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Intensive Care Management of Patients Prior to Liver Transplantation

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1. Introduction

Liver failure is a devastating illness with extremely high morbidity and mortality. With the advent of life-saving orthotopic liver transplantation, the mortality and morbidity due to liver failure has been significantly reduced. Many patients awaiting transplant are critically ill. The intensive care management of patients before liver transplantation is aimed at optimizing hepatic and extrahepatic organ function before the transplant operation, with a goal to favorably influence the perioperative and postoperative graft and patient survival.

Critical illness due to liver disease may present in the context of acute liver failure (ALF) or acute on chronic liver failure (ACLF). The differing pathophysiologic processes underlying these two categories of liver failure necessitate specific approaches to their intensive care management. In their extreme presentations, both types of liver failure result in multi-organ system failure; therefore, the intensive care management of these conditions requires a systematic multi-organ system approach to address hepatic and extrahepatic organ dysfunction (*Ford et al., 2010*). This chapter will provide a multi-organ system-based description of critical care management of ALF and ACLF before liver transplantation.

2. Acute liver failure

2.1 Definition and etiology

Acute liver failure (ALF) represents a clinical syndrome of varying etiologies that ultimately manifests as hepatic encephalopathy and coagulopathy (International Normalized Ratio [INR] greater than 1.5) in the setting of acute liver dysfunction. By definition, coagulopathy and hepatic encephalopathy occur within 6 months following the initial symptoms of hepatic dysfunction in a patient without chronic liver disease. The timing of development of hepatic encephalopathy after an initial presentation of jaundice helps further subdivide ALF into categories of hyper-acute (hepatic encephalopathy developing within 7 days of onset of jaundice), acute (8-28 days), and sub-acute (29-84 days).

The etiologies of ALF are numerous, and reversible causes must be actively sought. The most common etiology of ALF in the United States and United Kingdom is drug-induced, with acetaminophen toxicity the leading responsible agent. Other common classes of

medications known to provoke ALF in susceptible patients include antimicrobials, antidepressants, antiepileptics, anti-hypertensives, HIV therapy, chemotherapeutic agents, lipid-lowering agents, and glucose-lowering agents. Analgesics and recreational drugs are also known causes of drug-induced ALF.

Additional etiologies of ALF include viral infections, including Hepatitis A, B, C, D, and E, as well as herpes simplex virus, varicella zoster virus, cytomegalovirus, and Epstein-Barr virus. Toxins responsible for ALF include *amanita phalloides* (mushrooms), herbal preparations, organic solvents, and bacterial toxins, such as *bacillus cereus*. Pregnancy-related conditions include the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) and the acute fatty liver of pregnancy syndrome. Lymphoma, metastatic disease, hepatic ischemia, wilson disease, heat stroke, Budd-Chiari syndrome, autoimmune hepatitis, and extensive hepatic resection are other causes of ALF. Approximately 15-20% of patients with ALF have an undetermined cause.

2.2 Diagnosis and initial management considerations in ALF

Potential causes of ALF must be actively sought in the initial workup, as certain etiologies have specific life-saving treatments. Acetaminophen toxicity is treated with N-acetylcysteine, autoimmune hepatitis with corticosteroids, herpes simplex and varicella zoster viruses with intravenous acyclovir, acute fatty liver of pregnancy and HELLP syndrome by delivery of the fetus. Recent data suggests that the use of N-acetylcysteine (NAC) improves the outcome of patients with ALF, independent of the etiology (Lee *et al.*, 2009). Many transplant centers advocate the use of NAC for all patients with ALF. NAC can be administered intravenously at a dose of 150 mg/kg over 15 minutes followed by 50 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours. Adverse effects of NAC include bronchospasm and anaphylaxis and are managed by coadministration of antihistamines and corticosteroids as well as reduction of infusion rate. Oral preparations of NAC are also available. Discontinuation of NAC is appropriate following resolution of ALF or at the time of transplantation.

In addition to ruling out reversible causes of ALF, exclusion of chronic liver disease is crucial for appropriate management. Physical examination of patients presenting with liver failure should therefore focus on stigmata of chronic liver disease, including abdominal ascites, spider angiomas, or *caput medusae*. Hepatic imaging with ultrasound, CT or MRI is useful to evaluate for the presence of portal hypertension and chronic liver disease, as well as to evaluate hepatic size and vasculature, ascites, and hepatic masses. Recommended laboratory testing for potential etiologies of ALF include autoimmune markers, viral serologies, toxicology screen, and serum and urine testing for copper overload.

2.3 Patient stabilization

All patients with ALF should be monitored and treated in an intensive care unit. Many patients have progressed to multi-organ failure upon arrival, and immediate supportive measures should be undertaken. These may include interventions such as endotracheal intubation and mechanical ventilation, intravenous fluid resuscitation, placement of arterial and central venous lines, and vasoactive agent support.

2.4 Organ-specific management

2.4.1 Hepatic encephalopathy

Hepatic encephalopathy is defined by the presence of neuropsychiatric symptoms in the absence of other causes of altered mental status. Mental status changes range from subtle cognitive impairments to frank coma. The impaired hepatic clearance of ammonia and other toxins are poorly tolerated in patients with ALF, and result in astrocyte swelling and cytotoxic cerebral edema. Hepatic encephalopathy is divided into four grades based on the West Haven Criteria (Atterbury *et al.*, 1978); grade I denotes mild cognitive changes and attention deficits, grade II lethargy and apathy, grade III confusion and semi-stupor, and grade IV a comatose state.

Hepatic encephalopathy in ALF can result in cerebral edema, herniation, and death. Any patient with ALF and altered mental status should undergo an emergent head CT to rule out cerebrovascular accident, intracranial hemorrhage, or mass effect prior to treatment of hepatic encephalopathy. Those with grade III or IV encephalopathy should undergo elective endotracheal intubation and mechanical ventilation for airway protection, with maintenance of adequate sedation and patient-ventilator synchrony to reduce sudden increases in intracranial pressure. Neurosurgical placement of an intraparenchymal pressure monitor should then be strongly considered in order to continuously monitor and treat elevated intracranial pressure.

Intracranial hypertension is managed primarily with pharmacologic osmotherapy, with the goal to reduce intracranial pressure to less than 25 mmHg. Mannitol and hypertonic saline can be used for this purpose; if these measures fail, neuromuscular paralysis and therapeutic hypothermia with a target core body temperature of 32-33 degrees Celsius can be co-administered. In the setting of intracranial hypertension refractory to the above interventions, salvage therapy with barbiturate coma can be considered. Elevation of the head of the bed to 30 degrees is recommended for all patients. Furthermore, cerebral perfusion pressure, defined as the difference between mean arterial pressure and intracranial pressure, should be maintained at 60 mmHg or greater. In the setting of intracranial hypertension, this may require the use of vasoactive agents to increase the mean arterial pressure. Hyperventilation, formerly used to reduce intracranial pressure, may induce cerebral hypoxemia, and is no longer recommended for this purpose. Patients with grade I or II encephalopathy do not require intracranial pressure monitoring or endotracheal intubation for airway protection. However, serial neurologic exams are critical in these patients, as they can rapidly deteriorate to stage III or IV hepatic encephalopathy.

2.4.2 Coagulopathy

In addition to hepatic encephalopathy, *coagulopathy*, represented by an increasing INR, is a defining characteristic of progressing ALF. The synthetic function of the failing liver is diminished, and levels of clotting factors are reduced, resulting in elevations in the INR. In fact, the INR is considered the most sensitive indicator of hepatic function and is commonly used as a prognostic tool to aid prediction of spontaneous recovery or need for liver transplantation. Therefore, correction of the INR in the absence of bleeding is discouraged.

For invasive procedures, the INR can be temporarily corrected with recombinant Factor VIIa (Novo-7) at a dose of 40 µg/kg. Such therapy reduces the INR to below 1.5 within 30 minutes of administration, and allows approximately 90-120 minutes for the performance of invasive procedures. Vitamin K may reduce the INR if malnutrition is contributing to coagulopathy.

Despite the coagulopathic state observed in ALF, anticoagulant proteins such as protein C and S are reduced, and patients are at risk of venous thrombotic complications. Therefore, venous thromboembolism prophylaxis with subcutaneous heparin or low-molecular weight heparin formulations should be considered despite the presence of coagulopathy.

2.4.3 Renal impairment

Acute kidney injury in ALF usually results from impaired renal perfusion or direct renal insults. Hepatorenal syndrome, which occurs in the setting of portal hypertension and chronic liver disease, does not occur in ALF. Management of acute kidney injury includes avoidance of additional nephrotoxic insults, as well as supportive measures. In order to avoid increases in intracranial pressure and significant fluid shifts, if renal replacement therapy is necessary, continuous renal replacement therapy (CRRT) is preferred over conventional hemodialysis.

2.4.4 Infections

Infections occur in ALF from functional immunosuppression. Patients are susceptible to overwhelming bacterial and fungal sepsis, although clinical signs of infection may be absent. Empiric antibacterial and antifungal therapy should be considered in the setting of advanced hepatic encephalopathy, shock, or for patients listed for transplantation. Associated sepsis and septic shock are managed with broad-spectrum antibiotics, vasoactive agent support and high-dose corticosteroids.

2.4.5 Pulmonary complications

Respiratory disturbances, including acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), are frequent manifestations of ALF. In the setting of ALI and ARDS, lung-protective strategies with low tidal volume (6 cc/kg ideal body weight) ventilator settings and mild permissive hypercapnea are recommended. Hypoxemic respiratory failure portends a poor prognosis and is treated supportively. Severe hypercapnea, bronchoscopy, and patient-ventilator asynchrony can exacerbate intracranial hypertension; titration of the set respiratory rate to compensate for hypercapnea, as well as adequate sedation and analgesia to improve synchrony, are imperative. Neuromuscular-blocking paralytic agents may be necessary if patient-ventilator asynchrony persists despite adequate sedation.

2.4.6 Metabolic derangements

Metabolic derangements result both from impaired hepatic metabolic function and resulting multi-organ failure. Consequences include lactic acidosis and disturbances in arterial pH,

glucose, and electrolytes. Hypoglycemia results from impaired gluconeogenesis and glycogenolysis, and is managed via dextrose infusion and frequent glucose monitoring. Electrolyte disturbances include hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia, and should be corrected when recognized. However, the appearance of hypophosphatemia may indicate a favorable prognosis due to intracellular phosphorus consumption and hepatic regeneration. Finally, the high metabolic demands in ALF create a generalized catabolic state with resultant high nutritional needs. Enteric nutrition is recommended over parental routes to reduce gastrointestinal bacterial translocation and bleeding from stress ulceration.

3. Acute on chronic liver failure

3.1 Definition and etiology

Acute on chronic liver failure (ACLF), or decompensated cirrhosis, occurs when cirrhosis of any etiology is complicated by the development and sequelae of portal hypertension. Longstanding portal hypertension results from intrahepatic resistance to portal flow, and increased portal inflow from inappropriate splanchnic vasodilation. These pathophysiologic changes result in splanchnic and systemic derangements, including the development of gastroesophageal varices, hepatic encephalopathy, pulmonary decompensation, and hepatorenal syndrome. Given the importance of splanchnic vasodilation in the pathophysiology of ACLF, pharmacologic therapy with splanchnic vasoconstrictors plays a central role in the therapy of ACLF.

Etiologies of cirrhosis are numerous, and include alcoholic steatosis, chronic viral hepatitis, metabolic diseases (e.g. non-alcoholic fatty liver disease, hemochromatosis, wilson disease), autoimmune hepatitis and cholestatic liver diseases (e.g. primary biliary cirrhosis and primary sclerosing cholangitis).

3.2 Diagnosis

The diagnostic workup of a patient with suspected cirrhosis is similar to that of a patient presenting with ALF. Physical examination may reveal stigmata of chronic liver disease, including ascites and splenomegaly. Abdominal imaging with CT or MRI provides radiographic confirmation of chronic portal hypertension. Non-hepatic causes of portal hypertension, such as cardiac cirrhosis from longstanding heart failure, should also be excluded.

3.3 Organ-specific management

3.3.1 Hepatic encephalopathy

Hepatic encephalopathy in decompensated cirrhosis shares several qualities with the encephalopathy observed in ALF, including the grades of severity. However, major differences exist in clinical presentation and management of hepatic encephalopathy in ACLF. The chronicity of portal hypertension allows time for the development of ammonia fixation mechanisms and neuronal adaptation to ammonia. Thus, the hepatic encephalopathy of ACLF is not typically associated with cerebral edema. Treatment is

supportive and focuses on patient safety and avoidance of complications. As in ALF, patients with grade III or IV encephalopathy warrant elective intubation for airway protection. Causative factors of hepatic encephalopathy include dehydration, over-diuresis, infection, use of benzodiazepines and narcotics, gastrointestinal bleeding, constipation, electrolyte or acid-base imbalances, or recent transjugular intrahepatic portosystemic shunt (TIPS) procedure. Progression of underlying liver disease may be the only identifiable precipitant; when reversible causes are identified, they should be treated.

Medical treatment of hepatic encephalopathy consists of oral agents to assist in toxin elimination. Lactulose and other nonabsorbable disaccharides improve intestinal excretion of nitrogen and reduce production of ammonia by enteric bacteria. Intestinal decontamination with oral antibiotics such as rifaximin or metronidazole reduces the burden of ammonia-producing bacteria.

3.3.2 Gastroesophageal varices

Hemorrhage due to gastroesophageal variceal bleeding can be imminently fatal, and requires emergent therapy. Airway protection with endotracheal intubation reduces the risk of aspiration during massive hematemesis. Intravenous volume resuscitation or blood products should be administered carefully, as excess volume can increase portal pressures and exacerbate bleeding. An appropriate post-transfusion hemoglobin goal is 8 g/dL.

Infusion of the somatostatin analogue octreotide reduces portal pressure and can induce splanchnic vasoconstriction and facilitate hemostasis during variceal bleeding. Terlipressin, a vasopressin analogue, has been used with success in Europe to help control variceal bleeding. All patients should receive prophylactic antibiotics with either ceftriaxone or a fluoroquinolone, which have been shown to reduce infections, reduce the risk of rebleeding, and improve survival (Bernard *et al.*, 1999).

Following initiation of pharmacologic therapy, definitive therapy for gastroesophageal varices requires upper endoscopy with endoscopic band ligation or sclerotherapy. If these measures fail, or if gastric varices are detected, urgent TIPS can be used to achieve hemostasis and prevent the development of new varices. For severe uncontrolled bleeding, esophageal balloon tamponade may be necessary for temporary stabilization until definitive TIPS therapy is undertaken.

3.3.3 Cardiovascular impairments

Cardiovascular system derangements frequently complicate the hemodynamic picture of decompensated cirrhosis. Circulatory changes resemble those of septic shock, including increased cardiac output, reduced systemic vascular resistance, wide pulse pressure, and decreased mean arterial pressure. Patients are susceptible to sepsis-induced hypotension and septic shock. Norepinephrine is the preferred vasoactive agent in such patients, as it preserves cardiac output while increasing vascular resistance. Hypotension can also occur by decreased venous return if severe ascites produces compression of the inferior vena cava.

Finally, the phenomenon of cirrhotic cardiomyopathy with impaired systolic and diastolic dysfunction, and reduced response to inotropic therapy has been described (Zardi *et al.*, 2010). Several mechanisms for cirrhotic cardiomyopathy have been proposed, including myocardial apoptosis, involvement of circulating carbon monoxide and nitric oxide, and cardiomyocyte receptor impairments. If overt heart failure develops, consultation with a cardiologist is advisable.

3.3.4 Pulmonary complications

The pulmonary system derangements in decompensated cirrhosis are characterized by distinct disorders of varying severity. In the *hepatopulmonary syndrome* (HPS), excess vasodilation of the pulmonary vasculature system limits oxygen diffusion across the alveolar-capillary membrane. Vasodilation may occur through nitric oxide and other circulating vasodilators, or through arteriovenous malformations resulting in intrapulmonary shunts; the difference in these two mechanisms distinguish type I and type II HPS, respectively. Presenting symptoms include dyspnea, platypnea, orthodeoxia, cyanosis, and hypoxemia. Arterial blood gas and transthoracic double bubble echocardiogram or lung perfusion scans can help establish the diagnosis. Supplemental oxygen improves hypoxemia in type I HPS, whereas embolization of arteriovenous malformations can be performed in type II syndrome. In both forms, liver transplantation is the definitive treatment, and the presence of either form facilitates priority listing for transplantation.

Portopulmonary hypertension (PPH) is a form of pulmonary arterial hypertension occurring in the presence of portal hypertension, and portends a poor prognosis. The mechanism of the adverse effects of portal hypertension on the pulmonary vasculature remains unclear. Proposed explanations include endothelial remodeling in response to a hyperdynamic circulation, as well as inflammatory cascades related to cytokines. Patients present with exertional dyspnea, fatigue, chest pain, and signs of volume overload. Diagnosis is confirmed by right heart catheterization, which demonstrates a pulmonary artery pressure (PAP) of 25 mmHg or greater with a normal pulmonary capillary wedge pressure. The degree of PAP elevation correlates with mortality during liver transplant, and patients with moderate or severely elevated pressures generally are not candidates for transplantation. Continuous infusion of vasodilatory prostaglandins such as epoprostenol may improve hemodynamics and reduce PAP to allow patients improved likelihood of tolerating transplantation.

Hepatic hydrothorax refers to pleural effusions that occur when diaphragmatic defects allow the transudation of ascitic fluid into the pleural space. Dyspnea, cough, chest discomfort, and respiratory collapse can occur. Diagnostic and therapeutic thoracentesis should be performed to exclude infection, malignancy, and cardiopulmonary etiologies of pleural effusions. Diuretics such as furosemide and spironolactone can be administered, but patients with respiratory compromise should undergo therapeutic thoracentesis. Chest tubes are contraindicated in hepatic hydrothorax, as re-expansion pulmonary edema and hypovolemic shock can occur and are poorly tolerated in the cirrhotic patient. If hepatic hydrothorax is refractory to diuresis and thoracentesis, TIPS is indicated to help prevent the formation of ascites and subsequent transudation.

3.3.5 Renal impairments

Hepatorenal syndrome (HRS) is defined as an increase in creatinine to greater than 1.5 g/dL or a decrease in creatinine clearance to below 40 mL/min. HRS is a dreaded complication of cirrhosis, and can develop unexpectedly at any point in the course of illness. Splanchnic vasodilation in the setting of cirrhosis results in reduced effective blood volume and pre-renal acute kidney injury. HRS is a diagnosis of exclusion. Two forms exist; type I progresses rapidly, whereas type II progresses over a longer time period; both are fatal without transplant. When diagnosing HRS, other causes of acute kidney injury in cirrhosis must be excluded, including dehydration and over-diuresis, medication effects, and intrinsic renal insults. Diagnostic criteria for HRS include: cirrhosis with ascites, creatinine level of at least 1.5 mg/dL, lack of response to diuretic withdrawal and volume expansion, absence of shock, and absence of nephrotoxic and parenchymal renal etiologies.

A definitive curative treatment for HRS is limited to liver transplantation, but supportive measures aimed at correcting the pathophysiology are in trial. Terlipressin has been studied for HRS in addition to its use in variceal hemorrhage, and has demonstrated the ability to reverse Type 1 HRS. Octreotide and the alpha agonist midodrine can induce splanchnic vasoconstriction, thereby potentially reversing the pathophysiology of HRS. Avoidance of additional renal insults, including diuretics and other nephrotoxic agents, is essential. The TIPS procedure can be used to improve overall circulatory function through portal venous decompression. Finally, renal replacement therapy is often required while patients await transplant.

3.3.6 Infectious complications

Further complications of decompensated cirrhosis include a predisposition to infections, owing to a chronic low-grade inflammatory state produced by excess cytokines and reduced clearance of toxins. Impaired function of macrophages and antigen presenting cells and decreased levels of complement are also implicated. In the setting of septic shock, early goal-directed therapy is warranted, but over-resuscitation of volume can increase portal pressures and lead to exacerbation of portal hypertension. As in acute liver failure, patients with decompensated cirrhosis may benefit from use of glucocorticoids to supplement vasoactive agents (*Fernandez et al., 2006*). Bacterial pathogens are most typical, but fungal infections occur frequently in cirrhosis and should be considered in the differential diagnosis.

3.3.7 Ascites

Abdominal ascites is another notable manifestation of decompensated cirrhosis. Ascites can cause significant morbidity, including abdominal pain and discomfort, dyspnea and orthopnea, hepatic hydrothorax, spontaneous bacterial peritonitis, and abdominal compartment syndrome. Abdominal compartment syndrome is characterized by restrictive lung mechanics, renal and mesenteric vascular compromise, and hypotension due to compression of the inferior vena cava.

Ascites develops in response to renal hypoperfusion, which results in upregulation of the renin-angiotensin-aldosterone system to increase sodium and water retention. Elevated

portal pressures produce a capillary hydrostatic pressure gradient, forcing fluid into the abdominal interstitium. Sodium restriction and use of diuretics can be used to manage ascites. Refractory ascites can be managed with serial large-volume paracentesis or placement of a TIPS shunt.

3.3.8 Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is a frequent complication of ascites, and can precipitate hepatorenal syndrome. Common pathogens of SBP include *E coli*, *K pneumonia*, and *S pneumoniae*, although culture-negative SBP occurs as well. Recommended antibiotics include third-generation cephalosporins or fluoroquinolones; daily maintenance antibiotics are used for secondary prophylaxis. If SBP is suspected, treatment with antimicrobials while awaiting culture results is appropriate.

4. Indications for liver transplantation

Many patients with worsening ALF or ACLF are eligible for orthotopic liver transplant. Indications for transplant are numerous and include acquired or congenital etiologies, viral hepatitis, drug-induced ALF, cirrhosis, cholestatic diseases, metabolic disorders, vascular derangements, and hepatocellular carcinoma. Because the supply of donor grafts is exceeded by the demand for transplantation, organ allocation is critical. The process of organ allocation is defined by country-specific donor and recipient allocation schemes.

Several models for prognostic data in ALF have been proposed. Consensus exists in the belief that the degree and clinical trend of coagulopathy and hepatic encephalopathy remain the most important prognostic indicators, and are helpful in determining patient appropriateness for transplantation listing. ALF may resolve with supportive treatment, but frequently progresses to death in the absence of transplantation. Patients with ALF therefore have highest priority for liver transplantation.

Patients with decompensated cirrhosis are classified by the Model For End Stage Liver Disease (MELD) score (Murray and Carithers, 2005), which has largely replaced the Childs Pugh system, with higher MELD scores indicating higher mortality. Although exceptions are made, including for hepatocellular carcinoma, a MELD score of 15 or higher is generally required to list patients with end stage liver disease for transplantation.

Several contraindications for transplantation exist. Active alcohol or substance abuse, medical non-adherence, poor social support, extrahepatic malignancy, significant cardiopulmonary disease, uncontrolled sepsis, extrahepatic systemic infections, and uncontrolled psychiatric illness are examples of contraindications to liver transplantation.

5. Salvage mechanisms and bridges to transplant

Although liver transplantation is life-saving for acute and chronic liver failure, the immunosuppressant medications necessary to prevent rejection and allow optimal graft function following transplant are frequently accompanied by adverse metabolic effects, nephrotoxicity, and susceptibility to potentially fatal infections. In addition, the demand for

transplant greatly exceeds the supply of donor livers, and many patients either die while awaiting a donor or become too critically ill to qualify for transplant. The discrepancy in the supply and demand for organs, and the high pre-transplant mortality and post-transplant morbidity have generated interest in surgical techniques to avoid transplantation and chronic immunosuppression, and support systems to serve as a bridge to transplant or spontaneous recovery. Examples of these include auxiliary liver transplantation and liver assist devices.

5.1 Auxiliary liver transplantation

An alternative to traditional orthotopic liver transplantation for patients with ALF is that of auxiliary transplant, based on the well-established regenerative capacity of hepatocytes. Unlike traditional transplantation, where native hepatectomy is performed simultaneously with donor engraftment, in auxiliary transplants, the patient's native liver is left surgically intact, while a partial or smaller sized donor graft is transplanted. This procedure allows assumption of hepatic functions by the donor graft, resolution of multi-organ failure, and clinical stabilization of the patient. In turn, the native liver benefits both from additional time, as well as improved physiological conditions, thus maximizing the opportunity for hepatic regeneration. Younger patients (below 40 years of age) with ALF due to viral hepatitis or acetaminophen toxicity appear to have the best outcome with this strategy. After native hepatic function is demonstrated, the auxiliary graft can be removed, but is most frequently allowed to atrophy by withdrawal of immunosuppression. Complete cessation of immunosuppression can be achieved in many patients (*Boudjema et al., 1995*).

5.2 Artificial and bioartificial hepatic support systems

Mechanical hepatic support systems serve as a bridge to transplant in patients with ACLF, and as a bridge to transplant or spontaneous recovery in patients with ALF. These systems are designed to reproduce the detoxifying functions of the liver, and mimic the principles upon which renal replacement therapy is based. While conventional renal dialysis removes small toxins and water-soluble toxins, the liver detoxifies larger toxins and protein-bound toxins. Dialysis of these larger and protein-bound toxins through unbound human albumin solutions allows the removal from the patient's circulation.

Several artificial systems have been developed utilizing albumin dialysis. The Molecular Adsorbent Recirculating System (MARS), Single Pass Albumin Dialysis (SPAD), and Prometheus are examples; of these, MARS has been the most widely studied. MARS has been utilized for management of hepatic encephalopathy, cerebral edema, hepatorenal syndrome, treatment of drug overdoses, and as a bridge to transplantation (*Mitzner, 2011*). MARS has been shown to improve hemodynamic parameters and organ perfusion during circulatory collapse, and has been associated with improvement in hepatic synthetic function. For patients with ACLF, MARS can provide temporarily relief of intractable pruritis and fatigue.

Bioartificial systems work similarly to artificial systems to remove toxins by albumin dialysis, but additionally utilize human or porcine hepatocytes to mimic hepatic synthetic

function. Advances in the development of bioartificial systems have been limited by the challenges in maintaining hepatocyte viability.

6. Conclusion

Acute liver failure and acute on chronic liver failure are complex illnesses often culminating in multi-organ failure, and require meticulous care in the pre-transplant phase. Mortality in the absence of transplantation is high, but the advent of multi-disciplinary critical care has significantly improved the outcome in these disease processes. A protocolized approach to the intensive care management of patients prior to liver transplantation will favorably impact the pre-transplant and post-transplant status of these patients.

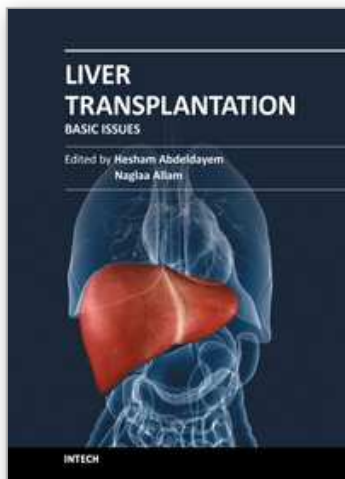
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This book covers a wide spectrum of topics including history of liver transplantation, ischemia-reperfusion injury, immunology of liver transplantation, viral hepatitis and liver transplantation, other indications for liver transplantation, prognostic factors and perioperative period. The authors of the chapters are experts in their respective fields. They are proponents covering different aspects of liver transplantation and come from many centers across the world. The interdisciplinary approach and the authority of the contributors resulted in a valuable reference to anyone interested in developing a global view in liver transplantation including medical students, residents, fellows, nurses, and practicing physicians and surgeons as well as researchers in the field of liver transplantation.

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