Acetaminophen Hepatotoxicity and Acute Liver Failure

Linda J. Chun, BS, Myron J. Tong, PhD, MD,† Ronald W. Busuttil, PhD, MD,‡ and Jonathan R. Hiatt, MD‡*

Abstract: Acetaminophen-induced hepatotoxicity is a common consequence of acetaminophen overdose and may lead to acute liver failure (ALF). Currently acetaminophen is the most common cause of ALF in both United States and United Kingdom, with a trend to increasing incidence in the United States. *N*-acetylcysteine is the most effective drug to prevent progression to liver failure with acetaminophen hepatotoxicity. Liver transplantation is the only definitive therapy that will significantly increase the chances of survival for advanced ALF. This communication reviews current information regarding causes and management of acetaminophen-induced hepatotoxicity and ALF.

Key Words: acute liver failure, drug toxicity, liver transplantation

(*J Clin Gastroenterol* 2009;43:342–349)

Acute liver failure (ALF) is defined as the presence of hepatic encephalopathy and coagulopathy in patients with no history of liver disease.[1,2] Acetaminophen-induced hepatotoxicity is an important cause of ALF. Acetaminophen is one of the most widely used analgesics with few side effects when taken in therapeutic doses,[3,4] and hepatotoxicity is a common consequence of acetaminophen overdose.[5] Acetaminophen hepatotoxicity causing ALF was not fully recognized in the United States until the mid-1980s; since then, studies have shown that the incidence is increasing.[6] This review considers current information regarding pathophysiology and management of acetaminophen-induced hepatotoxicity and ALF.

PATHOPHYSIOLOGY

Acetaminophen is considered a predictable hepatotoxin, where biochemical signs of liver damage will become apparent within 24 to 48 hours after the time of overdose and produce a dose-related centrilobular necrosis in the liver.[4,7] The lowest dose of acetaminophen to cause hepatotoxicity is believed to be between 125 and 150 mg/kg.[5,8] The threshold dose to cause hepatotoxicity is 10 to 15 g of acetaminophen for adults and 150 mg/kg for children.[5,9] Mechanisms of acetaminophen hepatotoxicity include generation of a toxic metabolite, mitochondrial dysfunction, and alteration of innate immunity.

From the *Albert Einstein College of Medicine; ‡Departments of Surgery; and †Medicine, Division of Digestive Diseases, Pfleger Liver Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA.

No disclosures or conflicts of interest for any author.

Reprints: Jonathan R. Hiatt, MD, Room 72-160 CHS, 650 C.E. Young Drive, South, Box 956904, 72-160 CHS, Los Angeles, CA 90095-6904 (e-mail: jhiatt@mednet.ucla.edu).

Acetaminophen Toxic Metabolite

Hepatotoxicity is a direct liver injury caused by the toxic metabolite of acetaminophen.[4] When taken in therapeutic doses, greater than 90% of acetaminophen is metabolized to phenolic glucuronide and sulfate in the liver by glucuronyltransferases and sulfotransferases and subsequently excreted in the urine.[9] Of the remaining acetaminophen, about 2% is excreted in the urine unchanged[9]; approximately 5% to 10% is metabolized by cytochrome P450, mainly the enzyme CYP2E1,[10] to *N*-acetyl-*p*-benzoquinoneimine (NAPQI),[11] a highly reactive, electrophilic molecule that causes harm by formation of covalent bonds with other intracellular proteins. This reaction is prevented by conjugation with glutathione and subsequent reactions to generate a water-soluble product that is excreted into bile.[12] With acetaminophen overdose, glucuronyltransferases and sulfotransferases are saturated, diverting the drug to be metabolized by cytochrome P450 and generating NAPQI in amounts that can deplete glutathione. If glutathione is not replenished, NAPQI will begin to accumulate in the hepatocytes.[7]

NAPQI can form covalent bonds with cellular proteins and modify their structure and function.[7] This cellular disturbance leads to a decrease in calcium ATPase activities and an increase in levels of cytosolic calcium.[12,13] Abnormal cellular calcium homeostasis can alter the permeability of the cell, causing the formation of blebs in the cell membrane and loss of membrane integrity.[7]

Mitochondrial Dysfunction

There is evidence that acetaminophen overdose can cause mitochondrial dysfunction either by covalent binding to mitochondrial proteins or by other mechanisms. The modified mitochondrial proteins and high levels of cytosolic calcium can depress mitochondrial respiration and adenosine triphosphate (ATP) synthesis and induce mitochondrial oxidant stress with increased production of peroxynitrite, a potent oxidant and nitrating agent. Peroxynitrite can generate additional covalent bonds with cellular proteins, causing further mitochondrial dysfunction. Eventually there is alteration of membrane permeability leading to collapse of mitochondrial membrane potential, disruption of ATP synthesis, release of mitochondrial proteins into the cell cytoplasm, and oncotic necrosis of hepatocytes.[12,13]

Alteration of Innate Immunity

The liver's innate immune system has been shown to play a major role in the progression of liver injury during acetaminophen hepatotoxicity. Endothelial cells within hepatic sinusoids lack a basement membrane, allowing ready access of immune cells from the blood stream to the underlying hepatocytes. Cell death caused by the toxic acetaminophen metabolites first activates Kupffer cells,

phagocytic macrophages of the liver, to release cytokines including interleukin-12, interleukin-18, and tumor necrosis factor-α that may activate natural killer (NK) and natural killer thymus lymphocytes. Activated natural killer and natural killer thymus cells may cause liver damage by cytotoxic activity, promoting further activation of Kupffer cells, and stimulating local production of chemokines. Inflammatory mediators, cytokines, and chemokines, recruit and accumulate neutrophils in the liver and exacerbate the hepatic injury.[14]

EPIDEMIOLOGY

National estimates for acetaminophen toxicity in the United States include 26,000 hospitalizations and more than 450 deaths annually.[15] A study in the United Kingdom reported fewer than 10% of patients with acetaminophen overdose would develop severe liver damage, and only 1% to 2% would develop ALF.[15] Despite the small fraction of acetaminophen overdoses that lead to complications, acetaminophen currently is the most common cause of ALF in both the United States and United Kingdom.[3,16]

In the 1970s and 1980s, hepatitis B was the most common cause of ALF in the United States. By the late 1990s, a multicenter report from the Acute Liver Failure Study Group identified acetaminophen toxicity as the cause of ALF in 20% of cases.[17] Subsequent studies reported acetaminophen overdose to be the most common cause of ALF, accounting for 39% to 42% of all cases, with suicidal intent in 27% to 44% and unintentional overdose in 48% to 61%.[3,18,19] Of the patients with acetaminophen-induced ALF, 74% to 79% were women, 88% to 90% were of white ethnicity, and the median age was 36 to 37 years.[3,18] One report showed an increase of incidence of acetaminophen-induced ALF from 28% in 1998 to 52% in 2003.[3] A multicenter prospective study of pediatric patients reported the most common cause of ALF to indeterminate (49%), with only 14% caused by acetaminophen overdose.[20]

In the United States, many acetaminophen overdoses are unintentional. Of patients with unintentional overdose in a study by Larson et al,[3] 79% reported that they were taking the analgesic specifically for pain, and 38% were taking 2 different preparations of the drug simultaneously. Of narcotic users, one-third were also ingesting over-the-counter acetaminophen. The most common prescription narcotic used for pain was the combination of acetaminophen and hydrocodone. This suggests that patients are not aware that their prescription pain medications also contain acetaminophen and may ingest an overdose using this medications combination with over-the-counter acetaminophen.[3] Morbidity and mortality seem to be greater with unintentional compared with intentional overdosage possibly because of delayed presentation and treatment.[6,21]

Recent studies using a new assay for the detection of acetaminophen-protein adducts have identified the possibility that unrecognized acetaminophen overdose may have been the cause of ALF in cases previously thought to be indeterminate. Acetaminophen-protein adducts were identified in 19% and 12.5%, respectively, of such indeterminate cases in reports by Davern et al[22] and James et al.[23]

Risk Factors

Many factors have been proposed to increase susceptibility to acetaminophen hepatotoxicity. Patients over the age of 40 have increased risk of ALF, death, and need for liver transplantation after acetaminophen overdose.[24] Genetic variations resulting in polymorphisms of the cytochrome isoenzymes may affect their ability to metabolize drugs.[9] Tobacco smoke was an independent risk factor for mortality after acetaminophen overdose in a retrospective study.[9] Susceptibility to acetaminophen-induced hepatotoxicity may be increased with chronic use of anticonvulsants[25] and antituberculous therapy, specifically isoniazid.[5] The fasting state exacerbates hepatotoxicity by depletion of glutathione stores and heightened activity of the enzyme CYP2E1.[9,26] Acute alcohol intake can be protective, because alcohol competes with acetaminophen as a substrate for cytochrome P450, but chronic alcohol ingestion stimulates CYP2E1 activity, inhibits the rate of glutathione synthesis, and increases toxicity.[9,27]

The clinical importance of these risk factors is controversial.[10,28] Later studies and recent reviews found insufficient evidence to support the link between chronic alcohol use and fasting with increased susceptibility to acetaminophen hepatotoxicity.[9,29]

CLINICAL PRESENTATION

The signs and symptoms of untreated acetaminophen overdose depend on the interval after ingestion and are defined in phases. Findings in phase 1 (first 24 h) include anorexia, abdominal pain, nausea, vomiting lethargy, malaise, and diaphoresis. In phase 2 (24 to 72 h), symptoms may improve or even disappear; whereas biochemical abnormalities [elevated transaminases and bilirubin and prolonged prothrombin time (PT)] will become evident. Patients may experience right upper quadrant abdominal pain, and hepatomegaly may be present. In phase 3 (72 to 96 h), nausea and vomiting reappear or worsen and are accompanied by malaise, jaundice, and central nervous system symptoms including confusion, somnolence, or coma. Hepatocellular injury and death most commonly occur in this stage. Oliguria secondary to dehydration or acute tubular necrosis may develop, and liver test abnormalities will reach their peaks at this stage. In phase 4 (4 to 14 d), there is resolution of liver damage and liver tests, with return of normal hepatic architecture within 3 months. Approximately 70% of patients who developed ALF will enter phase 4 and can recover completely. Approximately 1% to 2% of untreated patients with toxic acetaminophen levels will develop fatal hepatic failure. If the overdose is severe enough and there is no intervention, death will occur within 4 to 18 days after ingestion.[4,9,30]

Transaminases are particularly abnormal; aspartate aminotransferase can exceed 10,000 IU/L and alanine aminotransferase can exceed 1000 IU/L, although values may be lower than these extremes. There is a lesser increase in alkaline phosphatase. Total bilirubin may reach 4 mg/dL, with minimal elevation early after ingestion. Coagulation disturbances may be severe, with marked elevations of PT and international normalized ratio (INR). If liver biopsy is performed, histopathology shows extensive centrizonal necrosis without steatosis and light inflammatory infiltrate.[4,30] Metabolic disturbances include hypophosphatemia, hypoglycemia, and metabolic acidosis. In general, hypophosphatemia is a biochemical feature of acetaminophen overdose, with or without hepatotoxicity, and the degree of hypophosphatemia reflects the severity of the overdose.[5,31] Hypoglycemia may occur within the first 24 hours and reflects impaired hepatic gluconeogenesis,

inability to mobilize hepatic glycogen stores, and elevated levels of circulating insulin.[5] Metabolic acidosis occurs in as many as half of patients after acetaminophen overdose. Within the first 15 hours, metabolic acidosis is caused by direct inhibition of the uptake and metabolism of lactic acid by the liver and later due to worsening hepatic function and impaired hepatic clearance of lactic acid.[5] Lactic acidosis also reflects reduced oxygen extraction and increased anaerobic metabolism seen in patients with critical illness.[5,32]

ALF

ALF is a clinical syndrome defined by a severe decline in hepatic synthetic function with the rapid onset of hepatic encephalopathy.[33] The best indicator of liver damage is the PT,[34] and there is a relationship between the severity of the liver disease and the degree of coagulation abnormality.[35] Severe coagulopathy often precedes the development of hepatic encephalopathy, which usually occurs 2 to 4 days after ingestion.[5,33] Hepatic encephalopathy is graded from I to IV according to severity (Table 1).[36] The grade is correlated with survival and need for supportive treatment.[5,36]

Cerebral edema is present in as many as 80% of patients with ALF, and grade IV hepatic encephalopathy. With progressive edema and increased intracranial pressures, fatal uncal herniation may occur. Decerebrate posturing, systemic hypertension, and pupillary abnormalities are among the clinical signs of increased intracranial pressure but may be absent.[33]

Patients with ALF commonly have metabolic derangements including hypokalemia, hyponatremia, and hypophosphatemia.[33] Increased susceptibility to infection is a major source of mortality, with bacterial infections in 44% to 80% and fungal infections in 32%.[33] The mortality rate approaches 30% for patients with acetaminophen hepatotoxicity that develop ALF.[9]

DIAGNOSIS

Early diagnosis of acetaminophen hepatotoxicity is essential, as rapid deterioration is common, whereas current treatments are very effective in preventing morbidity and mortality. A detailed drug history including dosage, route of administration, and duration should be obtained. Physicians must recognize that acetaminophen is present in many drug products. In addition to usual laboratory testing, serial serum acetaminophen levels should be measured. Serum acetaminophen level above 300 mg/L at 4 hours after ingestion and above 50 mg/L at 15 hours predict 90% probability for the presence of severe or fatal liver damage.[30] Even with undetectable serum acetaminophen levels, acetaminophen cannot be excluded, as patients with unintentional overdose may present 3 to 4 days after ingestion of acetaminophen and often do not have detectable serum acetaminophen levels.[30,37]

TABLE 1. Grades of Encephalopathy

I	Changes in behavior with minimal changes in level of consciousness
II	Gross disorientation, drowsiness, possibly asterixis, inappropriate behavior
III	Marked confusion, incoherent speech, sleeping most of the time but arousable to vocal stimuli
IV	Comatose, unresponsive to pain, decorticate or decerebrate posturing

Adapted from *Hepatology*. 2005;41:1179–1197.[36]

CLINICAL MANAGEMENT

Interventions for acetaminophen overdose include inhibition of absorption, removal of acetaminophen from the blood, prevention of the conversion of acetaminophen into the toxic metabolite NAPQI, detoxification of NAPQI, and liver transplantation.[38] Choice of therapies depends upon the timing of presentation and the degree of hepatic decompensation.

Gastric lavage, activated charcoal ingestion, and induction of vomiting by ipecacuanha can reduce absorption within the first few hours after ingestion. Weak evidence shows activated charcoal to be the most effective of the 3 in preventing absorption.[38,39] Charcoal hemoperfusion has been proposed to remove acetaminophen from the blood but is unsupported by current evidence.[38] Cimetidine inhibits cytochrome P450 and might be used to inhibit the conversion of acetaminophen into the hepatotoxic metabolite NAPQI, but a quasi-randomized study has found no beneficial effect in using cimetidine with *N*-acetylcysteine (NAC).[38,40]

Agents to detoxify NAPQI include methionine, cysteamine, and NAC. Although all were shown to decrease risk of liver damage in randomized trials, methionine and cysteamine caused more adverse gastrointestinal and central nervous system effects when compared with NAC. NAC is now widely accepted as the antidote best able to reduce the risk of hepatotoxicity and also mortality in patients with ALF.[38] NAC works by replenishing glutathione stores, binding directly to acetaminophen toxic metabolite and enhancing nontoxic sulfate conjugation in liver cells.[41] The overall mortality rate for acetaminophen overdose had declined from as high as 5% to 0.7% with use of NAC. Liver transplantation is the only intervention that improves survival when there is irreversible liver damage causing ALF.[38]

Treatment With NAC

NAC may prevent hepatic failure in patients with acetaminophen overdose if administered early enough.[42] It is highly effective in protecting against severe liver damage, renal failure, and death if it is given within 8 to10 hours after ingestion[41,43,44] and can reduce the severity of liver damage even if given within 16 hours.[45] Currently, the recommended dose of NAC is 140 mg/kg, diluted to 5% solution orally, followed by 70 mg/kg orally every 4 hours for 17 doses. For patients unable to take NAC by mouth, the intravenous route may be used, with a loading dose of 150 mg/kg in 5% dextrose over 15 minutes and a maintenance dose of 50 mg/kg over 4 hours followed by 100 mg/kg over 16 hours.[9,36]

No studies have shown any difference in effectiveness between oral and intravenous routes of administration, and no randomized trials have demonstrated the optimal route or dose.[38] Oral NAC is associated with more adverse events than intravenous NAC. Oral NAC can cause mild to moderate side effects including nausea, vomiting, abdominal pain, diarrhea, and rash, whereas intravenous NAC can cause anaphylactoid reactions in very rare instances.[9,38]

Anaphylactoid reactions are treated by cessation of the infusion and IV antihistamines or corticosteroids for the severe cases. NAC infusion can be continued at a slower rate when the symptoms have subsided.[5]

Many studies show NAC to be both safe and beneficial when given up to 24 hours after overdose[5,41] or even later for patients with already established ALF.[46] Patients receiving NAC treatment beyond 48 hours after ingestion had higher survival rates and lower incidence of cerebral edema and cardiovascular dysfunction when compared with patients not receiving the agent.[47] NAC can increase oxygen consumption in patients with acetaminophen-induced ALF and may improve the distribution of blood in microcirculation or the ability of the tissues to use oxygen, possibly explaining beneficial effects on end-organ function and survival with established liver damage.[32]

The Rumack-Matthew nomogram was created to predict whether patients would develop hepatotoxicity after acetaminophen overdose and is intended as a guide for early management of a single acute overdose, as opposed to overdose from chronic ingestions. According to the nomogram, hepatotoxicity is predicted when the plasma acetaminophen concentration lies above the probable hepatotoxicity line, a semilogarithmic plot joining the acetaminophen concentration of 200 mg/L at 4 hours with the concentration of 50 mg/L at 12 hours. The Rumack-Matthew nomogram is now used as a guide to identify patients requiring treatment with NAC.

Current Recommended Management

For patients suspected to have an acute acetaminophen overdose, serum acetaminophen concentration is measured at the time of presentation to assess the risk of hepatotoxicity.[5] For patients taking acetaminophen chronically, serum acetaminophen concentration is used to verify ingestion but not to predict toxicity.[8] Other tests for severity of overdose include arterial pH, PT, serum creatinine, hemoglobin, platelet count, and serum amylase.[34]

Activated charcoal and gastric lavage can be used to prevent absorption of acetaminophen, but only are effective when used within 1 hour of ingestion for charcoal and 4 hours for gastric lavage.[5] For patients with a single acute overdose of acetaminophen, the initial measured acetaminophen plasma concentration is plotted on the Rumack-Matthew nomogram, and patients with values above the possible hepatotoxicity line should be started on NAC.[9] A lower treatment line that joins the acetaminophen concentration of 100 mg/L at 4 hours to 14 mg/L at 15 hours is used for patients that have factors that would make them more susceptible to acetaminophen hepatotoxicity.[8] Patients may be discharged without any treatment if the 4-hour acetaminophen level lies below the line of hepatotoxicity.[5]

If a serum acetaminophen concentration cannot be obtained or will not be available within 8 hours, patients should be treated if they ingested a toxic dose greater than 150 mg/kg or greater than 12 g. Treatment is stopped when the serum acetaminophen concentration falls below the necessary treatment line.[5] Measurement of transaminases also may be used in the absence of acetaminophen levels. Treatment should be given to patients with elevated aspartate aminotransferase and alanine aminotransferase and may be withheld if transaminases are not elevated.[48]

Patients should receive a full course of NAC if they have a questionable history regarding the acetaminophen dose or a nonacute overdose.[5] Nonacute overdoses are ingestions that occurred over a period longer than 4 hours, precluding use of the nomogram for treatment decisions. Most of these are supratherapeutic doses taken by patients with risk factors that increase susceptibility to developing acetaminophen-induced hepatotoxicity.[48] The ingested dose and the interval to presentation are the most important prognostic factors for nonacute overdoses. Presentation later than 24 hours after ingestion is associated with increased risk for hepatotoxicity. NAC treatment is required for ingestion of more than 150 mg/kg over 24 hours or 75 mg/kg over 24 hours for patients with risk factors that would increase susceptibility to developing acetaminophen-induced hepatotoxicity.[8]

Patients with coagulopathy or elevated creatinine level should be admitted for further monitoring including daily measurements of INR and creatinine and should receive NAC treatment at a dose of 150 mg/kg every 24 hours until INR falls below 2. Patients may be discharged from the hospital after they complete a full course of NAC treatment if it was begun within 8 hours of ingestion. For treatment begun after 8 hours, patients may be discharged only if asymptomatic and with normal serum creatinine concentration and liver tests.[5] Management decisions are based partly on serial measurements of INR, but cases exist where INR is increased without liver toxicity, possibly the consequence of interaction between clotting factors and NAC.[49,50] This possibility should be considered for patients with increased INR as the only sign of hepatotoxicity.[50] Figure 1 provides an overview of the current recommendation for treatment with NAC.

Medical Management for Established ALF

Patients with ALF require prompt intensive care to avoid rapid and irreversible decompensation.[36,51] Need for intensive care unit admission is determined by presence of mental status changes and coagulopathy (INR above 1.5).[51] Early communication with a transplant center for management and transfer decisions should be undertaken, and transfer to a transplant center should be considered for patients who develop early signs of progressive coagulopathy (INR > 2 at 24 h, INR > 4 at 48 h, or INR > 6 at 72 h after ingestion; or INR > 5 at any time), renal impairment with serum creatinine level > 2.3 mg/dL, metabolic acidosis with pH < 7.35 or $HCO_3^- < 18$ mmol/L, hypotension, encephalopathy, or hypoglycemia.[5] Because of the possibility of rapid deterioration, arrangements for transfer should be made early in the patient's course.[36]

ALF is a multisystem disorder with acute renal failure, hypotension, sepsis, coagulopathy, encephalopathy, and cerebral edema.[8] There are no proven therapies for ALF, and initial management consists mainly of intensive care support.[36] Patients should have central venous and arterial access for hemodynamic monitoring, as well as a urinary catheter. Coagulation parameters, blood counts, metabolic panels, and arterial blood gases are monitored frequently. The mental status is monitored closely, with computed tomography of the head to evaluate neurologic changes or suspected cerebral edema and intracranial pressure monitoring when intracranial hypertension is identified.[36,51,52] Table 2 provides an overview of the current recommendations for general intensive care for ALF.

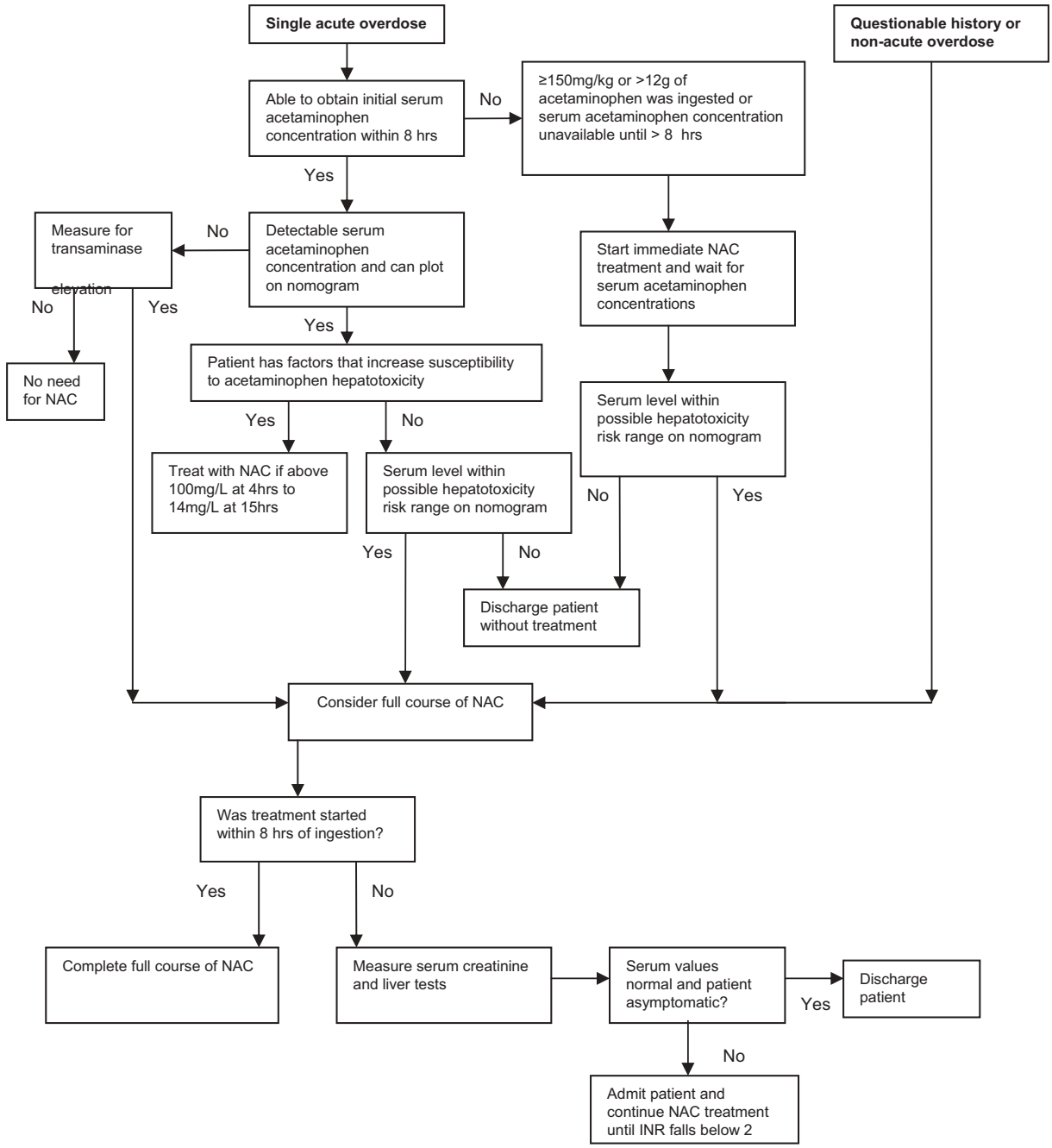

FIGURE 1. Algorithm showing current recommendations for *N*-acetylcysteine (NAC) treatment of acetaminophen overdose.

LIVER SUPPORT SYSTEMS

Liver support systems have been developed to replace liver functionality in patients with ALF and prolong survival until spontaneous recovery or as a bridge to transplantation.[36,53] At present none are recommended to be used outside of clinical trials.[36] Acellular and bioartificial cellular devices are available.

Acellular systems include hemodialysis, sorbent hemoperfusion, and albumin dialysis. Albumin dialysis is the most studied liver support modality, and the Molecular Reabsorbent and Recirculating System (MARS) is the most commonly used device for albumin dialysis. Earlier studies showed that MARS could improve hemodynamic stability, decrease hepatic encephalopathy and intracranial pressures, and decrease serum levels of bilirubin, creatinine, and bile acids.[54] More recently MARS was reported to be safe and efficacious as a bridge to liver transplantation,[55] but offered limited survival benefit without subsequent transplantation.[56]

Bioartificial liver support systems use extracorporeal liver perfusion through cell-based bioreactors. The bioreactor contains a semipermeable membrane that places human or porcine hepatocytes in contact with whole blood or plasma while excluding them from the patient's circulation.[53,54]

TABLE 2. General Intensive Care for Acute Liver Failure

Cerebral edema/intracranial hypertension
Grade I/II encephalopathy
Consider transfer to liver transplant facility and listing for transplantation
Brain computed tomography: rule out other causes of decreased mental status; little utility to identify cerebral edema
Avoid stimulation, avoid sedation if possible
Antibiotics: surveillance and treatment of infection required; prophylaxis possibly helpful
Lactulose: possibly helpful
Grade III/IV encephalopathy
Continue management strategies listed above
Intubate trachea (may require sedation)
Elevate head of bed
Consider placement of intracranial pressure monitoring device
Immediate treatment of seizures required; prophylaxis of unclear value
Mannitol: use for severe elevation of intracranial pressure or first clinical signs of herniation
Hyperventilation: effects short-lived; may use for impending herniation
Infection
Surveillance for and prompt antimicrobial treatment of infection required
Antibiotic prophylaxis possibly helpful but not proven
Coagulopathy
Vitamin K: give at least 1 dose
FFP: give only for invasive procedures or active bleeding
Platelets: give for platelet counts $< 10{,}000/mm^3$ or invasive procedures
Recombinant activated factor VII: possibly effective for invasive procedures
Prophylaxis for stress ulceration: give H_2 blocker or proton pump inhibitor
Hemodynamics/renal failure
Pulmonary artery catheterization
Volume replacement
Pressor support (dopamine, epinephrine, norepinephrine) as needed to maintain adequate mean arterial pressure
Avoid nephrotoxic agents
Continuous modes of hemodialysis if needed
N-acetylcysteine, prostacyclin: effectiveness unknown
Vasopressin: not helpful in acute liver failure; potentially harmful
Metabolic derangements
Follow closely: glucose, potassium, magnesium, phosphate
Consider nutrition: enteral feedings if possible or total parenteral nutrition

Adapted from *Hepatology*. 2005;41:1179–1197.[36]
FFP indicates fresh frozen plasma.

The first phase 2/3 randomized, multicenter controlled trial concluded that the use of a porcine hepatocytes in a bioartificial liver improved 30-day survival to 73% in patients with ALF, compared with 59% in the control group.[53] A more recent phase 3 randomized, controlled trial of an extracorporeal liver assist device using human hepatocytes in China showed significant improvement in survival for patients with acute-or-chronic liver failure due to hepatitis B and C. Further research is needed before the Food and Drug Administration will approve a phase 3 trial in the United States.[57]

LIVER TRANSPLANTATION

Liver transplantation remains the gold standard treatment and offers the best long-term survival for acetaminophen overdose patients who develop ALF.[33,58] Acetaminophen is the leading cause of drug-induced liver failure requiring liver transplantation,[59] contributing to 8% to 13% of all causes of ALF that required liver transplantation.[18,58]

Prognostic Indicators and Selection Criteria for Liver Transplantation

Very few patients with acetaminophen hepatotoxicity require liver transplantation. As transplantation is irreversible and obligates lifelong immunosuppression,[54] selection criteria based on prognostic indicators for ALF patient are used to identify patients for whom spontaneous recovery is unlikely and for whom transplantation will be life-saving.

The criteria from King's College Hospital (KCH) are the most widely accepted to select patients with ALF for liver transplantation.[8] Patients with acetaminophen-induced ALF who meet KCH criteria have mortality above 90% without transplantation.[54] The criteria were initially reported to have sensitivity of 72%, specificity of 98%, and overall positive predictive value of 89%.[60] Later studies challenged the sensitivity based on significant mortality for patients failing to meet the criteria.[61–63] A meta-analysis reported that the criteria had only moderate sensitivity of 69%, but a high specificity of 92%.[64]

Several modifications of KCH criteria have been proposed (Table 3). As patients with ALF and multiple organ dysfunction commonly have elevated blood lactate concentration reflecting systemic hemodynamic dysfunction and defects in oxygen utilization, a modification using arterial lactate levels has been proposed,[63] but also

TABLE 3. Liver Transplantation for Acetaminophen-induced Acute Liver Failure: King's College Hospital (KCH) Criteria and Proposed Modifications[59,62,65]

	Proposed Modifications	
KCH Criteria[59]	**Hyperlactatemia[62]**	**Pediatric Patients[65]**
pH < 7.30 (irrespective of grade of encephalopathy)	Strongly consider listing for transplantation if arterial lactate concentration > 3.5 mmol/L after early fluid resuscitation	pH < 7.30
or		or
Prothrombin time > 100 s and serum creatinine > 300 μmol/L in patients with grade III or IV encephalopathy	List for transplantation if: arterial pH < 7.3 or arterial lactate concentration > 3.0 mmol/L after adequate fluid resuscitation; or concurrently	Prothrombin time > 100 s and serum creatinine > 200 μmol/L in patients with grade III encephalopathy
	Serum creatinine > 300ímol/L, INR > 6.5, and encephalopathy of grade $\geq$ III	

challenged.[65] A modification of KCH criteria for pediatric patients was based on study showing the single best prognostic indicator to be encephalopathy grade $\geq$ III.[66]

OUTCOME

More than 90% of patients with acetaminophen overdose recover completely, whether or not they develop acetaminophen hepatotoxicity.[9] Overall survival for patients with acetaminophen hepatotoxicity is 78% to 80%, better than 80% if NAC is given within 12 hours after ingestion, but only 48% if NAC is not administered.[67] Patients who did not fulfill the KCH criteria had a survival rate of 90% to 93%.[61,67] The overall mortality is as high as 28% for patients who develop ALF, although better than comparable rates for ALF due to other causes. Reported survival rates for acetaminophen-induced ALF are 65% to 73% without liver transplantation.[3,18]

Many factors affect survival and the development of ALF after acetaminophen overdose. Patients who sought medical care within 24 hours of ingestion had significantly better survival compared with later presentation. With established ALF, patients with hepatic encephalopathy grade $\leq$II had survival better than 95%; survival decreases as the level of encephalopathy increases.[67] Pediatric patients with ALF had 100% survival with grade $\leq$II, but only 18% with grade $\geq$ III; the development of cerebral edema reduced survival to 22%.[66,67] Patients requiring inotropic support had poorer survival, and patients with metabolic acidosis that failed to respond to adequate fluid resuscitation had overall survival below 10%.[5] Serum creatinine concentrations and PT had close correlation with survival. A peak PT below 90 seconds predicted survival of 80%, falling to 8% for PT beyond 180 seconds.[68] Overall survival was 65% for patients with serum creatinine below 100 μmol/L, decreasing to 23% if above 300 μmol/L.[60]

Acetaminophen-induced ALF was less likely to require liver transplantation than ALF due to other causes,[19] with only 6% to 8% of patients receiving liver transplantation.[3,18,61] More than half of patients who fulfill transplant criteria are not listed because of significant alcohol or drug abuse history, psychiatric disorders, or untreatable sepsis, hypotension, or cerebral edema.[67] Many patients will improve with medical management alone, even when criteria for transplantation are fulfilled.[61] The overall survival rate after liver transplantation approaches 70%, with 1-year survival of 73% at 1 year and 67% at 5 years in one recent study. Most deaths after transplantation are due to sepsis, multiorgan failure, and neurologic complications.[58]

SUMMARY

Acetaminophen is a safe over-the-counter drug for pain relief and fever reduction but is a rare cause of hepatotoxicity and ALF if taken in toxic doses. Depletion of hepatocyte glutathione and accumulation of the toxic metabolite NAPQI are widely accepted as the mechanisms of acetaminophen toxicity. NAPQI can form covalent bonds to cellular macromolecules, affecting the general function of the cell and leading to liver damage. Newer hypotheses of the mechanism of toxicity include mitochondrial dysfunction from aberrant covalent bonds between acetaminophen and mitochondrial proteins and inflammatory hepatocyte damage from an innate immune response to the foreign protein. Currently acetaminophen is the most common drug to cause death from toxic ingestion and the most common cause of ALF in both United States and United Kingdom. Although many acetaminophen overdoses are intentional, an increasing number of cases in the United States are unintentional. Initial symptoms of acetaminophen hepatotoxicity may be vague gastrointestinal disturbances, with diagnostic suspicion raised by marked elevation of serum transaminase levels. NAC is the single most effective treatment to prevent further liver damage. Hepatotoxicity may progress to ALF and require meticulous intensive care support to prevent rapid and irreversible deterioration. KCH criteria may be helpful in determining which patients need liver transplantation. Acetaminophen-induced ALF has the highest rate of spontaneous recovery compared with other causes, and few patients require liver transplantation. For patients that do not recover, liver transplantation is currently the only therapy that will significantly increase rates of survival.

REFERENCES

1. Lee WM. Acute liver failure. *N Engl J Med*. 1993;329:1862–1872.
2. Hoofnagle JH, Carithers RL, Shapiro C, et al. Fulminant hepatic failure: summary of a workshop. *Hepatology*. 1995;21:240–252.
3. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology*. 2005;42:1364–1372.
4. Black M. Acetaminophen hepatotoxicity. *Gastroenterology*. 1980;78:382–392.
5. Makin AJ, Williams R. Acetaminophen-induced hepatotoxicity: predisposing factors and treatments. *Adv Intern Med*. 1997;42:453–483.
6. Lee WM. Acetaminophen and the U.S. Acute Liver Failure Study Group: lowering the risks of hepatic failure. *Hepatology*. 2004;40:6–9.
7. Lee WM. Drug-induced hepatotoxicity. *N Engl J Med*. 1995;333:1118–1127.
8. Dargan PI, Jones AL. Acetaminophen poisoning: an update for the intensivist. *Crit Care*. 2002;6:108–110.
9. Larson AM. Acetaminophen hepatotoxicity. *Clin Liver Dis*. 2007;11:525–548.
10. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. *J Toxicol Clin Toxicol*. 2002;40:3–20.
11. Nelson SD. Molecular mechanisms of the hepatotoxicity caused by acetaminophen. *Semin Liver Dis*. 1990;10:267–278.
12. Jaeschke H, Bajt ML. Intracellular signaling mechanisms of acetaminophen-induced liver cell death. *Toxicol Sci*. 2006;89:31–41.
13. Jaeschke H, Knight TR, Bajt ML. The role of oxidant stress and reactive nitrogen species in acetaminophen hepatotoxicity. *Toxicol Lett*. 2003;144:279–288.
14. Liu ZX, Kaplowitz N. Role of innate immunity in acetaminophen-induced hepatotoxicity. *Expert Opin Drug Metab Toxicol*. 2006;2:493–503.
15. Nourjah P, Ahmad SR, Karwoski C, et al. Estimates of acetaminophen (Paracetamol)-associated overdoses in the United States. *Pharmacoepidemiol Drug Safety*. 2006;15:398–405.
16. Bernal W. Changing patterns of causation and the use of transplantation in the United Kingdom. *Semin Liver Dis*. 2003;23:227–237.
17. Lee WM. Acute liver failure in the United States. *Semin Liver Dis*. 2003;23:217–226.
18. Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*. 2002;137:947–954.
19. Bower WA, Johns M, Margolis HS, et al. Population-based surveillance for acute liver failure. *Am J Gastroenterol*. 2007;102:2459–2463.

20. Squires RH, Shneider BL, Bucuvalas J, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr*. 2006;148:652–658.
21. Schiødt FV, Rochling FA, Casey DL, et al. Acetaminophen toxicity in an urban county hospital. *N Engl J Med*. 1997;337: 1112–1117.
22. Davern TJ II, James LP, Hinson JA, et al. Measurement of serum acetaminophen-protein adducts in patients with acute liver failure. *Gastroenterology*. 2006;130:687–694.
23. James LP, Alonso EM, Hynan LS, et al. Detection of acetaminophen protein adducts in children with acute liver failure of indeterminate cause. *Pediatrics*. 2006;118:e676–e681.
24. Schmidt LE. Age and paracetamol self-poisoning. *Gut*. 2005;54:686–690.
25. Bray GP, Harrison PM, O'Grady JG, et al. Long-term anticonvulsant therapy worsens outcome in paracetamol-induced fulminant hepatic failure. *Hum Exp Toxicol*. 1992;11:265–270.
26. Whitcomb DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. *JAMA*. 1994;272:1845–1850.
27. Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. *Hepatology*. 1995;22: 767–773.
28. Rumack BH. Acetaminophen misconceptions. *Hepatology*. 2004;40:10–15.
29. Kuffner EK, Dart RC, Bogdan GM, et al. Effect of maximal daily doses of acetaminophen on the liver of alcoholic patients: a randomized, double-blind, placebo-controlled trial. *Arch Intern Med*. 2001;161:2247–2252.
30. Salgia AD, Kosnik SD. When acetaminophen use becomes toxic. Treating acute accidental and intentional overdose. *Postgrad Med*. 1999;105:81–84, 87, 90.
31. Jones AF, Harvey JM, Vale JA. Hypophosphataemia and phosphaturia in paracetamol poisoning. *Lancet*. 1989;2:608–609.
32. Harrison PM, Wendon JA, Gimson AE, et al. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. *N Engl J Med*. 1991;324:1852–1857.
33. Han MK, Hyzy R. Advances in critical care management of hepatic failure and insufficiency. *Crit Care Med*. 2006;34: S225–S231.
34. O'Grady JG. Paracetamol-induced acute liver failure: prevention and management. *J Hepatol*. 1997;26(suppl 1):41–46.
35. Clark R, Borirakchanyavat V, Gazzard BG, et al. Disordered hemostasis in liver damage from paracetamol overdose. *Gastroenterology*. 1973;65:788–795.
36. Polson J, Lee WM; American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. *Hepatology*. 2005;41:1179–1197.
37. McClain CJ, Price S, Barve S, et al. Acetaminophen hepatotoxicity: an update. *Curr Gastroenterol Rep*. 1999;1:42–49.
38. Brok J, Buckley N, Gluud C. Interventions for paracetamol (acetaminophen) overdose. *Cochrane Database Syst Rev*. 2006; CD003328.
39. Underhill TJ, Greene MK, Dove AF. A comparison of the efficacy of gastric lavage, ipecacuanha and activated charcoal in the emergency management of paracetamol overdose. *Arch Emerg Med*. 1990;7:148–154.
40. Burkhart KK, Janco N, Kulig KW, et al. Cimetidine as adjunctive treatment for acetaminophen overdose. *Hum Exp Toxicol*. 1995;14:299–304.
41. Smilkstein MJ, Knapp GL, Kulig KW, et al. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). *N Engl J Med*. 1988;319:1557–1562.
42. Kozer E, Koren G. Management of paracetamol overdose: current controversies. *Drug Safety*. 2001;24:503–512.
43. Prescott LF, Illingworth RN, Critchley JA, et al. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. *Br Med J*. 1979;2:1097–1100.
44. Prescott LF. Treatment of severe acetaminophen poisoning with intravenous acetylcysteine. *Arch Intern Med*. 1981;141:386–389.
45. Rumack BH, Peterson RC, Koch GG, et al. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. *Arch Intern Med*. 1981;141:380–385.
46. Harrison PM, Keays R, Bray GP, et al. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. *Lancet*. 1990;335:1572–1573.
47. Keays R, Harrison PM, Wendon JA, et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *BMJ*. 1991;303:1026–1029.
48. Rowden AK, Norvell J, Eldridge DL, et al. Updates on acetaminophen toxicity. *Med Clin North Am*. 2005;89:1145–1159.
49. Schmidt LE, Knudsen TT, Dalhoff K, et al. Effect of acetylcysteine on prothrombin index in paracetamol poisoning without hepatocellular injury. *Lancet*. 2002;360:1151–1152.
50. Pol S, Lebray P. N-acetylcysteine for paracetamol poisoning: effect on prothrombin. *Lancet*. 2002;360:1115.
51. Rinella ME, Sanyal A. Intensive management of hepatic failure. *Semin Respir Crit Care Med*. 2006;27:241–261.
52. Stravitz RT, Kramer AH, Davern T, et al. Intensive care of patients with acute liver failure: recommendations of the U.S. Acute Liver Failure Study Group. *Crit Care Med*. 2007;35: 2498–2508.
53. Demetriou AA, Brown RS Jr, Busuttil RW, et al. Prospective, randomized, multicenter, controlled trial of a bioartificial liver in treating acute liver failure. *Ann Surg*. 2004;239:660–667.
54. Barshes NR, Gay AN, Williams B, et al. Support for the acutely failing liver: a comprehensive review of historic and contemporary strategies. *J Am Coll Surg*. 2005;201:458–476.
55. Doria C, Mandalá L, Scott VL, et al. Fulminant hepatic failure bridged to liver transplantation with a molecular adsorbent recirculating system: a single-center experience. *Dig Dis Sci*. 2006;51:47–53.
56. Wai CT, Lim SG, Aung MO, et al. MARS: a futile tool in centres without active liver transplant support. *Liver Int*. 2007;27:69–75.
57. Sullivan MG. Early data suggests merits of liver assist device. *Am Coll Surg: Surg News*. 2008;4:19.
58. Farmer DG, Anselmo DM, Ghobrial RM, et al. Liver transplantation for fulminant hepatic failure: experience with more than 200 patients over a 17-year period. *Ann Surg*. 2003;237:666–675.
59. Russo MW, Galanko JA, Shrestha R, et al. Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transplantation*. 2004;10:1018–1023.
60. O'Grady JG, Alexander GJ, Hayllar KM, et al. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology*. 1989;97:439–445.
61. Bernal W, Wendon J, Rela M, et al. Use and outcome of liver transplantation in acetaminophen-induced acute liver failure. *Hepatology*. 1998;27:1050–1055.
62. Anand AC, Nightingale P, Neuberger JM. Early indicators of prognosis in fulminant hepatic failure: an assessment of the King's criteria. *J Hepatol*. 1997;26:62–68.
63. Bernal W, Donaldson N, Wyncoll D, et al. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. *Lancet*. 2002;359:558–563.
64. Bailey B, Amre DK, Gaudreault P. Fulminant hepatic failure secondary to acetaminophen poisoning: a systematic review and meta-analysis of prognostic criteria determining the need for liver transplantation. *Crit Care Med*. 2003;31:299–305.
65. Schmidt LE, Larsen FS. Prognostic implications of hyperlactatemia, multiple organ failure, and systemic inflammatory response syndrome in patients with acetaminophen-induced acute liver failure. *Crit Care Med*. 2006;34:337–343.
66. Mahadevan SB, McKiernan PJ, Davies P, et al. Paracetamol induced hepatotoxicity. *Arch Dis Child*. 2006;91:598–603.
67. Makin AJ, Wendon J, Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987-1993). *Gastroenterology*. 1995;109:1907–1916.
68. Harrison PM, O'Grady JG, Keays RT, et al. Serial prothrombin time as prognostic indicator in paracetamol induced fulminant hepatic failure. *BMJ*. 1990;301:964–966.

