Contemporary Liver Transplantation
DOI 10.1007/978-3-319-05543-5_16-1

Fulminant Hepatic Failure: Diagnosis and Management

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Abstract

Fulminant hepatic failure (FHF) is a condition resulting in rapid deterioration of liver function often followed by a cascade of fatal consequences. This rare syndrome is incited by a catastrophic insult to the liver. The causes of FHF can be classified into six general categories: viral infections, drugs and toxins, and cardiovascular, metabolic, miscellaneous, and indeterminate causes. FHF can result in sudden onset of hepatic encephalopathy, coagulopathy, jaundice, and multisystem organ failure. An improvement in the morbidity and mortality associated with FHF has been seen over the last several years with an advanced understanding of the mechanisms of injury, early initiation of intensive medical therapy, and the use of orthotopic liver transplant. This chapter will review the topic of FHF with a focus on the etiologies and clinical management.

Keywords

Acute liver failure; Acute liver injury; Hepatic failure; Acetaminophen-induced liver injury; Liver support systems; Multisystem organ failure

Introduction

Fulminant hepatic failure (FHF), also known as acute liver failure, is a rare condition resulting in rapid deterioration of liver function often followed by a cascade of devastating consequences. The syndrome is incited by a catastrophic insult to the liver in an otherwise healthy individual. This liver injury can result in sudden onset of hepatic encephalopathy, often in association with coagulopathy, jaundice, and multisystem organ failure. FHF is a true medical emergency and carries a very high mortality rate. An improvement in the morbidity and mortality outcomes associated with FHF has not been seen until recently with advanced understanding, intensive medical therapy, and monitoring and the use of orthotopic liver transplant (Ostapowicz et al. 2002). The goal of this chapter is to review the topic of FHF with a focus on the etiologies and clinical management. Particular attention will be paid to the critical care management, the role of liver transplantation, and experimental therapies.

Definitions

The term “fulminant hepatic failure” was first introduced more than 30 years ago by Trey et al. to describe the onset of altered mental status within 8 weeks of initial symptoms in an individual with no previous history of liver disease (Sass and Shakil 2003; Polson and Lee 2005). Based on this, the most widely

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DOI 10.1007/978-3-319-05543-5_16-1

accepted definition includes evidence of coagulation abnormality, usually an INR ≥1.5, any degree of mental alteration in a patient without preexisting cirrhosis, and illness duration of <26 weeks (O'Grady et al. 1989; Sass and Shakil 2003). Patients with Wilson disease, vertically acquired hepatitis B infection (HBV), or autoimmune hepatitis may be included despite the possibility of cirrhosis if their disease has been recognized for <26 weeks.

Various modifications to the original use of the term have occurred. It has been suggested that the term "fulminant hepatic failure" be reserved for cases in which encephalopathy develops within 2 weeks of the onset of jaundice and that "subfulminant hepatic failure" be applied to cases in which encephalopathy develops beyond 2 weeks. Other terms signifying length of illness such as hyperacute (<1 week), acute (8–28 days), and subacute (29 days to 12 weeks) have been proposed (Hoofnagle et al. 1995; Sass and Shakil 2005). This classification reflects differences in survival rate for these groups with the best prognosis begin in the hyperacute group, possibly because most of these are due to acetaminophen toxicity (Ostapowicz et al. 2002).

Epidemiology

The actual incidence of FHF has never been fully established. The International Classification of Diseases, Ninth Revision (ICD-9), has no specific billing code for FHF which has limited the use of databases to derive an estimate (Hoofnagle et al. 1995; Lee et al. 2008). However, it is thought that FHF affects about 2,000 patients annually, as determined by evaluation of reports from liver transplant centers, population surveillance programs, and various counties (Lee et al. 2008). Additionally, based on a FHF workshop in 1995, it is thought that FHF represents 6 % of liver-related deaths and accounts for ~7 % of liver transplants (Lee et al. 2008).

Etiology

The etiology of FHF can result from a wide variety of causes and is often one of the best predictors of prognosis (Ostapowicz et al. 2002). Additionally, the etiology of FHF varies depending on patient demographics, geographic location, and timing of the event. The causes of FHF can be classified into six general categories: viral infections, drugs and toxins, and cardiovascular, metabolic, miscellaneous, and indeterminate causes (Polson and Lee 2005). In a historical series from the 1980s, viral hepatitis (predominately hepatitis B) was the most common etiology in the United States (USA); however, more recent data from the US Acute Liver Failure Study Group has identified acetaminophen (46 %), indeterminate (15 %), and idiosyncratic drug reactions (12 %) as the most frequent causes (Lee et al. 2008; Navarro 2009; Lee 2012).

Causes of FHF

A. Viral
HAV, HBV ± HDV, HEV, HSV, CMV, EBV, HVZ, adenovirus, hemorrhagic fever viruses
B. Drugs and toxins
Examples: Acetaminophen, CCl_4, yellow phosphorus, *Amanita phalloides*, sulfonamides, tetracycline, herbal remedies, halothane, INH, rifampicin, valproic acid, NSAIDs, disulfiram
C. Vascular
Right heart failure, Budd-Chiari syndrome, veno-occlusive disease, shock liver (ischemic hepatitis), heat stroke

(*continued*)

DOI 10.1007/978-3-319-05543-5_16-1

D. Metabolic
Acute fatty liver of pregnancy, Wilson disease, Reye's syndrome, galactosemia, hereditary fructose intolerance, tyrosinemia
E. Miscellaneous
Malignant infiltration (liver metastases, lymphoma), autoimmune hepatitis, sepsis
F. Indeterminate
Includes primary graft nonfunction in liver-transplanted patients

Abbreviations: HAV hepatitis A virus, *HBV* hepatitis B virus, *HDV* hepatitis D virus, *HEV* hepatitis E virus, *HSV* herpes simplex virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *HVZ* herpes varicella zoster virus, CCl_4 carbon tetrachloride, *INH* isoniazid, *NSAIDs* nonsteroidal anti-inflammatory drugs

Viral Hepatitis

Several viruses have been associated with FHF, particularly hepatitis A, B, C, D, and E. In addition, acute liver failure can be seen with herpes simplex virus, varicella zoster virus, Epstein-Barr virus, adenovirus, and cytomegalovirus (Lee et al. 2008; Lee 2008). Hepatitis serological testing should be done for identification of acute viral infection even when another possible etiology is identified. Acute viral hepatitis causes hepatic failure in ~1 % of cases of hepatitis A and B. FHF due to acute hepatitis C infection remains controversial and at most is very uncommon and occurs in <1 % of patients (Farci et al. 1996; Schiodt et al. 2003).

Overall during the past decade, viral hepatitis has become an infrequent cause of FHF in the USA, currently making up about ~10 % of cases (hepatitis B ~7 % and hepatitis A 3 %) (Ostapowicz et al. 2002). The role of nucleos(t)ide analogues in the management of FHF due to hepatitis B in the absence of immunosuppression is debated. Although several articles have suggested, based on case reports or historical controls, that nucleoside analogues are of value, a recent controlled trial by Seremba et al. (2007) has disputed this thought (Reshef et al. 2000; Teo et al. 2001; Tillmann et al. 2006; Kumar et al. 2007b; Liaw et al 2012).

Hepatitis B carriers undergoing immunosuppressive or cancer chemotherapy may experience reactivation of hepatitis B virus (HBV) replication, and this can lead to FHF. Prophylactic antiviral therapy is recommended for HBV carriers at the onset of cancer chemotherapy or for a finite course of immunosuppressive therapy (Liaw et al 2012). A high viral load at baseline is the most important risk factor for HBV reactivation.

In an endemic area such as Russia, Pakistan, Mexico, or India, hepatitis E remains an important cause of hepatic failure, particularly in the context of pregnancy (Jayanthi and Udayakumar 2008). The overall case fatality rate for hepatitis E is 0.5–3 % with mortality rate rising to 15–25 % in pregnant women (CDC 1987). Moreover, vertical transmission of hepatitis E from women with acute infection results in FHF in more than half of neonates. Certain hepatitis E genotypes have also been associated with more severe disease. Fortunately, HEV has not been an important cause of fulminant hepatitis in healthy individuals in the USA. From recent studies in the USA, it has been noted that infections with HEV can lead to hepatic decompensation in patients with preexisting liver disease and recipients of solid organ transplants and cause the development of infection (Hamid et al 2002; Kumar et al. 2007a; Kamar et al. 2008; Khuroo and Khuroo 2008). Therefore, pathogens like HEV should be considered early in the workup as potential viral syndromes in FHF and transplant recipients.

Herpes viruses, Epstein-Barr virus, varicella zoster virus, and others occasionally cause FHF usually in the setting of immunosuppression. Pregnancy has been implicated previously as increasing the risk that herpes virus infection will have a fulminant course (Peters et al. 2000). Obtaining a liver biopsy can be helpful in making a diagnosis in these cases. Treatment should be initiated with acyclovir in suspected or documented cases.

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DOI 10.1007/978-3-319-05543-5_16-1

Acetaminophen-Related Injury

No prescription drug is known to have caused as many deaths and near-fatal episodes as acetaminophen. Over the past two decades, the number of cases reported in the USA has increased as a percentage of the number of overall cases of FHF. While this may reflect a decline in the incidence of viral hepatitis A and B, it probably represents an increase in the number of cases as well. Acetaminophen overdose is the number one cause of FHF in the USA, Great Britain, and most of Europe, accounting for nearly 50 % of all cases of US acute liver injury. Fortunately, the prognosis for acetaminophen-induced liver failure is somewhat better than for most other causes but still carries 30 % mortality, making it linked to more deaths in the US Acute Liver Failure Registry than any other etiology (Ritt et al. 1969; Lee 2008). Liver injury due to acetaminophen is generally more commonly seen after unintentional than intentional overdose (Wolf et al. 2012).

The development of liver failure from acetaminophen is dose dependent; hepatic failure is more likely with ingested dosages >150 mg/kg. Various risk factors increase the probability of acute liver damage even at therapeutic doses of acetaminophen. These factors include: alcoholic abuse, malnutrition, and concurrent use of narcotic analgesics compounded with acetaminophen. Liver damage from acetaminophen leads to a characteristic pattern of pericentral necrosis due to cytochrome P450-mediated oxidative metabolism of acetaminophen to the highly reactive, intermediate metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI) (Moyer et al. 2011). Accumulation of NAPQI leads to cell death and hepatocellular necrosis. *N*-Acetylcysteine (NAC) is established as a treatment for acetaminophen-induced hepatotoxicity (Heard and Green 2012). NAC acts by replenishing glutathione that is depleted and detoxifies NAPQI. In addition, excessive NAC also provides substrates for hepatic ATP synthesis, thus supporting mitochondrial energy metabolism. The latter pathway may be particularly important in delayed administration of NAC. The administration of NAC should be given as early as possible but still may be of value 48 h or more after ingestion (Harrison et al 1990). Allergic reactions may be treated with antihistamines or epinephrine (Vale and Proudfoot 1995).

Establishing the diagnosis of acetaminophen poisoning is often easy if a clear history can be obtained. Obstacles that often delay the correct diagnosis include failure of the first medical contact to not elicit the correct history, the patient's altered mentation at the time of interview, covering up detail by the patient because of embarrassment, and simply ignorance of any risk involved from an over-the-counter preparation. The parent compound, acetaminophen, can readily be measured by several different methods, and these tests are available in most hospital laboratories. Despite this, acetaminophen levels are often undetectable at the time of presentation with liver failure due to delay in presentation. A characteristic pattern of very high enzyme elevations is observed in most cases in association with a low bilirubin, the classic hyperacute injury pattern which can suggest acetaminophen as the etiology (Lee 2008).

Drug Reactions

Unlike FHF due to acetaminophen, which is dose related, FHF due to idiosyncratic drug reactions (known as drug-induced liver injury [DILI]) is dose independent. DILI usually occurs within six months of drug initiation (O'Grady et al. 1993). Idiosyncratic drug reaction results in ~12 % of FHF cases (Lee 2012). Drugs commonly implicated in cases of DILI include antibiotics, nonsteroidal anti-inflammatory drugs, and anticonvulsants. Herbal medications and dietary supplements have also been associated with acute liver failure. Idiosyncratic drug reactions are likely the result of a specific alteration (genetic polymorphisms) in the metabolizing enzymes leading to a toxic by-product. The reaction is further enhanced by the patient's own innate immune response (Kaplowitz 2002,2005; Navarro and Senior 2006; Chang and Schiano 2007). In general, DILI cases evolve with a subacute course with lower aminotransferase levels than acetaminophen and much higher bilirubin. There are a few exceptions, particularly the quinolone antibiotics such as ciprofloxacin (Fuchs et al. 1994; Clay et al. 2006). Establishing the diagnosis is equally,

DOI 10.1007/978-3-319-05543-5_16-1

if not more, difficult with DILI in comparison to acetaminophen. Unfortunately, DILI-induced FHF cases carry a much poorer prognosis with less than 30 % spontaneous survival as compared with >65 % spontaneous survival following acetaminophen-induced FHF.

Cardiovascular Causes

Hypoperfusion of the liver can result in ischemic hepatitis and FHF in extreme cases. Hypoperfusion can result from systemic hypotension due to cardiac dysfunction, sepsis, Budd-Chiari syndrome (hepatic vein thrombosis), veno-occlusive disease, or the use of vasoconstricting drugs such as cocaine or methamphetamine. Documented hypotension is not always found. Simultaneous onset of renal dysfunction and muscle necrosis may be noted (Kisloff and Schaffer 1976; Hoffman et al. 1990; Silva et al. 1991; Taylor et al. 2012). Aminotransferase levels will be markedly elevated and respond rapidly to stabilization of the circulatory problem. Cardiovascular support is the treatment of choice in this setting.

The Budd-Chiari syndrome (acute hepatic venous outflow tract obstruction) is an uncommon cause of FHF accounting for about 1 % of cases (Menon et al. 2004; DeLeve et al. 2009). Right upper quadrant pain, hepatomegaly, and fluid retention characterize the initial clinical picture and may help distinguish this syndrome from other forms of FHF in which the liver parenchyma is collapsed and not tender. Therapeutic strategies have included anticoagulation, use of transjugular intrahepatic portocaval shunting, or transplantation (Kuo et al. 1996; Shrestha et al. 1997; Ryu et al. 1999). The ability to manage the cause of ischemia will determine the outcome for these patients as transplantation is rarely needed (Taylor et al. 2012).

Metabolic Causes

Metabolic disorders like Wilson disease (WD), HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, acute fatty liver of pregnancy, Reye's syndrome, galactosemia, hereditary fructose intolerance, and tyrosinemia may also cause FHF.

WD accounts for 6–12 % of all patients with FHF who are referred for emergency liver transplantation. FHF due to WD occurs predominantly in young women at a ratio of about 4:1 (EASL 2012). Diagnostic tests for WD should include ceruloplasmin, serum and urinary copper levels, total bilirubin/alkaline phosphatase ratio, slit lamp examination for Kayser-Fleischer rings, and quantitative hepatic copper levels obtained by liver biopsy when possible (Roberts and Schilsky 2008). High bilirubin (>20 mg/dL) and low alkaline phosphatase levels (including undetectable levels) due to profound hemolytic anemia help with its recognition. Liver transplantation is the only effective option for those with WD who present with FHF. One-year survival following liver transplantation ranges from 79 % to 87 %, with good long-term survival (Roberts and Schilsky 2008).

When a pregnant woman presents with FHF, some specific etiologies must be considered. The hepatic damage of HELLP syndrome is proposed to result from disordered placentation, leading to either the circulation of antiangiogenic factors and endothelial dysfunction, or cytokine production causing the characteristic periportal hemorrhage and fibrin deposition (Sánchez-Bueno et al. 2012). Acute fatty liver of pregnancy is a sudden catastrophic illness occurring most frequently in the third trimester, when mitochondrial dysfunction due to maternal and fetal fatty acid β-oxidation defects resulting in microvesicular fatty acid accumulation in hepatocytes (Song et al. 2012). There is an overlap of these two clinical syndromes, and they play a major role in the pathogenesis of preeclampsia and proteinuria. Early recognition of these syndromes and prompt delivery of care are critical in achieving good outcomes. Failure to recover from the illness should prompt urgent listing for liver transplantation (Bacq 2011).

DOI 10.1007/978-3-319-05543-5_16-1

Miscellaneous Causes

Some rare causes of FHF include heat shock, protracted seizures, amatoxin-containing mushroom poisoning, autoimmune hepatitis, and malignant infiltration (Broussard et al. 2001; Chavez-Tapia et al. 2007; Garcin et al. 2008; Magdalan et al. 2010).

Amatoxins are found in a variety of poisonous mushrooms (e.g., *Amanita phalloides*, *Amanita virosa*, and *Galerina autumnalis*) and are responsible for more than 90 % of fatalities caused by mushroom poisoning worldwide. The onset of signs and symptoms >6 h after mushroom consumption should increase suspicion for amatoxin-containing mushroom poisoning. The natural history of amatoxin poisoning has been grouped into three phases: gastrointestinal phase (vomiting and diarrhea), latency phase, and FHF phase (48–72 h after ingestion). In addition to urgent evaluation for liver transplant, therapy with amatoxin uptake inhibitor therapy such as intravenous silibinin or continuous infusion of penicillin G with oral silymarin should be started (Broussard et al. 2001; Magdalan et al. 2010).

FHF occurs in a small fraction of autoimmune hepatitis patients. The clinical picture is in the form of a subacute presentation, with intermediate elevation of enzyme levels and high bilirubin concentrations. Presence of autoantibodies and a compatible picture on biopsy help to confirm the diagnosis. Some cases of autoimmune hepatitis may respond well to steroid therapy, and others may still require transplantation (Chavez-Tapia et al. 2007).

The most common forms of malignant infiltration implicated in FHF are lymphoma, breast cancer, and melanoma (Dellon et al. 2006). It must be remembered that this is an extremely rare cause of FH-F. Diagnosis should be made by imaging and biopsy, and treatment appropriate for the underlying malignant condition is indicated.

Indeterminate Causes

About 15–20 % of FHF occurs without a cause being determined. These cases can include unrecognized idiosyncratic drug toxicity, non-A–E viral hepatitis, and possibly unrecognized metabolic and genetic diseases. The reasons for this misdiagnosis may include failure to obtain an adequate history, failure to perform the definitive diagnostic tests, or simply due to some other rare diagnoses. About 20 % of FHF of indeterminate cause is related to obscure acetaminophen toxicity as found through detection of acetaminophen-protein adducts, the by-products of the toxic reaction (Khandelwal et al. 2011).

Clinical Features and Management

As described previously in this chapter, the causes of FHF are variable; however, they all share the common mechanism of acute hepatocyte death and its resulting sequel. In most cases, FHF will result in multisystem organ failure with the development of coma. The general management of a patient with FHF includes ensuring the patient is being cared for in an intensive care setting at a center with an active liver transplantation program, monitoring for worsening liver failure, treating complications, and providing nutritional support (Fig. 1) (O'Grady et al. 1993). The mortality rate of FHF is as high as 40–50 %, depending on the cause and therapeutic management (Wang et al. 2013). In this section the various complications of FHF and their management will be reviewed.

Encephalopathy and Cerebral Edema

Cerebral edema presents clinically as hepatic encephalopathy and may vary from subtle changes in affect, insomnia, and difficulty with concentration (stage 1) to deep coma (stage 4) (Ede and Williams 1986; Hoofnagle et al. 1995). Cerebral edema is a common neurologic component of FHF with the vast majority of cases progressing to stage 4 (Table 1) (Ede and Williams 1986). Cerebral edema leading to intracranial

DOI 10.1007/978-3-319-05543-5_16-1

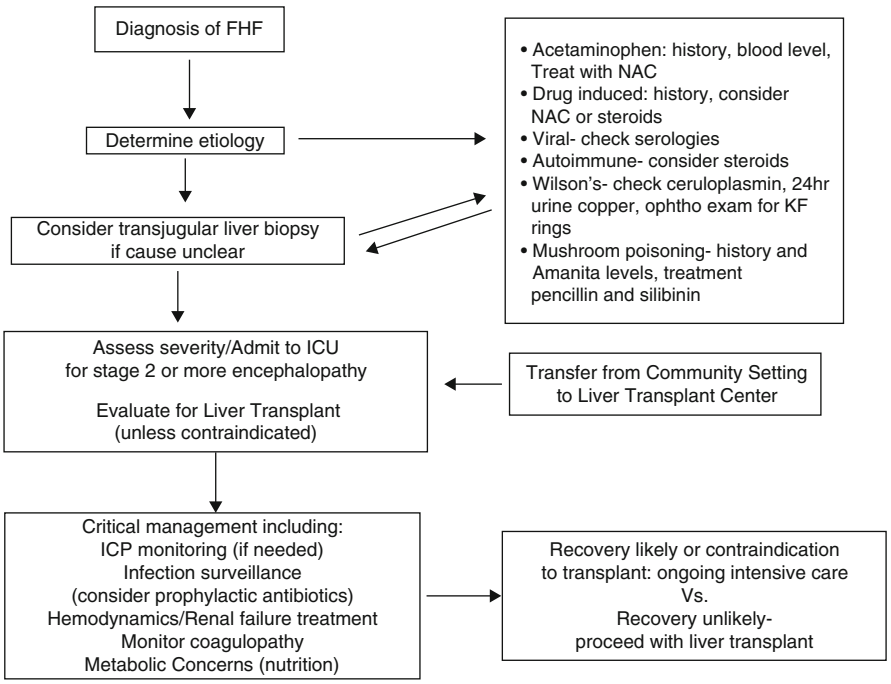

Fig. 1 Algorithm for management of FHF. *Abbreviations: FHF* fulminant hepatic failure, *ICP* intracranial pressure, *KF* Kayser-Fleischer

Table 1 Stages of hepatic encephalopathy

Stage	Mental status	Tremor	EEG
I	Euphoria; occasionally depression; fluctuant mild confusion; slowness of mentation and affect; untidy; slurred speech; disorder in sleep rhythm	Slight	Usually normal
II	Accentuation of stage I; drowsiness; inappropriate behavior; able to maintain sphincter control	Present (easily elicited)	Abnormal; generalized slowing
III	Sleeps most of the time but is arousable; speech is incoherent; confusion is marked	Usually present if patient can cooperate	Always abnormal
IV	Not arousable; may or may not respond to painful stimuli	Usually absent	Always abnormal

Adapted from Sass and Shakil (2003) and Trey and Davidson (1970)

hypertension (ICH) is one of the major causes of morbidity and mortality in patients with FHF, accounting for the cause of death in the majority of patients due to brain herniation (Gazzard et al. 1975; Ede and Williams 1986; Pathikonda and Munoz 2010). The pathogenesis of cerebral edema and ICH in FHF appears to be multifactorial. Ammonia is converted in brain white matter to active glutamine, which osmotically causes cerebral edema (Bjerring et al. 2009). Other factors such as impaired cerebral blood flow, impaired autoregulation, systemic inflammatory response, and ischemic injury have also been proposed as a mechanism for the formation of cerebral edema.

Basic interventions for the management of cerebral edema should be applied universally in patients with high-grade hepatic encephalopathy. These interventions include elevation of the head of the bed to 30°, maintenance of a neutral neck position, endotracheal intubation, minimizing painful stimuli, and control of arterial hypertension (Frontera and Kalb 2011; Wang et al. 2013). Propofol is a reasonable choice for sedation because it may protect from worsening ICH. Intracranial pressure (ICP) monitoring by placement of epidural, subdural, or parenchymal catheter should be considered in FHF patients with high-

DOI 10.1007/978-3-319-05543-5_16-1

grade hepatic encephalopathy, in centers with expertise in ICP monitoring, as well as in patients awaiting liver transplantation (Lidofsky et al. 1992). ICP monitoring can detect elevations in ICP to direct interventions, which may preserve brain perfusion and prevent cranial herniation. Generally, the goal of therapy in FHF is to maintain ICP less than 20 mmHg and cerebral perfusion pressure (CPP) more than 60 mmHg. CPP less than 40 mmHg for more than 2 h indicates reduced neurological blood flow to maintain intact brain function and could lead to poor posttransplantation prognosis (Hoofnagle et al. 1995). There are also several tools available for *indirect* measurement of cerebral blood flow, including jugular bulb catheter, transcranial Doppler, and xenon-enhanced computed tomography (Sundaram and Shaikh 2011). Factors that increase ICP need to be avoided and include hypercapnia, hyponatremia, frequent movements, neck vein compression, fluid overload, fever, hypoxia, coughing, sneezing, seizures, and endotracheal suctioning.

In patients with persistently elevated ICP, osmotic therapy with mannitol can be considered. Mannitol reduces ICP by osmotically drawing water from the brain parenchyma into the intravascular space (Larsen and Bjerring 2011). Hypothermia, although controversial, is thought to have some benefit in reducing ICP as it lowers brain energy metabolism, reduces arterial ammonia concentration and extraction of ammonia by the brain, and reverses systemic inflammatory reactions therefore reducing cerebral edema (Jalan et al. 1999). In addition to its neurological effect, studies have shown that hypothermia results in significant improvement of cardiovascular hemodynamics, as manifested by increased mean arterial pressure (MAP) and systemic vascular resistance, and reduction in noradrenaline requirements (Jalan et al. 1999; Vaquero and Blei 2004). Potential hazards include cardiac arrhythmias, infection, and bleeding complications (Stravitz and Larsen 2009). Therapeutic hypothermia (cooling to a core temperature of 34–35 °C) is probably well tolerated and effective, but randomized, controlled trials are needed to confirm the benefits of hypothermia before it is recommended routinely. Additionally, there may be challenges with the re-warming of patients.

Cardiovascular Dysfunction

FHF is characterized by a hyperdynamic circulation with high cardiac output, low mean arterial pressure (MAP), and low systemic vascular resistance (Siniscalchi et al. 2010). Due to poor oral intake, transudation of fluid into the extravascular space, and possibly gastrointestinal bleeding, most patients are volume depleted and require initial fluid resuscitation. The initial treatment of hypotension should involve intravenous infusion of normal saline and a volume challenge is recommended (Stravitz and Kramer 2009; Stravitz and Larsen 2009; Siniscalchi et al. 2010; Lee et al. 2011). With progressive renal failure and pulmonary edema, a Swan-Ganz catheter may be required to guide further management. The MAP should be maintained in a narrow range to achieve a CPP of 60–80 mmHg to prevent cerebral hypoperfusion and further cerebral hyperemia. Noradrenaline, with fewer β-adrenergic side effects, could increase hepatic blood flow in parallel with minimizing tachycardia and is often the preferred vasopressor (Stravitz and Kramer 2009). Patients with uncorrectable hypotension after volume repletion and vasopressor administration should be evaluated for adrenal insufficiency, which occurs frequently in the setting of liver failure (O'Beirne et al. 2007). Adrenal insufficiency can be corrected with stress doses of corticosteroids.

Renal Failure

The incidence of acute renal failure in FHF is as high as 50–70 %. Direct drug nephrotoxicity, hepatorenal syndrome, and acute tubular necrosis due to ischemia from hypotension are among the most important associated disease entities (Bihari et al. 1986). Management includes avoidance of nephrotoxic agents, treatment of infection, maintenance of adequate renal perfusion, and renal replacement therapy. Early targeted volume replacement and vasoactive agent administration are essential to avoid arterial hypotension and ensure adequate renal perfusion. Worsening renal failure needs to be addressed with renal

DOI 10.1007/978-3-319-05543-5_16-1

replacement therapy. Continuous renal replacement therapy is recommended, as most patients with FHF tolerate intermittent hemodialysis poorly because of circulatory instability, precipitous fluid shifts, and a rise in ICP (Davenport et al. 1993).

Coagulopathy

The liver plays a central role in the synthesis of the majority of coagulation factors and many inhibitors (Pereira et al. 1996). The principal hematologic abnormalities seen in FHF include platelet dysfunction and reduced levels of anticoagulant proteins (protein C/S or antithrombin III) and procoagulation factors (II, V, VII, IX, and X) due to failure of synthesis and consumption (Pereira et al. 1996). This causes a prolongation in the prothrombin time, as well as a tendency to develop thrombotic events such as disseminated intravascular coagulation (Langley and Williams 1992).

Bleeding generally occurs from superficial mucosal lesions, especially gastric erosions. Administration of proton pump inhibitors can decrease the risk of gastric mucosal bleeding. In general, infusion of fresh frozen plasma is indicated only for control of active bleeding or during invasive procedures. Cryoprecipitate is recommended in patients who have significant hypofibrinogenemia (<1 g/L). Platelet transfusion is indicated only to aid in controlling active bleeding or during invasive procedures if the count is $<50 \times 10^9$/L or prophylactically if $<20 \times 10^9$/L (Munoz et al. 2009). Finally, vitamin K (5–10 mg subcutaneously) should be considered in all patients with FHF, because its deficiency can occur in >25 % of patients.

Metabolic Abnormalities

Metabolic abnormalities in FHF include hypoglycemia, lactic acidosis, and electrolyte derangements. Patients are prone to develop hypoglycemia because hepatocyte necrosis causes glycogen depletion and defective glycogenolysis and gluconeogenesis. Rapid development of hypoglycemia can confound hepatic encephalopathy and contribute to poor ICP control (Schneeweiss et al. 1993). Serum phosphate, potassium, and magnesium are frequently low, requiring repeated supplementation. Owing to the hypercatabolic state of FHF, nutrition is vital and enteral feedings should be initiated early. If enteral feeding is contraindicated, parenteral nutrition may be considered on a case-by-case basis (Montejo González et al. 2011).

Infections and Sepsis

Infections, particularly bacterial respiratory and urinary tract, develop in as many as 80 % of patients with FHF (Wyke et al. 1982; Sass and Shakil 2005). FHF patients have enhanced susceptibility to infection because of the presence of indwelling lines and catheters, dysfunction of monocytes, impaired complement system, and impaired neutrophil and Kupffer cell function (Leber et al. 2012). Infectious organisms are mainly Gram-negative enteric bacilli, Gram-positive cocci, and *Candida* species (Rolando et al. 1996). In addition to infection inhibiting hepatic regeneration, it is associated with progression of hepatic encephalopathy and renal failure, reduces successful rate of liver transplantation, and increases mortality in FHF (Rolando et al. 1996). One must have a high index of suspicion for infection and obtain surveillance cultures in addition to chest radiographs if there is any unexpected deterioration in the patient's status. Empirical antibiotics should be considered upon presentation (Leber et al. 2012).

Role of Liver Transplantation

Liver transplantation (OLT) remains the only definitive treatment for patients with FHF and irreversible liver injury (Starzl et al. 1982). Before the use of OLT in the 1960s, approximately 15 % of patients with

DOI 10.1007/978-3-319-05543-5_16-1

FHF survived. With continued surgical refinement and better immunosuppressive agents, OLT for FHF offers about a 65 % survival but has been reported as high as 80 % (Ascher et al. 1993; Sass and Shakil 2005). In light of this, rapid evaluation for transfer to a transplantation center and consideration for liver transplantation are mandatory before contraindications develop. All patients meeting criteria for OLT may be listed as United Network for Organ Sharing Status 1A immediately upon arrival to the transplant center. Contraindications to OLT include: extrahepatic malignancy, uncontrolled extrahepatic sepsis, multisystem organ failure, irreversible brain damage, and unresponsive cerebral edema with a sustained elevation of ICP (>50 mmHg) and a decrease in CPP (<40 mmHg) (Sass and Shakil 2005).

The key factors affecting post-OLT survival are the severity of the pretransplantation illness of the recipient and the quality of the graft used (Bernal and Wendon 2004; Barshes et al. 2006). The more severe the encephalopathy at the time of surgery or severity of multisystem organ failure, the less likely that the surgery will be successful. Several risk factors have been associated with a decreased likelihood of patient survival after OLT, including history of life support, recipient age >50 years old, recipient BMI > =30 kg/m^2, and serum creatinine >2.0 mg/dL (Schiodt et al. 1999; Farmer et al. 2003). The additional risk to post-OLT patient survival posed by each of these risk factors was additive in terms of etiology; acetaminophen toxicity tends to have a more favorable outcome than do viral hepatitis or drug reactions (Farmer et al. 2003). The main causes of death in the posttransplantation period are sepsis and multiorgan failure (Farmer et al. 2003).

Role of Experimental Therapies and Liver Support Systems

Due to the low incidence and high mortality of FHF, few therapies have been evaluated in a controlled study. Besides the few etiologies of FHF with immediate and specific treatment [i.e., acetaminophen (NAC), HSV (acyclovir), Amanita (silibinin)], most other liver-focused therapies have proven ineffective. In this section, the two therapies which have shown the most promise, NAC and liver replacement therapy, will be reviewed.

Use of *N*-Acetylcysteine

It is well studied and known that NAC when given within the first 24 h after acetaminophen overdose can prevent or minimize liver damage (Hamlyn et al. 1978; Prescott and Critchley 1983). Promising research has found that treatment with NAC may benefit patients with other forms of acute liver failure, by improving systemic hemodynamics, tissue oxygen delivery, and other favorable effects on the acutely injured liver (Harrison et al. 1991; Walsh et al. 1998; Rank et al. 2000).

The US Acute Liver Failure Study Group reported the result of their experience with intravenous NAC in 2009 to treat acute liver failure due to etiologies other than acetaminophen. In this prospective, double-blind trial, patients with acute liver failure (nonacetaminophen), at 24 medical centers across the USA between 1998 and 2006, were randomized to receive NAC or placebo infusion for 72 h (Lee et al. 2009). Acute liver failure caused by DILI ($n = 45$) represented the single largest group among 173 patients who were randomized. Although the overall survival at 3 weeks was not significantly different between the groups, the transplant-free survival was significantly better among those patients randomized to NAC (40 vs. 27 %, $P = 0.043$). The benefits of transplant-free survival were confined to the 114 patients with coma grades I–II who received NAC (52 % compared with 30 % for placebo; 1-sided $P = 0.010$), while those with coma grades III–IV receiving NAC had a 9 % transplant-free survival versus 22 % in the placebo group (1-sided $P = 0.912$). When the overall and transplant-free survival of the four largest etiologic groups was considered, patients with DILI and hepatitis B virus (HBV) showed improved outcome in comparison with the AIH and indeterminate groups. In the DILI patients, transplant-free

DOI 10.1007/978-3-319-05543-5_16-1

survival was 58 % for those receiving NAC compared with 27 % for those receiving placebo (Lee et al. 2009). This study suggests that therapy with intravenous NAC should be considered in patients with early stage acute liver failure due to or thought to possibly be due to idiosyncratic DILI. Nausea and vomiting were the symptoms more frequent during treatment with NAC. Along with its excellent safety profile, NAC is easy to administer, does not require intensive care monitoring, and can be given in community hospitals.

Liver Support Systems

Extracorporeal supportive devices have been studied and developed to replace the liver function in FHF patients. Unfortunately, the complexity of liver metabolic, synthetic, detoxifying, and excretory functions makes the development of extracorporeal hepatic support extremely difficult. Currently available liver support systems are comprised of nonbiological (detoxification) systems and bioartificial systems. The most common techniques of nonbiological systems are the molecular adsorbent recirculating system (MARS) and Prometheus therapy. These systems are useful methods of removing the accumulated water-soluble/insoluble, protein-bound, and metabolic waste products in patients with FHF (Rademacher et al. 2011). Unfortunately, no survival benefit could be demonstrated compared with standard medical therapy (Oppert et al. 2009). Bioartificial liver systems rely on the use of actual liver cells to perform detoxification and secretion of hepatocyte-derived factors. To date, the C3A line, a subclone of the HepG2 hepatoblastoma cell line, is the only human-based cell line that has been tested clinically in a bioartificial liver device named ELAD™ (Millis et al. 2002; Duan et al. 2007). Of note, a multicenter, randomized trial of the ELAD device is ongoing to assess the safety and efficacy of this system in FHF. Preliminary data on the use of bioartificial devices suggest some improvement in encephalopathy. A systematic review that pooled 12 randomized controlled trials (with a total of 483 patients) using various bioartificial support systems concluded that overall they had no significant effect on mortality compared with standard medical therapy (Kjaergard et al. 2003; Liu et al. 2004).

Prognosis

The prognosis of FHF varies greatly with the underlying cause of liver injury and patient related factors. Limited organ availability and potential complications to lifelong immunosuppression make an accurate prognosis in FHF a major goal. Predicting the outcome of a patient with FHF is key and must be recognized early for the possibility of liver transplant if required (Sass and Shakil 2003). Several models have been developed for predicting the outcome in patients with FHF.

The King's College Criteria are the most widely used for selecting patients for liver transplantation (Table 2) (O'Grady et al. 1989). It was developed in a cohort of 588 patients with FHF who were managed medically between 1973 and 1985 (O'Grady et al. 1989). The predictors differ based on the etiology of FHF (acetaminophen vs. other causes). In patients with acute liver failure due to acetaminophen, recovery may be observed even in patients who have evidence of severe hepatocellular necrosis and synthetic dysfunction. In acetaminophen-induced acute liver failure, there are two broad criteria for referral for orthotopic liver transplantation: arterial pH of less than 7.30, irrespective of grade of encephalopathy or grade III or IV encephalopathy with both a prothrombin time (PT) greater than 100 s, and a serum creatinine concentration greater than 3.4 mg/dL. For other causes of FHF, poor prognosis predictors include PT greater than 100 s, irrespective of the grade of encephalopathy or any three of the following: age less than 10 or greater than 40 years, unfavorable disease etiology (such as non-A, non-B viral hepatitis, idiosyncratic drug reactions, Wilson disease), duration of jaundice before development of encephalopathy greater than seven days, PT greater than 50 s, or serum bilirubin greater than 18 mg/dL.

DOI 10.1007/978-3-319-05543-5_16-1

Table 2 The King's college criteria for liver transplantation

Acetaminophen	Nonacetaminophen
pH < 7.3 (irrespective of grade of encephalopathy)	PT > 100 s (INR > 6.5) (irrespective of grade of encephalopathy)
Or all three of the following	Or any three of the following
Grade III–IV encephalopathy	Age <10 or >40 years
PT > 100 s (INR > 6.5)	Etiology: (non-A, non-B hepatitis, halothane, idiosyncratic drug reaction, Wilson disease)
Serum creatinine >300 μmol/L (3.4 mg/dL)	Period of jaundice to encephalopathy >7 days
	PT > 50 s (INR > 3.5)
	Serum bilirubin >300 μmol/L (17.5 mg/dL)

Adapted from O'Grady et al. (1989)
Abbreviations: INR international normalized ratio, *PT* prothrombin time

The accuracy of the King's College Criteria has been evaluated in several studies. These studies have shown positive predictive values ranging from just below 70 % to nearly 100 % (Anand et al. 1997; Shakil et al. 2000; Bernal et al. 2002; Schmidt and Dalhoff 2002). Recently, the addition of arterial lactate levels in patients with APAP-induced FHF has been proposed to improve sensitivity of the criteria and identifies patients in need for OLT earlier (Bernal et al. 2002). The Clichy criteria are widely used in Northern Europe for FHF and takes into consideration coagulation factor V concentrations and patient age (Bernuau et al. 1986).

The model for end-stage liver disease (MELD) score has been used since 2002 by the United Network for Organ Sharing for allocation of grafts to adult patients with cirrhosis awaiting transplantation in the USA (Freeman et al. 2002). MELD is a severity score derived from the transformation of three biochemical parameters in a logarithmic formula, i.e., total serum bilirubin, prothrombin time, and creatinine. Studies have examined the MELD score at listing as a predictor of pretransplant and posttransplant survival in United Network for Organ Sharing Status 1 patients and compared survival among four diagnostic groups within the Status 1 designation (Kremers et al. 2004 and Yantorno et al. 2007). The four groups were comprised of FHF due to acetaminophen, FHF without acetaminophen toxicity, primary graft nonfunction within 7 days of transplantation, and hepatic artery thrombosis within 7 days of transplantation. They found, using Cox regression methodology, that the FHF-nonacetaminophen group had the poorest survival probability while awaiting OLT. This was negatively correlated with MELD score ($P = 0.0001$), which translated into the best survival benefit associated with OLT. The authors concluded that liver allocation within the Status 1 designation may need to be further stratified by diagnosis and that MELD score may be useful in prioritizing the FHF-nonacetaminophen group (Kremers et al. 2004 and Yantorno et al. 2007).

Liver histology (Fig. 2) and liver volume are often used by clinicians when trying to determine prognosis. There are a few limitations due to risk of bleeding with liver biopsy, a small potential for sampling error, and the fact that they can be overall misleading (Hanau et al. 1995). A small or shrinking liver on radiologic assessment can be of some value as this demonstrates collapse of the liver parenchyma (Hanau et al. 1995; Itai et al. 1997).

DOI 10.1007/978-3-319-05543-5_16-1

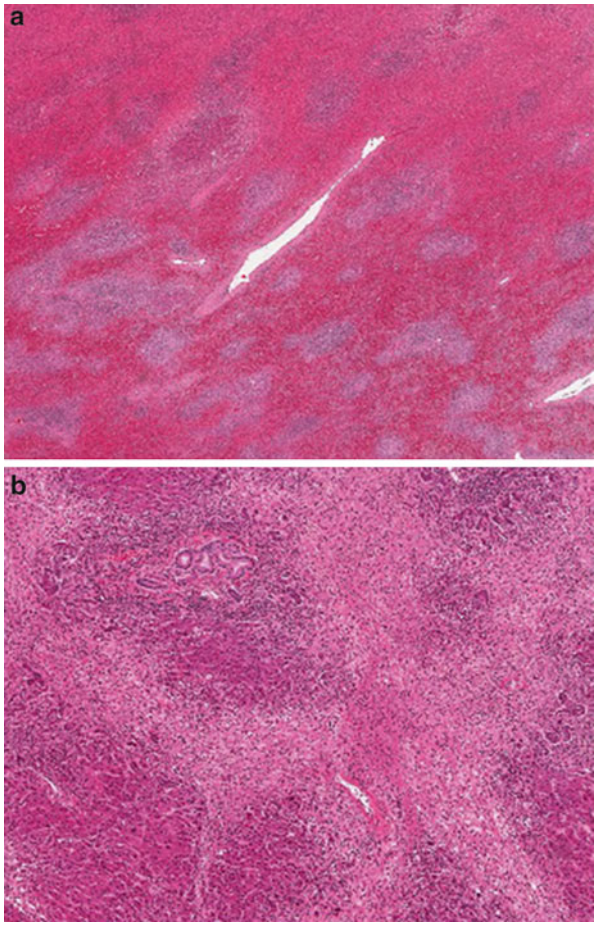

Fig. 2 Liver biopsy from a patient with FHF due to herbal supplement hepatotoxicity. (**a**) Low power: confluent hepatic necrosis (hematoxylin and eosin staining). (**b**) High power: centrilobular necrosis

Conclusion

FHF is a very challenging and serious medical condition. It tests our best clinical and surgical skills because of its rarity, rapid progression, and frequently poor outcomes. Early identification of FHF and the administration of etiology-specific treatment are crucial in its management. Patients with FHF are particularly vulnerable to infection, bleeding, and cerebral edema. The technique of liver transplantation has reduced the mortality rate associated with FHF. Rescue therapies that provide temporary liver support or other treatments short of transplantation may be of some benefit. Increased knowledge on the mechanisms of liver cell injury, hepatic regeneration, and the pathogenesis of encephalopathy and extrahepatic organ failure is needed. The greatest benefits in terms of reduced mortality and morbidity from FHF will result from public health measures to control drug-induced liver injury.

Cross-References

► Artificial Liver Treatment, When and Which One?
► Organ Procurement Organization
► Orthotopic Liver Transplantation: Complications

DOI 10.1007/978-3-319-05543-5_16-1

► Orthotopic Liver Transplantation: Indications and Contraindications
► Orthotopic Liver Transplantation: Surgical Techniques

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