A guide to managing acute liver failure

ABSTRACT

Nearly 2,000 cases of acute liver failure occur each year in the United States. This disease carries a high mortality rate, and early recognition and transfer to a tertiary medical care center with transplant facilities is critical. This article reviews the definition, epidemiology, etiology, and management of acute liver failure.

KEY POINTS

In the United States, the most common cause of acute liver failure is acetaminophen toxicity, followed by viral hepatitis.

Testing for the cause of acute liver failure needs to start as soon as possible so that specific treatment can be initiated and the patient can be placed on the transplant list if needed.

Acetylcysteine and either a proton pump inhibitor or a histamine H₂ receptor blocker should be given to all patients with acute liver failure. Liver transplant is the cornerstone of therapy in patients not responding to other treatments.

There are a number of prognostic scores for acute liver failure, but each has limitations.

DEFINITIONS

Acute liver failure is defined as a syndrome of acute hepatitis with evidence of abnormal coagulation (eg, an international normalized ratio > 1.5) complicated by the development of mental alteration (encephalopathy) within 26 weeks of the onset of illness in a patient without a history of liver disease. In general, patients have no evidence of underlying chronic liver disease, but there are exceptions; patients with Wilson disease, vertically acquired hepatitis B virus infection, or autoimmune hepatitis can present with acute liver failure superimposed on chronic liver disease or even cirrhosis.

The term acute liver failure has replaced older terms such as fulminant hepatic failure, hyperacute liver failure, and subacute liver failure, which were used for prognostic purposes. Patients with hyperacute liver failure (defined as development of encephalopathy within 7 days of onset of illness) generally have a good prognosis with medical management, whereas those with subacute liver failure (defined as development of encephalopathy within 5 to 26 weeks of onset of illness) have a poor prognosis without liver transplant.
NEARLY 2,000 CASES A YEAR

There are nearly 2,000 cases of acute liver failure each year in the United States, and it accounts for 6% of all deaths due to liver disease. It is more common in women than in men, and more common in white people than in other races. The peak incidence is at a fairly young age, ie, 35 to 45 years.

CAUSES

The most common cause of acute liver failure in the United States and other Western countries is acetaminophen toxicity, followed by viral hepatitis. In contrast, viral hepatitis is the most common cause in developing countries.

Acetaminophen toxicity

Patients with acetaminophen-induced liver failure tend to be younger than other patients with acute liver failure. Nearly half of them present after intentionally taking a single large dose, while the rest present with unintentional toxicity while taking acetaminophen for pain relief on a long-term basis and ingesting more than the recommended dose.

After ingestion, 52% to 57% of acetaminophen is converted to glucuronide conjugates, and 30% to 44% is converted to sulfate conjugates. These compounds are nontoxic, water-soluble, and rapidly excreted in the urine.

However, glutathione can become depleted after large doses of acetaminophen or in malnourished people, allowing this toxic metabolite to accumulate.

metabolism through this pathway.

Metabolism of acetaminophen through the cytochrome P450 pathway results in production of N-acetyl-p-benzoquinone imine (NAPQI), the compound that damages the liver. NAPQI is rendered nontoxic by binding to glutathione, forming NAPQI-glutathione adducts. Glutathione capacity is limited, however. With too much acetaminophen, glutathione becomes depleted and NAPQI accumulates, binds with proteins to form adducts, and leads to necrosis of hepatocytes (Figure 1).9,10

Acetylcysteine, used in treating acetaminophen toxicity, is a substrate for glutathione synthesis and ultimately increases the amount of glutathione available to bind NAPQI and prevent damage to hepatocytes.11

Acetaminophen is a dose-related toxin. Most ingestions leading to acute liver failure exceed 10 g/day (> 150 mg/kg/day). Moderate chronic ingestion, eg, 4 g/day, usually leads to transient mild elevation of liver enzymes in healthy individuals12 but can in rare cases cause acute liver failure.13

Whitcomb and Block14 retrospectively identified 49 patients who presented with acetaminophen-induced hepatotoxicity in 1987 through 1993; 21 (43%) had been taking acetaminophen for therapeutic purposes. All 49 patients took more than the recommended limit of 4 g/day, many of them while fasting and some while using alcohol. Acute liver failure was seen with ingestion of more than 12 g/day—or more than 10 g/day in alcohol users. The authors attributed the increased risk to activation of cytochrome P450 2E1 by alcohol and depletion of glutathione stores by starvation or alcohol abuse.

Advice to patients taking acetaminophen is given in Table 1.

Other drugs and supplements
A number of other drugs and herbal supplements can also cause acute liver failure (Table 2), the most common being antimicrobial and antiepileptic drugs.15 Of the antimicrobials, antitubercular drugs (especially isoniazid) are believed to be the most common causes, followed by trimethoprim-sulfamethoxazole. Phenytoin is the antiepileptic drug most often implicated in acute liver failure.

Statins can also cause acute liver failure, especially when combined with other hepatotoxic agents.16

The herbal supplements and weight-loss agents Hydroxycut and Herbalife have both been reported to cause acute liver failure, with patients presenting with either the hepatocellular or the cholestatic pattern of liver injury.17 The exact chemical in these supplements that causes liver injury has not yet been determined.

Acetylcysteine is the main drug used for treating acetaminophen toxicity

Viral hepatitis
Hepatitis B virus is the most common viral cause of acute liver failure and is responsible for about 8% of cases.18

Patients with chronic hepatitis B virus infection—as evidenced by positive hepatitis B surface antigen—can develop acute liver failure if the infection is reactivated by the use of immunosuppressive drugs for solid-organ or bone-marrow transplant or medications such as anti-tumor necrosis agents, rituximab, or chemotherapy. These patients should be treated prophylactically with a nucleoside analogue, which should be continued for 6 months after immunosuppressive therapy is completed.

Hepatitis A virus is responsible for about 4% of cases.18

**TABLE 1**

**Advice to patients taking acetaminophen**

Acetaminophen is used to treat pain and fever. Overall, it is safe, but if you take too much (more than 4,000 mg per day), it can damage the liver. If you are taking it, please do the following:

Read the label. Many medicines contain acetaminophen, so you could be taking too much without knowing.

Don’t drink. Drinking alcohol increases the likelihood of acetaminophen-induced liver toxicity.

Get help. If you or your child may have taken too much acetaminophen, call the American Association of Poison Control Centers hotline at 1-800-222-1222 right away.

Keep acetaminophen (and all drugs) out of the hands of children.

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Hepatitis C virus rarely causes acute liver failure, especially in the absence of hepatitis A and hepatitis B.\textsuperscript{3,19}

Hepatitis E virus, which is endemic in areas of Asia and Africa, can cause liver disease in pregnant women and in young adults who have concomitant liver disease from another cause. It tends to cause acute liver failure more frequently in pregnant women than in the rest of the population and carries a mortality rate of more than 20% in this subgroup.

TT (transfusion-transmitted) virus was reported in the 1990s to cause acute liver failure in about 27\% of patients in whom no other cause could be found.\textsuperscript{20}

Other rare viral causes of acute liver failure include Epstein-Barr virus, cytomegalovirus, and herpes simplex virus types 1, 2, and 6.\textsuperscript{6}

### Specific Causes

Other causes of acute liver failure include ischemic hepatitis, autoimmune hepatitis, Wilson disease, Budd-Chiari syndrome, and HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome.

#### Many Patients Need Liver Transplant

Many patients with acute liver failure ultimately require orthotopic liver transplant,\textsuperscript{21} especially if they present with severe encephalopathy. Other aspects of treatment vary according to the cause of liver failure (Table 3).

#### Specific Management

**Management of acetaminophen toxicity**

If the time of ingestion is known, checking the acetaminophen level can help determine the cause of acute liver failure and also predict the risk of hepatotoxicity, based on the work of Rumack and Matthew.\textsuperscript{22} Calculators are available, eg, [http://reference.medscape.com/calculator/acetaminophen-toxicity](http://reference.medscape.com/calculator/acetaminophen-toxicity).

If a patient presents with acute liver failure several days after ingesting acetaminophen, the level can be in the nontoxic range, however. In this scenario, measuring acetaminophen-protein adducts can help establish acetaminophen toxicity as the cause, as the adducts last longer in the serum and provide 100\% sensitivity and specificity.\textsuperscript{23} While most laboratories can rapidly measure acetaminophen levels, only a few can measure acetaminophen-protein adducts, and thus this test is not used clinically.

Acetylcysteine is the main drug used for acetaminophen toxicity. Ideally, it should be given within 8 hours of acetaminophen ingestion, but giving it later is also useful.\textsuperscript{1}

Acetylcysteine is available in oral and intravenous forms, the latter for patients who have encephalopathy or cannot tolerate oral intake due to repeated episodes of vomiting.\textsuperscript{24,25} The oral form is much less costly and is thus preferred over intravenous acetylcysteine in patients who can tolerate oral intake. Intravenous acetylcysteine should be given in a loading dose of 150 mg/kg in 5\% dextrose over 15 minutes, followed by a maintenance dose of 50 mg/kg over 4 hours and then 100 mg/kg given over 16 hours.\textsuperscript{1} No dose adjustment is needed in patients who have renal toxicity (acetaminophen can also be toxic to the kidneys).

#### Table 2

**Mechanism of toxicity of drugs and herbal supplements known to cause acute liver failure**

<table>
<thead>
<tr>
<th>Drug or supplement</th>
<th>Pattern of injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbinafine</td>
<td>Cholestatic and mixed</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Cholestatic or mixed</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Cholestatic or mixed</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Hepatocellular</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Hepatocellular, cholestatic, or mixed</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Hepatocellular</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Hepatocellular, cholestatic, or mixed</td>
</tr>
<tr>
<td>Herbalife</td>
<td>Hepatocellular</td>
</tr>
<tr>
<td>Hydroxycut</td>
<td>Hepatocellular, cholestatic, or mixed</td>
</tr>
<tr>
<td>Kava kava</td>
<td>Hepatocellular</td>
</tr>
<tr>
<td>OxyElite Pro</td>
<td>Hepatocellular</td>
</tr>
</tbody>
</table>

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Most patients with acetaminophen-induced liver failure survive with medical management alone and do not need a liver transplant. Cirrhosis does not occur in these patients.

**Management of viral acute liver failure**
When patients present with acute liver failure, it is necessary to look for a viral cause by serologic testing, including hepatitis A virus IgM antibody, hepatitis B surface antigen, and hepatitis B core IgM antibody.

Hepatitis B can become reactivated in immunocompromised patients, and therefore the hepatitis B virus DNA level should be checked. Detection of hepatitis B virus DNA in a patient previously known to have undetectable hepatitis B virus DNA confirms hepatitis B reactivation.

Patients with hepatitis B-induced acute liver failure should be treated with entecavir or tenofovir. Although this treatment may not change the course of acute liver failure or accelerate the recovery, it can prevent reinfection in the transplanted liver if liver transplant becomes indicated.

Herpes simplex virus should be suspected in patients presenting with anicteric hepatitis with fever. Polymerase chain reaction testing for herpes simplex virus should be done and if positive, patients should be given intravenous acyclovir. Despite treatment, herpes simplex virus disease is associated with a very poor prognosis without liver transplant.

**Autoimmune hepatitis**
The autoantibodies usually seen in autoimmune hepatitis are antinuclear antibody, antismooth muscle antibody, and anti-liver-kidney microsomal antibody, and patients need to be tested for them.

The diagnosis of autoimmune hepatitis can be challenging, as these autoimmune markers can be negative in 5% of patients. Liver biopsy becomes essential to establish the diagnosis in that setting.

Guidelines advise starting prednisone 40 to 60 mg/day and placing the patient on the liver transplant list.

**Wilson disease**
Although it is an uncommon cause of liver failure, Wilson disease needs special attention because it has a poor prognosis. The mortality rate in acute liver failure from Wilson disease reaches 100% without liver transplant.

Wilson disease is caused by a genetic defect that allows copper to accumulate in the liver and other organs. However, diagnosing Wilson disease as the cause of acute liver failure can be challenging because elevated serum and urine copper levels are not specific to Wilson disease and can be seen in patients with acute liver failure from any cause. In addition, the ceruloplasmin level is usually normal or high because it is an acute-phase reactant. Accumulation of copper in the liver parenchyma is usually patchy; therefore, qualitative copper staining on random liver biopsy samples provides low diagnostic yield. Quantitative copper on liver biopsy is the gold standard test to establish the diagnosis, but the test is time-consuming. Kayser-Fleischer rings around the iris are considered pathognomonic for Wilson disease when seen with acute liver failure, but

**TABLE 3**

<table>
<thead>
<tr>
<th>Management of acute liver failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer the patient to the intensive care unit in a tertiary care center with facilities for liver transplant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurologic complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2–3 encephalopathy: order computed tomography of the brain to rule out secondary causes of encephalopathy; avoid hyponatremia and use of sedatives</td>
</tr>
<tr>
<td>Grade 3–4 encephalopathy: intubate; elevate the head end of bed to 30 degrees; consider giving mannitol or hypertonic saline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infectious complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Give a broad-spectrum antibiotic if infection is suspected, and add an antifungal agent if there is no improvement with initial antibiotic coverage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Give a histamine H₂ receptor blocker or a proton pump inhibitor to prevent upper gastrointestinal bleeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Determining the cause of acute liver failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain a thorough history of ingestion of drugs from the patient and family</td>
</tr>
</tbody>
</table>

| Laboratory testing, including toxicology screen, acetaminophen or acetaminophen-protein adduct levels; serologic testing for hepatitis A, hepatitis B, hepatitis C, herpes simplex virus, autoimmune hepatitis, and serum and urine copper and serum ceruloplasmin levels |
ACUTE LIVER FAILURE

Clinical features of acute liver failure

Cerebral edema due to elevated intracranial pressure

High-output cardiac failure

Hypoglycemia, lactic acidosis, coagulopathy

Pancreatitis, particularly in acetaminophen-induced acute liver failure

Acute respiratory distress syndrome

Upper gastrointestinal bleeding from stress-related ulcers and coagulopathy

Hypoadrenalism: lack of glucocorticoid and mineralocorticoid production

Acute kidney injury

Infectious diseases from impaired leukocyte function

FIGURE 2.

they are seen in only about 50% of patients.33

A unique feature of acute Wilson disease is that most patients have very high bilirubin levels and low alkaline phosphatase levels. An alkaline phosphatase-to-bilirubin ratio less than 2 in patients with acute liver failure is highly suggestive of Wilson disease.34

Another clue to the diagnosis is that patients with Wilson disease tend to develop Coombs-negative hemolytic anemia, which leads to a disproportionate elevation in aminotransferase levels, with aspartate aminotransferase being higher than alanine aminotransferase.

Once Wilson disease is suspected, the patient should be listed for liver transplant because death is almost certain without it. For patients awaiting liver transplant, the American Association for the Study of Liver Diseases guidelines recommend certain measures to lower the serum copper level such as albumin dialysis, continuous hemofiltration, plasmapheresis, and plasma exchange, but the evidence supporting their use is limited.

NONSPECIFIC MANAGEMENT

Acute liver failure can affect a number of organs and systems in addition to the liver (Figure 2).

General considerations

Because their condition can rapidly deteriorate, patients with acute liver failure are best managed in intensive care.

Patients who present to a center that does not have the facilities for liver transplant should be transferred to a transplant center as soon as possible, preferably by air. If the patient may not be able to protect the airway, endotracheal intubation should be performed before transfer.

The major causes of death in patients with acute liver failure are cerebral edema and in-
fection. Gastrointestinal bleeding was a major cause of death in the past, but with prophylactic use of histamine H₂ receptor blockers and proton pump inhibitors, the incidence of gastrointestinal bleeding has been significantly reduced.

Although initially used only in patients with acetaminophen-induced liver failure, acetylcysteine has also shown benefit in patients with acute liver failure from other causes. In patients with grade 1 or 2 encephalopathy on a scale of 0 (minimal) to 4 (comatose), the transplant-free survival rate is higher when acetylcysteine is given compared with placebo, but this benefit does not extend to patients with a higher grade of encephalopathy.35

Cerebral edema and intracranial hypertension

Cerebral edema is the leading cause of death in patients with acute liver failure, and it develops in nearly 40% of patients.36

The mechanism by which cerebral edema develops is not well understood. Some have proposed that ammonia is converted to glutamine, which causes cerebral edema either directly by its osmotic effect37,38 or indirectly by decreasing other osmolytes, thereby promoting water retention.39

Cerebral edema leads to intracranial hypertension, which can ultimately cause cerebral herniation and death. Because of the high mortality rate associated with cerebral edema, invasive devices were extensively used in the past to monitor intracranial pressure. However, in light of known complications of these devices, including bleeding,40 and lack of evidence of long-term benefit in terms of mortality rates, their use has come under debate.

Treatments. Many treatments are available for cerebral edema and intracranial hypertension. The first step is to elevate the head of the bed about 30 degrees. In addition, hyponatremia should be corrected, as it can worsen cerebral edema.41 If patients are intubated, maintaining a hypercapneic state is advisable to decrease the intracranial pressure.

Of the two pharmacologic options, mannitol is more often used.42 It is given as a bolus dose of 0.5 to 1 g/kg intravenously if the serum osmolality is less than 320 mOsm/L.1 Given the risk of fluid overload with mannitol, caution must be exercised in patients with renal dysfunction. The other pharmacologic option is 3% hypertonic saline.

Therapeutic hypothermia is a newer treatment for cerebral edema. Lowering the body temperature to 32 to 33°C (89.6 to 91.4°F) using cooling blankets decreases intracranial pressure and cerebral blood flow and improves the cerebral perfusion pressure.43 With this treatment, patients should be closely monitored for side effects of infection, coagulopathy, and cardiac arrhythmias.1

L-ornithine L-aspartate was successfully used to prevent brain edema in rats, but in humans, no benefit was seen compared with placebo.44,45 The underlying basis for this experimental treatment is that supplemental ornithine and aspartate should increase glutamate synthesis, which should increase the activity of enzyme glutamine synthetase in skeletal muscles. With the increase in enzyme activity, conversion of ammonia to glutamine should increase, thereby decreasing ammonia circulation and thus decreasing cerebral edema.

Patients with cerebral edema have a high incidence of seizures, but prophylactic antiseizure medications such as phenytoin have not been proven to be beneficial.46

Infection

Nearly 80% of patients with acute liver failure develop an infectious complication, which can be attributed to a state of immunodeficiency.47 The respiratory and urinary tracts are the most common sources of infection.48 In patients with bacteremia, Enterococcus species and coagulase-negative Staphylococcus species are the commonly isolated organisms. Also, in patients with acute liver failure, fungal infections account for 30% of all infections.50

Infected patients often develop worsening of their encephalopathy51 without fever or elevated white blood cell count.49,52 Thus, in any patient in whom encephalopathy is worsening, an evaluation must be done to rule out infection. In these patients, systemic inflammatory response syndrome is an independent risk factor for death.53

Despite the high mortality rate with infection, whether using antibiotics prophylactically in acute liver failure is beneficial is controversial.54,55

Drinking and fasting increase the risk of acetaminophen overdose

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ACUTE LIVER FAILURE

Gastrointestinal bleeding

The current prevalence of upper gastrointestinal bleeding in acute liver failure patients is about 1.5%. Coagulopathy and endotracheal intubation are the main risk factors for upper gastrointestinal bleeding in these patients. The most common source of bleeding is stress ulcers in the stomach. The ulcers develop from a combination of factors, including decreased blood flow to the mucosa causing ischemia and hypoperfusion-reperfusion injury.

Pharmacologic inhibition of gastric acid secretion has been shown to reduce upper gastrointestinal bleeding in acute liver failure. A histamine H₂ receptor blocker or proton pump inhibitor should be given to prevent gastrointestinal bleeding in patients with acute liver failure.

EXPERIMENTAL TREATMENTS

Artificial liver support systems

Membranes and dialysate solutions have been developed to remove toxic substances that are normally metabolized by the liver. Two of these—the molecular adsorbent recycling system (MARS) and the extracorporeal liver assist device (ELAD)—were developed in the late 1990s. MARS consisted of a highly permeable hollow fiber membrane mixed with albumin, and ELAD consisted of porcine hepatocytes attached to microcarriers in the extracapillary space of the hollow fiber membrane. Both systems allowed for transfer of water-soluble and protein-bound toxins in the blood across the membrane and into the dialysate. The clinical benefit offered by these devices is controversial, thus limiting their use to experimental purposes only.

Hepatocyte transplant

Use of hepatocyte transplant as a bridge to liver transplant was tested in 1970s, first in rats and later in humans. By reducing the blood ammonia level and improving cerebral perfusion pressure and cardiac function, replacement of 1% to 2% of the total liver cell mass by transplanted hepatocytes acts as a bridge to orthotopic liver transplant.

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Prognostic scores of acute liver failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>King's College criteria</td>
</tr>
<tr>
<td>Age</td>
<td>Yes</td>
</tr>
<tr>
<td>Cause of acute liver failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Presence of encephalopathy</td>
<td>Yes</td>
</tr>
<tr>
<td>Presence of coagulopathy</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum bilirubin level</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum creatinine level</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Sensitivity** to predict poor outcome without liver transplant
- Acetaminophen-induced acute liver failure: 69%
- Acute liver failure from other causes: 68%

**Specificity** to predict poor outcome without liver transplant
- Acetaminophen-induced acute liver failure: 82%
- Acute liver failure from other causes: 92%

APACHE II = Acute Physiology and Chronic Health Evaluation II; MELD = Model for End-State Liver Disease.
PROGNOSIS

Different criteria have been used to identify patients with poor prognosis who may eventually need to undergo liver transplant.

The King’s College criteria system is the most commonly used for prognosis (Table 4). Its main drawback is that it is applicable only in patients with encephalopathy, and when patients reach this stage, their condition often deteriorates rapidly, and they die while awaiting liver transplant.37,66,67

The Model for End-Stage Liver Disease (MELD) score is an alternative to the King’s College criteria. A high MELD score on admission signifies advanced disease, and patients with a high MELD score tend to have a worse prognosis than those with a low score.68

The Acute Physiology and Chronic Health Evaluation (APACHE) II score can also be used, as it is more sensitive than the King’s College criteria.6

The Clichy criteria can also be used.

Liver biopsy. In addition to helping establish the cause of acute liver failure, liver biopsy can also be used as a prognostic tool. Hepatocellular necrosis greater than 70% on the biopsy predicts death with a specificity of 90% and a sensitivity of 56%.70

Hypophosphatemia has been reported to indicate recovering liver function in patients with acute liver failure.71 As the liver regenerates, its energy requirement increases. To supply the energy, adenosine triphosphate production increases, and phosphorus shifts from the extracellular to the intracellular compartment to meet the need for extra phosphorus during this process. A serum phosphorus level of 2.9 mg/dL or higher appears to indicate a poor prognosis in patients with acute liver failure, as it signifies that adequate hepatocyte regeneration is not occurring.

REFERENCES

28. Yu JW, Sun LJ, Yan BZ, Kang P, Zhao YH. Lamivudine treatment is as-


