ACUTE LIVER FAILURE

Definitions

Acute liver failure (ALF) is defined as the development of hepatic encephalopathy (HE) and coagulopathy in a patient with no history of previous liver disease, with the onset HE within 26 weeks of jaundice (1). It should be stressed that ALF is not a disease, but rather a clinical syndrome triggered by numerous etiologic agents. There are three possible outcomes after ALF: spontaneous survival without orthotopic liver transplantation (OLT), OLT, or death. In the U.S. ALF Study Group Registry consisting of more than 2,000 enrollees between 1998 and 2013, 30% of patients died, one-quarter underwent OLT, and 50% recovered spontaneously (W. M. Lee, personal communication). Etiology of ALF is the single, most important factor in determining outcome. In patients with acetaminophen (APAP) overdose, spontaneous recovery is the rule (63% in the ALF Study Group Registry). Patients with acute hepatitis A, ischemic hepatitis, and pregnancy-related ALF—assuming prompt delivery of the fetus—also have high rates of spontaneous survival (>50%). Patients with ALF from all other causes have very poor rates of recovery without OLT, approximately 25% for those with indeterminate cause, acute hepatitis B, and idiosyncratic drug reactions (2). The shorter the interval between jaundice and the development of HE, the higher the likelihood of spontaneous survival; conversely, the longer this interval, the more likely is death without OLT (3).

Epidemiology

In the ALF Study Group Registry, APAP accounts for approximately 45% of cases, half of those due to ingestion of a single large dose with suicidal intent, and the other half as “therapeutic misadventures” (3). The second most common cause of ALF remains indeterminate even after extensive serologic and historical evaluation (12% of cases), followed by idiosyncratic drug reactions (11%) and acute hepatitis B (7%), with autoimmune hepatitis, acute hepatitis A, hepatic vein thrombosis (Budd–Chiari syndrome), ischemic hepatitis, fulminant Wilson disease, malignant infiltration of the liver, and pregnancy-associated ALF (acute fatty liver and HELLP [hemolysis, elevated liver enzymes, and low platelets] syndrome) constituting fewer than 5% of cases each. The initial laboratory and procedural evaluation of patients with ALF to determine cause is indicated in Table 127.1 (4).

Pathophysiology

Multiorgan System Failure

Multiorgan system failure (MOSF) is the most common cause of death in patients with ALF. The pathogenesis of MOSF in ALF is not well understood, but early activation of proinflammatory cytokine pathways followed by compensatory anti-inflammatory responses are both involved (5). Although the systemic inflammatory response syndrome (SIRS) is the clinical expression of the proinflammatory response and accompanies MOSF, the compensatory anti-inflammatory response may be responsible for the subsequent development of sepsis and death (5). Highly prothrombotic microparticles derived from multiple parent cells (platelets, hepatocytes, endothelial cells, and monocytes) may also play a role in the MOSF of ALF, and may explain why ALF is a relatively prothrombotic state despite the general assumption by clinicians that these patients had a bleeding tendency (6).

Hepatic Encephalopathy and Intracranial Hypertension

A manifestation of MOSF peculiar to ALF is the development of HE, which may signify progression to cerebral edema. Cerebral edema becomes increasingly likely as the level of consciousness declines, and occurs in 38% to 81% of cases of grade 3 or 4 HE, respectively (7). The pathophysiology of cerebral edema in ALF has been studied extensively and is unique compared to other causes of raised intracranial pressure (ICP) (Fig. 127.1). Although both cytotoxic (intracellular) and vasogenic (extracellular) edema coexist, the former predominates, coinciding with the observation that most swelling localizes to gray matter astrocytes. Although there may be increased permeability to water and various other molecules, there is no widespread breakdown of the blood–brain barrier (8).

Elevated serum ammonia, produced primarily by gut microorganisms and inadequately cleared by the liver, has long been recognized to contribute to the development of cerebral edema in ALF. Patients who develop cerebral herniation have substantially higher serum ammonia levels—usually more than 200 μmol/L—and greater cerebral ammonia uptake. Conversely, herniation rarely occurs when serum ammonia levels remain below 150 μmol/L (9). Ammonia readily crosses the blood–brain barrier and is taken up by astrocytes, where it combines with glutamate to form glutamine, which in turn contributes to an osmotic gradient that draws water into the intracellular space. Although the brain usually compensates for such an osmotic challenge by extruding organic osmolytes—for example, myoinositol—the rapidity of its development in ALF often does not allow time for compensation to occur, as it would with chronic liver failure (10,11).

Increased cerebral blood flow (CBF) is an important factor in the formation of cerebral edema. Although the cerebral metabolic rate is low in patients with ALF, CBF rises with the accumulation of ammonia and is frequently excessive relative to energy expenditure (12). Early in the course of disease, CBF may be appropriately low to match the reduced cerebral metabolic rate, but with progression of hepatic failure, hyperemia ensues (13). Systemic inflammation often coincides

...
Cerebral perfusion pressure: Rather than remaining constant in the face of varying levels of
results from impairment in cerebrovascular autoregulation. Abnormal CBF in patients with ALF also
with increases in CBF and ICP, suggesting that it may have a pathogenic role (14). Abnormal CBF in patients with ALF also
results from impairment in cerebrovascular autoregulation. Rather than remaining constant in the face of varying levels of
cerebral perfusion pressure:

\[ \text{CPP} = \text{mean arterial pressure (MAP)} - \text{ICP} \]

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results from impairment in cerebrovascular autoregulation. Rather than remaining constant in the face of varying levels of
cerebral perfusion pressure:

\[ \text{CPP} = \text{mean arterial pressure (MAP)} - \text{ICP} \]

Diagnosis

Prognostic schemes have been developed to predict death without OLT in patients with ALF. The King's College Criteria (17),
retrospectively analyzed outcomes in patients with ALF according to cause and subsequently validated the model in a test
population. For patients with APAP-induced ALF, predictors of death included acidosis on admission (arterial pH < 7.30), or
azotemia, severe coagulopathy, and high-grade HE (grade 3 or 4). In patients with ALF due to other causes, severe coagulopa-
thy or any three of the criteria listed in Table 127.2 also predicted death. Although the original series using these criteria
reported a predictive accuracy for death without OLT of more than 85%, subsequent analyses have suggested that they are
less accurate (18). Consequently, other prognostic parameters continue to be applied to individual patients with ALF during
the weighty decision of whether to proceed with OLT.

Treatment

Etiology-Specific Management

N-acetylcysteine (NAC) has become widely administered to patients with ALF due to APAP on the basis of both laboratory and clinical data (29,30); however, randomized, placebo-controlled studies documenting the efficacy of NAC in APAP overdose have never been performed. Several rules of administration require emphasis. First, although nomograms describing the probability of hepatotoxicity after a single APAP ingestion have been used widely to determine whether NAC should be administered, the time of ingestion frequently cannot be determined accurately, and ingestions are often multiple. Therefore, NAC should be administered whenever there is uncertainty about timing or dose. Second, intravenous NAC should be administered when a patient has higher than grade 1 HE, or in patients who do not tolerate oral dosing

![Pathogenesis of cerebral edema and intracranial hypertension in acute liver failure. BBB: blood-brain barrier; Ca\(^2+\): calcium; CBF: cerebral blood flow; CPP: cerebral perfusion pressure; HO-1: heme-oxidase-1; ICP: intracranial pressure; NO: nitric oxide; SIRS: systemic inflammatory response syndrome.](image-url)
Finally, since the administration of NAC, even late after ingestion, appears to confer survival benefit, dosing should continue until evidence of severe liver injury resolves (international normalized ratio [INR] less than 1.5 and resolution of HE) (32).

**Other Etiology-Specific Treatments**

Specific medications may be considered in patients with ALF due to non-APAP etiologies, and are outlined in Table 127.3. It should be emphasized that studies to support the use of these therapies do not exist; one using lamivudine for acute hepatitis B found no benefit versus placebo (33). Another randomized, placebo-controlled trial suggested improved transplant-free survival of patients with non-APAP ALF and low-grade (stage I-II) HE who received NAC (34).

### Management of HE, Cerebral Edema, and Seizures

Considering the central importance of ammonia in the pathogenesis of HE and cerebral edema, clinicians often use therapies aimed at lowering serum ammonia levels in patients with ALF. The most commonly used agents in chronic liver disease, nonabsorbable disaccharides (e.g., lactulose) and oral antibiotics (neomycin, rifaximin, or metronidazole), have not been studied in patients with ALF but probably have little effect on outcome. A computed tomographic (CT) scan of the head should be considered early in the course of ALF to exclude other causes of altered mental status, especially intracerebral hemorrhage. Although a head CT may also detect cerebral edema, a normal scan does not rule out clinically important

### TABLE 127.2 Schemes for Predicting Poor Prognosis and the Need for Orthotopic Liver Transplantation in Patients with Acute Liver Failure (ALF)

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Cause of ALF</th>
<th>Criteria for Liver Transplantation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>King’s College criteria</td>
<td>Acetaminophen</td>
<td>Arterial pH &lt; 7.30 Or All of the following: Prothrombin time &gt; 100 s Creatinine &gt; 3.4 mg/dL Grade 3/4 encephalopathy PT more than 100 s (INR &gt; 6.6)</td>
<td>O’Grady et al., 1989 (17)</td>
</tr>
<tr>
<td>Non-acetaminophen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor V</td>
<td>Viral</td>
<td>Age &lt; 30 yr; factor V &lt; 20% Or Any age; factor V &lt; 30% and grade 3/4 encephalopathy</td>
<td>Bernuau et al., 1986; 1991 (19,20)</td>
</tr>
<tr>
<td>Factor VIII/V ratio</td>
<td>Acetaminophen</td>
<td>Factor VIII/V ratio &gt; 30</td>
<td>Pereira et al., 1992 (21)</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Mixed</td>
<td>Hepatocyte necrosis &gt; 70%</td>
<td>Donaldson et al., 1993 (22)</td>
</tr>
<tr>
<td>Arterial phosphate</td>
<td>Acetaminophen</td>
<td>&gt; 1.2 mmol/L</td>
<td>Schmidt and Dalhoff, 2002 (23)</td>
</tr>
<tr>
<td>Arterial lactate</td>
<td>Acetaminophen</td>
<td>&gt; 3.5 mmol/L</td>
<td>Bernal et al., 2002 (24)</td>
</tr>
<tr>
<td>Arterial ammonia</td>
<td>Mixed</td>
<td>&gt; 150-200 μmol/L</td>
<td>Clemmesen et al., 1999 (25)</td>
</tr>
<tr>
<td>APACHE II/III score</td>
<td>Acetaminophen</td>
<td>&gt; 15</td>
<td>Mitchell et al., 1998 (26,27)</td>
</tr>
<tr>
<td>MELD score</td>
<td>Non-acetaminophen</td>
<td>&gt; 32</td>
<td>Parkash et al., 2005 (28)</td>
</tr>
</tbody>
</table>


### TABLE 127.3 Potential Etiology-Specific Therapy of Patients with Acute Liver Failure

<table>
<thead>
<tr>
<th>Cause</th>
<th>Therapy</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>NAC oral: 140 mg/kg load, then 70 mg/kg every 4 hr</td>
<td>Smilkstein et al., 1988 (30)</td>
</tr>
<tr>
<td></td>
<td>NAC IV: 150 mg/kg load, then 12.5 mg/kg/h x 4 hr, then 6.25 mg/kg/hr</td>
<td>Buckley et al., 1999 (35), Smilkstein et al., 1991 (31)</td>
</tr>
<tr>
<td>Amanita&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Penicillin G: 1 g/kg/d IV &amp; NAC (as in APAP overdose)</td>
<td>Brousard et al., 2001 (36)</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Acyclovir: 30 mg/kg/d IV</td>
<td>Peters et al., 2000 (37)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Methyprednisolone 60 mg/d IV</td>
<td>Ichai et al., 2007 (38), Karkhanis et al. (39)</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Lamivudine 100–150 mg/d PO</td>
<td>Kumar et al., 2007 (33)</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Plasmapheresis, D-penicillamine</td>
<td>Rodriguez et al., 2003 (40)</td>
</tr>
<tr>
<td>AFLP/HellP</td>
<td>Delivery of fetus</td>
<td>Castro et al., 1999 (41)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Amanita refers to mushroom intoxication.

AFLP/HellP: acute fatty liver of pregnancy/hemolysis-elevated liver enzymes-low platelet syndrome.
intracranial hypertension (Fig. 127.2) (42). The specific management of cerebral edema in patients with ALF resembles that of other causes of intracranial hypertension, with the important caveat that hyperemia plays an important additional pathogenic role in the former (Fig. 127.3). Chest physiotherapy and suctioning should be temporarily minimized. The head of the bed should be elevated to at least 30 degrees, as this reduces ICP and decreases the risk of hospital-acquired pneumonia (43). The duration of time that a patient is placed supine or in Trendelenburg position for procedures should be minimized, especially if ICP is not monitored. Endotracheal intubation and mechanical ventilation must be implemented in a timely fashion to avoid the potentially injurious effects of hypoxemia and hypercapnia, while also reducing aspiration risk and facilitating management of intracranial hypertension. Laryngoscopy and intubation may cause transient elevations in ICP and fluctuations in blood pressure. Appropriate measures should be taken to minimize these physiologic derangements, including the appropriate use of sedation and neuromuscular blockade.

Adequate analgesia and sedation must be administered to manage intracranial hypertension in ALF. In general, shorter-acting agents are preferred, such that patients can be more quickly awakened and re-examined. Increased levels of endogenous benzodiazepine like molecules and GABAergic neurotransmission have been implicated in the pathogenesis of HE (44). Therefore, sedatives with GABAergic properties may exacerbate HE; propofol is preferred over benzodiazepines by some authors (45).

Hyperventilation causes cerebral vasoconstriction and a reduction in cerebral blood volume, effects that can be used therapeutically to reduce ICP (46). Patients with HE often spontaneously hyperventilate, with resultant respiratory alkalosis. If the PaCO₂ suddenly normalizes because of sedation or respiratory exhaustion, rebound vasodilatation may occur, with consequent elevated ICP. Thus, initial ventilator settings should probably be set to match the previous, spontaneous minute ventilation of the patient, and either arterial blood gases or end-tidal CO₂ should be closely monitored. The major concern with using hyperventilation as a means to lower ICP is that vasoconstriction may be severe enough to cause cerebral ischemia.

Osmotic agents, including mannitol and hypertonic saline (HTS), lower ICP most effectively in the setting of global—rather than unilateral—cerebral edema with an intact blood–brain barrier, which characterizes ALF (47). In small human and animal studies, mannitol effectively lowered ICP and appeared to improve survival (48,49). A general indication for the administration of mannitol includes persistently (more than 10 minutes) elevated ICP (more than 20 mmHg if monitor present; see below in “Controversies”) after ensuring proper calibration of the ICP monitor. The optimal dose of mannitol remains untested, but smaller boluses (e.g., 0.25–0.5 g/kg every 4 to 6 hours) appear to be as effective as larger ones. Apart from potentially causing hypovolemia, the accumulation of mannitol may be nephrotoxic, an important consideration given that many patients with ALF have abnormal renal function. Consider maintaining serum osmolality below 320 mOsm/L, but this threshold is arbitrary, is frequently exceeded without adverse effect in other neurocritical care patients, and does not predict an increased risk of renal failure.

HTS is increasingly being used in various settings as an alternative to mannitol to treat cerebral edema (47). Theoretical advantages over mannitol include the following: (a) the blood–brain barrier is less permeable to HTS, making it a more effective osmotic agent; (b) it is a volume expander rather than a diuretic; and (c) there is no proven nephrotoxicity. HTS can be administered as boluses of 3% to 30% saline every 3 to 4 hours, or as a continuous infusion. In one randomized, controlled trial of patients with ALF and high-grade
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Management of Cardiopulmonary Complications

Patients with ALF frequently develop SIRS, regardless of whether or not their course is complicated by infection (54). Vasoplegia is common in ALF and can be complicated by sedatives, mechanical ventilation, and relative adrenal insufficiency (55). Norepinephrine is currently the preferred vasopressor for vasodilatory shock (56). The goal MAP should be individualized to optimize organ perfusion, rather than choosing an arbitrary number, but is generally kept above 65 mmHg. CPP should be maintained above 50 to 60 mmHg, since CBF auto-regulation fails below these levels in most individuals; if an ICP monitor is not placed, clinicians should err on the side of higher blood pressure. Although there are theoretical concerns that vasopressin may exacerbate ICH, it may be used as a second-line vasopressor (57). In patients with relative adrenal insufficiency, treatment with low-dose corticosteroids (e.g., hydrocortisone 50 to 100 mg IV every 6 to 8 hours, or 8 to 10 mg/hr as a continuous IV infusion) reduces vasopressor requirements, although the impact on outcome is uncertain.

As many as 37% of patients with ALF develop acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) (58). With established ALI or ARDS, tidal volumes should be limited to 6 mL/kg of predicted body weight, although increases in PaCO₂ cannot be tolerated in the setting of cerebral edema and intracranial hypertension. Given the high risk of developing ARDS, it may be advisable to limit tidal volumes even in the absence of established ALI/ARDS. Positive end-expiratory pressure (PEEP/CPAP) settings should be sufficient to achieve adequate oxygenation, while concomitantly ensuring that ICP, blood pressure, and cardiac output are not compromised.

Management of Acute Kidney Injury

Acute kidney injury (AKI) complicates up to 50% of cases of ALF, and is more prevalent in acetaminophen-induced ALF (59,60). Hypovolemia, hypotension, and the use of nephrotoxins—including aminoglycosides, nonsteroidal anti-inflammatory drugs, and intravenous contrast—should be minimized. Patients with ALF can develop hepatorenal syndrome (HRS) as a consequence of intense renal vasoconstriction (see Acute-on-Chronic Liver Failure, below). The decision to initiate renal replacement therapy (RRT) must consider the magnitude of renal dysfunction, metabolic derangements, and volume overload. Continuous renal replacement therapy (CRRT) is preferred over intermittent hemodialysis (IHD) by many clinicians, largely because of more stable volume management and greater time-averaged dialysis dose. Even transient hypotension is poorly tolerated in patients with cerebral edema; not only does the CPP decrease, but cerebral vasodilation may increase, with further increases in CBF and ICP (61). Excessively rapid correction of metabolic acidosis with bicarbonate-based dialysate may transiently increase cerebral spinal fluid CO₂, reduce central nervous system (CNS) pH, and promote more cerebral vasodilatation (62). Good results have been achieved with CRRT in patients with ALF (63). Regardless of the mode of RRT, an adequate hemofiltration or

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Management of Infections

ALF is associated with reticuloendothelial dysfunction and impaired immunity, with reduced complement levels, abnormal opsonization, and ineffective phagocytosis. ALF patients are, therefore, at high risk of nosocomial infections with both bacterial and fungal pathogens, which occur in almost 40% of these patients (65). Early diagnosis can be difficult since patients often have subtle manifestations of infection, but is vital because of the high associated morbidity and mortality. Daily surveillance cultures (urine, blood, sputum) and chest radiography should be considered, as they may improve early diagnosis of infection and guide selection of antimicrobial agents (66). Prophylactic antibiotics (enteral and parenteral) have not shown consistent impact rates of bacteremia or survival in ALF (67). Nevertheless, many clinicians prefer to use them, especially in patients listed for transplantation. Empiric broad-spectrum antibiotics (including vancomycin and an antifungal agent, as indicated) should be considered in any patient with ALF who develops significant isolates on surveillance cultures, unexplained progression of HE, or signs of SIRS, as these frequently predict sepsis in patients with ALF (14, 54).

Management of Coagulopathy

Despite a deficiency of clotting factors, low fibrinogen, thrombocytopenia, and platelet dysfunction, clinically important spontaneous bleeding is relatively infrequent in patients with ALF, being seen in less than 10% of patients (68). Therefore, the routine use of blood products to correct these abnormalities is not justified since they are unnecessary, ineffective, and perhaps most importantly, interfere with the prognostic utility of the INR. Although treatment of coagulopathy may be considered in anticipation of invasive procedures, global hemostasis in patients with ALF is usually normal or even hypercoagulable (69), and transfusion of plasma may exacerbate a prothrombotic state characterized by profusely high von Willebrand factor and factor VIII, and deficient fibrinolysis (67, 70, 71). Vitamin K deficiency has been reported to contribute to the coagulopathy of ALF (72) and should be repleted parenterally (10 mg subcutaneously [SC] or slow [over 30 minutes] IV). Coagulopathy and mechanical ventilation are well-established indications for gastrointestinal (GI) stress ulcer prophylaxis, which has been shown to decrease the risk of GI bleeding in ALF patients (73). Deep venous thrombosis prophylaxis is recommended; although there are no published data, low-dose unfractionated heparin or low–molecular-weight heparin can be safely used (Richard T. Stravitz, personal observations).

Management of Metabolic Derangements

ALF is a catabolic state, with increased energy requirements and negative nitrogen balance, which may in turn contribute to immunosuppression (74). Higher-than-usual caloric intake is therefore recommended, with 35 to 40 kcal/kg/day and 0.8 to 1 g/kg/day of protein, preferably provided via the enteral route. Reduced hepatic glycogen stores and impaired gluconeogenesis are responsible for the frequent development of hypoglycemia, which often requires treatment with intravenous dextrose. Conversely, hyperglycemia may contribute to increases in ICP and other complications. Thus, blood glucose values must be closely monitored and maintained within the normal range with intravenous short-acting insulin.

Liver Transplantation for ALF

OLT remains the treatment of last resort for ALF. The decision to list a patient with ALF for OLT requires careful clinical and psychosocial assessment and should be started immediately on recognition of poor prognosis as discussed above. In addition to usual clinical evaluation, patients with ALF due to APAP overdose often present with histories of suicidal ideation or substance abuse, which may preclude their consideration as viable OLT candidates. Because OLT candidates with ALF are generally younger and healthier than their counterparts with chronic liver disease, the pretransplant evaluation can usually be abbreviated to include echocardiography, duplex ultrasonography of the liver, and routine pretransplant laboratories (e.g., total anti-CMV, HIV antibody).

Criteria for listing a patient with ALF for OLT change and current criteria may be found at UNOS.ORG in Policy 3.6. Presently, patients with ALF are given priority to receive a cadaveric organ over all patients with chronic liver disease (Status 1). Candidates must have a life expectancy without OLT of less than 7 days, have onset of HE within 8 weeks of the first symptoms of liver disease, and no history of pre-existing liver disease. In addition, patients must be in the ICU and must fulfill one of the following three criteria: (i) be ventilator dependent; (ii) require dialysis or CRRT; or (iii) have an INR more than 2.0. Patients with acute decompensated Wilson disease may also be listed as Status 1 in consideration with their extremely poor prognosis for spontaneous survival. Before transporting a patient with ALF to the operating room for OLT, a detailed review of the patient’s neurologic status must be made so that OLT is not performed when likelihood of neurologic recovery is poor. Specifically, it has been observed that severe, sustained intracranial hypertension predicts brainstem herniation during OLT or poor neurologic recovery after OLT, and patients with ICP greater than 40 mmHg or CPP less than 40 mmHg for more than 2 hours appear to be particularly vulnerable to these disastrous outcomes (75).

Early (3-month) mortality after OLT for ALF is higher than for patients transplanted for all causes of chronic liver disease—about 20% versus 10%, respectively, reflecting the acuity and severity of disease at the time of transplant. Thereafter, however, 5- and 10-year survival after OLT for ALF approximates 70% and 65%, respectively (76). Well-selected APAP-ALF patients with careful review of psychosocial factors potentially have outcomes similar to patients with chronic liver disease patients (77).

Controversies

Intracranial Pressure Monitoring

ICP cannot accurately be determined noninvasively and carries important prognostic implications for spontaneous survival and neurologic recovery after OLT, many experts advocate ICP monitor placement in OLT candidates with stage III or IV HE (78). Although there is a perception that ICP monitoring significantly improves the outcome of patients with ALF, no prospective, randomized studies exist to support the practice, and retrospective studies in fact refute this perception (79).
The invariable presence of coagulopathy in patients with ALF increases the bleeding risk of ICP monitor placement, and earlier studies reported bleeding complications in up to 20%. However, the clinical significance of many of these bleeding complications was probably negligible (78), and more recent series have found lower bleeding rates (5%) (79). Although placement of ICP monitors into the epidural space may minimize the risk of hemorrhage, the accuracy of this practice, compared with other methods of ICP monitoring, has not been well studied.

**Therapeutic Hypothermia in ALF**

Fever increases ICP and is an independent predictor of worse outcome in brain-injured patients, such that hyperthermia should be avoided (80). The induction of mild hypothermia may interfere with several steps in the pathogenesis of cerebral edema. Specifically, hypothermia attenuates the osmotic gradient created by increased astrocytic glutamine, normalizes extracellular glutamate and lactate, decreases CBF, restores autoregulation, and reduces ICP (81). Temperatures of 32°C to 33°C have been used to control intracranial hypertension in patients with ALF refractory to standard care. However, a recent controlled study failed to show significant benefit with the potential exception of younger acetaminophen patients (82). Important potential adverse effects of hypothermia in the setting of ALF include interference with coagulation, an increased risk of infection, and cardiac dysrhythmias.

**ACUTE-ON-CHRONIC LIVER FAILURE**

**Definitions**

Patients with cirrhosis, the fibro-inflammatory alteration of hepatic architecture resulting in portal hypertension, usually die from acute hepatic decompensation (AD), which triggers MOSF. The term AD is often invoked in a patient with cirrhosis who develops ascites, hepatic encephalopathy, GI hemorrhage, and/or bacterial infection, without progression to MOSF (83). By contrast, acute-on-chronic liver failure (ACLF) has recently been defined as AD with MOSF (83,84). The natural history and clinical manifestations of ACLF have been recently described in order to study the entity, and a prognostic score for ACLF was later developed and validated, which included entries for the number of organs failed, age, and white blood cell (WBC) count (85,86) (available online at http://www.clif-consortium.com). A North American consortium subsequently proposed a second definition of ACLF, including grade III/IV hepatic encephalopathy, hypotension despite adequate volume repletion, and/or a requirement for mechanical ventilation or RRT (87). Transplant-free mortality at 28 and 90 days is 33% and 51%, respectively, in patients with ACLF, but only 2% and 10%, respectively, in those with AD (86). The most common extrahepatic manifestation of ACLF is renal failure, which also portends the worst prognosis.

**Pathophysiology**

According to the Scientific Registry of Transplant Recipients, the most common cause of end-stage liver disease in the United States is chronic hepatitis C, with or without a contribution from alcohol abuse (seen in about 40% of cases). Patients with alcoholic cirrhosis and indeterminate (cryptogenic) causes, many of whom have nonalcoholic steatohepatitis (NASH), occupy second and third most frequent causes, respectively. Other less common etiologies include chronic hepatitis B, immune-mediated liver diseases—autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis—and hereditary liver diseases—hemochromatosis, alpha-1-antitrypsin deficiency.

Patients with cirrhosis decompensate as a result of contributions from two basic pathogenic mechanisms: portal hypertension and hepatocellular insufficiency. Complications of portal hypertension include hemodynamic alterations, functional renal failure, ascites, and GI bleeding, most commonly from variceal hemorrhage. Complications of hepatocellular insufficiency include coagulopathy and hepatic encephalopathy, although it should be appreciated that the latter also occurs as a result of portosystemic shunting.

The pathophysiology of ACLF is the subject of intense ongoing research; however, the topic remains poorly understood largely because the syndrome required formal definition and recognition as a clinical entity. Although the definitions of ACLF noted above were not used in most of the studies exploring pathogenesis, a consensus of experts has summarized the available data (86). ACLF usually occurs after a triggering event in a patient with stable cirrhosis, such as alcoholic hepatitis, superimposed viral hepatitis, drug-induced liver injury, or a complication of cirrhosis itself, most often infection, in turn, often due to bacterial translocation from the gut.

A fundamental feature of cirrhosis critical to the pathogenesis of AD and ACLF is an abnormal hemodynamic state characterized by low systemic vascular resistance (SVR), systemic hypotension, and splanchnic vasodilation. Consequently, arterial underfilling of critical regulatory vascular beds in the renal arterial and hypothalamic circulations result in the elaboration of compensatory neurohumoral effectors, such as renin, angiotensin, vasopressin, and norepinephrine. The primary mechanism underlying low SVR includes release of vasodilatory mediators such as endothelins and nitric oxide by the portal endothelium, which is exacerbated by triggers of ACLF (86). The normal compensatory mechanisms which occur in response to low SVR underlie the formation of ascites, the functional renal failure of cirrhosis—HRS—and hyponatremia. HRS and cirrhotic ascites have the same basic pathogenesis (Fig. 127.4). As outlined above, renal arterial constriction occurs in normal compensation for systemic hypotension. Poor renal perfusion results in sodium retention, plasma volume expansion, and, in the presence of hepatic sinusoidal hypertension, the transudation of lymph across the Glisson capsule as low-protein ascites (88). HRS can be considered an exaggeration of this renal vasoconstriction, often in the setting of cardiac hypocontractility (89).

**Diagnosis**

**Cardiovascular Manifestations**

In addition to the circulatory and neurohumoral features of AD and ACLF discussed above, patients with decompensated cirrhosis have impaired cardiac contractility, particularly after infection or GI bleeding (90). Myocardial failure was
formerly ascribed to the ethanol toxicity or iron deposition in myocardium; however, cirrhotic cardiomyopathy, depressed myocardial contractility as a complication of cirrhosis per se, has been recognized as a distinct clinical entity. Diagnostic criteria of cirrhotic cardiomyopathy include blunt inotropic and chronotropic responses to stress, diastolic dysfunction, and prolonged QT interval on electrocardiogram (ECG). A pathogenic role of cirrhotic cardiomyopathy has been documented in patients with HRS, particularly in the setting of infection, and in the circulatory dysfunction after large volume paracentesis without adequate plasma expansion (89, 91, 92).

Renal Manifestations

AKI in patients with decompensated cirrhosis is an independent predictor of death in the ICU (93), frequently signals the onset of infection (94), and is an integral component of ACLF (86, 95). The definition of AKI in cirrhosis is based upon the modified Risk, Injury, Failure, Loss, End-stage renal disease (RIFLE) criteria rather than a fixed serum creatinine (96). The differential diagnosis of AKI in patients with cirrhosis includes prerenal azotemia, HRS, and acute tubular necrosis (ATN). Analysis of urine sediment and sodium differentiate the above possibilities: the former two diagnoses present with normal urine sediment and low (<10 mEq/L) urine sodium, and the latter with renal tubular cell debris and high urine sodium. The distinction of these causes of renal failure remains paramount, since in its late stages, HRS portends a very poor prognosis and is generally irreversible without OLT, in contrast to prerenal azotemia and ATN. In practical terms, the diagnosis of HRS is often made after the exclusion of septic shock, intrinsic renal disease, obstructive uropathy, and most important, prerenal azotemia, the latter after a 1.5-L IV fluid challenge—normal saline with or without colloid (Table 127.4) (97).

Infectious Manifestations

Bacterial infections represent the most common trigger for ACLF and remain one of the two primary causes of death (84, 95). Risk factors for bacterial infections in hospitalized patients with cirrhosis include ICU admission and GI bleeding (98). Patients with cirrhosis are relatively immunocompromised as a result of portal hypertension and immune dysfunction. Portal hypertension results in the formation of a low-protein ascites, which is susceptible to infection because of its low complement concentration and, thus, low opsonic activity (99). In addition, gut congestion from portal hypertension increases the likelihood of bacterial translocation into blood, which seeds the ascites secondarily, the so-called spontaneous bacterial peritonitis (SBP) (100).

Most studies of bacterial infections in patients with cirrhosis were performed in the 1980s, during which community-acquired, gram-negative infections (urinary tract infections and SBP) predominated. More recent studies, however, have documented an evolution of the epidemiology of infection in patients with cirrhosis. SBP remains the most common bacterial infection in patients admitted to the ICU, but a shift toward gram-positive infections has occurred. In one major hepatic disease ICU, 77% of isolates were gram-positive, which was ascribed to the widespread use of prophylactic fluoroquinolones in cirrhotic patients with low-protein ascites (101), and to the frequent use of invasive procedures, including IV catheter insertion and variceal band ligation (102).

**TABLE 127.4 Diagnostic Criteria of Hepatorenal Syndrome**

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low GFR (creatinine &gt;2.5 mg/dL; CrCl &lt;20 mL/min)</td>
<td>Oliguria (less than 400 mL/d)</td>
</tr>
<tr>
<td>Absence of shock, infection, nephrotoxins</td>
<td>Urine sodium less than 10 mEq/L</td>
</tr>
<tr>
<td>Absence of improvement after a 1.5-L fluid challenge</td>
<td>Serum sodium less than 130 mEq/L</td>
</tr>
<tr>
<td>Absence of intrinsic renal disease</td>
<td>GFR, glomerular filtration rate; CrCl, creatinine clearance.</td>
</tr>
</tbody>
</table>

**Gastrointestinal Manifestations**

Acute upper gastrointestinal (UGI) bleeding, presenting as hematemesis and/or melena, remains one of the three most common indications for admission of patients with cirrhosis to the ICU and a common precipitant of ACLF. Esophageal varices account for most UGI bleeds in patients with cirrhosis, with gastric varices accounting for approximately 5% to 10% (103), and nonvariceal UGI pathology (gastric or duodenal mucosal lesions) noted in up to 30%. Other uncommon causes of UGI bleeding associated with cirrhosis include portal hypertensive gastropathy and gastric antral vascular ectasia, which more often present with occult GI bleeding and anemia (104). Therefore, upper endoscopy must be performed in all patients admitted to the ICU with acute UGI bleeding to identify its source as well as administer therapy.

**Pulmonary Manifestations**

Respiratory failure accounts for up to 40% of admissions of cirrhotic patients to the ICU. The differential diagnosis of respiratory distress in patients with cirrhosis may be categorized into complications of cirrhosis, pulmonary vascular diseases resulting from portal hypertension, and primary liver diseases with cardiopulmonary manifestations (Table 127.5) (105). Pulmonary complications of cirrhosis include massive ascites with compression of the lungs and diaphragm, and hepatic hydrothorax (HH), the accumulation of extracellular fluid with similar protein characteristics as ascites (low-protein) within the pleural space (106). HH usually occurs in the right pleural space (85%) and may occur in the absence of obvious ascites as a result of negative intrathoracic pressure during inspiration. Pulmonary vascular complications may also cause respiratory failure in patients with cirrhosis. The hepatopulmonary syndrome (HPS) is defined as a widened alveolar–arterial oxygen gradient due to intrapulmonary vasodilation in a patient with liver disease. The pathogenesis of HPS remains obscure but likely results from the release of vasoactive mediators from the liver, which increase intrapulmonary nitric oxide production (Fig. 127.5). In a patient with cirrhosis and resting hypoxemia (PaO2 <70 mmHg while breathing an FiO2 of 0.21), the diagnosis is confirmed by a contrast echocardiogram, in which agitated saline administered intravenously delivers microbubbles into the left ventricle at least three heartbeats after their appearance in the right ventricle (107).

In contrast to HPS, portopulmonary hypertension (PPH) is the development of increased pulmonary vascular resistance due to vasoconstriction and subsequent vascular remodeling in a patient with portal hypertension (Fig. 127.6) (108). Screening with transthoracic echocardiography reveals evidence of pulmonary hypertension—right ventricular systolic pressure greater than 50 mmHg—but the diagnosis must be confirmed with right heart catheterization showing elevated mean pulmonary artery (PA) pressure (PAP >25 mmHg) as well as high pulmonary vascular resistance—more than 240 dynes/second per cm²—and normal pulmonary capillary wedge pressure (109).

**Neurologic Manifestations**

Changes in mental status frequently accompany admission of patients with cirrhosis to the ICU and should not automatically suggest the presence of HE (Table 127.6). Usually, HE presents as a global decline in cognition and intellect, but focal neurologic
deficits and signs of cerebral edema—decrebrate posturing and seizures—have also been described (110). After screening for toxic and metabolic derangements, a severely obtunded patient should undergo non–contrast-enhanced head CT to rule out intracranial bleeding. HE may then be diagnosed on clinical grounds after ruling out the above; high serum ammonia levels may help confirm, but are not necessary to make, the diagnosis.

The presentation of a patient with advanced-grade HE to the ICU should prompt a search for precipitating factors, particularly infection and UGI bleeding (Table 127.7). The administration of broad-spectrum antibiotics should be considered until negative cultures have returned, and fluid and electrolyte abnormalities should be corrected. If sedation is required for procedures, benzodiazepines should be used with caution, since they can exacerbate even subclinical HE.

**Treatment**

**Cardiovascular Complications**

The treatment of heart failure in the setting of decompensated cirrhosis remains poorly defined; due to the underlying hemodynamic abnormalities, afterload reduction with angiotensin-converting enzyme inhibitors may precipitate profound hypotension and renal failure, and cardiac glycosides and β-adrenergic agonists have been shown to be relatively ineffective.

**Renal Complications and Ascites**

The treatment of ascites and azotemia will be considered together, since they share common pathogenic mechanisms. Ascites in the ICU is usually approached first with sodium restriction, and the judicious administration of diuretics, as long as the patient does not have marked azotemia (creatinine >2 g/dL), electrolyte abnormalities, or hypotension. A combination of furosemide and spironolactone has been shown to effect a diuresis better than either agent alone; a ratio of 40 mg of the former to 100 mg of the latter administered by mouth has been shown empirically to preserve potassium balance in most patients with cirrhosis (111); the administration of IV albumin (12.5 g/day) may improve the efficacy of diuretics. Large-volume paracentesis should be performed if ascites interferes with ventilation of the patient or if diuretics result in azotemia or...

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**TABLE 127.6 Differential Diagnosis of Altered Mental Status in Patients with Cirrhosis**

- Hepatic encephalopathy
- Electrolyte abnormalities
  - Hyponatremia
  - Hypokalemia
  - Hypomagnesemia
  - Hypoglycemia
- Uremia
- Intracranial bleeding
  - Subdural hematoma
  - Subarachnoid hemorrhage
- Alcohol and/or drugs
  - Intoxication
  - Withdrawal

**TABLE 127.7 Precipitating Events and Mechanisms of Hepatic Encephalopathy in Patients with Cirrhosis**

<table>
<thead>
<tr>
<th>Event</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive protein ingestion</td>
<td>↑ Gut ammonia production</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td></td>
</tr>
<tr>
<td>Portosystemic shunting</td>
<td>↓ Neurotoxin clearance (ammonia, endogenous benzodiazepines)</td>
</tr>
<tr>
<td>Fever, Infection</td>
<td></td>
</tr>
<tr>
<td>Dehydration, azotemia</td>
<td>↓ Renal excretion of ammonium</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td></td>
</tr>
<tr>
<td>Sedatives (benzodiazepines)</td>
<td>↑ Inhibitory neurotransmission (gamma-aminobutyric acid)</td>
</tr>
</tbody>
</table>

---

**FIGURE 127.6** Pathophysiology and diagnostic algorithm of portopulmonary hypertension. ECG, electrocardiogram; JVD, jugular venous distention; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PFT, pulmonary function testing; PVR, pulmonary vascular resistance; RVH, right ventricular hypertrophy; TR, tricuspid valve regurgitation.
Any patient with cirrhosis admitted to an ICU with clinical
Infectious Complications

any patient with cirrhosis admitted to an ICU with clinical
Infectious Complications

epidemiology of high prevalence and risk factors. The experts also
make recommendations for the prevention and management of
hospita infections in cirrhosis patients admitted to the ICU, including
with invasive Aspergillus, Candida species also rarely infect cirrhotic
cases, and refractory shock in such patients may respond to stress
dooses of corticosteroids (124).

Gastrointestinal Complications

Although the trend toward improved survival after variceal
hemorrhage in the last two decades (125), each episode still carries
a mortality risk of 10% to 20%, and rebleeding remains an
important concern especially during the first few days after
the index bleed (Fig. 127.8). General resuscitative measures
on admission to the ICU should include correction of hypotension,
repletion of blood—not to exceed a hemoglobin of
approximately 8 to 9 g/dL, as further repletion increases portal
pressure—and consideration of endotracheal intubation before
doscopy (Table 127.8). A recent prospective, randomized
study of transfusion strategies in patients with UGI bleeding
has suggested that a restrictive strategy, in which patients
received red blood cell transfusion only when hemoglobin
dropped to less than 7 g/dL, was associated with significantly
higher survival, fewer complications, and lower portal pres-
ures in patients with Child-Pugh A/B class cirrhosis compared
to a more liberal transfusion strategy, administered when the

electrolyte abnormalities. IV colloid administration—albumin
6 to 8 g for each liter of ascites removed—should accompany
paracentesis of 5 L or more to prevent postparacentesis circula-
tory dysfunction (112). The insertion of a transjugular intrahe-
patic portosystemic shunt (TIPS) may be considered in patients
who have failed medical therapy (113). In an ICU setting, how-
ever, patients are often too ill to consider TIPS for this indica-
tion, although not necessary for the indication of refractory
variceal bleeding (see below).

The optimal treatment of HRS remains undefined. Figure
127.7 outlines potential treatments, not mutually exclusive,
related to the pathogenic mechanisms of HRS. The ultimate
treatment of the hemodynamic abnormalities of cirrhosis is
OLT, which can completely reverse HRS if performed rela-
tively soon after its onset (114). Albumin infusions (25 to
50 g/day) are commonly administered. Vasoconstrictor ther-
apy holds promise for reversing HRS by reversing the state
of systemic vasodilatation. The oral α-adrenergic agonist mido-
drine (5 to 10 mg orally thrice daily) was found to be effective
in one widely cited but preliminary study, when used in com-
bination with octreotide (100 μg subcutaneously twice daily)
which increases systemic blood volume and thus renal blood
flow by countereacting splanchnic vasodilation (115). Terlip-
ressin, an intravenously administered vasopressin analog with
fewer ischemic complications, also reverses systemic vasodi-
lation and has been found to effectively reverse HRS, but is
not yet available in the United States; it may be more effec-
tive than midodrine/octreotide (116); norepinephrine, which
is readily available, may be an effective alternative (117).
Electrolyte abnormalities should be corrected; hyponatremia and
hypomagnesemia result from furosemide administration, and
hyperkalemia from spironolactone administration. Hypona-
tremia also results from hemodilution in the setting of high
vasopressin release from the neurohypophysis, exacerbates
hepatic encephalopathy, and portends a poor prognosis (118).

Infectious Complications

Any patient with cirrhosis admitted to an ICU with clinical
suspicion of sepsis should immediately receive empiric IV
antibacterial agents to cover gram-positive as well as gram-
negative organisms until cultures and sensitivities allow
narrowing of the regimen; empiric vancomycin should be con-
sidered in patients who have been instrumented. The choice of
coverage for gram-negative bacilli should be a third genera-
tion cephalosporin—cefotaxime (2 g IV every 8 hours) or cef-
triaxone (1 g IV every 24 hours) (111,119)—aminoglycosides
should be avoided except in serious infections with a multiply
resistant organism because of the susceptibility of cirrhotic
patients to aminoglycoside nephrotoxicity. Determinants of
in-hospital mortality of cirrhotic patients with sepsis include
inappropriate or delayed empiric antimicrobial therapy, and
the use of a single rather than combined agents (120).

Diagnostic paracentesis should be performed on all cir-
rhotic patients admitted to the ICU with ascites and renal
failure, HE, or any evidence of infection (111). Localization
symptoms and signs of peritonitis—abdominal pain, fever,
rebound tenderness—may be absent in up to 30% of patients
with SBP. Ascites should be immediately inoculated into cul-
ture bottles at the bedside, which has been shown to increase
culture yields (121); however, even bedside inoculation with a
large volume of ascites (20 mL) yields positive cultures in only
40% to 50% (102). Therefore, the diagnosis of SBP should
rely on a PMN count 250 cells/μL or more; culture-negative
neutrocytic ascites—with 250 or more PMNs/μL—should be
considered the equivalent of SBP (122). Patients with ascites
and this PMN count should receive a third-generation cepha-
losporin and IV albumin—1.5 g/kg at diagnosis and 1.0 g/kg
48 hours after diagnosis—which has been shown both to
decrease the incidence of HRS and to improve mortality
(123). A similar diagnostic and therapeutic algorithm should
be followed for spontaneous bacterial empyema, the infectious
equivalent of SBP in patients with HH. The incidence of fun-
gal infections also increases in cirrhotic patients admitted to
the ICU, including with invasive Aspergillus, Candida species
also rarely infect cirrhotic ascites, but with disastrous outcome
when it occurs.

The mortality of cirrhotic patients admitted to the ICU with
infection remains high, with death usually from hepatic failure,
HRS, or refractory septic shock. As with patients with ALF, rel-
ative adrenal insufficiency commonly accompanies decompens-
ated cirrhosis and sepsis, and refractory shock in such patients
may respond to stress doses of corticosteroids (124).
varices and controls active bleeding in more than 75% of cases when combined with vasoactive therapy (131); recurrent bleeding should prompt a second attempt at endoscopic treatment in most cases. In patients with recurrence after a second endoscopic treatment, or in any recurrence with hemodynamic instability, emergent insertion of a TIPS should be considered. Recent series have also shown that early TIPS in cirrhotics with a high risk of failure of medical management—Child C cirrhosis, or Child B cirrhosis with active bleeding on EGD—is associated with much lower failure to control bleeding, rebleeding, and borderline higher survival than continued medical management (132). Patients with acute hemorrhage from fundic gastric varices present a particular therapeutic challenge because the bleeding is more profuse and interventions have been less successful in controlling the acute bleed (103). Vasoactive therapy should be administered as for bleeding from esophageal varices, and tissue adhesive therapy may be attempted with cyanoacrylate glue (133). In the absence of endoscopic and vasoactive control of gastric variceal bleeding, insertion of a large tamponade balloon (Linton tube) can temporize control before a TIPS procedure.

In previous periods, bacterial infection complicated acute variceal bleeding in 40% of patients and contributed to renal failure and recurrent early bleeding (134). Antibiotic prophylaxis after variceal hemorrhage has been shown to decrease the incidence of infection, as well as variceal rebleeding, resulting in improved survival (134, 135). Although oral or IV fluoroquinolones—norfloxacin 400 mg orally/day or ofloxacin 200 mg IV twice daily—have been more thoroughly studied for this purpose, a randomized trial has suggested superior efficacy of cephalosporins—for example, ceftriaxone, 1 g IV daily—because of the widespread development of resistance to the former (136); however, local resistance patterns should be considered.

**Pulmonary Complications**

The prognosis of patients who develop refractory HH, which is diagnosed by the serum-to-ascites albumin gradient similar to the serum-to-ascites albumin gradient (SAAG) (137), is very poor unless the patient undergoes OLT (137). The basic treatment of HH includes diuretic administration as for ascites, and therapeutic thoracocentesis. Placement of a TIPS in patients with refractory HH may be considered but is not universally effective, and relapse-free 1-year survival is only 35% (138). Chest tube placement and pleurodesis are relatively contraindicated in refractory HH as they often contaminate the pleural space, precluding OLT (139). An infectious complication of HH, spontaneous bacterial empyema, should be diagnosed and managed similarly to SBP, and has a very high mortality (140).

### TABLE 127.8 Specific Management of Acute Variceal Hemorrhage and Its Complications

<table>
<thead>
<tr>
<th>Therapeutic Maneuver</th>
<th>Dose/Route/Indication</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion of RBC</td>
<td>To hemoglobin of 7–8 g/dL</td>
<td>Villanueva et al., 2013 (152)</td>
</tr>
<tr>
<td>Octreotide</td>
<td>100 μg IV bolus, then 50 μg/h for 5 d</td>
<td>Corley et al., 2001 (130)</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>EVL preferred over EVS</td>
<td>De Franchis and Primignani, 1999 (153)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Pantoprazole 40 mg IV or PO/d for 9 d</td>
<td>Shaheen et al., 2005 (128)</td>
</tr>
<tr>
<td>Antibiotic prophylaxis</td>
<td>Norfloxacin 400 mg/d for 7 d, or ceftriaxone</td>
<td>Bernard et al., 1999 (135); Fernandez et al., 2006 (136)</td>
</tr>
<tr>
<td>TIPS</td>
<td>After two failed therapeutic endoscopies</td>
<td>Mihas and Sanyal, 2004 (154)</td>
</tr>
</tbody>
</table>

RBC, red blood cells; EVL, esophageal variceal ligation; EVS, endoscopic variceal sclerotherapy; TIPS, transjugular intrahepatic portosystemic shunt.
Supplemental oxygen usually bridges patients with HPS to OLT, which improves or reverses the process in 85% of patients (141). Patients with HPS have increased transplant waiting-list mortality when compared to patients with normal gas exchange; consequently, patients with HPS and PaO2 less than 60 mmHg on room air are allowed increased priority for OLT under the current organ allocation system in the United States. Perioperative mortality after OLT in patients with HPS varies according to the degree of shunting and hypoxemia (141,142). The optimal treatment of PPH—indicated when mean PAP is more than 35 mmHg—not has been well defined (109); prostacyclin analogs (epoprostenol titrated via PA catheter; inhaled iloprost [5 μg six times daily]) phosphodiesterase inhibitors, endothelin receptor antagonists, or combination therapy appear to be effective (143). PPH does not always reverse after OLT, and therefore, patients with mean PAP more than 35 mmHg after maximal medical treatment are often not offered transplant.

Management of Neurologic Complications

The specific treatment of HE poses special challenges in the ICU. The standard therapy, oral lactulose, must be administered via nasogastric tube in an intubated patient, cannot be given if there is an ileus, and its overzealous administration risks aspiration pneumonia, gaseous distention of the bowel, toxic megacolon, and electrolyte imbalance. Rectal lactulose offers an alternative route of administration, but its efficacy over tap water or saline enemas is unknown. The “nonabsorbable” antibiotic neomycin should be avoided, as the absorption of even small quantities from the gut risks renal injury. Rifaximin, a rifampin derivative that also decreases gut flora production of neurotoxins, appears to be as effective as lactulose, and has a good safety profile (144). The benzoazolepine receptor antagonist flumazenil (1 mg IV) improves HE, but the benefit wanes within 2 hours (145). Extracorporeal albumin dialysis also improves HE in refractory cases and may be considered as a bridge to OLT (146).

Controversies

A major source of controversy in managing patients with decompensated cirrhosis revolves around the perception of bleeding risk. Patients with stable cirrhosis develop AD and ACLF as a result of bleeding, usually from the UGI tract. However, management of this type of bleeding, which results from portal hypertension, is not very controversial. The controversy lies in whether patients who present with a variceal bleed should have their INR and platelet count treated, and if so, the goals of treatment, especially since the transfusion of high volumes of plasma raises portal pressures, and may increase the risk of rebleeding (147). Major controversy continues to involve the prophylactic use of platelets and plasma in patients with cirrhosis before invasive procedures. Research in the last 10 years has started to help make clinicians more comfortable with conservative repletion of factors and blood products, beginning with the seminal observations by Tripodi et al. (148), who described in vitro assay conditions that demonstrated that patients with cirrhosis generate as much thrombin as normal healthy controls. A second landmark study by the same group showed that a platelet count of approximately 60 × 10⁹ cells/L was sufficient to preserve thrombin generation at or near the 90th percentile of normal healthy controls (149).

Subsequent studies in patients with cirrhosis have suggested that, despite the consequences of portal hypertension that lead to bleeding, patients may in fact be hypercoagulable (150). Although many questions remain unanswered, and guidelines to help the clinician remain undefined, the area is being vigorously studied.

Key Points

- ALF is a clinical syndrome with more than a dozen causes, few of which have etiology-specific treatments. N-acetylcysteine may be an appropriate treatment for all etiologies.
- The roles of direct ICP monitoring and therapeutic hypothermia in managing patients with ALF and cerebral edema remain very controversial.
- The three most common causes of death in patients with ALF are cerebral edema/intracranial hypertension/brainstem herniation, infection, and multiorgan system failure.
- OLT is a highly effective treatment for ALF but must be judiciously applied, as many patients recover spontaneously, organs are scarce, and long-term complications of OLT remain considerable. Therefore, prediction of death without OLT is of paramount importance.
- Patients with cirrhosis are admitted to the ICU most commonly as the result of acute hepatic decompensation, presenting as infection and/or portal hypertensive UGI bleeding.
- ACLF has recently been recognized as a distinct clinical entity consisting of acute hepatic decompensation in the presence of extrahepatic organ failure.
- ACLF has a high short-term mortality, which parallels the degree of multiorgan system failure. The most common extrahepatic manifestation of ACLF, renal failure, portends the worst prognosis.
- Patients with ACLF should receive empiric, multiple antimicrobial agents as soon as possible, until screening tests for infection (including diagnostic paracentesis) have either returned negative or identified a responsible source and organism.

References

33. Kumar M, Satapathy S, Monga R, et al. A randomized controlled trial of
30. Parkash O, Munoz RJ, Wanless IR, et al. Glutamine, myo-inositol, and brain edema in acute liver fail-
35. Buckley NA, Whyte IM, O’Connell DL, Dawson AH. Oral or intrave-
rous N-acetylcysteine: which is the treatment of choice for acetaminophen
34. Cordoba J. Glutamine, myo-inositol, and brain edema in acute liver fail-
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rous N-acetylcysteine: which is the treatment of choice for acetaminophen
34. Cordoba J. Glutamine, myo-inositol, and brain edema in acute liver fail-
Lidofsky SD, Bass NM, Prager MC, et al. Intracranial pressure monitor -
MacDougall BR, Williams R. H2-receptor antagonist in the prevention
Pereira SP, Rowbotham D, Fitt S, et al. Pharmacokinetics and efficacy of
Runyon BA, Montano AA, Akriviadis EA, et al. The serum-ascites albumin
Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a dis-
Stravitz RT, Larsen FS. Therapeutic hypothermia for acute liver failure.
Munoz SJ, Moritz MJ, Bell R, et al. Factors associated with severe intra-
Karvellas CJ, Safinia N, Auzinger G, et al. Medical and psychiatric out-


