Pharmacological Considerations in Acute and Chronic Liver Disease

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Abstract

Acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) have profound effects on human physiology that extend well beyond hepatic considerations. Virtually every organ system is affected to some degree, as are the medications used to treat both chronic and acute conditions for these organ systems. Even a small therapeutic misadventure can precipitate an acute decompensation in liver failure patients, further emphasizing the importance of appropriate drug dosing. Liver disease results in significant alteration in the pharmacokinetic and pharmacodynamic characteristics of medications. While the magnitude of these alterations is dependent upon the extent of liver disease and the physiochemical characteristics of a given medication, the effect of most medications will be amplified as a result of liver disease. This chapter provides a practical overview of drug dosing considerations, with a focus on basic pharmacokinetic and pharmacodynamics principles, in the context of ALF and ACLF. This is followed by medication considerations organized by organ system, with a focus on neurology, pulmonary, cardiovascular, renal, hematologic, gastrointestinal, and endocrine. Infectious disease considerations are also reviewed. The use of objective monitoring tools and the establishment of therapeutic goals will help facilitate the optimal use of drug therapy for each organ system. In many cases, treatment guidelines are lacking for the management of acute and chronic disease observed concurrently in patients with liver failure. Avoiding medications that have unpredictable pharmacokinetic profiles, or that are prone to drug-drug interactions, will reduce sequela. Employing evidence-based pharmacotherapy should yield improved outcomes. Practical considerations for the aforementioned are provided.

Keywords

Liver failure • Cirrhosis • Pharmacokinetic • Pharmacodynamic • Metabolism • Drug dosing Analgesia • Pain • Sedation • Agitation • Antiepileptic • Synthetic prostacyclin • Phosphodiesterase inhibitor • Endothelin receptor antagonists • Vasopressor • Beta-blocker Antiarrhythmic • Hepatorenal syndrome • HRS • Stress ulcer prophylaxis • Proton pump inhibitor • Histamine-2 receptor antagonists • Anti-emetic • Venous thromboembolism

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prophylaxis • VTE • Anticoagulation • Heparin-inducted thrombocytopenia • HIT Infectious disease • Antibiotic • Glycemic control • Thyroid • Relative adrenal insufficiency RAI • Steroid • Continuous renal replacement therapy • CRRT • Extracorporeal liver support • ECLS • Extracorporeal membrane oxygenation • ECMO

Learning Objectives

- Describe the basic pharmacokinetic and pharmacodynamic alterations that occur in patients with liver disease.
- Identify key medications that require dosing adjustments in patients with liver failure.
- Given a patient case with liver disease, select the most appropriate therapeutic recommendation.
- Discuss the effect of extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy (CRRT) and extracorporeal liver support systems on medications in patients with liver failure.

17.1 Pharmacokinetics/ Pharmacodynamics

Liver disease results in significant alteration in the pharmacokinetic and pharmacodynamic characteristics of medications. Unfortunately there are no endogenous markers of hepatic clearance, and the most common scoring tool used for characterizing liver disease, the Child-Pugh classification, does not correlate well with hepatic clearance or drug metabolism in liver disease. While the magnitude of these alterations is dependent upon the extent of liver disease and the physiochemical characteristics of a given medication, the effect of most medications will be amplified as a result of liver disease.

17.1.1 Absorption

Delayed gastric emptying in patients with liver dysfunction can result in delayed absorption; this is a minor determinant in the extent of absorption [1, 2]. More significant is the affect that changes in first-pass metabolism have on bioavailability. Drugs absorbed from the gastrointestinal tract are exposed to the metabolizing enzymes and bile excretory transport system of the liver before reaching systemic circulation [3]. In patients with normal liver function, drugs with a moderate to high extraction ratio will undergo significant first-pass metabolism, which is a function of mesenteric blood flow passing through the liver. Liver dysfunction leads to porto-systemic shunting and subsequently decreased activity of drug-metabolizing enzymes, resulting in a substantial increase in systemic bioavailability. This effect is further exacerbated in patients with a transjugular intrahepatic porto-systemic shunt (TIPS). Orally administered midazolam bioavailability can be increased tenfold in cirrhotic patients with TIPS compared to cirrhotic patents without [4]. This is largely the result of decreased intestinal cytochrome P450 (CYP) 3A activity [5]. It should be noted that first-pass metabolism is bypassed altogether when medications are administered intravenously and therefore should not affect bioavailability.

17.1.2 Distribution

The distribution of medications is predominantly altered by changes in volume and protein binding [3]. Patients with hepatic cirrhosis are often volume overloaded as a result of fluid retention and ascites. This results in an increased volume of distribution (Vd) which has the greatest effect on hydrophilic (water soluble) medications. Beta-lactam drugs can have a Vd as much as threefold larger [6]. This necessitates an increased dose, and perhaps a loading dose, in order to achieve and maintain therapeutic serum concentrations. Circulating plasma proteins are also low in patients with liver disease, especially chronic disease. Highly protein bound drugs are most affected, resulting in greater circulating free drug in the serum. This is predominantly due to decreased binding to albumin and α1-acid glycoprotein as a result of decreased protein synthesis, qualitative changes in protein blinding sites, and accumulation of endogenous compounds, such as bilirubin, that inhibit plasma protein binding [7]. This is particularly problematic for medications with narrow therapeutic range and necessitates increased monitoring.

17.1.3 Metabolism and Elimination

Most data about drug metabolism are derived from patients with stable chronic liver disease; studies in patients with ALF are largely underrepresented. In general the degree of drug metabolism and elimination impairment parallels the degree of liver disease, but more specifically it is determined by the intrinsic hepatic drug clearance, hepatic blood flow, and the extent of plasma protein binding of a given drug.

Intrinsic hepatic drug clearance represents the metabolism of unbound drug by the liver, though not all metabolic pathways are affected equally [3, 8]. Phase II conjugative metabolism is relatively less affected than phase I oxidative metabolism, which consists of the enzymes CYP and nicotinamide adenine dinucleotide phosphate (NADPH)-dependent CYP reductase. In general these enzymes are more sensitive to changes in liver function because of their dependence on oxygen [9]. Further declines in liver blood flow as a result of disease progression or placement of a TIPS may compound these effects. The Model for End-Stage Liver Disease (MELD) score has been correlated with CYP activity.

Hepatic blood flow is another important determinant of drug metabolism by the liver, especially for drugs with a high extraction ratio. The hepatic extraction ratio of a drug, which can be categorized as low (<0.3), intermediate (0.3–0.6), or high (>0.6), indicates the efficiency with which the liver can eliminate a given compound from the circulation, and is determined by intrinsic drug clearance and protein binding. Drugs with high extraction ratio are highly dependent on liver blood flow and demonstrate increased bioavailability in low-flow states, but are less influenced by changes in the activity of drug metabolizing enzymes and protein binding. Conversely, the metabolism of drugs with low extraction ratio is much more sensitive to changes in hepatic enzyme function and protein binding and relatively less affected by decreased hepatic blood flow. Drugs with intermediate extraction ratio may have variable bioavailability but generally exhibit decreased clearance in the setting of reduced liver function.

The changes in protein binding associated with acute and chronic liver disease can have variable effects on drug metabolism because they can influence both Vd and extraction ratio of a drug. Highly protein-bound drugs in the setting of hypoalbuminemia will distribute more extensively into tissues, making less total drug available in the circulation. Increased unbound fraction can lead to potentially increased clinical effects due to higher free drug concentrations, but can also increase hepatic clearance by presenting more unbound drug to the liver for metabolism. This would be especially true for drugs with low extraction ratio. The ultimate clinical effects are therefore difficult to predict, but generally speaking drugs with low protein binding and low intrinsic hepatic clearance are most likely to demonstrate reduced hepatic clearance in liver failure. In addition to decreased metabolism, extrahepatic drug elimination may also decrease as liver function declines. Cholestasis may result in reduced biliary excretion of certain medications. Additionally, the development of renal dysfunction, such as hepatorenal syndrome (HRS), is common in decompensated liver disease.

17.2 Neurology

Management of neurologic derangements is common and challenging in patients with liver disease, and may include the chronic management of psychiatric and seizure medications, and the acute management of analgesia, sedation, and delirium. The Society of Critical Care Medicine has provided evidence-based clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit (ICU) [10]. There are no specific recommendations made for patients with liver disease, however the guidelines are largely generalizable and it is reasonable to apply basic principles to this population. The practice of monitoring for safety and efficacy and establishing therapeutic goals is universal, whereas medication selection requires greater appreciation for disease- and patient-specific variables. When selecting drug therapy one must consider the altered pharmacokinetic profile imposed by end-stage liver disease (ESLD) and dose medications appropriately to avoid adverse events. Tables 17.1

Table 17.1 Analgesia summary of recommendations

Medication	Place in therapy	Considerations
Acetaminophen	Preferred agent	• Well tolerated in patients with liver disease including cirrhosis.
		• Limit daily dose to 2 g/day (up to 3 g/day for short-term use).
Tramadol	Use sparingly with caution	• Can precipitate or worsen hepatic encephalopathy, but potentially less than opioids, and may be preferred.
		• Dose reduction is required.
Opioids	Use sparingly with caution	• All opioids can precipitate or worsen hepatic encephalopathy.
		• Variable effect and response dependent on individual agent.
		• Fentanyl preferred (short-acting agents with minimal accumulation).
		• Hydromorphone is an alternative.
		• Dose reduction is required.
NSAIDs	Avoid use	• Bioavailability increased in patients with liver impairment.
		• Increased risk of gastrointestinal bleed, variceal hemorrhage, acute kidney injury, and development of diuretic-resistant ascites.
Other	Patient-specific consideration	• Anticonvulsants and antidepressants are generally avoided due to concern for altered mentation.
		• Nortriptyline and desipramine appear less sedating and are preferred if absolutely necessary.

Table 17.2 Sedative summary of recommendations

Medication	Place in therapy	Considerations
Lorazepam	Preferred agent for intermittent sedation	• Metabolic pathway less affected by cirrhosis compared to other benzodiazepines.
		• No active metabolites.
Propofol	Preferred agent for continuous sedation	• Well tolerated in patients with cirrhosis.
		• Pharmacokinetic profile is minimally altered in liver failure.
		• Concern for hypotension and deep sedation.
Dexmedetomidine	Relative contraindication - avoid use	• Clearance significantly reduced by liver dysfunction.
		• Hypotension and bradycardia are common.
Midazolam	Relative contraindication - avoid use	• Clearance significantly reduced by liver dysfunction.
		• Renally-cleared active metabolite with an unpredictable half-life.
		• Concern for hypotension and deep sedation.

and 17.2 provide recommendations for the management of pain and agitation. The most common, often preventable complications include hepatic encephalopathy, acute kidney injury, and gastrointestinal bleeding. Severity of these adverse effects range from mild to serious and can sometimes be fatal [11]. Guidelines for the management of psychiatric and seizure medications in the context of liver failure are not available, but the same basic principles apply when selecting drug therapy. Considerations for drug selection and monitoring will be discussed further.

17.2.1 Analgesics

17.2.1.1 Monitoring

Patients in the ICU, including those in liver failure, routinely experience pain [10]. The etiology is multifactorial and can include injuries incurred prior to admission, surgery, procedures, line placement, endotracheal tube placement, or other routine ICU cares. As such, pain should be routinely monitored in all patients using an objective and validated tool. The Numeric Pain Score (NPS) and the Visual Analogue Scale (VAS) are most reliable and should be used in patients who can assess and communicate their own pain [10]. For those patients with altered mentation, including encephalopathic patients, the Behavioral Pain Scale (BPS) or Critical-Care Pain Observation Tool (CPOT) is recommended [10]. Rather than using non-specific symptoms and physiologic signs such as vital signs, perspiration, or nausea and vomiting, these tools use more specific criteria such as facial expression, body movement, muscle tension, and vocalization or compliance with mechanical ventilation. Regular use of these validated tools can lead to optimal use of medications and better pain management, thereby facilitating improved clinical outcomes in critically ill patients [10, 12, 13].

17.2.1.2 Acetaminophen

Acetaminophen (APAP) is a known hepatotoxin and is the leading cause of drug-induced ALF, accounting for nearly 50% of all cases of ALF in the United States [14]. These findings may lead prescribers to avoid APAP use in patients with known liver disease [15]. Data suggests that short-term therapeutic doses of ≤4 g/day of APAP do not result in drug accumulation in patients with nonalcoholic cirrhosis, nor do they cause significant changes in liver function tests; rather, unintentional APAP intoxication over a long period of time is the most common cause of ALF [14, 16–18]. APAP can produce dose-related hepatocellular necrosis, particularly in the setting of chronic alcohol consumption, in which even prescribed doses of APAP are sufficient to produce acute hepatitis [19, 20]. Those with alcoholic cirrhosis are particularly vulnerable to APAP-induced hepatotoxicity as they experience an increase in N-acetyl p-benzoquinone imine (NAPQI, a hepatotoxic metabolite), production via enzymatic induction and decreased levels of glutathione which neutralizes NAPQI [16, 17, 21]. APAP use in patients with alcoholic cirrhosis should be used at the lowest effective dose, not to exceed 2 g/day (up to 3 g/day for short-term use), and chronic use should be avoided. For moderate to severe pain, the short-term use of appropriately-dosed APAP is preferred over other analgesics that are associated with more serious adverse effects, such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids [15].

17.2.1.3 Opioid

Opioids should be used cautiously in patients with chronic liver disease because they can precipitate or contribute to worsening hepatic encephalopathy [16, 17, 22–24]. In the setting of acute liver injury, opioids should be used even more sparingly. When opioid use is unavoidable, fentanyl is the preferred opioid as its pharmacokinetic profile, relative to other opioids, remains unchanged [22, 23]. Bearing in mind the

quick onset and short duration of action, therapy should be initiated at a reduced dose and given less frequently, then titrated to effect. Hydromorphone demonstrates increased bioavailability and a prolonged half-life but is a viable alternative to fentanyl at a reduced dose. Codeine requires metabolism via CYP to be converted to morphine. Reduced metabolism in patients with liver disease makes codeine ineffective as an analgesic. Morphine should be avoided in patients with liver disease; it is metabolized by the liver to an active metabolite which is heavily dependent upon renal function for clearance. This, along with increased bioavailability, results in a prolonged half-life and exaggerated pharmacologic effect fostering unpredictable kinetics and potentially unsafe use. Similarly, oxycodone demonstrates a prolonged half-life in liver disease and may accumulate. Meperidine exhibits similar pharmacokinetic changes, but accumulation of neurotoxic metabolites makes it an especially poor choice for pain management during liver disease. The clearance of methadone is reduced in ESLD, though it is free from active metabolites. Because of this, some advocate for its use in moderate liver failure despite its difficulty to use in healthy adults because of its highly variable and unpredictable pharmacokinetic profile. To date a consensus has not been reached on the role of methadone in liver disease. Opioid-dependent patients present a unique challenge in the context of acute, decompensated liver failure. Opioids should be prescribed sparingly in the context of encephalopathy but consideration must be paid to the risk of withdrawal. The lowest effective dose of opioid, preferably fentanyl, should be used and titrated to effect.

17.2.1.4 Other

Several other medications have been evaluated in patients with liver disease as opioid alternatives for the management of acute and chronic pain, especially neuropathic pain. Tramadol, which has both a hepatic metabolic and renal elimination component, has been recommended as a treatment option before proceeding to opioids based on its favorable safety profile [11]. As with other medications, a dose reduction and increased monitoring is warranted. Other medications such as anticonvulsants (carbamazepine, gabapentin, pregabalin) and tricyclic antidepressants (TCA) are common for chronic pain management, but are generally avoided in liver failure given concern for altered mentation. However, if a TCA is deemed necessary, nortriptyline and desipramine appear less sedating and are preferred.

17.2.1.5 NSAIDS

The risk of NSAID use in the setting of liver dysfunction is often underestimated. Health care professionals frequently endorse the use of NSAIDs in this population while recommending the avoidance of APAP use in patients with liver disease or cirrhosis [15]. Although occurrences are rare, these agents can independently produce idiosyncratic acute hepatocellular necrosis or cholestatic damage, which could precipitate an episode of ACLF [19, 25, 26]. More concerning is their deleterious effect on renal function. Mediated by prostaglandin (PG) synthesis inhibition, NSAIDs impair their protective renal vasodilating effect. Though not generally a concern in normotensive adults, inhibition of PG synthesis leads to renal decompensation in scenarios such as cirrhosis where renal and systemic hemodynamics are dependent on the availability of PGs [27]. This may result in blunting of the natriuretic effect of diuretics, as well as decreased sodium and water excretion, creatinine clearance, and glomerular filtration rate, both in patients with compensated disease and decompensated cirrhosis [28–34]. NSAIDs have also been associated with variceal bleeding in patients with liver failure [35]. In summary, these adverse effects are generally considered a class effect and NSAIDs should be avoided in patients with hepatic cirrhosis.

17.2.2 Sedatives

Critically ill patients are frequently anxious and agitated due to procedures and invasive therapies, such as mechanical ventilation and invasive lines. Sedatives reduce agitation and anxiety, thereby keeping patients more comfortable and safe during their ICU encounter [10]. There are several therapeutic options available to prescribers to establish and maintain safe and effective sedation, but selection of therapy must be patient-specific, taking into consideration how acute and chronic diseases will affect the pharmacokinetic profile of the drug.

17.2.2.1 Therapeutic Goals

Depth of sedation should be routinely monitored in all patients using an objective and validated tool. The Sedation Agitation Scale (SAS) and the Richmond Agitation Sedation Scale (RASS) are validated in critically ill patients, though not specifically in patients with liver disease [10]. Light sedation (SAS 3–4 or RASS 0 to −1) is preferred to deep sedation as it has been associated with decreased duration of mechanical ventilation and lower mortality. Once sedation goals are established, the least amount of sedative necessary to maintain patient comfort and safety should be used.

17.2.2.2 Propofol

Propofol is an intravenous general anesthetic that exerts its effect through agonism of gamma-Aminobutyric acid (GABA) receptors and perhaps reduced glutamatergic activity through N-Methyl-D-aspartic acid (NMDA) receptor blockade. It is a short-acting medication that is cleared rapidly and linear pharmacokinetics have been observed with infusion in healthy patients [36–38]. Its pharmacokinetic

profile does not appear to significantly change in patients with moderate hepatic cirrhosis, defined as those without ascites or encephalopathy [37]. Although the recovery time was longer in patients with cirrhosis and Vd at steady state was larger, total body clearance and terminal elimination half-life were unchanged. While the drug undergoes extensive hepatic metabolism, additional extra-hepatic metabolism prevents significant drug accumulation in patients with cirrhosis. Short-term propofol use during endoscopic procedures in patients with liver failure has demonstrated an incidence of adverse effects similar to other sedative agents and does not precipitate hepatic encephalopathy, but post anesthetic recovery following procedural sedation may be delayed compared to healthy subjects [39–42]. Cessation of propofol infusion results in a more rapid return to baseline function compared to midazolam [43–46]. Common but serious side effects include respiratory depression, hypotension (attributed to systemic vasodilation which is more pronounced in hypovolemic patients), hypertriglyceridemia, and cardiac dysrhythmias. Hypotension, which can also lower intracranial pressure, may theoretically worsen hepatic encephalopathy, is generally proportional to dose and rate of administration. Propofol infusion syndrome (PRIS) is defined as metabolic acidosis and cardiac dysfunction, along with one of the following: rhabdomyolysis, hypertriglyceridemia, or renal failure [47]. PRIS is a rare but life-threatening complication with mortality rates ranging from 18 to 83% [48, 49]. Liver disease has not been identified as a risk factor for PRIS, but rate and duration of infusion are strong predictors. For this reason it is recommended that infusions greater than 65 mcg/kg/min for longer than 48 h be avoided [49]. Propofol should immediately be discontinued if PRIS is suspected, although complications and even death may ensue after propofol discontinuation, because there is no known antidote. All things considered, propofol appears to be safe and effective in liver failure and is the preferred agent for sedation due to its short half-life, fast onset, and decreased recovery time compared to other agents [50–53].

17.2.2.3 Dexmedetomidine

Dexmedetomidine is a centrally-acting alpha-2 receptor agonist that is routinely used in the ICU to provide light sedation for patients requiring mechanical ventilation. Data suggests that dexmedetomidine is a safe and effective alternative to a midazolam infusion and may yield a shorter duration of mechanical ventilation and ICU length of stay, and potentially lower incidence of delirium, which together can significantly lower total ICU costs in critically ill patients [54–57]. Dexmedetomidine is extensively metabolized in the liver by CYP and glucuronidation to inactive metabolites. Since it is a high-extraction ratio drug, changes in hepatic blood flow can significantly affect clearance. Dexmedetomidine use in liver dysfunction, marked by increased aspartate aminotransferase (AST) and bilirubin, is associated with delayed clearance and prolonged half-life, which may lead to significant delays in emergence from sedation, and an exaggerated side-effect profile [58–60]. Reduction in sympathetic tone caused by dexmedetomidine may be particularly problematic in patients with vasoplegia caused by hepatic failure, as the compensatory mechanisms are impaired, resulting in profound bradycardia and hypotension. Given these risks, dexmedetomidine should be judiciously dosed and monitored if used in patients with liver dysfunction, or avoided all together.

17.2.2.4 Benzodiazepine

Prior to the introduction of newer sedative agents like propofol and dexmedetomidine, benzodiazepines were the mainstay of sedative therapy for critically ill patients [10, 61]. Lorazepam and midazolam have been the most commonly prescribed benzodiazepines for this purpose, where midazolam has traditionally been used for short-term sedation and lorazepam for long-term sedation. However, all benzodiazepines are metabolized by the liver. This results in reduced metabolism and prolonged elimination in patients with liver dysfunction, especially when compared to propofol [43–46, 62–64]. These altered pharmacokinetic parameters are further augmented in elderly patients or those concurrently administered medications that inhibit CYP enzyme systems and/or glucuronide conjugation in the liver. Taken together, these characteristics can result in prolonged sedation and may precipitate or worsen hepatic encephalopathy [10, 65, 66]. Hepatorenal syndrome is a common complication in acutely ill hepatic cirrhosis patients. Given that midazolam has an active metabolite which is renally eliminated, the use of midazolam in patients with combined liver and kidney impairment can further prolong sedation and should be avoided [67–70]. Should a benzodiazepine be necessary, lorazepam is generally thought to be the drug of choice because its primary mechanism of metabolism, conjugation, is a process less affected by liver dysfunction [71–73]. When using lorazepam in patients with liver disease, the dose should be empirically reduced and given less frequently, thus utilizing the lowest effective dose to minimize undesirable adverse effects. Midazolam use should be avoided.

17.2.3 Antiepileptics

Antiepileptic drug (AED) therapy warrants detailed clinical assessment in the setting of liver failure because some of these agents (phenytoin, carbamazepine, oxcarbazepine, lamotrigine, valproate, etc.) are known to cause liver failure. Even if not the cause of liver failure, most AEDs are hepatically metabolized to some extent and necessitate dose adjustments in the setting of liver failure [74–76]. The ability to balance the effects of these agents on the liver while continu-

ing to ensure safe and effective seizure control can be challenging. During the initial workup and management of ALF all medications, especially AEDs, should be screened as a potential etiology [77]. Any drug thought to be associated with causing ALF should be immediately discontinued and alternative therapy considered. Consideration for alternative therapy should primarily include AED outcome data for the patient's specific seizure type. In addition, one must also consider mechanism of action, drug interactions, and side effect profile with particular attention paid to the potential of worsening hepatic encephalopathy [78]. However, this can be difficult given that most AEDs are hepatically metabolized to some extent [74–76].

Phenytoin, levetiracetam, and more recently lacosamide, are three AEDs commonly used in contemporary practice. Phenytoin has a narrow therapeutic window and demonstrates non-linear kinetics in healthy adults; this is further amplified in patients with liver disease due to its high protein binding, low extraction ratio, and CYP2C9 and CYP2C19 metabolic pathways [74, 75, 79]. Lower doses should be used during liver failure and therapeutic drug monitoring of free phenytoin levels should be employed. Phenytoin also has many significant drug-drug interactions which further complicate its roles in therapy. In general, newer agents yield similar efficacy to older agents but have a more favorable adverse drug reaction profile and fewer drug-drug interactions. Levetiracetam exhibits low protein binding and a low extraction ratio with approximately 24% metabolized via hydrolysis; the remainder is excreted unchanged by the kidneys. Dose adjustments are not necessary in liver dysfunction, but drug accumulation has been observed in renal failure and warrants dose reduction. Few drug-drug interactions and a favorable adverse effect profile make levetiracetam a first-line agent. Similar to levetiracetam, lacosamide exhibits low protein binding and a low extraction ratio, but is slightly more dependent upon the liver for metabolism through the CYP2C9, CYP2C19, and CYP3A4 pathways [74, 75, 79]. Drug accumulation does occur as liver function decreases so empiric dose reductions are recommended.

17.3 Cardiovascular

Cirrhosis is a hyperdynamic state and patients frequently exhibit low systemic vascular resistance, increased cardiac output and heart rate, and low mean arterial pressure (MAP) at baseline. The constellation of findings indicative of the structural abnormalities as well as functional changes that can be found in cirrhotic patients have been termed cirrhotic cardiomyopathy. These changes include the previously mentioned alterations in hemodynamic parameters as well as systolic and diastolic dysfunction and electrophysiological changes. The presence of cirrhotic cardiomyopathy can have a significant effect on how patients respond in periods of increased stress such as critical illness, surgery, and infection and can make management of hemodynamics in the critical care setting challenging as the hemodynamic manifestations are often enhanced. Extensive discussion regarding cardiovascular pathophysiology in liver disease is discussed in detail elsewhere in this textbook. Many of the parenteral cardiovascular medications used in the ICU setting have a fast onset, short duration, and readily measurable effects and can be dosed to a clinical goal such as blood pressure. This makes it easier to determine if liver disease is affecting the response to these medications and if dosing modifications are indicated.

17.3.1 Vasopressors

Vasopressors are frequently required to maintain adequate perfusion in critically ill patients with both ALF and ACLF. Shock can be the result of a variety of insults including, but not limited to, decompensated liver failure resulting in a vasodilatory state, septic shock, and hemorrhagic shock. Norepinephrine is considered the vasopressor of choice for distributive shock in patients with cirrhosis as its stimulation of both alpha and beta-receptors increases MAP due to vasoconstrictive effects while preserving cardiac output with little increase in stroke volume compared with dopamine. There are no dosing recommendations specific to patients with liver disease and vasopressors can be titrated to patient-specific hemodynamic goals. Dopamine should generally be avoided because it could cause vasodilation of the splanchnic circulation thereby worsening portal hypertension [80].

Vasopressin has been used as an adjunct to catecholamines for the treatment of shock and has been found to be catecholamine-sparing in the setting of septic shock [81]. Vasopressin may be of particular benefit in patients who also have HRS as it has been shown to improve outcomes related to that disease state [82].

17.3.2 Beta-adrenoreceptor Antagonists and Calcium Channel Blockers

Beta-adrenoreceptor antagonists (more commonly referred to as beta blockers or β-blockers) are used in the critical care setting for a variety of indications including hypertension, tachycardia, and arrhythmias. Metoprolol is a commonly used selective β-blocker which is metabolized by the liver via several different metabolic pathways [83]. It is a high extraction ratio medication so bioavailability is increased in liver disease (from 50% in normal subjects to 80% in cirrhosis). In addition, the area under the curve (AUC) was markedly increased and the elimination half-life was prolonged follow-

ing both oral and intravenous doses [84]. Dose reduction by a factor of two to three has been recommended [83]. Labetalol, a nonselective β-blocker commonly used in the ICU setting, is also hepatically metabolized and has a high extraction ratio [2]. Therefore, similar consideration should be given to a possible prolonged half-life and need for dose reduction.

17.3.3 Calcium Channel Blockers

Nicardipine is a calcium channel blocker which is primarily used in its parenteral form as a continuous infusion for hypertensive emergency or urgency in the critical care setting. It undergoes extensive hepatic metabolism and has a high extraction ratio [2]. The pharmacokinetics of nicardipine can be described as a three-compartment model. The alpha and beta half-lives are both short at under one hour, however the terminal half-life is over 12 h which is seen with long-term infusions. Due to its hepatic metabolism, this is even longer in patients with liver disease. Although, titration to specific clinical goals is appropriate, titration should occur slowly with close hemodynamic monitoring and dose reduction may be necessary in patients with liver disease.

17.3.4 Antiarrhythmics

The majority of antiarrhythmics are metabolized by the liver and have a narrow therapeutic index making dose adjustments clinically significant in this patient population. This section will focus on the more commonly used antiarrhythmics in the non-cardiac critical care setting such as those used for atrial fibrillation. Amiodarone is likely the most commonly used antiarrhythmic in non-cardiac ICUs and is available as both oral and parenteral formulations. It is extensively metabolized by the liver and has a very long half-life in patients without liver disease after prolonged oral administration (25–53 days) [85, 86]. Although there are no data specific to amiodarone in liver disease, it can be assumed that metabolism would be impacted resulting in an even longer half-life [83]. Diltiazem, a class IV antiarrhythmic used for rate control in atrial fibrillation, is available in an oral form but is usually used in the ICU in its parenteral form as a continuous infusion. It is extensively metabolized by the liver resulting in decreased clearance in patients with liver dysfunction. A small study of long-term oral administration in cirrhosis demonstrated a slightly prolonged half-life and increased AUC of diltiazem and one of its active metabolites [87]. An empiric dose reduction by a factor of two has been suggested [83].

An additional cardiovascular consideration in patients with cirrhosis is QT interval prolongation which is frequently associated with cirrhotic cardiomyopathy and can worsen as severity of cirrhosis worsens. The prevalence of QT prolongation has been reported to be as high as 60% in patients with Child-Pugh grade C cirrhosis [88]. Therefore, evaluation of the baseline QT interval and continued monitoring is vital as is assessment of medications with risk of QT prolongation.

17.4 Pulmonary

Pulmonary complications are common in ESLD [1, 2, 89]. Standard supportive care medication therapies for dyspnea and hypoxia (e.g. albuterol, inhaled steroids, etc.) can commonly be prescribed in this patient population without need for dosing adjustments. However, more severe complications, such as portopulmonary hypertension may require treatment with pulmonary vasodilatory therapies such as synthetic prostacyclins, phosphodiesterase inhibitors and endothelin receptor antagonists [21, 89–94]. These particular medications may require more thoughtful monitoring and dosing adjustments in the ESLD patient population as described below.

17.4.1 Synthetic Prostacyclins

Synthetic prostacyclins such as epoprostenol, treprostinil, and iloprost have established efficacy in the treatment of portopulmonary hypertension [89]. However, the pharmacokinetics of these agents, particularly clearance, may be significantly altered in patients with hepatic impairment.

The pharmacokinetics of intravenous iloprost was evaluated in eight hospitalized patients suffering from liver cirrhosis. Pharmacokinetic parameters were collected throughout the inpatient treatment course [95]. The study demonstrated that iloprost clearance was one-half in patients with hepatic impairment. The authors concluded that initial starting doses should be reduced by at least one-half the standard dose and patients should receive dose titrations based on individual parameters.

Epoprostenol has the shortest half-life amongst the synthetic prostacyclins, which is estimated to be approximately six minutes [96]. However, given the lack of available chemical assay to assess the *in vivo* pharmacokinetics of epoprostenol, no specific studies to date exist evaluating the impact of hepatic impairment on this medications pharmacokinetics.

To date, treprostinil has the most data specifically focused on use in hepatic impairment. According to its package insert, both intravenous and subcutaneous treprostinil is documented to have decreased clearance in patients with hepatic impairment [97]. It is recommended that for the treatment of pulmonary hypertension, that the initial dose be decreased to 0.625 ng/kg/min ideal body weight in patients with mild to

moderate hepatic impairment. However, there are no formalized studies to date that evaluate the use of intravenous or subcutaneous treprostinil in patients with severe hepatic impairment.

Most recently, oral treprostinil was approved by the United States Food and Drug Administration. The availability of an oral prostacyclin provides a simplified administration route of therapy for patients with pulmonary hypertension. However, there are limited data for the use of this particular synthetic prostacyclin in portopulmonary hypertension. Regardless, there is significant potential that this therapy will be used in the future for treatment of this unique subset of patients. Fortunately, this agent has the most robust data evaluating its pharmacokinetics in the liver disease patient population. Peterson and colleagues completed a small evaluation of the pharmacokinetics of oral treprostinil, treprostinil diolamine, in thirty subjects with various degrees of hepatic impairment [98]. With increasing severity of hepatic impairment, the mean treprostinil clearance decreased, resulting in increased levels of treprostinil. Adverse effects, such as headache, nausea, etc., were more commonly experienced in the patients with hepatic impairment. In clinical practice, oral treprostinil should be dose cautiously, and patients should be monitored closely for adverse effects.

Clinical interpretation of these data indicates the need to start synthetic prostacyclins, except epoprostenol, at lower doses in patients with hepatic impairment. Similarly, clinicians should cautious titrate doses while monitoring closely for adverse effects. However, epoprostenol's uniquely short half-life makes it the likely exception to this rule and can likely be initiated and titrated regardless of hepatic function.

17.4.2 Phosphodiesterase Inhibitors

There is increasing evidence supporting the use of sildenafil and tadalafil in patients with portopulmonary hypertension [89, 94].

Sildenafil undergoes metabolism via CYP3A4 and CYP2C9 to form an active metabolite [99]. It would be anticipated that this metabolism would be altered in a patient with hepatic impairment. Although the manufacturer of Revatio®, sildenafil marketed for pulmonary hypertension, provides no dose adjustment recommendations, the manufacturer for Viagra®, sildenafil marked for erectile dysfunction, suggests a lower starting dose in patients with hepatic dysfunction [99, 100]. Therefore, it may be pertinent to be cautious with aggressive dosing of sildenafil, regardless of indication, in patients with hepatic impairment.

Similarly to sildenafil, tadalafil is primarily metabolized by CYP3A. According to the tadalfil package insert, initial pharmacokinetics studies have shown that mild to moderate hepatic impairment did not impact the amount of tadalafil exposure the patient experiences [101]. However, in patients with Child Pugh Class A or B hepatic impairment, the manufacture recommends to consider starting at a dose of 20 mg once per day or less. However, they state that due to lack of literature evaluating the use of tadalafil in patients with severe hepatic impairment, it should be avoided.

Apart from manufacturer recommendations, tadalafil pharmacokinetics in patients with hepatic impairment was evaluated by Forgue and colleagues [102]. This study evaluated tadalafil pharmacokinetics in a total of twenty-five patients with some degree of hepatic impairment. However, only one patient was classified as having severe impairment. Their evaluation found a trend towards lower tadalafil concentrations and prolongation in half-life with increasing severity of impairment; however, no statistical association was found.

Data regarding the use of both sildenafil and tadalafil in patients with hepatic impairment are limited and inconsistent. Error on the side of caution and starting at lower doses is likely most appropriate in most patients, but more aggressive dosing is not excluded by the data published to date.

17.4.3 Endothelin Receptor Antagonists

The most robust data supporting pharmacologic therapy for the treatment of portopulmonary hypertension appears to be with endothelin receptor antagonists. However, these agents are hepatically metabolized and are known to cause hepatotoxicity, so caution must be used in a patient with hepatic impairment.

Bosentan has been associated with an improvement in symptoms in a retrospective study of patients with portopulmonary hypertension [103]. This study also completed a subset pharmacokinetic analysis of five patients with moderate hepatic impairment. The analysis showed an increase in bosentan exposure in this specific patient population; however, this was not related to patient outcomes. One of the major concerns associated with the use of bosentan is its potential to cause liver toxicity [104]. In line with this, Savale *et al.* did identify a 5.5% risk of elevated liver enzymes in their retrospective analysis [103]. Based on these data, it is appropriate to use caution when imitating this agent in patients with hepatic impairment given the increase risk for elevated bosentan levels. Frequent liver function monitor is also clinically appropriate in this patient population.

Macitentan has the most robust data supporting its use in the pulmonary arterial hypertension patient population in the form of a randomized controlled trial showing statistically significant improvement in morbidity and mortality [105]. In regards to the safety of this agent, this study found that there was no variation in liver function abnormalities between varying doses in patients with hepatic dysfunction. However, it is still recommended to obtain liver function tests at base-

line and repeated periodically during the first six months and then as clinically indicated [106].

Ambrisentan has been evaluated in a small prospective, observational, cohort study of portopulmonary hypertension, showing positive outcomes in pulmonary hemodynamics [107]. In regards to safety outcomes, this study did not identify any change in liver function tests throughout the twelve month study period. This would indicate the likelihood that ambrisentan can safely be used in patients with hepatic impairment, however, patients should be closely monitored for adverse effects.

As a whole, the endothelin-receptor antagonist group appears to have decent support for use in the portopulmonary hypertension patient population. It is prudent to monitor these patients for not only hemodynamic adverse effects, but also for direct liver injury indicated by an elevation in liver function tests.

17.5 Renal

Renal dosing adjustments are required for many medications; however, these adjustments are significantly complicated by the pharmacokinetic alterations, particularly fluctuations in distribution and metabolism that occur in patients with hepatic impairment. Patients with an increased Vd secondary to ascites may potentially have a decreased renal clearance of medications given the kidney's decreased access to the medication to be able to clear it. Also, medications that are usually protein bound typically can have a greater renal clearance in patients with hepatic impairment secondary to decreased protein production, and therefore a greater free concentration available for elimination by the kidney.

HRS is a potential complication associated with ESLD. Agents such as midodrine, octreotide and albumin may potentially be used for the treatment of HRS. None of these commonly used agents require dose adjustments based on pharmacokinetic alterations in patients with hepatic impairment.

17.6 Gastrointestinal

Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are commonly prescribed agents for hospitalized ESLD patients. These agents are commonly prescribed for one of two indications: stress ulcer prophylaxis or treatment of gastro-esophageal variceal hemorrhages [9]. Apart from inpatient use, these two classes of medications are readily available as over-the-counter products that patients may be taking without consultation with a prescriber, so it is important to discuss the concerns with these medications with all patients with hepatic impairment.

17.6.1 Proton Pump Inhibitors

There is no evidence to date to recommend one PPI over another for any indication. However, secondary to the fact that most PPIs undergo CYP metabolism, pharmacokinetic alterations caused by hepatic impairment may warrant the selection of one agent over the others.

17.6.1.1 Omeprazole

As one of the oldest available PPIs, omeprazole is a commonly used agent. However, caution is necessary when prescribing this agent for patients with hepatic impairment. In a pharmacokinetic analysis of omeprazole in patients with cirrhosis, it was found that omeprazole exposure was increased regardless of the severity of hepatic impairment [17]. These data would suggest that omeprazole has significantly decreased clearance in the ESLD patient and should likely be avoided if possible.

17.6.1.2 Esomeprazole

A small pharmacokinetic evaluation of esomeprazole in patients with hepatic impairment has been described by Sjövall and colleagues [108]. This study identified a minimal risk of increased esomeprazole exposure in patients with mild or moderated hepatic impairment. However, increase drug levels were noted to be significantly elevated in patients with severe hepatic dysfunction. This concern has been noted by the drug manufacturer, such that in patients with severe hepatic impairment, a dose reduction to 20 mg daily is recommended [109]. Therefore, dosing recommendations remain unchanged for patients with mild to moderate hepatic impairment, but caution should be executed when prescribing esomeprazole for patients with severe hepatic impairment.

17.6.1.3 Lansoprazole

The pharmacokinetics of lansoprazole was evaluated in a single-dose study, which the results are significantly limited by the lack of repeat dosing [110]. It was found that there is an increase in half-life and drug exposure with increase severity of liver disease. Patients with severe hepatic impairment were found to have marked changes in the pharmacokinetic profile. These data suggest that lansoprazole should likely be avoided in patients with hepatic impairment, particularly in patients with severe hepatic impairment.

17.6.1.4 Pantoprazole

Although pantoprazole undergoes CYP metabolism, it has been shown that the pharmacokinetics and tolerability of pantoprazole are similar independent of the severity of hepatic impairment [111]. Therefore, it is unnecessary to dose adjust pantoprazole regardless of the degree of hepatic impairment. This evidence makes pantoprazole the most favorable PPI for use in patients with ESLD.

17.6.2 Histamine-2 Receptor Antagonists

Famotidine appears to have a more favorable pharmacokinetic profile in this patient population in comparison to ranitidine. In one pharmacokinetic evaluation of famotidine use in the ESLD patient population, famotidine clearance was unchanged compared to those patients without hepatic impairment [112]. However, famotidine does require dose adjustments for renal impairment, such that patients with HRS should be appropriate dose reduced [113]. Ranitidine has documented increased neuropsychiatric complications in patients with ESLD and should likely be avoided in this patient population [114].

17.6.3 Anti-emetics

Decreased gastrointestinal motility, nausea, and vomiting are also common complications associated with ESLD [115].

17.6.3.1 Metoclopramide

Metoclopramide is a commonly used agent given its promotility and antiemetic effects. However, given the fact that metoclopramide is subject to first-pass metabolism, has significant plasma protein binding properties and undergoes significant hepatic metabolism, dose reductions should be considered in the ESLD patient population [116–120]. Also, given metoclopramide's renal clearance property, a dose reduction is also crucial in patients with concomitant renal dysfunction. A 50% dose reduction is appropriate in patients with cirrhosis.

17.6.3.2 Ondansetron

Ondansetron is mainly eliminated via hepatic metabolism [121]. Clearance of ondansetron is related to the degree of hepatic impairment, such that worsening liver impairment leads to significantly decreased ondansetron clearance [122]. Caution should be used when prescribing ondansetron in patients with hepatic impairment. It can also be recommended that for patients with severe hepatic impairment daily doses of ondansetron should be limited to 8 mg.

17.7 Hematology

17.7.1 Venous Thromboembolism Prophylaxis and Anticoagulation

Historically, the endogenous coagulopathy in patients with ESLD due to decreased production of vitamin K clotting factors and platelets was thought to be protective against the development of venous thromboembolism (VTE) [123]. More recent studies have called this theory of "autoanticoagulation" into question and demonstrated that these patients also have decreased production of anticoagulation factors and may actually be at an increased or similar risk of VTE compared to hospitalized patients without ESLD [124]. Literature evaluating the safety of pharmacologic prophylaxis in ESLD is limited but does raise concern for an increased risk of bleeding complications [125, 126]. In addition, evidence-based VTE prophylaxis guidelines provide no specific recommendations for patients with liver disease but advise against the use of pharmacologic prophylaxis in patients with significant bleeding risk which includes risk factors such as platelet count <50,000/μL, liver failure, and international normalized ratio (INR) >1.5 [127]. It should be noted that there are limited data in critically ill cirrhotic patients. A recent retrospective study of 798 patients found that the incidence of VTE in critically ill cirrhotic patients was not statistically different from that in noncirrhotic patients although rates were relatively low at 2.7% and 7.6%, respectively. Cirrhotic patients were less likely to receive pharmacologic prophylaxis [128]. ESLD and associated coagulopathy (elevation in INR) alone should not be considered a contraindication to pharmacologic prophylaxis and critically ill patients with ESLD should receive pharmacologic prophylaxis as a default unless there are specific contraindications. Certainly, careful evaluation of risk versus benefit should be done on a patient-by-patient basis.

As a result of the increased risk of VTE, anticoagulation therapy is being increasingly utilized in patients with ESLD. There are limited data on the safety of therapeutic anticoagulation in the hospital setting in patients with ESLD, especially in critically ill patients.

If pharmacologic prophylaxis or therapeutic anticoagulation is initiated with unfractionated heparin there are no dosing considerations specific to patients with liver dysfunction. Many of these patients will have concomitant renal dysfunction and given that low molecular weight heparins (with the exception of dalteparin) are renally eliminated, they present a higher risk for bleeding complications.

Patients with ALF and ACLF frequently have an acute coagulopathy and elevated INR from baseline and are at high risk of bleeding complications. There are no data evaluating the use of VTE prophylaxis or therapeutic anticoagulation in this population. Mechanical prophylaxis only should be recommended during the acute phase of the disease process.

17.7.2 Heparin-Induced Thrombocytopenia

The development of heparin-induced thrombocytopenia (HIT) in a patient with liver disease presents a complex situation because evidence-based guidelines recommend therapeutic anticoagulation for four weeks in the setting of isolated HIT without thrombosis and for three months if

there is associated thrombosis [129]. Of course, the increased risk of thrombosis associated with HIT would have to be balanced with the risk of bleeding in order to make a decision about therapeutic anticoagulation in individual patients. Of the medications that would be used for initial anticoagulation in the setting of HIT, argatroban is the only one with pharmacologic considerations in liver dysfunction. Argatroban is a direct thrombin inhibitor that is hepatically metabolized primarily by CYP3A4/5 to non-active metabolites. The elimination half-life is approximately 45 min in healthy volunteers but is increased by threefold in patients with moderate hepatic impairment (Child-Pugh score > 6) along with a fourfold decrease in systemic clearance. Furthermore, anticoagulant responses returned to baseline in 2–4 h in healthy volunteers but took at least six hours (up to 20 h) in patients with hepatic impairment [130]. As a result, the recommended starting dose of argatroban per the manufacturer is decreased from 2 to 0.5 mcg/kg/min in patients with moderate or severe hepatic impairment [126]. A retrospective study supporting this reduced starting dose also recommended delaying the monitoring of the activated partial thromboplastin time (aPTT) to at least four to five hours after initiation or dose adjustments (compared with the standard of two hours) due to the longer time required to achieve steady state concentrations [131]. Retrospective studies of argatroban in critically ill patients describe significantly reduced dosing requirements [132, 133]. One study found a 57% reduction in dose compared with non-critically ill patients and that dose requirements were inversely related to Sequential Organ Failure Assessment (SOFA) score [132]. The authors of a second study in patients with multiple organ dysfunction syndrome (MODS) again found markedly reduced dose requirements but additionally, found a significantly lower mean argatroban dose in patients with hepatic insufficiency than in those without [133]. Accordingly, a starting dose of one tenth to one eighth of the standard starting dose is recommended for critically ill patients with MODS. To reduce the risk of bleeding complications, consideration should be given to the selection of alternative agents in patients with significant hepatic dysfunction. However, if argatroban is utilized in this patient population, a starting dose at the low end of this range is advised (e.g. 0.125 mcg/kg/min).

17.8 Infectious Disease

Infection in ESLD is associated with significant morbidity and mortality, including the development of ACLF [134]. In fact, patients with cirrhosis who develop infections have been found to have a fourfold increase in mortality compared to similar patients with cirrhosis without infection [135]. Infection either exists on admission or is acquired during hospitalization in approximately 25–30% of patients with ESLD which is four to five times higher than the general population [136, 137]. Independent risk factors for infection in patients with cirrhosis include previous infection in the past 12 months, a MELD score of 15 or greater, and protein malnutrition [138]. Patients with both ALF and ESLD are at significant risk of various types of infections although spontaneous bacterial peritonitis (SBP) and urinary tract infections are most common [136, 137, 139–141]. As in the general ICU population, multi-drug resistant (MDR) pathogens are of increasing prevalence in ESLD and should be taken into consideration when selecting antibiotics for nosocomial infections [136]. As a result of the increased incidence of infection as well as the risk of MDR bacteria, utilization of antimicrobials, including broad-spectrum agents, in this patient population is significant. Hepatic dysfunction affects several pharmacokinetic parameters which impacts antimicrobial dosing, including decreased protein binding, metabolism, and renal elimination. As previously mentioned, a significant portion of these patients will have concomitant renal dysfunction which will impact the dosing of the majority of antimicrobials. In contrast to the available literature to guide dosing of antimicrobials in renal dysfunction, there is a shortage of literature on the pharmacokinetics of antimicrobials in liver dysfunction. The antimicrobials used in the ICU that have specific dosing recommendations in the package labeling based on Child-Pugh score are limited to metronidazole, tigecycline, caspofungin, and voriconazole. A recently published review extensively evaluated the pharmacokinetic literature for commonly used antibiotics that undergo hepatic or mixed renal-hepatobiliary clearance [142]. In addition, to noting recommendations that exist in product labeling, the authors make additional dose adjustment recommendations by Child-Pugh score based on the available pharmacokinetic literature. Antibiotics that have recommendations for dose adjustments which are pertinent to the ICU setting include clindamycin, metronidazole, nafcillin, rifampin, and tigecycline. Clindamycin should have a 50% dose reduction in Child-Pugh class C. The dosing interval for metronidazole 500 mg dosing should be changed from every 8 h to every 12–24 h for all Child-Pugh classes. It's noted that nafcillin likely needs a dose adjustment although no specific recommendations are provided. For rifampin, a 50% dose reduction should be considered in all Child-Pugh classes. Finally, a 50% dose reduction should be made for tigecycline in Child-Pugh class C.

Recent literature has highlighted the inadequacy of standard antibiotic dosing regimens in the critically ill. Specifically, the ability to achieve desired concentrations is decreased which has been associated with adverse patient outcomes [143]. It is well known that both ESLD and critical illness are associated with increased Vd, therefore hydrophilic drugs, such as β-lactam antibiotics, are of concern due to the risk of decreased plasma concentrations and thus efficacy. Increased loading doses should be considered [144].

In addition, ESLD has been reported to be a risk factor for several antibiotic related toxicities including β-lactam-induced neutropenia and aminoglycoside-related nephrotoxicity [145, 146].

17.9 Endocrine

The incidence of nonalcoholic steatohepatitis (NASH) continues to grow and is one of the most common etiologies of liver cirrhosis [147]. Its growth parallels the global increase in diabetes mellitus (DM), obesity, and metabolic syndrome [147]. Endocrine abnormalities are common, and often significant, in patients with liver disease because the liver is the predominant organ responsible for the metabolism and catabolism of many proteins, hormones, cytokines, and interleukins [148]. In many cases these abnormalities are associated with worse outcomes and necessitate pharmacotherapeutic intervention for the management of DM, thyroid disorder, and relative adrenal insufficiency (RAI).

17.9.1 Glycemic Control

Diabetes mellitus is associated with increased risk of hepatic complications, including encephalopathy, portal hypertension, ascites, SBP, renal dysfunction, hepatocellular cancer, and death, in patients with chronic liver disease and cirrhosis [149]. It is thought that DM may promote inflammation and fibrosis via increased mitochondrial oxidative stress, mediated by adipokines. Effective glycemic control may mitigate the development of these adverse effects, though outcome data are lacking [149]. Intensive glycemic control (serum glucose 80–110 mg/dL) has been evaluated during critical illness and was found to significantly increase the risk of hypoglycemia and conferred no overall mortality benefit [150]. Specific to patients with acute decompensated cirrhosis, hypoglycemia is associated with increased mortality, and intraoperative hypoglycemia may also be indicative of post-hepatectomy liver failure [151, 152]. It has not been established whether hypoglycemia is partly responsible for the increased short-term mortality of patients with acute decompensated liver cirrhosis or rather merely a consequence of the severity of the disease or its complications. Nevertheless, conservative management dictates the avoidance of treatments associated with increased hypoglycemia risk. As such, the American Diabetes Association recommends that insulin therapy be initiated for treatment of persistent hyperglycemia, starting at a threshold of 180 mg/dL and titrated to a target glucose range of 140–180 mg/dL for the majority of critically ill patients [153]. While patients with liver failure are not specifically addressed by these guidelines, it is reasonable to apply these recommendations to that patient population. An insulin infusion has been shown to be the best method for achieving glycemic targets; therapy should be initiated with an intravenous insulin infusion using a validated written or computerized protocol that allows for predefined adjustments in the infusion rate, followed by a transition to "sliding scale" insulin when clinically appropriate. Patients with liver disease may initially require higher doses of insulin to control serum glucose because of insulin resistance in muscle, liver, and adipose [154]. However, as the disease progresses and metabolic function deteriorates, insulin requirements may decrease as gluconeogenesis slows. Oral agents are not ideal for chronic management and are contraindicated in the acute management of DM; they are often hepatically metabolized and can therefore accumulate in these patients and cause toxicity, including hypoglycemia and lactic acidosis [149, 153, 154]. DM is difficult to manage in patients with liver disease, given that both hyper- and hypo-glycemia are associated with poor outcomes and close clinical monitoring is warranted.

17.9.2 Thyroid

The liver is primarily responsible for the peripheral conversion of tetraiodothyronine (T4) to triiodothyroinine (T3), as well as the synthesis of many proteins, including thyroid binding proteins. Therefore, dysregulation and dysfunction of thyroid hormones are anticipated in patients with cirrhosis [148, 155]. The incidence of thyroid abnormalities in the setting of liver disease is variable, ranging from 13 to 61%. Hypothyroidism is most common and presents most frequently as low T3 and low free T3, although hyperthyroidism can also occur [155, 156]. In the critically ill cirrhotic patient admitted to the ICU, more than half had some form of Euthyroid Sick Syndrome [157]. While thyroid dysfunction has been associated with decreased short- and long-term survival of patients with liver cirrhosis, data are not conclusive [158]. A retrospective study found that liver function in patients with a hypothyroid state tended to be better than in those with a euthyroid state [159]. Given that the appropriate treatment of Euthyroid Sick Syndrome is unclear in patients with normal liver function, the additional layer of complexity imposed by liver dysfunction, along with inconclusive outcome data, makes it difficult to establish a treatment plan. Additionally, levothyroxine has been associated with an increased risk of hypoglycemia in patients with liver impairment [160]. The pharmacokinetic profile of levothyroxine is not significantly altered by liver disease, but given our understanding of the consequences of hypoglycemia in this patient population, conservative thyroid management is warranted.

17.9.3 Adrenal Insufficiency

RAI, sometimes referred to as hepatoadrenal syndrome, is common in critically ill patients, but it also has been reported in patients with uncompensated and stable cirrhosis, including those with and without septic shock [148, 161–163]. The reported incidence is variable, ranging from 7.2 to 60%, in part due to wide variability in laboratory technique and test criteria used for diagnosis [148, 164, 165]. Despite this variability, most studies have demonstrated RAI to be associated with poor prognosis in cirrhotic patients. A relationship appears to exist between the severity of the liver disease and the presence of RAI, though neither the mechanism nor the exact prevalence of RAI is fully understood [161, 163]. The diagnosis of RAI also remains controversial. Meta-analyses have evaluated the role of low- (1 mcg) and standard-dose (250 mcg) corticotropin test in the diagnosis of RAI, finding that both tests performed well but were not without limitations [166, 167]. Endocrine Society Guidelines recommend the use of standard-dose (250 mcg) corticotropin as the "gold standard" diagnostic tool to establish the diagnosis, although liver disease affects how the test is interpreted. Alterations in serum free and total cortisol levels have been observed in both chronic and severe acute hepatitis as a result of decreased protein binding [168, 169]. Serum free cortisol or free cortisol index may be preferred for the evaluation of RAI compared to serum total cortisol in these patients [168, 169]. Guidelines recommend the use of a low diagnostic (and therapeutic) threshold in acutely ill patients, as well as in patients with predisposing factors, such as liver disease [170]. A few studies have evaluated the role of corticosteroids in the treatment of RAI in patients with liver cirrhosis, with and without septic shock [159, 162, 163, 171, 172]. For all studies the intervention was hydrocortisone dosed at 200–300 mg per day, sometimes referred to "stress-dose", with outcomes focused on vasopressor dose and duration, shock resolution, shock recurrence, adverse effects including infection and gastrointestinal bleed, and hospital survival. Outcome data are mixed, as are expert opinions, similar to the data set and expert opinions representative of septic patients without liver cirrhosis. Endocrine guidelines recommend fludrocortisone 0.1 mg daily and hydrocortisone 15–25 mg given two to three times daily in adults with RAI, though this is a broad recommendation and not specific to patients with liver disease [170]. This dose is considerably lower than what has been studied in liver cirrhosis, and what is recommended by the Surviving Sepsis Guidelines (hydrocortisone 200 mg daily) [173]. The dose of hydrocortisone need not be adjusted in patients with liver failure. Additional high-quality data are needed to make strong recommendations, though the administration of glucocorticoids, and perhaps mineralocorticoids, may improve outcomes in patients with liver cirrhosis, including when accompanied by septic shock.

17.10 Special Populations

17.10.1 Continuous Renal Replacement Therapy

There is a potential for critically ill patients with hepatic impairment to require continuous renal replacement therapy (CRRT). Dose adjustments are commonly necessary for medications with specific pharmacokinetic properties [174] (Table 17.3). It is critical to understand that these properties may be significantly altered from baseline in patients with hepatic impairment. Medication clearance is also significantly influence by CRRT modality and effluent rate. In order to appropriately dose medications in patient with hepatic impairment receiving CRRT, critical evaluation of each medication's pharmacokinetic properties in relation to both hepatic clearance and CRRT clearance is essential.

17.10.2 Extracorporeal Liver Support Systems

Accumulation of various toxins that otherwise would be metabolized by the liver contribute to many of the complications seen in ALF and ACLF. Several of these toxins (e.g. ammonia and endogenous benzodiazepines) are involved in some of the most significant manifestations of ALF and ACLF, cerebral edema and hepatic encephalopathy, respectively. Others (e.g. pro-inflammatory cytokines) may play a role in cardiovascular and renal dysfunction.

Extracorporeal liver support (ECLS) systems, or liver assist devices, can act as a bridge to liver recovery (since the liver can maintain the ability to regenerate, especially in ALF) or liver transplantation by mimicking the function of the liver and assisting with various hepatic functions. There are two types of ECLS systems: artificial and bioartificial. Artificial systems eliminate albumin-bound and water soluble substances, including bilirubin and various toxins, with technologies utilizing exogenous albumin and artificial membranes similar to those used in hemodialysis. Examples of artificial systems include the Molecular Adsorbent Recirculating System (MARS [Teraklin AG, Rostock, Germany]), single-pass albumin dialysis (SPAD), Prometheus (Fresenius, Hamburg, Germany), and high-volume plasmapheresis (HVP). Bioartificial systems differ because they use living hepatocytes and therefore provide some synthetic and metabolic function in addition to detoxification. Examples of bioartificial

Table 17.3 Example of some drug attributes to increase likelihood of removal via CRRT

Drug attribute
Low percent protein binding
Small volume of distribution
Small molecular weight

systems include the Extracorporeal Liver Assist Device (ELAD, Vital Therapies, Inc., San Diego, USA) and HepatAssist (Arbios, USA). MARS is the most frequently used ECLS system in the United States as well as the most extensively studied, although HVP is the only ECLS system to demonstrate an improvement in transplant-free survival in ALF thus far [175]. Study outcomes related to the use of ECLS systems in both ALF and ACLF have been recently extensively reviewed [176].

17.10.2.1 Drug Considerations

Given that artificial ECLS systems eliminate albumin-bound and water soluble substances, removal of drugs which have these qualities is a special consideration in determining appropriate dosing. In addition, timing of the administration of the drugs in relation to the timing of ECLS system treatment can have a significant impact on drug removal. Since MARS is the most commonly used ECLS system in the United States, this section will focus on drug dosing considerations during MARS and will review the available pharmacokinetic data for drugs utilized in the ICU. MARS employs albumin dialysis to remove both albumin bound and water soluble substances. It should be noted that MARS is used in conjunction with CRRT (see the chapter entitled *Use of Extra-corporeal Liver Support Therapies* for detailed information regarding MARS mechanisms and system set-up). Drugs can be removed by the MARS system in addition to clearance from CRRT making dosing complicated. Also, drugs with both high and low protein binding can be removed given the two different mechanisms of removal. There is very little literature describing the impact of MARS on drug removal and therefore very little guidance on appropriate dosing.

One study utilized an *in vitro* model to examine the effects of MARS on the removal of several different drugs with varying pharmacokinetic characteristics compared with removal via continuous venovenous hemodialysis (CVVHD) [177]. Ceftriaxone (low Vd) and teicoplanin (high Vd) are both highly albumin bound antibiotics. Ceftriaxone concentrations decreased by 71% in 6 h with MARS compared with 20% with CVVHD. Similarly, teicoplanin concentrations decreased by 90% with MARS and 58% with CVVHD which demonstrates significant removal via both therapies. Both ceftazidime (low Vd) and levofloxacin (high Vd) have negligible albumin binding and as a result were shown to have similar removal during MARS and CVVHD which was primarily driven by CVVHD clearance. Ceftazidime concentrations decreased by 98.4% in CVVHD and 99.8% in MARS. Likewise, levofloxacin concentrations decreased by 99.3% in both CVVHD and MARS.

A second study also using an *in vitro* model described the removal of moxifloxacin and meropenem [178]. Moxifloxacin is moderately albumin-bound and meropenem demonstrates low albumin binding. The concentrations of both moxifloxacin and meropenem decreased by approximately 50% 1 h after the initiation of MARS. Both medications were found in all portions of the MARS system as well as the dialysate demonstrating removal by the MARS component as well as the dialysis component.

Piperacillin-tazobactam removal during MARS has also been described in two case reports [179, 180]. In one case report, a patient receiving MARS for APAP-induced ALF received a single dose of piperacillin-tazobactam 4.5 gm administered over three hours [180]. Piperacillin-tazobactam is known to be cleared via CRRT and is moderately protein bound. Piperacillin concentrations decreased by approximately 32% from one hour after the end of the infusion to three hours later. The half-life was calculated to be 1.53 h which was 3.7-fold shorter than that reported with CVVHD alone demonstrating additional removal via MARS [181]. In the second case report, one patient received MARS for refractory hepatic encephalopathy and a second patient received MARS for hepatic failure (including encephalopathy) after hepatectomy [179]. The first patient had piperacillin concentrations measured after the first dose of 3.375 gm administered over four hours. The second patient had piperacillin concentrations measured during two different three-hour extended infusion piperacillin-tazobactam dosing regimen: 4.5 gm every 8 h and 3.375 gm every 8 h. All serum concentrations taken from both patients (including at the end of MARS therapy and the dosing interval) exceeded that which would be desired for treatment of the involved organisms per the MIC breakpoints recommended by the 2014 Clinical Laboratory Standards Institute guidelines [182].

One case report describes negligible removal of tacrolimus during MARS despite the fact that it has a low-molecular weight and is highly protein-bound [183]. Finally, MARS has been used for the management of acute poisoning from a variety of drugs and substances which has been recently extensively reviewed [184].

Clinicians should anticipate significant removal of any highly protein bound drug during MARS treatment sessions and ideally time the administration of those drugs for after MARS treatment sessions are complete if using intermittent sessions. Using extended or continuous infusion times could be considered for certain drugs, especially if MARS is being run continuously. Utilizing therapeutic drug monitoring when available can provide significant guidance on appropriate dosing given the lack of pharmacokinetic data.

17.10.3 Extracorporeal Membrane Oxygenation

The use of extracorporeal membrane oxygenation (ECMO), which often requires therapeutic anticoagulation with mechanical support, is not common in the context of liver

failure due to its association with underlying coagulopathy, but when employed it poses an additional layer of complexity for drug dosing. Several mechanisms account for alternations in pharmacokinetic parameters during ECMO. The larger apparent Vd, as a product of larger circulatory volume, disproportionally affects drugs with small Vd (hydrophilic) and thereby results in lower maximum concentration (Cmax) and increased elimination [185]. Furthermore, this may be complicated by ongoing fluid removal either via forced diuresis or CRRT, which results in a dynamic Vd and variable drug concentrations. Drug inactivation, sequestration, or adsorption by the various components of the ECMO circuit also influences pharmacokinetics. The Vd, degree of protein binding, and the extent of equilibrium between tissue and plasma concentration upon initiation of ECMO will dictate the degree of pharmacologic impact ECMO has on these drugs [185–190].

Patients requiring ECMO often necessitate increased analgesic and sedative doses, including morphine, fentanyl, and midazolam [185, 190, 191]. This may be in part due to the deeper sedation goals to optimize oxygenation and minimize agitation-related sequale such as ECMO circuit complications, but it is also related to pharmacokinetic changes during ECMO. While analgesics, sedatives, inotropes, vasopressors, diuretics, and anticoagulants may be titrated to measureable endpoints, no real time target exists for antibiotics [192]. Due to the multiple variables that may influence the pharmacokinetic profile of drugs in critically ill patients, drug regiments should be individualized. Initial does should be based on population pharmacokinetics and increased frequency of therapeutic drug monitoring with subsequent adjustments should be employed whenever possible [185, 192, 193].

Conclusion

The management of a chronic disease complicated by an acute exacerbation is challenging enough without having to consider potential clinically important changes in the pharmacokinetics and pharmacodynamics of drug therapy. In the context of liver disease, the drugs used to treat the condition are altered significantly by the disease itself and can further complicate drug therapy. Avoidance of some drugs and dose adjustments in others are necessary to avoid drug misadventures and further deterioration of an already fragile disease state. Basic considerations for drug therapy have been reviewed, including a deeper assessment organized by organ system. Additionally, consideration has been given to devices that will further alter the pharmacokinetics and pharmacodynamics in the setting of liver disease. Drug therapy should be based on evidence-based outcome data, and guidelines when available, along with the side effect profile of a given medication. Dosing of medications in patients with liver disease should be based on population kinetics in patients with liver disease, and not extrapolated from other patient populations. When possible, therapeutic drug monitoring should be implemented and therapy should be customized to each individual patient.

17.11 Chapter Assessment Questions (Bold Emphasis Answers are Correct)

1. Which of the following best describes the effect of acute liver failure (ALF) on drug distribution?
   Increased volume of distribution
   Decreased volume of distribution
   Increase in protein binding
   Decrease in the fraction of free drug available
2. Which of the following sedative agents appears to be the safest agent to use in patients with ESLD?
   Dexmedetomidine
   Lorazepam
   Midazolam
   Propofol
3. Based on medication half-life, which synthetic prostacyclin does not require cautious dosing or dose adjustments for the treatment of portopulmonary hypertension?
   Bosentan
   Epoprostenol
   Iloprost
   Treprostinil
4. Which of the following beta-blockers should be dosed cautiously in patients with ALF secondary to increased bioavailability, area-under-the-curve, and elimination half-life?
   Esmolol
   Metoprolol
   Nadolol
   Propranolol
5. Which proton pump inhibitor does NOT require dose adjustments in patients with severe ESLD?
   Esomeprazole
   Lansoprazole
   Omeprazole
   Pantoprazole
6. Which of the following statements is true regarding pharmacologic venous thromboembolism prophylaxis in patients with end-stage liver disease (ESLD)?
   Autoanticoagulation in ESLD negates the need for pharmacologic prophylaxis.
   ESLD and associated coagulopathy alone should not be considered a contraindication to pharmacologic prophylaxis and critically ill patients with ESLD should receive pharmacologic prophylaxis as a default unless there are specific contraindications.

Evidence supports that ESLD patients should only receive pharmacologic prophylaxis if the platelet count is greater than 100,000/μL and the INR is less than 2.5.

Low-molecular weight heparin prophylaxis is the preferred agent for pharmacologic prophylaxis in all ELSD patients.

7. Which of the following antimicrobial medications requires a 50% dose reduction for all classifications of Child Pugh classes?

Clindamycin

Metronidazole

Rifampin

Tobramycin

8. What pharmacokinetic properties make a medication likely to be removed via continuous renal replacement therapy (CRRT)?

Large volume of distribution, high protein binding, large molecular weight

Large volume of distribution, low protein binding, large molecular weight

Small volume of distribution, high protein binding, small molecular weight

Small volume of distribution, low protein binding, small molecular weight

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