Fulminant hepatic failure: etiology and indications for liver transplantation

Daniel Gotthardt¹, Carina Riediger¹, Karl Heinz Weiss¹, Jens Encke¹, Peter Schemmer², Jan Schmidt² and Peter Sauer¹

¹Department of Internal Medicine IV, University Hospital of Heidelberg, Im Neuenheimer Feld 410, 69120 Heidelberg and ²Department of Surgery, University Hospital of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany

Abstract
Fulminant hepatic failure is characterized by the development of severe liver injury with impaired synthetic capacity and encephalopathy in patients with previous normal liver or at least well compensated liver disease. The etiology of fulminant hepatic failure refers to a wide variety of causes, of which toxin-induced or viral hepatitis are most common. In spite of specific therapeutic options in distinctive etiologies, orthotopic liver transplantation is the only therapy proven to improve patient survival in the majority of patients. The outcome is determined by the complications like severe coagulopathy, infections, renal impairment or increased intracranial pressure. The decision for transplantation depends on the possibility of spontaneous hepatic recovery, which may be estimated by several factors. The most important variables for predicting the need of transplantation in fulminant hepatic failure are the degree of encephalopathy, patients age and the underlying cause of liver failure.

Keywords: fulminant hepatic failure; liver transplantation

Main Text

Overview
Fulminant hepatic failure (FHF) or acute liver failure (ALF) is defined as the rapid development of acute liver injury with severe impairment of the synthetic function and hepatic encephalopathy in a patient without obvious, previous liver disease. The time interval of onset of symptoms like jaundice and the appearance of encephalopathy led to several definitions of FHF [1,2]. Although hyper acute, fulminant and subfulminant hepatic failure may differ in their clinical features, like the incidence of cerebral edema, renal failure or portal hypertension, in clinical practice the different sub-definitions were not generally accepted [3].

FHF is not one of the major indications for orthotopic liver transplantations (OLT), but remains the only therapeutic option for patients, without sufficient regeneration of hepatocytes proven to improve survival. Before liver transplantation had become a reasonable option survival rates of acute liver failure were as low as 15%, but had achieved rates of 60% up to 80% in different series in the last decade [4]. Since the liver is capable of regenerating to a large extent and in several cases the underlying cause of hepatocyte injury may be removed or at least can be controlled with supportive medical therapy, FHF in principle may resolve in a complete recovery. The decision for transplantation depends upon the estimation of the probability of spontaneous recovery and may be very difficult, weighing the advantages of an early transplantation against the disadvantages of an unnecessary transplantation with all consequences. Therefore prognostic scores have been developed as decision support systems for indication and optimal time point of liver transplantation. Overall about 5 to 10% of annual liver transplantations are due to acute liver failure. In the UNOS/OPTN registry, in 2004, 491 out of 5845 transplantations were due to FHF (8.4%) [5]. In 2005 in the German registry 87 out of 1401 transplantations were reported to be associated with FHF (6.2%) [6] (see Table 1).

Etiology of acute liver failure
Generally FHF is defined by reduced synthesis parameters of the liver, usually INR ≥1.5 and reduced detoxification resulting in any degree of encephalopathy. This is accepted by the exclusion of preexisting
 ongoing controversy of the initiation of antiviral response leading to elimination of HBV, led to an failure, the reduced possibility of complete immune treatment strategies against HBV may avoid fatal liver regions. Since there is evidence, that new antiviral incidence of viral hepatitis in different geographic in different reports, again reflecting the overall routine serology [9]. The overall incidence varies widely since precore or pre-S mutant viruses may escape by of FHF and the incidence may be underestimated, Hepatitis B is probably the most common viral cause of FHF and the incidence may be underestimated, if the disease has been known for less than 26 weeks [1]. If FHF is due to autoimmune hepatitis, Wilson’s disease, and vertically acquired HBV infection, the possibility of preexisting cirrhosis may be neglected, if the disease is known for less than 26 weeks [7]. FHF can result from a wide variety of causes, but viral or toxin-induced hepatitis are the most common (see Table 2).

### Drug induced liver failure

One of the most common causes of FHF is a substance that by itself is cytotoxic or after metabolizing is able to trigger a cascade of cytotoxic and/or autoimmune phenomena. The most important drug is acetaminophen not accounting only for the majority of drug induced ALF, but also being the most common reason for acute liver failure. In several cases the incidence of acetaminophen induced FHF varies among geographic regions, which mostly is due to the local incidence of the different forms of viral hepatitis [4,8,9]. Mushroom poisoning such as Amanita phalloides can cause acute liver failure as well, which should be excluded explicitly during initial evaluation of suspected patients. These intoxications are often preceded by severe gastrointestinal disease, like abdominal pain, diarrhea and vomiting.

### Viral hepatitis

Hepatitis B is probably the most common viral cause of FHF and the incidence may be underestimated, since precore or pre-S mutant viruses may escape by routine serology [9]. The overall incidence varies widely in different reports, again reflecting the overall incidence of viral hepatitis in different geographic regions. Since there is evidence, that new antiviral treatment strategies against HBV may avoid fatal liver failure, the reduced possibility of complete immune response leading to elimination of HBV, led to an ongoing controversy of the initiation of antiviral treatment [10]. Although hepatitis A is the most common cause of acute viral hepatitis, a progression to FHF is observed in rare cases. Hepatitis C virus seems to be a cause of FHF only in a few cases. [4, 11]. Hepatitis E, which is more severe in pregnant women and is endemic in specific areas can cause FHF, thus travel history is important during initial presentation [12,13]. Other viral infections leading to ALF and requiring OLT have been described, e.g. Herpes Virus, but are often caused by immunosuppressive treatment, which was initiated before.

### Vascular origin

The different blood supply related to the liver can be involved in FHF. Budd-Chiari syndrome, hepatic vein thrombosis, which is more common in females with a medium age of 35 may lead to FHF. [14,15]. Portal vein thrombosis may be the reason for FHF, but often is associated with cirrhosis of the liver or a pancreatic process. Veno-occlusive disease i.e. in the course of hematopoetic cell transplantation and ischemic hepatitis due to reduced arterial perfusion can also be a reason for FHF. Therefore abdominal imaging including assessment of arterial, portal and venous perfusion is strongly recommended starting with ultrasound examination. In most cases further imaging modalities like CT-scan or MRI are required.

### Wilson’s disease

A rare cause of acute liver failure is an acute manifestation of Wilson’s disease (WD). It can occur as FHF or as acute-on-chronic event. Together with autoimmune hepatitis it is generally considered that WD comply with the criteria of acute liver failure, although in most cases a chronic disease is present.

---

**Table 1. Indications for Liver transplantsations**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Percentage</td>
</tr>
<tr>
<td>Non-cholestatic cirrhosis</td>
<td>3527</td>
<td>60.3</td>
</tr>
<tr>
<td>Cholestatic liver disease/Cirrhosis</td>
<td>498</td>
<td>8.5</td>
</tr>
<tr>
<td>FHF</td>
<td>491</td>
<td>8.4</td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>187</td>
<td>3.2</td>
</tr>
<tr>
<td>Metabolic diseases</td>
<td>173</td>
<td>3.0</td>
</tr>
<tr>
<td>Malignant Diseases</td>
<td>395</td>
<td>6.8</td>
</tr>
<tr>
<td>Other</td>
<td>574</td>
<td>9.8</td>
</tr>
<tr>
<td>Total</td>
<td>5845</td>
<td>100</td>
</tr>
</tbody>
</table>

Data from the UNOS database (2004) and data from the German registry (DSO 2005) were grouped to match classification [5,6].

---

**Table 2. Etiology of fulminant hepatic failure**

<table>
<thead>
<tr>
<th></th>
<th>Viral</th>
<th>Idiosyncratic</th>
<th>Toxic Dose-dependent</th>
<th>Toxic synergistic</th>
<th>Metabolic</th>
<th>Associated with pregnancy</th>
<th>Vascular</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hepatitis A,B,C,D,E, CMV HSV, EBV, VZV, HJV 6, Parvo-virus B19, Parainfluenza, Yellow Fever, and others</td>
<td>Halogenated hydrocarbons, Coumarins, Methyldopa, Phenytoin, Carbamazepin, Valproic acid, Rifampicin, Penicillin, Sulfonamides, Chinolones, etc.</td>
<td>Acetaminophen (Paracetamol), Isoniazid, Tetracycline, Methotrexat, Carbon tetrachloride, Amphetamine, Amanita phalloides-Toxin</td>
<td>Ethanol + Acetaminophen, Barbiturate + Acetaminophen, Isoniazid + Rifampicin</td>
<td>M. Wilson, alpha-1-AT-deficiency, Galactosemia, Tyrosinemia, Reye-Syndrome, NASH</td>
<td>Acute fatty liver of pregnancy, HELLP-Syndrome</td>
<td>Budd-Chiari-Syndrome, veno-occlusive disease, shock, heart failure</td>
<td>Autoimmune-hepatitis, malignant infiltration, hyperthermia, sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
which has not been recognized. Therefore a manifest liver fibrosis or even cirrhosis is not considered to be an exclusion criteria for listing as an acute liver failure.

**Rare causes of ALF**

A number of metabolic related disorders other than Wilson’s disease have been reported to be associated with FHF including acute fatty liver of pregnancy and Reye’s syndrome. In addition FHF has also been reported in patients with autoimmune hepatitis, sepsis or malignant infiltration of the liver. The etiolog of FHF can be determined in up to 80% of cases [3], which is important since it may influence treatment options and may help to determine the prognosis and requirement of OLT.

**Treatment options**

The management of patients with FHF requires a thorough infrastructure and understanding to deal with the complications that may be present, including renal failure, circulatory dysfunction, coagulopathy, gastrointestinal bleeding, encephalopathy, cerebral edema and metabolic disturbances like metabolic acidosis and hypoglycemia. In the course of these complexities, patients with FHF should be managed in an intensive care unit and should be transferred as soon as possible to centers with a liver transplant program [16]. Liver transplantation remains the main promising option of treatment of FHF. However, depending on the etiology, specific therapies may be used. For example, N-acetylcysteine can significantly improve prognosis of patients with acetaminophen intoxication [17]. Other interventions may be helpful in other specific settings as: forced diuresis, silybin and activated charcoal in patients with amanita phalloides poisoning. Due to the development of new antiviral medication Hepatitis B virus infection can be treated even in the acute phase [18]. Acyclovir may improve prognosis in patients with herpes virus infection and FHF. Transjugular intrahepatic portosystemic stent shunt is the treatment of choice in patients presenting with FHF due to acute Budd-Chiari syndrome. Liver support systems that substitute in part the functions including detoxification and homeostasis of metabolism have been developed and tested. The efficacy has been demonstrated in only a small number of patients [19].

**Prognostic scores and indication for orthotopic liver transplantation**

In patients with FHF, the decision to transplant depends on the probability of spontaneous hepatic recovery, which is variable and cannot be predicted reliably. The most important factors for predicting survival in FHF are the degree of encephalopathy, the patient’s age, and the cause of FHF. As an example, spontaneous recovery is more likely with lower grades of encephalopathy [20], which is between 65 to 70 percent in patients with encephalopathy grade I-II and is less than 20 percent in patients with encephalopathy grade IV [20]. Patients older than 40 or less than 10 years are less likely to show spontaneous recovery compared to patients between these ages. Patients with FHF due to acetaminophen intoxication, hepatitis A, hepatitis B have a better prognosis than those with idiosyncratic drug reactions or Wilson’s disease [21]. Several other variables have been used to predict the probability of recovery but their predictive value have not been established so far: the prothrombin time in addition with serum bilirubin concentration and arterial pH [22], low serum phosphate levels [23], high arterial ammonia levels [24]. Liver histology has not been shown to be reliable for predicting recovery, and is not recommended routinely in patients with FHF [25].

Statistical models have been developed for predicting the outcome in patients with FHF [26–29]. The most commonly used scoring system are the King’s College Hospital criteria (KCC) [20]. The model was developed in a series of 588 patients with acute liver failure who were managed without transplantation between 1973 and 1985 [20]. These criteria discriminate between acetaminophen induced liver failure and other etiologies (see Table 3). In acetaminophen-induced FHF, there are two important criteria for indication to liver transplantation: an arterial pH of less than 7.3, irrespective of grade of encephalopathy; or a prothrombin time (PT) greater than 100 seconds and a serum creatinine concentration greater than 3.4 mg/dL (301 μmol/L) in patients who have grade III or IV encephalopathy. In other causes of FHF, liver transplantation is indicated in patients who have either a PT greater than 100 seconds, irrespective of the grade of encephalopathy, or any three of following variables: age less than 10 or greater

**Table 3. King’s College Hospital criteria for liver transplantation in fulminant hepatic failure**

<table>
<thead>
<tr>
<th>Acetaminophen-induced disease</th>
<th>All other causes of fulminant hepatic failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Arterial pH &lt;7.3 (independent of the grade of encephalopathy)</td>
<td></td>
</tr>
<tr>
<td>• Grade III or IV encephalopathy and</td>
<td>Any three of the following variables (independent of the grade of encephalopathy)</td>
</tr>
<tr>
<td>• Prothrombin time &gt;100 s and</td>
<td>1. Age &lt;10 years or &gt;40 years</td>
</tr>
<tr>
<td>• Serum creatinine &gt;3.4 mg/dL (301 μmol/l)</td>
<td>2. Etiology: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions</td>
</tr>
<tr>
<td></td>
<td>3. Duration of jaundice before onset of encephalopathy &gt;7 days</td>
</tr>
<tr>
<td></td>
<td>4. Prothrombin time &gt;50 s</td>
</tr>
<tr>
<td></td>
<td>5. Serum bilirubin &gt;18 mg/dL (308 μmol/l)</td>
</tr>
</tbody>
</table>

From [20].
than 40, non-A, non-B hepatitis, idiosyncratic drug reactions, duration of jaundice before development of encephalopathy greater than seven days, PT greater than 50 seconds, or serum bilirubin greater than 18 mg/dL. The accuracy of the King’s College Criteria has been evaluated in separate cohorts. Although, relatively low negative predictive values have been shown for these criteria no other scores have been shown to be superior [30,31].

Summary

Fulminant hepatic failure is characterized by the rapid development of severe liver injury with impaired synthetic function and encephalopathy. Most common, FHF is caused by toxin-induced or viral hepatitis, but can result from a wide variety of causes. The mainstay of therapy is orthotopic liver transplantation. Therefore, patients with liver failure should be transferred as soon as possible to a transplant center, to ensure management of complications. The decision for transplantation depends on the probability of hepatic recovery, which is difficult to predict. The most important factors, which in part are included in the King’s College Criteria, for predicting the outcome in FHF are the degree of encephalopathy, the patient’s age, and the underlying cause of fulminant hepatic failure.

Conflict of interest statement. None declared.

References

13. Khuroo MS, Kamili S, Yattoo GN. Hepatitis E virus infection may be transmitted through blood transfusions in an endemic area. J Gastroenterol Hepatol 2004; 19: 778–784
29. Lake JR, Sussman NL. Determining prognosis in patients with fulminant hepatic failure: when you absolutely, positively have to know the answer. Hepatology 1995; 21: 879–892