Rudis MI, Bond CA. Critical care pharmacy services in United States hospitals. *Ann Pharmacother.* 2006;40(4):612–618. [PubMed: 16569803]

97. Kane-Gill SL, Dasta JF, Buckley MS, et al. Clinical Practice Guideline: Safe medication use in the ICU. *Crit Care Med.* 2017;45(9):e877–e915. [PubMed: 28816851]

98. Valentin A, Capuzzo M, Guidet B, et al. Errors in administration of parenteral drugs in intensive care units: Multinational prospective study. *BMJ.* 2009;338(7700):928–931.

99. Kane-Gill SL, O'Connor MF, Rothschild JM, et al. Technologic Distractions (Part 1): Summary of approaches to manage alert quantity with intent to reduce alert fatigue and suggestions for alert fatigue metrics. *Crit Care Med.* 2017;45(9):14811488. [PubMed: 28682835]

100. Lee H, Ryu K, Sohn Y, Kim J, Suh GY, Kim E. Impact on patient outcomes of pharmacist participation in multidisciplinary critical care teams: A systematic review and meta-analysis. *Crit Care Med.* 2019;47(9):1243–1250. [PubMed: 31135496]

101. Wang T, Benedict N, Olsen KM, et al. Effect of critical care pharmacist's intervention on medication errors: A systematic review and meta-analysis of observational studies. *J Crit Care*. 2015;30(5):1101–1106. [PubMed: 26260916]

102. Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA.* 1999;282(3):267–270. [PubMed: 10422996]

103. Shulman R, McKenzie CA, Landa J, et al. Pharmacist's review and outcomes: Treatment-enhancing contributions tallied, evaluated, and documented (PROTECTED-UK). *J Crit Care*. 2015;30(4):808–813. [PubMed: 25971871]

104. Rudall N, McKenzie C, Landa J, Bourne RS, Bates I, Shulman R. PROTECTED-UK - Clinical pharmacist interventions in the UK critical care unit: Exploration of relationship between intervention, service characteristics and experience level. *Int J Pharm Pract.* 2017;25(4):311–319. [PubMed: 27699912]

105. Rech MA, Adams W, Smetana KS, et al. PHarmacist Avoidance or Reductions in Medical Costs in Patients Presenting the EMergency Department: PHARM-EM Study. *Crit care Explor.* 2021;3(4):e0406. [PubMed: 33912836]

106. Bosma LBE, Hunfeld NGM, Quax RAM, et al. The effect of a medication reconciliation program in two intensive care units in the Netherlands: A prospective intervention study with a before and after design. *Ann Intensive Care*. 2018;8(1):19. [PubMed: 29417295]

SELF-ASSESSMENT QUESTIONS

1. Which of the following statements regarding medication use in critical care compared to other settings is the *most correct*?

   A. More critically ill patients have chronic diseases (eg, heart failure, diabetes melltius, chronic kidney disease) than hospital ward patients.

   B. Acute liver dysfunction is more common in the community setting than in the critical care environment.

   C. A greater proportion of patients on the hospital ward require use of organ support devices such as dialysis than in the critical care environment.

   D. Critical care patients are at higher risk for more severe complications from sedating medications than hospital ward patients.

The following case pertains to questions 2-5.

GB is a 47-year-old man who presents to the Emergency Department (ED) with large-volume hematemesis in the setting of alcoholic cirrhosis with active alcohol misuse. He has an altered mental status and vital signs that include a blood pressure of 74/42 mm Hg, a heart rate of 119 beats/min, a respiratory rate of 23 respirations/min and a temperature of 37.8°C. Pertinent laboratory data includes a hemoglobin of 5.2 g/dL (52 g/L; 3.23 mmol/L), platelets of 120,000/µL (120 × 10^9/L), white blood cell count (WBC) of 11,200/µL (11.2 × 10^9/L), serum creatinine of 1.1 mg/dL (97 µmol/L), aspartate aminotransferase (AST) of 137 IU/L (2.28 µkat/L), alanine aminotransferase (ALT) of 66 IU/L (1.10 µkat/L), and an international normalized ratio of 1.8.

2. What is the *most appropriate* interpretation of GB's laboratory data?

   A. Vitamin K deficiency from poor nutrition in alcohol use disorder.

   B. Congestive hepatopathy in the setting of cirrhosis.

   C. Chronic liver disease due to alcohol use disorder.

   D. Hypoxic hepatitis secondary to shock.

3. What is the expected impact of GB's current hepatic function on his chronic venlafaxine XR 75 mg daily use (a hepatically cleared medication), and how should his dosing regimen be adjusted?

   A. GB has known alcoholic cirrhosis and thus his venlafaxine dose should be reduced to XR 37.5 mg daily.

   B. Because of GB's laboratory evidence of hypoxic hepatitis, his venlafaxine dose should be reduced by 50% to XR 37.5 mg daily.

C. With resuscitation GB's liver function will improve; thus, his dose should be increased to XR 150 mg daily.

D. GB has altered mental status and end organ dysfunction thus his venlafaxine should be held in the acute setting.

4. Which of the following phases of critical illness is GB currently experiencing?

A. Rescue.

B. Optimization.

C. Stabilization.

D. De-escalation.

5. GB is given 2 liters of lactated Ringer's in the ED and transferred to the ICU. Given his current state, what pharmacokinetic changes are expected in the ensuing hours?

A. Intramuscular lorazepam would exhibit heightened absorption.

B. Intravenous ceftriaxone would have an increased free fraction.

C. Intravenous octreotide would have a decreased volume of distribution.

D. Subcutaneous enoxaparin levels would be low due to improving end-organ function.

6. Which of the following is an *advantage* of inhaled medication administration?

A. Contemporary nebulizer technology has increased aerosol medication delivery to the site of action in the lungs to ≥ 50%.

B. Medication costs for inhaled medications are generally much less than for intravenous agents.

C. The toxicity profile for inhaled medications is more favorable than systemic therapy.

D. Several medications can be administered concurrently via the inhaled route to increase efficiency.

7. Which of the following statements is *most correct* regarding aerosolized antibiotics for pneumonia?

A. For patients with community acquired pneumonia, monotherapy with aerosolized tobramycin is recommended for patients with *Klebsiella pneumoniae*.

B. In patients with hospital-acquired pneumonia with *Acinetobacter baumannii*, aerosolized colistin is recommended as an adjunct to systemic polymixins.

C. For patients with ventilator-associated pneumonia from methicillin-resistant *Staphylococcus aureus*, aerosolized vancomycin is recommended as an adjunct to systemic therapy.

D. The guidelines for pneumonia recommend against the use of inhaled antibiotics because of very low-quality evidence.

The following case pertains to questions 8-10.

EA is a 35-year-old woman (weight 60 kg) admitted to the ICU with severe shortness of breath, tachypnea, hypotension, and altered mental status. In the emergency room, EA received 6 liters of 0.9% sodium chloride, was intubated and started on antimicrobials, sedation, and vasopressors. Her medical history is remarkable for treated hypothyroidism. Chest radiography reveals diffuse, bilateral opacities suggestive of pneumonia and pulmonary edema. Her physical examination is significant for anasarca. EA has a nasogastric tube (NGT) in place. In the ICU, she is mechanically ventilated and deeply sedated. Her current medications include norepinephrine at 20 µg/min (0.33 µg/kg/min), vasopressin at 0.04 units/min, fentanyl infusion at 100 µg/hr, propofol at 30 µg/kg/min, famotidine 20 mg per NGT twice daily, home levothyroxine 50 µg per NGT daily, enoxaparin 40 mg subcutaneously daily, azithromycin 500 mg intravenously daily, and ceftriaxone 1 g intravenously daily.

8. Given EA's current state, which of the following physiologic changes are *most likely* to be observed?

   A. Decreased α-1 glycoprotein concentrations.

   B. Decreased albumin concentrations.

   C. Increased subcutaneous blood flow.

   D. Increased splanchnic perfusion.

9. Based on EA's clinical status, which of the following would be the most appropriate pharmacotherapeutic recommendation?

   A. Change the dose of enoxaparin to 40 mg subcutaneously twice daily.

   B. Change azithromycin to tablet to be crushed per NGT.

   C. Change famotidine and levothyroxine to intravenous administration.

   D. Change famotidine to pantoprazole suspension per NGT.

EA's respiratory status continues to decline 12 hours later. Results of an arterial blood gas are pH 7.26, $PaCO_2$ 65 mm Hg (8.6 kPa), PaO_2 50 mm Hg (6.7 kPa), HCO_3 16 mEq/L (mmol/L), and SaO_2 84% (0.84) while receiving mechanical ventilation set at assist control/volume control, tidal volume 300 mL (6 mL/kg), respiratory rate 35 breaths/min, and positive end-expiratory pressure 15 cm H_2O (1.5 kPa). EA has received neuromuscular blockade and continues to be deeply sedated. It is decided to initiate venovenous extracorporeal membrane oxygenation.

10. What would you expect to happen to plasma concentrations of propofol (a highly lipophilic medication) and ceftriaxone (a highly protein bound medication) as a result of the addition of the extracorporeal circuit?

    A. Propofol plasma concentrations decrease and ceftriaxone plasma concentrations increase.

    B. Propofol plasma concentrations increase and ceftriaxone plasma concentrations decrease.

    C. Both propofol and ceftriaxone plasma concentrations decrease.

    D. Both propofol and ceftriaxone plasma concentrations increase.

11. A patient is transferring to your ICU for initiation of molecular adsorbent recirculating system (MARS®) for fulminant hepatic failure and altered mental status. The team would like to start fosphenytoin for empiric seizure coverage until the electroencephalogram is available. Which one of the following actions is preferred to optimize medication delivery in this patient?

    A. Infuse fosphenytoin while MARS is running.

    B. Empirically double the dose.

    C. Infuse fosphenytoin after MARS is completed.

    D. Empirically half the dose.

12. What medication characteristics would *most likely* lead to subtherapeutic plasma concentrations if administered concurrently with therapeutic plasma exchange?

    A. Large volume of distribution.

    B. High protein binding.

    C. Low molecular weight.

D. High lipid solubility.

13. Medications that have a low-hepatic extraction ratio would be most affected by which of the following?

A. Hepatic blood flow.

B. Large-volume fluid resuscitation.

C. Intrinsic hepatic clearance.

D. Gastric motility.

The following case pertains to question 14.

MB is a 21-year-old man (72 kg) admitted to your ICU after sustaining multiple fractures from a motor vehicle crash. He has no significant medical history. He is currently intubated and receiving his fifth liter of 0.9% sodium chloride and has undergone a massive transfusion of blood products. His current medications include norepinephrine at 10 µg/min (0.14 µg/kg/min), hydromorphone at 2 mg/hr, famotidine 20 mg intravenously twice daily, and piperacillin/tazobactam 4.5 g over 30 minutes intravenously four times daily. His laboratory values include: sodium 145 mEq/L (mmol/L), potassium 3.1 mEq/L (mmol/L), chloride 97 mEq/L (mmol/L), carbon dioxide 18 mEq/L (mmol/L), blood urea nitrogen 10 mg/dL (3.6 mmol/L), serum creatinine 0.3 mg/dL (27 µmol/L), WBC 20,000/µL (20×10^9/L), hemoglobin 6 g/dL (60 g/L; 3.72 mmol/L), platelets of 230,000/µL (230×10^9/L). His urine output is 110 mL/hr.

14. Which of the following would explain a subtherapeutic plasma concentration of piperacillin/tazobactam in MB?

A. Decreased volume of distribution.

B. Augmented renal clearance.

C. Hemodynamic instability.

D. Decreased gut motility.

15. A new clinical decision support software package is being considered to alert ICU clinicians to the risk of developing kidney injury. Which of the following strategies would maximize the value of the alert?

A. Selectively apply the alert to dialysis patients to limit alert fatigue.

B. Select and implement a commercially available alert package to the local environment to ensure maximal functionality.

C. Deploy the new alert technology into the pharmacy workflow and in six months, review alert metrics and ask pharmacists about their experience with the program.

D. Integrate the patient medication profile into the clinical decision support to enhance specificity of the alert.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Critically ill patients have a heightened susceptibility to severe complications from medications (D is correct). Patients across the care continuum have chronic comorbidities (A is incorrect). Critically ill patients have a higher prevalence of acute organ dysfunction (B is incorrect) and a greater need for organ support (C is incorrect) than patients in the community or hospital ward.

2. **C.** The elevated hepatic enzymes with a 2:1 AST/ALT ratio and decreased synthetic function are most consistent with chronic liver disease associated with alcohol use disorder (C is correct). While poor nutrition is common in patients with alcohol use disorder and can lead to an increased INR, nutritional deficiencies alone would not be expected to contribute to the hepatic enzyme abnormalities (A is incorrect). The patient is hypovolemic thus hepatic congestion is unlikely (B is incorrect). Profound elevations in hepatic enzymes in the thousands would be more

suggestive of hepatic hepatitis thus while this pattern is not consistent, he would be at risk (D is incorrect).

3. **D.** In the setting of altered mental status, an unstable gastrointestinal bleed, and potential for acute on chronic end-organ dysfunction it is appropriate to temporarily hold the venlafaxine for 24 to 48 hours and monitor for signs and symptoms of withdrawal (D is correct). Although it is recommended to dose reduce venlafaxine in mild-to-moderate chronic liver impairment, this is described as a chronic medication that the patient has been tolerating so alone this would not be an indication to dose reduce (A is incorrect). Hypoxic hepatitis is more associated with profound elevations in hepatic enzymes in the thousands and thus his pattern is not consistent with "shock liver" (B is incorrect). With resuscitation end-organ dysfunction can improve, but with the GB's underlying cirrhosis residual hepatic impairment is expected (C is incorrect).

4. **A.** GB likely has an upper gastrointestinal bleed secondary to varices in the setting of cirrhosis. The time from the onset of illness is hours, and he has evidence of hypovolemic shock as evidenced by hypotension, tachycardia, and end-organ dysfunction (ie, altered mental status) thus he warrants rescue and resuscitation with fluid and blood products to a target hemoglobin of 7 g/dL (70 g/L; 4.34 mmol/L) (A is correct). Once the patient has been adequately resuscitated and has begun to achieve hemodynamic stability he would be considered in the optimization and stabilization phase (B and C are incorrect) and as he achieves source control for his bleed and is able to transfer out of the ICU he would be considered in the de-escalation phase (D is incorrect).

5. **B.** In the acute phase of critical illness and shock where the patient is being resuscitated and "rescued," there is decreased protein binding for albumin-bound medications and an increase free fraction (B is correct). Other key pharmacokinetic changes during this phase include decreased enteral, subcutaneous, and intramuscular absorption (A is incorrect), an increased volume of distribution especially with fluid resuscitation and increased vascular permeability (C is incorrect), and increased risk for evolving end-organ dysfunction which can lead to medication accumulation (D is incorrect).

6. **C.** Aerosolized medications generally have a more favorable toxicity profile than systemic therapies, with cough and bronchospasm as the primary side effects (C is correct). Even with optimal medication delivery conditions, only 10%–30% of a medication dose will reach the target site within the lungs (A is incorrect). Several drugs including anti-infectives such as inhaled tobramycin and inhaled ribavirin can be prohibitively expensive relative to the systemic route (B is incorrect). Use of several concurrent medications, especially not commercially prepared combinations, can lead to incompatibilities and decreased medication effectiveness (D is incorrect).

7. **B.** Guidelines recommend use of aerosolized colistin as an adjunct to systemic therapy for hospital-acquired pneumonia from *Acinetobacter* spp. or other gram-negative species sensitive only to polymixins (B is correct). It is one of the four scenarios where inhaled antimicrobials are recommended as part of combination therapy for pneumonia (D is incorrect). Monotherapy with inhaled gram-negative agents are not indicated for pneumonia (A is incorrect). Sparse literature has studied inhaled vancomycin, but it is poorly tolerated and not recommended (C is incorrect).

8. **B.** In critical illness, serum concentrations of albumin decrease (B is correct). In contrast, concentrations of α-1 glycoprotein increase (A is incorrect). Given the degree of shock as evidenced by high-dose vasopressors, she is likely to experience shunting of blood from nonvital tissues such as the gastrointestinal tract and subcutaneous tissue to vital organs such as the brain and heart (C and D are incorrect).

9. **C.** Critical illness, perfusion abnormalities from septic shock, and decreased gastric emptying from fentanyl may lead to unpredictable rates of enteral absorption. The best course of action would be to deliver medications intravenously (C is correct) to ensure 100% bioavailability (B and D incorrect). Adequate peripheral perfusion is required for subcutaneous absorption. Empiric dose increases of enoxaparin without clear documentation of low anti-factor Xa concentrations may increase the risk for bleeding complications (A is incorrect).

10. **C.** Lipophilic and high-protein-bound medications are expected to have decreased concentrations at the initiation of ECMO due to circuit sequestration (C is correct; A, B, and D are incorrect). The plasma concentrations of both agents will be further reduced due to dilution from the circuit priming solution (increased Vd).

11. **C.** Medications that are highly protein bound such as fosphenytoin have increased clearance with liver support systems that use albumin, such as MARS. It would be most ideal to administer fosphenytoin after MARS therapy is completed (C is correct). Alternatively, if a highly protein-bound medication needs to be administered during MARS, it should be infused into the post albumin dialysis line of the circuit. Administering a highly protein medication during MARS may lead to subtherapeutic levels and clinical failure (A is incorrect). However, empiric dose adjustments for narrow therapeutic window medications without the support of medication levels are not recommended due to the risks associated with both high and low levels (B and D are incorrect). This is especially true for medications such as fosphenytoin which exhibit nonlinear pharmacokinetics.

12. **B.** Medications that highlight protein bound and have a low volume of distribution have the greatest likelihood of being removed during therapeutic plasma exchange (B is correct). Medications with a large volume of distribution, high lipophilicity, or a low molecular weight will not be susceptible to removal with therapeutic plasma exchange (A, C, and D are incorrect).

13. **C.** Metabolism of medications with a low-hepatic extraction ratio are largely dependent on intrinsic hepatic clearance (C is correct) and less so on hepatic blood flow (A is incorrect). Medication metabolism is not primarily affected by large-volume resuscitation or gastric motility (B and D are incorrect).

14. **B.** Predictors of augmented renal clearance in MB include young age and trauma (B is correct). Hemodynamic instability or decreased gut motility will not affect plasma concentrations of medications administered intravenously (C and D are incorrect). Since this patient received a large-volume resuscitation his volume of distribution would be increased (A is incorrect).

15. **D.** Patient level data can enhance alert specificity while preserving sensitivity (D is correct). The tool is designed to predict future acute kidney injury risk, therefore restriction to dialysis patients would not be in alignment with the goal of the tool (A is incorrect). Commercially available alert packages should be customized to local practice (B is incorrect). End users should be engaged before implementation to optimize alert design and minimize counterbalances and workflow interruptions (C is incorrect).