Hepatic Failure

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Acute Liver Failure

Definition, Epidemiology, and Causes

Acute liver failure (ALF) refers to the rapid deterioration of liver function that is seen in previously healthy patients. Its defining characteristics include the development of coagulopathy, with an international normalized ratio (INR) >1.5, as well as alteration of mental status (encephalopathy). It occurs in individuals without preexisting cirrhosis and with an illness of no more than 26 weeks duration.

There are some minor differences that are associated with duration of symptoms, and therefore ALF can be further subdivided into hyperacute (less than 7 days), acute (7–21 days), or subacute (more than 21 days and less than 26 weeks). Hyperacute and acute liver failures are more commonly associated with cerebral edema, while patients with subacute failure can present with ascites, portal hypertension-related bleeding, and renal failure.

Approximately 2,300 patients experience ALF in the United States [1]. Half of these cases are associated with drug toxicity, most of them related to acetaminophen. Viral hepatitis accounts for one fifth of the cases, the remaining being different metabolic and vascular disorders (Table 18.1) [2].

Clinical Manifestations

The rapid compromise of hepatic physiologic function results in clinical features that can affect several organ systems and can be variable in their presence and intensity.

Neurologic System

Nonspecific complaints such as fatigue, malaise, lethargy, nausea, vomiting, headache, and anorexia are frequently present in patients with liver failure. As a defining characteristic, patients with ALF present with various degrees of encephalopathy, ranging from slight confusion to coma. In order to characterize the severity of the impairment, several grading scales have been described [3]. Most commonly used is the West-Haven criteria (Table 18.2) [4]. For moderate to severe cases of encephalopathy, the Glasgow Coma Scale can also be used.

The mechanism by which these changes occur has not been fully identified; however, there are some generally

Table 18.1 Causes of acute liver failure

Medications	Acetaminophen (paracetamol)
	Tetracycline
	Troglitazone
	Isoniazid
	Aspirin
Toxins	*Amanita* mushrooms
	Lepiota helveola
Infectious	Hepatitis A
	Hepatitis B
	Hepatitis C (very uncommon)
	Cytomegalovirus
	Epstein-Barr virus
Metabolic	Acute fatty liver of pregnancy
	Wilson's disease
	Reye's syndrome
Vascular	Budd-Chiari syndrome
	Portal vein thrombosis
	Veno-occlusive disease
	Ischemic hepatitis
Parenchyma replacement or loss	Breast cancer
	Melanoma
	Small cell lung cancer
	Hepatectomy
	Necrosis

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Table 18.2 West-Haven criteria for grading hepatic encephalopathy

Grade I	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impaired performance of addition
Grade II	Lethargy or apathy
	Minimal disorientation for time or place
	Subtle personality change
	Inappropriate behavior
	Impaired performance of subtraction
Grade III	Somnolence to semistupor but responsive to verbal stimuli
	Confusion
	Gross disorientation
Grade IV	Coma (unresponsive to verbal or noxious stimuli)

accepted theories that revolve around impaired detoxification of substances normally cleared by the liver.

- Ammonia
- The metabolism of nitrogen-containing compounds in the gastrointestinal system results in the production of ammonia. In its normal state, the liver converts this neurotoxic product into glutamine and urea. Impaired liver function results in elevated blood ammonia. Astrocytes contain the enzyme glutamine synthetase in their endoplasmic reticulum as a means of handling excessive ammonia. Accumulation of glutamine within the astrocytes results in cell swelling which leads to a series of events that result in a neuroinhibitory state [5].
- False Neurotransmitters
- The failing liver results in the production of false neurotransmitters. These molecules may interfere with normal brain functioning and have a net inhibitory effect [6].
- Amino Acid Imbalance
- Patients with hepatic failure have decreased plasma levels of the branched-chain amino acids (BCAA) valine, leucine, and isoleucine while experiencing increased levels of aromatic amino acids (AAA) phenylalanine, tryptophan, and tyrosine. This is thought to be related to increased muscle catabolism and therefore increased BCAA metabolism as well as decreased breakdown of AAA by the compromised liver. The end result is an imbalance that leads to an increased influx of AAA in the brain which has an inhibitory effect in the nervous system [7].
- GABA receptor
- Thought to be mediated by inflammatory cells, neurosteroids are produced by myelinated glial cells. This results in positive modulation of GABA receptors that in turn enhance the inhibitory tone [8].

Besides the astrocyte swelling that is seen with the accumulation of glutamine explained above, overall neurologic dysfunction results in loss of autoregulation of intracranial pressure as well as reduced cerebral blood flow. The result of these changes may result in further neurologic derangement and compromise [9].

Besides hepatic encephalopathy, patients with ALF can also present with cerebral edema. There is an overlap with the clinical features that are seen with encephalopathy and include nausea, vomiting, headache, and agitation. In advanced cases which can progress to brain herniation, hypertension, bradycardia, changes in pupillary exam or reflexes, as well as respiratory depression can be seen [10].

Table 18.3 Respiratory complications seen in acute liver failure

Infectious	Upper respiratory infections
	Pneumonia
Noninfectious	Pulmonary edema
	Pleural effusion
	Pneumothorax
	Hepatopulmonary syndrome
	Acute respiratory distress syndrome
	Acute lung injury
	Depressed central respiratory drive

Respiratory System

Patients with ALF may present with nonspecific respiratory symptoms including dyspnea on exertion, orthopnea, anxiety, and air hunger. The affecting processes involved are very broad and can range from a simple pleural effusion to acute respiratory distress syndrome (ARDS) [11]. The spectrum of respiratory pathology that is seen can be grouped in to two major categories: infectious and noninfectious (Table 18.3).

Pulmonary edema can be of cardiogenic or noncardiogenic etiology. The prevalence of pulmonary edema appears to be higher in those patients with cerebral edema, suggesting the accumulation of osmotic substances within the lung parenchyma and outside the vasculature [12]. Molecular imbalance and injury to endothelial cells, accompanied by a decrease in oncotic pressure, may play a role in the development of this disease.

Hepatopulmonary syndrome can be seen in both ALF and chronic liver failure. It is thought to arise from microscopic shunting from arteriovenous dilations that occur in the pulmonary vasculature [13]. The precise mechanism is unknown; however, it is thought that the elevated levels of nitric oxide seen in patients with liver failure may mediate the abnormal vasodilation that occurs in the pulmonary parenchyma. The result is an overperfusion with maintenance of ventilation; a VQ mismatch occurs that ultimately leads to hypoxemia [14].

Cardiovascular and Hematologic System

As part of the pathophysiology associated with ALF, there is low systemic vascular resistance and a hyperdynamic

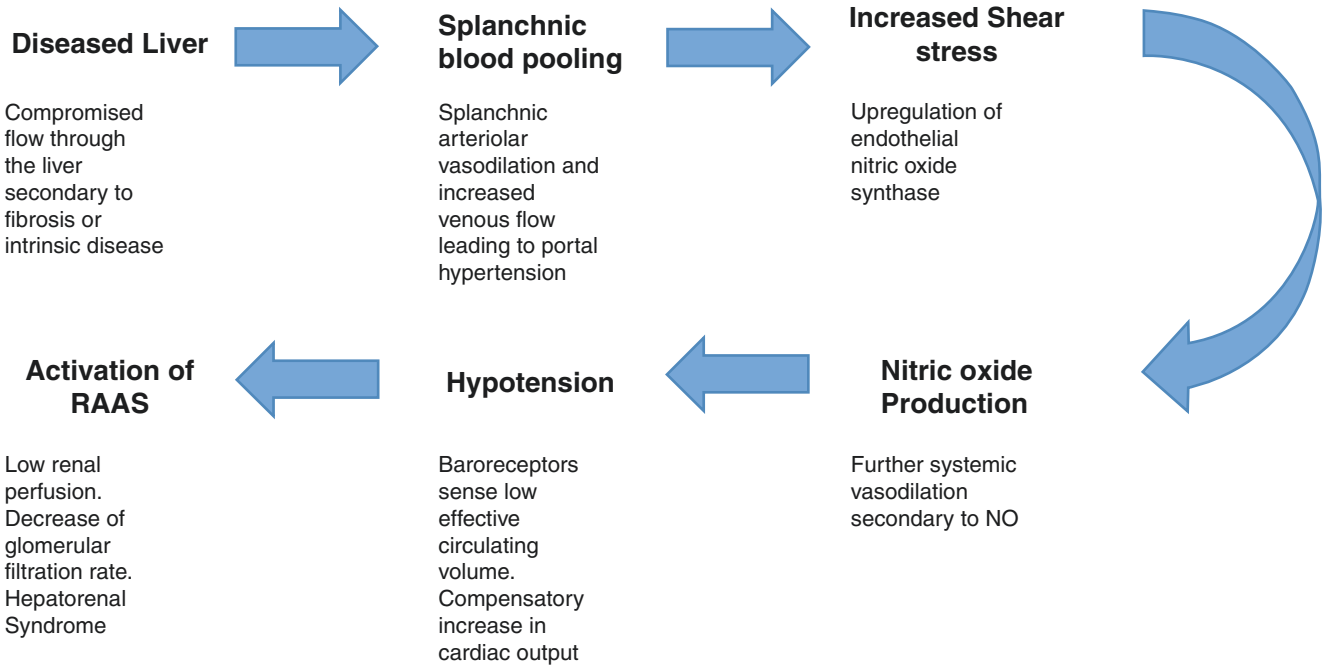

Fig. 18.1 Physiologic changes that occur in patients with liver failure

circulation with elevated cardiac output. The pathophysiology is multifactorial but vasoactive substances are thought to mediate the process [15]. While the underlying pathophysiology may differ, hemodynamic variables appear very similar to those seen in sepsis and septic shock.

In the failing liver, there is an increase in splanchnic blood pooling that is associated with the increased resistance of flow through the liver. This results in increased shear stress in the splanchnic circulation that causes upregulation of endothelial nitric oxide synthase (eNOS) and ultimately nitric oxide (NO) production [15, 16]. There is further systemic vasodilation causing a low effective circulating volume and relative hypotension despite an overall elevated intravascular volume. The systemic baroreceptors are unloaded and there is a compensatory increase in cardiac output as well as activation of the renin-angiotensin-aldosterone system (RAAS) that may ultimately affect the renal system (Fig. 18.1) [15].

Patients with ALF usually present with varying degrees of coagulopathy. As the liver fails, there is decrease in the synthesis of factors involved in both coagulation and anticoagulation, specifically fibrinogen, prothrombin, protein C, protein S, and factors V, VII, VIII, IX, X, and XI. The end result is an increased in prothrombin and activated partial thromboplastin times as well as elevation of INR [17].

Overt bleeding is not typically seen, as there is a decrease in both coagulation and anticoagulation factors. However, mucosal bleeding from the oropharynx or the gastrointestinal mucosa can be frequently seen. This is compounded by the underlying platelet dysfunction that can occur in patients with liver failure.

Gastrointestinal and Endocrine Systems

Right upper quadrant pain, gastrointestinal bleeding, ascites, nausea, and vomiting can be seen in patients with ALF. These symptoms are nonspecific and can be multifactorial.

Patients with acute viral or autoimmune hepatitis may experience liver parenchyma inflammation as part of the normal response to infection. This leads to an increase in the overall volume of the liver. The liver capsule may be unable to accommodate acute volume changes, and stretching of it results in activation of pain receptors and right upper quadrant pain. Discomfort in this area can also be related to direct trauma causing bleeding.

Abdominal distention may be associated with ascites. The neurohumoral alterations are seen with ALF leading to excessive sodium retention and ultimately plasma volume expansion. This, combined with a decrease in the overall circulating proteins due to compromised liver function, leads to overflow of fluid into the peritoneal cavity [18]. Tense ascites can result in compromise of respiratory, renal, and cardiovascular function due to direct compression of the diaphragm and vasculature.

As part of its normal physiologic function, the liver is responsible for gluconeogenesis as well as glycogen storage. As liver function worsens, these two key metabolic functions are compromised. In up to 40 % of patients, hypoglycemia is seen and treatment is warranted [19].

Renal System and Electrolytes

Acute kidney injury can be present in 30–70 % of patients with ALF [20, 21]. The etiology can be variable: prerenal azotemia, drug toxicity, and acute tubular necrosis have all been implicated. Hepatorenal syndrome, especially type 1, has also been associated with the progression of this disease. Acute kidney injury can be divided into oliguric vs. anuric failure, with the latter making fluid management difficult in the critical care setting [15].

Accompanying this derangement we can also see electrolyte disturbances: hyperkalemia, hyperphosphatemia, hypophosphatemia, hypercalcemia, and hypomagnesaemia that can lead to secondary arrhythmias and mental status changes [22].

Lactic acidosis can be seen in patients with ALF. The accumulation of tissue lactate is multifactorial. The effective blood pressure is usually lower in those patients with liver failure. This causes a generalized tissue hypoxia that leads to the production of lactate. The compromised liver is unable to uptake and process the lactate, leading to its accumulation [23–25]. In addition, acute kidney injury can further contribute to the underlying acidosis due to failure of fixed acid clearance [22].

Infectious Disease

Kupffer cells can be found around the hepatic sinusoids. Because of their location, they are constantly exposed to gut bacteria and endotoxins. They play a key role in clearing these pathogens and in maintaining normal homeostasis. In patients with liver failure, their function is impaired, and there is an increased susceptibility to develop Gram-positive and Gram-negative bacterial infections as well as possible fungal and viral infections [26].

Hepatic encephalopathy has been linked to an increased incidence of infection [27]. Although the mechanism behind this has not been clearly elucidated, it is thought that CNS depression alters the immune system modulation. In ALF, there is also a change in the production as well as clearance of different cytokines in patients with liver failure and compromised neutrophil function. These problems will lead to decreased bacterial opsonization and clearance. These alterations ultimately contribute to the immunologic impairment [26–28].

Up to three quarters of patients with ALF will develop a bacterial infection. The organisms that are most commonly seen include Gram-negative-bacteria, *Streptococcus*, *Staphylococcus*, and *Candida*. They may develop a systemic inflammatory response syndrome (SIRS) that will be undistinguishable from noninfectious conditions including necrotic hepatocytes from the failing liver [29–31].

Other Systems

Jaundice and pruritus are common complaints of patients with ALF. Although not specific to liver failure, the presence of both symptoms should raise suspicion of compromised excretion of bilirubin by hepatocyte failure.

A normal by-product of the metabolism of heme, bilirubin is usually excreted in bile and urine. The liver is responsible for conjugating glucuronic acid with bilirubin in order to make a soluble compound. As a result, conjugated bilirubin passes into the colon and is eventually eliminated. In the failing liver, there is a severe compromise of the ability to metabolize and excrete bilirubin secondary to the undergoing cell necrosis. There is buildup of unconjugated bilirubin in the blood resulting in eventual deposition of these molecules in mucous membranes, skin, and conjunctiva, what is known as jaundice [32]. Because of the yellow color of the pigment, the physical appearance of the patient changes, directly correlating with bilirubin levels.

Besides bilirubin, there is also accumulation and deposition of bile acids in the skin. This has been associated with pruritus. Other mechanisms that may explain this symptom include the endogenous opioids theory which proposes that the liver failure patient has elevated opioid levels secondary to decrease clearance and metabolism. These molecules activate the mu opioid receptor which may produce pruritus [33–35].

Workup and Initial Management

As explained throughout this chapter, the management strategies for patients with ALF are different from those of patients that have chronic liver failure with an acute decompensation. It is imperative to determine what form of failure the patient is experiencing. For those with ALF, early recognition and transfer to a transplant center will improve outcomes and mortality.

On initial presentation, a patient's mental status will be affected to different degrees; however it may deteriorate further. Getting a thorough history during the first encounter is therefore important as it can elucidate the possible cause of the acute failure.

The intensivist should review all medications that the patient ingested in the last 7 days. Specific questions about ingestion of acetaminophen should be asked. Dietary intake should also be explored, playing close attention to any exposure to mushrooms. Exact time of ingestion is key in order to determine treatment and further steps in management.

Social history should also be reviewed in detail. Recent travel to viral hepatitis endemic areas as well as contact with other patients that have required hospital visits should be evaluated. Focus on alcohol and drug use, sexual behaviors, and vaccination status can help determine the causative mechanism for the liver failure.

Past medical history plays a key role in determining if the patient has chronic liver disease or if they are experiencing an acute failure. A history of hepatitis, ascites, jaundice, asterixis, and gynecomastia and family history of a metabolic

Table 18.4 Laboratory exams that should be part of the initial evaluation of patients with acute liver failure

Infectious	White blood cell count
	Hemoglobin and hematocrit
	Platelet count
	Hepatitis A IgM
	Hepatitis B surface antigen
	Hepatitis B surface antibody
	Hepatitis B core antibody IgM
	Hepatitis B e antigen
	Hepatitis C antibody
Coagulopathy	Prothrombin time
	Activated thromboplastin time
	INR
	Type and screen
Renal and metabolic	Serum electrolytes (Na, K, Cl, CO2, Mg, PO4, Ca)
	Glucose
	BUN and creatinine
	AST
	ALT
	Alkaline phosphatase
	Total bilirubin
	Direct bilirubin
	Albumin
	Amylase
	Lipase
	Arterial blood gas
	Serum lactate
	Ammonia
	Ceruloplasmin
Toxin	Acetaminophen level
	Toxicology screen
Autoimmune	ANA
	ASMA
	Immunoglobulin levels

disorder favor chronic liver disease with an acute exacerbation. History of malignancy and lack of screening for colorectal cancer should also make the intensivist suspicious for metastatic malignancy. Physical exam may disclose important findings that can elicit cause. An effort to identify the clinical manifestations described previously should be done.

Laboratory values that should be routinely obtained are listed in Table 18.4.

When testing for hepatitis B, it is important to evaluate for immunity (hepatitis B surface antibody), infectivity (hepatitis B e antigen), and the presence of an acute infection (hepatitis B core antibody IgM). Although hepatitis C can cause ALF, it is usually associated with chronic liver failure [36].

BUN and CO2 can usually be lower than reference values in patients with ALF. This is secondary to poor muscle mass as well as a respiratory alkalosis experienced by these patients. Presentation with concomitant renal failure will alter most serum electrolytes.

Elevation of liver enzymes can be indicative of acute hepatitis and ALF. However, values that are within reference range may be markers of poor prognosis as it may be reflective of decreased effective liver mass [26, 34].

Workup should be started on presentation, even if patient is going to be transferred to a liver center. Early identification of the etiology and early treatment can significantly improve outcome. It can also identify those patients that will need liver transplantation in order to treat their disorder.

If during the history and physical assessment a cause can be clearly identified, treatment should be started empirically. Waiting for laboratory values can be detrimental and result in further deterioration of the patient. Consultation with hepatology/gastroenterology, transplant surgery, and the intensivist should be done upon determination of liver failure of any cause.

Management

The development of ALF has very different etiologies as well as presentations. As such, the management may differ from patient to patient. Identification of the causative agent and treatment of it is important. However, supportive care in the intensive care unit is critical for ensuring a positive outcome.

Patients that have evidence of encephalopathy will require intensive care unit (ICU) admission and management while those with no neurologic derangement can be followed on a regular ward with close monitoring. Patients should have frequent checks of their coagulation parameters, arterial blood gases, complete blood counts, metabolic panels, serum aminotransferases, alkaline phosphatase, and bilirubin levels. Derangements warrant further investigation. Hemodynamic monitoring, precise fluid management, and monitoring for infections are all essential.

Encephalopathy, Cerebral Edema, and Intracranial Hypertension

The grade of hepatic encephalopathy guides the management and treatment of the neurologic system in ALF. This is because intracranial hypertension (ICH) and cerebral edema characterize the severity of patient presentation. Those with mild forms (grades I and II) very rarely develop these devastating complications while 25–35 % of patients with grade III and 65–75 % of those with grade IV present with ICH [11].

For those patients with grades I and II, frequent neurologic assessments should be performed to follow possible neurological progression. Maintaining the patient in a quiet environment helps minimize agitation. Sedation should be minimized; however, if needed minimal doses of short-acting

benzodiazepines should be used [37]. For patients who present with or develop grade III and IV neurological symptoms, securing an airway should be the first treatment strategy followed by mechanical ventilation. For sedation, propofol should be used since there is evidence that it decreases cerebral blood flow and allows for frequent ongoing neurological assessment [38].

Intracranial pressure (ICP) monitoring devices are used in some ICUs in patients with ALF and grade III or grade IV encephalopathy [39]. The main reason for its use is the early identification of ICH and subsequent treatment. Also, not all patients present with Cushing's trial of systemic hypertension, bradycardia, and irregular respirations. Several trials have shown that ICP monitoring can be performed safely and successfully be used to manage ICH [40–42]. However, no trial has demonstrated a survival benefit. Bleeding has been associated with the placement of monitors; however, recent literature reports that there is a decrease prevalence of this particular complication. The incidence of bleeding after placement of ICP monitor device has been less than 1 % [43].

CT scan of the brain should be considered in those patients with an acute mental status change and those with coagulopathy in order to rule out intracranial bleed. This imaging modality does not diagnose cerebral edema or ICH in all patients, and therefore, it is not needed in every case of encephalopathy. Patients at risk of encephalopathy should also have the head of their bed elevated at 30° [44], minimize ET suctioning, and minimize pain as these factors can lead to ICH [37].

For those patients with elevated ammonia levels (greater than 75 ug/dL) and ALF, administration of lactulose can lower the incidence of cerebral edema and decrease mortality [45]. Prior to prescribing this drug, the route of drug administration must be considered as the patient's ability to tolerate PO intake may be compromised. Other compounds studied include L-ornithine L-aspartate but have failed to demonstrate any survival improvement [46].

Phenytoin has been proposed as a possible prophylactic measure to prevent cerebral edema. An initial study that involved evaluation of brain at autopsy showed that patients who were treated with prophylactic phenytoin had a decrease in cerebral edema [47]. Follow-up trials were unable to replicate these results and more importantly, there was no survival improvement when this agent was used prophylactically [48].

The administration of intravenous mannitol has been shown to transiently decrease cerebral edema and may be helpful in cases in which ICH is <60 mmHg [49]. A dose of 0.5–1 g/kg may be beneficial and it may be repeated if serum osmolality is below 320 mOsm/L. The use of hypertonic saline has also been suggested. There is a lower incidence of ICH in patients with ALF that are treated with hypertonic if it is used to achieve a serum sodium level between 145 and 155 mEq/L [50]. Use of hypertonic saline can be limited by renal failure. A newer treatment technique that has been proposed to prevent ICH is hypothermia. It is thought to mediate this benefit by preventing hyperemia [51]. Concerns regarding the use of hypothermia in the treatment of ALF include worsening coagulopathy and compromise of hepatocyte recovery [52].

Hyperventilation and use of corticosteroids have been proposed as a management option to reduce ICP. The former may achieve this goal via vasoconstriction. However, trials suggest that although there is a delay in the onset of cerebral herniation, there is no reduction in the incidence of cerebral edema and no survival benefit [53]. Hyperventilation should only be used after all other resources have failed.

Respiratory Management

While hypoxemia in patients with ALF arises from many causes, it is treated with supplemental oxygen. If the patient has grade III or IV hepatic encephalopathy, a definite airway should be established. During intubation, *cis*-atracurium is the agent of choice since it does not increase ICP [54].

Pleural effusions can be observed and may or may not be contributing to hypoxemia or other respiratory problems. The use of diuretics should be carefully considered as these patients are usually in a very delicate hemodynamic state. Overuse of diuretics can precipitate renal failure [34].

Hepatopulmonary syndrome (HPS) has been traditionally resistant to medical therapies [15]. Oxygen supplementation for hypoxemia is recommended. Transjugular intrahepatic portosystemic shunt (TIPS) has been reported to improve HPS; however, it is not currently recommended as its outcomes are variable [55, 56]. Liver transplantation is the only therapy that has been shown to improve oxygenation and decrease oxygen requirement [57]. The diagnosis of HPS should prompt immediate referral to a transplant center.

Cardiovascular and Hematologic Management

Decreases in blood pressure lead to compromised renal and brain perfusion. It is imperative to be attentive to blood pressure and heart rate values in order to ensure adequate hemodynamics and, most importantly, adequate perfusion. Patients with ALF should be resuscitated initially with crystalloid before considering vasoactive agents.

The generally accepted goal mean arterial pressure is 65 mmHg [58]. If after adequate volume resuscitation the patient is still hypotensive and not meeting blood pressure goals, vasopressors should be considered. Norepinephrine should be initiated and titrated to effect [59]. For resistant hypotension consideration to vasopressin should be given, although it should be used with caution as it has been associated with cerebral vasodilation and increased ICH [60, 61]. Terlipressin has also been suggested as adjuvant treatment but it is currently not available in the United States [60]. Other causes of hypotension resistant to vasopressor therapy

should also be entertained including adrenal failure and severe acidosis.

During liver transplantation, ICH and hemodynamics improve immediately after hepatectomy, probably secondary to removal of vasoactive cytokines. Hepatectomy can improve these derangements for up to 48 h [62]. Hepatectomy is currently recommended only as a last resort and when a liver graft in the process of being delivered to the transplant institution [37].

Despite the derangements of coagulation laboratories in patients with ALF, their coagulation status remains in equilibrium and overall hemostasis. In the absence of bleeding, no correction of laboratory parameters should be performed [63]. Transfusion should be discouraged because treatment with FFP may precipitate pulmonary problems including hypoxia, and transfusion also prevents the use of INR as a marker of hepatocyte recovery [37].

If an invasive procedure is planned or if there is evidence of significant bleeding, correction of coagulopathy should be done. FFP can be used for this purpose; however, careful volume management should also be achieved. The use of plasmapheresis and recombinant activated factor VII (rFVIIa) can help in the correction of coagulopathy. rFVIIa has been proposed as it effectively corrects derangements without volume overload [64]. However, administration does carry the risk of myocardial infarction and portal vein thrombosis [65]. ALF has also been associated with vitamin K deficiency and it should be administered routinely in these patients [66].

Thrombocytopenia has also been reported in patients with ALF. Platelets should not be administered in the absence of bleeding. If the patient has platelet counts that are greater than 10,000/mm^3, no prophylactic transfusion should be given [67]. If an invasive procedure is planned, platelets between 50,000/mm^3 and 70,000/mm^3 have been proposed, and in those bleeding, the intensivist should consider transfusion if platelets drop below 50,000/mm^3 [67, 68].

Gastrointestinal and Endocrine Management

Bleeding from intestinal mucosa is rare but has been reported in patients with ALF. Histamine-2 receptor blockers have been used in critically ill patients as prophylaxis of gastrointestinal (GI) bleeding with great success [69]. Also, proton pump inhibitors (PPI) have contributed to the reduced incidence of upper GI bleeding in patients with liver dysfunction [70]. It is therefore recommended that ALF patients are started on prophylaxis while in the ICU.

Nutrition can be compromised in patients with ALF; therefore, enteral feedings should be started early unless there are contraindications. There is no evidence that using branched-chain amino acid formulas has benefits over other enteral tube feeds [71]. Protein supplementation should not be restricted but rather limited to 60 g per day in most patients. If gastrointestinal feeding is contraindicated, parenteral nutrition may be considered. There is also evidence that the risk of GI bleeding is reduced in patients that are on enteral feeding [72].

Hypoglycemia should be actively treated in patients with ALF. The intensivist should consider adding dextrose to crystalloids in the form of D5. If hypoglycemia is severe, central replacement with D20 concentration should be used. Frequent glucose checks should be performed in order to assess the response to glucose administration. Improvement and eventually weaning can be achieved in those patients that experience hepatocyte recovery.

Right upper quadrant pain can be treated with narcotics. Judicious doses should be used as metabolism of medications can be compromised with the failing liver [37]. The management of ascites will be discussed with chronic liver failure.

Renal Management

Close urine output monitoring is paramount in patients with ALF. Hemodynamic changes and alterations in the cardiovascular system make the kidneys susceptible to injury. Insertion of a urinary catheter should be performed upon determination of hepatic failure.

Besides serum electrolytes, measurement of urinary sodium and creatinine is necessary. High or normal urine sodium may indicate the presence of acute tubular necrosis, while a low urine sodium may indicate prerenal azotemia or hepatorenal syndrome. Several electrolyte derangements may occur and correction should be attempted. Accumulation of lactate may result from tissue hypoxia and combined with renal failure may cause life-threatening acidosis.

Renal replacement therapy may be necessary in these patients. When indicated, continuous dialysis should be used as studies have shown that it provides cardiovascular as well as intracranial pressure stability when compared to intermittent dialysis [73].

Infectious

The development of an infection in a patient with ALF has been associated with worsening encephalopathy and cerebral edema. Also, the presence of bacterial or fungal infections may compromise any attempts at performing a liver transplantation. Because of the impact that it has, prophylactic antimicrobials have been proposed as a prevention strategy for these patients [74].

Prophylactic antibiotics have been used and shown to decrease the incidence of infections in patients with ALF. In a prospective control trial by Rolando N et al., patients with fulminant liver failure were randomized to receive either selective parenteral and enteral antimicrobials vs. no treatment until clinically indicated. 104 patients were included in this study. Thirty-four percent of those patients randomized

to receive prophylactic antibiotics developed an infection compared to 61 % of those that were treated when clinically indicated ($p<0.005$). However, this did not translate into a survival benefit [75]. It is currently recommended that if no prophylactic antibiotics are used, periodic sputum, urine, and blood cultures are performed to determine if there are bacterial infections [37].

The use of antifungals has also been studied [76]. It is routine practice of the authors to use prophylactic enteric fluconazole in patients that are expected to be in the ICU for more than 3 days, given that there is a decrease in fungal infections in high-risk critically ill surgical patients [77].

It is paramount to perform an infectious workup to any patient with liver failure that develops a change in mental status as it may be a change precipitated by infection.

Specific Management

Acetaminophen Toxicity

The most common cause of ALF in the United States is acetaminophen (paracetamol) toxicity [78]. Over-the-counter availability and the fact that it can be found in combination with other medications make it the cause of voluntary or involuntary overdoses that compromise liver function and may result in fulminant liver failure.

Acetaminophen is usually taken orally and absorbed via the gastrointestinal system. Its half-life is usually 2–4 h with one exception being extended release preparations in which it is increased to more than 4 h. Total doses should not exceed 4 g per day. Ingesting doses less than 7.5 g per day is unlikely to result in acute toxicity; however, it can vary depending on underlying liver function [79].

The metabolism of acetaminophen is performed in the liver. Most of the compound, approximately 90 %, is conjugated with sulfate or glucuronide and excreted in the urine. Five percent of the remaining medication is excreted unchanged in the urine. The remaining acetaminophen is subject to metabolism by the cytochrome P450 pathway. It is converted into N-acetyl-p-benzoquinoneimine (NAPQI), a highly reactive and toxic compound that is immediately conjugated with hepatic glutathione and excreted in the urine.

When glutathione levels drop below 20 % physiologic levels, NAPQI forms covalent bonds via cysteine groups with hepatic molecules and proteins, leading to irreversible hepatocyte damage. A decrease in glutathione levels, enhanced cytochrome P450 activity secondary to medication use, acetaminophen overdose, or decreased liver function from chronic disease make patients more susceptible to developing toxicity.

The clinical presentation of acetaminophen toxicity can be divided into four different stages (Table 18.5).

Stage I includes a series of nonspecific GI symptoms that start shortly after ingestion. No liver abnormality can be seen. During stage II, there is usually transaminitis with a high AST/ALT ratio. Stage III is characterized by the clinical evidence of liver failure and, in some patients, renal failure. Mortality is higher at this stage. Those patients that survive this stage progress to stage IV in which there is normalization of most of their lab derangements.

Because patients may not show symptoms up to 24 h after ingestion, it is very important to obtain a detailed history. Standard workup should be initiated as discussed previously. Contacting poison control will help coordinate efforts to treat and eventually transfer patient to a liver center [37].

In order to determine the severity of the poisoning, a serum acetaminophen concentration (4 h post ingestion or later) should be plotted against time on the modified Rumack-Matthew nomogram (Fig. 18.2) [80, 81]. Patients with acetaminophen levels below the treatment line can be discharged home after psychiatric and social evaluation. All other patients should be admitted to the intensive care unit [82].

For those patients that ingested a single dose of acetaminophen of more than 7.5 g less than 4 h prior to presentation, administration of activated charcoal should be considered. Review of several small studies demonstrated that activated charcoal was the best available option to reduce absorption [83–85]. Also, there is a decreased risk of developing liver injury if charcoal is given prior to other forms of treatment [85]. If patient has an unstable airway, charcoal should not be administered until the airway is controlled.

The antidote of choice for acetaminophen toxicity is N-acetylcysteine (NAC). The exact mechanism of action is unclear; however, it appears to restore glutathione levels

Table 18.5 Clinical stages of acetaminophen toxicity

Stage	Onset	Symptoms	Laboratory values
Stage I	0–24 h	Nausea, vomiting, malaise	Elevated acetaminophen levels
Stage II	24–72 h	RUQ pain, nausea, vomiting	Elevated AST, ALT, ALP, total bilirubin, lactate, and creatinine
Stage III	72–96 h	Encephalopathy, jaundice	Elevated AST, ALT, ALP, total bilirubin, PT, INR, PTT, lactate, and creatinine
			Hypoglycemia
Stage IV	5 days	Improvement in confusion, resolution of GI symptoms	Normalization of above values

[86, 87]. Indications for administration include a serum acetaminophen level above the treatment line, ingestion of more than 7.5 g, serum acetaminophen level >10 mcg/mL if time of ingestion is unknown, evidence of liver injury, and a history of acetaminophen ingestion regardless of time of ingestion [86–88].

Oral and IV administration of NAC have been studied and both appear effective [86]. The main factor determining the mode of treatment should be the mental status of the patient. If the patient is confused or has evidence of encephalopathy, oral administration should be avoided. If the oral protocol is used, a loading dose of 140 mg/kg should be given followed by 17 doses of 70 mg/kg given every 4 h. If IV NAC is used, a loading dose of 150 mg/kg is given over 1 h. A second dose of 50 mg/kg is then given over 4 h and finally a third dose of 100 mg/kg is given over 16 h.

An alternative to NAC is hemodialysis. This method effectively removes acetaminophen [89]. However, because of the effectiveness of NAC, it should be reserved for cases in which the antidote is not available.

Acetaminophen toxicity is best managed in a multidisciplinary setting with assistance from hepatology and surgery teams.

Amatoxin Intoxication

Ingestion of poisonous mushrooms can lead to lethal emergencies including ALF. *Amanita phalloides*, *Amanita bisporigera*, *Amanita verna*, and other mushroom species may cause ALF. These mushrooms do not express repulsive smells or tastes, and they can be found throughout midsummer in moist oak forests.

Alpha-amanitin is the amatoxin responsible for liver failure. After gastrointestinal absorption, enterohepatic circulation is responsible for transportation into the liver, where via active transport it concentrates in hepatocytes. The toxin will bind to RNA polymerase and inhibit protein synthesis, ultimately leading to apoptosis [90].

The clinical presentation of patients that ingest amatoxin includes an initial asymptomatic period of a few hours. This is followed by gastrointestinal symptoms that include abdominal pain, nausea, vomiting, and diarrhea that can be bloody. Liver enzymes will be elevated and will continue to increase. One to two days after ingestion, the second phase of the presentation begins with an apparent recovery with continuing elevation of AST and ALT. In severe poisonings, coagulopathy and possible DIC and renal failure may ensue. The last phase includes ALF and typically starts 3 days after ingestion. Hypoglycemia and multi-organ failure can be seen.

Workup of a patient with suspected amanita ingestion should proceed as indicated earlier in this chapter. Detection of amatoxin can be performed in urine samples using enzyme-linked immunoassay (ELISA); this test is not readily available in all institutions and awaiting results should not preclude supportive treatment [91].

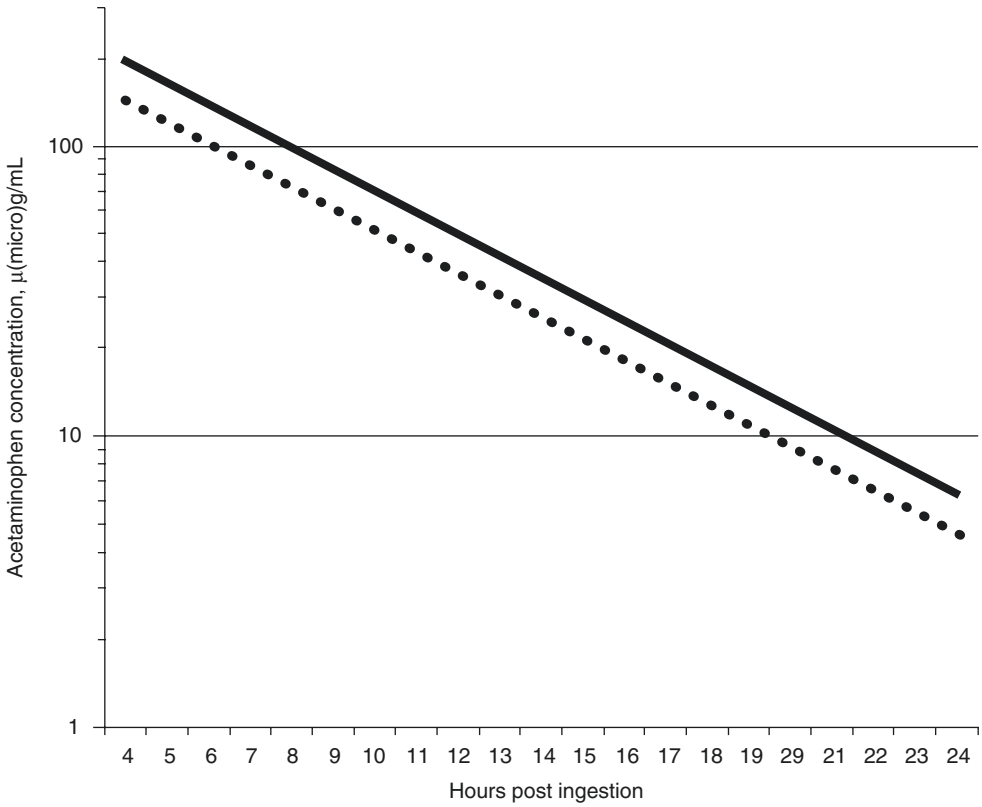

Fig. 18.2 Modified Rumack-Matthew nomogram. The *X axis* represents the number of hours after ingestion of acetaminophen and the *Y axis* the concentration of the medication in the blood. Levels are measured at least 4 h after ingestion. The *solid line* represents concentrations that are toxic. The *dotted line* represents a 25 % reduction in the toxic levels and it accounts for possible errors in acetaminophen assays. If the level is above the *dotted line*, NAC therapy should be started. If below, the patient can be safely discharged after medical evaluation (Data from Rumack and Matthew [80] and Rumack [81])

Supportive treatment should be started immediately after presentation. In addition, an effort to minimize toxin absorption should be attempted. Activated charcoal can bind amatoxin, and if given in repeated doses, it can reduce mortality significantly by increasing elimination via gastrointestinal tract [37].

Medications that can inhibit uptake of this toxin have also been described. These include penicillin G and silymarin. The former is given as a continuous infusion and has been show to decrease mortality [92, 93]. The latter is a more potent inhibitor and is available in IV and PO formats. Silymarin has been shown to minimize damage to hepatocytes [92, 94, 95].

NAC has also been used in the treatment of amatoxin intoxication. Mortality appears to improve with implementation of protocols very similar to those of acetaminophen toxicity [92, 96].

Wilson's Disease

Wilson's disease poses a different presentation from frank ALF. It normally occurs in the background of chronic liver disease that has been unrecognized. Treatment varies when presentation of this disease is acute, and this will be the focus of this section.

A genetically recessive disease, it is estimated that 2–3 % of ALF cases are related to Wilson's disease [97]. The majority of copper that is ingested is transported into the liver where it is incorporated into enzymes and copper-binding proteins (ceruloplasmin). Excess copper is combined with apometallothionein and excreted into bile. In Wilson's disease, the incorporation into ceruloplasmin is compromised and copper is accumulated in the liver. As the disease progresses, other organs are affected. Besides parkinsonian movements and tremors, Kayser-Fleischer rings, psychiatric alterations, and renal problems, Wilson's disease will present with liver disease: cirrhosis, chronic failure without cirrhosis, and acute liver failure.

Laboratory workup should include serum ceruloplasmin, which is usually low, as well as serum copper level (above 200 mcg/dL) [97]. In patients with evidence of ALF, low transaminases, low alkaline phosphatase, hypokalemia, glycosuria, hypophosphatemia, and renal tubular acidosis, the diagnosis of Wilson's disease should be considered.

In patients with acute failure, the aim should be to remove copper. Hemodialysis and peritoneal dialysis can successfully achieve this goal [98]. Albumin dialysis and the molecular absorbent recirculating system (MARS) device have also been used with promising results [99, 100]. Penicillamine, zinc, and other medications used for treatment of Wilson's disease do not play a role in ALF.

Viral Hepatitis

The development of ALF from viral hepatitis may occur after acute infection; Ostapowicz et al. estimated that the etiology of 12 % of those patients that were diagnosed with ALF was viral hepatitis [101]. Most of the clinical deteriorations that are seen in patients with this etiology of disease are related to chronic liver infection. ALF is more common with hepatitis B but it can also present in patients with hepatitis A, C, and E [34].

Presentation of viral hepatitis is described in four phases. Phase 1 is characterized by lack of symptoms but changes in laboratory studies that may be suggestive of viral hepatitis. Phase 2 marks the development of symptoms that include nausea, vomiting, abdominal pain, arthralgias, and possible fevers. The next phase includes clinical characteristics of ALF including right upper quadrant pain, becoming icteric, and possible coagulopathy. The last phase, 4, leads to the normalization of laboratory values and resolution of symptoms.

Diagnosis of viral hepatitis relies on serum laboratories. Acute hepatitis A is diagnosed by the presence of IgM antibody against the hepatitis A virus. Presence of IgG implies previous infection and resolution.

Hepatitis B has several important antigens and antibodies. Hepatitis B surface antigen (HBsAg) is usually found in patients with acute infection. A second antigen, associated with infectivity, is hepatitis B e antigen. The first antibody that can be detected in patients acutely infected and that indicates acute presentation of disease is IgM anti-HBcAg. Resolution of acute infection and recovery results in IgG antibodies against this antigen. Finally, anti-HBsAg appears in the serum several months after infection, indicating resolution. They will also be found in patients with hepatitis B vaccine.

IgG anti-hepatitis C virus has been used to diagnose exposure to this viral infection. It can usually be found in the serum several months after an acute infection and contrary to anti-HBsAg, it does not confer immunity to Hepatitis C. Use of ELISA and RIBA testing for diagnosis has fallen out of favor. HCV RNA PCR assays were developed in order to detect the presence of the virus. It has been successful in not only establishing the diagnosis but also the presence of an acute infection.

Treatment of acute hepatitis A is limited to supportive care as there are no medications that improve outcome. Hepatitis B treatment usually follows the same principles as most antiviral therapy is directed toward treatment of chronic disease. However, recent studies have suggested that acute hepatitis B may benefit from administration of lamivudine [102]. Finally, acute hepatitis C has been treated with IFN therapy with resolution of HCV RNA after several months of treatment [103].

Ischemic Hepatitis

Low perfusion pressure to the liver may result in clinical manifestations of ALF known as ischemic or hypoxic hepatitis. It is an uncommon cause of liver failure, with a prevalence of 1 per 1,000 hospital admissions [104]. This can be a direct

consequence of global hypoperfusion, hemodynamic instability, direct vascular occlusion during surgical procedures, hepatic artery disease (occlusion, dissection, thrombosis) in patients with portal vein thrombosis, or hepatic sickle cell crisis [105]. Hepatocytes in zone 3 become ischemic and eventually necrotic leading to liver insufficiency.

Prognosis of ischemic hepatitis is poor. Raurich et al. described an in-hospital mortality of 61.5 % in all patients that were diagnosed with this disease process. In those patients with concomitant septic shock and those that experienced cardiac arrest, mortality rates were higher, at 83.3 % and 77.7 %, respectively. Risk factors for mortality included an elevated INR, need for renal replacement therapy, and diagnosis of septic shock. Non-survivors were more likely to be on vasopressors and to require mechanical ventilation [106].

Patients with hepatitis secondary to shock present with several symptoms related to their hemodynamic instability including altered mental status, respiratory distress, severe hypotension, and renal failure. Patients with a history of cardiac compromise may present with nausea, vomiting, right upper quadrant pain, and malaise. Up to 14 % of patients with septic shock will also have ischemic hepatitis, presenting with fevers and severe hypotension [106].

Laboratory examination reveals elevated aminotransferase levels, usually above 1,000 IU/L. The ratio of serum alanine aminotransferase to LDH less than 1.5 suggests ischemic hepatitis [107]. If hypoperfusion is chronic in nature, synthetic function may be preserved and coagulation studies may be normal; however, in acute cases, there is severe derangements that continue to progress with time. If ischemic hepatitis is suspected, a right upper quadrant ultrasound with Doppler should be immediately performed as it may reveal the etiology of the insufficiency.

There is no specific treatment for ischemic hepatitis. Management is centered around restoring cardiac output and reestablishing hepatic perfusion. Appropriate resuscitation is necessary. Excessive fluid administration may lead to vascular congestion which can in turn compromise perfusion of hepatocytes and aggravate the presentation. Judicious use of diuretics should be exercised as diuresis may exacerbate hypoperfusion and therefore liver failure. Intensivists should rule out ischemic hepatitis in any patient that presents with septic shock and has elevated aminotransferases [106]. Prompt recognition of hypoperfusion state may lead to early intervention and possible better outcomes.

Chronic Liver Disease

Definition, Epidemiology, and Causes

Continuous hepatic injury that persists for more than 6 months is considered chronic liver disease (CLD). The liver parenchyma suffers continuous inflammation and potential destruction. The hepatic insult does not only result in damage but also in attempts of repair. Ultimately this leads to a broad spectrum of clinical manifestations including fibrosis, cirrhosis, and hepatocellular carcinoma. These changes are accompanied by alterations in serum liver function tests and can include physical exam finding suggestive of physiologic alterations.

Table 18.6 Causes of chronic liver disease

Infectious	Chronic hepatitis B
	Chronic hepatitis C
	Brucellosis
	Syphilis
	Echinococcosis
	Schistosomiasis
Drugs and toxins	Alcohol
	Amiodarone
	Isoniazid
	Methotrexate
Metabolic (acquired and genetic)	Nonalcoholic fatty liver disease (NAFLD)
	Hemochromatosis
	Wilson's disease
	α1-Antitrypsin deficiency
Vascular	Right heart failure
	Veno-occlusive disease
	Hereditary hemorrhagic telangiectasia
Other	Primary biliary cirrhosis
	Primary sclerosing cholangitis
	Autoimmune hepatitis

In the United States, the most common causes of cirrhosis leading to liver transplantation are alcoholic liver disease, chronic viral hepatitis, and nonalcoholic liver disease (Table 18.6) [108]. This last etiology has increased significantly in incidence. Most patients are generally asymptomatic until decompensation occurs, making the calculation of prevalence difficult. Approximately 49,500 deaths in 2010 where associated with CLD [109].

Clinical Manifestations

Patients with CLD may present with compensated or uncompensated hepatic failure. The former may be asymptomatic prior to evaluation, but patients usually report nonspecific symptoms such as weight change, fatigue, and lack of appetite. Those patients with an acute decompensation may show signs of active bleeding, confusion, and skin changes. Because of the broad spectrum of the disease, presentation will vary between different patients. Due to similar underlying pathophysiology, symptoms and findings may be similar to those described previously during the acute liver failure presentation.

Nervous System

Patients with CLD may present with varying degrees of hepatic encephalopathy. Classification and underlying pathophysiology are similar to those described previously in the ALF section. An acute exacerbation with an underlying chronic liver dysfunction can cause rapid progression from confusion to coma.

Respiratory System

Shortness of breath, dyspnea, and other nonspecific respiratory symptoms may also be reported. As with acute dysfunction, the etiology may be of infectious, metabolic, or of cardiac etiology. Hepatopulmonary syndrome can also play a role in underlying hypoxemia [15]. The mechanisms that lead to the respiratory derangements in CLD are similar to those described in acute liver compromise.

Cardiovascular and Hematologic System

Figure 18.1 explains the molecular mechanism behind the underlying decreased effective perfusion pressure seen in patients with liver failure. As a result, patients will have a lower than baseline blood pressure, with some of them transitioning from hypertensive to normotensive.

The cardiac output in patients with liver disease is usually high; however it is important to understand that myocardial cells are actually depressed from exposure to the changes in cytokines and other molecules. There is a slightly elevated heart rate that compensates for the depression and overall results in increase cardiac output, in a normal-sized man, often in the range of 10–12 L/min [15].

Patients with CLD may present with anemia, leukopenia, thrombocytopenia, and coagulopathy [110]. The pathophysiology behind anemia is multifactorial, and it may include episodes of gastrointestinal bleeding associated with portal hypertension and coagulopathy. There may also be nutritional deficiencies such as folate deficiency that can lead to compromised production of red cells and vitamin K deficiency that can lead to decreased production of coagulation factors [17]. Aplastic anemia, hypersplenism, and hemolysis may contribute to the anemia experienced by patients with chronic failure [111].

Thrombocytopenia is associated with portal hypertension: an enlarged spleen can sequester the majority of the circulating platelet mass and lead to a decrease platelet count. It has also been described that patients with liver disease have decreased levels of thrombopoietin that will also lead to thrombocytopenia [112].

Gastrointestinal and Endocrine Systems

Patients experiencing CLD can present with abdominal distention and pain, anorexia, nausea, and vomiting. Physical exam may also show ascites, hypogonadism, hypersplenism, and evidence of gastrointestinal (GI) bleeding such as hematemesis, hematochezia, and melena. GI bleeding can be the result of mucosal injury and thrombocytopenia or a more severe and life-threatening event such as variceal hemorrhage. An umbilical hernia may be seen when ascites becomes prominent.

For those patients with CLD, there are significant changes in the hemodynamics of the portal vein. The hepatic microcirculation, sinusoids, undergoes constriction secondary to architectural changes that compromise the lumen of these systems. Furthermore, there is active contraction of myofibroblasts and active smooth muscle secondary to cytokine changes (increased levels of intrahepatic ET-1) that cause even more restriction in the radius of these sinusoids [113, 114]. These changes lead to an increase in portal pressure.

A second factor that impacts the pressure of the portal vein is the increased in blood flow in the portal vein. As shown in Fig. 18.1, there is a splanchnic arteriolar vasodilation that leads to increase venous outflow and, therefore, increased flow that results in further increases of portal pressure and eventually portal hypertension (PHT) [15].

The elevated blood pressure and flow are partially relieved by decompressing the inflow into the portal vein into systemic collaterals. The esophageal submucosal veins are a preferred method of decompression and may result in esophageal varices. As flow increases so does the vessel radius [115]. This ultimately leads to an increase in wall tension that may end up in rupture and variceal bleeding [114, 116].

Ascites is also closely related to PHT. In fact, patients without evidence of PHT do not develop ascites even in the presence of cirrhosis. The threshold for formation of ascites appears to be 12 mmHg at the level of the portal vein [117]. As a response to this increase in pressure, there is splanchnic vasodilation leading to a decrease in effective arterial blood volume that is mediated by several molecules including nitric oxide (NO). There is subsequently an activation of the renin-angiotensin-aldosterone system that increases renal sodium retention and plasma expansion that ultimately leads to accumulation of fluid in the peritoneal cavity [118]. The low levels of circulating protein secondary to liver compromise may also favor the formation of ascites.

On physical exam, we can find evidence of PHT by placing a stethoscope over the epigastrium. If there are collateral connections between the portal system and the umbilical vein, a murmur can be auscultated. This finding is known as Cruveilhier-Baumgarten murmur.

Dizziness, diaphoresis, and overall malaise may be reflective of underlying hypoglycemia. Patients with CLD undergoing an acute exacerbation may see decreased levels of circulating glucose with corresponding changes in neurologic exam.

Male and female patients with CLD can report abnormalities related to infertility, impotence, and in the case of women chronic anovulation. Physical exam may show evidence of

testicular atrophy in men, while ultrasound and other imaging may show atrophic ovaries and uterus. There are several possible mechanisms that explain these findings. The increased levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) observed in some patients suggest the primary dysfunction of the testicles or ovaries. An alternative mechanism suggests suppression of the hypothalamic-pituitary function. The dysfunction may be secondary to decreased clearance of estrogen, testosterone, prolactin, and other substances [119, 120].

Male patients with CLD may complain of loss of male pattern pubic hair, chest and axillary hair loss, and gynecomastia. This finding is thought to be related to an overall increase in estradiol: the adrenal glands produce and increase quantities of androstenedione that undergoes aromatization into estrone and eventually to estradiol [120].

Renal System

Similar to patients with ALF, patients with CLD can present with renal pathology. These may manifest as decreased urine output, arrhythmias, generalized body edema, and overall malaise. Most of the changes are associated with the underlying liver dysfunction.

In hospitalized patients with CLD, it is estimated that approximately 10 % of them will develop hepatorenal syndrome (HRS). The pathophysiology of HRS follows the development of PHT. As explained in Fig. 18.1, there is dilation of the splanchnic circulation, leading to a decrease in perfusion pressure. The response is cardiac compensation as well as activation of the renin-angiotensin-aldosterone system. There is also vasoconstriction mediated by the sympathetic nervous system. These changes ultimately lead to low renal perfusion and a significant decrease of the glomerular filtration rate [16].

Electrolyte abnormalities can accompany the changes that are seen on the renal system. Hyperkalemia, hyperphosphatemia, and hyponatremia can be detected in serum electrolytes. Symptoms may be variable and depend not only on severity of derangement but acuity. Dizziness, weakness, and palpitations may be reflections of these abnormalities.

Infectious Disease

CLD leads to acquired immune deficiency and makes these patients prone to developing infections. The mechanism by which the immune response is compromised includes the deficiency of serum complement [121] as well as the compromised activity and function of phagocytes such as macrophages, PMNs, and Kupffer cells [122, 123]. Certainly, the presence of fevers should make the intensivist suspicious for an infectious process and further investigation is warranted in order to determine additional symptoms that may guide further treatment. However, patients who present with decompensated liver failure may have an infection causing the decompensation. Thus, suspicion for the presence of infection should be high, and the threshold for obtaining cultures is low in any patient with liver failure who is acutely ill.

Abdominal pain that worsens and fevers should raise the suspicion for spontaneous bacterial peritonitis (SBP) in those patients with evidence of ascites. Up to 30 % of these patients may develop SBP [124]. Patients with cirrhosis have an increased intestinal permeability as well as altered intestinal motility. This may lead to the bacterial overgrowth and infection of ascites [125]. The most common organism seen is *Escherichia coli*; however, other organisms have also been described [126]. Typically SBP is monomicrobial and a polymicrobial infection should prompt consideration of a perforated viscous.

Other Systems

Similar to ALF, skin and urine color can change in patients with CLD. The increase in bilirubin secondary to compromised liver function leads to the accumulation in the skin leading to jaundice as well as dark appearance of urine. These changes are usually undetectable if the serum bilirubin is less than 2 mg/dL.

Another change that can be appreciated in the skin of patients with CLD includes palmar erythema. It is thought to be the consequence of altered sex hormone metabolism which may lead to capillary vasodilation [127].

Careful examination of the skin can also reveal vascular lesions characterized by the presence of a central arteriole with surrounding smaller vessels. These are called spider angiomata and their appearance is related to an increase in estradiol levels. The number as well as size of these lesions is related to the severity of liver disease although they are not specific for it [128].

As an additional route to decompress the portal vein during PHT, the umbilical vein may open leading to shunting into abdominal wall veins. These vessels engorge significantly making them very easy to identify during physical exam. This finding is known as caput medusa.

Workup and Initial Management

Initial workup and management of patients with CLD should begin with a thorough history. Onset of symptoms and identification of disease progression helps determine the pathophysiologic manifestations of the disease. Previous medical diagnosis including viral hepatitis should be assessed. A thorough review of all medications that the patient takes can help identify potential additional mechanisms of liver injury. Hospitalizations and transfusions should be reviewed.

Social history including exposure to high-risk behaviors such as intravenous drug use and alcohol abuse should be performed. Family history of liver disease and personal

history of malignancy (including oncologic treatment and surveillance studies) also play a key role in the development of disease and should be explored.

A complete physical exam should be performed and an attempt to determine if any of the clinical manifestation discussed previously are present. The exam should include neurologic, rectal, and skin exam. Assessment of vital signs in order to identify possible hypotension, hypoxemia, as well as end-organ perfusion should be performed.

There is no serologic test that can diagnose CLD accurately. Laboratory abnormalities that are identified could be related to ALF or another etiology with some degree of liver dysfunction. Besides serologic tests, evaluation of the degree of liver fibrosis and additional characteristics of CLD can be investigated with radiologic studies.

The initial serologic studies that are performed as well as initial management are similar to those described in Table 18.4 in the ALF section. In addition, studies from ascitic fluid should also be performed when it is desired to identify etiology of fluid and possibility of infection. After paracentesis with removal of 50 mL of ascites in a sterile fashion, the intensivist should send the fluid for cell count, cytology, albumin, total protein, triglycerides, amylase, adenosine deaminase, as well as culture [129]. This should be accompanied by a serum albumin in order to calculate the serum-ascites albumin gradient (SAAG). This is done by subtracting the albumin in the ascitic fluid from the serum value. Based on such studies, the etiology of ascites can be determined (Table 18.7).

Imaging studies that are routinely used include ultrasonography (US), CT scan, and magnetic resonance imaging (MRI). US can help identify morphologic changes such as nodularity. With Doppler US, patterns of flow as well as possible occlusions can be identified. CT and MRI are able to identify nodularity and changes in volume of liver mass (hypertrophy or atrophy) as well as assess the portal vasculature [130]. Evaluation of collateral circulation, varices, and tumors can also be performed. Since US does not use contrast, this can be very helpful in those patients with renal compromise [131, 132].

If after a thorough workup, the diagnosis of CLD cannot safely be established, liver biopsy should be considered. Identifying changes consistent with CLD may be very beneficial as it may prevent delays in therapy and potential worsening of the patient [133–135]. Surgery and interventional radiology teams should be involved in order to determine the safest and least invasive method that can render a diagnosis.

Table 18.7 Ascitic fluid studies and etiology of disease

Chylous ascites	Triglycerides
Peritoneal tuberculosis	Adenosine deaminase
Pancreatic ascites	Amylase and protein
Spontaneous bacterial peritonitis	Cell count
	Culture
Malignant ascites	Cytology
SAAG >1.1 g/dL	Portal hypertension
SAAG <1.1 g/dL	Nephrotic syndrome
	Tuberculosis
	Pancreatic ascites
	Malignancy

Suspicious findings for CLD should prompt consultation with hepatology/gastroenterology and transplant surgery in order to determine if the patient will benefit from additional therapies and workup including possible transplantation.

Evidence of encephalopathy, compromised ventilation, hypotension, hypoperfusion, active bleeding, sepsis, and SBP should prompt admission to the ICU. Consideration of additional hemodynamic monitors such as an arterial line and central access may be considered in every patient. A Foley catheter should be placed in all patients with hemodynamic instability or with poor renal function but avoided in those with anuria to prevent a urinary tract infection.

It is also helpful to classify the severity of liver disease. The Child-Turcotte Pugh (CTP) classification divides patients into three groups based on serum labs and clinical presentation. It can help in determining possible surgical treatments or additional therapies [136, 137]. This specific scoring system is presented in Table 18.8.

Another classification system that is used for the allocation of organs in the Unites States is the model for end-stage liver disease (MELD). It consists of a formula that will assign a score to a patient and that accurately predicts mortality within 3 months. The formula is based on three laboratory values (bilirubin, INR, and creatinine) and it is modified by etiology. The formula is shown below [138]:

$$\mathrm{MELD} = 3.78\times\ln\left(\text{serum bilirubin}\left(\frac{\text{mg}}{\text{dL}}\right)\right)+11.2\times\ln\left(\text{INR}\right)+9.57$$
$$\times\ln\left(\text{serum creatinine}\left(\frac{\text{mg}}{\text{dL}}\right)\right)+6.43\times\text{etiology}$$

Table 18.8 Child-Turcotte-Pugh (CTP) classification

	Points		
Measurement	1	2	3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Bilirubin (mg/dL)	1–2	2–3	>3
Ascites	Absent	Slight	Moderate
Encephalopathy grade	None	1 and 2	3 and 4
PT	1–4	4–6	>6
or			
INR	<1.7	1.7–2.3	>2.3

If the disease process is alcohol, 1 is assigned to etiology. If the liver failure is secondary to a cholestatic process, 0 is assigned instead. Several factors can modify the calculated MELD score for allocation purposes, and these include dialysis and the presence of hepatocellular carcinoma.

The CTP and MELD system have been compared in several studies in order to determine which provides a better answer to prognosis for patients. Although some studies show superiorities of MELD, others show no difference and good predictions with both systems [139–142]. A systematic review, suggested that the MELD was better for predicting 3-month mortality but otherwise the systems were similar [143]. Because of its use with United Network for Organ Sharing (UNOS) lists for allocation of organs, MELD has become more popular.

Management

Encephalopathy

Hepatic encephalopathy (HE) is a diagnosis of exclusion, and therefore, an effort to identify other etiologies of altered mental status should be performed. It is also necessary to determine the precipitating event leading to the neurologic derangement which includes bleeding, renal failure, electrolyte abnormalities, changes in diet, and changes in medication [144].

Treatment principles are similar to those described in the ALF section. They should be based on supportive care, attempts to correct precipitating factors, minimizing GI nitrogen intake, and establishment of therapy.

Admission to an ICU is important as patients with HE need constant neurologic assessments for progression or resolution. For grade III and grade IV HE, establishment of definite airway should be the first step in management. Laboratory studies are key in order to identify possible precipitating events.

A decrease in nitrogen production as well as nitrogen delivery should be attempted with medication. The most common therapy used is lactulose, which reduces the absorption of ammonia. Twenty-five milliliter should be given twice a day and should be titrated to achieve two soft bowel movements [145].

Rifaximin has also been used as an add-on therapy to lactulose. It is an antibiotic with activity against Gram-positive and Gram-negative aerobes and anaerobes. The usual dose is 400 mg three times a day. Trials have shown benefit in the treatment of HE when rifaximin is used in addition to lactulose [146]. Another antibiotic that has been use is neomycin. This alternative treatment has been used for the treatment of overt hepatic encephalopathy [147]. However, because it has been associated with complications such as ototoxicity and nephrotoxicity, neomycin is used less commonly today [145].

An assessment of nitrogen intake by assessing a patient's diet is also very important. If a patient's HE is unresponsive to the therapies described above, oral branched-chain amino acids (BCAA) should be considered in an attempt to reduce the hepatically metabolized nitrogen load. A recent meta-analysis showed that BCAA-enriched formulations may be beneficial in some patients with HE and CLD [71]. The daily protein intake should be 1.2–1.5 g/kg/day as severe restriction may be detrimental in the catabolic state of CLD [145].

Ascites

The first step in management of a patient with CLD and ascites should be sodium restriction to no more than 2,000 mg per day [129]. This should also be accompanied by oral spironolactone and possibly furosemide in order to perform natriuresis while maintaining normokalemia. Spironolactone inhibits sodium reabsorption in the distal tubule and collecting ducts but it can lead to gynecomastia and hyperkalemia. Furosemide is a loop diuretic and inhibits the luminal Na-K-2Cl symporter causing natriuresis and also hypokalemia when used alone. Combination therapy has been used more effectively in achieving sustained results. If the serum sodium is less than 125 mmol/L, fluid restriction to no more than 1.2 L per day should also be done [148].

For those patients that are not responsive to diuretic therapy, serial paracenteses can be performed in order to relieve symptoms [149]. In carefully selected patients, transjugular intrahepatic portosystemic shunt (TIPS) should be considered. Trials have demonstrated that there is better control of ascites and overall survival with this procedure; however, there is worsening hepatic encephalopathy [150]. Referral to a transplant center should be done for patients with refractory ascites.

Tense ascites with respiratory compromise and abdominal discomfort can also be the initial presentation of patients

with CLD. Prior to sodium restriction, paracentesis should be performed. For large volume (>5 L) removal, albumin replacement should be done [151]. Replacement of 6–8 g of albumin per L of fluid removed has been shown to improve survival [129].

Replacement after paracentesis has remained a controversial topic. In one study performed by Gines et al., patients with tense ascites were randomized to receive albumin or no replacement. Those that did not receive albumin had more changes in serum electrolytes, plasma renin, and creatinine but had no survival advantage [152]. There has been no study up to date demonstrating decreased survival in patients without replacement when compared to albumin [153].

In a meta-analysis by Bernardi et al., 1,225 patients from 17 trials were analyzed. Albumin was shown to be superior to other plasma expanders, with an infusion between 5 and 10 g of albumin per liter removed [154].

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, and nonsteroidal anti-inflammatory agents should be avoided in patients with CLD and ascites: prostaglandin inhibition can severely affect renal hemodynamics as well as natriuresis.

It is important to evaluate patients with ascites for ventral and umbilical hernias. For those patients with ascites, hernia repair should only be attempted after medical treatment of ascites. For those with refractory ascites, repair should be deferred until after liver transplantation. If the patient has an incarcerated or strangulated hernia, emergency repair is warranted, but special attention to the ascites postoperatively must be made.

Spontaneous Bacterial Peritonitis

The diagnosis of spontaneous bacterial peritonitis (SBP) is established with studies sent from ascitic fluid revealing one of the following three findings:

1. Leukocyte count of more than 500 per mm^3
2. Polymorphonuclear count of more than 250 per mm^3
3. Positive bacterial culture

The causative organism is usually a Gram-negative enteric bacteria; if more than one organism is identified, secondary peritonitis should be considered. *Escherichia coli* and *Klebsiella* are responsible for more than 50 % of the cases [155]. Therapy is tailored based on the most likely causative agent.

If the patient has not been on empiric antibiotics prior to presentation, an intravenous third-generation cephalosporin should be started, preferably cefotaxime 2 g every 8 h. If the patient has been exposed prior to this medication, coverage should be based on hospital antibiogram [129]. Therapy should be started if there is a high suspicion for infection while cultures are pending.

The recurrence rate of SBP can be as high as 70 % and therefore prophylaxis is advocated. Long-term antibiotic therapy, norfloxacin 400 mg daily, is recommended [156]. Trimethoprim/sulfamethoxazole can be used as a second-line agent for those patients with sensitivities [129].

Variceal Hemorrhage

The presence of esophageal varices in patients with CLD warrants prophylactic therapy. The most effective medication has been propranolol that inhibits stimulation of the beta-2 venodilator receptors seen in varices. It should be started at low doses, 5 mg orally twice a day, and titrated to reduction of pulse rate by 25 %. If patients cannot take propranolol, isosorbide mononitrate can be used. If the patient is unable to tolerate medical therapy, esophagogastroduodenoscopy (EGD) and variceal banding should be performed [157].

Three principles govern the management of an acute variceal bleed: stabilization and resuscitation, identification and treatment of bleeding, and prevention of recurrence. If a patient presents with evidence of GI bleeding, immediate type and cross should be performed, and if needed, transfusion of untyped and uncrossed blood should begin. Waiting for laboratory values to show anemia may worsen the overall clinical condition of the patient.

Upper GI bleeding in a patient with presumed CLD prompts urgent endoscopy to identify possible bleeding esophageal or gastric varices. If during endoscopy, no varices are seen, repeat evaluation should be done in 3 years. If varices are identified but not bleeding, follow-up endoscopy should be done after 1 year. If active bleeding is encountered and it appears to involve esophageal varices, an attempt at controlling the bleeding varices should be done. Banding followed by sclerotherapy are the two most common methods of achieving control. If after appropriate attempts bleeding does not stop, a Sengstaken-Blakemore tube should be inserted. TIPS and surgical shunts should be considered if all previous methods fail. TIPS has shown improved outcomes [129]; however, it is associated with HE [157]. Surgical shunts carry a high morbidity and should be considered a last resort.

CLD patients with GI bleeding are at risk of developing bacterial infections. Some advocate the use of ceftriaxone for 7 days while patients are GI bleeding [158, 159]. If the patient stabilizes and tolerates oral intake, changing to norfloxacin is reasonable.

Hepatorenal Syndrome

The diagnostic criteria for hepatorenal syndrome (HRS) are shown in Table 18.9.

HRS is a diagnosis of exclusion and it is important to rule out other etiologies including prerenal azotemia, intrinsic renal disease, and post renal failure. In order to diagnose HRS, all major criteria in Table 18.9 must be met. Minor

criteria are not required; however, they provide supportive evidence that the pathophysiology is consistent with HRS. Identification of precipitating event is also instrumental in the management of HRS as additional therapy can be instituted.

When performing large volume (>5 L) paracentesis, it is recommended to replace volume with albumin (see ascites section above) as this procedure may lead to HRS. Evaluation for possible SBP as well as workup for GI bleeding should be considered as they are well-established risk factors for the development of this syndrome.

There are two manifestations of HRS: type I and type II. The former shows a rapid decline in renal function with either an initial creatinine of greater than 2.5 mg/dL or a 50 % reduction in the creatinine clearance. Type II usually leads to moderate renal failure that progresses slowly and is manifested as diuretic-resistant ascites [160].

Liver transplantation is the preferred treatment for patients with HRS. Any patient with evidence of this syndrome should be referred to a liver transplantation center in order to be listed for transplantation [161]. Bridging with pharmacotherapy is necessary in most patients as there is rapid decompensation, especially in those with type I HRS.

The basic principle behind the management of HRS is reversal of renal vasoconstriction and splanchnic vasodilation. Dopamine, fenoldopam, and prostaglandins have been used in an attempt to cause direct renal vasodilation [15]. Results of several trials have not favored any of these agents as none have improved outcome [160–162].

Splanchnic vasoconstriction, in an attempt to reduce portal blood flow and decrease pressure, has been attempted with vasopressin, ornipressin, terlipressin, norepinephrine, and midodrine [15]. Ornipressin, with some promising results, resulted in an increase rate of ischemic events [163]. Terlipressin in combination with albumin has shown the most promising results, with improvements in renal function although its use has not been approved in the United States [164]. Norepinephrine and vasopressin have been used with improvement of renal function and successful bridging to transplantation [60].

Hemodialysis may be required in the treatment of these patients, especially those with type 1 disease. Those patients that are hospitalized in an ICU should receive continuous dialysis rather than intermittent as it minimizes changes of abrupt hemodynamic changes and further compromise of these frail patients [73].

Table 18.9 Criteria for diagnosis of hepatorenal syndrome

Major criteria
Chronic or acute liver disease with advanced hepatic failure and portal hypertension
Low glomerular filtration rate
Serum creatinine >1.5 mg/dL
or
24 h creatinine clearance <40 mL/min
Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs
Absence of GI fluid losses
Absence of renal fluid losses in response to diuretic therapy
No sustained improvement in renal function after diuretic withdrawal and expansion of plasma volume with 1.5 L of plasma expander
Proteinuria <500 mg/day
No obstructive uropathy, parenchymal renal disease, microhematuria
Minor criteria
Urine volume <500 mL/day
Urine sodium <10 mEq/L
Urine osmolality greater than plasma osmolality
Urine RBCs <50/high-power field
Serum sodium concentration <130 mEq/L

Liver Transplantation

Patients with ALF and CLD may benefit from liver transplantation. This therapeutic option should be considered when medical therapy has failed and when there is progression of disease. Referral to transplant center should occur once the patient has experienced ascites, variceal hemorrhage, HRS, and HE. Consultation with hepatology and transplant surgery teams ensures early consideration for transplantation. Table 18.10 presents poor prognostic factors from the King's College Criteria that may suggest that the need for transplantation is increased.

Prior to transplantation, a thorough evaluation is performed on patients regardless of etiology. This includes assessment of cardiac function, possible occult malignancy, identification of infection, contraindications to chronic steroid therapy, and appropriate social support.

The rapidly progressive nature of ALF designates that these patients are currently listed as Status 1 by the United Network for Organ Sharing (UNOS) [165]. Approximately

Table 18.10 King's College criteria that suggests poor prognosis

Non-acetaminophen
INR greater than 6.5 or
Three of the following five criteria:
Patient age of less than 11 or greater than 40
Serum bilirubin of greater than 300 μmol per liter
Time from onset of jaundice to the development of coma of greater than 7 days
INR greater than 3.5
Drug toxicity, regardless of etiology of ALF
Acetaminophen
Arterial pH <7.3
INR greater than 6.5
Creatinine greater than 300 μmol per liter
Encephalopathy (grade III or IV)

40 % of patients with ALF will undergo liver transplantation, 25 % of them will improve with supportive care, and 35 % will not survive their presentation; of those that have a liver transplant performed, the 3-year survival is approximately 75 % [165]. Patients with failure secondary to viral hepatitis usually have better outcomes than those with drug reactions or metabolic causes. Also, patients with ALF have worst outcomes when compared with patients with CLD.

The 1-year survival for patients with CLD that undergo liver transplantation is 90 % [166]. Timing is not standard and is usually dependent on severity of MELD. Living donors have been used secondary to decrease in organ availability and it has been successful. This therapy has not been studied in patients with ALF.

Other Therapies

Liver replacement therapies (LRT), also known as liver dialysis, have been studied and used as a bridging therapy to transplant [167–170]. Several methods have been developed and they can be grouped into artificial and bioartificial devices. Regardless of the mode of action, they attempt to clear toxins that are free and protein bound, as well as to regenerate or replace proteins that are affected by the liver failure process.

Among the artificial methods, the most studied is the molecular adsorbent recirculation system (MARS). It effectively clears several toxic compounds and causes a dramatic improvement in serum laboratories and in some symptoms such as pruritus [171]. Unfortunately, this has not translated into clinical benefits [172].

Biologic methods include devices with porcine hepatocytes and with human hepatoblastoma cells [167, 171–173]. Their theoretical advantage is the production of proteins and compounds produced by a normal liver as well as detoxification functions. As opposed to artificial systems, technology is not readily available. The results from different trials have been promising, showing improvement in survival to transplantation and normalization of serum laboratories [167].

An alternative to liver transplantation is hepatocyte transplantation. This consists of injecting human hepatocytes into the portal vein with an attempt to restore hepatic function [174]. It has been principally used to correct errors of metabolism, and trials have shown improvement in encephalopathy and ammonia and serum laboratories in patients with ALF that undergo this therapy [175]. More trials are needed in order to establish the role of this treatment option.

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