TABLE 154.1

<table>
<thead>
<tr>
<th>Cause</th>
<th>Prevalence (%)</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>APAP</td>
<td>45</td>
<td>History; APAP level</td>
</tr>
<tr>
<td>HBV</td>
<td>7</td>
<td>anti-HBs (IgM and total), HBsAg, anti-HBs, HBV DNA, anti-HDV</td>
</tr>
<tr>
<td>AIH</td>
<td>5</td>
<td>ANA, ASMA, anti-LKM, immunoglobulins</td>
</tr>
<tr>
<td>HAV</td>
<td>4</td>
<td>anti-HAV (IgM and total)</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>3</td>
<td>Serum ceruloplasmin and copper; urine copper; slitlamp eye exam</td>
</tr>
<tr>
<td>BCS</td>
<td>2</td>
<td>Doppler ultrasound of liver</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
<td>Contrast-enhanced CT, MRI (preferred)</td>
</tr>
<tr>
<td>AFLP/HELLP</td>
<td>1</td>
<td>Pregnancy test</td>
</tr>
<tr>
<td>HSV</td>
<td>0.5</td>
<td>Anti-HSV 1/2, HSV DNA</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>Anti-HCV/HCV RNA, anti-CMV/CMV DNA, anti-EBV/EBV DNA, toxoscopy screen</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>14</td>
<td>All of above negative</td>
</tr>
<tr>
<td>Idiosyncratic drug</td>
<td>13</td>
<td>History, all of above negative</td>
</tr>
</tbody>
</table>

APAP, acetaminophen; HBV, hepatitis B virus; HDV, hepatitis D virus; AIH, autoimmune hepatitis; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; anti-LKM, anti-liver kidney microsomal antibody; HAV, hepatitis A virus; BCS, Budd-Chiari syndrome; CT, computed tomography; MRI, magnetic resonance imaging; AFLP/HELLP, acute fatty liver of pregnancy/hemolysis-elevated liver enzymes-low platelet syndrome; HSV, herpes simplex virus; HCV, hepatitis C virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

N = approximately 1,000 at the time of publication. (W.M. Lee, personal communication.)

Suggested evaluation of patients with idiosyncratic drug hepatotoxicity and indeterminate ALF should include all of the tests listed, since these are diagnoses of exclusion.

It remains doubtful that acute hepatitis C virus infection causes ALF, but chronic hepatitis C may increase a patient’s susceptibility to ALF after a different acute insult (6). The initial laboratory and procedural evaluation of patients with ALF to determine cause is indicated in Table 154.1 (7).

Assessment of Prognosis

Outcomes of ALF

Two general rules improve the prediction of outcome in patients with ALF. First, the cause of ALF is the single, most important prognostic factor. In patients with APAP overdose, spontaneous recovery is the rule (63% in the ALFSG cohort). Patients with acute hepatitis A, shock liver, and pregnancy-related AFLP—assuming prompt delivery of the fetus—also have relatively high rates of spontaneous survival (more than 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). Second, 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 (8). Patients with APAP overdose and acute hepatitis A usually have hyperacute progression (jaundice-HE interval within 7 days) and have a relatively good prognosis, whereas most idiosyncratic drug reactions have a more subacute presentation (jaundice-HE interval of more than 28 days) and dismal prognosis without OLT.

Prognostication Schemes

To anticipate the need for OLT, prognostic schemes have been developed to predict death without OLT in patients with ALF. The most time-honored scheme, the King’s College Criteria (9), 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 less than 7.30), or azotemia, severe coagulopathy, and high-grade HE (grade 3 or 4). In patients with ALF due to other causes, severe coagulopathy or any three of the criteria listed in Table 154.2 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 (10). Consequently, other prognostic parameters continue to be applied to individual patients with ALF during the weighty decision of whether to proceed with OLT.

Complications and Treatment

General Management

ALF commonly causes multiorgan dysfunction, such that management requires close collaboration between intensivists, hepatologists, transplant surgeons, and other specialists (11). Improvements in critical care practice have resulted in improved mortality over past decades, even in patients who do not
TABLE 154.2
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>APAP</td>
<td>Arterial pH &lt; 7.30 or</td>
<td>O’Grady et al., 1989 (9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>all of the following:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. PT &gt; 100 s</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Creatinine &gt; 3.4 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Grade 3/4 encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Non-APAP</td>
<td></td>
<td>PT &gt; 100 s (INR &gt; 6.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>any 5 of the following:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. NANB/drug/halothane etiology</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Jaundice to encephalopathy &gt; 7 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Age &lt; 10 or &gt; 40 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. PT &gt; 50 s</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Bilirubin &gt; 17.4 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Factor V</td>
<td>Viral</td>
<td>Age &lt; 30 y: factor V &lt; 20% or</td>
<td>Bernaau et al., 1986; 1991 (202,203)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any age: Factor V &lt; 30% and grade</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/4 encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Factor VIII ratio</td>
<td>APAP</td>
<td>Factor VIII ratio &gt; 10</td>
<td>Pereira et al., 1992 (204)</td>
</tr>
<tr>
<td>Arterial phosphate</td>
<td>APAP</td>
<td>&gt; 1.2 mmol/L</td>
<td>Schmidt and Dalhoff, 2002 (206)</td>
</tr>
<tr>
<td>Arterial lactate</td>
<td>APAP</td>
<td>&gt; 3.5 mmol/L</td>
<td>Berna et al., 2002 (207)</td>
</tr>
<tr>
<td>Arterial ammonia</td>
<td>Mixed</td>
<td>&gt; 150–200 μmol/L</td>
<td>Clemmesen et al., 1999 (24)</td>
</tr>
<tr>
<td>APACHE II/III score</td>
<td>APAP</td>
<td>&gt; 15</td>
<td>Berna et al., 1998, Mitchell et al., 1998 (208,209)</td>
</tr>
<tr>
<td>MELD score</td>
<td>Non-APAP</td>
<td>&gt; 30</td>
<td>Rosario et al., 2005 (210)</td>
</tr>
</tbody>
</table>

Abbreviations per legend of Table 154.1, as well as: PT, prothrombin time; INR, international normalized ratio; NANB, non-A, non-B viral hepatitis; APACHE, Acute Physiology and Chronic Health Evaluation; MELD, model for end-stage liver disease.


undergo OLT (12,13). Since the progression of complications can be rapid, patients should be transferred to a liver transplant center; in general, higher-volume centers have superior outcomes. Sedation should initially be minimized to avoid confusing the effects of drugs with deteriorating mental status. Worsening hepatic encephalopathy (HE) is a clear indication for admission to the ICU; the likelihood of spontaneous survival decreases with a worsening coma grade at admission (9,14).

**Cause-Specific Management**

Acetaminophen. The administration of N-acetylcysteine (NAC) has become widely applied to patients with ALF due to APAP on the basis of both laboratory and clinical data (15,16); 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 multiple. Therefore, NAC should be administered “whenever there is doubt concerning the timing, dose ingested, or plasma concentration, since the use of the antidote is much less hazardous than the consequences of withholding it” (17). Second, intravenous NAC should be administered when a patient has higher than grade 1 HE, or in patients who do not tolerate oral dosing (16). 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), rather than by completion of a set number of doses of the drug (18).

Other Cause-Specific Treatments. Specific medications that should be considered in patients with ALF due to other causes are outlined in Table 154.3. It should be emphasized that randomized, controlled studies to support these therapies do not exist, and most of these recommendations are made only on the basis of case reports, expert opinion, and a high therapeutic threshold.

**Management of Specific Complications of ALF**

**Neurologic Complications**

Pathophysiology. By definition, patients with ALF develop varying degrees of HE (Table 154.4). Worsening mental status...
TABLE 154.3

CAUSE-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>APAP</td>
<td>NAC Oral: 140 mg/kg load, then 70 mg/kg every 4 hrs</td>
<td>Smilkstein et al., 1988 (15)</td>
</tr>
<tr>
<td></td>
<td>NAC IV: 150 mg/kg load, then 12.5 mg/kg/h × 4 hrs, then 6.25 mg/kg/hr</td>
<td>Buckley et al., 1999 (212), Smilkstein et al., 1991 (16)</td>
</tr>
<tr>
<td>Amanita</td>
<td>Penicillin G: 1 g/kg/d IV &amp; NAC</td>
<td>Brussard et al., 2001 (213)</td>
</tr>
<tr>
<td>HSV</td>
<td>Acyclovir: 30 mg/kg/d IV</td>
<td>Peters et al., 2000 (214)</td>
</tr>
<tr>
<td>AIH</td>
<td>Methylprednisolone 60 mg/d IV</td>
<td>Kessler et al., 2004 (215)</td>
</tr>
<tr>
<td>HBV</td>
<td>Lamivudine 100 to 150 mg/d PO</td>
<td>Tillmann et al., 2006 (216)</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Lamivudine, D-penicillamine</td>
<td>Rodríguez et al., 2003 (217)</td>
</tr>
<tr>
<td>AFLP/HELLP</td>
<td>Delivery of fetus</td>
<td>Castro et al., 1999 (218)</td>
</tr>
</tbody>
</table>

APAP, acetaminophen; NAC, N-acetylcysteine; Amanita refers to mushroom intoxication; HSV, herpes simplex virus; AIH, autoimmune hepatitis; HBV, hepatitis B virus; AFLP/HELLP, acute fatty liver of pregnancy/hemolysis–elevated liver enzymes–low platelet syndrome.

May be a consequence of progression to cerebral edema, which is present in 38% to 81% of cases of grade 3 or 4 encephalopathy and becomes increasingly likely as the level of consciousness declines (19,20). The pathophysiology of cerebral edema in ALF has been studied extensively and is unique compared with other causes of raised intracranial pressure (ICP) (Fig. 154.1). 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 (21–23).

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 (24). 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 (25). Although the brain usually compensates for such an

TABLE 154.4

HEPATIC ENCEPHALOPATHY GRADES AND RELATIONSHIP TO CEREBRAL EDEMA AND PROGNOSIS IN ACUTE LIVER FAILURE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mental status</th>
<th>Cerebral edema</th>
<th>Spontaneous recovery without liver transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Euphoria, mild confusion, dysarthria, abnormal sleep rhythm</td>
<td>Rare</td>
<td>52% overall</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>87% APAP</td>
</tr>
<tr>
<td>II</td>
<td>Accentuation of stage I, lethargy, moderate confusion, incontinence</td>
<td>35% drug reaction</td>
<td>18% indeterminate cause</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>38% other cause</td>
</tr>
<tr>
<td>III</td>
<td>Severe confusion, incoherent speech</td>
<td>40%–80%</td>
<td>33% overall</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50% APAP</td>
</tr>
<tr>
<td>IV</td>
<td>Coma or near coma</td>
<td>12% drug reaction</td>
<td>16% indeterminate cause</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27% other cause</td>
</tr>
</tbody>
</table>

APAP, acetaminophen.

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-oxygenase-1; ICP, intracranial pressure; NO, nitric oxide; SIRS, systemic inflammatory response syndrome.

Management of HE, Cerebral Edema, and Seizures. Considering the central importance of ammonia in the pathogenesis of hepatic encephalopathy 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 adequately studied in patients with ALF but appear to have little effect on outcome (40). Nevertheless, if lactulose is administered, the dose should be adjusted to achieve no more than three to four bowel movements per day, and care must be taken to avoid excessive abdominal distention, volume depletion, and hypernatremia. Even though oral neomycin is minimally absorbed from the gastrointestinal tract, it has been reported to cause acute renal failure and is therefore not recommended (41).

A computed tomography (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 intracranial hypertension (Fig. 154.2) (42,43). Since 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 (7,44). 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 (45). The invariable presence of coagulopathy 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 (CPP = mean arterial pressure [MAP] – ICP), CBF tends to vary directly with blood pressure (46,37). Thus, although excessive CBF contributes to worsening cerebral edema (38), patients are also especially vulnerable to ischemia if hypotension occurs. Furthermore, despite global increases in CBF, there may be important regional variations, such that blood flow is excessive in some areas and insufficient in others (39). Thus, it is important that CPP be carefully controlled, and extremes avoided.

Management of HE, Cerebral Edema, and Seizures. Considering the central importance of ammonia in the pathogenesis of hepatic encephalopathy 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 adequately studied in patients with ALF but appear to have little effect on outcome (40). Nevertheless, if lactulose is administered, the dose should be adjusted to achieve no more than three to four bowel movements per day, and care must be taken to avoid excessive abdominal distention, volume depletion, and hypernatremia. Even though oral neomycin is minimally absorbed from the gastrointestinal tract, it has been reported to cause acute renal failure and is therefore not recommended (41).
FIGURE 154.2. Head computed tomography (CT) scans of a 32-year-old man with acute liver failure who died of progressive cerebral edema. At admission (left), the CT scan was normal; 48 hours later (right), there was diffuse loss of gray-white differentiation, effacement of sulci, and obliteration of the basal cisterns, consistent with severe diffuse edema and transtentorial herniation with brainstem compression.

important additional pathogenic role in the former (Fig. 154.3). Patients should be cared for in a calm, quiet environment, with limited stimulation. Chest physiotherapy and suctioning should be temporarily minimized. The head of the bed should be elevated to at least 30°, as this reduces ICP and decreases the risk of hospital-acquired pneumonia (48–50). 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 hypercarbia, 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. Although controversial, intravenous lidocaine may further attenuate the rise in ICP from laryngoscopy (51,52).

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 GABA-ergic neurotransmission have been implicated in the pathogenesis of HE (53). Therefore, sedatives with GABA-ergic properties may exacerbate HE; propofol is preferred over benzodiazepines by some authors (54). However, if used over several days, the dose of propofol should be limited to less than 5 mg/kg per hour to decrease the risk of the potentially fatal propofol infusion syndrome, and appropriate adjustments to the patient’s caloric intake should be made (55).

Hyperventilation causes cerebral vasoconstriction and a reduction in cerebral blood volume, effects that can be used therapeutically to reduce ICP. Patients with hepatic encephalopathy often spontaneously hyperventilate, with resultant respiratory alkalosis (56). If the PaCO₂ suddenly normalizes because of sedation or respiratory exhaustion, rebound vasodilatation may occur, with consequent elevated ICP (57). 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. In fact, this effect has been demonstrated even with moderate hyperventilation in patients with traumatic brain injury, a condition where CBF is usually reduced (58,59). In the setting of cerebral hyperemia, one might expect that hyperventilation would be particularly effective in controlling ICP; indeed, one study found that hyperventilation improved CBF autoregulation in ALF (60).

Jugular venous oximetry may be useful to guide therapy, with a high jugular venous oxygen saturation (or low arteriojugular venous oxygen difference [AVjDo₂]) used as evidence that hyperventilation is safe (61). While this method provides a more objective approach to gauging the effects of hyperventilation, jugular venous oximetry has proven relatively insensitive to the detection of even relatively large areas of cerebral ischemia (60,62). Since heterogeneity of CBF may sensitize some regions of the brain to ischemia in ALF (39) and another controlled trial found no clinical benefit (63), the routine use of hyperventilation in the management of ALF patients with HE cannot be advocated. However, spontaneous hyperventilation of patients with ALF should not be discouraged.

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 (64,65), which characterizes ALF. In small human and
HTS is increasingly being used in various settings as an alternative to mannitol to treat cerebral edema (64,70). 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 encephalopathy, a HTS infusion (30% saline, 5–20 mL/hour) maintained serum sodium levels of 145 to 155 mmol/L effectively acted as prophylaxis against intracranial hypertension (71). However, great caution must be taken when HTS is weaned or discontinued to ensure that the serum sodium falls very slowly to avoid precipitating rebound cerebral edema. Apart from the potentially beneficial effects of inducing mild hypernatremia, it is perhaps more important to avoid hyponatremia. Approximately two thirds of patients with ALF present with serum sodium levels less than 135 mmol/L and one third have levels less than 130 mmol/L. The presence of hyponatremia may contribute to the development of cerebral edema early in the course of ALF (72) and is an independent predictor of worse outcome (73,74). Hyponatremia should therefore be corrected, but serum sodium levels should not be raised more quickly than 0.3 to 0.5 mmol/L/hour to minimize the risk of osmotic demyelination. HTS can cause local tissue damage and phlebitis, and therefore—whenever possible—should be administered through a central venous catheter.

High-dose barbiturates (pentobarbital [3–5 mg/kg IV loading bolus followed by 1–3 mg/kg per hour IV infusion], or thiopental [5–10 mg/kg loading bolus followed by 3–5 mg/kg per hour]) can be used as rescue therapy when other interventions have been maximized but the ICP remains more than 20 mm Hg (75). Electroencephalography (EEG) should be performed to guide dosing, with the goal being to achieve a burst-suppression pattern. Although effective at reducing ICP, barbiturates have numerous deleterious effects, including hypotension, electrolyte disturbances, and immunosuppression. It is also unclear that there is any additional benefit to using barbiturates when an EEG already demonstrates burst suppression with the use of other sedatives (e.g., propofol). Indomethacin (25 mg IV bolus) constricts intracerebral blood vessels and has also been reported to be effective at lowering ICP. Considering the potential of untoward gastric mucosal and renal side effects, however, the use of indomethacin requires further study (76). Corticosteroids are of no value in treating intracranial hypertension in ALF and should not be used for this purpose (66).

Fever increases ICP (77) and is an independent predictor of worse outcome in brain-injured patients (78), such that euthermia should be maintained. Conversely, the induction of mild hypothermia is a promising intervention in ALF, since it interferes with several steps in the pathogenesis of cerebral edema. Specifically, hypothermia attenuates the osmotic gradient created by increased astrocytic glutamate (79), normalizes extracellular glutamate and lactate (80), decreases CBF (81), restores autoregulation (82), and reduces ICP (83). Temperatures of 32°C to 33°C have been used to control intracranial hypertension in patients with ALF refractory to standard care (84). Several novel methods of maintaining hypothermia, both surface-based and intravascular, are available to achieve consistent temperature control (85,86). Important potential adverse
effects of hypothermia in the setting of ALF include interference with coagulation and an increased risk of infection. Current models of hepatic encephalopathy suggest that early in the course, cerebral edema is largely due to ammonia-induced cytotoxic edema, whereas subsequent increases in ICP are associated with increased CBF and hyperemia (33). In the former case, osmotic therapy may be most appropriate and effective, whereas in the latter situation, various measures to reduce CBF, including hyperventilation, deeper sedation, greater head-of-bed elevation, or hypothermia may be preferred. Thus, knowledge of CBF potentially helps predict deterioration and guide therapy. Determining CBF has long been largely a research tool, but an increasing number of bedside monitors have been developed, although it is important for clinicians to be familiar with their limitations. Transcranial Doppler (TCD) flow velocities are easiest to measure over the middle cerebral artery (MCA) and are dependent on CBF, vessel caliber, and the angle of insonation (operator technique) (87). Jugular venous oximetry is relatively simple to perform, with normal saturation levels (SjO2) having a relatively broad range from as low as 55% to as high as 75% (AVjDO2 = 3–6 mL/100 mL). Assuming that cerebral oxygen consumption remains constant, one would expect SjO2 to vary with CBF, with levels more than 75% suggestive of hyperemia, and less than 55%, ischemia (88). However, as discussed earlier, there is a wide range of “normal” values, and this is a global measure that cannot exclude regional ischemia. If parenchymal ICP monitors are used, there is little additional risk in placing a brain Po2 (PbPo2) monitor or microdialysis catheter, although experience with these modalities specifically in the setting of ALF is limited (76). Nonconvulsive seizures are a potential cause of worsening cerebral edema and secondary brain injury. A small study using 2-channel—rather than the usual 16 to 20 channels—EEG suggested that nonconvulsive seizures are relatively common in ALF, although the criteria used for electrographic seizures were not described (89). Given the frequency of nonconvulsive seizures and status epilepticus among comatose patients in general, routinely obtaining an EEG in patients with hepatic encephalopathy, particularly when there is a clinical change in neurologic status, may be useful (90). However, there is currently insufficient evidence to justify the routine use of prophylactic phenytoin (89,91). Furthermore, sedation with propofol or benzodiazepines is likely to provide more effective antiseizure prophylaxis than phenytoin.

Cardiopulmonary Complications

Patients with ALF frequently develop systemic inflammatory response syndrome (SIRS), regardless of whether or not their course is complicated by infection (35). Hypoventilation is typical of patients with ALF and can be ascribed to low systemic vascular resistance, the use of sedatives, mechanical ventilation, and relative adrenal insufficiency (92,93). Even though overall energy expenditure is increased (94), peripheral oxygen extraction may be impaired (95). Lactic acidosis is an important prognostic marker in ALF, but the mechanism is not primarily dysxia, but rather impaired hepatic clearance and increased splanchic production (96). Dopamine and norepinephrine are currently the preferred vasopressors for vasodilatory shock (97). Most patients with severe ALF will require an arterial catheter, and various tools are available to optimize volume status and cardiac output (98). The goal MAP should be individualized to optimize organ perfusion, rather than choosing an arbitrary number, but is generally kept above 60 to 65 mm Hg. CPP should be maintained above 50 to 60 mm Hg, since CBF autoregulation fails below these levels in most individuals; if an ICP monitor is not placed, clinicians should err on the side of a slightly higher blood pressure. In patients with relative adrenal insufficiency, treatment with low-dose corticosteroids (e.g., hydrocortisone 50–100 mg IV every 6–8 hours, or 8–10 mg/hour as a continuous IV infusion) reduces vasopressor requirements, although the impact on outcome is uncertain (93).

As many as 37% of patients with ALF develop acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) (99). Although liver failure may have a direct effect, the cause may also include neurogenic pulmonary edema, aspiration pneumonitis, nosocomial pneumonia, or extrapulmonary infection. 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 (100). Given the high risk of developing ARDS, it may be advisable to limit tidal volumes even in the absence of established ALI/ARDS (101). Positive end-expiratory pressure settings should be sufficient to achieve adequate oxygenation, while concomitantly ensuring that ICP, blood pressure, and cardiac output are not compromised.

Renal Failure

Acute renal failure complicates up to 50% of cases of ALF, and is even more frequent when the cause of ALF is acetaminophen intoxication (102,103). 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 vasospasm (104) (see Chronic Liver Failure, below). The decision to institute 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 (105). Even transient hypotension is poorly tolerated in patients with cerebral edema; not only does the CPP decrease, but cerebral vasodilatation may increase, with further increases in CBF and ICP (106). Excessively rapid correction of metabolic acidosis with bicarbonate-based dialysate may transiently increase cerebrospinal fluid CO2, reduce central nervous system (CNS) pH, and promote more cerebral vasodilatation (107). Good results have been achieved with CRRT in patients with ALF (108). However, when performed using carefully designed protocols, hemodynamic stability can also be achieved with IHD (109). Regardless of the mode of RRT, an adequate hemodilution or dialysis dose should be used (110), while blood pressure—and preferably ICP—are carefully monitored and maintained. With CRRT, regional, rather than systemic, anticoagulation is more often used to improve filter longevity, most often with citrate. Since citrate accumulates with poor hepatic function, ionized calcium levels must be regularly monitored (111).

Infections

ALF is associated with reticuloendothelial dysfunction and impaired immunity, with reduced complement levels, abnormal

Infections

ALF is associated with reticuloendothelial dysfunction and impaired immunity, with reduced complement levels, abnormal
opsonization, and ineffective phagocytosis (112,113). ALF patients are, therefore, at high risk of nosocomial infections with both bacterial and fungal pathogens, which occur in almost 40% of these patients (114). Early diagnosis can be difficult since patients often have subtle manifestations of infection but is vital because of the high associated morbidity and mortality (34,115). 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 (115). Although prophylactic antibiotics (enteral and parenteral) decrease the risk of infection in ALF, they have not been shown to improve survival and may promote infection with resistant pathogens (116). 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 administered to any patient with ALF who develops significant isolates on surveillance cultures (114), unexplained progression of HE (34), or signs of SIRS (35), as these frequently predict sepsis in patients with ALF.

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. Therefore, the routine use of blood products to correct these abnormalities is not justified since they are unnecessary, ineffective, and interfere with the prognostic utility of the INR. Correction of coagulopathy should be performed in the setting of significant bleeding, or as an anticipatory measure (117). Vitamin K deficiency has been reported to contribute to the coagulopathy of ALF (118) and should be repleted parenterally. rFVIIa (40 μg/kg) may be considered in patients with life-threatening bleeding and prior to placement of an ICP monitor or performance of a liver biopsy (46,119). If the INR is more than 2.0. Patients with acute decompensated Wilson disease may also be listed as status 1 in consideration for liver transplantation. Empiric broad-spectrum antibiotic therapy is necessary for patients transplanted for all causes of chronic liver disease—status 1. Candidates must have a life expectancy without OLT of less than 7 days, have onset of hepatic encephalopathy 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) have a platelet count less than 50,000/μL, (ii) 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.

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 (5), which may preclude their consideration as viable OLT candidates. Since 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 prertransplant 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 hepatic encephalopathy 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) have a platelet count less than 50,000/μL, (ii) 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.

Definition and Immediate Concerns

Almost all patients with chronic liver failure have underlying cirrhosis, the fibroinflammatory alteration of hepatic architecture that results from numerous chronic insults to the liver. Immediate concerns regarding every patient with chronic liver failure on presentation to the ICU include assessment for possible infection and upper gastrointestinal bleeding, which precipitate most admissions (128).

Overview

Patients with chronic liver disease develop liver failure (decompensation) as a result of portal hypertension and hepatocellular
insufficiency. Complications of portal hypertension include hemodynamic alterations, functional renal failure, ascites, and gastrointestinal bleeding, most commonly from variceal hemorrhage. Complications of hepatocellular insufficiency include coagulopathy and hepatic encephalopathy, although it should be appreciated that the latter occurs also as a result of portosystemic shunting. An important trend in recent management of patients admitted to the hospital for decompensated cirrhosis has been an increasing use of ICUs (from 18%–24% of hospitalizations in one major center over 10 years) (128).

**Etiology**

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 (about 40% of cases) (129). Patients with alcoholic cirrhosis and inderminate (cryptogenic) causes, many of whom have nonalcoholic steatohepatitis (NASH), occupy second and third most frequent causes, respectively. Other less common causes 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).

**Assessment of Prognosis in Cirrhotic Patients Admitted to the ICU**

The assessment of prognosis in cirrhotic patients admitted to the ICU is essential to identify patients in whom aggressive treatment is likely futile. Several prognostic schemes have been assessed (Table 154.5), and those using general organ system assessments, such as the Sequential Organ Failure Assessment (SOFA) score, appear to be more accurate than liver-specific schemes (130–132). Indeed, the number of organ systems (cardiovascular, respiratory, hepatic, renal, coagulation, and neurologic) failing 24 hours after ICU admission strongly predicts in-hospital mortality, from 55% in patients with failure of one organ to 97% in those with failure of three or more organs (131,132). It should be emphasized that, in the absence of OLT as a therapeutic option, cirrhotic patients admitted to the ICU have a very poor long-term prognosis, with 89% 1-year mortality and median survival of only 1 month (133). In such patients, a high APACHE III score, vasopressor use, mechanical ventilation, and jaundice predict in-hospital mortality (133,134).

**TABLE 154.5**

<table>
<thead>
<tr>
<th>Organ system (criterion)</th>
<th>0 Points</th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
<th>4 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (PaO₂/FiO₂)</td>
<td>&gt;400</td>
<td>301–400</td>
<td>201–300</td>
<td>101–200</td>
<td>≤100 [ventilated]</td>
</tr>
<tr>
<td>Hemostatic (platelets)</td>
<td>&gt;150</td>
<td>101–150</td>
<td>51–100</td>
<td>21–50</td>
<td>≤20</td>
</tr>
<tr>
<td>Hepatic (bilirubin [mg/dL])</td>
<td>&lt;1.2</td>
<td>1.2–1.9</td>
<td>2.0–5.9</td>
<td>6.0–11.9</td>
<td>&gt;12.0</td>
</tr>
<tr>
<td>Cardiovascular (hypotension)</td>
<td>MAP &gt;20 mm Hg</td>
<td>MAP &gt;70 mm Hg</td>
<td>Dopamine ≤5 or dobutamine</td>
<td>Dopamine &gt;5 or epinephrine &gt;0.1</td>
<td>Dopamine &gt;0.1 or epinephrine &gt;0.1</td>
</tr>
<tr>
<td>Neurologic (Glasgow coma score)</td>
<td>15</td>
<td>13–14</td>
<td>10–12</td>
<td>6–9</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Renal (creatinine [mg/dL])</td>
<td>&lt;1.2</td>
<td>1.2–1.9</td>
<td>2.0–3.4</td>
<td>3.5–4.9</td>
<td>&gt;5.0</td>
</tr>
</tbody>
</table>

PaO₂/FiO₂, arterial oxygen tension/fractional inspired oxygen; MAP, mean arterial pressure; epi, epinephrine; norepi, norepinephrine.

A SOFA score with a cutoff of 8 points had a sensitivity of 95%, specificity of 88%, overall correctness of 91%, PPV of 87%, and NPV of 96% for predicting in-hospital mortality.

*Adrenergic agents in μg/kg/min.


**Management of Complications of Chronic Liver Failure in the ICU**

**Evaluation of Abdominal Pain**

The development of abdominal pain in a patient with end-stage liver disease often denotes a life-threatening complication of cirrhosis or portal hypertension. Certain causes of abdominal pain have increased prevalence in patients with cirrhosis and deserve particular emphasis because of high morbidity and mortality, as well as often subtle presentation (Table 154.6). A diagnostic paracentesis should be performed immediately in any patient with ascites and abdominal pain to diagnose spontaneous bacterial peritonitis (SBP), and look for evidence of gastrointestinal tract perforation into ascites. The latter may be distinguished from SBP by its higher total protein and LDH concentration, the isolation of more than one organism (including anaerobes and *Candida*), lower glucose, and trend toward higher white blood cell (WBC) and polymorphonuclear (PMN) leucocyte counts (135). Hemoperitoneum from spontaneous rupture of a mesenteric varix (136) or hepatocellular carcinoma (137) may also be rapidly detected by diagnostic paracentesis, in which case the patient should be referred for emergent interventional angiography.

The diagnosis and treatment of intra-abdominal catastrophes in patients with cirrhosis remains challenging. Specifically, complicated gallstone and peptic ulcer disease may present
less acutely in patients with cirrhosis, delaying diagnosis; in those requiring surgical intervention, morbidity and mortality remain very high (138,139). Acute portal vein thrombosis, which may complicate cirrhosis and often denotes development of hepatocellular carcinoma (HCC), should be suspected in patients with abdominal pain, GI bleeding, and ileus (140), and should prompt screening with Doppler ultrasound. However, if the thrombus propagates acutely into the superior mesenteric vein, bowel ischemia and infarction, and death, usually ensue.

**Cardiovascular Complications**

The resting hemodynamic state in decompensated cirrhosis consists of systemic hypotension due to systemic and splanchic arterial dilation (141,142). Consequently, patients with decompensated cirrhosis have marked arterial underfilling of systemic vascular beds in the renal arterial and hypothalamic circulations, resulting in the elaboration of compensatory neurohumoral hormones such as renin, vasopressin, and norepinephrine. The primary pathogenic mechanism underlying this hyperdynamic state includes release of vasodilatory mediators such as endothelin and nitric oxide by the portal endothelium.

In addition, patients with decompensated cirrhosis have impaired cardiac contractility in response to stress, in particular, infection or GI bleeding (143). Such myocardial failure was formerly ascribed to the myocardial toxicity of ethanol or iron in patients with cirrhosis due to alcohol abuse or hemochromatosis, respectively. Recently, cirrhotic cardiomyopathy, depressed myocardial contractility as a complication of cirrhosis per se, has been proposed to explain the hemodynamic collapse in cirrhotics who experience a complication of their disease (143).

Diagnostic criteria include blunted isotropic and chronotropic responses to stress, diastolic dysfunction, and prolonged QT interval on electrocardiogram (ECG). A pathogenic role of cirrhotic cardiomyopathy has also been documented in patients with the hepatorenal syndrome (144), particularly in the setting of infection (145), and in the circulatory dysfunction after large volume paracentesis without adequate plasma expansion (143,146). 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 (143).

**Ascites and Renal Complications**

Acute renal failure (ARF) in patients with decompensated cirrhosis is an independent predictor of death in the ICU (147) and frequently denotes the onset of infection (148). The differential diagnosis of acute renal failure in a decompensated cirrhotic includes prerenal azotemia, hepatorenal syndrome (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 (less than 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 1.5-2 L IV fluid (normal saline with or without colloid) challenge (Table 154.7) (104). HRS and cirrhotic ascites have the same basic pathogenesis (Fig. 154.4). 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...

### Table 154.6

**Differential Diagnosis of Abdominal Pain in Patients with Cirrhosis**

<table>
<thead>
<tr>
<th>Cause of abdominal pain</th>
<th>Etiologic associations</th>
<th>Clinical presentation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>Low protein azotemia</td>
<td>Fever, rebound tenderness, HE, azotemia</td>
<td>Runyon, 2004 (150)</td>
</tr>
<tr>
<td>Incarcerated hernia (umbilical, inguinal)</td>
<td>Ascites, recanalization of the umbilical vein</td>
<td>Localized pain, bowel obstruction</td>
<td>Carbonell et al., 2005 (219)</td>
</tr>
<tr>
<td>Cholethiasis and complications</td>
<td>Pigmented gallstones</td>
<td>Localized pain, jaundice, fever, pancreatitis</td>
<td>Silva and Wong, 2005 (138); Perkins et al., 2004 (220)</td>
</tr>
<tr>
<td>Peptic ulcer and complications</td>
<td>Decompensated cirrhosis, Helicobacter infection</td>
<td>UGI bleeding, perforated viscus</td>
<td>Calvet et al., 1998 (221); Lehneri and Herfarth, 1993 (139); Mosnier et al., 1992 (222)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Spontaneous rupture</td>
<td>Hemoperitoneum (rare)</td>
<td>Castells et al., 2001 (137)</td>
</tr>
<tr>
<td>Portal/mesenteric venous thrombosis</td>
<td>Hepatocellular carcinoma</td>
<td>Bowel ischemia, GI bleeding, ileus</td>
<td>Amirano et al., 2004 (140)</td>
</tr>
<tr>
<td>Rupture of mesenteric varix</td>
<td>Recent large-volume paracentesis</td>
<td>Hemoperitoneum</td>
<td>Akriviadis, 1997 (223); Arnold et al., 1997 (136)</td>
</tr>
</tbody>
</table>

HE, hepatic encephalopathy; UGI, upper gastrointestinal; GI, gastrointestinal.

In addition to the usual causes of abdominal pain and acute abdomen in the general ICU population, all of the above have been described with higher prevalence in patients with cirrhosis. Appropriate screening tests for the above include diagnostic paracentesis, duplex ultrasonography, contrast-enhanced abdominal computerized tomography (CT), and/or upper endoscopy.
hypertension, the transudation of lymph across the Glisson capsule as low-protein ascites (149). HRS can be considered an exaggeration of this renal vasoonconstriction, often in the setting of cardiac hypococontractility (144).

The treatment of ascites in the ICU should include judicious administration of diuretics in subjects without marked azotemia (creatinine >2.0 mg/dL), electrolyte abnormalities, or hypotension. A combination of furosemide and spironolactone has been shown to better effect a diuresis than either agent alone; a ratio of 40 mg of the former to 100 mg of the latter has been shown empirically to preserve potassium balance in most patients with cirrhosis (150), and administered by mouth has been shown to improve the efficacy of diuretics (151). Large-volume paracentesis should be performed if ascites interferes with ventilation of the patient or if diuretics result in azotemia or electrolyte abnormalities. IV colloid administration (albumin 6–8 g for each liter of ascites removed) should accompany paracentesis of greater than or equal to 5 L to prevent postparacentesis circulatory dysfunction (152). The insertion of a transjugular intrahepatic portosystemic shunt (TIPS) may be considered in patients who have failed medical therapy (104). In an ICU setting, however, patients are often too ill to consider TIPS for this indication (Table 154.8).

Relative contraindications for TIPS include severe liver failure (MELD >20; PT >20 s; creatinine >2.0 mg/dL; bilirubin >3.0 mg/dL), active systemic infection (risk of TIPS infection ["endo-TIPSitis"]), recent/severe hepatic encephalopathy, current hemodynamic instability, congestive heart failure, chronic renal failure, pulmonary hypertension, and adverse outcomes. Does not improve long-term patient survival for any indication and has not been shown to prevent recurrence of indication for placement (for rescue in variceal bleeding about 5%, refractory ascites 15%–60%, hepatic hydrothorax 30%–40%).

TIPS, transjugular intrahepatic portosystemic shunt; MELD, model for end-stage liver disease; PT, prothrombin time.


**TABLE 154.7**

<table>
<thead>
<tr>
<th>Diagnostic Criteria of Hepatorenal Syndrome (HRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>Low GFR (creatinine &gt;2.5 mg/dL; CrCl &lt;20 mL/min)</td>
</tr>
<tr>
<td>Absence of shock, infection, nephrotoxins</td>
</tr>
<tr>
<td>Absence of improvement after 1.5 L fluid challenge</td>
</tr>
<tr>
<td>Absence of intrinsic renal disease</td>
</tr>
<tr>
<td>Proteinuria &lt;500 mg/dL</td>
</tr>
<tr>
<td>Normal renal ultrasound</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
</tr>
<tr>
<td>Oliguria (&lt;500 mL/d)</td>
</tr>
<tr>
<td>Urine sodium &lt;10 mEq/L</td>
</tr>
<tr>
<td>Serum sodium &lt;130 mEq/L</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; CrCl, creatinine clearance


**TABLE 154.8**

<table>
<thead>
<tr>
<th>Relative Contraindications and Adverse Outcomes Associated with Placement of TIPS or Salvage Therapy of Acute Variceal Hemorrhage, Refractory Ascites, or Refractory Hepatic Hydrothorax</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative Contraindications</strong></td>
</tr>
<tr>
<td>Severe liver failure (MELD &gt;20; PT &gt;20 s; creatinine &gt;2.0 mg/dL; bilirubin &gt;3.0 mg/dL)</td>
</tr>
<tr>
<td>Active systemic infection (risk of TIPS infection [&quot;endo-TIPSitis&quot;] )</td>
</tr>
<tr>
<td>Recurrent/severe hepatic encephalopathy</td>
</tr>
<tr>
<td>Current hemodynamic instability</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td><strong>Adverse Outcomes</strong></td>
</tr>
<tr>
<td>Does not improve long-term patient survival for any indication</td>
</tr>
<tr>
<td>TIPS-induced hemolytic anemia</td>
</tr>
<tr>
<td>Worsening or precipitation of hepatic encephalopathy</td>
</tr>
</tbody>
</table>

**TABLE 154.4**


**FIGURE 154.4** Pathogenesis of ascites, hepatorenal syndrome, and hyponatremia in patients with decomposed cirrhosis. Vasoactive substances are shown in italics. ADH, antidiuretic hormone/vasopressin; HRS, hepatorenal syndrome; NO, nitric oxide. (Adapted from Sandhu BS, Sanyal AJ. Management of ascites in cirrhosis. Clin Liver Dis. 2005;9[4]:715–732, viii.)
The optimal treatment of HRS remains undefined (154). Figure 154.5 outlines potential treatments, not mutually exclusive, related to the pathogenetic mechanism of HRS. The ultimate treatment of the hemodynamic abnormalities of cirrhosis is OLT, which can completely reverse HRS if performed relatively soon after its onset (155). Vasooconstrictor therapy holds promise for reversing HRS by reversing the state of systemic vasodilatation. The oral u-adrenergic agonist midodrine (5–10 mg orally thrice daily) was found to be effective in one widely cited but preliminary study, when used in combination with octreotide (100 μg subcutaneously twice daily), which increases systemic blood volume and thus renal blood flow by counteracting splanchnic vasodilatation (156). Terlipressin, an intravenously administered vasopressin analogue with fewer ischemic complications, also reverses systemic vasodilatation and has been found to effectively reverse HRS in Europe, but is not yet available in the United States (154). The administration of intravenous colloid, specifically albumin, serves to improve renal vascular perfusion (154–156). Finally, patients with decompensated cirrhosis should not receive even small therapeutic doses of NSAIDs (e.g., for fever), since these agents exacerbate renal vasocstruction by inhibiting production of endogenous vasodilatory renal prostaglandins.

Electrolyte abnormalities frequently accompany ARF in cirrhosis and complicate the treatment of ascites. Hyponatremia and hypomagnesemia result from furosemide administration, and hyponatremia and hyperkalemia from spironolactone administration. Hyponatremia also results from hemodilution in the setting of high vasopressin release from the neurohypophysis and portends a poor prognosis (157).

**Infectious Complications**

Bacterial infections represent the most common cause of admission of cirrhotic patients to the ICU and remain one of the two primary causes of death (158). Risk factors for bacterial infections in hospitalized patients with cirrhosis include ICU admission and GI bleeding (159). Patients with cirrhosis are relatively immunosuppressed 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 (160). In addition, gut congestion from portal hypertension increases the likelihood of bacterial translocation into blood, which seeds the ascites secondarily, so-called spontaneous bacterial peritonitis (SBP) (150).

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 diseases ICU, 77% of isolates were Gram-positive, which was ascribed to the widespread use of prophylactic fluoroquinolones in cirrhotic patients with low-protein ascites (161), and to the frequent use of invasive procedures, including IV catheter insertion and vascular band ligation (128). Therefore, any patient admitted to an ICU with clinical suspicion of sepsis should be empirically given 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 considered in patients who have been instrumented. The choice of coverage for Gram-negative bacilli should be a third-generation cephalosporin (e.g., cefotaxime [2 g IV every 8 hours] or ceftriaxone [1 g IV every 24 hours]) (162); aminoglycosides should be avoided except in serious infections with a multiply-resistant organism because of the susceptibility of cirrhotic patients to aminoglycoside nephrotoxicity (163).

Diagnostic paracentesis should be performed on all cirrhotic patients admitted to the ICU with ascites and renal failure, HE, or any evidence of infection. Localizing symptoms and signs of peritonitis—abdominal pain, fever, rebound tenderness—may be absent in up to 30% of patients with this process. Blood and ascites should be immediately inoculated into culture bottles at the bedside, which has been shown to increase culture yields (164). However, even with bedside inoculation of a large volume of ascetic fluid (20 mL), culture yields may be as low as 40% (128). Therefore, the diagnosis of SBP should rely solely on a PMN leukocyte count of greater than or equal to 250 cells/μL and culture-negative neutrocytic ascites—that is, with more than 250 PMNs/μL—should be considered the equivalent of SBP (165). Patients with ascetic fluid PMN count of equal to or more than 250 cells/μL should receive a third-generation cephalosporin (as above) and IV albumin (1.5 g/kg at diagnosis.
2316 Section XV: Gastrointestinal Disease and Dysfunction

and 1.0 g/kg 48 hours after diagnosis), which has been shown both to decrease the incidence of HRS after SBP and to improve mortality (166). A similar diagnostic and therapeutic algorithm should be followed for spontaneous bacterial empyema, the infectious equivalent of SBP in patients with hepatic hydrothorax (see below) (167).

The incidence of fungal infections also increases in cirrhotic patients admitted to the ICU. Although not classically as immunosuppressed as after cancer chemotherapy, patients with Child’s C cirrhosis have been reported to spontaneously develop invasive aspergillosis in the ICU (168). Candida species also rarely infect cirrhotic ascites, with disastrous outcome. The mortality of cirrhotic patients admitted to the ICU with infection remains high, with death usually from hepatic failure, HRS, or refractory septic shock (128,169). As with patients with ALF, relative adrenal insufficiency commonly accompanies decompensated cirrhosis and sepsis, and refractory shock in such patients may respond to stress doses of corticosteroids (see Cardiovascular Complications, in ALF section above) (170).

Gastrointestinal Bleeding

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 (171). Esophageal varices account for most UGI bleeds in patients with cirrhosis, with gastric varices accounting for approximately 5% to 10%, and nonvariceal UGI pathology (gastric or duodenal mucosal lesions) noted in up to 30% (172). 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 (173). 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.

Patients with cirrhosis who present with acute UGI bleeding should be considered for ICU admission to deliver intensive nursing care and to manage the bleed as well as its complications. Despite the trend toward improved survival after variceal hemorrhage in the last two decades (174), each episode still carries a mortality risk of 10% to 20%, and the risk of rebleeding remains highest during the first few days after the index event (Fig. 154.6). General resuscitative measures on admission to the ICU should include correction of hypotension, repletion of blood (not to exceed a hemoglobin of approximately 8–9 g/dL), and consideration of endotracheal intubation before endoscopy (Table 154.9). A recent retrospective study has shown that endotracheal intubation prior to endoscopy may decrease the risk of fatal massive aspiration of blood, but does not decrease the risk of aspiration pneumonia (175). Factors that should contribute to the decision of whether to intubate a cirrhotic patient with an UGI bleed should include the rate of bleeding, hemodynamic instability, and degree of hepatic encephalopathy. Suppression of gastric acid secretion with proton pump inhibitors has been shown to decrease the number, size,
and complications from post-band ligation esophageal ulcers (176).

In the last 20 years, three major improvements in the management of acute variceal hemorrhage have increased survival of patients with cirrhosis: the early administration of vasoactive agents to decrease portal pressure, the widespread use of variceal band ligation, and antibiotic prophylaxis at the time of acute bleed (Table 154.9). Vasopressin, formerly used for lowering portal pressure for this indication, has fallen from favor due to vasoplastic adverse effects; although the vasopressin analogue terlipressin has a better safety profile and appears to improve control of acute variceal bleeding (177), it has not yet been approved for use in the United States. The somatostatin analogue octreotide (100 μg IV bolus followed by 50 μg/hour as an IV infusion; Table 154.9) also has a favorable safety profile, and meta-analysis has demonstrated improved rates of sustained bleeding control after acute hemorrhage from esophageal varices (178). Octreotide should be administered as early as possible in a cirrhotic patient with acute UG bleeding, preferably during transport to the hospital.

Endoscopic therapy after stabilization of the patient remains the definitive treatment for bleeding esophageal varices and controls active bleeding in more than 75% of cases when combined with vasoactive therapy (179). Endoscopic band ligation and sclerotherapy yield similar rates of control of active bleeding, but band ligation results in fewer local complications (esophageal ulcers, recurrent bleeding) and is therefore preferred (180). Recurrent bleeding should prompt a second attempt at endoscopic treatment in most cases (181). In patients with recurrence after a second endoscopic treatment, or in any recurrence with hemodynamic instability, emergent insertion of a TIPS should be considered (181). In such dire situations, the relative contraindications for TIPS placement, outlined in Table 154.7, become less important. 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 (172). Vasoactive therapy should be administered as for bleeding from esophageal varices, and sclerotherapy may be attempted. Cyanoacrylate glue injection has been shown to control acute bleeding from varices in the gastric fundus or cardia but is not widely available in the United States (182); in the absence of endoscopic and vasoactive control of gastric variceal bleeding, insertion of a large tamponade balloon (Linton tube) can temporize control before insertion of a TIPS (172).

In previous periods, bacterial infection complicated acute variceal bleeding in 40% of patients (174) and contributed to renal failure and recurrent early bleeding (183). Antibiotic prophylaxis after variceal hemorrhage has been shown to decrease the incidence of infection as well as variceal rebleeding, resulting in improved survival (183,184). 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 recent 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 (185); however, local resistance patterns should be considered.

**Pulmonary Complications**

Respiratory failure accounts for up to 40% of admissions of cirrhotic patients to the ICU (132). 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 154.10) (186). Complications of cirrhosis include massive ascites, and hepatic hydrothorax (HH), the accumulation of extracellular fluid with similar protein characteristics as ascites (low-protein, high-albumin gradient as compared to serum) within the pleural space (167). 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. The treatment of HH includes diuretic administration as for ascites, and therapeutic thoracentesis. Placement of a TIPS in patients with refractory HH may be considered but is not universally effective, and relapsethree 1-year survival is only 35% (187,188). Chest tube placement and pleurodesis are relatively contraindicated in refractory HH as they often contaminate the pleural space, precluding OLT. An infectious complication of HH, spontaneous bacterial empyema, should be diagnosed and managed similarly to SBP, but has a high mortality (167).

Two relatively uncommon, insidiously presenting pulmonary vascular complications may cause respiratory failure in patients with cirrhosis. The hepatic pulmonary syndrome (HPS) may be defined as a widened alveolar-arterial oxygen tension due to intrapulmonary vasodilatation 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. 154.7) (186). In a patient with cirrhosis and resting hypoxemia (PaO2 less than 70 mm Hg while breathing an FiO2 of 0.21), the diagnosis is confirmed by a contrast echodensitogram, in which agitated saline administered intravenously delivers microbubbles into the left ventricle at least three heartbeats after their appearance in the right ventricle (186). Supplemental oxygen usually bridge patients with HPS to OLT, which improves or reverses the process in 85% of patients (189). Patients with HPS have increased transplant waiting list mortality when compared to patients with normal gas exchange; consequently, patients with

---

**TABLE 154.10**

**DIFFERENTIAL DIAGNOSIS OF RESPIRATORY DISTRESS AND HYPOXEMIA IN PATIENTS WITH CIRRHOSIS**

<table>
<thead>
<tr>
<th>Complications of cirrhosis</th>
<th>Massive ascites</th>
<th>Hepatic hydrothorax</th>
<th>Muscle wasting</th>
<th>Aspiration pneumonia</th>
<th>Pulmonary vascular disorders due to portal hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatopulmonary syndrome</td>
<td>Portopulmonary hypertension</td>
<td>Liver diseases with cardiopulmonary manifestations</td>
<td>Alpha-1-antitrypsin deficiency (basilar emphysema)</td>
<td>Sarcoidosis (restrictive lung disease, cardiomyopathy)</td>
<td>Hemosiderosis (cardiomyopathy)</td>
</tr>
</tbody>
</table>


---

**Chapter 154: Liver Failure: Acute and Chronic**

---

2317
**Pathophysiology**

**Vasoactive mediators**
- Pulmonary NO

**Precapillary vasodilation**
- A-V shunting
- Hypoxemia

**Diagnosis**

**Dyspnea**
- Clubbing
- Cyanosis
- ABG: PaO$_2$ <70 mm Hg
- CXR: clear
- PFT: normal spirometry
- Contrast echo: shunting
- Chest CT: peripheral vasodilation

**FIGURE 154.7. Pathophysiology and diagnostic algorithm of hepatopulmonary syndrome.**

**Portal hypertension**
- Vasoactive mediators
  - (e.g., endothelins)

**Pulmonary arteriolar constriction**

**Medial hypertrophy of pulmonary arterioles**

**Obstruction of pulmonary arterioles**

**FIGURE 154.8. Pathophysiology and diagnostic algorithm of portopulmonary hypertension.**

**Neurologic Complications**

Changes in mental status frequently accompany admission of patients with cirrhosis to the ICU and should not automatically suggest the presence of hepatic encephalopathy (HE) (Table 154.11). Usually, HE presents as a global decline in cognition and intellect, but focal neurologic deficits and signs of cerebral edema—decerebrate posturing and seizures—have also been described rarely (194). 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. Most important, 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 154.12). The HPS and PaO$_2$ less than 60 mm Hg on room air are allowed increased priority for OLT under the current organ allocation system in the United States (190). Perioperative mortality after OLT in patients with HPS varies according to the degree of shunting and hypoxemia (190,191).

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. 154.8) (192). Screening with transthoracic echocardiography reveals evidence of pulmonary hypertension (right ventricular systolic pressure greater than 50 mm Hg), but the diagnosis must be confirmed with right heart catheterization showing elevated mean pulmonary artery pressure (PAP) more than 25 mm Hg), as well as high pulmonary vascular resistance (greater than 240 dynes/second per cm$^{-5}$) and normal pulmonary capillary wedge pressure (192,193). The treatment of PPH—indicated when mean PAP is more than 35 mm Hg—has not been well defined (192); prostacyclin analogues (epoprostenol titrated via pulmonary artery [PA] catheter; inhaled iloprost [5 μg six times daily]), phosphodiesterase inhibitors (sildenafil, 20 mg PO thrice daily), or combination therapy appear to be effective in small case series (192). Unfortunately, the prognosis of patients with PPH is sufficiently poor after OLT that many patients with a mean PAP more than 35 mm Hg are not offered transplant.

**FIGURE 154.7. Pathophysiology and diagnostic algorithm of hepatopulmonary syndrome.**

**ABG,** arterial blood gas; **A-V,** arteriovenous; **CT,** computed tomography; **CXR,** chest x-ray film; **echo,** echocardiogram; **NO,** nitric oxide; **PFT,** pulmonary function testing.
administration of broad-spectrum antibiotics (e.g., ceftriaxone) should be considered until cultures have returned negative, and fluid and electrolyte abnormalities should be corrected. If sedation is required for procedures, benzodiazepines should be used with caution, since they exacerbate even subclinical HE (195).

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 offers an alternative route of administration, but its efficacy to prevent toxic megacolon, and electrolyte imbalance. Rectal lactulose risks aspiration pneumonia, gaseous distention of the bowel, given if there is an ileus, and its overzealous administration cannot be tolerated via nasogastric tube in an intubated patient, cannot be given if there is an ileus, and its overzealous administration.

The administration of broad-spectrum antibiotics (e.g., ceftriaxone) should be considered until cultures have returned negative, and fluid and electrolyte abnormalities should be corrected. If sedation is required for procedures, benzodiazepines should be used with caution, since they exacerbate even subclinical HE.

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 offers an alternative route of administration, but its efficacy to prevent toxic megacolon, and electrolyte imbalance. Rectal lactulose risks aspiration pneumonia, gaseous distention of the bowel, given if there is an ileus, and its overzealous administration.

The administration of broad-spectrum antibiotics (e.g., ceftriaxone) should be considered until cultures have returned negative, and fluid and electrolyte abnormalities should be corrected. If sedation is required for procedures, benzodiazepines should be used with caution, since they exacerbate even subclinical HE.

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 offers an alternative route of administration, but its efficacy to prevent toxic megacolon, and electrolyte imbalance. Rectal lactulose risks aspiration pneumonia, gaseous distention of the bowel, given if there is an ileus, and its overzealous administration.

The administration of broad-spectrum antibiotics (e.g., ceftriaxone) should be considered until cultures have returned negative, and fluid and electrolyte abnormalities should be corrected. If sedation is required for procedures, benzodiazepines should be used with caution, since they exacerbate even subclinical HE.

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 offers an alternative route of administration, but its efficacy to prevent toxic megacolon, and electrolyte imbalance. Rectal lactulose risks aspiration pneumonia, gaseous distention of the bowel, given if there is an ileus, and its overzealous administration.
In the United States, patients with chronic liver failure constitute an increasing proportion of ICU admissions, principally due to the maturation of the hepatitis C epidemic, which is not expected to peak until 2018. The trend may accelerate as a new wave of patients with cirrhosis due to nonalcoholic steatohepatitis decompensates, since obesity and the metabolic syndrome affect approximately one third of the U.S. population. Therefore, intensivists can expect to manage more patients with chronic liver failure to bridge them to OLT, which remains the only effective long-term therapy. In contrast to chronic liver failure, ALF patients constitute a small and numerically stable minority of patients admitted to the ICU. For intensivists, the importance of a thorough understanding of the management of ALF lies in its very high morbidity and mortality, which can be improved by vigorous intensive care as a bridge to OLT.

Stress Points: Acute Liver Failure

1. ALF is a clinical syndrome with a high mortality that affects almost every organ system.
2. The three most common causes of death in patients with ALF are cerebral edema/intracranial hypertension/brain-stem herniation, infection, and multiorgan system failure.
3. 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 (4). Therefore, prediction of death without OLT is of paramount importance.

Stress Points: Chronic Liver Disease

1. Patients with chronic liver disease are admitted to the ICU most commonly as the result of infection and/or upper GI bleeding, which results in hepatic decompensation.
2. Iatrogenic injury to a patient with decompensated chronic liver disease admitted to the ICU represents a major source of preventable morbidity and mortality. Sources of significant iatrogenic injury include nephrotoxic medications (e.g., aminoglycosides, NSAIDs) and unnecessary invasive procedures, particularly insertion of central venous and intraarterial catheters.
3. The prognosis of patients with cirrhosis admitted to the ICU is poor, with in-hospital mortality paralleling the degree of multiorgan system failure. Long-term prognosis of cirrhotic patients admitted to the ICU is also poor without OLT.

References

flow autoregulation, and hepatic encephalopathy in fulminant hepatic fail-
38. Dehdashti F, Koudas GN, Hamamoto RA, et al. Effects of peritumoral cystic chan-
ning and ammonia infusion on cerebral flow autoregulation in the late
40. Cremer OL, Moons KG, Bouman EA, et al. Long-term propofol infusion
42. Herrine S, Northup B, Bell R, et al. The effect of head elevation on cere-
46. Stream VAM, Caldwell SH, Hospehler EE, et al. Rectal monitor in acute
47. Kearvy BT, Alexander GJ, Williams R. The safety and value of intra-
48. Bemis S, Nothig E, Bell R, et al. The effect of head elevation on cere-
49. Li J, Lee Y, Wang HB. Effects of head posture on cerebral hemodyn-
53. Stream VAM, Caldwell SH, Hospehler EE, et al. Rectal monitor in acute
54. Kearvy BT, Alexander GJ, Williams R. The safety and value of intra-
55. Bemis S, Nothig E, Bell R, et al. The effect of head elevation on cere-
56. Li J, Lee Y, Wang HB. Effects of head posture on cerebral hemodyn-
60. Stream VAM, Caldwell SH, Hospehler EE, et al. Rectal monitor in acute
61. Jalan R, Olde Damink SW, Neuvonen PJ, et al. Moderate hypothermia pre-
63. Jalan R, Damink SW, Deute HE, et al. Moderate hypothermia for uncon-
2322 Section XV: Gastrointestinal Disease and Dysfunction


Acute pancreatitis has an annual incidence of 5 to 40 per 100,000 (1,2) with an overall mortality of 1.5 per 100,000 (1). The clinical course of acute pancreatitis is often self-limited and results in little, if any, structural alteration of the gland and requires no intervention. Approximately one third of patients, however, develop pancreatic necrosis, which has an associated mortality rate that can be as high as 30% (1,3). All complications of this disease are potentially lethal and may require aggressive intervention to control or abort the process, and support the patient until the condition is resolved. Because of this, acute pancreatitis can be among the most difficult of clinical entities to treat. Very few, if any, other conditions present with such a myriad of origins, diagnostic difficulties, clinical manifestations, risk of multisystem involvement, and indeterminate prognosis for such a prolonged period. Severe acute pancreatitis often demands an extended stay in the intensive care unit and hours on hours of multidisciplinary care. Numerous causative factors of acute pancreatitis have been recognized. The most important risk factors for pancreatitis in adults are gallstones and excessive alcohol use, although clinically detectable pancreatitis never develops in most persons with these risk factors. The incidence of gallstone pancreatitis is increased among white women older than the age of 60 years (4,5) and is highest in patients with gallstones <5 mm in diameter (5,6). Other causes include metabolic derangements such as hypertriglyceridemia, duct obstruction (for example, related to tumor or pancreas divisum), medications (i.e., aminopyrine, thiazides, and estrogen), and trauma. About 20% of cases remain idiopathic, although this classification is expected to become less common as factors of genetic predisposition and environmental susceptibility are elucidated (7).

Trypsin is the key enzyme in the activation of pancreatic zymogens. Underlying the pathophysiology of acute pancreatitis is the inappropriate conversion of trypsinogen to trypsin and a lack of prompt elimination of active trypsin inside the pancreas (7). Activation of other pancreatic enzymes causes injury to the gland and results in an inflammatory process that seems to be out of proportion to the response of other organs to a similar insult, possibly due to disturbances in the microcirculation of the pancreas and the exquisite sensitivity of the pancreas to ischemia (8). In addition to further significant tissue damage as a direct result, the inflammatory process may extend beyond the pancreas and result in the systemic inflammatory response syndrome, multiorgan failure, and ultimately, death.

At times, diagnosing acute pancreatitis may be as difficult as predicting the course or defining the treatment. Even with history, physical examination, laboratory values, radiographic studies, and special procedures, a conclusive diagnosis of acute pancreatitis and its complications is often elusive. The best approach may be to elucidate the history of a similar attack or hospitalization and identify associated etiologic factors, most commonly alcohol abuse or biliary tract disease.

The recurrence rate of acute pancreatitis has been reported to be as high as 33% (9) and can be even higher in the alcoholic population (10). Disease isolated to the head or tail of the pancreas may result in pain localized to the right or left upper quadrant with diaphragmatic irritation and referred pain to the subcapsular areas. The classic presentation of epigastric pain that radiates through to the back may be present in only 50% of patients presenting with acute pancreatitis. After the patient develops peritoneal signs, pancreatitis can mimic all other acute abdominal crises, especially those necessitating emergent surgery.

Of the biochemical diagnostic criteria, the most commonly used is the serum amylase level (11). Serum amylase levels that are more than three times the upper limit of normal are almost