

## REVIEW ARTICLE

## CRITICAL CARE MEDICINE

## Acute Liver Failure

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**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).<sup>1-3</sup>

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

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## THE CLINICAL PROBLEM

## DEFINITION AND PRESENTATION

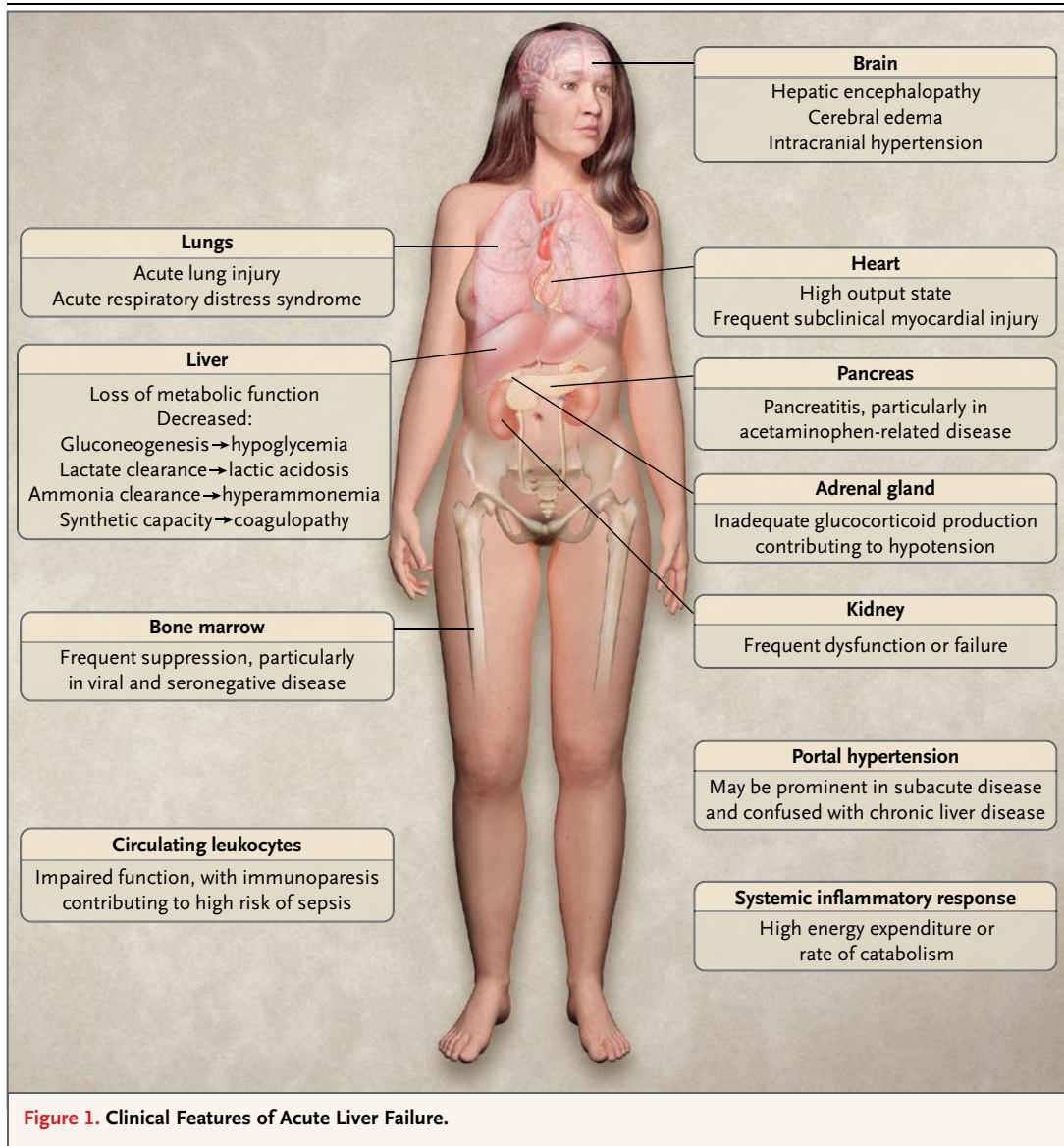
The original term “fulminant hepatic failure,” defined as “a severe liver injury, potentially reversible in nature and with onset of hepatic encephalopathy within 8 weeks of the first symptoms in the absence of pre-existing liver disease,”<sup>6</sup> remains relevant today. More modern definitions recognize distinct disease phenotypes and quantify the interval between the onset of symptoms and the development of encephalopathy<sup>7</sup> (Fig. 2). This interval provides clues to the cause of disease, likely complications, and prognosis with supportive medical care alone.<sup>8-10</sup> 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.<sup>11,12</sup> Acute liver failure may also occur after hepatitis B infection,<sup>13</sup> 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 effec-

tive in prevention.<sup>14</sup> Other rare viral causes of acute liver failure include herpes simplex virus, cytomegalovirus, Epstein-Barr virus, and parvoviruses.<sup>15</sup>

#### *Drug-Induced Liver Injury*

Drug-induced liver injury is responsible for approximately 50% of cases of acute liver failure in the United States.<sup>16,17</sup> 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.

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.<sup>18</sup> Malnourished patients and patients with alcoholism are at increased risk.<sup>19</sup> 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.<sup>20,21</sup>

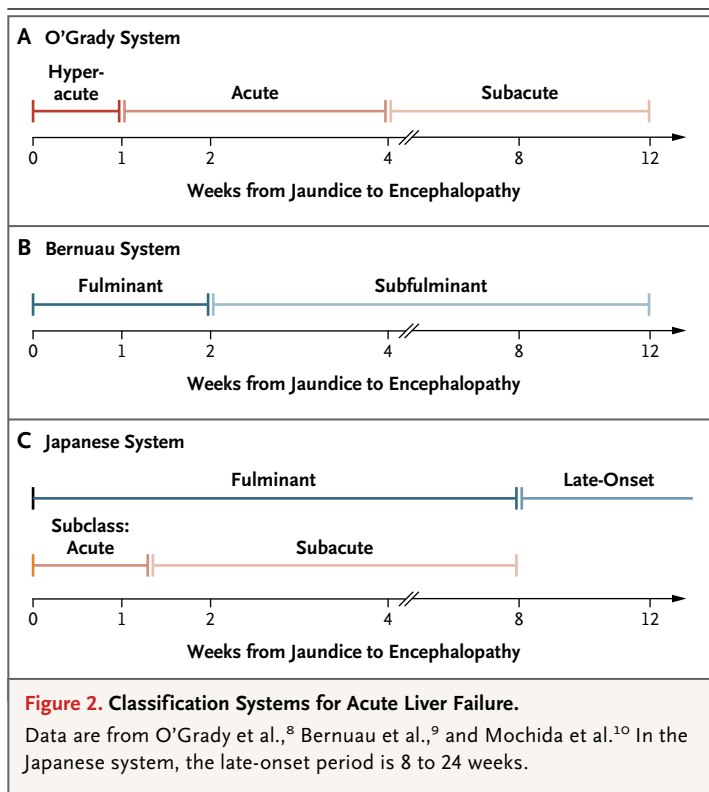
Idiosyncratic drug-induced liver injury is rare, even among patients who are exposed to potentially hepatotoxic medication, and few patients with drug-induced liver injury have progression to encephalopathy and acute liver failure.<sup>22</sup> Factors such as an older age, increased elevations in blood aminotransferase and bilirubin levels, and coagulopathy are associated with an increased risk of death.<sup>17,23</sup>

**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.<sup>24,25</sup> This condition primarily requires supportive cardio-respiratory 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, heat-stroke, mushroom ingestion, and metabolic diseases such as Wilson’s disease.<sup>15,16</sup> 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



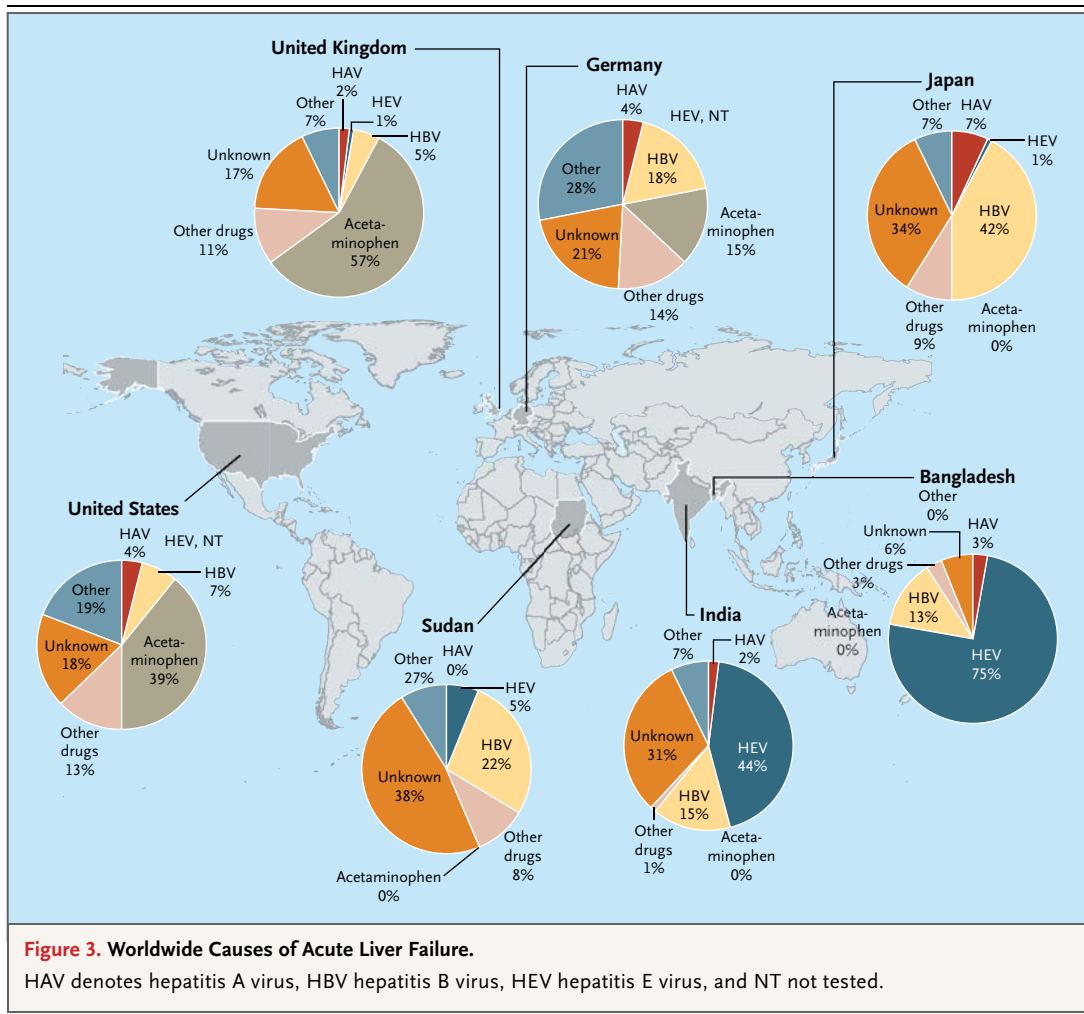
virus or exposure to a toxin. These cases often follow a subacute presentation, and rates of survival are poor without transplantation.

**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.<sup>18,26</sup> 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.<sup>27</sup>

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.<sup>28,29</sup> A later pattern of functional immunosuppression may be seen with secondary nosocomial sepsis and impaired

hepatic regeneration.<sup>30</sup> 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.<sup>31,32</sup> Since serial evaluation of laboratory coagulation variables (e.g., the international normalized ratio and prothrombin time) is central to prognostic evaluation, the adminis-

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

Organ System and Common Conditions	Assessment	Specific Elements of Care
<b>Cardiovascular system</b>		
Hypotension	Invasive monitoring for all conditions; echocardiography for low cardiac output and right ventricular failure	
Intravascular volume depletion		Correction of volume depletion
Vasodilatation		Vasopressors
Low cardiac output and right ventricular failure		Inotropic support
<b>Hepatic system</b>		
Evolving hepatic dysfunction	Serial biochemical and coagulation testing	Intravenous acetylcysteine
<b>Respiratory system</b>		
Risk of aspiration pneumonitis	Neurologic observation to monitor level of consciousness	Early tracheal intubation for depressed level of consciousness
<b>Metabolic and renal systems</b>		
Hypoglycemia	Serial biochemical testing	Maintain normoglycemia
Hyponatremia		Active fluid management
Renal dysfunction, lactic acidosis, hyperammonemia		Renal-replacement therapy
Impaired drug metabolism		Review drug administration
<b>Central nervous system</b>		
Progressive encephalopathy	Neurologic observation; monitoring of serum ammonia level; transcranial ultrasonography; consideration of intracranial-pressure monitoring	Treatment of fever and hyponatremia; screening for sepsis High-grade encephalopathy: endotracheal intubation; avoidance of $Paco_2$ of <30 mm Hg or >45 mm Hg; target for serum sodium, 145–150 mmol/liter; risk assessment for intracranial hypertension
Intracranial hypertension		Interventions for pressure surges: osmotherapy (mannitol, hypertonic saline); temperature control; rescue therapies (indomethacin, thiopentone)
<b>Hematologic system</b>		
Coagulopathy	Laboratory coagulation testing	No routine correction of coagulation abnormalities, only for invasive procedures (including platelets and fibrinogen)
<b>Immunologic system</b>		
High risk of sepsis	Clinical evaluation	Antibiotic prophylaxis

\*  $Paco_2$  denotes partial pressure of arterial carbon dioxide.

tration of coagulation factors 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.

## COMPLICATIONS

**CARDIORESPIRATORY DYSFUNCTION**

Circulatory dysfunction and hypotension are common in patients with acute liver failure and are often multifactorial in origin. The effective blood volume may initially be low owing to poor oral intake and fluid losses through vomiting and the development of vasodilatation, leading to a condition consistent primarily with hypovolemic shock.

Approaches to cardiovascular support in patients with acute liver failure do not differ markedly from those used in patients with other critical illnesses and focus on early restoration of circulating volume, systemic perfusion, and oxygen delivery. In patients who continue to have hypotension despite volume repletion, norepinephrine is the preferred vasopressor, with or without adjunctive use of vasopressin or vasopressin analogues.<sup>33</sup> Myocardial function should be assessed by means of echocardiography, since hypoxic hepatitis may result from impaired cardiac function. Relative adrenal insufficiency may be present in patients with cardiovascular instability and is associated with increased mortality, but whether supplemental glucocorticoids improve survival is unclear.<sup>34</sup>

Although endotracheal intubation is often required to manage a reduced level of consciousness, respiratory dysfunction is uncommon early in the clinical course of acute liver failure. It is more common later, during the phase of hepatic regeneration or in association with nosocomial sepsis. The goals of respiratory care are similar to those in other critical illnesses; hyperventilation to induce hypocapnia may be used for emergent control of intracranial hypertension if the condition is associated with cerebral hyperemia, but sustained hyperventilation should be avoided. Spontaneous hyperventilation is averted by means of appropriate sedation and mandatory modes of ventilation.

**NEUROLOGIC CONDITIONS**

The central place of encephalopathy in the definition of acute liver failure reflects its key prognostic importance, and its development reflects critically impaired liver function (Table S2 in the Supplementary Appendix). However, depending on the speed with which encephalopathy develops, its presence has differential prognostic importance.

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.<sup>5</sup>

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.<sup>35,36</sup> Encephalopathy can be precipitated by infection and may occur in patients with low systemic blood pressure and vasodilatation.<sup>37,38</sup> 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.<sup>39</sup>

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  $\mu\text{mol}$  per liter (255 to 340  $\mu\text{g}$  per deciliter).<sup>37,40</sup> 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.<sup>35,36</sup> 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.<sup>35,36</sup> Treatments that are used in chronic liver disease may be inappropriate in acute liver failure. In particular, the role of neomycin, rif

axamin, 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 L-ornithine-L-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.<sup>41</sup>

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.<sup>42</sup> 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.<sup>35</sup> 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.<sup>43,44</sup> 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.<sup>45</sup> 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  $\mu\text{mol}$  per liter or a sustained

level of at least 150  $\mu\text{mol}$  per liter despite treatment, an age of 35 years or less, and concurrent renal or cardiovascular organ failure.<sup>37,38,40</sup>

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.<sup>46</sup>

#### 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.<sup>47</sup> Although renal dysfunction is associated with increased mortality, the resolution of liver failure is accompanied by a return to pre-existing levels in most cases.<sup>48</sup> In patients requiring renal-replacement therapy, continuous rather than intermittent forms are generally used to achieve greater metabolic and hemodynamic stability.<sup>49</sup> 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.

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### TREATMENT

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#### 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 hyponatremia 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.<sup>50,51</sup> 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 multiorgan failure results in deterioration in many patients who are awaiting transplantation, candidates for transplantation should be identified as quickly as possible.<sup>52</sup>

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.<sup>53,54</sup> 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 transplantations are performed in patients with acute liver failure.<sup>52,55</sup> 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.<sup>55</sup> 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.<sup>55,56</sup> Early impaired liver-graft function is poorly tolerated in critically ill patients and predisposes them to intracranial hypertension and sepsis.<sup>56</sup>

#### 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.<sup>57</sup> 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.<sup>58,59</sup> The most extensively studied device

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

Factor	King's College Criteria	Clichy Criteria	Japanese Criteria
Age†	Yes	Yes	Yes
Cause	Yes	No	No
Encephalopathy†	Yes	Yes	Yes
Bilirubin level	Varies	No	Yes
Coagulopathy†	Yes	Yes	Yes

\* The King's College criteria are from O'Grady et al.,<sup>8</sup> the Clichy criteria from Bernuau et al.,<sup>9</sup> and the Japanese criteria from Mochida et al.<sup>10</sup> 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.<sup>59</sup> 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.<sup>60</sup> 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.<sup>61</sup> 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.<sup>62</sup>

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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