Acute Liver Failure

William Bernal, M.D., and Julia Wendon, M.B., Ch.B.

A CUTE LIVER FAILURE IS A RARE BUT LIFE-THREATENING CRITICAL ILLNESS that occurs most often in patients who do not have preexisting liver disease. With an incidence of fewer than 10 cases per million persons per year in the developed world, acute liver failure is seen most commonly in previously healthy adults in their 30s and presents unique challenges in clinical management. The clinical presentation usually includes hepatic dysfunction, abnormal liver biochemical values, and coagulopathy; encephalopathy may develop, with multiorgan failure and death occurring in up to half the cases (Fig. 1).

1-3 The rarity of acute liver failure, along with its severity and heterogeneity, has resulted in a very limited evidence base to guide supportive care.4 However, rates of survival have improved substantially in recent years through advances in critical care management and the use of emergency liver transplantation.5 In this review, we outline the causes and clinical manifestations of acute liver failure and discuss current approaches to patient care.

THE CLINICAL PROBLEM

DEFINITION AND PRESENTATION

The original term “fulminant hepatic failure,” defined as “a severe liver injury, potentially reversible in nature and with onset of hepatic encephalopathy within 8 weeks of the first symptoms in the absence of pre-existing liver disease,”6 remains relevant today. More modern definitions recognize distinct disease phenotypes and quantify the interval between the onset of symptoms and the development of encephalopathy7 (Fig. 2). This interval provides clues to the cause of disease, likely complications, and prognosis with supportive medical care alone.8-10 In hyperacute cases, this interval is a week or less, and the cause is usually acetaminophen toxicity or a viral infection. More slowly evolving, or subacute, cases may be confused with chronic liver disease and often result from idiosyncratic drug-induced liver injury or are indeterminate in cause. Patients with subacute causes, despite having less marked coagulopathy and encephalopathy, have a consistently worse outcome with medical care alone than those in whom the illness has a more rapid onset.

CAUSES

Acute liver failure is much less common in the developed world than in the developing world, where viral infections (hepatitis A, B, and E) are the predominant causes. Public health measures (e.g., vaccination and improved sanitation) are among the factors resulting in the reduced incidence of these infections in the United States and much of Western Europe, where drug-induced liver injury is the most common cause of acute liver failure (Fig. 3).

Viruses

Globally, hepatitis A and E infections are probably responsible for the majority of cases of acute liver failure, with rates of death of more than 50% reported from the...
developing world. Acute liver failure may also occur after hepatitis B infection, which is a common cause in some Asian and Mediterranean countries. Particularly poor survival has been seen in patients with reactivation of previously stable subclinical infection with the hepatitis B virus without established chronic liver disease. This scenario is most common in patients with treatment-induced immunosuppression during or after therapy for cancer. The identification of at-risk patients and the use of antiviral prophylaxis before the initiation of chemotherapy, immunotherapy, or glucocorticoid therapy are effective in prevention. Other rare viral causes of acute liver failure include herpes simplex virus, cytomegalovirus, Epstein–Barr virus, and parvoviruses.

Drug-Induced Liver Injury

Drug-induced liver injury is responsible for approximately 50% of cases of acute liver failure in the United States. Such injury may be dose-dependent and predictable, as exemplified by acetaminophen-induced hepatotoxicity, which is the most common cause of acute liver failure in the United States. It may also be idiosyncratic, unpredictable, and probably independent of dose.

Figure 1. Clinical Features of Acute Liver Failure.
Although acute liver failure after acetaminophen ingestion can occur after consumption of a single large dose, the risk of death is greatest with substantial drug ingestion staggered over hours or days rather than at a single time point. Acute liver failure is more common with late presentation to medical attention because of unintentional rather than deliberate self-poisoning. Malnourished patients and patients with alcoholism are at increased risk. Acetaminophen is also a potential cofactor for hepatic injury in patients taking the drug for the relief of symptoms from hepatic illness of other causes.

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

Other Causes
Acute ischemic hepatocellular injury, or hypoxic hepatitis, may occur in critically ill patients with primary cardiac, circulatory, or respiratory failure. It may be caused by severe sepsis accompanied by signs of cardiac failure and major, transient elevations in blood aminotransferase levels. This condition primarily requires supportive cardiorespiratory management rather than specific interventions targeted at the liver injury. The prognosis depends on both the cause of hepatic hypoxia and the severity of liver injury. A similar liver-injury pattern may also be seen in drug-induced liver injury caused by recreational drugs such as MDMA (3,4-methylenedioxy-N-methylamphetamine, also known as ecstasy) or cocaine.

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

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

**Focus of Critical Care**

**Initial Care**

Recognition of hepatic injury may be delayed if confusion or agitation is the dominant presenting sign, particularly in hyperacute cases in which jaundice is minimal or in subacute cases, which may be mistaken for chronic liver disease. Early discussion with specialists at a liver center may be crucial to guide management (Table 1) and expedite the safe transfer of suitable patients.

Early restoration of intravascular volume and systemic perfusion may prevent or mitigate the severity of organ failure. In patients with severe acetaminophen poisoning, the interval between drug ingestion and treatment with acetylcysteine is closely related to the outcome. Acetylcysteine has complex antioxidant and immunologic effects that may also benefit patients with non–acetaminophen-related acute liver failure. In a randomized, controlled study involving such
patients, treatment with intravenous acetylcysteine improved survival rates, but only among patients with low-grade encephalopathy.\textsuperscript{27}

Encephalopathy may progress rapidly, particularly in patients with hyperacute disease. For patients with progression to agitation or coma, we recommend early endotracheal intubation and sedation for airway control in order to facilitate general care, control oxygen and carbon dioxide levels, and prevent aspiration pneumonitis, although practice varies according to center.

A low arterial blood pressure with systemic vasodilatation with or without confirmed sepsis is common in patients with acute liver failure and is associated with more severe encephalopathy and increased mortality.\textsuperscript{28,29} A later pattern of functional immunosuppression may be seen with secondary nosocomial sepsis and impaired hepatic regeneration.\textsuperscript{30} In the absence of an evidence base to guide practice, we administer antibiotics preemptively in patients who have coagulopathy and organ failure or encephalopathy and those in whom illness progression is considered likely. High standards of infection control should be practiced to minimize the risks of nosocomial sepsis.

Overt bleeding is uncommon in patients with acute liver failure and reflects a balanced hemostatic defect. In most cases, the loss of hepatic synthesis of procoagulant factors is paralleled by the loss of hepatically derived anticoagulants. Functional testing indicates no major bleeding tendency and may even indicate the presence of a procoagulant state.\textsuperscript{31,32} Since serial evaluation of laboratory coagulation variables (e.g., the international normalized ratio and prothrombin time) is central to prognostic evaluation, the adminis-
Critical care medicine should be avoided, except when needed to treat bleeding or before invasive procedures.

**Subsequent Care**

The severity of illness, rapidity of change, and extent of extrahepatic organ involvement require early critical care. The cause of liver injury should be sought, since specific therapies may be available for some causes of acute liver failure (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). However, inappropriately prolonged investigation and medical therapy may make transplantation impossible if surgery becomes contraindicated because of the progression of multiorgan failure and development of sepsis.

### Table 1. Common Management Issues and Condition-Specific Elements of Care in Acute Liver Failure.*

<table>
<thead>
<tr>
<th>Organ System and Common Conditions</th>
<th>Assessment</th>
<th>Specific Elements of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>Invasive monitoring for all conditions; echocardiography for low cardiac output and right ventricular failure</td>
<td>Correction of volume depletion</td>
</tr>
<tr>
<td>Intravascular volume depletion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasodilatation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low cardiac output and right ventricular failure</td>
<td></td>
<td>Inotropic support</td>
</tr>
<tr>
<td><strong>Hepatic system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evolving hepatic dysfunction</td>
<td>Serial biochemical and coagulation testing</td>
<td>Intravenous acetylcysteine</td>
</tr>
<tr>
<td><strong>Respiratory system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of aspiration pneumonitis</td>
<td>Neurologic observation to monitor level of consciousness</td>
<td>Early tracheal intubation for depressed level of consciousness</td>
</tr>
<tr>
<td><strong>Metabolic and renal systems</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Serial biochemical testing</td>
<td>Maintain normoglycemia</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction, lactic acidosis, hyperammonemia</td>
<td>Laboratory coagulation testing</td>
<td>Renal-replacement therapy</td>
</tr>
<tr>
<td>Impaired drug metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive encephalopathy</td>
<td>Neurologic observation; monitoring of serum ammonia level; transcranial ultrasonography; consideration of intracranial-pressure monitoring</td>
<td>Treatment of fever and hyponatremia; screening for sepsis High-grade encephalopathy; endotracheal intubation; avoidance of Paco2 of &lt;30 mm Hg or &gt;45 mm Hg; target for serum sodium, 145–150 mmol/liter; risk assessment for intracranial hypertension</td>
</tr>
<tr>
<td>Intracranial hypertension</td>
<td></td>
<td>Interventions for pressure surges: osmotherapy (mannitol, hypertonic saline); temperature control; rescue therapies (indomethacin, thiopentone)</td>
</tr>
<tr>
<td><strong>Hematologic system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Laboratory coagulation testing</td>
<td>No routine correction of coagulation abnormalities, only for invasive procedures (including platelets and fibrinogen)</td>
</tr>
<tr>
<td><strong>Immunologic system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk of sepsis</td>
<td>Clinical evaluation</td>
<td>Antibiotic prophylaxis</td>
</tr>
</tbody>
</table>

* Paco2 denotes partial pressure of arterial carbon dioxide.
In patients with subacute presentations, even low-grade encephalopathy indicates an extremely poor prognosis, whereas in hyperacute disease, high grades of encephalopathy may clearly indicate a poor prognosis. The goal of clinical strategies is to prevent the onset of encephalopathy, limit its severity when it develops, and reduce the risk of cerebral edema. Intracranial hypertension from severe cerebral edema remains a feared complication and is a leading cause of death worldwide among patients with acute liver failure. In many centers, intracranial hypertension is seen in only a minority of patients. However, among patients in whom intracranial hypertension develops, the rate of survival without transplantation remains poor.

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

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

Neurologic care focuses on the prevention of infection, the maintenance of stable cerebral perfusion, and the control of circulating ammonia and its cerebral metabolism. The drug t-ornithine–t-aspartate enhances ammonia detoxification to glutamine in muscle. However, in a large, randomized, controlled trial, the drug did not lower circulating ammonia levels, reduce the severity of encephalopathy, or improve survival rates among patients with acute liver failure.41 In patients with established encephalopathy, treatment is focused on minimizing the risk of intracranial hypertension by lowering cerebral ammonia uptake and metabolism through the use of sedation and prophylactic osmotherapy. In a randomized, controlled trial involving patients with high-grade encephalopathy, treatment with intravenous hypertonic saline solution delayed the onset of intracranial hypertension.42 Hypothermia affects multiple processes involved in the development of cerebral edema; by slowing body metabolism, it lowers systemic production of ammonia and cerebral uptake and metabolism, in addition to having hemodynamic stabilizing effects and reducing cerebral blood flow.35 Clinical observations have suggested that moderate hypothermia (32 to 33°C) improves hemodynamics and controls refractory intracranial hypertension, but a multicenter trial of prophylactic moderate hypothermia (34°C) in patients with high-grade encephalopathy did not show a delay in or reduced severity of intracranial hypertension.43,44 A pragmatic approach to temperature management is to avoid fever and maintain a core body temperature of 35 to 36°C.

The most effective mode of neurologic monitoring to guide therapy in patients with high-grade encephalopathy is not clear. Direct measurement of intracranial pressure is associated with uncommon but definite risks, particularly intracranial hemorrhage.45 In view of the potential complications and the decreasing incidence of intracranial hypertension, we monitor intracranial pressure only in patients with clinical signs or evidence of evolving intracranial hypertension. Other indicators of increased risk include an arterial ammonia concentration of more than 200 μmol per liter or a sustained level of at least 150 μmol per liter despite treatment, an age of 35 years or less, and concurrent renal or cardiovascular organ failure.37,38,40

We treat sustained increases in intracranial pressure with a bolus of intravenous hypertonic saline (at a dose of 20 ml of 30% sodium chloride or 200 ml of 3% sodium chloride, keeping serum sodium at <150 mmol per liter) or mannitol (at a dose of 2 ml of 20% solution per kilogram of body weight, maintaining serum osmolality at <320 mOsm per liter). Hypothermia at 32 to 34°C may be used in patients with resistant cases, and a bolus of intravenous indomethacin (at a dose of 0.5 mg per kilogram) may be used when cerebral hyperemia is also present.46

**RENAL DYSFUNCTION**

Substantial renal dysfunction may occur in more than 50% of patients with acute liver failure. This complication is more common in the elderly and in patients with acetaminophen-induced acute liver failure.47 Although renal dysfunction is associated with increased mortality, the resolution of liver failure is accompanied by a return to preexisting levels in most cases.48 In patients requiring renal-replacement therapy, continuous rather than intermittent forms are generally used to achieve greater metabolic and hemodynamic stability.49 In addition to indications for the use of renal-replacement therapy in other forms of critical illness, such therapy may be used to control hyperammonemia and other biochemical and acid–base disturbances.

**TREATMENT**

**METABOLIC AND NUTRITIONAL SUPPORT**

The goal of treatment is to achieve overall metabolic and hemodynamic stability, with the reasonable, though yet unproven, idea that such therapy will greatly improve conditions for hepatic regeneration and minimize the risk of complications. In patients with acute liver failure, this type of support is provided as it is for other critically ill patients, with specific caveats. Patients with acute liver failure are at increased risk for hypoglycemia, which can be prevented by an intravenous glucose infusion. Large-volume infusions of hypotonic fluids, which may result in hypotension and cerebral swelling, should be avoided. Patients with acute liver failure have high energy
expenditure and protein catabolism, requiring nutritional support to preserve muscle bulk and immune function. Pragmatically, in patients with encephalopathy, we administer 1.0 to 1.5 g of enteral protein per kilogram per day while frequently measuring blood ammonia levels, with a lowered protein load for short periods in patients with worsening hyperammonemia or otherwise at high risk for intracranial hypertension.

**PROGNOSTIC EVALUATION**

Early identification of patients who will not survive with medical therapy alone is of great practical importance in identifying potential candidates for transplantation. Since the progression of multorgan failure results in deterioration in many patients who are awaiting transplantation, candidates for transplantation should be identified as quickly as possible.

Various prognostic evaluation systems, most of which have features derived from analyses of historical patient cohorts that were treated without transplantation, are in use worldwide. Although the details of these systems differ, they share common features (Table 2). The presence of encephalopathy is a key indicator, with further consideration given to the patient's age and the severity of liver injury, as assessed by the presence of coagulopathy or jaundice. The most well characterized evaluation system is the King's College Criteria, with meta-analyses confirming that these criteria have clinically acceptable specificity but more limited sensitivity.

To address these limitations, a wide variety of alternate prognostic systems and markers have been proposed. To date, none have achieved universal acceptance, though the need for improved identification of candidates for transplantation is clear.

**TRANSPLANTATION**

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

Early impaired liver-graft function is poorly tolerated in critically ill patients and predisposes them to intracranial hypertension and sepsis.

**OTHER THERAPIES**

The limited availability of liver transplantation has led to the evaluation of other therapies in patients with advanced disease. Hepatocyte transplantation involves intraportal or intraperitoneal infusion of isolated human hepatocytes to augment liver function. The procedure has been used successfully in neonates and children with inborn errors of metabolism, but to date the experience in pediatric acute liver failure has been limited. The cell mass that is infused represents only 5% of the theoretical liver mass, which is insufficient in patients with massive hepatic necrosis, and the technique remains experimental.

Other therapies seek to support the failing liver through the removal of circulating toxic mediators, to stabilize the clinical conditions of the patients while they await definitive transplantation, or to facilitate native liver regeneration. Among such extracorporeal liver-assist devices are nonbiologic dialysis-based systems for systemic detoxification and bioartificial devices that incorporate hepatic cells of porcine or human origin to replace both detoxification and synthetic functions.

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**Table 2. Criteria for the Selection of Patients with Acute Liver Failure for Transplantation.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>King's College Criteria</th>
<th>Clichy Criteria</th>
<th>Japanese Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cause</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Encephalopathy†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bilirubin level</td>
<td>Varies</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Coagulopathy†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*The King’s College criteria are from O’Grady et al., the Clichy criteria from Bernaua et al., and the Japanese criteria from Mochida et al.* Yes indicates that the factor is included as a criterion, and No that the factor is not included; Varies indicates that the criterion is used only in cases not associated with acetaminophen.

†This factor is common to all prognostic models.
is the molecular adsorbent recirculating system, with case series suggesting biochemical improvements during its use. A multicenter, randomized, controlled trial involving patients with acute liver failure showed no survival benefit, but the study was confounded by a transplantation rate of 75% soon after enrollment. The porcine hepatocyte–based HepatAssist device appeared to be safe in a randomized, controlled trial but did not show a survival benefit except on secondary analysis. For now, the use of extracorporeal devices should be restricted to clinical trials. Preliminary reports suggest that high-volume plasma exchange may be a promising therapy.

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REFERENCES


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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplementary Materials: Critical Care Medicine Series - Acute Liver Failure

Authors: Dr William Bernal, Prof. Julia Wendon.

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Table S1: Therapies for specific etiologies of Acute Liver Failure.

Table S2: Grading Scales for encephalopathy.

References.

Table S1. Therapies for specific etiologies of Acute Liver Failure

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Intervention (s)</th>
<th>RCT</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Nucleoside Analogues</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Herpes Simplex</td>
<td>Acyclovir / Foscarnet</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Gancyclovir / Foscarnet</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Immunosupression</td>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td>Budd Chiari</td>
<td>Anti-coagulation / TIPSS</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td><em>Amantia phalloides</em></td>
<td>Penicillin G / Silymarin</td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Anti-neoplasics</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>N-acetyl Cysteine</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Other DILI</td>
<td>Drug withdrawal</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Note: RCT; Randomised controlled trial evidence to support use.

DILI; Non-acetaminophen Drug induced Liver Injury
Table S2. Modified West Haven Criteria for grading of encephalopathy with comparable Glasgow Coma Scale (GCS) in Acute Liver Failure.

<table>
<thead>
<tr>
<th>Grade</th>
<th>GCS</th>
<th>Conscious level and Cognitive Function</th>
<th>Clinical and Neuro-psychiatric Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14-15</td>
<td>Impaired computation</td>
<td>Shortened attention span</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild confusion</td>
<td>Minor lack of awareness</td>
</tr>
<tr>
<td>2</td>
<td>12-15</td>
<td>Inattentive</td>
<td>Irritability,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disorientation for time</td>
<td>Disinhibition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate confusion</td>
<td>Asterixus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Slurred Speech</td>
</tr>
<tr>
<td>3</td>
<td>7-12</td>
<td>Somnolent but rousable</td>
<td>Inappropriate / bizarre behaviour.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marked confusion</td>
<td>Paranoia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aggression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Asterixus &amp; Ataxia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Slurred Speech</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypo- or hyper-reflexia</td>
</tr>
<tr>
<td>4</td>
<td>&lt;7</td>
<td>Unrousable</td>
<td>Unresponsive to pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pupillary abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Flexor / extensor posturing</td>
</tr>
</tbody>
</table>

Note: Grades 1-2 ‘low Grade’, Grades 3-4 ‘High grade’. After Amodio et al.\textsuperscript{8} . Assessment of encephalopathy grade should be undertaken when other causes of reduced consciousness have been accounted for.
References


1. The most common cause of acute liver failure globally is
   a. acetaminophen toxicity
   b. hepatitis A and E  
   c. hepatitis B
   d. hepatitis C
   e. CMV

2. The leading cause of death among acute liver failure patients is
   a. sepsis
   b. uncontrolled hemorrhage
   c. respiratory insufficiency
   d. intracranial hypertension

True or False

3. INR >3 should prompt therapy with fresh frozen plasma to prevent bleeding

4. Most patients with acute liver failure are hypertensive

5. In acetaminophen liver injury, risk of death is greater with ingestion of one large dose rather than overdose staggered over several days.

6. In patients with subacute failure, low grade encephalopathy carries a grave prognosis

7. Norepinephrine is the preferred vasoactive agent to support blood pressure in ALF

8. Lactulose and rifaximin are the preferred treatments for elevated ammonia in ALF

9. Subacute liver failure has a better prognosis than acute or hyperacute cases

10. Hepatitis A is the most common cause of acute liver failure in the US

11. Ecstasy and cocaine can cause a pattern of liver injury similar to acute ischemic hepatocellular injury

12. In encephalopathic patients, intubation keeping pCO₂ levels between 30 and 45mm Hg is recommended

13. Use of hypertonic saline, hypothermia and sedation are the preferred therapies to manage encephalopathy and increased intracranial pressure in ALF

14. Liver transplant success rates are similar in ALF as for other conditions

15. In acute liver failure, there is a close relationship between arterial ammonia level and development of encephalopathy, risk is greatest when ammonia > 255 ug/dL

16. Acetylcysteine may improve outcomes in ALF, patients with severe encephalopathy benefit the most