Acute liver failure (ALF) is an uncommon, but dramatic, clinical syndrome defined by the onset of coagulopathy (international normalized ratio \([\text{INR}] > 1.5\)), and mental status changes within 8 to 26 weeks of presentation \([1,2]\). The cause of ALF usually is established rapidly by patient history, laboratory tests, and imaging studies but remains unknown in up to 20% of cases \([3]\). Acetaminophen overdose is the most common cause of ALF in Western countries, and its incidence seems to be increasing. Fortunately, most patients who have acetaminophen overdose recover with early N-acetylcysteine (NAC) therapy and supportive care, but regulatory actions are needed to prevent future cases. Many patients who have ALF develop infectious, cardiopulmonary, or renal complications that can progress to multiorgan failure. In addition, cerebral edema is notoriously difficult to diagnose and treat and can lead to irreversible brain ischemia and eventual death. Emergency liver transplantation is associated with a 70% 1-year patient survival, but less than 10% of patients who have ALF are listed, and up to 20% of listed patients die awaiting liver transplantation. Therefore, early referral of patients who have a poor prognosis to a liver transplant center is essential to optimize clinical outcomes.

**Etiology in the United States**

The low annual incidence of ALF in the United States, estimated at 2800 cases per annum, makes it difficult to collect reliable data on the causes, risk factors, and outcomes of this clinical syndrome \([2,4]\). This low annual incidence also can lead to referral bias, selection bias, and ascertainment...
bias in single-center reports. ALF occurs in patients of all ages, but the causes and prognosis in adults and in infants and children differ markedly [2,5]. In addition, for reasons that are unclear, a predominance of female patients has been reported consistently for nearly all causes of ALF (Table 1).

The United States Acute Liver Failure Study Group (ALFSG) is a network of 23 tertiary care centers that have studied the causes and outcomes of ALF prospectively since 1998 [3]. A recent analysis of 1033 consecutive adult patients enrolled through July 2007 demonstrates that acetaminophen overdose accounts for 46% of cases, followed by indeterminate ALF (15%) and idiosyncratic drug reactions (12%) (Fig. 1). During the past 8 years, an increasing frequency of acetaminophen overdose cases and a decreasing frequency of indeterminate cases and cases caused by hepatitis A virus (HAV) have been noted [6,7]. Other identifiable causes of ALF include acute hepatitis B virus (HBV) infection (7%), autoimmune hepatitis (5%), ischemic hepatitis (4%), and various other causes (5%). Overall survival was 67% at 3 weeks after presentation, with 46% of patients improving spontaneously and 25% requiring emergency liver transplantation [3]. The likelihood of spontaneous recovery was highest in patients who had acetaminophen overdose, HAV, and pregnancy (58%–64%). Patients who had Wilson’s disease, indeterminate ALF, and drug reactions had the worst prognosis (0–30%).

Table 1
Clinical features in 1033 consecutive adults with who had acute liver failure in the United States (1998–2007)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Acetaminophen N = 475</th>
<th>Drug N = 119</th>
<th>Indeterminate N = 151</th>
<th>Hepatitis A virus N = 31</th>
<th>Hepatitis B virus N = 75</th>
<th>Other N = 182</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age (years)</td>
<td>36</td>
<td>43</td>
<td>37</td>
<td>47</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>74</td>
<td>67</td>
<td>56</td>
<td>45</td>
<td>44</td>
<td>76</td>
</tr>
<tr>
<td>Jaundice (days)</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>3</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Median serum alanine transferase level (IU/L)</td>
<td>4149</td>
<td>571</td>
<td>851</td>
<td>2404</td>
<td>1601</td>
<td>677</td>
</tr>
<tr>
<td>Median bilirubin level (mg/dL)</td>
<td>4.5</td>
<td>21.6</td>
<td>23.0</td>
<td>11.9</td>
<td>20.8</td>
<td>15.2</td>
</tr>
<tr>
<td>Outcomes at 3 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant (%)</td>
<td>9</td>
<td>40</td>
<td>42</td>
<td>29</td>
<td>47</td>
<td>35</td>
</tr>
<tr>
<td>Spontaneous survival (%)</td>
<td>64</td>
<td>26</td>
<td>27</td>
<td>58</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Overall survival (%)</td>
<td>71</td>
<td>63</td>
<td>65</td>
<td>84</td>
<td>64</td>
<td>60</td>
</tr>
</tbody>
</table>

The diagnosis of ALF is based on the physical examination (altered mental status) and laboratory findings (INR > 1.5). The initial evaluation should include rapid identification of the underlying cause, with an emphasis on treatable conditions (Table 2). In addition to serologic testing, a urine toxicology screen, and liver imaging, a careful review of all ingested medications is important. ALF occasionally is confused with other clinical entities such as sepsis, systemic disorders with hepatic and brain involvement (eg, systemic lupus erythematosus, thrombotic thrombocytopenic purpura), and acute decompensation of chronic liver disease. Alcoholic hepatitis or flares of chronic HBV may be mistaken for ALF, but a careful review of the patient’s medical history, laboratory tests, and imaging studies should differentiate these conditions. Septic patients who have intrahepatic cholestasis and disseminated intravascular coagulation typically have low factor VIII levels, whereas patients who have ALF typically have normal factor VIII levels but low factor V levels [8].

ALF usually presents initially with nonspecific symptoms such as nausea, vomiting, and malaise. Severe acute liver injury often leads to impaired elimination of bilirubin, manifesting as jaundice immediately before or shortly after presentation. In addition, the depressed synthesis and excessive consumption of clotting factors results in a complex coagulopathy. A diminished synthesis of glucose, increased intracellular lactate production, and
reduced hepatic uptake of lactate can lead to hypoglycemia and metabolic acidosis. Thirty percent to 40% of patients who have ALF present with impaired renal function and associated azotemia and oliguria [9].

Mental status changes or encephalopathy are defining criteria of ALF. They are believed to be caused by cerebral edema, particularly in patients

<table>
<thead>
<tr>
<th>Cause</th>
<th>Etiology</th>
<th>Evaluation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td>Hepatitis B</td>
<td>HBsAg, anti-HBc IgM</td>
<td>Lamivudine, entecavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV-DNA by PCR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatitis D</td>
<td>HDV-RNA, anti-HDV IgM</td>
<td>Lamivudine, entecavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV-DNA by PCR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus</td>
<td>CMV-DNA PCR, CMV-IgM, biopsy</td>
<td>Ganciclovir, valganciclovir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epstein-Barr virus</td>
<td>EBV-DNA PCR, serology, biopsy</td>
<td>Steroids, acyclovir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Herpes simplex virus</td>
<td>HSV-DNA PCR, anti-HSV IgM, biopsy</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Wilson’s disease</td>
<td>Ceruloplasmin, urinary and hepatic copper, slit lamp examination</td>
<td>Chelating agents? plasmapheresis</td>
</tr>
<tr>
<td></td>
<td>Acute fatty liver of pregnancy, HELLP syndrome</td>
<td>Preeclampsia findings (hypertension, edema, proteinuria)</td>
<td>Emergency delivery of infant</td>
</tr>
<tr>
<td></td>
<td>Autoimmune hepatitis</td>
<td>ANA, ASMA, IgG, IgM, IgA liver biopsy</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>Metastatic malignancy</td>
<td>Imaging, liver biopsy</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Acute leukemia/lymphoma</td>
<td>Bone marrow aspiration, liver biopsy</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Drugs/Toxins</td>
<td>Acetaminophen toxicity</td>
<td>Medication history, serum acetaminophen level, acetaminophen-cysteine adducts (?)</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td></td>
<td>Idiosyncratic drug reaction</td>
<td>Temporal relationship</td>
<td>Withdraw suspect medication</td>
</tr>
<tr>
<td></td>
<td>Amanita poisoning</td>
<td>Recent mushroom ingestion, severe gastrointestinal symptoms</td>
<td>Gastric lavage, charcoal, penicillin G, silymarin, hemodialysis</td>
</tr>
<tr>
<td>Vascular</td>
<td>Budd-Chiari syndrome</td>
<td>Liver ultrasound with Doppler, angiogram</td>
<td>Heparin, low molecular weight heparin</td>
</tr>
<tr>
<td></td>
<td>Ischemic hepatitis</td>
<td>Systemic hypotension (cardiogenic shock, pulmonary embolism, hypovolemia)</td>
<td>Reversal of hypotension, inotropes</td>
</tr>
</tbody>
</table>

Abbreviations: ANA, antinuclear antibodies; anti-HGe, anti-hepatitis B core; ASMA, anti-smooth muscle antibody; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HbsAg, hepatitis B surface antigen; HDV, hepatitis D virus; HELLP, hemolysis, elevated liver enzymes, and low platelet count; HSV, herpes simplex virus; PCR, polymerase chain reaction.
who have rapid-onset ALF, whereas portosystemic shunting of toxins is implicated in patients who have subacute ALF. The complications of ALF, such as hypoglycemia, sepsis, fever, and hypoxia/hypotension, also contribute to neurologic abnormalities. The West Haven criteria for encephalopathy frequently are applied to patients who have ALF, although the Glasgow coma score is more useful for intubated patients. Patients who have grade 1 encephalopathy have only subtle changes in affect, altered sleep patterns, or difficulties in concentration. Patients who have stage 2 encephalopathy have drowsiness, disorientation, and confusion. Stage 3 is marked by somnolence and incoherence. Patients who have stage 4 have frank coma with minimal (4A) or no (4B) responses to noxious stimuli. Patients who have ALF often have asterixis or tremors in stages 1 or 2 and hyperreflexia, clonus, or muscular rigidity in stages 3 or 4. Although worrisome, these upper motor neuron signs are reversible with hepatic recovery. Patients progressing to stage 3 or 4 encephalopathy have a poorer outcome than those who have a maximum of stage of 1 or 2 encephalopathy (70% survival in patients who have stage 2 encephalopathy versus 20% survival in patients who have stage 4 encephalopathy) [10].

**Diagnosis of acetaminophen hepatotoxicity**

Acetaminophen overdose is the leading cause of ALF in the United States and in other Western countries and recently has been increasing [3,6]. There are an estimated 60,000 cases of acetaminophen overdose annually, most of which are intentional suicide gestures [11]. Nearly 26,000 patients who have acetaminophen overdose are hospitalized each year; an estimated 1% of these patients develops severe coagulopathy or encephalopathy. The mortality attributed to acetaminophen overdose is 500 per annum, and at least 20% of these deaths occur in patients who have unintentional acetaminophen overdose [11]. Nearly half of acetaminophen-related cases of ALF are therapeutic misadventures [6]. The increasing incidence of acetaminophen-induced ALF may, in part, reflect a shift from aspirin to acetaminophen-based products to treat acute febrile illnesses, the presence of acetaminophen in numerous over-the-counter and prescription medications, and underappreciation of its hepatotoxicity [12].

Acetaminophen is a dose-dependent hepatotoxin that can cause severe acute hepatocellular injury. The injury leads to a characteristic pattern of pericentral necrosis because of the cytochrome P-450–mediated oxidative metabolism of acetaminophen to the highly reactive intermediate metabolite, N-acetyl-p-benzoquinone imine (NAPQI) (Fig. 2) [13]. Although there are intracellular mechanisms to detoxify NAPQI, excessive production can deplete intrahepatic glutathione stores and bind to intracellular proteins, leading to hepatocellular necrosis. Chronic consumption of alcohol can induce cytochrome P-450 2E1 (CYP2E1) activity and increase the rate of NAPQI formation with therapeutic dosing [14]. Short-term studies of
therapeutic doses of acetaminophen in recently abstinent alcoholics have not demonstrated hepatotoxicity, however [15]. Ingestion of other cytochrome P-450 inducers, such as phenytoin and isoniazid, can lower the threshold for acetaminophen hepatotoxicity [16]. Many patients who have unintentional acetaminophen overdose report short-term fasting and/or poor nutritional status immediately preceding the event, but prospective studies of hepatic glutathione stores at presentation with ALF are unavailable [17].

The hallmark of acetaminophen hepatotoxicity is the presence of elevated serum aminotransferase levels (up to 400 times the upper limit of normal) with concomitant hypoprothrombinemia, metabolic acidosis, and renal failure. Most patients have normal or minimally elevated serum bilirubin levels at presentation because of the acuity of the liver injury. The diagnosis of acetaminophen hepatotoxicity requires a high index of suspicion (Box 1). Some patients present with unexplained nausea and vomiting and are noted to have only mild aminotransferase elevations, metabolic acidosis, or isolated hypoprothrombinemia. Others present with obtundation following a witnessed or unwitnessed overdose. The minimal dose of acetaminophen
that produces liver injury varies from 4 to 10 g. Recent prospective studies demonstrate evidence of mild biochemical liver injury with therapeutic dosing of 1 g of acetaminophen every 6 hours in healthy volunteers [18]. Acetaminophen hepatotoxicity therefore should be considered whenever the dose exceeds 4 g/d.

Patients who have unintentional acetaminophen overdose often present with 2 to 3 days of nonspecific symptoms superimposed on the acute or chronic medical condition for which they were taking an acetaminophen-based analgesic [6,19]. Patients who have taken an unintentional overdose generally have been exposed over several days, have low or undetectable serum acetaminophen levels, and have more advanced encephalopathy at presentation. In addition to a serum and urine toxicology screen for illicit substances, a careful review of all prescription and over-the-counter medications is critical (Tables 3, 4).

Serum acetaminophen levels can help estimate the risk of liver injury following a single ingestion [13,20]. A low serum level does not exclude significant overdose, however, and repeated serum samples at 4 to 12 hours may be needed to define the hepatic risks. Serum bilirubin levels exceeding 10 to 15 mg/dL can lead to false-positive acetaminophen levels with some colorimetric assays [21]. Given these limitations, detection of serum acetaminophen-cysteine protein adducts that emanate from the liver may prove to be a more sensitive and specific biomarker [22,23]. Although the diagnostic and prognostic significance of adduct levels is still evolving, this assay may prove particularly useful in patients unable to provide a medication history or in patients presenting after multiple ingestions over time. Furthermore, detection of adducts in patients who have virally mediated ALF, in which acetaminophen may be a toxic cofactor, could permit more rapid administration of NAC.

Management of acetaminophen overdose

Standard medical therapy of known or suspected acetaminophen overdose includes induction of emesis by ipecac syrup, gastric lavage of pill fragments, and administration of activated charcoal to reduce absorption (see Box 1) [24]. In patients who have a single ingestion, the likelihood of subsequent hepatotoxicity is estimated by the Rumack nomogram.

Patients who have known or suspected intentional acetaminophen overdose should be hospitalized to assess their suicidal risk. Patients who have unstable hemodynamics, renal failure, or altered mental status should be monitored in an ICU and transferred to a liver transplant center early, if deemed potential transplant candidates. NAC should be administered immediately to patients at risk for hepatotoxicity based on the initial serum acetaminophen level, elevated serum aminotransferase level, or INR level. Oral NAC is given as a loading dose of 140 mg/kg followed by a maintenance dose of 70 mg/kg for up to 72 hours or until the INR has become

ACUTE LIVER FAILURE

767
Box 1. Diagnosis and management of acetaminophen overdose

**Diagnosis**
- Ingestion of a toxic dose of acetaminophen-containing product(s)
  - Review intake of all over-the-counter and prescription medications
  - Intake of more than 4 g (usually > 10 g) of acetaminophen in 24 hours
  - Consider in all patients who have an unexplained serum alanine aminotransferase levels higher than 1000 IU/mL
  - Obtain serum acetaminophen level for single-dose ingestion (Rumack nomogram)
  - Bilirubin level higher than 10 mg/dL may lead to false-positive serum acetaminophen levels
  - Check urine toxicology screen for other toxins/illicit substances
    - Exclude acute hepatitis A virus, hepatitis B virus, and ischemia

**Management and treatment**
- Within 4 hours of ingestion administer
  - Ipecac syrup/nasogastric lavage
  - Activated charcoal, 1 g/kg
- Admit to hospital if there is potential for hepatotoxicity, coagulopathy, altered mentation, or intentional overdose with suicide attempt.
- Admit to ICU if there is encephalopathy, metabolic acidosis, renal failure.
  - Arrange early transfer to transplant center if there is grade 2 encephalopathy or other adverse prognostic criteria
- Obtain serum liver biochemistries, arterial blood gas and lactate, prothrombin time/international normalized ratio, and factor V levels at admission and every 12 hours
- Administer oral N-acetylcysteine
  - Loading dose: 140 mg/kg
  - Maintenance dose: 70 mg/kg every 4 hours for 17 doses or until international normalized ratio is less than 1.5
- Nausea and vomiting are seen in 20% of patients.
  - Mix N-acetylcysteine with carbonated beverage to improve gastrointestinal tolerance.
• Intravenous N-acetylcysteine is approved by the Food and Drug administration for acetaminophen overdose.
• Indications: gastrointestinal intolerance of oral N-acetylcysteine, ileus, pancreatitis, bowel obstruction, short gut syndrome, and pregnancy
• Contraindications: known sulfa allergy
• Loading dose: 150 mg/kg in 250 mL dextrose 5% over 1 hour
• Maintenance dose: 50 mg/kg in 500 mL dextrose 5% over 4 hours; then 125 mg/kg in 1000 mL dextrose 5% over 19 hours; 100 mg/kg in 1000 mL dextrose 5% over 24 hours for 2 days or until the international normalized ratio is less than 1.5
• Telemetry monitoring is needed during infusion.
  • Hypersensitivity/anaphylactoid reactions occur in 3% of patients.
  • For a mild hypersensitivity reaction, reduce the infusion rate by 50% and consider intravenous diphenhydramine or corticosteroids

lower than 1.5 [13]. Most patients tolerate oral NAC, with the coadministration of antiemetics, but an intravenous formulation is available for patients who cannot tolerate oral NAC [25]. Most experts recommend continuous intravenous infusion of NAC until the INR is less than 1.5. This formulation is particularly useful in pregnant women, patients who have a short gut, or patients who have an ileus. This drug should be administered in a monitored unit, because up to 3% of patients receiving intravenous NAC develop a hypersensitivity reaction. Patients who experience a mild to moderate infusion reaction should have the infusion rate decreased by 50% and receive antihistamines and/or corticosteroids.

Unintentional acetaminophen overdose

The ALFSG recently demonstrated that nearly 50% of acetaminophen-related ALF occurs without an overt suicide intent [6]. In most of these patients, the amount of acetaminophen ingested exceeded the maximal daily recommended dose of 4 g/d. Nearly 50% of these patients, however, reported ingesting only 4 to 10 g/d, and 38% of patients ingested a multitude of products. Contrary to earlier reports, these patients were not more likely to be taking antidepressants or to have a history of alcohol abuse [14,19]. Nonetheless, patients who had an unintentional overdose had more advanced encephalopathy at presentation, presumably because of frequent narcotic administration. Fortunately, 95% of these patients received
NAC, and their rate of spontaneous survival was similar to that of patients who had taken an intentional overdose (64% versus 66%).

Because acetaminophen hepatotoxicity is the leading cause of ALF but is completely preventable, some experts have recommended regulatory changes regarding the labeling and dispensation of acetaminophen-containing products [12,26]. In the United Kingdom, blister packaging and restrictions on the dispensation of acetaminophen tablets have led to a reduction in the number of patients taking an intentional overdose and in those referred for liver transplantation [27,28]. The Food and Drug Administration (FDA) recently proposed changes in the labeling of all over-the-counter products that contain acetaminophen as well as nonsteroidal anti-inflammatory drugs [29]. Additional limitations on the dispensing of prescription acetaminophen-narcotic congeners and on reducing or eliminating the acetaminophen

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Acetaminophen content of selected narcotic analgesics a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription analgesics</td>
<td>Acetaminophen per dose (mg) b</td>
</tr>
<tr>
<td>Anexia (hydrocodone bitartrate)</td>
<td>325–660 mg</td>
</tr>
<tr>
<td>Capital with Codeine Suspension (codeine phosphate)</td>
<td>120 mg/5 ml</td>
</tr>
<tr>
<td>Darvocet-N50 (propoxyphene napsylate)</td>
<td>325 mg</td>
</tr>
<tr>
<td>Darvocet-N100 (propoxyphene napsylate)</td>
<td>650 mg</td>
</tr>
<tr>
<td>Darvocet-A500 (propoxyphene napsylate)</td>
<td>500 mg</td>
</tr>
<tr>
<td>Endocet (oxycodeone hydrochloride)</td>
<td>325–650 mg</td>
</tr>
<tr>
<td>Esic Plus (butalbital/caffeine)</td>
<td>500 mg</td>
</tr>
<tr>
<td>Fioricet (butalbital/caffeine)</td>
<td>325 mg</td>
</tr>
<tr>
<td>Fioricet with Codeine (butalbital/caffeine/codeine phosphate)</td>
<td>325 mg</td>
</tr>
<tr>
<td>Lorcet (hydrocodone bitartrate)</td>
<td>325–750 mg, 500 mg/15 ml</td>
</tr>
<tr>
<td>Lortab (hydrocodone bitartrate)</td>
<td>325–500 mg 500 mg/15 ml</td>
</tr>
<tr>
<td>Maxidone (hydrocodone bitartrate)</td>
<td>750 mg</td>
</tr>
<tr>
<td>Norco (hydrocodone bitartrate)</td>
<td>325 mg</td>
</tr>
<tr>
<td>Panadol #3 and #4 (codeine phosphate)</td>
<td>300 mg</td>
</tr>
<tr>
<td>Percocet/Oxyct (oxycodeone hydrochloride)</td>
<td>325–650 mg</td>
</tr>
<tr>
<td>Phenaphen with Codeine (codeine phosphate)</td>
<td>325–650 mg</td>
</tr>
<tr>
<td>Roxicet (oxycodeone hydrochloride)</td>
<td>325–500 mg, 325 mg/5 ml</td>
</tr>
<tr>
<td>Sedapap (butalbital)</td>
<td>650 mg</td>
</tr>
<tr>
<td>Talacen (pentazocine hydrochloride)</td>
<td>650 mg</td>
</tr>
<tr>
<td>Tylenol #2, #3, and #4 (codeine phosphate)</td>
<td>300 mg</td>
</tr>
<tr>
<td>Tylox (oxycodeone hydrochloride)</td>
<td>500 mg</td>
</tr>
<tr>
<td>Ultracet (tramadol hydrochloride)</td>
<td>325 mg</td>
</tr>
<tr>
<td>Vicodin (hydrocodone bitartrate)</td>
<td>500 mg</td>
</tr>
<tr>
<td>Vicodin ES (hydrocodone bitartrate)</td>
<td>750 mg</td>
</tr>
<tr>
<td>Vicodin HP (hydrocodone bitartrate)</td>
<td>660 mg</td>
</tr>
<tr>
<td>Wygesic (propoxyphene napsylate)</td>
<td>650 mg</td>
</tr>
<tr>
<td>Zydone (hydrocodone bitartrate)</td>
<td>400 mg</td>
</tr>
</tbody>
</table>

a This list does not contain all acetaminophen-containing prescription products.
b Contact Poison Control Center for exact dosage of other constituents.
Table 4
Acetaminophen content of selected over-the-counter medications

<table>
<thead>
<tr>
<th>Over-the-counter medications</th>
<th>Acetaminophen per dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actifed products (triprolidine/</td>
<td>325–500 mg</td>
</tr>
<tr>
<td>pseudoephedrine)</td>
<td></td>
</tr>
<tr>
<td>Alka Seltzer products (sodium bicarbonate)</td>
<td>250–325 mg</td>
</tr>
<tr>
<td>Allerest products (naphazoline)</td>
<td>325–500 mg</td>
</tr>
<tr>
<td>Anacin, Anacin-3 (aspirin/caffeine)</td>
<td>80–500 mg, 100 mg/ml, 160 mg/5 ml</td>
</tr>
<tr>
<td>Arthritis Foundation Aspirin-Free</td>
<td>500 mg</td>
</tr>
<tr>
<td>(acetaminophen)b</td>
<td></td>
</tr>
<tr>
<td>Benadryl Allergy/Cold Tablets</td>
<td>500 mg</td>
</tr>
<tr>
<td>(diphenhydramine hydrochloride)</td>
<td></td>
</tr>
<tr>
<td>Children’s Tylenol products (acetaminophen)b</td>
<td>80–160 mg, 160 mg/5 ml</td>
</tr>
<tr>
<td>Comtrex products (pseudoephedrine,</td>
<td>325–1000 mg, 500 mg/5 ml, 500 mg/15 ml, 650 mg/oz, 1000 mg/oz, 1000 mg/5ml</td>
</tr>
<tr>
<td>chlorpheniramine)</td>
<td></td>
</tr>
<tr>
<td>Datril Extra (acetaminophen)b</td>
<td>325–500 mg, 130 mg/5 ml</td>
</tr>
<tr>
<td>Drixoral products (dextromethorphan,</td>
<td>325–500 mg</td>
</tr>
<tr>
<td>pseudoephedrine)</td>
<td></td>
</tr>
<tr>
<td>Excedrin Migraine Products</td>
<td>250–500 mg</td>
</tr>
<tr>
<td>(aspirin/caffeine)</td>
<td></td>
</tr>
<tr>
<td>Goody’s Extra Strength Headache Powder</td>
<td>130–500 mg, 260 mg per powder paper</td>
</tr>
<tr>
<td>(aspirin/caffeine)</td>
<td></td>
</tr>
<tr>
<td>Liquiprin (acetaminophen)b</td>
<td>80 mg/0.8 ml, 80 mg/1.66 ml, 80 mg/2.5 ml</td>
</tr>
<tr>
<td>Midrin (dichloralphenazone,</td>
<td>325 mg</td>
</tr>
<tr>
<td>isometheptene mucate)</td>
<td></td>
</tr>
<tr>
<td>NyQuil (dextromethorphan, pseudoephedrine,</td>
<td>250 mg, 167 mg/5 ml, 1000 mg/packet, 1000 mg/30 ml</td>
</tr>
<tr>
<td>doxylamine)</td>
<td></td>
</tr>
<tr>
<td>Pamprin (ibuprofen)</td>
<td>250–500 mg, 650 mg/packet</td>
</tr>
<tr>
<td>Panadol (acetaminophen)b</td>
<td>80–500 mg, 60 mg/0.6 ml, 80 mg/0.5 ml</td>
</tr>
<tr>
<td>Percogesic (phenyltoloxamine)</td>
<td>325–500 mg</td>
</tr>
<tr>
<td>Sine-Aid Sinus Medicine (ibuprofen,</td>
<td>500 mg</td>
</tr>
<tr>
<td>pseudoephedrine)</td>
<td></td>
</tr>
<tr>
<td>Sinutab products (pseudoephedrine,</td>
<td>325–500 mg, 1000 mg/oz</td>
</tr>
<tr>
<td>chlorpheniramine)</td>
<td></td>
</tr>
<tr>
<td>Sominex Pain Relief Formula</td>
<td>500 mg</td>
</tr>
<tr>
<td>(diphenhydramine)</td>
<td></td>
</tr>
<tr>
<td>St. Joseph’s Aspirin Free Products</td>
<td>80–500 mg, 60 mg/0.6 ml, 80 mg/0.8 ml, 80 mg/2.5 ml, 120 mg/5 ml, 160 mg/5 ml</td>
</tr>
<tr>
<td>(acetaminophen)b</td>
<td></td>
</tr>
<tr>
<td>Sudafed Sinus Products</td>
<td>325–500 mg</td>
</tr>
<tr>
<td>(pseudoephedrine hydrochloride)</td>
<td></td>
</tr>
<tr>
<td>Tempra products (acetaminophen)</td>
<td>80, 160 mg/5 ml</td>
</tr>
<tr>
<td>TheraFlu products (dextromethorphan,</td>
<td>325–650 mg, 650–1000 mg/packet</td>
</tr>
<tr>
<td>pseudoephedrine)</td>
<td></td>
</tr>
<tr>
<td>Tylenol products (acetaminophen)b</td>
<td>325–650 mg, 250 mg/5 ml, 650 mg/30 ml, 650–1000 mg/packet, 1000 mg/30 ml</td>
</tr>
<tr>
<td>Vanquish products (aspirin, caffeine)</td>
<td>194 mg</td>
</tr>
</tbody>
</table>

\(^{a}\) This list does not contain all over-the-counter products that contain acetaminophen.

\(^{b}\) Only active ingredient is acetaminophen.
component of these products have been suggested but not yet implemented [12]. In the interim, health care providers and pharmacies should be aware of the acetaminophen content in many compound medications.

**Acute liver failure related to viral hepatitis**

Severe acute HAV, HBV, and hepatitis E virus (HEV) infections occasionally produce ALF. The diagnosis of HAV-related ALF depends on the detection of anti-HAV IgM. Young children, persons more than 50 years old, and individuals who have underlying liver disease may be more prone to develop severe acute HAV. The overall incidence of ALF from acute HAV infection is less than 1% [7,30]. A recent analysis of the United Network for Organ Sharing (UNOS) transplant database and the ALFSG confirmed a significant decline in the incidence of fulminant HAV in the United States between 1998 and 2005 [7]. This decline presumably results from more widespread HAV vaccination and the reduced incidence of sporadic acute infection. Of note, the Centers for Disease Control and Prevention liberalized recommendations for HAV and HBV vaccination in 2007 so that now any individual is eligible for vaccination [31].

Fulminant HBV infection occurs in less than 1% of acutely infected individuals. It is diagnosed by the presence of detectable hepatitis B surface antigen (HBsAg) and/or anti-hepatitis B core (HBc) IgM antibody. Some patients who have chronic HBV may develop transiently detectable anti-HBc IgM during a disease flare, however [32,33]. Patients who have fulminant HBV occasionally have hepatitis D virus (HDV) coinfection or superinfection as confirmed by detection of anti-HDV antibodies. Although early studies suggested that pre-core and core-promoter variants of HBV were associated with ALF, recent studies have failed to demonstrate this association [32,33]. The role of HBV genotypes and host factors in determining susceptibility to HBV-related ALF is unclear. Patients who have HBV-related ALF have only a 30% likelihood of survival [33,34]. Although fulminant HBV is believed to be caused by an overwhelming immune response to infected hepatocytes, the use of oral antiviral agents such as lamivudine or entecavir has been proposed [34]. A recent randomized, controlled trial of lamivudine in patients in India who had severe acute HBV failed to demonstrate any clinical benefit, however [35]. A retrospective review of the ALFSG experience from 1995 to 2006 also failed to demonstrate any benefit from antiviral therapy in 76 patients who had HBV-related ALF [36]. Nonetheless, many experts use oral antiviral agents for fulminant HBV because of their relative safety [2].

Severe acute HEV infection is a leading cause of ALF in tropical countries. It occurs most commonly in pregnant women [37,38]. It is diagnosed by detection of anti-HEV IgM antibody. The treatment is supportive. Recently, a recombinant protein vaccine for HEV was shown to be safe and effective in preventing acute infection in a high-risk population from Nepal.
Rarely, other nonhepatotropic viruses including Epstein-Barr virus, cytomegalovirus, herpes simplex virus (HSV), varicella zoster virus, human herpes virus-6, and parvovirus B-19 can cause ALF [40–42]. Whether these rare causes of ALF are caused by viral variants or an aberrant host immune response is unclear. Diagnosing ALF caused by one of these nonhepatotropic viruses frequently is difficult and often requires histologic confirmation as well as polymerase chain reaction testing. In particular, most patients who have HSV-related ALF have no skin lesions at presentation [43,44]. Severe acute Epstein-Barr virus, cytomegalovirus, or HSV should be considered as causes of ALF because they can be treated successfully with antiviral therapy (see Table 2).

**Idiosyncratic drug reactions**

Drug-induced liver injury (DILI) is a leading cause for the discontinuation of drugs in development and for regulatory actions on previously approved drugs [45]. DILI is rare (1 in 10,000 to 1 in 1,000,000 patient years) and is thought to be caused by host metabolic idiosyncrasy [46,47]. Most patients who have severe DILI experience acute hepatocellular injury resulting in jaundice, but some patients develop severe DILI from severe cholestatic hepatic injury [48,49]. Multiple case series demonstrate a preponderance of women in patients who have DILI and in patients progressing to ALF [3,48]. Whether women are more susceptible to idiosyncratic drug-induced ALF because of differences in body weight, drug dosing, or metabolizing/detoxification enzyme activity is unknown.

Idiosyncratic drug reactions are characterized by variable latency after initial administration but usually occur within 12 months of drug initiation. Genetically determined variability in host toxification, detoxification, and regeneration pathways is implicated in the pathogenesis and outcome of idiosyncratic DILI, but supportive data are limited [47]. The roles of medication dose, drug–drug interactions, alcohol consumption, host immune response, and other environmental cofactors are largely unknown [50,51]. The Drug Induced Liver Injury Network should provide insight into the etiologies and mechanisms of DILI by prospectively collecting biologic samples from well-phenotyped cases (see http://dilin.dcri.duke.edu for additional information) [52].

The primary treatment of drug-induced ALF is discontinuing the suspected drug to avoid further hepatic injury [53]. A recent uncontrolled series suggested a potential role for corticosteroids in some patients who have severe DILI, but this approach is controversial [54]. In addition, corticosteroids were not beneficial in large, randomized controlled studies of patients who had ALF [55]. DILI is notoriously difficult to diagnose because patients usually lack immunologic or allergic features at presentation, often are taking multiple drugs, and a confirmatory laboratory test is not available. Liver histology in severe DILI usually is not beneficial.
except for excluding other treatable causes. Therefore, DILI is a diagnosis of exclusion that requires causality assessment instruments that have substantial limitations [56,57].

In addition to prescription drugs, a careful history of herbal, complementary, and alternative medicines is needed in patients who have unexplained ALF. For example, green tea, ephedra, and various weight-loss agents have been associated with ALF [58–60]. Unfortunately, herbal products are not regulated closely during development, manufacturing, or marketing, and in many mixtures the specific hepatotoxic ingredient(s) cannot be identified.

Development of jaundice in combination with high serum aminotransferase levels in patients who have DILI has an estimated mortality rate of 10% (Hy’s rule) [61]. A recent retrospective review of 784 Swedish DILI cases confirmed that serum aspartate aminotransferase and bilirubin levels at presentation are the most important predictors of mortality or liver transplantation in severe hepatocellular DILI [48]. A recent review of 95 Japanese DILI cases also identified high serum bilirubin level at presentation and a prolonged latency period to be risk factors for mortality [62]. A review of the UNOS liver transplantation database from 1990 to 2002 highlighted the causes and outcomes of 270 adult liver transplant recipients who had drug-induced ALF [63]. A striking female predominance was reported (76%), the mean age was 35 years, and acetaminophen was the culprit in 49% of cases. Commonly implicated medications in the idiosyncratic DILI group included isoniazid (17.5%), propylthiouracil (9.5%), phenytoin (7.3%), and valproate (7.3%) [63]. In the US ALFSG, two thirds of the patients who had DILI were female. Most presented with high serum bilirubin levels (median, 22 mg/dL) and had symptoms for an average of 10 days before presentation (see Table 1). Implicated medications included antituberculosis drugs (20%), sulfa compounds (12%), phenytoin (10%), and various herbs (10%) (personal communication, WM Lee, MD, 2007). Overall, patients who had idiosyncratic DILI resulting in ALF had a poor prognosis, with a spontaneous survival rate of only 26% at 3 weeks. Therefore, any patient who develops jaundice with coagulopathy or encephalopathy from suspected DILI should be referred urgently to a liver transplant center.

**Other identifiable causes of acute liver failure**

Autoimmune hepatitis rarely causes ALF [64]. Autoimmune serologies and liver biopsy can aid in the diagnosis, but many of these patients have low titer or undetectable autoantibodies. The benefit of corticosteroids in fulminating autoimmune hepatitis is unclear. Early identification of ALF caused by autoimmune hepatitis is important, however, because of the low rate of spontaneous survival (Fig. 1). ALF is a well-known complication of several pregnancy-related liver diseases including acute fatty liver of pregnancy (AFLP) and the syndrome of hemolysis, elevated liver enzyme levels and low platelet count (HELLP) [65–67]. Treatment of these conditions is directed
toward prompt delivery of the fetus. The hallmark of AFLP is the rapid development of microvesicular steatosis in the third trimester with resultant mitochondrial dysfunction, metabolic acidosis, and coagulopathy, with only mild to moderate serum aminotransferase elevations. Women who have long-chain fatty acid metabolic defects are at increased risk of developing AFLP, but only 25% of women who have AFLP exhibit an identifiable mutation [68]. Although most women who have AFLP or HELLP improve with prompt delivery, some require emergency liver transplantation. Severe acute viral hepatitis and HSV hepatitis should also be considered in pregnant women who have ALF, particularly in the third trimester, because these conditions are associated with a poor prognosis even with prompt delivery.

Sudden hepatic outflow obstruction caused by occlusion of all three hepatic veins (Budd-Chiari syndrome) is a rare but potentially treatable cause of ALF [69]. Patients usually present with recent onset of abdominal pain, hepatomegaly, and ascites. More than 80% of patients have an identifiable thrombophilia that may be treated with anticoagulation, but many require liver transplantation [70]. Arterial hypoperfusion to the liver caused by cardiogenic shock or hypovolemia can lead to ischemic hepatitis and may progress to ALF [71]. The outcome in these patients is determined primarily by the underlying cardiopulmonary disease, and liver transplantation rarely is required or indicated.

*Amanita phalloides* mushroom poisoning is a rare cause of ALF that often presents with severe gastrointestinal symptoms and diarrhea. Assays for amanita toxin are unavailable. Patients can be treated with successfully intravenous penicillin G, silymarin, and dialysis, although many require liver transplantation [72,73].

**Metabolic and infiltrative diseases**

Wilson’s disease is a hereditary disorder of impaired biliary excretion of copper that presents as ALF in up to 25% of adolescent or young-adult patients [74]. Clues to fulminant Wilson’s disease include the presence of Kayser-Fleischer rings on slit-lamp examination in up to 50% of cases, low serum alkaline phosphatase levels, hemolytic anemia with hyperbilirubinemia, and low serum ceruloplasmin levels (although these levels are normal in 15% of patients) [75]. Elevated serum and urinary copper levels often occur, but these tests may not be feasible because of the frequent presence of concomitant renal failure. A transjugular liver biopsy can establish the diagnosis definitively by detecting elevated quantitative hepatic copper levels and advanced hepatic fibrosis, but this biopsy is not always feasible. Because fulminant Wilson’s disease has 100% mortality in the absence of liver transplantation, all these patients should be listed quickly for transplantation.

Acute Hodgkin’s and non-Hodgkin’s lymphoma, metastatic carcinoma (eg, lung, breast, melanoma), and several variants of leukemia are rare infiltrative causes of ALF [76,77]. Although a diagnosis of fulminant malignancy may be suspected based on history, laboratory tests, or imaging,
liver biopsy frequently is required for confirmation. These patients have a poor prognosis and are not candidates for liver transplantation [3].

**Indeterminate acute liver failure**

No cause is identified in up to 20% of adult patients who have ALF and in 50% of children who have ALF [3,5,78]. Prior studies failed to demonstrate occult infection with HBV, HEV, parvovirus B-19, HSV, or SEN virus in US ALFSG adult patients who had indeterminate ALF [33,43,79,80]. Other proposed causes include occult autoimmune hepatitis, undiagnosed acetaminophen hepatotoxicity, or DILI [23]. In the ALFSG, 19% of the patients who had indeterminate ALF had detectable serum acetaminophen-cysteine adducts; these patients tended to have higher serum aminotransferase levels and lower bilirubin levels at presentation than adduct-negative patients who had indeterminate ALF [23]. Whether acetaminophen was the primary cause of ALF or merely a cofactor in these cases is unclear, however. Patients who have indeterminate ALF have a poor likelihood of spontaneous recovery and should be evaluated rapidly for liver transplantation.

**Management of acute liver failure**

A key principle in management is the unpredictable and rapid manner in which patients who have ALF can deteriorate. Therefore, patients who have ALF should be monitored in an ICU for frequent neurologic and hemodynamic assessment [2]. If the prognosis is poor, early transfer to a liver transplant center is recommended.

**General management measures**

A rapid evaluation for treatable causes of ALF allows the initiation of specific, appropriate therapy (see Table 2). Except for liver transplantation, however, no single medical intervention has been shown to be beneficial for all patients who have ALF. Corticosteroids or intravenous prostaglandin E1 infusions failed to decrease morbidity or mortality in randomized, controlled trials [55,81,82]. NAC is of proven benefit in patients who have acetaminophen hepatotoxicity [13,20]. Some physiologic studies suggest that NAC may be beneficial in non-acetaminophen ALF, possibly because of improved tissue oxygenation [83,84]. Preliminary results from the ALFSG multicenter, double-blind study of NAC in non-acetaminophen ALF recently demonstrated a survival benefit only in patients who had grade 1 or 2 encephalopathy [85]. Therefore, this simple and widely available therapy may be useful in some patients who have ALF.

An experienced hepatologist, transplant surgeon, and intensivist should work as a team to direct the management of patients who have ALF. Evaluation for liver transplantation includes obtaining diagnostic serologies,
a chest roentgenogram, a bedside echocardiogram, and psychosocial evaluation. Placement of central venous access and arterial lines can allow fluid resuscitation, infusion of medications, frequent laboratory monitoring, and titration of acid/base status. Routine laboratory tests including serial lactate, factor V, INR, and liver biochemistries should be obtained at least every 8 to 12 hours. Glucose levels should be monitored hourly and supplemented as needed.

### Neurologic features

Continuous assessment of neurologic status is critical. Classical signs of intracranial hypertension, such as papilledema, loss of pupillary reflexes, and clonus, do not correlate reliably with intracranial pressure (ICP) measurements or grade of encephalopathy (Box 2). Similarly, head CT findings of cerebral edema frequently occur late and are not adequately sensitive or reliable to detect intracranial hypertension (Fig. 3) [86,87]. Moreover, the scanning time and transportation logistics usually preclude use of MR imaging in critically ill patients who have ALF. The pathogenesis of cerebral edema in patients who have ALF may involve the “glutamine hypothesis,” wherein detoxification of ammonia by astrocytes leads to the conversion of glutamate to glutamine that can increase tissue osmolarity and cause edema [88]. Alternatively, cerebral edema may develop from failure of intracerebral vascular autoregulation with resultant increases in brain water and brain volume, particularly in patients who have advanced encephalopathy [89,90].

Although invasive, ICP monitoring is the most reliable means to monitor changes in ICP in patients who have ALF [91]. Information from an ICP monitor helps guide management decisions regarding the use of mannitol and paralytic agents. Controversy exists, however, about whether ICP monitoring should be used only in liver transplant candidates, only in patients enrolled in clinical trials, or in all patients who have grade 3 or grade 4 encephalopathy. Sedation should be withheld for at least 2 to 4 hours in intubated patients who have ALF who are being considered for placement of an ICP monitor to assess brain function. A preoperative head CT is recommended to exclude spontaneous hemorrhage. Although parenchymal catheters have a greater risk of intracranial bleeding, they provide more reliable pressure readings [91,92]. ICP measurements can help intensivists maintain an adequate cerebral perfusion pressure (CPP) (ie, > 50 mm Hg) by the introduction of vasopressors to raise the mean arterial pressure (MAP) or maneuvers to lower the elevated ICP (ie, CPP = MAP – ICP).

To prevent exacerbation of cerebral edema, the head of the bed should be elevated more than 30° from horizontal in all patients who have ALF [93]. Vigorous suctioning or other Valsalva maneuvers should be avoided to prevent surges in ICP. Prophylactic intravenous lidocaine may be of value [5,93]. Mechanical ventilation with high levels of positive end-expiratory pressure should be avoided. Cooling blankets can be used to keep the
Box 2. Management of cerebral edema in acute liver failure

**Grade 1 or 2 encephalopathy**
- Grade 1: Mild changes in mood and speech, disordered sleep
- Grade 2: Inappropriate behavior, mild irritability, agitation, or somnolence
  - Hyperreflexia, clonus, asterixis (may or may not be present)
- Transfer patient to ICU for frequent monitoring and neurologic checks.
  - Maintain a quiet environment with minimal environmental stimuli.
  - Avoid sedatives/hypnotics.
- Administer dextrose 10% drip with hourly blood glucose monitoring.
- Lactulose may be of benefit in patients who have subacute acute liver failure (see text).
  - Toxicities: megacolon, volume depletion, hypernatremia

**Grade 3 or 4 encephalopathy**
- Grade 3: Patient is somnolent but arousable to verbal command and demonstrates marked confusion, incoherent speech.
- Grade 4: Patient is not arousable by painful stimuli.
  - Avoid medications with sedative properties (eg, narcotics, benzodiazepines) unless patient is intubated
- Elevate head of bed to 30° from horizontal.
  - Avoid Valsalva maneuvers, vigorous straining, or suctioning.
  - Use cooling blankets to keep core temperature at 37°C or lower.
- Consider intubation to protect airway, hypoxia, respiratory failure.
  - If intubated, propofol or midazolam are preferred for sedation.
- Obtain a head CT to rule out intracranial hemorrhage.
- Consider placement of an intracranial pressure monitor.
  - Correct coagulopathy (international normalized ratio < 1.5) with fresh frozen plasma or recombinant factor VIIa.
  - Balance risk of procedure versus benefit of accurate data (eg, epidural versus subdural versus parenchymal) in selecting type of intracranial pressure catheter used.

**Measures for elevated intracranial pressure**
- Maintain cerebral perfusion pressure above 50 mm Hg (cerebral perfusion pressure = mean arterial pressure – intracranial pressure).
patient’s core temperature below 37.0°C. Sedative medications, especially long-acting benzodiazepines, narcotics, and diphenhydramine, should be avoided in nonintubated patients because they can obscure neurologic changes. If sedation is required for patient comfort and safety, agents with a short half-life, such as midazolam or propofol, are preferred.

If a patient deteriorates clinically or has an ICP exceeding 20 mm Hg for more than 5 to 10 minutes, several measures should be undertaken. Initially, hyperventilation of intubated patients to a PCO₂ of 28 to 30 mm Hg is recommended to induce cerebral vasoconstriction [94]. Lactulose can help lower systemic ammonia levels in cirrhotic patients by its osmotic activity and acidification of stool, but lactulose has not been tested prospectively in patients who have ALF. In addition, lactulose raises concerns about free water depletion and potential abdominal distention with associated bowel ischemia. Nonetheless, many centers use lactulose, particularly for patients who have subacute liver failure who have evidence of portosystemic shunting [2].

Mannitol (0.5–1.0 g/kg) is a first-line therapy for management of ICP surges exceeding 20 mm Hg that do not respond to hyperventilation [95]. Mannitol reduces intracranial volume by drawing fluid into the intravascular space. Mannitol infusions should be withheld in patients who have renal failure or fluid overload until these problems have been addressed. Monitoring of serum osmolarity also is recommended to avoid a hyperosmolar state.
Recent data suggest that hypertonic saline infusion, with a target serum sodium level of 145 to 155 mmol/L, may reduce the incidence and severity of intracranial hypertension, but further studies are needed because of the narrow therapeutic index [96].

Thiopental and pentobarbital are centrally acting hypnotics that reduce brain oxygen use. They represent a second-line therapy for severe intracranial hypertension [97]. Pentobarbital, administered as a 100- to 150-mg bolus over 15 minutes followed by continuous infusion at 1 to 3 mg/kg/h, should be monitored to maintain serum drug levels at 20 to 35 mg/L. Because barbiturate infusions can cause systemic hypotension, dopamine may be required to maintain an adequate CPP. Propofol has been used to reduce ICP. It may be advantageous because of its low risk of systemic hemodynamic effects [98].

Moderate hypothermia can reduce cerebral hyperemia and decrease ICP in patients who have ALF refractory to medical therapy [99–101]. Reducing the core body temperature to 33°C or 35°C reduces cerebral oxygen use and blood flow. Whole-body hypothermia can be achieved by external cooling blankets, intravascular cooling devices, and body suits with core body temperatures monitored by a rectal or intravascular thermometer. Sedation with a paralytic agent such as atracurium may be needed to prevent reflexive

Fig. 3. Head CT findings in a patient who has acute liver failure with cerebral edema. A 39-year-old man ingested an unknown quantity of acetaminophen, zolpidem, and lamotrigine in a suicide attempt 48 hours before presentation. His initial acetaminophen level was 87 μg/mL, his alanine aminotransferase level was above 9000 IU/L, his international normalized ratio was 8.9, and his factor V level was less than 15%. He also had a severe lactic acidosis with hypotension requiring the use of pressors and intubation. (A) At the time he was list for liver transplantation, a head CT showed loss of the gray–white matter interface, but an intracranial pressure monitor revealed an opening pressure of only 12 to 15 mm Hg. After an uneventful liver transplantation, the patient did not wake up. (B) A follow-up head CT showed diffuse changes of worsening cerebral edema and the patient was pronounced brain dead after the absence of intracranial blood flow was determined on a Technitium-99 albumin scan.
Shivering, but propofol or deep sedation also may be effective. The optimal means to rewarm hypothermic patients who have ALF safely have not been established. Because of the potential risks of hypothermia, including cardiac arrhythmias, worsening coagulopathy, hypotension, and impaired liver regeneration, randomized, controlled trials of therapeutic and prophylactic hypothermia with ICP monitoring are needed before this investigational therapy can be recommended routinely.

Seizures in patients who have ALF may be difficult to detect, particularly in patients receiving deep sedation or barbiturates. In one study of 42 intubated patients who had ALF, 31% had subclinical seizure activity. The incidence was lower in patients who received prophylactic phenytoin [102]. Some experts recommend continuous or intermittent electroencephalogram monitoring for patients who have grade 3 or grade 4 coma, but this practice has not been adopted widely. Hypoglycemia and electrolyte disturbances should be excluded as precipitating factors for seizure development and treated aggressively if detected. Phenytoin, infused as an 18-mg/kg loading dose over 30 minutes followed by 100 mg every 8 hours, is the first-line treatment for seizures; pentobarbital, 3 mg/kg, is reserved for refractory seizures [102].

Infections

Infectious complications are common in patients who have ALF and are a leading cause of mortality. Eighty percent of patients who have ALF develop bacterial infections, and 20% to 30% develop fungal infections during their hospitalization [103]. Therefore, daily surveillance cultures of blood, urine, and sputum are recommended on admission to the ICU [103]. A diagnostic paracentesis should be performed on all patients who have ALF at presentation with ascites, unexplained fever, or leukocytosis. Patients commonly are infected with staphylococcal species, streptococcal species, or gram-negative rods [2,103]. Coverage with broad-spectrum antibiotics should be initiated if the patient develops fever, leukocytosis, or unexplained deterioration in clinical status. Frequently a quinolone or third-generation cephalosporin is used. Vancomycin can be added for patients suspected of having line infection or further deterioration. Enteral decontamination with poorly absorbed orally administered antibiotics does not seem to alter the outcome of patients who have ALF who receive parenteral antibiotics. Fluconazole or amphotericin should be added for suspected or proven fungal infection.

Renal failure and fluid management

Acute renal failure in ALF usually is multifactorial with components of acute tubular necrosis (ATN), hypovolemia, and even hepatorenal syndrome. Renal failure is particularly common in patients who have acetaminophen toxicity and portends a poor prognosis [104]. In addition to
monitoring of central pressures, a urinalysis and urine electrolytes can help distinguish ATN from hepatorenal or prerenal causes of renal failure. Lactic acidosis is a common complication of ALF that can be worsened by hypovolemia, infection, and poor perfusion pressures [105]. Infusion of normal saline or other colloids may help in the management of hypovolemia. Avoidance of nephrotoxic agents, including aminoglycosides, nonsteroidal anti-inflammatory drugs, and intravenous contrast dye, is critical in patients who have ALF. Enteral feedings are preferred to parenteral nutrition because of the high rate of infectious and metabolic complications with the latter method. Hyponatremia is a poor prognostic sign. In addition, serum sodium levels below 125 mmol/L should be avoided because hyponatremia can exacerbate cerebral edema.

If progressive renal failure ensues with oliguria, azotemia, or fluid overload, continuous venovenous hemofiltration is preferred to standard hemodialysis because of the less dramatic fluid shifts and higher perfusion pressures [106]. Citrate anticoagulation may be preferred to heparin in patients who have liver disease, but randomized, controlled trials have not been completed.

**Hemodynamic monitoring and inotropes**

ALF is characterized by a hyperdynamic circulation with high cardiac output, low MAP, and low systemic vascular resistance. Following fluid resuscitation, dopamine or norepinephrine may be used to maintain an adequate MAP and a CPP higher than 50 mm Hg [2,88]. Vasopressin and its analogue terlipressin should be avoided, because they produce cerebral vasodilation and increased cerebral blood flow leading to worsening intracranial hypertension [107]. Placement of a Swan-Ganz catheter is helpful when inotropes or ICP monitors are used. Surges in systemic hypertension and bradycardia (Cushing’s reflex) may herald impending uncal herniation. In terminal ALF, patients can become refractory to inotropes and die from circulatory failure. A Technitium-99 albumin scan can document the absence of blood flow in patients who have ALF and refractory cerebral edema so that these patients can be removed from the liver transplant waiting list.

**Coagulopathy and bleeding**

Serial INR and factor V levels provide useful prognostic information. Routine correction of elevated INR levels with fresh frozen plasma (FFP) is not recommended unless there is evidence of active bleeding or an invasive procedure is planned (Box 3). A therapeutic trial of vitamin K, 10 mg, subcutaneously for 3 consecutive days is recommended at presentation, because many patients who have ALF are vitamin K deficient. Before an invasive procedure, such as placement of a central line or an ICP monitor or liver biopsy, FFP is infused in an attempt to decrease the INR below 1.5. The
volume of infused FFP needs to be monitored carefully to avoid exacerbation of fluid overload and cerebral edema. Similarly, immediately before invasive procedures the platelet count should be maintained above 50,000 platelets/mL by means of platelet infusions [108]. Cryoprecipitate can be administered if the fibrinogen level is less than 100 mg/dL. Acid suppression with a proton-pump inhibitor rather than sucralfate or histamine-2 receptor blockers is used to prevent upper gastrointestinal bleeding in intubated patients who have ALF [2,109].

Recombinant activated factor VII (rFVIIa) has been used before invasive procedures in patients who have severe coagulopathy, but it is not FDA approved for this indication [110,111]. The goal of rFVIIa infusion is to promote localized clot formation in areas of tissue factor release. Because of its cost and risks, most centers reserve rFVIIa infusion for patients who have an INR higher than 1.5 despite infusion of at least 4 units of FFP who require an invasive procedure. Typically a single dose of 80 ug/kg is infused rapidly to enhance clot formation and to normalize the INR for 2 to 12 hours. Contraindications include Budd-Chiari syndrome; known or suspected malignancy; a history of deep venous thrombosis, pulmonary embolism, or thrombophilia; pregnancy; and hypersensitivity to vitamin K. The medication should be administered immediately before invasive procedures. Repeating coagulation parameters immediately thereafter is not recommended because of its short half-life. It is unclear whether additional doses or continuous infusions of rFVIIa prevent spontaneous bleeding in patients who have ALF.

Prognosis in acute liver failure

Before the widespread availability of liver transplantation, the reported survival of patients who had ALF was 3% to 18% [2,112]. Later studies reported survival of 14% to 25% without liver transplantation and 41% to 49% with liver transplantation [113]. Among transplant recipients, the 1-year patient survival rate now varies between 60% and 80% [114,115]. The severity of encephalopathy and coagulopathy correlate inversely with survival [116,117]. Numerous prognostic scales have been proposed to identify patients who have the greatest need for liver transplantation.

King’s College criteria

The King’s College criteria were developed from a retrospective cohort of 588 medically managed patients who had ALF and then were validated prospectively in an additional 175 patients who had ALF [118]. Readily obtained clinical and laboratory parameters were selected to enhance their clinical usefulness in patients who had acetaminophen and non-acetaminophen–related ALF. In the acetaminophen cohort, an arterial pH below 7.3 or INR higher than 6.5, a serum creatinine level higher than 3.4 mg/dL, and
Box 3. Management of coagulopathy in acute liver failure

**Multifactorial causes**
- Hypoprothrombinemia caused by reduced hepatic synthesis of coagulation factors and disseminated intravascular coagulation/hypofibrinogenemia
- Thrombocytopenia caused by reduced hepatic thrombopoietin production, consumption, acute portal hypertension, and reduced marrow production (e.g., aplastic anemia, acute viral illness)
- Vitamin K deficiency caused by poor oral intake and jaundice/cholestasis

**Assessment**
- Obtain prothrombin time/international normalized ratio, partial thromboplastin time, complete blood cell and platelet count, and fibrinogen every 12 hours.
- Serial international normalized ratio and factor V levels have prognostic value.
- Approximately 10% of patients who have acute liver failure have clinically significant bleeding.
- Mucocutaneous hemorrhage, gastrointestinal bleeding, and bleeding at insertion sites

**Management**
- Prophylaxis for gastrointestinal bleeding is recommended in all patients treated with a proton-pump inhibitor or histamine 2 blocker.
- Vitamin K (10 mg) subcutaneously for 3 days is recommended for all patients.
- Prophylactic fresh frozen plasma infusions are not recommended in the absence of active bleeding.
- Concerns about volume overload/worsening cerebral edema
- Lose prognostic value of international normalized ratio
- If there is active bleeding or a planned procedure, administer
- Fresh frozen plasma to maintain international normalized ratio below 1.5
- Platelet infusion to maintain a level higher than 50,000 platelets/mL
- Cryoprecipitate to maintain fibrinogen level higher than 100 mg/dL
- Consider recombinant factor VIIa only if an invasive procedure such as placement of an intracranial pressure monitor will be performed and the international normalized ratio is below 1.5 after 4 units of fresh frozen plasma.
grade 3 or grade 4 encephalopathy had prognostic significance. In the non-acetaminophen cohort, an INR higher than 6.5 or three or more of the following five parameters were independent predictors of poor outcome [118]:

1. Unfavorable causes (non-A, non-B hepatitis, DILI)
2. Jaundice for more than 7 days before encephalopathy
3. Age under 10 years or over 40 years
4. INR higher than 3.5
5. Serum bilirubin level higher than 17.5 mg/dL

The positive predictive value of these criteria for mortality was 84% in the acetaminophen cohort and 98% in the non-acetaminophen cohort; the negative predictive values were 86% and 82%, respectively [118]. This prognostic model has been tested in other patient cohorts, and lower positive predictive values and negative predictive values were found [119,120]. Recently, the value of early arterial lactic acid levels in conjunction with the standard King’s College criteria have been studied in patients who have acetaminophen-induced ALF. A postresuscitation arterial lactate level higher than 3.0 mmol/L and an “early” level higher than 3.5 mmol/L had negative predictive values of 97% and 99%, respectively, but had positive predictive values of only 79% and 74%, respectively [105].

Other prognostic models

The Model for End Stage Liver Disease (MELD) score, consisting of serum creatinine level, total bilirubin level, and INR, was shown to predict 3-month survival better than the Child-Turcotte-Pugh score in liver transplant candidates who had cirrhosis [121]. The MELD score has become the means by which liver allografts are allocated to cirrhotic patients in the United States. In patients who have non-acetaminophen ALF, MELD scores identified patients who have the worst prognosis; other patients had a high rate of spontaneous recovery independent of MELD score [122].
Global assessment models have been proposed to predict outcome [123]. Larson and colleagues [6] recently showed that admission APACHE II scores were superior to the King’s College criteria or MELD scores in predicting outcomes in patients who had acetaminophen-induced ALF. Other potential prognostic laboratory markers include serum phosphate levels, which decline in patients who have rapid hepatic regeneration [124]. Similarly, serum alpha-fetoprotein levels increase in patients undergoing rapid liver regeneration, and increasing levels indicate a better prognosis [125,126]. Although these biochemical parameters probably have inadequate predictive power independently, they may be useful clinically in combination with other prognostic variables. Abdominal CT scanning to assess liver volume and liver biopsy to assess hepatic histopathology also have been proposed, but both methods have limited sensitivity, specificity, and feasibility [127,128]. Because the cause of ALF is an important, consistent predictor of outcome, disease-specific prognostic models may prove useful for non-acetaminophen as well as acetaminophen-related ALF [7].

Liver transplantation

Emergency liver transplantation is the only intervention with known survival benefit in patients who have ALF carrying a poor prognosis [114]. Outcome after liver transplantation is linked closely to the severity of the pretransplant illness and the nature of the graft used. Currently, the 1-year survival of patients undergoing transplantation for ALF is lower than that of patients undergoing transplantation for chronic liver failure (70% versus 85%), probably because of the emergent nature of the surgery, concomitant organ failure, and higher incidence of immunologically mediated graft dysfunction.

Rapid medical and surgical evaluation is required for all ALF transplant candidates before listing to exclude significant cardiopulmonary disease, malignancy, or other conditions that negatively affect patient outcomes [2]. In addition, a comprehensive psychosocial evaluation of patient compliance, family support, and substance abuse is extremely important in patients who have acetaminophen overdose. Ongoing evaluation of the need and the suitability of patients listed for transplantation because of ALF is necessary because of the unstable nature of this patient population and the potential development of contraindications. The frequent delay in securing a suitable donor liver renders medical decisions complex and difficult. Most centers consider refractory systemic hypotension or intracranial hypertension, uncontrolled sepsis, or progressive multiorgan failure to be contraindications to transplantation.

To facilitate rapid distribution of livers for life-saving transplantation, the UNOS developed a special status 1 designation for patients who have a high short-term risk of death. Patients eligible for status 1 designation include patients who have ALF with onset of illness in the prior 8 weeks,
patients who have fulminant Wilson’s disease, and transplant recipients who have primary graft nonfunction or early hepatic artery thromboses. Status 1 patients move ahead of all other listed patients who have chronic liver failure. Grafts are allocated to status 1 patients based on blood type, geography, and waiting time [122,129]. In August 2005, the status 1 category was modified to include specific clinical and laboratory criteria for fulminant hepatic failure, hepatic artery thromboses, and primary graft nonfunction. Donor livers are offered initially to status 1A adults or children; a status 1B category was developed for pediatric patients who had chronic liver disease requiring intensive care, nonmetastatic hepatoblastoma, or metabolic disease. In calendar years 2004 and 2005, 1529 patients were listed as UNOS status 1 [130]. Fifteen days after listing, 54.2% of patients had undergone transplantation, 16.1% were dying or too sick to undergo transplantation, 11.6% had recovered, 8.7% were still listed for transplantation, and 9.1% had been delisted. Extrapolating these data to the overall population, less than 10% of the 2800 patients who have ALF receive a liver transplant each year in the United States.

**Artificial and bioartificial liver devices**

Artificial and bioartificial liver-support devices are under development for patients who have acute and acute on chronic liver failure. These devices may be ideally suited for patients who have ALF as a bridge to spontaneous recovery during native liver regeneration. The design of a clinical trial design is difficult, however, because of variable spontaneous recovery rates and variable availability of liver transplantation. The ideal liver replacement device should perform normal hepatocyte functions including detoxification, metabolism, and synthesis of critical proteins. Early attempts at artificial liver detoxification included hemodialysis, hemofiltration, exchange transfusion, plasma exchange, and resin hemoperfusion, but none of these interventions improved outcome [131,132]. Newer artificial detoxification devices, such as the Molecular Absorbent Recirculating System, use charcoal or other adherent particles in an extracorporeal circuit [132,133]. These artificial devices provide only the filtration function, however. The need for arterial and venous cannulation, anticoagulation, and extracorporeal perfusion can cause complications.

Bioartificial liver support devices use human or other mammalian-derived hepatocytes in an extracorporeal circuit [132]. In theory, these systems can synthesize proteins and metabolize xenobiotics in addition to performing filtration and detoxification. Maintaining viable, sterile hepatocytes for continuous extracorporeal use is a formidable challenge, however. Concerns have been raised regarding transmission of hepatocytes to the host, transmission of zoonoses, activation of the clotting cascade, and immunologic reactions with development of xenoantibodies [134]. In the largest randomized, controlled trial, 171 patients who had fulminant or subfulminant liver failure or primary graft nonfunction following liver
transplantation were assigned randomly to receive a daily 6-hour treatment with the a device that contains 100 g of porcine hepatocytes loaded in a dialysis cartridge in series with charcoal filters, versus standard care [135,136]. Overall, 30-day survival was similar in both treatment groups (71% in the group treated with the porcine hepatocyte device versus 62% in the control group; $P = .26$). This landmark study highlights the difficulties of performing clinical trials in ALF and the need for appropriate patient inclusion criteria and clinically relevant end points. Further refinements of device components and perfusion circuitry and an improved understanding of liver regeneration are needed to improve these devices for use in patients who have ALF.

Summary

ALF remains a dramatic and highly unpredictable clinical syndrome. Studies of its causes and natural history are hampered by its low incidence, variable terminology, and variable clinical management. In the United States, acetaminophen is the leading cause of ALF, and the incidence of unintentional acetaminophen overdose seems to be increasing. ALF is a clinical syndrome of coagulopathy and encephalopathy ensuing from a multitude of infectious, immunologic, vascular, infiltrative, and metabolic diseases (see Table 2). Proven treatments for specific causes of ALF include NAC for acetaminophen overdose and delivery in pregnancy-related ALF. In addition, because of their generally safe medication profile, antiviral agents frequently are recommended for HBV- and HSV-related ALF. Intravenous NAC for non-acetaminophen–related ALF seems promising, but the available data indicate that corticosteroids should not be used in indeterminate ALF or DILI. Cerebral edema is a hallmark of ALF that requires specialized management by a group of experienced intensivists, hepatologists, and transplant surgeons. A low threshold for broad-spectrum antibiotics is recommended, because patients who have ALF are at high risk of bacterial and fungal infections. Patients who have advanced encephalopathy or an otherwise unfavorable prognosis should be referred promptly to a liver transplant center for further evaluation. Emergency liver transplantation can have a favorable outcome but requires coordinated intensive care and constant reassessment.

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References

ACUTE LIVER FAILURE


