Care of the Patient with Liver Failure Requiring Transplantation

55

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Introduction and Preoperative Care

Patients undergo liver transplantation to address chronic liver failure, acute fulminant liver failure, or primary liver cancer. Depending on acuity, patients with decompensated chronic or acute fulminant liver failure generally require preoperative intensive care unit (ICU) admission to manage organ dysfunction.

Those with chronic liver failure are allocated an organ based on waiting list position determined by their local organ procurement organization (OPO). This position is dependent upon blood type and Model for End-Stage Liver Disease (MELD) score. MELD is determined by a weighting of serum bilirubin, creatinine, and international normalization ratio (INR). Those with a high MELD score have a greater risk of mortality and thus are given priority to transplantation. Patients with a MELD score of 40 have a 75% chance of death within 3 months. This is particularly important given the transplantation is typically performed on those with high MELD scores in large urban areas such as ours in the greater Los Angeles area. These patients thus are critically ill and require preoperative ICU monitoring and care.

Patients with hepatocellular carcinoma (HCC) who require liver transplantation are given a MELD exception and rarely require preoperative ICU care. The patient's ability to undergo liver transplant in the setting of HCC is determined by the Milan criteria or the University of California, San Francisco (UCSF) criteria. HCC patients with a single tumor <5 cm, up to three tumors <3 cm, absence of macroscopic vascular invasion, and absence of extrahepatic spread may undergo liver transplantation based on the Milan criteria.

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Preoperative Care of Patients with Decompensated Chronic Liver Failure

Neurologic

Altered level of consciousness is common in patients with decompensated cirrhosis. This is a result of portosystemic shunting and hepatocellular dysfunction/toxin production that results in hepatic encephalopathy. Most severe or accelerated changes in the level of consciousness are the result of a precipitating event such as a significant upper gastrointestinal bleed and resultant uremia or a new infection. Encephalopathy can be exacerbated by the administration of medications such as benzodiazepines that are generally avoided in the routine treatment of this patient population. Those with low-grade encephalopathy, manifested by mild confusion and tremors, are administered agents such as lactulose to decrease ammonia absorption by acidifying bowel content and increase transit of the bowel contents. Rifaximin is also commonly used to diminish the presence of urease and protease-splitting bacteria. It is important to remember to discontinue lactulose therapy in advance of anticipated liver transplantation to avoid intraoperative diarrhea and possible bowel distention.

Cardiac

Systemic and splanchnic arteriolar vasodilation is a well-known physiologic derangement in patients with end-stage liver disease. As a result, these patients have hyperdynamic and low systemic vascular resistance cardiac profiles and often require vasopressor therapy—whether oral (e.g., midodrine) or intravenous (e.g., norepinephrine)—to maintain adequate mean arterial pressures (MAP) of >65 mmHg. It is important to consider that hypotension may be multifactorial, resulting from active hemorrhage, infection, and/or systemic inflammatory response (SIRS). Further, cardiac contractile function may be impaired in patients with long-standing cirrhosis or in those with associated ischemic cardiac disease. Routine use of beta blockade as prophylaxis in those with varices may also cause hypotension. If hemor-

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rhage and SIRS response have been addressed and ruled out, refractory hypotension could be a result of adrenal insufficiency; this is a common pathophysiology in end-stage liver disease patients. There is little additional role for invasive cardiac monitoring in cirrhotic patients for the diagnosis and treatment of shock over echocardiography and other noninvasive means. In general, the treatment of shock does not depart much from that in other patients. Patients should be approached similarly with crystalloid resuscitation and early goal-directed therapy; there is little evidence that albumin should be the resuscitative fluid of choice. Monitoring base deficit and lactate is as prognostic and useful to guide resuscitative efforts in patients with decompensated liver disease as it is for the general ICU population.

Pulmonary

Patients with advanced liver disease may have other associated pulmonary disorders, including hepatic hydrothorax, emphysema from alpha-1-antitrypsin deficiency, hepatopulmonary syndrome (HPS), and portopulmonary hypertension (PPH).

Hydrothorax is typically the result of tense abdominal ascites and should be addressed by paracentesis, thoracentesis, and total body volume management. Draining of pulmonary effusions should be limited to those with impending respiratory failure due to the risk of infection and hemorrhage associated with invasive procedures and re-accumulation. Definitive treatment of pulmonary effusions is with liver transplantation.

HPS is caused by intrapulmonary shunting and does not result in right heart failure. Patients with HPS will classically experience positional hypoxia. PPH on the other hand results from pulmonary vascular vasoconstriction and can ultimately lead to thrombosis and fibrosis. In contrast to HPS, right heart failure is typical in PPH.

It is important to distinguish between HPS and PPH. In general, liver transplantation is curative of the former and, until recently, was contraindicated in the latter. However, the introduction of many new agents and classes of agents to treat pulmonary hypertension may render liver transplantation possible in centers of excellence with careful pre- and intraoperative monitoring. Although noninvasive monitoring is helpful and new modalities are being developed, the most expeditious and accurate modality to differentiate between HPS and PPH is right heart catheterization. HPS, PPH, and CHF can all cause elevated pulmonary artery pressures. However, pulmonary artery wedge pressure (PAWP) is low in HPS and PPH (and elevated in CHF). Pulmonary vascular resistance (PVR) is normal to decreased in HPS but elevated in PPH. Thus, cardiac output is elevated in HPS and normal to decreased in PPH.

Renal

One of the major causes of AKI in patients with advanced cirrhosis and ascites is the phenomenon of hepatorenal syndrome (HRS) or acute renal failure without other etiology. There are two subtypes of HRS, types I and II. The first type generally progresses with a rapid decrease in renal function and is characterized with doubling in serum creatinine within that period of time. It may be precipitated by spontaneous bacterial peritonitis, gastroenteritis with high-volume diarrhea, volume loss from gastrointestinal bleed, or large-volume paracentesis without appropriate volume repletion. Type I HRS can be fatal and often leads to multi-system organ failure. Type II HRS demonstrates a more indolent course of renal failure, often precipitated by ascites refractory to diuretic treatment [1]. HRS develops due to splanchnic circulation vasodilation, intravascular hypovolemia, and renal vasoconstriction and is most often a diagnosis of exclusion after investigating for other causes of renal failure. The treatment approach includes strict intake and output monitoring, serum creatinine monitoring, and following changes from baseline or within the past 48 h. If the patient develops oliguria with elevated serum creatinine greater than 50% from a reference value or baseline serum creatinine level, suspect AKI. Multiple diagnostic variable are used to diagnose HRS in patients with cirrhosis (Fig. 55.1). These patients may require combined liver and renal transplant and/or intraoperative renal replacement therapy to assist with volume status, correcting acidosis, and electrolyte abnormalities. The mainstay of treatment for HRS is liver transplantation, after which a majority of patients demonstrate a return to adequate renal function. Consideration should be given to a combined liver/kidney transplantation in those who have required dialysis for greater than 2 months, although this time period is controversial. A variety of approaches can be used to increase intravascular volume and MAP including albumin and vasopressors (norepinephrine, terlipressin). Intermittent paracentesis may be necessary to manage third spacing of fluids in hepatorenal syndrome prior to liver transplant [2, 3]. Type 1 HRS requires multiple therapeutic strategies and therapies; please refer to Fig. 55.2 for a detailed algorithm.

Infectious Disease

The presence of infection in a cirrhotic patient quadruples mortality and worsens liver function. Those with chronic liver failure are functionally immunosuppressed and are often colonized with multiresistant organisms. The most common infection in these patients is spontaneous bacterial peritonitis. Strict attention should be paid to removing unnecessary catheters and avoiding intubation/mechanical ventilation, when possible. Patients require prophylactic antibiotics for spontaneous bacterial peritonitis after a variceal bleed; however, there is little need for general broad-spectrum antimicrobial therapy.

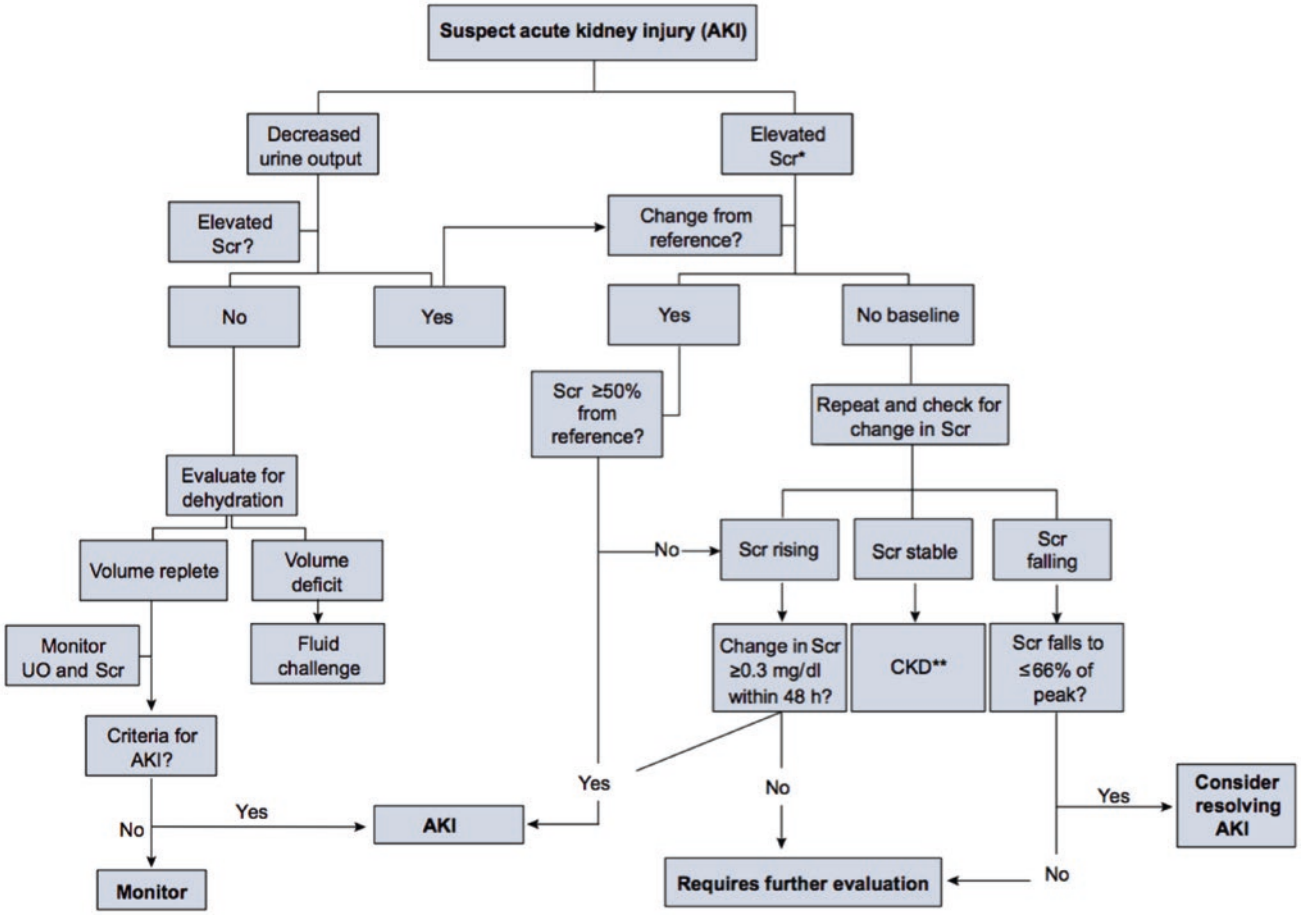

Fig. 55.1 Diagnostic algorithm to evaluate acute kidney injury in the hospitalized patient with cirrhosis. AKI acute kidney injury, Scr serum creatinine, UO urine output, CKD chronic kidney disease, RRT renal replacement therapy, Na sodium (Reproduced with permission from Nadim et al. "Management of the critically ill patient with cirrhosis: A multidisciplinary perspective")

Preoperative Care of the Patient with Acute Fulminant Liver Failure

Patients with fulminant liver failure receive a MELD exemption in listing—the appropriateness of transplantation may be determined by King's criteria (Table 55.1). In general, patients experience toxic necrosis of the liver on a baseline of normal function, most commonly due to intentional or inadvertent ingestion of large doses of acetaminophen. Thus, the abnormalities noted are lactic acidosis, marked elevation of INR, and high-grade encephalopathy. Ascites and hepatorenal syndrome are often not present given the acuity of presentation. Creatinine, however, is often elevated due to ATN. If time of ingestion is known, and within 8 h, N-acetylcysteine should be administered to prevent further toxicity in acute liver failure patients. If the patient fails medical management with progression of liver failure, liver transplantation will be required. The most significant risk of mortality to a patient with fulminant liver failure is that of cerebral edema and subsequent death from cerebral herniation. Intracranial monitoring remains controversial given severe coagulopathy, thrombocytopenia, and risk of infection. Serum sodium of 145–150 meq/L should be maintained with hypertonic saline to decrease the amount of cerebral edema. If renal dialysis is required, a continuous mode is preferred to avoid rapid fluid shifts that may exacerbate cerebral edema.

Postoperative Care

Patients having undergone liver transplantation will require postoperative intensive care unit (ICU) admission. Close communication and coordination of care between the surgeons, anesthesiologists, intensivists, and nursing staff are essential to the management of the patient in this setting. Liver transplantation typically entails a lengthy surgical procedure requiring significant amounts of blood product transfusion and risk of postoperative respiratory insufficiency. Preoperatively, many of these patients have neurologic, cardiopulmonary, and renal dysfunction requiring

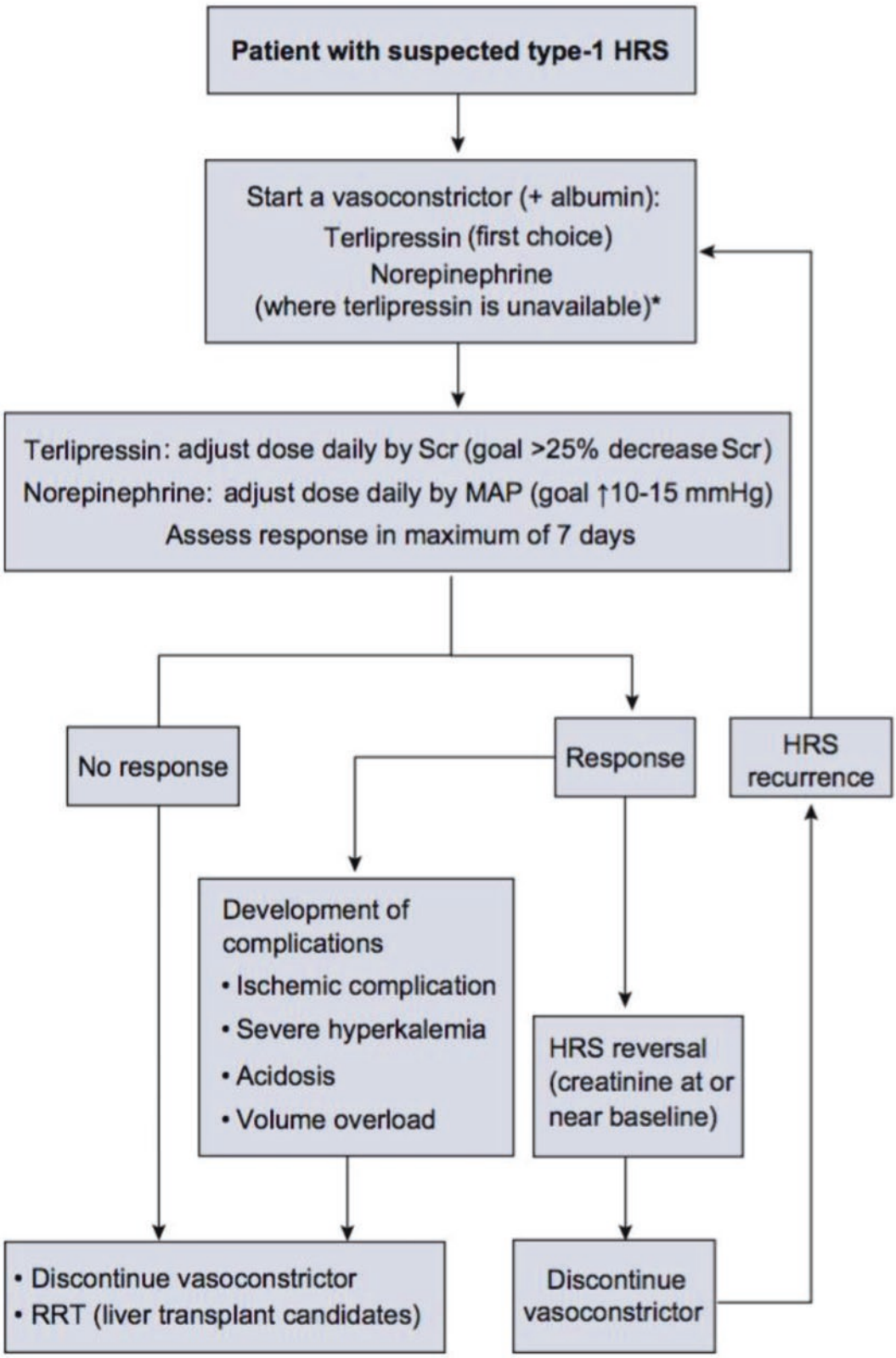

Fig. 55.2 Algorithm for patients with suspected type 1 HRS. HRS hepatorenal syndrome, RRT renal replacement therapy. *The authors recommend a trial of octreotide IV and midodrine for a maximum of 3 days prior to the initiation of norepinephrine (Reproduced with permission from Nadim et al. "Management of the critically ill patient with cirrhosis: A multidisciplinary perspective")

Table 55.1 King's College criteria for patients with acute liver failure

Acetaminophen	Non-acetaminophen
Lactate >3.5	INR > 6.5 regardless of encephalopathy
pH < 7.3	3 out of 5 of the following
Grade 3 or 4 encephalopathy	Bilirubin >3.0
INR > 6.5	INR > 3.5
Creatinine >3.0	Age < 10 or >40
	Cause indeterminate or drug induced
	Jaundice to encephalopathy >7 days

ICU admission prior to the transplant. Pre-liver transplant patients that are in renal failure requiring dialysis, in respiratory failure requiring mechanical ventilation, and/or admitted to the ICU prior to transplant have a higher risk of postoperative complications and prolonged ICU length of stay (LOS) [4].

Neurologic

Fentanyl, a narcotic, is the first-line agent for the treatment of pain and agitation given its rapid onset and short duration of action in postoperative transplant patient. Those who require additional sedation for agitation not controlled with narcotic analgesia benefit from the use of dexmedetomidine over benzodiazepines given a decreased risk of iatrogenic delirium and decreased length of mechanical ventilation [5]. Dexmedetomidine is an alpha-2 adrenoreceptor agonist and should be used in caution with patients with hypotension and baseline bradycardia as it can exacerbate both conditions. With the use of spontaneous awakening trials (SATs), Richmond Agitation and Sedation Score (RASS), and Confusion Assessment Method for the ICU (CAM-ICU), patients have decreased episodes of delirium, duration of mechanical ventilation, and ICU and hospital length of stay [6]. In this particular population, however, sustained delirium and encephalopathy may be the result of poor functioning of liver transplant graft, infection, intracranial hemorrhage or cerebral ischemia, seizures, and/or immunosuppressant toxicity. There should be a low threshold to pursue diagnostic CT scan of head, cultures including cerebral spinal fluid, and electroencephalography (EEG) in the posttransplant patient with change in mental status.

Encephalopathy due to cerebral edema associated with fulminant liver failure and elevated ammonia levels in patients with end-stage liver disease should be corrected with an adequately functioning liver transplant graft. If an intracranial monitor was placed preoperatively, it should be maintained until the INR is corrected and the liver is functioning well.

Respiratory Failure and Insufficiency

In the past decade, early recovery after surgery or "fast-track" programs have been implemented in a variety of disciplines, including hepatobiliary and colorectal patients after elective surgery with no worsening of postoperative outcomes and improvement in patient satisfaction. Liver transplant patients may be eligible for fast-track extubation immediately postoperative in the operating room and upon arrival to the ICU. Patients that successfully undergo fast-track extubation have been shown to benefit from decreased rates of re-intubation and tracheostomy along with improved survival [7]. Patients that are likely not candidates for fast-track extubation include those with preoperative acute liver failure, re-transplantation, Child's C cirrhosis, and intraoperative red blood cell transfusion >6 units [7]. Patients that require continued mechanical ventilation upon arrival to the ICU should be placed on ventilator settings of tidal volume 6 mL/kg and FiO2 < 0.4 [8]. Patients who may exhibit transfusion-related lung injury after receiving a significant amount of blood products require ventilation strategies similar to patients with acute respiratory distress syndrome (ARDS); in this case, target tidal volumes of 6 mL/kg with supplemental oxygen and positive end-expiratory pressure (PEEP) [9]. Infections of the lower respiratory tract require broad-spectrum antibiotics and antifungals until species and sensitivities are established. The liver transplant patients who remain hemodynamically stable and require minimal mechanical ventilation settings with resolved encephalopathy should undergo daily spontaneous breathing trials (SBT) and subsequent evaluation for possible extubation to reduce the duration of mechanical ventilation and ICU length of stay [10]. Early mobilization and aggressive chest physiotherapy are performed to prevent complications of atelectasis and inadequate ventilation.

Cardiovascular

Centers may opt to monitor patients intraoperatively with pulmonary artery catheters and/or transesophageal echocardiography. Once stable and resuscitated, patients should be liberated from these devices. Steroids are routinely administered as a part of early immunosuppression regimen after liver transplant and may require a prolonged course in treating hypotension secondary to adrenal insufficiency.

Hematology

Liver transplantation patients remain at risk for postoperative hemorrhage due to thrombocytopenia, fibrinolysis, and deficiency of coagulation factors. Abnormal coagulation tests and

platelet count are not good predictors of bleeding; thus aggressive correction of these coagulopathies should be avoided. Therapy should also include practical measures as avoiding hypothermia and persistent acidosis. Aggressive correction of coagulopathy and thrombocytopenia may also put patients at higher risk of hepatic artery, portal vein, and deep vein thrombosis. Typical target ranges include hemoglobin of 8 g/dl and platelet count >20 × 10^9/l [11]. Thromboelastography (TEG) may be useful in dictating guided blood product resuscitation in the post-liver transplant patients to decrease blood loss and transfusion requirements [12]. Liver transplant patients with hemorrhage that are undergoing appropriate blood product resuscitation and become hemodynamically unstable or develop abdominal compartment syndrome should return immediately to the operating room.

Nutrition

Patients with advanced cirrhosis are often malnourished and as such are at higher risk for infections, worsening encephalopathy, and decompensation. Though these patients may appear grossly overweight, their usual or dry weight is often masked by massive ascites and edema secondary to hypoalbuminemia. The American and European Society for Clinical Nutrition and Metabolism and the European Society for Clinical Nutrition and Metabolism (ASPEN [13] and ESPEN [14], respectively) have compiled an extensive set of guidelines, both of which provide a subset of consensus statements for patients with hepatic failure.

The primary goals of nutrition for patients with hepatic failure include (1) identifying and assessing patients at risk for undernutrition, (2) calculating nutritional needs and incorporating adequate protein and high-calorie formulas, and (3) considering dobhoff placement if encephalopathy precludes voluntary enteral nutrition or short-term parenteral nutrition if unable to provide enteral feeds secondary to ileus or malabsorption.

Dry or usual weight may be difficult to ascertain given the chronicity of liver disease, thus complicating calculations for caloric needs. Poor oral intake may be a result of underlying encephalopathy, gastroparesis, and overall decreased gastrointestinal motility. In prior years, protein restriction was emphasized to mitigate the effects on worsening hepatic encephalopathy. However, given the already reduced lean muscle mass of this vulnerable patient population, protein-restricted diets can worsen hepatic failure. Recommended protein intake is 1.2–1.5 g/kg/day, with a total energy intake of 35–40 kcal/kg/day. Dobhoff placement is recommended if the patient is unable to meet his/her caloric needs per os; percutaneous endoscopic gastrostomy or open gastrostomy tube is otherwise not recommended given an increased risk of complications [14].

Renal

Post-liver transplant acute kidney injury (AKI) is a frequent event with reports of up to 52% of patients developing AKI [15]. Factors such as increased Child-Pugh score, pre-existing diabetes, and large number of intraoperative transfusions increase the risk of AKI in the post-liver transplant. The development of post-liver transplant AKI leads to prolonged ICU and hospital length of stay, increased mortality, and decreased duration of liver graft function [15]. In patients that develop AKI post-liver transplantation, treatment includes the prevention of hypotension and decreased use of unnecessary blood products. The use of renal replacement therapy is reserved for patients that develop significant volume overload, uremia, and electrolyte abnormalities. The most effective treatment of postoperative liver transplant AKI is prevention. Preventive strategies include delayed initiation of calcineurin inhibitors, avoiding nephrotoxic agents such as IV contrast, and ensuring adequate control of hyperglycemia [15].

Infection

The most common cause of morbidity and mortality after liver transplantation is infection, accounting for 60% of the deaths after liver transplantation [16]. Prolonged and complicated operations, multiple catheter insertions, immunosuppression, and large quantities of fresh frozen plasma can all increase the risk of infectious complications [17]. Diagnosis of infections in this patient population may be difficult due to the lack of signs and symptoms such as fever, chills, cellulitis, and leukocytosis due to an immunosuppressed status. Early postoperative infections in liver transplant patients are typically bacterial and related to the donor's status (previous infections from advanced cirrhosis), the surgical procedure itself, prolonged use of invasive catheters, and duration of mechanical ventilation. Perioperative antibiotics are typically broad spectrum and may include third-generation cephalosporins. Early removal of invasive catheters, early mobility, pulmonary toilet, vigilant monitoring of patient's surgical wounds and drains, and early discharge from the ICU may decrease these infectious complications. Liver transplant patients are at risk of developing opportunistic infections given the initial burst of immunosuppression with high-dose steroid therapy and, as such, should be initiated on prophylactic trimethoprim-sulfamethoxazole (TMP-SMX) to prevent *Pneumocystis carinii* pneumonia and ganciclovir to prevent cytomegalovirus infection.

Complications

Technical Errors

Besides surgical and coagulopathic bleeding, other postoperative complications can occur; these include postoperative hepatic artery thrombosis (3%) or portal vein thrombosis (< 1%) [11]. The resulting lack of blood flow and developing ischemia and necrosis from hepatic artery thrombosis present with signs and symptoms similar to fulminant liver failure patients with elevated liver serum tests, coagulopathy, and severe metabolic acidosis. Doppler ultrasound of the hepatic artery and portal vein is routinely employed within the first 24–48 h after liver transplant to diagnose possible vascular complications prior to the development of ischemia and necrosis of the liver transplant graft. These patients are at high risk for continued ischemia and necrosis of the graft with the need for urgent relisting and re-transplantation. Compared to patients with hepatic artery thrombosis, those with portal vein thrombosis do not present with such critical signs and symptoms as a rapid rise in liver function tests and disruption in synthetic function. Although portal vein thrombosis leads to elevation in liver serum tests, signs and symptoms are less dramatic and may consist of mesenteric venous congestion, gastrointestinal hemorrhage, and the development of ascites. Although these patients may require re-transplantation, they can typically be managed with thrombectomy, shunt, or revision of the portal vein anastomosis. Biliary duct complications, which include anastomosis stricture or leak, affect 5–25% of liver transplant patients and are often delayed diagnoses [18]. Thrombosis of the liver transplant hepatic artery can also lead to non-anastomotic stricture [18]. Biliary duct complications can be evaluated with ultrasound of the liver transplant graft looking for biloma and biliary duct dilation. Similarly, internal to external drains placed during the liver transplantation may show biliary drainage during the first several postoperative days. Elevated serum liver tests specifically bilirubin will elevate or fail to appropriately decrease after liver transplant, and the patients may develop signs and symptoms of infection. Magnetic resonance cholangiopancreatography (MRCP) may be used as a noninvasive diagnostic modality to look for biliary anastomosis complications. Endoscopic retrograde cholangiopancreatogram (ERCP) can be used for the diagnosis of biliary anastomosis leak and stricture, in addition to possible treatment with sphincterotomy and/or biliary stent [19]. Endoscopic treatment is often preferred over percutaneous management of biliary leaks and stricture. Treatment options include endoscopic dilation and stenting and have excellent success rates approaching 75% [20]. Surgical revision of the biliary anastomosis due to stricture or leak may be required in 10–20% of patients [18, 21]. The use of broad-spectrum antibiotics for treatment or prophylaxis is recommended due to the high risk of cholangitis and intra-abdominal sepsis [22]. 30–50% of patients with biliary stricture will have to undergo re-transplantation due to chronic biliary cirrhosis due to obstruction even with adequate treatment [19, 22].

Nontechnical

Primary graft nonfunction and hyperacute rejection can occur in the immediate or acute postoperative setting. Primary graft nonfunction occurs in 2–14% of orthotopic liver transplants and typically presents similar to fulminant liver failure with significant metabolic acidosis, elevated liver enzymes, coagulopathy, and lack of bile production [11, 23]. Intraoperative hemodynamic instability, reperfusion injury of the liver transplant graft, marginal livers, and advanced age of donors and recipient are factors that may lead to primary graft nonfunction. Once diagnosed, the only treatment indicated is for relisting and liver re-transplantation. Development of hyperacute rejection (HAR) after liver transplant is a rare complication that may develop intraoperatively or in the immediate postoperative period, which is antibody-mediated and due to ABO crossmatch incompatibility. Patients with HAR typically present with progressive encephalopathy and weakness, elevated bilirubin, severe coagulopathy, thrombocytopenia, metabolic acidosis, and shock. Diagnosis is confirmed with Doppler ultrasound that displays portal vein thrombosis and absence of biliary duct stricture. Along with critical care supportive therapy, patients can be managed with plasma exchange for antibody removal and intravenous immunoglobulin [11]. Overall, patients that develop HAR will need immediate relisting and re-transplantation. Acute cellular rejection after liver transplant may occur within the first 6–8 weeks, and the patients are often out of the ICU and no longer critically ill. Patients with acute cellular rejection typically are not critically ill and may present with fever, weakness, and elevated liver function tests. Prior to treating the patients for acute cellular rejection, one must rule out all possible acute infections that could account for the signs and symptoms given that the treatment of acute cellular rejection requires immunosuppression with pulse-dose glucocorticoids and adjustment of other immunosuppression medications.

Immunosuppression

Glucocorticoids are the first-line therapy for the prevention and treatment of acute cellular rejection. Common glucocorticoids used for liver transplant include prednisone, hydrocortisone, and methylprednisolone with the first dose given while in surgery. Intravenous hydrocortisone is typically administered in the immediate postoperative period until the patient is taking enteral nutrition and can transition to oral prednisone. Most patients will undergo a glucocorticoid taper and either transitioned off of glucocorticoids or to a low maintenance dose, typically over a 6-month to 2-year

period [24]. Glucocorticoids have a significant number of side effects including poor wound healing, increased infection risks, hyperglycemia, and hypertension; these patients may need judicious adjustment of insulin sliding scale for hyperglycemia. Glucocorticoid-free immunosuppression is possible and may be of benefit in patients with cirrhosis due to hepatitis C virus. [25, 26]

Calcineurin inhibitors (CNI), including cyclosporine and tacrolimus, are used to prevent and treat acute rejection and liver transplant graft loss. Both provide immunosuppression by inhibiting interleukin-2 and interferon-gamma production and require monitoring of blood levels to reach appropriate therapeutic levels. Potential side effects including altered mental status, seizures, neuropathy, renal failure, electrolyte abnormalities, and others should be monitored for and treated appropriately. Tacrolimus is currently the CNI of choice and has demonstrated superiority in preventing acute rejection and graft loss with decreased mortality [27, 28]. Posterior reversible encephalopathy syndrome (PRES) is a rare syndrome and side effect of CNI that is diagnosed with clinical exam and CT or MRI. Patients with PRES most commonly present with seizures but may also have symptoms such as headache, delirium, and visual changes. Head CT or MRI typically demonstrates vasogenic edema of the parietal or occipital lobes; however MRI may be more sensitive in diagnosing PRES. Treatment of PRES most often involves discontinuing the offending CNI and supportive care.

Mycophenolate mofetil (MMF, CellCept) is an antimetabolite that inhibits purine and pyrimidine synthesis with the active by-product of mycophenolic acid (MPA). MPA ultimately inhibits the proliferation of T lymphocytes for immunosuppression. MMF is typically used long term to reduce the dose or replace glucocorticoids. As such, the use of MMF will avoid common CNI side effects, such as nephrotoxicity and neurotoxicity, though it can cause other side effects, including abdominal pain, nausea, vomiting, anorexia, diarrhea, and bone marrow suppression. MMF as a monotherapy after the acute phase of liver transplant has shown similar results to glucocorticoids and CNI for prevention of chronic rejection and mortality [29, 30].

Mammalian target of rapamycin (mTOR) inhibitors (everolimus and sirolimus) inhibit the proliferation of lymphocytes. The use of mTOR inhibitors allows for immunosuppression while avoiding renal dysfunction and has shown potential benefit in patients undergoing liver transplant for HCV. Common complications of dyslipidemia and oral ulcers are typically easy to manage.

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