

Acute Liver Failure and the Neurological Complications: Theoretical Review

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Abstract
This study aimed at theoretically reviewing the Acute Liver Failure (ALF) and the Neurological Complications by reviewing the related studies in this area. As the problem of this study lies in exploring the neurological complications caused by Acute Liver Failure, and defining the causes of Acute Liver Failure, besides Diagnosing of Acute Liver Failure and the treatment processes of Acute Liver Failure. And the study concluded that the management of acute liver failure addresses the individual pathophysiological processes that occur in this condition. It improves chances of survival in patients awaiting liver transplantation and dramatically reduces the risk of death from neurological complications.

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1.1 Introduction

Acute liver failure (ALF) (*see figure 1*) is a rare but life-threatening critical illness that occurs most often in patients who do not have preexisting liver disease. With an incidence of fewer than 10 cases per million persons per year in the world, acute liver failure is seen most commonly in previously healthy adults in their 30s and presents unique challenges in clinical management. The clinical presentation usually includes hepatic dysfunction, abnormal liver biochemical values, and coagulopathy; encephalopathy may develop, with multi-organ failure and death occurring in up to half the cases (Bernal, William, and Julia, 2013).

Brain swelling is an important complication from acute liver failure (ALF), and it is a frequent cause of death in patients who suffer this complication. Some cases of acute liver failure spontaneously recover and some are so destructive that a liver transplant would be required to achieve survival. In either scenario, deterring brain swelling and optimizing brain perfusion when brain swelling does occur is a critical element in creating the option of good survivorship in patients with ALF (Jalan, Olde Damink, Deutz, Hayes & Lee, 2001).

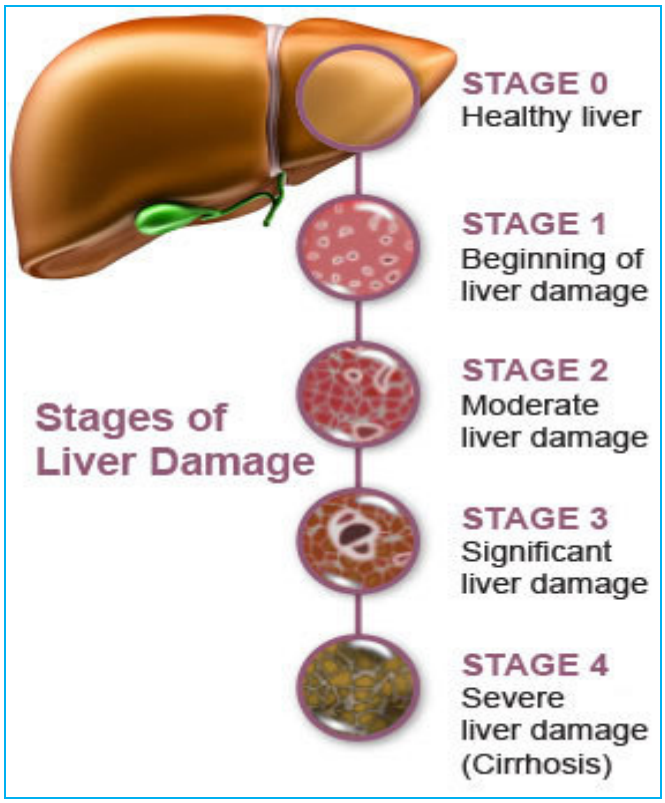

Figure (1): Stages of Liver damage

The rarity of acute liver failure, along with its severity and heterogeneity, has resulted in a very limited evidence base to guide supportive care (Lee, Stravitz & Larson, 2011).

However, rates of survival have improved substantially in recent years through advances in critical care management and the use of emergency liver transplantation (Bernal, Hyyrylainen & Gera, 2013).

In this review, the authors will outline the causes and clinical manifestations of acute liver failure and discuss current approaches to patient care (Bernal, Auzinger, Dhawan & Wendon, 2010).

One of the major causes of mortality in patients with acute liver failure (ALF) is the development of hepatic encephalopathy (HE) which is associated with increased intracranial pressure (ICP). High ammonia levels, increased cerebral blood flow and increased inflammatory response have been identified as major contributors to the development of HE and the related brain swelling. The general principles of the management of patients with ALF are straightforward. They include identifying the insult causing hepatic injury, providing organ systems support to optimize the patient's physical condition, anticipation and prevention of development of complications. Increasing insights into the pathophysiological mechanisms of ALF are contributing to better therapies (Mpabanzi & Jalan, 2012).

The outcomes of ALF in developed countries have improved dramatically in the last 25 years, owing to better understanding of its aetiopathogenesis, and the advent and availability of emergency LT for those who progress to severe liver failure. Parallel advancements and evolving standards of care in evidence-based practices in organ-system support in the liver units and the intensive care units (ICU) have played a vital complimentary role in managing these complex patients.

This has culminated in a significantly improved outcome for patients managed with medical treatment alone and those who received LT for the treatment of ALF, the latter showing a vast improvement in 1-year post LT survival rates from 36% in 2014 to approximately 80% currently in world (Privitera, Agarwal & Jalan, 2014).

Acute liver failure is the development of sudden, severe hepatic dysfunction from an acute insult to the liver, associated with the onset of hepatic encephalopathy and coagulation abnormalities. The most widely accepted definition from the American Association for the Study of Liver Diseases (AASLD) is “evidence of coagulation abnormality, usually an international normalized ratio above 1.5, and any degree of mental alteration (encephalopathy) in a patient without preexisting liver disease and with an illness of less than 26 weeks’ duration. A select group of patients, such as those with Wilson’s disease, vertically acquired hepatitis B virus, or autoimmune hepatitis, maybe be classified as having ALF despite the possibility of underlying cirrhosis if their disease has been recognized for less than 26 weeks (Arvind & Narayanan, 2017).

The terms *fulminant hepatic failure* and *sub-fulminant hepatitis* have been used for patients with ALF. Fulminant hepatic failure has been used to describe patients who develop hepatic encephalopathy within 8 weeks

of the onset of illness. Sub-fulminant hepatitis has been used to describe patients who develop hepatic encephalopathy more than 8 weeks but less than 26 weeks of the onset of illness. However, the term *acute liver failure* is most suitable as it encompasses all clinical presentations (Murali, Devarbhavi, Venkatachala, Singh & Sheth, 2014).

1.2 Problem statement

Acute liver failure (ALF) occurs when many of the cells in the liver die or become very damaged in a short period of time. This causes the liver to fail to work normally, and as a result, patients may develop a change in level of alertness or even coma. Because this condition develops so fast, getting care quickly is critical. One of the major causes of mortality in patients with acute liver failure (ALF) is the development of hepatic encephalopathy (HE) which is associated with increased intracranial pressure (ICP). Therefore, the problem of this study lies in exploring the neurological complications caused by Acute Liver Failure, defining the causes of Acute Liver Failure, besides Diagnosing of Acute Liver Failure and the treatment processes of Acute Liver Failure.

1.3 Classification of Acute liver failure (ALF)

O'Grady and colleagues (O'Grady, Schalm & Williams, 1993) classify ALF into 3 categories (*see figure 2*) based on the interval between the development of jaundice and the onset of encephalopathy.

1. Hyperacute liver failure: the onset of encephalopathy less than 7 days after the development of jaundice.
2. Acute liver failure: the onset of encephalopathy 8 to 28 days after the development of jaundice.
3. Sub-acute liver failure: the onset of encephalopathy more than 5 weeks but less than 12 weeks after the development of jaundice.

This classification may help to inform the etiology of the liver failure. For example, hyperacute liver failure is usually from acetaminophen toxicity or viral infections, while subacute liver failure is usually caused by an idiosyncratic drug-induced liver injury, autoimmune hepatitis or Wilson's disease. However, the classification does not have a prognostic significance that is distinct from the etiology of the illness itself.

TYPE	INTERVAL	CEREBRAL EDEMA	PROGNOSIS	CAUSES
HYPERACUTE	<7 days	common	moderate	Hep A,B Acetaminophen
ACUTE	8-28 days	common	poor	Non-A/B/C, drugs
SUBACUTE	29days-24 wks	rare	poor	Non-A/B/C, drugs

Figure (2): O'Grady Classification of Acute liver failure (ALF)

1.4 Etiologies of Acute liver failure (ALF)

Acute liver failure has many etiologies (*see table 1*). The most common cause of ALF in the developed countries is drug-induced liver injury. In developing countries, viral hepatitis is the predominant cause of ALF.[6] Emphasis on vaccination and improved public sanitation measures have reduced the incidence of infectious hepatitis in the developed counties.

Table (1): Etiologies of Acute liver failure (ALF)

Acetaminophen-induced liver injury
Drug-induced Liver injury (non-acetaminophen) - Antibiotics: amoxicillin-clavulanate, ciprofloxacin, nitrofurantoin, minocycline, dapsone, doxycycline, trimethoprim-sulfamethoxazole, efavirenz, didanosine, abacavir - Anti-epileptics: valproic acid, phenytoin, carbamazepine - Anti-tuberculosis drugs: isoniazid, rifampin-isoniazid, pyrizinamide - Miscellaneous: propylthiouracil, amitryptiline, statins, amiodarone, methotrexate, methyldopa - NSAID: Diclofenac, ibuprofen, indomethacin, naproxen - Herbs: ma huang, kava kava, herbalife
Viral hepatitis - Hepatitis A, B, C and E - CMV, EBV, herpes virus, varicella zoster viruse
Pregnancy specific liver diseases - Acute fatty liver of pregnancy - HELLP syndrome - Preeclampsia-associated liver diseases
Ischemic hepatitis - Systemic hypotension - Budd-Chiari syndrome
Reversible causes - Autoimmune hepatitis - Leptospirosis, hepatic amoebiasis, malaria, rickettsial diseases
Miscellaneous - Wilson's disease - Malignant infiltration - Mushroom poisoning

Identifying the etiology of ALF is important for defining the treatment approach and prognosis. For example, the timely use of antidotes for several forms of acute liver injury depends on identifying the inciting agent.

1.5 Signs and Symptoms of Acute Liver Failure

Symptoms of acute liver failure can be like those of a virus, such as upset stomach (nausea), a tired feeling all the time (fatigue) or vomiting. This can rapidly progress to jaundice (yellowing of the skin: *see figure 3*) and encephalopathy.

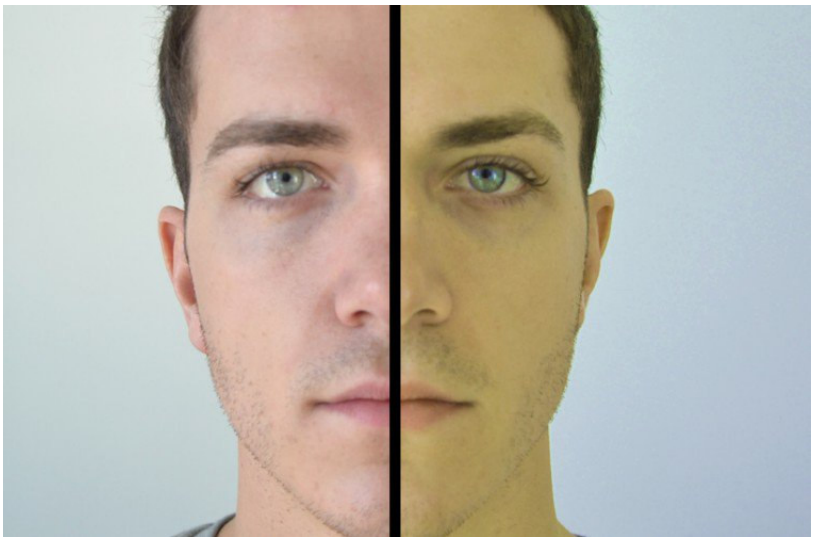

Figure (3): Yellowing of the skin

Encephalopathy is a condition in which the brain does not work properly. This happens when the liver is not able to break down or get rid of toxic products in the liver. (A liver that is working properly is able to break down toxins and carry them out of the liver.)

Encephalopathy always occurs when a child has sudden and severe liver failure. Infants up to 28 days old may not have many noticeable signs of encephalopathy, although they will have jaundice symptoms.

Infants older than 28 days may be irritable, have crying spells and can't be made to feel better, or they might want to sleep more during the day than at night. Older children may seem angry, have a hard time falling asleep, be forgetful or confused, or feel drowsy (Tripodi & Mannucci, 2011).

1.6 Causes of Acute Liver Failure

Acute liver failure is much less common in the developed world than in the developing world, where viral infections (hepatitis A, B, and E) are the predominant causes. Public health measures (e.g., vaccination and improved sanitation) are among the factors resulting in the reduced incidence of these infections in the United States and much of Western Europe, where drug-induced liver injury is the most common cause of acute liver failure (Bernal, William, & Julia, 2013).

1.6.1 Viruses

Globally, hepatitis A and E (*see figure 4*) infections are probably responsible for the majority of cases of acute liver failure, with rates of death of more than 50% reported from the developing world. Acute liver failure may also occur after hepatitis B (*see figure 4*) infection, which is a common cause in some Asian and Mediterranean countries. Particularly poor survival has been seen in patients with reactivation of previously stable subclinical infection with the hepatitis B virus without established chronic liver disease. This scenario is most common in patients with treatment-induced immunosuppression during or after therapy for cancer.

The identification of at-risk patients and the use of antiviral prophylaxis before the initiation of chemotherapy, immunotherapy, or glucocorticoid therapy are effective in prevention. Other rare viral causes of acute liver failure include herpes simplex virus, cytomegalovirus, Epstein–Barr virus, and parvoviruses (Ichai & Samuel, 2008).

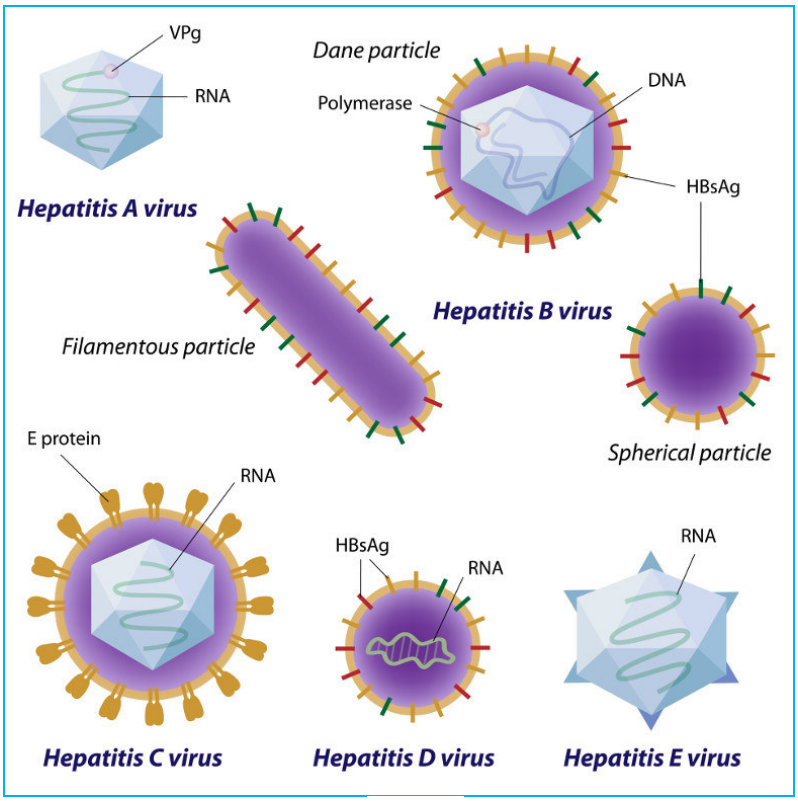

Figure (4): Hepatitis Viruses

1.6.2 Drug-Induced Liver Injury

Drug-induced liver injury is responsible for approximately 50% of cases of acute liver failure in the United States (Reuben, Koch & Lee, 2010).

Such injury may be dose-dependent and predictable, as exemplified by acetaminophen-induced hepatotoxicity, which is the most common cause of acute liver failure in the United States. It may also be idiosyncratic, unpredictable, and probably independent of dose.

Although acute liver failure after acetaminophen ingestion can occur after consumption of a single large dose, the risk of death is greatest with substantial drug ingestion staggered over hours or days rather than at a single time point. Acute liver failure is more common with late presentation to medical attention because of unintentional rather than deliberate self-poisoning. Malnourished patients and patients with alcoholism are at increased risk. Acetaminophen is also a potential cofactor for hepatic injury in patients taking the drug for the

relief of symptoms from hepatic illness of other causes (Khandelwal, James, Sanders, Larson & Lee, 2011).

Idiosyncratic drug-induced liver injury is rare, even among patients who are exposed to potentially hepatotoxic medication, and few patients with drug-induced liver injury have progression to encephalopathy and acute liver failure. Factors such as an older age, increased elevations in blood aminotransferase and bilirubin levels, and coagulopathy are associated with an increased risk of death (Bjornsson & Olsson, 2005).

1.6.3 Other Causes

Acute ischemic hepatocellular injury, or hypoxic hepatitis, may occur in critically ill patients with primary cardiac, circulatory, or respiratory failure. It may be caused by severe sepsis accompanied by signs of cardiac failure and major, transient elevations in blood aminotransferase levels (Lescot, Karvellas, Beaussier & Magder, 2012).

This condition primarily requires supportive cardiorespiratory management rather than specific interventions targeted at the liver injury. The prognosis depends on both the cause of hepatic hypoxia and the severity of liver injury. A similar liver-injury pattern may also be seen in drug-induced liver injury caused by recreational drugs such as MDMA (3,4-methylenedioxy-*N*-methylamphetamine, also known as ecstasy) or cocaine.

Other causes of acute liver failure are neoplastic infiltration, acute Budd–Chiari syndrome, heatstroke, mushroom ingestion, and metabolic diseases such as Wilson's disease. Acute liver failure that occurs during pregnancy may require early delivery of the fetus; management should be discussed with specialists at a referral center that has capabilities for both neonatal care and intensive management of the mother's liver disease.

In many cases, the cause of acute liver failure remains unknown, despite intensive investigation; potential causes include infection with a novel virus or exposure to a toxin. These cases often follow a subacute presentation, and rates of survival are poor without transplantation.

1.7 Complications

1.7.1 Cardiorespiratory Dysfunction

Circulatory dysfunction and hypotension are common in patients with acute liver failure and are often multifactorial in origin. The effective blood volume may initially be low owing to poor oral intake and fluid losses through vomiting and the development of vasodilatation, leading to a condition consistent primarily with hypovolemic shock.

Approaches to cardiovascular support in patients with acute liver failure do not differ markedly from those used in patients with other critical illnesses and focus on early restoration of circulating volume, systemic perfusion, and oxygen delivery. In patients who continue to have hypotension despite volume repletion, norepinephrine is the preferred vasopressor, with or without adjunctive use of vasopressin or vasopressin analogues. Myocardial function should be assessed by means of echocardiography, since hypoxic hepatitis may result from impaired cardiac function. Relative adrenal insufficiency may be present in patients with cardiovascular instability and is associated with increased mortality, but whether supplemental glucocorticoids improve survival is unclear (Etogo-Asse, Vincent & Hughes, 2012).

Although endotracheal intubation is often required to manage a reduced level of consciousness, respiratory dysfunction is uncommon early in the clinical course of acute liver failure. It is more common later, during the phase of hepatic regeneration or in association with nosocomial sepsis. The goals of respiratory care are similar to those in other critical illnesses; hyperventilation to induce hypocapnia may be used for emergent control of intracranial hypertension if the condition is associated with cerebral hyperemia, but sustained hyperventilation should be avoided. Spontaneous hyperventilation is averted by means of appropriate sedation and mandatory modes of ventilation.

1.7.2 Neurologic Conditions

The central place of encephalopathy in the definition of acute liver failure reflects its key prognostic importance, and its development reflects critically impaired liver function. However, depending on the speed with which encephalopathy develops, its presence has differential prognostic importance. In patients with subacute presentations, even low-grade encephalopathy indicates an extremely poor prognosis, whereas in hyperacute disease, high grades of encephalopathy may clearly indicate a poor prognosis. The goal of clinical strategies is to prevent the onset of encephalopathy, limit its severity when it develops, and reduce the risk of cerebral edema. Intracranial hypertension from severe cerebral edema remains a feared complication and is a leading cause of death worldwide among patients with acute liver failure. In many centers, intracranial hypertension is seen in only a minority of patients. However, among patients in whom intracranial hypertension develops, the rate of survival without transplantation remains poor.

The pathogenesis of encephalopathy and cerebral edema in acute liver failure is only partly understood; there is evidence that both systemic and local inflammation and circulating neurotoxins, particularly ammonia, play a role.35,36 Encephalopathy can be precipitated by infection and may occur in patients with low systemic blood pressure and vasodilatation. Inflammatory mediators may trigger or worsen encephalopathy through the

alteration of cerebral endothelial permeability to neurotoxins or the initiation of inflammatory responses and altered cerebral blood flow (Butterworth, 2011).

In liver failure, the normal detoxification of ammonia to urea is impaired, and levels of circulating ammonia increase. There is a close relationship between an elevated arterial ammonia level and the development of encephalopathy, with the risk of intracranial hypertension greatest when there is a sustained level of ammonia of 150 to 200 μmol per liter (255 to 340 μg per deciliter). Ammonia increases intracellular osmolarity through its cerebral metabolism to glutamine and induces changes in neurotransmitter synthesis and release and in mitochondrial function; altered cerebral function and swelling result. The speed of development of hyperammonemia is such that the usual osmotic compensatory mechanisms are ineffective in cases of acute liver failure — in contrast to cases of subacute or chronic disease, in which these compensatory mechanisms are functioning and intracranial hypertension is uncommon. Treatments that are used in chronic liver disease may be inappropriate in acute liver failure. In particular, the role of neomycin, rifaxamin, and other non-absorbable antibiotics is unclear, and treatment with lactulose is potentially deleterious.

Neurologic care focuses on the prevention of infection, the maintenance of stable cerebral perfusion, and the control of circulating ammonia and its cerebral metabolism. The drug l-ornithine–l-aspartate enhances ammonia detoxification to glutamine in muscle. However, in a large, randomized, controlled trial, the drug did not lower circulating ammonia levels, reduce the severity of encephalopathy, or improve survival rates among patients with acute liver failure (Acharya, Bhatia, Sreenivas, Khanal & Panda, 2009).

In patients with established encephalopathy, treatment is focused on minimizing the risk of intracranial hypertension by lowering cerebral ammonia uptake and metabolism through the use of sedation and prophylactic osmotherapy. In a randomized, controlled trial involving patients with high-grade encephalopathy, treatment with intravenous hypertonic saline solution delayed the onset of intracranial hypertension. Hypothermia affects multiple processes involved in the development of cerebral edema; by slowing body metabolism, it lowers systemic production of ammonia and cerebral uptake and metabolism, in addition to having hemodynamic stabilizing effects and reducing cerebral blood flow. Clinical observations have suggested that moderate hypothermia (32 to 33°C) improves hemodynamics and controls refractory intracranial hypertension, but a multicenter trial of prophylactic moderate hypothermia (34°C) in patients with high-grade encephalopathy did not show a delay in or reduced severity of intracranial hypertension. A pragmatic approach to temperature management is to avoid fever and maintain a core body temperature of 35 to 36°C.

The most effective mode of neurologic monitoring to guide therapy in patients with high-grade encephalopathy is not clear. Direct measurement of intracranial pressure is associated with uncommon but definite risks, particularly intracranial hemorrhage. In view of the potential complications and the decreasing incidence of intracranial hypertension, we monitor intracranial pressure only in patients with clinical signs or evidence of evolving intracranial hypertension. Other indicators of increased risk include an arterial ammonia concentration of more than 200 μmol per liter or a sustained level of at least 150 μmol per liter despite treatment, an age of 35 years or less, and concurrent renal or cardiovascular organ failure.

We treat sustained increases in intracranial pressure with a bolus of intravenous hypertonic saline (at a dose of 20 ml of 30% sodium chloride or 200 ml of 3% sodium chloride, keeping serum sodium at <150 mmol per liter) or mannitol (at a dose of 2 ml of 20% solution per kilogram of body weight, maintaining serum osmolality at <320 mOsm per liter). Hypothermia at 32 to 34°C may be used in patients with resistant cases, and a bolus of intravenous indomethacin (at a dose of 0.5 mg per kilogram) may be used when cerebral hyperemia is also present (Wendon & Lee, 2008).

1.7.3 Renal Dysfunction

Substantial renal dysfunction may occur in more than 50% of patients with acute liver failure. This complication is more common in the elderly and in patients with acetaminophen-induced acute liver failure. Although renal dysfunction is associated with increased mortality, the resolution of liver failure is accompanied by a return to preexisting levels in most cases. In patients requiring renal-replacement therapy, continuous rather than intermittent forms are generally used to achieve greater metabolic and hemodynamic stability. In addition to indications for the use of renal-replacement therapy in other forms of critical illness, such therapy may be used to control hyperammonemia and other biochemical and acid–base disturbances.

1.8 Treatment

1.8.1 Metabolic and Nutritional Support

The goal of treatment is to achieve overall metabolic and hemodynamic stability, with the reasonable, though yet unproven, idea that such therapy will greatly improve conditions for hepatic regeneration and minimize the risk of complications. In patients with acute liver failure, this type of support is provided as it is for other critically ill patients, with specific caveats. Patients with acute liver failure are at increased risk for hypoglycemia, which can be prevented by an intravenous glucose infusion. Large-volume infusions of hypotonic fluids, which may result in hyponatremia and cerebral swelling, should be avoided. Patients with acute liver failure have high energy

expenditure and protein catabolism, requiring nutritional support to preserve muscle bulk and immune function. Pragmatically, in patients with encephalopathy, we administer 1.0 to 1.5 g of enteral protein per kilogram per day while frequently measuring blood ammonia levels, with a lowered protein load for short periods in patients with worsening hyperammonemia or otherwise at high risk for intracranial hypertension.

1.8.2 Prognostic Evaluation

Early identification of patients who will not survive with medical therapy alone is of great practical importance in identifying potential candidates for transplantation. Since the progression of multi-organ failure results in deterioration in many patients who are awaiting transplantation, candidates for transplantation should be identified as quickly as possible (Simpson, Bates & Henderson, 2009).

Various prognostic evaluation systems, most of which have features derived from analyses of historical patient cohorts that were treated without transplantation, are in use worldwide. Although the details of these systems differ, they share common features.

The presence of encephalopathy is a key indicator, with further consideration given to the patient's age and the severity of liver injury, as assessed by the presence of coagulopathy or jaundice. The most well characterized evaluation system is the King's College Criteria, with meta-analyses confirming that these criteria have clinically acceptable specificity but more limited sensitivity. To address these limitations, a wide variety of alternate prognostic systems and markers have been proposed. To date, none have achieved universal acceptance, though the need for improved identification of candidates for transplantation is clear.

1.8.3 Transplantation

Although transplantation is a treatment option for some specific causes of acute liver failure, such treatment is not universally available, and less than 10% of liver transplantations are performed in patients with acute liver failure. In such patients, especially those who are at risk for intracranial hypertension, intraoperative and postoperative management is challenging, and rates of survival are consistently lower than those associated with elective liver transplantation. However, outcomes have improved over time, with registry data reporting current rates of survival after transplantation of 79% at 1 year and 72% at 5 years. Most deaths after transplantation for acute liver failure occur from infection during the first 3 postoperative months. The risk of death is higher among older recipients and among those receiving older or partial grafts or grafts from donors without an identical ABO blood group. Early impaired liver-graft function is poorly tolerated in critically ill patients and predisposes them to intracranial hypertension and sepsis (Bernal, Cross & Auzinger, 2009).

1.9 Conclusion

A multimodal approach to the management of acute liver failure addresses the individual pathophysiological processes that occur in this condition. It improves chances of survival in patients awaiting liver transplantation and dramatically reduces the risk of death from neurological complications.

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