Acute liver failure (ALF), also known as fulminant hepatic failure (FHF), embraces a spectrum of clinical entities characterized by acute liver injury, severe hepatocellular dysfunction, and hepatic encephalopathy. This condition is uncommon but not rare; it affects approximately 2000 to 2800 people annually in the United States, with a mortality of 3.5 per million despite intensive support. Loss of hepatocyte function sets in motion a vicious multiorgan dysfunction syndrome, with ensuing death even when the liver has begun to recover. Complications of FHF include encephalopathy, cerebral edema, sepsis, acute respiratory distress syndrome (ARDS), hypoglycemia, coagulopathy, gastrointestinal bleeding, pancreatitis, and acute renal failure (ARF). Acetaminophen toxicity, idiosyncratic drug reactions, and hepatotropic viruses remain the most common cause of FHF in the United States. FHF accounts for 5% to 6% of liver transplantation, which is currently the only proven and definitive treatment option for patients who are unlikely to recover spontaneously. Unfortunately, many patients die before a suitable organ can be identified. Thus, the dominant medical interventions for acute liver failure in the critical care setting are supportive. Alternative “liver replacement” therapeutic strategies are under clinical investigation.

**Definitions**

The terms fulminant hepatic failure and acute liver failure are often used interchangeably. FHF is defined as the presence of encephalopathy (regardless of grade) and coagulopathy (international normalized ratio [INR] > 1.5) within 26 weeks of the appearance of symptoms in patients with no previous history of underlying liver disease. Since the original definition of FHF proposed by Trey and Davidson in 1970, several other classifications have emerged (Box 102-1). In different classifications, the interval between the onset of symptoms or jaundice and the appearance of encephalopathy allows grouping of patients with similar causes, clinical characteristics, and prognosis.

**Etiology**

Viral hepatitis remains the most common identifiable cause of FHF in the developing world, whereas acetaminophen toxicity and idiosyncratic drug reactions have replaced viral hepatitis as the most frequent apparent causes of FHF in the United States and Europe. Both prognosis and management are determined in part by the underlying etiology of FHF.

**ACETAMINOPHEN TOXICITY**

Acetaminophen overdose is now the leading cause of FHF in the United States and accounts for 40% to 50% of cases. This type of liver injury occurs both after attempted suicide by acetaminophen overdose and after unintentional “therapeutic misadventures” caused by use of the drug for pain relief in excess of the dose specified in the package labeling, typically over a period of several days. A careful medical history clarifies the quantity ingested; blood levels can be confirmatory but may not be elevated in cases of unintentional overdose. Doses considered nontoxic (<4 g/day in adults, <8 mg/kg in infants) might cause hepatotoxicity if other concurrent factors exist, such as alcohol ingestion, fasting, or malnutrition. Hepatotoxicity usually develops 1 to 2 days after the overdose, and circulating alanine aminotransferase (ALT) levels and INR values reach their peak around day 3. A continued increase of INR after day 3 is associated with a 90% mortality rate. Acetaminophen is also nephrotoxic, and renal failure may occur in the absence of liver necrosis.

Acetaminophen undergoes phase 1 metabolism by hepatic cytochrome P450 2E1 (CYP2E1) enzymes to a toxic intermediate compound, N-acetyl-p-benzoquinone imine (NAPQI), which is rapidly detoxified by hepatic glutathione into a nontoxic metabolite. Under normal conditions, little NAPQI accumulates. However, in an overdose, owing to depletion of glutathione stores, unconjugated NAPQI accumulates and causes hepatocellular necrosis. The amount of liver injury is directly related to the amount of ingested acetaminophen and the amount of NAPQI produced. In a recent study, the dose of acetaminophen ingested did not correlate with the overall prognosis. Enzyme inducers such as alcohol, antiepileptic drugs, and cigarette smoke can enhance acetaminophen-mediated hepatotoxicity. Chronic alcohol consumption induces synthesis of CYP2E1 enzymes and, to a lesser extent, depletes glutathione stores. Substrate competition for CYP2E1 occurs between ethanol and acetaminophen when the two drugs are taken simultaneously. During the metabolism of acetaminophen, NAPQI formation is diminished when alcohol is present. The rate at which CYP2E1 degrades is also slowed, and the half-life of the enzyme increases from 7 hours to 37 hours. As long as ethanol remains in the body, there is competition between acetaminophen and ethanol for CYP2E1; however, once ethanol is removed, NAPQI formation is enhanced, resulting in enhanced hepatic injury in the 24 hours after cessation of alcohol consumption. Genetic variability within the population affecting expression of the cytokine, tumor necrosis factor alpha (TNF-α), also has been implicated as a determining factor in the severity of drug reactions related to acetaminophen.

**IDIOSYNCRATIC DRUG REACTIONS**

Drug-induced liver damage is a significant cause of death in patients with FHF in Western countries (Box 102-2). The most common implicated drugs are antibiotics, central nervous system (CNS) agents, herbal/dietary supplements, and immunomodulatory agents. Hepatocellular injury is common in younger patients, whereas a cholestatic picture is more common in the elderly. Dose, duration, and the hepatic metabolism of the drug all may play a role in the development of drug-induced liver injury.

Most idiosyncratic drug reactions are due to single agent, but multiple medications are implicated in some patients. Women generally predominate among patients with idiosyncratic drug-induced liver injury. Other risk factors for drug-induced hepatotoxicity include extremes of age, abnormal renal function, obesity, preexisting liver disease, and concurrent use of other hepatotoxic drugs. Idiosyncratic drug toxicities are immunologically mediated by the drug itself or its metabolites. Most idiosyncratic reactions occur within 4 to 6 weeks after initiation of treatment, although rare cases have occurred months or years later.

Idiosyncratic hepatic injury is mediated by several mechanisms, including disruption of intracellular calcium homeostasis, injury to canalicular transport pumps, such as multidrug resistance–associated protein 3 (MRP3), T cell–mediated immunologic injury, triggering of apoptotic pathways by TNF-α, and inhibition of mitochondrial beta oxidation. Isoniazid, pyrazinamide, antimicrobials...
Whereas viral hepatitides remain the most common identifiable cause of FHF worldwide, considerable geographic variation exists in the subtype of hepatitides. Thus, hepatitis B virus (HBV) is a common cause of FHF in the Far East, and hepatitis E virus (HEV) is more prevalent in the Indian subcontinent. In the United States, approximately 12% of FHF referred for liver transplants are due to hepatitis A and B. Occurrence of FHF within the larger number of patients with viral hepatitis, however, is rare (0.2%-0.4% for hepatitis A, 1%-4% for hepatitis B).

Hepatitis A virus (HAV) is associated with a higher risk of developing FHF if infection is acquired in older adulthood. Thus, vaccination is recommended for adults traveling from developed countries to endemic areas. The relevance of HAV as a cause of FHF in patients with preexisting chronic liver disease has been recognized recently. HAV vaccination in this high-risk group has been suggested. Postexposure prophylaxis with immune serum globulin may reduce the incidence of hepatitis A, but only when administration occurs within 14 days after exposure.

HBV can result in FHF through several mechanisms: acute primary HBV infections, reactivation of hepatitis B in patients with chronic HBV, or superinfection with hepatitis D virus. Acute HBV infection is diagnosed by the detection of immunoglobulin M (IgM) antibodies against hepatitis B core antigen (HbcAg), because a substantial number of patients have negative serum hepatitis B surface antigen (HBsAg) and serum HBV-DNA. Low or absent levels of HBsAg and HBV-DNA are associated with better prognosis and lower rate of recurrence after orthotopic liver transplantation (OLT). FHF after reactivation of chronic hepatitis B has been described mainly in immunosuppressed male patients; this form of the disease usually has a subfulminant course and a poor prognosis.

Most studies indicate that hepatitis C virus (HCV) infection alone does not result in FHF. However, isolated cases of HCV-RNA in serum or tissue of patients with FHF and negative markers for other viruses have been noted in Western countries. Involvement of HCV in FHF is slightly more common in the Far East. An increased risk of FHF in patients with chronic hepatitis B and superinfection by HCV has been suggested.

FHF is seen in 2.5% to 6% of hepatitis D virus cases. Coinfection with HBV and hepatitis D virus (HDV) or superinfection by HDV in patients with chronic hepatitis B also can cause FHF. The increased risk of coinfection is higher when intravenous (IV) drug abuse is present. Diagnosis of acute infection by HDV is made by the presence of HDV antigen, anti-HDV IgM antibody, or HDV-RNA.

Infection by hepatitis E virus (HEV) is uncommon in Western countries but occurs in travelers to endemic areas. Pregnant women infected by HEV seem to have a special propensity for developing FHF. Diagnosis is made by detection of anti-HEV IgM antibodies. Other viruses have been implicated in the pathogenesis of FHF of indeterminate etiology. These viruses include cytomegalovirus (CMV), human herpesvirus-6 (HHV-6), Epstein-Barr virus (EBV), hepatitis G virus (HGV), herpes simplex virus (HSV), varicella-zoster virus (VZV), parovirus B19 in children, and togavirus, adenovirus, paramarvovirus, yellow fever, Q fever, and most recently, SEN virus and TT virus. Although these causes are rare, they must be excluded, because some patients may benefit from specific antiviral therapy.

Miscellaneous cardiovascular, metabolic, and other disorders account for 2% to 10% of cases of FHF. Acute liver ischemia secondary to shock states can result in hepatocellular necrosis; however, the prognosis remains good if the primary condition can be corrected. The prognosis is worse when FHF is due to other causes such as Budd-Chiari syndrome, veno-occlusive disease, or malignancies associated with impaired hepatic blood flow. Rarely, the first manifestation of Wilson’s disease is FHF, which sometimes occurs in patients without evidence of chronic liver disease. Death is universal without OLT. Acute fatty liver of pregnancy is rare, occurring in the third trimester of pregnancy, and usually responds well to fetal delivery. Other causes of FHF are autoimmune hepatitis, non-Hodgkin’s lymphoma, or Reye syndrome, the last being less common in the pediatric population since aspirin use has been curtailed.
nature of complications, and duration of illness. Patients with grade IV encephalopathy have a higher than 80% mortality without OLT. The successful use of OLT in FHF has created a need for early prognostic indicators to select patients most likely to benefit from OLT. Various prognostic scoring systems exist (Box 102-3), However, many of these are subject to debate because of bias and equating death with liver transplant, which falsely elevates the positive predictive value of any prognosticitation method. 21

For patients with acetaminophen overdose, HAV infection, shock liver, or pregnancy-related acute liver failure, the short-term survival without transplantation is over 50%. Short-term transplant-free survival is lower (<25%) for patients with FHF of indeterminate cause or FHF caused by these factors: drugs other than acetaminophen, HBV infection, autoimmune hepatitis, Wilson’s disease, Budd-Chiari syndrome, or cancer. The King’s College prognostic criteria are the most widely used. These criteria provide a reasonable prediction of the likelihood of death and the need for transplantation in FHF patients. 22 The criteria are different for acetaminophen and non-–acetaminophen-induced FHF (see Box 102-3), and experts have criticized the King’s College criteria on the basis of low sensitivity and negative predictive value, especially for causes of FHF other than acetaminophen poisoning. The APACHE II system has been found to be equal to King’s College criteria for accuracy in predicting death in acetaminophen-induced FHF.23 Other approaches include the Cliché criteria, 26 which use factor V assay, factor VIII/V ratio, serial α-fetoprotein levels, and plasma group-specific component protein (Gc globulin) levels. 27,28 Liver volume decreases with progression of the disease, and its measurement with computed tomography (CT) may help assess prognosis. Other proposed prognostic tools include the proportion of necrosis as assessed by histologic examination of specimens obtained by liver biopsy, amount of fresh frozen plasma (FFP) required to correct coagulopathy, or determination of somatosensory evoked potentials. Other proposed markers for poor prognosis include serum levels of phosphate above 1.2 mmol/L on day 2 or 3, blood lactate concentration over 3.0 mmol/L, or Model for End-stage Liver Disease (MELD) score higher than 32. 29,31

**Box 102-2**

**ETIOLOGIC CLASSIFICATION OF ACUTE LIVER FAILURE**

<table>
<thead>
<tr>
<th>Acetaminophen Toxicity</th>
<th>Combination agents with enhanced hepatotoxicity:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiosyncratic Drug Injury</td>
<td>Alcohol-acetaminophen</td>
</tr>
<tr>
<td>Infrequent agents:</td>
<td>Trinitrophenylmethane-2-sulphoximine</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Rifampicin-isoniazid</td>
</tr>
<tr>
<td>Valproate</td>
<td>Amoxicillin-clavulanic acid</td>
</tr>
<tr>
<td>Halothane</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Phenytion</td>
<td>Reye syndrome</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Acute fatty liver of pregnancy</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Dapsone</td>
<td></td>
</tr>
<tr>
<td>Bromfenac</td>
<td></td>
</tr>
<tr>
<td>Troglitazone</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
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<tr>
<td>Lamivudine</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
</tr>
<tr>
<td>Gatifloxicin</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous agents:</td>
<td></td>
</tr>
<tr>
<td>Ecstasy</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
</tr>
<tr>
<td>Phencyclidine</td>
<td></td>
</tr>
<tr>
<td>Rare agents:</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Olofoxacin</td>
<td></td>
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<tr>
<td>Ketocozazole</td>
<td></td>
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<tr>
<td>Lisinopril</td>
<td></td>
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<tr>
<td>NICOTINIC ACID</td>
<td></td>
</tr>
<tr>
<td>Labelalol</td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td></td>
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<tr>
<td>Interferon alfa</td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td></td>
</tr>
<tr>
<td>Tolcapone</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td></td>
</tr>
</tbody>
</table>

**Viral Hepatitides**

<table>
<thead>
<tr>
<th>Hepatitis A, B, C, D, E, G</th>
<th>Herpes simplex virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human herpesvirus</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Hepatitis A, B, C, D, E, G</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Parvovirus B19</td>
</tr>
<tr>
<td>Paramyxovirus</td>
<td>Adenovirus</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>Togavirus</td>
</tr>
<tr>
<td>SEN virus</td>
<td>Parvovirus</td>
</tr>
<tr>
<td>TT virus</td>
<td>SEN virus</td>
</tr>
<tr>
<td>Yellow fever virus</td>
<td>SEN virus</td>
</tr>
</tbody>
</table>

**Toxins**

<table>
<thead>
<tr>
<th>CCL4</th>
<th>Amanita phalloides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow phosphorus</td>
<td>Herbal products</td>
</tr>
</tbody>
</table>

**Vascular**

<table>
<thead>
<tr>
<th>Ischemic</th>
<th>Yellow phosphorus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veno-occlusive disease</td>
<td>Herbal products</td>
</tr>
</tbody>
</table>

**Miscellaneous**

<table>
<thead>
<tr>
<th>Wilson’s disease</th>
<th>Autoimmune hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute fatty liver of pregnancy</td>
<td>Wilson’s disease</td>
</tr>
</tbody>
</table>

**Role of Liver Biopsy**

Liver biopsy can confirm the suspected cause of FHF and determine the degree of hepatocyte necrosis. Greater than 70% necrosis in a liver biopsy specimen is associated with 90% mortality without transplantation. 24,25 Because severe coagulopathy precludes safe percutaneous liver biopsy, the transjugular approach is often preferred. Although a liver biopsy is not mandatory, it can be valuable for determining prognosis, ruling out the presence of cirrhosis, and making the decision for early transplantation. Liver biopsy can help exclude occult malignancy in enigmatic cases and also can be used to assess the liver for evidence of regeneration, as manifested by the presence of liver cell mitosis. In rare cases, the liver biopsy can provide etiologic information that enables specific therapy to be instituted, as in the cases of HSV, CMV, adeno- virus, and paramyxovirus hepatitis infections. Because of the variable nature of liver biopsies in patients with FHF, a minimum of three, and ideally six, specimens of the hepatic parenchyma should be obtained for histologic evaluation. In addition, if Wilson’s disease or hepatic iron
The presence of encephalopathy is the essential clinical feature that differentiates FHF from acute severe hepatitis, and the time to onset after the appearance of jaundice distinguishes FHF from SFHF. The onset of encephalopathy is often abrupt and occasionally may precede the appearance of jaundice. Agitation, delusional ideas, and hyperkinesis are common but short-lived symptoms; coma rapidly ensues. The overall prognosis for those with stable grade I or II encephalopathy is good, whereas the prognosis for patients with grade III or IV encephalopathy is much poorer. In cases of acetaminophen overdose, encephalopathy usually occurs on the third or fourth day after ingestion and rapidly progresses to grade IV within 24 to 48 hours.

The pathophysiology of hepatic encephalopathy is poorly understood and is probably multifactorial. Ammonia buildup in the brain is believed to be the main offender. Elevated serum ammonia concentration is exacerbated by decreased urea synthesis in the injured liver. Endogenous substances, false neurotransmitters, short-chain fatty acids, benzodiazepines, and γ-aminobutyric acid are additional factors that lead to encephalopathy. The electroencephalogram (EEG) typically shows diffuse slowing of cortical activity and high-amplitude waveforms at 5 to 7 cycles per second. Subclinical seizure activity is often present in patients with grade III and IV encephalopathy, emphasizing the importance of EEG monitoring in these patients. Prophylactic therapy with phenytoin has been shown to reduce seizure activity and reduce cerebral edema. Seizure activity in FHF has been linked to excessive CNS glutamine, the main excitatory neurotransmitter in the brain. Newly synthesized glutamine is transported from the cytoplasm into mitochondria and is metabolized by glutaminase, yielding glutamate and ammonia. The generation of ammonia in the small mitochondrial compartment may reach extremely high levels, leading to induction of the mitochondrial permeability transition (MPT), production of free radicals, and potentially to oxidative damage of mitochondrial constituents. Thus, glutamine acts like a “Trojan horse,” serving as a carrier of ammonia into mitochondria. The glutamine-derived ammonia within mitochondria leads to astrocyte dysfunction, including cell swelling.

**CEREBRAL EDEMA**

Cerebral edema is estimated to occur in 75% to 80% of patients who progress to grade IV encephalopathy, and it is the leading cause of death in these patients. The mechanism(s) responsible for cerebral edema are only partially understood. Possible contributing factors include cerebral hyperemia, vasogenic edema due to disruption of the blood-brain barrier with rapid accumulation of low-molecular-weight substances, cytotoxicity due to the osmotic effects of ammonia, glutamine, and other amino acids, as well as the deleterious effects of pro-inflammatory cytokines and dysfunction of the sodium-potassium ATPase pump with loss of autoregulation of cerebral blood flow. Intracranial blood flow is markedly reduced in patients with chronic hepatic encephalopathy; the decrease in perfusion appropriately matches the reduction in cerebral metabolic rate (CMR). However, patients with FHF often develop either relative or absolute cerebral hyperemia; thus, perfusion is not well matched to the reduced CMR present in evolving or established hepatic coma. An early indicator of this pathologic process is either a decrease in the transcranial oxygen content difference (arterial oxygen content – jugular bulb oxygen content) to less than 4 mL/dL or an increase in middle cerebral artery systolic blood flow velocity. Serial transcranial Doppler ultrasonographic monitoring of cerebral blood flow velocity helps detect early cerebral hyperperfusion or hypoperfusion suggesting impaired cerebral autoregulation. Cerebral ischemia and permanent neurologic sequelae may occur (even after OLT) if cerebral perfusion pressure (CPP), calculated as mean systemic arterial blood pressure minus intracranial pressure, is not maintained above 40 to 50 mm Hg. However, there have been some reports of full neurologic recovery after OLT, despite high ICP and low CPP. CT of the brain often fails to demonstrate cerebral edema in patients with elevated ICP. Late clinical stages of cerebral edema include systemic hypertension, decerebrate rigidity, hyperventilation, papillary dilation, seizures, and brainstem herniation. An arterial ammonia level above 200 μg/dL in grade III and...
grade IV encephalopathy is a strong predictor of brain herniation.43 Full recovery of cerebral function is the rule if normal liver function returns, but permanent brain damage has been observed in patients making an otherwise complete hepatic recovery.

COAGULOPATHY

Severe alterations in coagulation are typical of FHF and are due to impaired hepatic synthetic function, leading to inadequate production of coagulation factors. Decreased levels of factors II, V, VII, IX, and X account for the prolongation of INR and activated partial thromboplastin time (APTT). Full recovery may occur in patients with FHF and carries a poor prognosis. Hyponatremia, alkalosis, hypokalemia, and lactic acidosis are common. Ionized hypocalcemia may indicate concomitant pancreatitis. Acute renal failure is seen in 30% to 70% of patients with acute liver failure and results from a combination of several factors such as intravascular volume depletion, sepsis, DIC, or direct nephrotoxicity from drugs such as acetaminophen or NSAIDs. Adrenal insufficiency has been described in up to 62% of patients with FHF when assessed by levels of the vitamin K–dependent factor VII by 25% after IV administration of vitamin K suggests that hepatic synthetic reserve is inadequate.44 Many anticoagulation factors, such as proteins C and S, are synthesized by the liver, and activated coagulation factors are removed by the liver. Disruption of the balance between procoagulant and anticoagulant factors may result in excessive thrombosis and disseminated intravascular coagulation (DIC), and the laboratory distinction between the two is often difficult. Platelet counts are below 100,000/μL in two-thirds of patients at some point in their clinical course, and platelet function is altered. Hemorrhage from the gastrointestinal tract or elsewhere is common in FHF and most often correlates with a low platelet count; platelet transfusion may be necessary for patients with counts less than 50,000/μL. FFP has not been shown to be of value in the absence of bleeding.

METABOLIC DERANGEMENTS

FHF results in myriad metabolic abnormalities. Hypoglycemia is seen in up to 45% of patients with FHF. This abnormality is caused by depletion of hepatic glycogen stores and impaired glucoseogenesis and may be refractory to infusion of IV dextrose solution. Hepatic insulin resistance and impaired peripheral insulin sensitivity are often present.45 Metabolic acidosis is common in acetaminophen-induced FHF and carries a poor prognosis. Hyponatremia, alkalosis, hypokalemia, hypophosphatemia, and lactic acidosis are common. Ionized hypocalcemia may indicate concomitant pancreatitis. Acute renal failure is seen in 30% to 70% of patients with acute liver failure and results from a combination of several factors such as intravascular volume depletion, sepsis, DIC, or direct nephrotoxicity from drugs such as acetaminophen or NSAIDs. Adrenal insufficiency has been described in up to 62% of patients with FHF when assessed by levels of the vitamin K–dependent factor VII by 25% after IV administration of vitamin K suggests that hepatic synthetic reserve is inadequate.44 Many anticoagulation factors, such as proteins C and S, are synthesized by the liver, and activated coagulation factors are removed by the liver. Disruption of the balance between procoagulant and anticoagulant factors may result in excessive thrombosis and disseminated intravascular coagulation (DIC), and the laboratory distinction between the two is often difficult. Platelet counts are below 100,000/μL in two-thirds of patients at some point in their clinical course, and platelet function is altered. Hemorrhage from the gastrointestinal tract or elsewhere is common in FHF and most often correlates with a low platelet count; platelet transfusion may be necessary for patients with counts less than 50,000/μL. FFP has not been shown to be of value in the absence of bleeding.

CARDIOVASCULAR, HEMODYNAMIC, AND RESPIRATORY COMPLICATIONS

Circulatory dysfunction accompanying FHF often mimics sepsis. Typically, patients are hyperdynamic, and calculated systemic vascular resistance is low. Vasodilation is thought to be due to the proinflammatory effects of circulating endotoxin and cytokines. Relative hypovolemia secondary to reduced systemic vascular resistance can make it difficult to assess the adequacy of intravascular volume, prompting insertion of pulmonary artery catheters. Cardiac arrhythmias occur frequently, owing to either electrolyte imbalances or increased circulating levels of catecholamines (from endogenous release or deliberate infusion). Severe peripheral shunting has been observed in FHF and may result from the plugging of small vessels by platelets, interstitial edema, or abnormal vasomotor tone, although the exact mechanism is unclear. Severely diminished tissue oxygen extraction is more common in nonsurvivors. An abnormal pattern of oxygen supply dependency results in oxygen extraction over a wider than normal range of oxygen delivery, presumably as a compensatory mechanism. Prostacyclin, which has microcirculatory vasodilatory effects, has been shown to increase peripheral oxygen uptake.47

Hyperventilation, hypercapnia, and respiratory alkalosis occur during acute liver failure and may worsen encephalopathy. Arterial hypoxemia is universal and is caused by a combination of intrapulmonary shunting, ventilation/perfusion mismatching, sepsis, aspiration, and ARDS.

SEPSIS

FHF is associated with impaired host resistance to and enhanced risk for bacterial and fungal infections. Common infections are aspiration pneumonia and primary bloodstream infections, including those caused by Candida spp. The tryptophan-removing bacteria (Staphylococcus aureus, enterococci), enteric gram-negative bacilli (Escherichia coli, Klebsiella spp.), and Candida spp. Diminished hepatic reticuloendothelial function and opsonic activity, defective polymorphonuclear leukocyte function, and impaired cell-mediated and humoral immunity are the major predisposing mechanisms. In one prospective study of 30 patients, 80% had culture-proven infection, and in half of the remaining patients, infection was suspected but cultures were negative.46 Regular microbial surveillance and aggressive treatment of presumed infection are essential, because prophylactic antibiotic regimens have shown little benefit.

Management

Optimal management of FHF begins with the recognition that any patient with acute liver disease can die suddenly and is best cared for in an intensive care unit (ICU), preferably in a transplant center. Because the transportation of patients with advanced levels of coma is hazardous and the disease often worsens rapidly, transfer to a liver transplantation center should be considered at the time of admission of any patient with FHF. Because the liver has a unique ability to regenerate after acute, self-limited injury, treatment is limited to general supportive measures. Failure of the cause of hepatic failure allows some patients to benefit from specific therapies and may influence posttransplant management if a transplant is performed.

THERAPY DIRECTED AT THE SPECIFIC ETIOLOGY OF FHF

Depending on the suspected or confirmed FHF etiology, a number of therapies may exist that can ameliorate or reverse the degree of liver injury. NAC should be given to all patients with FHF, regardless of the cause. NAC is a specific antidote for acetaminophen overdose; if given within the first 8 to 10 hours after an acute overdose, it replenishes glutathione stores and prevents development of hepatotoxicity. The efficacy of NAC declines progressively thereafter, but NAC may be effective up to 72 hours after acetaminophen ingestion.47 IV NAC is preferred over the enteral route. The dose is 150 mg/kg over 15 minutes, followed by 50 mg/kg given over 4 hours, followed by 100 mg/kg administered over 16 hours. Some experts recommend continued treatment until the INR normalizes. However, prolonged NAC therapy has been shown to impair murine liver regeneration and may impair liver regeneration following acetaminophen poisoning.48 Currently, the optimal duration of treatment with NAC remains unclear.

Benefits of NAC on survival, brain edema, hemodynamics, oxygen delivery, and oxygen consumption were found in patients with established FHF.48 A randomized, controlled trial of NAC by the U.S. Acute Liver Failure Study Group in patients with non–acetaminophen-induced FHF documented improved transplant-free survival.13

In Amanita intoxication, beneficial effects have been reported with the use of penicillin G (250 mg/kg/d) or sildinbin, 20 to 50 mg/kg/h for a total of 1400 mg/d for 3 to 4 days.15,16,21 (Enjalbert et al) (Karlson-Stüber et al) These drugs may be useful if they are given early after mushroom ingestion. In severe cases, OLT is often required.

Hepatitis secondary to HSV may be missed because of its nonspecific presentation and the absence of typical mucocutaneous lesions. Most patients with HSV hepatitis are immunoincompetent hosts. If
HSV hepatitis is suspected, treatment with parenteral acyclovir or ganciclovir should be started.

In patients with Wilson's disease, plasma exchange with FFP replacement is preferred, because this intervention can remove relatively large amounts of copper in a short period of time. Net copper removal is proportional to plasma concentration and can reach 12 mg per session. However, plasmapheresis only helps to bridge patients to transplant and carries no survival benefit. Chelating agents like penicillamine are ineffective in the setting of Wilson's disease–induced FHF. Hemofiltration and albumin dialysis also have been described as temporizing measures before OLT. The role of corticosteroids such as methylprednisolone (40 to 60 mg every 6 hours) or immunosuppressive agents in the setting of autoimmune hepatitis has not been well established. Patients who do not respond to treatment after 2 weeks (as evidenced by persistently elevated bilirubin and aminotransferase levels) often die without liver transplantation. Acute fatty liver of pregnancy usually responds to fetal delivery, and maternal mortality is improved after aggressive maternal care and early delivery. Fetal mortality, on the other hand, is only minimally improved after early delivery. Urgent chemotherapy is indicated for FHF caused by massive infiltration of the liver by lymphoma. Acute Budd-Chiari syndrome may be amenable to thrombolytic therapy or to transjugular intrahepatic portosystemic shunt (TIPS) placement. Administration of L-ornithine-L-aspartate (LOLA) in patients with FHF was ineffective in reducing circulating ammonia levels or improving survival. Patients who were treated with LOLA had a trend towards increased seizure activity. L-Ornithine phenylacetate is a promising agent that facilitates excretion of glutamine and may serve as a temporizing measure until transplantation is done.

HEPATIC ENCEPHALOPATHY

The treatment of encephalopathy associated with FHF is directed at limiting gut ammonia production and the avoidance of aggravating factors such as infection, ileus, obstipation, gastrointestinal hemorrhage, and other CNS depressants. Endotracheal intubation for grade III and IV hepatic encephalopathy (see Chapter 101) is essential. Lactulose (30 g every 1-2 hours) may be useful in the treatment of patients with grade I or II encephalopathy; however, administration of lactulose does not improve survival in advanced encephalopathy. The efficacy of lactulose in FHF has not been tested in clinical trials. This agent should be used with caution because of the risk of hypernatremia, dehydration due to diarrhea, and ileus. Lactulose by enema (300 g in 700 mL saline every 4-6 hours) remains an option in FHF patients who are unable to tolerate oral or nasogastric administration. Oral metronidazole (500 mg/d), neomycin (4–12 g/day), and rifaximin (800–1200 mg/d) directed against ammonia-producing gut flora have been employed. However, metronidazole may be neurotoxic in hepatic failure; and neomycin, although minimally absorbed, can still cause nephrotoxicity and ototoxicity. Rifaximin is very expensive, and comparative studies, especially studies of cost-effectiveness, should be conducted before it is recommended for routine use.

Endogenous benzodiazepine-like substances have been identified in the cerebrospinal fluid of patients with hepatic encephalopathy. Fluazam, a benzodiazepine receptor antagonist, has been used (0.2–20 mg) with some success to provide short-term improvement in patients with hepatic encephalopathy. Various experimental therapies such as exchange transfusion, charcoal hemoperfusion, and plasmapheresis have been used to lower circulating ammonia levels; however, none of these treatment approaches has been shown to improve survival.

CEREBRAL EDEMA

The optimal management of cerebral edema requires maintaining the delicate balance between mean arterial pressure (MAP) and ICP to preserve adequate cerebral perfusion (Box 102-4). Combined cerebral edema and intracranial hypertension is the most common cause of death in patients with FHF when ICP is above 30 mm Hg. An arterial ammonia level over 200 µg/dL predicts brain herniation. ICP monitoring may help to diagnose intracranial hypertension and guide management, especially in grade III or IV encephalopathy, although its use has never been shown to decrease mortality. Induced coma with propofol or pentobarbital titrated to burst suppression of 5–10 cycles/sec, endotracheal intubation for grade III or IV hepatic encephalopathy

<table>
<thead>
<tr>
<th>General Measures</th>
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<td>Head of bed elevation to 30-degree angle, and maintain patient’s neck in neutral position.</td>
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| Preventive and Therapeutic Interventions for Patients with Cerebral Edema and Intracranial Hypertension |

**Box 102-4**

**General Measures**

- Head of bed elevation to 30-degree angle, and maintain patient’s neck in neutral position.
- Endotracheal intubation for grade III or IV hepatic encephalopathy
- Minimize tactile and tracheal stimulation, including airway suctioning.
- Avoid hypovolemia and hypervolemia.
- Avoid hypothermia.
- Avoid hypoproteinemia and hypoalbuminemia.
- Monitor and maintain CPP < 15 mm Hg.
- Maintain CPP > 50 mm Hg.
- Monitor and maintain SvO2, between 55% and 85%.
- Use serial transcranial Doppler monitoring to titrate therapy.

**Management of Intracranial Hypertension**

- Mannitol boluses, 0.5–1.0 g/kg body weight
- Hyperventilation titrated to a PaCO2 of 28–30 mm Hg
- Induced moderate hypothermia to 32°C–33°C
- Achieve serum sodium levels of 145–155 mEq/L
- Induced coma with propofol or pentobarbital titrated to burst suppression of 5–10 cycles/sec
- CVH for oliguria and hyperosmolality (>310 mOsm/L)

**Other Unproven Therapies**

- Prophylactic phenytoin
- Indomethacin, 25 mg intravenous bolus
- Plasmapheresis with...
COAGULOPATHY

Despite severe coagulopathy, patients with FHF seldom have spontaneous hemorrhage. Routine use of FFP is not recommended unless spontaneous bleeding occurs or an invasive procedure is being contemplated. Platelets should be transfused before invasive procedures if the platelet count is less than 50,000 cells/µL. Administration of FFP does not increase survival, or may cause intravascular volume overload compared with FFP; however, more studies using this agent are needed.67 Prophylactic infusion of phenytoin has been studied in two controlled studies which gave different conclusions in regard to its efficiency in preventing seizures, cerebral edema, and survival.37 (Bhatia et al)

ACUTE RENAL FAILURE

Renal failure develops in up to 70% of patients with FHF, and the presence of FHF and renal failure has a grave prognosis without renal support. Mechanisms leading to acute tubular necrosis (ATN) include renal hyperperfusion (due to intravascular volume depletion and reduced mean arterial pressure), systemic inflammatory response syndrome (SIRS), hepatorenal syndrome, and direct toxic effects of the etiologic agent responsible for liver injury (e.g., acetaminophen). The presence of SIRS predicts renal failure in non–acetaminophen-induced FHF.68 Optimal fluid balance is paramount in patients with FHF to avoid prerenal azotemia and progression to ATN. Frequent monitoring of serum creatinine level, urinary output, and serum sodium concentrations is required. Diuretics and “renal dose” dopamine (2–4 µg/kg/min) have no protective value in the therapy for acute renal failure and are potentially harmful. Nephrotoxic drugs such as aminoglycosides or radiographic contrast agents should be avoided. Continuous veno¬ nous hemofiltration (CVVH) is preferred over intermittent hemodialysis, because this modality avoids the rapid fluid shifts and abrupt changes in ICP that are associated with intermittent dialysis.71

MISCELLANEOUS THERAPY

Glycemic control is vital in patients with deep encephalopathy. Constant infusion of 10% to 20% glucose is preferable to bolus administration for maintenance of euglycemia. FHF is a catabolic state, and protein-caloric malnutrition develops quickly. Thus, nutrition should be started soon and adjusted individually to maintain an adequate caloric intake. Enteral nutrition through a nasogastric or nasojugal tube is preferred to parenteral nutrition. Although aromatic amino acid–free enteral formulas are commercially available, their clinical efficacy and cost-effectiveness are not established. Correction of hypomagnesemia, hypokalemia, or hypophosphatemia is accomplished by supplementation of these formulations. H2-receptor antagonists, proton pump inhibitors, or sucralfate are used to reduce the incidence of gastrointestinal ulceration or erosive gastritis.

A high index of suspicion should be maintained for the presence of infection, because fever and leukocytosis may indicate a source of infection. The infection rate is 50% of infected patients. Infection must be suspected in the presence of any sudden clinical deterioration, such as worsening encephalopathy or hemodynamic instability, especially when liver function has started to recover.72 Microbiological cultures should be obtained from appropriate sites, and empirical antibiotics covering both enteric gram-negative and gram-positive bacteria should be started. Antifungal coverage should be initiated, particularly in patients already on broad-spectrum antibacterial coverage who have new-onset clinical deterioration. There are no generally accepted guidelines regarding use of prophylactic antibiotics. Their use is supported by recent studies that suggest that infection and progression to deep encephalopathy are highly correlated.72,75 Selective enteral decontamination may reduce the risk of infection due to gram-negative bacilli, but there are insufficient data to support its routine use.72 (Salmerón et al)

HEPATIC REPLACEMENT THERAPIES

Liver Transplantation

OLT is the only measure that can radically influence the course of FHF. FHF accounts for about 5% to 10% of liver transplants performed in the USA. Spontaneous survival has improved from 15% to 40% thanks to advances in critical care support. The survival rate is 60% improved to 60% after OLT. However, transplantation is an expensive and high-risk procedure with considerable morbidity. Moreover, OLT commits the patient to a lifetime of iatrogenic immunosuppression. In most series, patients transplanted for FHF have a lower 1-year survival than those transplanted for other causes, in part because of their poor clinical condition at the time of the procedure. Clinical liver transplantation continues to evolve, but availability of this therapy is hampered by continued shortages in donor organs. Contraindications to transplantation include irreversible brain damage, uncontrolled infection, severe pancreatitis, and malignancy. Early identification of patients who are likely to survive without OLT is a very important objective. Both the King’s College and the Cliché criteria are used most often to identify such patients (see Box 102–3). Liver biopsy, although not mandatory, may help decide the need for early transplantation. In general, patients with ≤60% are likely to survive without the need for transplantation, whereas those with ≥90% necrosis are unlikely to survive without transplantation.76,77 The prognosis without transplantation is less clear for patients in between these boundaries. These patients require the most aggressive care and attention.

Decisions regarding transplantation do not have to be made at the time of admission, but rather at the time a donor organ has been identified. This is because the typical waiting time for a donor organ for a United Network for Organ Sharing (UNOS) status 1 patient (those with FHF) is 2 to 3 days or more in the United States.78 Various surgical options exist for liver transplantation in patients with FHF (Box 102–5). The most frequently utilized procedure is cadaveric whole organ transplantation, with the donor organ being placed in the orthotopic position. However, continued efforts are being made to assess ways of expanding the donor pool by using marginal donors, living donor liver transplantation, cadaveric split liver transplantation, and various hepatic support systems to prolong survival long enough for the patient to undergo liver transplantation. Therapeutic hepatectomy with temporary portocaval Anastomosis in FHF has been reported to stabilize FHF patients until a suitable liver donor was available.
Hepatic Replacement Therapeutic Options Available to Patients with Fulminant Hepatic Failure

Liver Transplantation
- Cadaveric transplantation
- Whole liver
- Reduced-size liver
- Split liver
- Auxiliary partial liver
- Orthotopic position
- Heterotopic position
- Auxiliary whole liver
- Heterotopic position
- Living-related transplantation
- Left lateral segment
- Left lobe
- Extended left lobe
- Right lobe

Artificial Liver Assist Devices
- Non–cell-based systems
- Charcoal hemoperfusion
- High-volume plasmapheresis
- Continuous high-frequency hemodiafiltration
- Molecular adsorbent recirculating system (MARS)
- Cell-based systems (bioartificial liver assist devices)
- Primary porcine hepatocytes
- Human hepatoblastoma cells
- (Extracorporeal liver assist device [ELAD])

Hepatocyte Transplantation

Procured. The anhepatic periods were 14 hours in two cases and 66 hours in a third report.

Artificial and Bioartificial Liver Assist Devices

The use of artificial and bioartificial liver support devices in FHF has been shown to improve biochemical and physiologic indices of liver function (e.g., serum bilirubin concentration, INR, ICP, and CPP). However, the use of these devices has never been shown to improve transplant-free or overall survival. The MARS system utilizes a hollow-fiber, double-sized, albumin-impregnated dialysis membrane to extract protein-bound toxins into an albumin-containing dialysate. The Prometheus system utilizes fractionated plasma separation and adsorption. Bioartificial systems can use either porcine hepatocytes or human hepatoblastoma cells, and studies are underway to evaluate the role of these approaches in the management of FHF.

Hepatocyte Transplantation

Hepatocyte transplantation has been attempted in patients with FHF to accomplish the same goals as with the hepatic liver assist systems. The rationale is to deliver a sufficient supply of hepatocytes to maintain liver function until regeneration of native liver occurs or a graft for organ transplantation becomes available. Human hepatocytes from livers not used for transplantation can be cryopreserved, making them readily available if needed. Experimental studies in models of FHF showed engraftment and function of transplanted hepatocytes and increased survival. In patients with grade III and IV encephalopathy and severe coagulopathy, intraparenchymal or intrahepatic injection of human hepatocytes has been performed. In two studies, improvements have been noted in several parameters, including encephalopathy score, hemodynamic parameters, and serum ammonia and bilirubin levels. Pulmonary embolism of hepatocytes occurred when the injection was intraportal but not when hepatocytes were injected into the splenic artery. Other concerns about this technique include transplantation and acquisition of an adequate number of hepatocytes (only 0.15–80 g have been injected compared with 300 g [20% of normal liver mass required] to replace liver function), use of immunosuppression in FHF, and the need for a 48-hour period for engraftment and function. New sources of hepatocytes (e.g., stem cells and/or progenitor cells) are needed to increase the number of patients who might be candidates for hepatocyte transplantation. Future trials using this concept are likely if results with hepatocyte liver assist systems prove disappointing.

Conclusion

FHF remains a rare but a devastating illness with high mortality. The treatment of FHF poses a great challenge to intensive care clinicians. Early transfer to a transplant center is preferable not only because of the availability of transplantation, but also because of the availability of experienced clinician as these specialized centers. A multidisciplinary approach to critical care management is clearly required to address the multitude of organ derangements that are sequelae of FHF. Currently, only liver transplantation can radically alter the course of the disease process. Although transplant surgery including immunosuppressive therapy has considerably advanced over the past decade, this intervention is expensive and associated with complications related both to the procedure and the need for lifelong immunosuppression. Therefore, liver replacement strategies that are less invasive and permanent are urgently required. The current experience with nonbiological and biological artificial devices are encouraging but clearly require validation of their safety and efficacy by randomized controlled trials.
11. Continuous venovenous hemofiltration is the preferred method for artificial renal replacement to avoid hemodynamic fluctuations, which can aggravate cerebral hyperperfusion or hypoperfusion.

12. Liver transplantation is the only proven liver replacement therapy to reduce mortality. Both biological and nonbiological artificial liver replacement therapies remain unproven to reduce transplant-free mortality.

ANNOTATED REFERENCES


The classic paper that established the most widely used criteria (Kings College Criteria) for predicting liver transplant-free mortality in a large cohort of patients with either acetaminophen- or non-acetaminophen-induced FHF.


A comprehensive review with many references related to management of acute liver failure.


A comprehensive review of the treatment strategies currently available in animal models of acute liver failure.

Ding GK, Buckley NA. Evidence and consequences of spectrum bias in studies of criteria for liver transplant in paracetamol hepatotoxicity. QJM 2008;101:723-9.

A review of prognostic models for predicting poor outcome in acute liver failure and their limitations.


Review of the role of acetylcysteine in the management of acute liver failure.


Great review of the pathogenesis of cerebral edema in the setting of ALF.


A comprehensive review of hypothermia’s role in treatment of acute liver failure-induced cerebral edema.

REFERENCES

Access the complete reference list online at http://www.expertconsult.com
REFERENCES