Fulminant hepatic failure in children

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Fulminant hepatic failure (FHF) in children is a rare but often fatal event. Our knowledge of this disorder is limited by the rarity of the disorder at any single center. Initiatives are underway to accumulate the experience of several large centers in a multicenter study of pediatric FHF in children funded by the NIH (the Pediatric Acute Liver Failure Study Group). Most FHF cases in children remain without a cause. The mechanisms whereby hepatocytes undergo cell death are unknown, as is an understanding of the events leading to FHF and its progression. Therapy has focused on supportive care in an attempt to ameliorate complications, and early referral to a liver transplant center remains crucial. Outcomes are dependent upon the etiology and the degree of CNS involvement. Clinical trials of liver assist devices, hepatocyte transplantation and use of N-acetylcysteine for nonacetaminophen-induced FHF may hold promise for the future.

Hepatic failure is a syndrome that reflects the consequences of severe hepatocyte dysfunction. Fulminant hepatic failure (FHF) implies the absence of pre-existing liver disease. The loss of hepatocyte function sets in motion a multi-organ response, characterized by hepatic encephalopathy, a complex coagulopathy, derangements of intrahepatic metabolic pathways, and complications of renal dysfunction, cerebral edema, susceptibility to infection, and hemodynamic disturbances.

Once the diagnosis has been contemplated, the methods of diagnosis and prognostic considerations should have emphasis on the appropriate selection of patients who are candidates for liver transplantation.

Definitions
Traditionally, the definition of FHF has been based on the development of hepatic encephalopathy within 8 weeks of the first symptoms of illness without any previous history of underlying liver disease [1]. FHF is further subclassified into [2]:

- Hyperacute liver failure for cases in which encephalopathy occurs within 7 days of the onset of jaundice
- Acute liver failure (ALF) for cases with an interval of 8–28 days
- Subacute liver failure for patients in whom encephalopathy supervenes within 5–12 weeks of the onset of jaundice

The distinction between these groups may seem arbitrary, but many investigators have found paradoxically that those patients with the most rapid onset of encephalopathy have the best chance of spontaneous recovery, despite a high incidence of cerebral edema. This observation has also been seen in children. Rivera-Pen- era and colleagues found that children surviving FHF without transplant were admitted to the hospital sooner after the onset of illness (mean: 8 days) than nonsurvivors (mean: 22 days), and experienced prompt transfer to a transplant center (1.9 versus 12.2 days) [3].

This definition is inadequate for children, because the early stages of encephalopathy are difficult to assess, and encephalopathy may not be apparent until terminal stages of ALF in infants. Furthermore, the duration of illness can be difficult to assess, particularly in infants who present with ALF in the first few weeks of life, secondary to a condition that may be caused by unrecognized metabolic diseases (e.g., mitochondrial disease or a defect of fatty acid oxidation). In an effort to address the ambiguity associated with the definition of ALF in children, the Pediatric Acute Liver Failure Study Group (PALFSG) came to a consensus regarding the definition of ALF in children. The PALFSG defined ALF as:

- Biochemical evidence of liver injury
- No history of known chronic liver disease
- Coagulopathy not corrected by vitamin K administration
- An International Normalized Ratio (INR) greater than 1.5 if the patient has encephalopathy, or greater than 2.0 if the patient does not have encephalopathy
A scale to assess encephalopathy in children younger than 4 years of age was developed by the PALFSG (Table 1). As the pathophysiology of liver failure becomes better understood, definitions should reflect disease mechanisms rather than clinical descriptions. Until then, the consensus definition can be used to identify children with ALF.

In infants and young children, the inclusion of encephalopathy as a cardinal feature of FHF presents a problem, since it is difficult to determine on the basis of behavioral or mental status changes whether such a patient is manifesting early signs of encephalopathy; therefore, the early signs for infants and toddlers should include irritability, poor feeding, listlessness, seizures (often due to hypoglycemia) and loss of normal infantile reflexes. In neonates less than 30 days old, a distinction is made between neonatal liver failure developing in utero from that which appears to have developed in the perinatal period [4]. In these patients, more emphasis is placed on laboratory signs of failing hepatic synthetic or metabolic function.

Pathology
With severe hepatocellular injury, liver metabolic functions are impaired. Patients have compromised glucose homeostasis, increased lactate production, impaired synthesis of coagulation factors and reduced capacity to eliminate drugs, toxins and bilirubin. As a result, patients develop coagulopathy, hypoglycemia and acidosis, all of which increase the risk of gastrointestinal bleeding, seizures and myocardial dysfunction. Bacterial and fungal infections often complicate ALF. Bacteria may enter the systemic circulation from the gut as a result of impaired liver macrophage cell function or in association with the insertion of catheters and endotracheal tubes [5–8]. Depressed production of complement and acute-phase reactants may contribute to decreased response to infection. The combination of a decreased integrity of the immune system, exposure to antibiotics and insertion of catheters increases the risk of fungal infection.

Etiology
Viral hepatitis
A summary of the etiology is provided in Boxes 1–4. Hepatitis A, B, C, D and E, and non-A, non-B and non-C infections, are important causes of ALF, and may be the case in up to 50% of patients [10–15]. The relative incidence of each varies based on patient age, geographic location and risk factors for infection. It is anticipated that vaccination strategies and the ability to screen blood products will decrease the incidence of hepatitis A, B, C and D infections causing acute hepatic failure. The survival from each type varies, with the highest survival rates seen in acute hepatitis A infection, and lowest with non-A, non-B and non-C hepatitis in patients who have not received a transplant [3,16]. The median survival following the onset of grade 3 encephalopathy in patients with viral hepatitis who ultimately die is 4–5 days after hospital admission [17].

### Table 1. Stages of hepatic encephalopathy.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical manifestations</th>
<th>Asterixis/reflexes</th>
<th>Neurologic signs</th>
<th>EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confused, mood changes</td>
<td>Absent/normal</td>
<td>Tremor, apraxia</td>
<td>Diffuse slowing</td>
</tr>
<tr>
<td>II</td>
<td>Drowsy, decreased inhibitions</td>
<td>Present/ hyper-reflexic</td>
<td>Dysarthria, ataxia</td>
<td>Abnormal, general slowing</td>
</tr>
<tr>
<td>III</td>
<td>Stupor, sleepy but arousable</td>
<td>Present/Babinski sign</td>
<td>Muscle rigidity</td>
<td>Triphasic waves</td>
</tr>
<tr>
<td>IV</td>
<td>Coma</td>
<td>Absent</td>
<td>Decerebrate or decorticate</td>
<td>Very slow δ-activity</td>
</tr>
</tbody>
</table>

Data taken from [58,74,80].
Survival rates in patients with hepatitis A or B without liver transplantation are influenced by coexisting complications. Survival rates are 67% if cerebral edema or renal involvement is absent, 50% in patients with isolated cerebral edema, and 30% with both cerebral edema and renal failure [17].

In India and Asia, hepatitis E virus is an important cause of ALF, especially in pregnant females. Hepatitis E virus has recently been identified in the USA as a cause of ALF. Travelers to Mexico and other areas where the disease is endemic are at risk for infection [18].

Other viruses, such as echovirus (types 6, 11, 14 and 19), Coxsackie, herpes, parvovirus, cytomegalovirus and adenovirus, have been described as causes of FHF.

Severe hepatitis in the context of disseminated fatal herpes simplex virus (HSV) infection has been reported rarely in infants, children and adults. Neonatal infection is usually severe, generalized and characteristically associated with retrograde spread of HSV-2 genital infection in the mother [19]. Infants are particularly at risk if infection is primary and/or active at the time of delivery. In older children and adults, infections have been reported in renal transplant patients treated with immunosuppressive drugs, children with kwashiorkor and in patients with primary or secondary immunodeficiency [20]; however, there have also been rare reports of apparently immunocompetent children whose deaths were attributed to fatal HSV hepatitis [21].

Rare fatal causes of Epstein–Barr virus (EBV)-associated fulminant hepatitis have been reported in children [22,23]. In most of these cases, sensitive serologic or immunoperoxidase tissue-staining methods were not employed to rule out other hepatotropic viruses and, therefore, the association is suspect.

Male children with an X-linked recessive lymphoproliferative syndrome can develop massive hepatic necrosis during EBV infection, suggesting that immunodeficiency states are a prerequisite for the development of FHF secondary to EBV. However, using in situ DNA probes, investigators have recently shown highly concentrated EBV-specific DNA in the liver tissue of children with FHF.

Fatal echovirus types 6, 11, 14 and 19 causing massive hepatic necrosis mimicking HSV infection has been documented [24,25].

In immunocompromised hosts, adenoviral infection can cause fulminant hepatitis. Adenovirus has been isolated in 5–20% of patients undergoing bone marrow transplantation, and has been reported to cause invasive disease in 20% of these patients [26,27].

**Drug reactions**

In pediatric series, toxin- or drug-induced liver injury represents 15–20% of cases of FHF [3,10]. Liver toxicity due to medications may be dose related, as seen with acetaminophen, aspirin, azathioprine and cyclosporine, or may represent an idiosyncratic reaction seen with valproic acid, phenytoin, isoniazid, chlorpromazine and halothane [28–30]. Some medications, such as methotrexate, may result in chronic dose-related liver damage. Before liver transplantation was available, the survival rate of patients

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**Box 1. Etiology of fulminant liver failure in neonates and early infancy.**

**Infections**
- Cytomegalovirus
- Epstein–Barr virus
- Echovirus (types 6, 11, 14, 19)
- Hepatitis B
- Herpes simplex virus
- Syphilis

**Metabolic**
- Galactosemia
- Hereditary fructose intolerance
- Hereditary tyrosinemia
- Mitochondrial disease
- Neonatal hemochromatosis
- Niemann–Pick disease type C
- Zellweger syndrome

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**Box 2. Etiology of fulminant liver failure in late infancy and childhood.**

**Infections**
- Epstein–Barr virus
- Hepatitis A, B, C, D, E, non-A, non-B, non-C
- Varicella zoster

**Ischemia**
- Congestive heart failure, pericardial tamponade, hepatic artery thrombosis
- Budd–Chiari syndrome/hepatic vein thrombosis
- Veno-occlusive disease

**Malignancy**
- Hemophagocytic lymphohistiocytosis, leukemia, lymphoma, hemangioendothelioma, nephroblastoma

**Metabolic/miscellaneous**
- Autoimmune hepatitis, sickle-cell disease

**Toxin**
- Aflatoxin, *Amanita phalloides*, copper intoxication, iron
developing FHF with grade 3 or 4 encephalopathy due to idiosyncratic drug reactions or halothane hepatitis was 12.5%, compared with 53% for other causes [17].

The most common cause of drug-related FHF in adolescents and young adults is intentional acetaminophen overdose [31]. The median survival after acetaminophen ingestion for patients who ultimately die is 6–7 days, with a range of 3–56 days [17]. Poor prognostic factors include: cerebral edema, oliguric renal failure and uncompensated metabolic acidosis. Patients without any of these factors have almost a 100% survival rate. The presence of cerebral edema decreases the survival rate to 71%; coexisting cerebral edema and renal failure decreases the survival rate to 53%. If uncompensated metabolic acidosis is present, the survival rate decreases to 7% [17].

**Box 3. Etiology of fulminant hepatic failure in adolescents and young adults.**

**Infections**
- Bacillus cereus
- Hepatitis A, B, C, D, E
- Parvovirus

**Metabolic/miscellaneous**
- Autoimmune hepatitis
- Pregnancy
- Wilson’s disease

**Acetaminophen**

Acetaminophen injures hepatocytes in a dose-dependent fashion, so that the administered dose is a stronger determinant of the likelihood of a reaction than the host's drug-clearance system. Acetaminophen-induced ALF accounts for more than 50% of the cases in adults, and usually occurs within 48 h of an intentional overdose.

ALF from acetaminophen occurs as a result of conversion of acetaminophen to the highly reactive metabolite N-acetyl-p-benzoquinoneimine (NAPQI) through the CYP system [30]. NAPQI is detoxified by conjugation with glutathione. With depletion of hepatic glutathione stores, NAPQI binds to cysteine groups on protein, forming hepatotoxic protein adducts.

Although reported cases of acetaminophen-related ALF reflect single, acute ingestions, others have suggested that liver failure may result from chronic use of acetaminophen with therapeutic intent [32–34]. In either case, serum aminotransferase levels are typically high, exceeding 3500 IU/l. In a patient who has sudden marked elevation of serum aminotransferase levels out of proportion to jaundice, acetaminophen toxicity should be considered as a cause, even when historic evidence is lacking. The measurement of plasma acetaminophen levels predicts the risk of hepatotoxicity only after a single, acute overdose where the time of the ingestion is known. By contrast, plasma levels do not reliably foretell risk in the setting of therapeutic misadventures or with ingestions in the presence of other risk factors such as fasting or concurrent therapy with CYP2E1-inducing drugs (e.g., ethanol and isoniazid). In the latter situations, the diagnosis and treatment are dependent on historical and clinical laboratory findings. Liver injury occurring as a result of idiosyncratic reactions to drugs is characterized by a latency period ranging from 5 to 90 days from the initial ingestion of the drug. If liver failure occurs, the outcome is poor: liver transplantation or death in 75% of cases [35].

**Anticonvulsants**

Drug-induced ALF may occur as a result of exposure to the anticonvulsants phenytoin, carbamazepine and phenobarbital [36,37]. Liver injury occurs within 6 weeks of exposure, and is almost always accompanied by severe rash and eosinophilia indicating an immune-mediated injury. Familial risk and increased risk in African–Americans for anticonvulsant hypersensitivity has been recognized, suggesting that the clinical condition occurs in genetically susceptible

**Box 4. Drugs that may cause idiosyncratic liver injury leading to fulminant hepatic failure.**

- Isoniazid, isoformurane, sulfonamides, lisinopril, phentoin, nicotinic acid, statins, imipramine, propylthiouracil, gemtuzumab, halothane, amphetamine, valproic acid, labelalol, amiodarone, etoposide, dapsone, flutamine, herbs, toldapolone, didanosine, quetiapine, efavirenz, nefazodore, metformin, allopurinol, ofloxacin, methildopa, pyrazoloacidine, ketoconazole, troglitazone, diclofenac

- **Combination agents with enhanced toxicity**
  - Trimethoprim–sulfamethoxazole
  - Rifampin–isoniazid
  - Amoxicillin–clavulanate

- **Some herbal products/dietary supplements associated with hepatotoxicity**
  - Kava kava, chaparrai, skullcap, germander, pennyroyal, Jin Bu Huan, heliotrope, rattleweed, comfrey, sunnhemp, senecio, impila, greater celandine, gum thistle, He Shon, Wu Ma Huang, lipokinetz, Bai-Fang herbs

Adapted from [80].
patients [38]. Although the specific gene associated with risk has not been identified, in vitro studies suggest that abnormal metabolite detoxification is the basis for inherited susceptibility [39]. Phenytoin is metabolized by the CYP system, with the production of a highly reactive intermediate. Neoantigens develop if the reactive metabolite binds covalently to tissue macromolecules, and the antigens precipitate immune-mediated injury [39]. Autoantibodies recognizing liver microsomes have been detected in the sera from patients who have hypersensitivity reactions to anticonvulsants, whereas no autoantibodies have been detected in sera from healthy control subjects or patients receiving chronic phenytoin therapy without toxicity [39].

**Immune dysregulation**

Autoimmune hepatitis (AIH) can present as ALF in children, and is an example of immune dysregulation [40–42]. AIH should be considered early in the presentation, as treatment with corticosteroids may permit survival without liver transplantation. AIH occurs as a result of an immune reaction to liver cell antigens, possibly triggered by a mechanism of molecular mimicry or loss of self tolerance. With the acute presentation, autoantibodies may be absent, and liver histology shows severe hepatic necrosis accompanied by interface hepatitis and plasma cell infiltration.

Evidence suggests that ALF in some patients may reflect a disproportional immune response to a common stimulus, characterized by impaired cell-mediated and humoral immunity, increased risk for infectious complications and aplastic anemia. Patients may present with findings consistent with systemic inflammatory response syndrome. Hemophagocytic lymphohistiocytosis (HLH) may be a prototype for ALF caused by a disproportional immune response [43]. HLH is a disorder of immune regulation characterized by decreased natural killer (NK) cell function, uncontrolled macrophage activation and increased proinflammatory cytokines (IFN-γ, TNF-α, IL-1 and IL-2 receptor). NK cells comprise a central component of the innate immune system. They mediate cell–cell killing by the perforin and granzyme pathways, and are responsible for maintaining self tolerance. NK cells constitute a high proportion of innate resident immune cells in the liver, and play a pivotal role in maintaining inflammatory homeostasis at the port of entry of gut-originating antigens. It remains to be seen if disturbed NK cell function comprises a fraction of patients who have ALF of indeterminate cause. Nevertheless, it is tempting to speculate that such an immune disturbance may play a role in situations other than systemic HLH. Targeted anti-inflammatory therapy in early stages of disease might promote recovery and mitigate the need for transplantation. Further studies will be necessary to characterize the complex immune responses associated with various causes of ALF, particularly those of indeterminate cause.

**Metabolic**

An expanding number of inborn errors of metabolism can present with FHF, often within the first year of life. It seems clear that liver failure starts in utero in some of these entities (neonatal hemochromatosis and mitochondrial respiratory chain defects), whereas the clinical manifestations of others depend on postnatal exposure to nutritional substrates or conditions of catabolic stress (galactosemia, hereditary fructose intolerance, tyrosinemia and fatty acid oxidation defects). These inborn errors of metabolism lead to an acute or progressive intoxication from accumulation of toxic compounds proximal to the metabolic block.

**Mitochondrial hepatopathies**

Although often considered to be disorders of the CNS, muscle or heart, mitochondrial disorders of the respiratory chain can present in the neonatal period with liver failure [44]. Neonatal liver failure has been reported in association with selective deficiencies, including complex IV (cytochrome-C oxidase), and complexes I and III [45,46].

In other infants, liver failure is due to DNA depletion syndrome [47]. Liver failure due to DNA depletion appears to be predominantly a disease of infancy, with most patients presenting in the first 6 months of life [48,49].

A key laboratory feature to be noted is the presence of significant lactic acidemia and an elevated molar ratio of plasma lactate:pyruvate (normally less than 20:1). Serum β-hydroxybutyrate levels are generally elevated, with an increased ketone body molar ratio of β-hydroxybutyrate:acetate (normally less than 2:1). The observation of persistent hyperlactatemia (>2.5 mM), particularly in the postabsorptive period, is highly suggestive of a respiratory-chain defect. Definitive diagnosis depends on the demonstration of reduced activity of respiratory-chain enzymes in fresh frozen liver tissue, quantification of mitochondrial DNA compared with nuclear DNA, and screening for mitochondrial DNA deletions or point mutations using molecular techniques.
Fatty acid oxidation disorders

Several of more than 20 known disorders of intrahepatic fatty acid oxidation (FAO) have been described, presenting with episodes of hepatic failure in infants and young children. As FAO does not play a major role in energy production until late in fasting, affected patients may remain asymptomatic until provoked beyond the usual period of fasting, or until the need for FAO and ketone body production is accelerated by catabolic stress. These disorders present with a variety of clinical manifestations, including metabolic decompensation during fasting, or with viral infections, hypoketotic hypoglycemia and abnormal function of fatty acid-dependent tissues, particularly the heart, muscle and liver. In general, disorders that affect the most proximal steps in FAO result in more profound reductions in ketone body production and less recovery of clinical manifestations associated with ketogenesis, more severe hypoglycemia and more precipitous presentation after a shorter period of fasting. Thus, defects affecting long-chain fatty acid transport across the plasma membrane (carnitine palmityltransferase 1 deficiency and carnitine transport deficiency) and those affecting the intramitochondrial β-oxidation of long-chain fatty acids (very-long-chain acyl-CoA-dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA-dehydrogenase deficiency) are most likely to present in the first few months of life with life-threatening episodes of vomiting, hypoketotic hypoglycemia, coma, marked hepatomegaly, liver dysfunction, hypotonia and cardiomyopathy. The laboratory evaluation is usually characterized by normal serum bilirubin, mild elevation of serum aminotransferases, mild acidosis, hyperammonemia and coagulopathy, as well as marked elevations in serum uric acid levels and creatine phosphokinase levels. Long-chain fatty acid metabolites in the urine and blood offer a clue to the diagnosis.

Acute ischemic injury

Ischemic hepatitis may meet criteria for ALF [50–52]. Liver histology is characterized by centrilobular necrosis with preservation of the periportal zone. Serum aminotransferase levels may reach 5000–10,000 IU/l, and coagulopathy is found in 25–50% of patients. Aminotransferase levels decrease rapidly in response to stabilization of the circulation. The rapid decrease in aminotransferase levels in the absence of increasing serum bilirubin or worsening coagulopathy may distinguish ischemic hepatitis from viral or toxic hepatitis. Prognosis depends on correction of the underlying cause of hypotension.

Wilson's disease

Children with Wilson's disease can present with FHF or cirrhosis. Wilson's disease is a frequent indication for pediatric liver transplantation [3]. Decreased serum ceruloplasmin levels, elevated 24-h urine copper, hemolytic anemia, the presence of Kayser–Fleischer rings, and renal and neurologic abnormalities characterize Wilson's disease. Serum ceruloplasmin levels may be elevated to normal levels in patients with Wilson's disease, and urinary copper excretion may be elevated in patients with liver failure from other causes. Urinary copper excretion after d-penicillamine challenge and serum alkaline phosphatase:total bilirubin ratio of less than 2.0 may be helpful in differentiating Wilson's disease from other causes of FHF [53]. The gene for Wilson's disease, inherited in an autosomal-recessive manner, is located on chromosome 13.

Manifestations of liver failure

Portal hypertension

Patients with FHF do not usually have evidence of severe portal hypertension like patients with chronic liver failure. Portal hypertension in patients with FHF is secondary to increased hepatic resistance to hepatic blood flow due to sinusoidal collapse and distortion of the liver cell architecture, and microcirculation after extensive liver cell necrosis [54,55].

Although important prognostic information can be obtained by liver biopsy in acute liver injury, biopsy is associated with a high rate of complications and may not alter management. The presence of ascites at admission is a poor prognostic factor in children with FHF who do not undergo liver transplantation [3].

Circulatory changes

Acute liver failure is associated with a hyperdynamic circulation—a high cardiac output and decrease in systemic vascular resistance and mean arterial pressure [55]. Dilatation of the splanchnic circulation will result in increased hepatic vascular pressure, especially in the context of increased hepatic vascular resistance. The cause of systemic vasodilatation may be the accumulation of vasoactive substances of splanchnic origin in the systemic circulation that are either metabolized by a normal liver or abnormally released during acute injury [55].

Electrolyte changes & renal failure

Hypoglycemia (blood glucose of less than 40 mg/dl) is due to depletion of hepatic glycogen...
stores and impaired gluconeogenesis with massive hepatic necrosis or end-stage liver disease [56]. Other factors include elevated serum insulin levels, as a result of decreased liver catabolism, and abnormal glucagon and growth hormone.

Hyponatremia is frequently present in patients with acute and chronic liver disease because of decreased water excretion, increased renal sodium retention (due to stimulation of the renin–angiotensin–aldosterone system), and decreased activity of the sodium–potassium pump. Hypokalemia often accompanies hyponatremia and may be due to renal losses and hyperaldosteronism. With severe renal impairment, hyperkalemia may develop. Other abnormalities include hypocalcemia and hypomagnesemia. Serum calcium levels should be corrected for corresponding serum albumin levels.

Renal failure is present in 40% of patients with ALF and may be due to an imbalance between neurohumoral factors, renal vasoconstrictors and vasodilators [10]. Patients have marked renal vasoconstriction despite systemic vasodilation.

Plasma renin activity is typically increased, and renal prostaglandin activity is decreased, in patients with FHF. An elevated serum creatinine on admission is a poor prognostic sign in patients with acute liver injury. Serum creatinine levels are significantly higher after acetaminophen overdose than with other causes of FHF [16].

Acidosis at admission is also a poor prognostic sign. Acid–base disturbances may be present in up to 60% of children with FHF [10]. Renal excretion of sodium is significantly decreased in patients and may contribute to ascites formation.

**Hepatic encephalopathy & cerebral edema**

Hepatic encephalopathy is graded I to IV (Table 2). In one pediatric series, encephalopathy developed within 3 weeks of the initial symptoms of hepatitis in 88% of children with FHF. The survival in many series of ALF correlates directly with the degree of encephalopathy, with 60% survival with grade I, and decreasing to 5–25% with grade IV, disease [57]. There is a rapid progression through the stages of encephalopathy in children with FHF. In a pediatric series before the availability of orthotopic liver transplantation for FHF, the mean interval between the onset of encephalopathy and death was 4.2–8.4 days [10,12]. Jaundice of longer than 7 days duration before the development of hepatic encephalopathy is associated with poor outcome [16]. Severe encephalopathy may be associated with electrolyte abnormalities and hypotension, making affected patients less suitable for transplantation [3]. Because of the short interval between the onset of encephalopathy and patient death in patients with FHF, rapid transfer to a center able to perform emergency liver transplantation and early listing is essential to improve survival [5,58]. As stated above, in young children (<4 years old) and infants encephalopathy may not be easy to recognize, so all patients who do not have known liver disease and who present with elevated aminotransferase levels or conjugated hyperbilirubinemia should be evaluated for coagulopathy and evidence of encephalopathy. If there is biochemical evidence of liver injury, no history of known chronic liver disease, and coagulopathy or change in mental status, the child should be admitted to the hospital, preferably to a center that has expertise in the care of ALF and the capability to perform liver transplantation.

Even with early listing and successful transplantation, there may be neurologic sequelae in patients with advanced encephalopathy who undergo transplantation. Neurologic disease is a significant cause of post-transplant morbidity and mortality in patients receiving transplants for FHF.

It is generally accepted that hepatic encephalopathy is due to ammonia-induced alteration of the brain neurotransmitter balance, especially at the astrocyte–neuron interface [59]. Several authors have postulated that activation of the GABA/benzodiazepine inhibitory neurotransmitter system plays an important role in the pathogenesis of hepatic encephalopathy. GABA, the principal inhibitory neurotransmitter of the brain, is normally generated in the intestinal tract and degraded in the liver. During liver failure, GABA may escape hepatic metabolism and induce an increase in the number of its own receptors [57]. Intravenous administration of flumazenil, a benzodiazepine antagonist, has not been effective in reversing clinical or electrophysiologic brain abnormalities in children with FHF [58]. Other postulated mechanisms of hepatic encephalopathy include depletion of excitatory neurotransmitters, such as norepinephrine or dopamine, production of false neurotransmitters, such as octopamine, increased permeability of the blood–brain barrier, allowing toxic substances access to the CNS, and astrocyte dysfunction [60].

Cerebral edema is frequently present in patients with FHF and hepatic encephalopathy [57,59]. Brain edema occurs in 45% or more of patients with FHF, and is the major cause of morbidity and mortality [16,60]. It may develop concurrently with other symptoms of hepatitis, or its development
may be delayed [12]. Papilledema is usually absent in patients with FHF and cerebral edema, unlike patients with cerebral edema from other causes.

Cerebral blood flow adjusted for CO₂ levels correlates with cerebral swelling and mortality in patients with FHF. The presence of cerebral edema is a worse prognostic factor than renal failure, gastrointestinal bleeding or infection; only a serum bilirubin level higher than 20 mg/dl is a worse prognostic sign. In a series of children not undergoing liver transplant for FHF, cerebral edema by CT scan was seen in 50% of non-survivors, but never seen in survivors [3]. CT changes occur late and are absent in the majority of patients with increased intracranial pressure (ICP) by epidural monitoring [61].

Epidural ICP monitors appear to be more effective than CT scanning to detect increased ICP in patients with FHF, and they appear to be safe even in patients with markedly prolonged coagulation studies without associated thrombocytopenia (<50,000 platelets) [62]. This type of monitor can identify rises in ICP not associated with clinical symptoms. Complications of ICP monitoring include hemorrhage, infection and cerebrospinal fluid leak. Epidural monitors appear to be safer than subdural bolts or parenchymal monitors, which are associated with a higher rate of complications.

### Pulmonary disease

Adult respiratory distress syndrome (ARDS) frequently complicates acute or chronic liver failure and is often irreversible, despite medical therapy. Sepsis appears to be an important risk factor for the development of ARDS in patients with liver failure; patients with liver failure may have impaired Kupffer cell function, normally responsible for detoxification of gut-derived bacteria and their products [63]. Although the prognosis of ARDS associated with liver failure is very poor, ARDS has been shown to rapidly resolve following liver transplantation [63].

Pulmonary arteriovenous shunting with hypoxemia is frequently present in children with chronic liver disease and portal hypertension, but rarely seen in FHF [64]. This condition is reversible following liver transplantation.

### Coagulopathy

The liver is responsible for the synthesis of factors II, V, VII, VIII, IX and X. Reduced levels of these factors and other proteins important in coagulation reflect abnormalities of protein synthesis and impaired post-translational modification of vitamin K-dependent proteins (factors II, VII, IX and X; proteins C and S). Factor VIII is synthesized in the liver and endothelial cells; levels are increased in acute and chronic liver disease, including FHF. A high concentration of Factor VIII is the result of damaged vascular endothelial cells. The levels of all the other factors are typically decreased in liver disease, usually to an average of 20% or less of normal [53]. Factor V, which is vitamin K independent, may be the most sensitive single indicator of outcome in FHF. A rapid decrease in the level of this factor, which has a half-life of 12–24 h, reflects impaired synthesis due to rapidly developing liver damage [65]. Factor V levels are significantly decreased in nonsurvivors as compared with survivors [10,53]. The degree of decrease varies with the cause of FHF. In children with FHF due to viral hepatitis or drug injury, Factor V levels were higher in survivors without liver transplant (28 and 11%) than in children who died (13 and 7%) or received a transplant (18 and 5%). In patients with acetaminophen overdose, admission levels less than 10% were 91% sensitive, but only 55% specific in predicting fatal cases [65]. The specificity increased to 91% if the admission Factor V level of less than 10% was combined with grade III or IV encephalopathy. Admission values of these factors could be used to select patients who would benefit from early listing for liver transplantation.

The prothrombin time (PT) is an important prognostic sign in patients with fulminant and chronic hepatic failure, and is used to determine the timing of listing for liver transplant [66]. With intact vitamin K stores, PT is a reliable indicator of hepatic synthetic capacity. In children with FHF due to viral hepatitis or toxin injury, PTs are usually less than 14–20% of normal [53]. In one pediatric series of FHF, only patients with a PT of less than 90 s survived, although 60% of non-survivors had PTs of less than 90 s [12]. In the case of acetaminophen overdose, the PT at admission is not helpful in differentiating survivors and

### Table 2. Coma stage for children younger than 4 years.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical signs</th>
<th>Reflexes</th>
<th>Neurologic signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (I and II)</td>
<td>Inconsolable crying, sleep reversal, inattention to task</td>
<td>Hyper-reflexic</td>
<td>Untestable</td>
</tr>
<tr>
<td>Mid (III)</td>
<td>Somnolence, stupor, combativeness</td>
<td>Hyper-reflexic</td>
<td>Most likely untestable</td>
</tr>
<tr>
<td>Late (IV)</td>
<td>Comatose, arouses with painful stimuli (IVa) or no response (IVb)</td>
<td>Absent</td>
<td>Decerebrate or decorticate</td>
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nonsurvivors [65]. Fibrinogen levels are in the range of 0.8 g/l in children with FHF, and, when associated with increased fibrinogen degradation products, indicate fibrinolysis and disseminated intravascular coagulation.

Management
Care of a patient with FHF may be optimized by hospitalization at a transplant center. Survival is significantly better in patients undergoing early rather than late transfer [3].

Patients with liver failure have an increased glucose requirement, which can usually be satisfied by administration of dextrose 10–20% to maintain serum glucose of more than 60 mg/dl. Higher concentrations of glucose are required for persistent or symptomatic hypoglycemia. Maintaining normal blood glucose levels is especially challenging in those patients who require fluid restriction because of total body sodium and fluid overload, and frequently have hypokalemia due to diuretic therapy and impaired renal function.

In patients unable to take fluids orally, intravenous fluid is usually administered at a rate to replace insensible losses, while maintaining adequate blood glucose levels. Supplementation of intravenous fluid with calcium and magnesium is often required [57]. Hyponatremia should not be corrected with hypertonic saline, which worsens hepatic encephalopathy and total body fluid overload. Potassium-sparing diuretics such as spironolactone are helpful in patients with ascites due to hyperaldosteronism [67]. Severe renal dysfunction may be associated with the development of hyperkalemia. In patients with chronic liver failure, a sodium-restricted diet is an important adjuvant to diuretic therapy [68]. Medication administration to patients with acute and chronic liver disease and renal impairment should be modified accordingly.

Adequate nutritional intake is essential in patients with liver failure. Enteral nutrition is preferred. Infants are given formulas with higher concentrations of medium-chain triglycerides, which do not require incorporation into bile acid containing mixed micelles for intestinal absorption [69]. Care should be taken to avoid formulas that predispose patients to essential fatty acid deficiency or dicarboxylic aciduria [70]. Patients with biliary tract obstruction should receive supplementation of fat-soluble vitamins (A, D, E and K) because of deficient bile acid reabsorption. Complications of fat-soluble vitamin deficiency include xerosis, night blindness, rickets, osteoporosis, peripheral neuropathy, ataxia, ophthalmoplegia, impaired immune function and coagulopathy [69,70]. Patients with chronic liver disease and hepatic encephalopathy may benefit from oral protein restriction, but they may require a daily intake of 0.8–1.0 g/kg/day to maintain nitrogen balance [71]. Occasionally, parenteral nutrition may be required, and patients usually tolerate solutions containing a standard amino acid mixture [72]. Abnormalities have been noted in amino acid profiles in cirrhotics, and it has been hypothesized that decreased concentrations of branched-chain amino acids and increased concentrations of aromatic amino acids result in the production of false neurotransmitters [73]. Randomized, controlled trials using branched-chain amino acid solutions have noted a short-term beneficial effect on mental recovery from hepatic encephalopathy, with conflicting results on case fatality rates [72].

The primary goal in patients with FHF is to keep ICP lower than 25 mmHg. Intracranial pressures lower than 25 mmHg are associated with improved cerebral perfusion and a decreased rate of herniation. The cerebral perfusion pressure should be higher than 40–50 mmHg. Cerebral perfusion pressure is the calculated difference between the mean arterial pressure and the ICP. Because of coagulation abnormalities, many patients will be unable to undergo invasive monitoring and will be monitored by CT scans instead of a bolt or epidural monitor. Methods to reduce ICP include elective intubation, mannitol infusion and sodium and fluid restriction.

Vitamin K, 5–10 mg, is administered in patients with depleted hepatic stores. The dose is 1 mg/kg/year of age/day for three consecutive days, and then every other day [56]. Fresh frozen plasma (FFP) may be administered in asymptomatic patients with severe prolongation of their PT (>25–35 s), but is almost always used for patients with active bleeding with a prolonged PT and decreased Factor V levels, or before invasive procedures [74]. Administration of FFP increases the difficulty of following PT and Factor V levels as prognostic indicators. Volumes of FFP administered may be limited by fluid overload.

Early trials suggested that charcoal hemoperfusion would significantly improve survival in patients with FHF. Charcoal is an effective adsorbent for a wide range of soluble molecules and toxins that accumulate in FHF [17]. In controlled trials, charcoal hemoperfusion does not provide an additional benefit over specialized intensive care unit care. Plasmapheresis has been shown to have limited beneficial effect in children with FHF and hepatic encephalopathy [60]. Plasmapheresis
should be initiated early in the course of hepatic failure to be of benefit [60]. Complications of plasmapheresis include thrombocytopenia and catheter-related infections.

*N*-acetylcysteine replenishes depleted glutathione stores in acute acetaminophen overdose, thereby decreasing hepatotoxicity. If administered more than 15 h after the overdose, this agent is thought to be ineffective. Continuous intravenous *N*-acetylcysteine administration has been shown to improve mean arterial blood pressure and oxygen consumption and extraction in patients with FHF [75].

**Liver transplantation**

Survival after liver transplantation has improved dramatically since the early 1980s, when ciclosporin use for liver transplantation became common. Between 1987 and 1994, the United Network of Organ Sharing database reported 5-year actuarial patient and graft survivals after pediatric orthotopic liver transplantation of 75.8 and 59.9%, respectively. More recently, the combination of new immunosuppressive modalities with innovative surgical techniques has allowed pediatric 1-year survival rates to reach close to 90% in many large centers.

Biliary atresia is the most common indication for orthotopic liver transplantation in children. Even with the timely performance of biliary drainage procedure, 75% of children with biliary atresia require liver transplantation before 5 years of age.

Recent advances in surgical techniques, such as reduced liver and split liver grafts, have reduced waiting times and pretransplant morbidities for pediatric orthotopic liver transplantation candidates. Liver transplantation for FHF places the patient at the top of the transplant waiting list for a deceased donor graft. Unfortunately, with the donor organ shortage, this does not guarantee a donor organ will be available in time to prevent the complications of FHF. In order to attempt to decrease the morbidity and mortality associated with FHF, auxiliary liver transplants and hepatocyte transplants for patients with FHF have been utilized with some success [76,77].

**Experimental therapies**

While liver transplantation has proven to be a life-saving procedure for patients with FHF, the shortage of organs and unpredictability of organ availability for liver transplantation makes this option unattainable for many individuals. One potential solution to this problem is the use of an extracorporeal liver support system.

Artificial liver support has been attempted for over 40 years. Temporary systems have been developed to endeavor to expedite recovery from acute decompensation, facilitate regeneration or serve as a bridge to liver transplantation. Various nonbiological approaches have met with limited success, presumably because of the role of the liver in synthetic and metabolic functions that are inadequately replaced in these systems. Hemodialysis, hemoperfusion over charcoal or with resins or immobilized enzymes, plasmapheresis and plasma exchange have all been utilized. Purely biological approaches have shown encouraging results, but have been difficult to implement in the clinical setting. These have included whole-organ perfusion and perfusion of liver slices.

Bioartificial devices typically incorporate isolated cells in a bioreactor to simultaneously promote cell survival and function, as well as to provide for a level of transport seen *in vivo*. Several different systems differing in their geometry, cells and perfusate have been evaluated in clinical trials.

The HepatAssist™ system [101] is an extracorporeal liver failure therapy device in which the function of porcine liver cells is supplemented by a detoxification column filled with charcoal particles. Demetriou and colleagues published the only prospective, randomized, multicenter, controlled trial of liver assist therapy utilizing the HepatAssist system [78]. A total of 171 (86 control and 85 bioartificial liver) patients with fulminant/subfulminant hepatic failure or primary graft nonfunction following liver transplantation were enrolled, and included 147 patients with fulminant or subfulminant hepatic failure and 24 patients with ALF due to primary nonfunction after liver transplantation. Survival for the entire patient population at 30 days was 71% for bioartificial liver versus 62% for control (p = 0.26). After exclusion of primary graft nonfunction patients (n = 24), survival was 73% for bioartificial liver versus 59% for control (p = 0.12; n = 147). The study demonstrated safety and improved survival in the subset of patients with fulminant/subfulminant liver failure compared with controls. Exclusion of patients with primary nonfunction was rationalized, since these patients were much less likely to develop neurologic sequelae of liver failure, such as cerebral edema, herniation and brain death. Despite this favorable report, US FDA approval of this BAL device was not obtained. Research in this field remains active. However, there are no BAL devices yet
approved for clinical use outside of an experimental protocol. Use of these systems in children has been limited to case reports in the literature.

In summary, liver-assist devices have the potential to serve in the treatment of previously healthy patients with FHF. Current data, including the trial by Demetriou and colleagues, indicate a role for liver-assist devices as a treatment for acute hepatic encephalopathy. Enhancements to the liver-assist devices, such as design provisions for continuous therapy and increasing the number of metabolically active hepatocytes, are likely to be associated with greater efficacy in future clinical trials. Whether liver-assist devices can ever achieve a status in the treatment of liver failure that is comparable to the status of hemodialysis in the treatment of renal failure remains uncertain.

Financial & competing interests disclosure
Dr Philip Rosenthal is on the Scientific Advisory Board of Arbios. Arbios is the manufacturer of a bioartificial liver support device. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Executive summary

Definition of fulminant hepatic failure

- Fulminant hepatic failure (FHF) implies the absence of pre-existing liver disease.
- FHF includes development of hepatic encephalopathy within 8 weeks of the first symptoms of illness, which can be problematic in infants and young children, since it is difficult to assess behavioral and mental changes in these patients.
- FHF includes coagulopathy and severe hepatic necrosis.

Etiologies of fulminant hepatic failure

- Hepatitis viruses, including hepatitis A–E, echovirus, Coxsackie, herpes, parvovirus, cytomegalovirus, Epstein–Barr virus and adenovirus, have all been implicated.
- Toxin- or drug-induced liver injury represents 15–20% of all cases of FHF in children.
- Inborn errors of metabolism, including galactosemia, hereditary fructose intolerance, tyrosinemia, fatty acid oxidation defects, mitochondrial hepatopathies and Wilson's disease, may present with FHF.
- Indeterminate causes for FHF continue to represent a significant number of children with FHF, requiring better methods at diagnosis and prevention.

Manifestations of fulminant hepatic failure

- Hyperdynamic circulation with a high cardiac output and decreased systemic vascular resistance and mean arterial pressure may occur.
- Hypoglycemia, hyponatremia and hypokalemia may be observed.
- Renal failure may progress and subsequent hyperkalemia may ensue.
- Hepatic encephalopathy and cerebral edema will ultimately determine outcome success.
- Pulmonary disease may include the adult respiratory distress syndrome.
- The liver is responsible for the synthesis of vitamin K-dependent clotting factors, and these will be impaired with FHF, resulting in a coagulopathy and significant risk for bleeding.

Management

- Maximal supportive care is necessary in order to achieve good outcomes for FHF.
- Early referral to a specialized liver transplant center is encouraged and preferable.
- Administration of intravenous glucose solutions to prevent hypoglycemia and seizures is often necessary.
- Adjustment of fluids and electrolytes is often necessary.
- Maintaining appropriate intracranial pressure may require placement of a monitoring device and administration of mannitol, intubation and hyperventilation, sodium and fluid restriction, and elevation of the head of the bed.
- Liver transplantation has significantly improved the outcome for patients with FHF.
- The donor organ shortage has led to the development of liver-assist devices and use of auxiliary and hepatocyte transplantation for patients with FHF.

Future perspective

- A better understanding of the mechanisms responsible for hepatocyte death and injury should lead to improved and targeted therapies.
- The use of liver-assist devices to allow a bridge to transplantation and regeneration and recovery of the native liver will become a reality.
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Bibliography
