

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Complications of Acute Liver Failure



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G&H How is acute liver failure defined?

SM The definition of acute liver failure (ALF) has evolved. It used to be the onset of liver disease in a person who did not have evidence of chronic liver disease who developed hepatic encephalopathy within 8 weeks of the onset of disease. That was the classic definition for over 50 years. More recently, the definition has changed. It now includes symptoms of severe liver dysfunction with a duration of no more than 26 weeks developing in a person without evidence of underlying chronic liver disease. The specific manifestations of liver dysfunction must include coagulopathy and some degree of hepatic encephalopathy.

G&H What are the signs and symptoms of ALF?

SM The primary symptoms involve 1 or more of the various manifestations of hepatic encephalopathy, such as confusion, disorientation, lethargy, and, sometimes, up to profound coma. The severity of the symptoms varies considerably. The signs of ALF on physical examination may or may not include jaundice in addition to the signs of neurologic dysfunction. Importantly, by definition, there should be no signs of chronic liver disease.

G&H How common is ALF?

SM Generally, ALF is considered to be a relatively uncommon disorder. However, the frequency of this condition depends on the setting. For instance, in the community, ALF is fairly uncommon. However, physi-

cians in liver transplant centers likely would say that ALF is not uncommon because many (but not all) patients with ALF are promptly referred to centers that have a focus on liver replacement.

G&H What are the risk factors for ALF?

SM The risk factors are those associated with the various causes of ALF. For instance, residence in an area where hepatitis B virus (HBV) is endemic would be considered a risk factor for developing ALF from acute HBV infection. Other risk factors involve an etiology related to drug-induced liver disease. In fact, over 50% of ALF cases in the United States are caused by medicines that are toxic to the liver. For instance, a relatively common cause is related to acetaminophen overdose. Polypharmacy could be considered a risk factor because 1 of the medications could be harmful to the liver and eventually cause liver disease, possibly including ALF.

G&H How high is the mortality rate for ALF, and has it changed over time?

SM ALF has historically had a fairly high mortality, ranging from 60% to 80%. However, over the past 2 decades, there has been a bit of a trend to improved survival. Although this change has not been dramatic, it is commonly attributed to improvements in the general critical care provided in intensive care units (ICUs). Thus, the mortality of ALF has decreased but remains in excess of 50%, a reminder that this condition is still serious.

G&H What are the most common and serious complications of ALF?

SM If patients with ALF do not respond to general intensive medical treatment in an ICU, they often begin to experience a number of severe complications. The most common complication is infection. Bacteremia, pneumonia, urosepsis, cellulitis, and fungal infection are common, typically quite severe, and often end up becoming the immediate cause of death.

Another severe complication seen in patients with ALF is swelling of the brain, which may lead to intracranial hypertension and, ultimately, to uncal and cerebellar herniation, causing death.

The third group of complications involves multi-organ failure. If the patient's liver does not begin to regenerate soon or does not respond to treatment, or the patient does not receive a liver transplant in time, then, essentially, all of the critical body systems begin to malfunction and ultimately fail. The patient would develop cardiovascular failure, pulmonary failure, and kidney failure, ultimately leading to death.

G&H Are any complications caused by the treatment of this condition?

SM There are relatively few complications that can be directly attributed to the medical treatments of ALF. The use of intracranial transducers to continuously and directly monitor the intracranial pressures of a patient with ALF is, for instance, still a source of controversy due to the 10% to 20% rate of bleeding complications that occurs in relation to the insertion of the monitors. I believe that the risk/benefit ratio justifies the use of these monitors in patients with ALF and hepatic coma, but approximately half of all hepatologists prefer not to use intracranial monitors due to the fear of bleeding complications. Overall, I think that the main complication of the current medical therapies for ALF is that they often do not work and fail to reverse the progression of the condition.

G&H How can ALF be prevented in the first place?

SM The obvious way would be not to exceed therapeutic doses of acetaminophen both in prescribed medications and in the over-the-counter setting. The reduction of acetaminophen-related ALF would probably have a major impact on prevention and would perhaps avoid up to one-third of ALF cases in the United States. Prevention of acetaminophen-related ALF is still an unmet need and requires further educational efforts of the public and health providers alike. Secondly, it is important to make sure that patients with chronic liver disease are immunized

against hepatitis A and B; if a patient with a chronic liver condition acquires acute hepatitis A or B, ALF severity is often exacerbated.

G&H Are there ways to prevent the complications of ALF?

SM The main way to prevent complications of ALF is to implement rapid transfer of a patient suspected of having ALF to a liver center equipped with hepatologists and emergency transplant capability. This is desirable for at least the following 3 reasons: hepatology intensive therapy is specialized and often includes emergency liver transplant, these teams often care for this type of patient (who is uncommon in the community), and complications of ALF can develop and sometimes be fatal within a few hours. Physicians in the community can best help these patients by learning to recognize the early signs of a severe acute liver disease (such as hepatitis) and expeditiously transfer the patients to the nearest liver center of their choice.

G&H What are the main treatments for ALF?

SM There are 2 aspects to ALF treatment. One aspect is general and hepatologic intensive care management. Every patient with ALF needs to be in an ICU setting, not in the general medical ward, intermediate or telemetry unit, or the standard hospital room.

The second aspect is that, for a few causes of ALF, specific treatments are available. Not many causes of ALF have a specific treatment, but when a patient is identified with 1 of these disorders, the specific treatment should be considered. One example is ALF caused by acetaminophen overdose (both unintentional or suicidal) and its antidote, intravenous n-acetyl cysteine (NAC). Furthermore, relatively recent work by the US ALF Study Group has shown that NAC is also helpful in early ALF not caused by acetaminophen. This is relatively new knowledge that can be used in the community hospital while the patient is awaiting transfer to a liver center; in my opinion, there is still not sufficient awareness of this therapeutic tool. Any patient diagnosed with ALF—whether or not it is related to acetaminophen—is a potential candidate to be treated with NAC.

G&H Why is the US ALF Study Group important?

SM ALF is an uncommon condition with a very high mortality. To learn more about this condition, a consortium of academic liver centers around the country was formed approximately 20 years ago and established as the US ALF Study Group. From this entity's prospective data-

base, a large number of papers have been published from which much has been learned about ALF. Prior to this group, research on this condition consisted of relatively small numbers of patients in single centers.

G&H What are other specific treatments for ALF?

SM If the etiology of the patient's ALF is autoimmune hepatitis, then the specific treatment is to try a high dose of corticosteroids, but recent data suggest that the value of this therapy is unclear in this setting. If the cause of the ALF is cytomegalovirus, the patient would receive ganciclovir, a specific antiviral for that virus.

If ALF is caused by acute HBV, the patient could be treated with tenofovir or entecavir, potent medicines for chronic HBV. However, this is controversial because the severity of HBV-related ALF is perhaps mediated not only by direct viral toxicity but also by immune mechanisms, so these antiviral agents may not be enough to rescue the liver from shutdown.

The last specific etiology of ALF that has a specific treatment is rare variants of Budd-Chiari syndrome. This would be treated with transjugular intrahepatic portosystemic shunt stent placement.

If all of these measures fail—or the patient has progressive ALF from an etiology for which there is no treatment other than general intensive care management—the only backup treatment is emergency liver transplantation.

G&H What are the main treatment options for ALF complications?

SM As previously noted, the most common complication in most centers is infectious complications. That is the reason why patients are preemptively pancultured and many liver centers have a low threshold to start patients on broader-spectrum antibiotics and antifungal medications. It is not advisable to wait for patients to develop a fever because many of them are so ill that even if they have an infection, they might not be able to mount a febrile response. If the clinician sees that the patient's white cell count is elevated, the patient should be promptly started on antibiotics, with diligent surveillance cultures of the patient's body fluid (blood serum, urine, and sputum) obtained to try to detect any infection very early. This is the policy in many liver centers, given the lack of evidence-based data to determine exactly when and how to use prophylactic antibiotics.

The second most common complication is brain swelling. After 2 decades of study, this is still a controversial area of management, with hepatologists approximately evenly divided into 2 groups. One group—which I side with—believes in implanting a transducer in the skull of

the patient to have a direct, continuous reading of intracranial pressure and then uses medications and various maneuvers to treat any increases in intracranial pressure. The other group believes that there is not enough evidence to support this treatment and that the risks of implanting a monitor in the skull are greater than the potential benefits. These physicians, therefore, do not use transducers but monitor their patient's mental status and use computed axial tomography scans to determine when to use any of the available treatments for brain swelling. The currently available treatments include moderate hypothermia, in which the core temperature of the patient is lowered to approximately 35°C; osmotic therapy with mannitol and/or hypertonic saline; and continuous infusion of barbiturates in cases of poor response. These patients need to be in a head-up position to decrease their intracranial pressure and should be appropriately sedated because agitation and combativeness increase intracranial pressure.

The third group of complications, multi-organ failure, calls for standard support of each of the organ failures. For instance, for acute kidney failure, the patient may need temporary renal dialysis; for heart failure, the patient may need medical therapy to support the contractile function of the heart and pressors for arterial hypotension or shock; and for lung failure, the patient may need to be intubated and oxygenated via mechanical ventilation.

G&H What are the next steps in research for the treatment of ALF and its complications?

SM This is an exciting area because, after many years of work, we may be getting closer to an artificial liver support device. This extracorporeal liver assist device (ELAD, Vital Therapies, Inc) would assist the liver during the regeneration process, which, in the case of ALF, means responding to intensive hepatologic care or assisting liver function on a temporary basis if the patient is awaiting emergency liver transplantation.

In the ELAD, live, human-derived liver cells are placed within 4 cartridges, representing a significant proportion of the normal human liver mass. In the ICU, a blood ultrafiltrate from the patient's blood is perfused through these cartridges and then returned to the patient. Thus, the liver cells inside the cartridges perform their normal functions detoxifying the patient's fluid and adding clotting factors and other key liver-made substances. There is a need for quite a bit of equipment to keep the liver cells alive in their cartridges for a week or so, in terms of temperature, oxygen consumption, pH, function, glucose consumption, and other parameters. This device is certainly more complex than, for instance, a kidney dialysis machine because of the live liver cell components, in addition to a membrane, across which some chemicals flow back and forth.

Currently, there are several devices that assist other failing organs, for instance, the left ventricular assist device for the heart, mechanical ventilators to support the lungs, and the renal dialysis machine to assist the kidneys. We still do not have such a device for the liver when it fails in ALF. However, the ELAD is very promising and currently entering phase 3 clinical trials, so it may be an option in the not-so-distant future.

Dr Munoz has no relevant conflicts of interest to disclose.

Suggested Reading

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