

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Highlights From the ACG Guidelines for Acute Liver Failure



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### G&H Why were guidelines recently released for acute liver failure?

**AS** The previous North American guidelines on acute liver failure had been released over a decade ago from the American Association for the Study of Liver Diseases, so there was a need to review the updated literature on this disease since then. The goal was to incorporate recent advances in the medical field and how they relate to the management of acute liver failure. A group from the American College of Gastroenterology (ACG) reviewed scientific evidence using the Grading of Recommendations, Assessment, Development and Evaluation process to develop recommendations. These acute liver failure guidelines were published in the July 2023 issue of the *American Journal of Gastroenterology*, and I was lucky enough to be the first author of this publication.

### G&H According to the ACG guidelines, what is the definition of acute liver failure?

**AS** The definition of acute liver failure includes the development of acute liver injury that produces hepatic dysfunction, usually defined by an international normalized ratio of greater than 1.5 and the development of hepatic encephalopathy. The timeline of the liver injury development is important, as less than 26 weeks has been proposed as a cutoff, which helps to differentiate acute liver failure from a number of other liver diseases.

### G&H Why is acute alcoholic hepatitis not counted as liver failure?

**AS** Acute liver failure usually has a very grave prognosis with high 7-day mortality rates without liver transplantation. Although alcoholic hepatitis can cause acute-on-

chronic liver failure, it rarely leads to rapidly progressive disease with acute cerebral edema. In addition, studies have shown that the majority of patients presenting with alcoholic hepatitis have underlying cirrhosis and thus chronic liver disease. If patients are not upfront about their alcohol use, axillary testing such as phosphatidylethanol can be used to evaluate for recent alcohol use, and a liver biopsy can sometimes help confirm the diagnosis if doubt exists.

### G&H Why is it important to differentiate acute liver injury from failure?

**AS** It is helpful to think of liver injury as a spectrum that ranges from acute liver injury to severe acute liver injury to acute liver failure. Acute liver injury usually implies acute liver inflammation, can be due to many etiologies, and has variable prognosis based on those etiologies. The majority of patients with acute liver injury will have a benign course with identifiable and treatable causes. Severe acute liver injury is defined as the presence of acute liver injury and coagulopathy, which usually develops as liver dysfunction progresses and hepatocyte necrosis ensues. If untreated or unrecognized, severe acute liver injury can progress to acute liver failure marked by the development of hepatic encephalopathy. The likelihood of recovery is higher the sooner acute liver injury is identified and treated in order to prevent progression to severe acute liver injury and ultimately acute liver failure.

### G&H How can acute liver failure be differentiated from acute-on-chronic liver failure?

**AS** This is not a straightforward issue, as many physicians frequently have trouble differentiating between

the two. The ACG guidelines include a helpful table that outlines the differences between acute liver failure and acute-on-chronic liver failure. Specifically, patients with acute-on-chronic liver failure, by definition, have a history of chronic liver disease, and they tend to be older and frequently have signs of chronic liver disease on examination (eg, spider angiomas), imaging (eg, portal hypertension), and history. On the other hand, patients with acute liver failure tend to be younger and have no history of chronic liver disease. There is some overlap in precipitating factors for acute liver failure and acute-on-chronic liver failure, including drug-induced liver injury and viral hepatitis. However, patients with acute-on-chronic liver failure usually have a presenting complaint of infection or gastrointestinal bleeding, whereas infection develops

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late in the course of acute liver failure and gastrointestinal bleeding is uncommon in that scenario. The pattern of hepatic encephalopathy is also different. Patients with acute liver failure tend to develop cerebral edema with increased intracranial pressure; this rarely occurs (although it still can) in acute-on-chronic liver failure. Also, hepatic encephalopathy in patients with acute-on-chronic liver failure responds well to traditional hepatic encephalopathy therapies such as lactulose and rifaximin. In addition, acute liver failure patients often have renal failure because of hypoperfusion and acute tubular necrosis, whereas acute-on-chronic liver failure patients tend to develop hepatorenal syndrome–acute kidney injury. Furthermore, acute respiratory distress syndrome is rare in patients with acute liver failure but is commonly seen in patients with acute-on-chronic liver failure.

#### **G&H** What are the current recommendations for the best diagnostic methods for acute liver failure?

**AS** Most important is obtaining a history of the patient's presenting illness, as this may contain key answers as to

whether it is indeed an acute presentation. The guidelines recommend a broad initial workup that encompasses investigations for common and known precipitants of acute liver failure, such as testing for drug levels/toxicology, viral hepatitis, acetaminophen levels, autoimmune markers, and Wilson disease. Abdominal imaging should be obtained promptly, ideally contrasted cross-sectional imaging, but ultrasound with Doppler is also acceptable. Broad infectious workup should also be obtained, as these patients are at high risk for infections.

#### **G&H** When do the guidelines recommend obtaining a biopsy, and which method should be used?

**AS** Unfortunately, there is not a lot of supporting evidence (which is true of most acute liver failure–related issues) to have a firm evidence-based answer. Because most patients with acute liver failure are quite coagulopathic, transjugular liver biopsy is preferred considering its lower risk profile in general. A biopsy can be obtained if it will change management of the patient (eg, in cases where infiltrative malignancy or cirrhosis is suspected). For most patients with acute liver failure, biopsy may not be required.

#### **G&H** What is the current recommendation for when patients should be referred for liver transplant?

**AS** This is one of the points that we tried to emphasize in the ACG guidelines. Patients with acute liver failure and even those with severe acute liver injury should be transferred to the transplant center as soon as possible. We recommended contacting the transplant center for guidance as early as within the first few hours of patient presentation to the emergency room because of the logistics of referral, the time that the transport may take, and the high risk of quick deterioration of these patients.

#### **G&H** What do the guidelines note about different prognostic models for liver transplant in this patient population?

**AS** In several studies, the King's College Criteria have been shown to have good sensitivity for predicting which patients are at high risk of mortality, but the specificity of these criteria may not be as good. The Model for End-Stage Liver Disease (MELD) score can be used as well; however, MELD cutoff values have varied in studies. Whichever model is used, applying it early in the patient's disease course, as well as contacting the transplant center fast, is important.

## G&H Are there any other important liver transplant recommendations in the guidelines?

**AS** The decision for acute liver failure transplant listing needs to be made quickly, and transplant centers should have protocols for expedited evaluation and waitlisting of these patients for an organ in a timely manner. Most patients listed for liver transplant for acute liver failure will receive an organ offer quite fast owing to Status 1A listing (highest priority). Living donor liver transplant for

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acute liver failure patients has been reported in the literature with noninferior outcomes. The guidelines point out that living donor liver transplant may be a possibility for acute liver failure patients who do not receive an organ offer in a timely manner, but should only be undertaken by centers with a plethora of living donor liver transplant experience and well-developed protocols for this type of transplant in patients with acute liver failure.

## G&H What are the key recommendations for system-wide management of patients with acute liver failure?

**AS** One of the key recommendations of the ACG guidelines is the initiation of continuous renal replacement therapy for the indication of significant hepatic encephalopathy and hyperammonemia in addition to traditional indications of renal failure and volume overload. There

needs to be multidisciplinary communication between hepatology, intensive care unit, and nephrology personnel. Prophylactic correction of coagulopathy is discouraged, and patients should be monitored for any evidence of infection. Some literature suggests that infectious workup should be repeated routinely in these patients, as most of them will not have symptoms in the early course of infection; however, the frequency of such workup is unclear.

## G&H Could you summarize the main recommendations for initial management of patients with acute liver failure?

**AS** There are certain management strategies that may be beneficial in acute liver failure management. For example, early initiation of N-acetylcysteine in both acetaminophen and nonacetaminophen acute liver failure may be of benefit. In addition, in patients with viral symptoms, initiation of intravenous acyclovir can be considered until results are obtained for herpes simplex virus polymerase chain reaction (usually within 24 hours).

## G&H Are any treatment strategies noted in the guidelines as requiring stronger evidence before they can be recommended?

**AS** There is not a lot of evidence supporting the use of thromboelastography in coagulopathy assessment for patients with acute liver failure, but it is likely that this evidence will emerge soon. Evidence is also lacking for prophylactic antibiotic administration.

### Disclosures

*Dr Shingina has no relevant conflicts of interest to disclose.*

### Suggested Reading

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