A 63-Year-Old Man With Worsening Liver Failure

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A 63-year-old man who has profound deterioration in his condition is brought to his primary care physician by his family.

History

The patient has significant liver disease of at least 5 years' duration. It was first discovered by abnormalities found as a result of liver function testing but has become more clinically severe over time. About 3 years prior to presentation, the patient was admitted to the hospital with hepatomegaly and abdominal pain associated with alcohol binge drinking. A comprehensive evaluation, including a liver biopsy, had revealed alcoholic hepatitis at that time. A background history taken at that hospitalization had revealed heavy, long-term alcohol misuse involving an excess of 5 drinks of spirits per day. Since then, attempts to break the alcohol addiction have been in place with varying degrees of adherence.

About 18 months prior to his current presentation, ascites had appeared, which had initially responded to diuretic therapy. Over the last 2 months, the patient had been consuming large amounts of alcohol. His family reported increased edema of the feet and lower extremities, increased abdominal girth, decreased mental acuity with lethargy, and yellowing of the skin.

Physical examination

On hospital day 1, the patient exhibited confusion and had obvious jaundice. His temperature was elevated at 38 °C and blood pressure was low at 100/70 mm Hg. His skin had many spider telangiectasia and was deeply jaundiced. He had significant ascites with a caput medusae. A firm liver edge and spleen tip were palpable despite the ascites. There was 4+ edema of the feet and lower extremities to the knee. There was mild mental confusion and asterixis.

Diagnostic testing

Initial results from laboratory testing revealed a low hemoglobin level of 11.0 g/dL, an elevated white blood cell count of 18,000/µL that was predominantly neutrophils, and a low platelet count of 89,000 × 103/µL. His serum sodium level was low at 112 mEq/dL, potassium level was low at 2.9 mEq/dL, and serum albumin level was low at 2.3 g/dL. His prothrombin time (PT) was elevated at 30 s with an elevated international normalized ratio (INR) of 4.0. His aspartate aminotransferase level was 225 U/L and alanine aminotransferase level was 80 U/L with an elevated alkaline phosphatase level of 411 U/L. His blood alcohol level was 0.

Treatment and management

The patient was admitted to the hospital with initiation of general measures, including gentle diuresis to lower his body weight by 0.5 to 1.0 kg/d, antibiotics in the form of ceftriaxone (all cultures on hospital day 3 were negative, and paracentesis showed an ascitic fluid neutrophil count of < 100 cells/µL), and oral lactulose. Specific therapy in the form of prednisolone was also initiated.

On hospital day 7, there was some modest improvement in mentation, but the physical findings had otherwise minimally changed. Repeat laboratory test results showed an elevated bilirubin level of 18 mg/dL, a low albumin level of 2.1 g/dL, and an elevated creatinine level of 2.7 mg/dL. His PT remained elevated at 30 s with an INR of 4.0.

Which of the following is the optimal approach to managing this patient?

A. In addition to ongoing maneuvers to address reversible precipitating events, discuss liver transplantation (if feasible) as having the best long-term survival.
B. He should receive a transjugular intrahepatic portosystemic shunt

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(TIPS) procedure as prophylaxis against hemorrhage from esophageal varices.

C. He should receive more aggressive diuretics to more quickly remove the ascites and improve the edema.

D. Corticosteroids should be continued at least for 30 days with expectation for significant clinical and mortality benefit.

Correct Answer: A

The presented case opens a discussion about the clinical entity traditionally termed "end-stage chronic liver disease" and, more specifically, the clinical findings and natural history when such patients descend into liver failure. These are the patients who are known to have severe chronic liver disease with cirrhosis—be it induced by hepatitis C virus or, like the presented patient, by alcohol—yet are to some degree getting along and functional until some intercurrent event(s) causes a rapid and profound deterioration both biochemically (eg, escalating PT/INR and bilirubin level) and clinically (eg, hepatic encephalopathy hepatorenal syndrome), which often results in mortality.

Many years ago, when a patient would present similar to the clinical vignette, we would "round up the usual suspects" of precipitating events (see discussion below) in an attempt to find something reversible and treatable. The pathophysiological mechanisms and connections between such events and precipitous deterioration were unknown. Newer research now exists that more clearly elucidates how and why these things happen.[1] A main process that has been shown to be significant is systematic inflammation.[2] The inflammatory cascades can be triggered by infection, acute alcoholic hepatitis, and even severe hemorrhage (eg, bleeding varices). Very good direct correlations of systematic inflammation and its degree with the presence and severity of multiorgan failure in patients with chronic liver disease has been demonstrated.[2] To go even deeper, cellular mitochondrial dysfunction similarly correlates with the degree of inflammation in these patients as well.[3] As these pathophysiological and biochemical/cellular correlates and events are more clearly elucidated, perhaps more specific therapeutics to blunt and reverse these correlates may become available in the future.

For the present, however, we are left with 2 basic tactical therapeutics when confronted with such patients. One is to find and treat any of the classical precipitating events. The second is to support the patients and their failing organ systems long enough for some degree of recovery to occur.

So, initially there needs to be evaluation of where the patient is prognostically. For this, the well-validated Model for End-Stage Liver Disease (MELD) score can be used. This schema involves a calculation using creatinine, bilirubin, and serum sodium levels as well as INR to generate a number from less than 9 to 100, which portends a more ominous 3-month mortality as the calculation goes higher: Less than 9, -2% to 4%; 20 to 24, 20% to 29%; 52 to 75, 30% to 40%, and more than 75, more than 40%.4 The MELD score obviously is helpful prognostically but also plays a role in choices of therapy.

Regarding precipitating events, the major players are infection (usually bacterial), acute variceal bleeding, and acute alcoholic hepatitis.[1] Diagnostic testing would include appropriate cultures (including ascitic fluid), monitoring for gastrointestinal bleeding, and accurate history taking for recent alcohol binging. Of course, a complete set of blood studies with particular attention and monitoring of bilirubin, albumin, and serum sodium levels as well as PT/INR are required. Note that in these patients with end-stage "chronic" liver disease, it is the hepatocellular function and synthesis that are the main factors being tested rather than hepatocellular inflammation/destruction (eg, transaminases). The latter are more important in acute liver failure situations such as acetaminophen toxicity and fulminant hepatitis.

Once a defined trigger is identified, specific tactical therapeutics can be initiated as appropriate. These include early and aggressive use of antibiotics with coning down the choice as the source is identified, transfusion support, vasoconstrictor and endoscopic management bleeding varices if identified, and steroid therapy in selected patients with alcoholic hepatitis using yet another numerical scheme (the Lille score) to determine if and when to do so.[1,5,6]

These conditions are difficult to treat and, as stated above, have ominous prognosis. As alluded to previously, supportive measures are often required for days, if not weeks, to keep the patients alive meanwhile. Often, intensive care unit (ICU) monitoring is needed. Key items of support include airway protection and lactulose to lighten the degree of hepatic encephalopathy and significant support of the cardiovascular system. Once referred to as hepatorenal syndrome, which meant the progression of renal failure and refractory hypotension, it is now referred to as acute kidney injury. It is essentially the most ominous complication encountered in patients with end-stage liver disease. Attention to volume renal function, fluid/albumin status, and blood pressure in the ICU by experts is indicated. Often there will be a need for dialysis, which is quite ominous.[1]

To complete the discussion with a potentially more optimistic view, there seems to be a potential role for liver transplantation in select patients. Sundaram and colleagues have demonstrated that patients with acute-on-chronic liver disease who have 3 or more organ failures (eg, encephalopathy, renal failure, and circulation/blood pressure) have a 1-year survival of less than 20%, but if they undergo a liver transplantation, their 1-year survival increases to 80%.[7]

As to the question proposed above, Answer B is not appropriate on several counts. First, there is no gastrointestinal bleeding in our patient, and to undergo

What's The Take Home?

End-stage liver disease remains a common problem despite treatment advancements for hepatitis C virus and other etiologies. Often this occurs in so-called acute-on-chronic liver failure situations, wherein some significant acute clinical event complicates the pre-existing cirrhotic situation. This syndrome is seen in roughly 30% of hospitalized patients with cirrhosis,[1] and some form of systemic inflammation seems to be a pathophysiologic triggering mechanism. Precipitating events of note include infections, acute variceal hemorrhage, and alcoholic hepatitis. Subsequent lifethreatening sequelae include acute kidney injury, cardiovascular collapse with hypotension, and severe encephalopathy in a variety of other multiorgan failures. Identification and treatment of such precipitating events is key to therapy, but overall prognosis is guarded. There are a variety of schemes and scores available to predict prognosis and guide therapy. There is encouraging data that liver transplantation can prolong survival when feasible in these patients.

such a formidable prophylactic procedure in a patient who is so unstable carries more risk than benefit. Secondly, the validated indication of TIPS is multiple episodes of gastrointestinal bleeding, not primary prevention, which is actually a contraindication. Our patient does not have a history of gastrointestinal bleeding. Answer C, the acute and aggressive use of diuretics, is potentially dangerous here because the patient's renal function is tenuous and may be deteriorating. His blood pressure is tenuous as well, such that gentle diuresis seems to be effective for now with fluid removal without hypotension. Of note, it is not unusual for such patients to require volume expansion in this setting, and too-aggressive diuresis should be avoided. Answer D is a point specific one, perhaps, unfair to nonspecialists. There has been decades-long controversy over the role of steroids in alcoholic hepatitis, which is what he has. The Lille score scheme seems predictive as to who will benefit from them and compares day 0 scores with day 7 scores. This patient did not show a response to prednisolone at day 7 with a Lille score of 0.81 and, therefore, would not fulfill criteria to continue 30 days of therapy.[5,6]

Patient Outcome

The patient continued a stormy course of downward projection. The renal function progressively worsened, and dialysis was performed several times. Hypotension became a problem as well. On hospital day 16, melena was noted, and transfusions were administered. Meanwhile, no improvement was evident in bilirubin level or PT/INR. Although liver transplantation was discussed and there were certainly hepatic indications making it the seemingly best option, the requirement of alcohol abstinence for 6 months in patients with alcoholic cirrhosis remained an issue. The patient's family and attending physicians discussed, and agreed, that the supportive measures required to reach that point were essentially impossible, and comfort care was put in place. The patient died on hospital day 20.

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