65-Year-Old Woman With Abdominal Pain and Jaundice

Mitchell M. Pitlick, MD; Dharma B. Sunjaya, MD; and Christopher R. Stephenson, MD

A 65-year-old woman with no previous medical history was admitted to the hospital for management of abdominal pain of 2 weeks' duration. She described the pain as dull and diffuse but worst in the right upper quadrant without radiation to the back or shoulder. Her pain was associated with nausea, nonbloody diarrhea, anorexia, early satiety, and increased abdominal girth. She reported no medication or intravenous drug use. Her social history was notable for daily alcohol use since the age of 16 years, with recent consumption of approximately 2 L of vodka every 10 to 12 days.

On physical examination, the patient was afebrile with a heart rate of 99 beats/min and a blood pressure of 104/61 mm Hg. She appeared frail with notable jaundice of the upper extremities, face, and sclerae. Her abdomen was markedly distended and diffusely tender with a palpable liver edge. There was no rebound tenderness or guarding. She was alert and oriented without asterixis. Laboratory studies were notable for the following (reference ranges provided parenthetically): creatinine, 2.1 mg/dL (0.59-1.04 mg/dL); hemoglobin, 8.5 g/dL (11.6-15.0 g/dL); white blood cell count, 32 $\times$ 10^9/L (3.4-9.6 $\times$ 10^9/L); aspartate aminotransferase (AST), 149 U/L (8-43 U/L); alanine aminotransferase (ALT), 23 U/L (7-45 U/L); alkaline phosphatase, 289 U/L (35-104 U/L); γ-glutamyltransferase, 670 U/L (5-36 U/L); total bilirubin, 7.4 mg/dL ($\leq$1.2 mg/dL); direct bilirubin, 5.1 mg/dL (0.0-0.3 mg/dL); international normalized ratio (INR), 1.7 (0.9-1.1); and albumin, 2.8 g/dL (3.5-5.0 g/dL). Abdominal ultrasonography revealed the presence of gallbladder sludge without cholelithiasis or biliary duct dilation. The liver was smooth with no abnormalities. There was small to moderate ascites with slow flow in the left, right, and main portal veins, consistent with portal hypertension.

1. **Which *one* of the following is the *most appropriate* next test to evaluate this patient's abdominal pain?**
   a. Endoscopic retrograde cholangiopancreatography
   b. Computed tomography (CT) of the abdomen and pelvis
   c. Esophagogastroduodenoscopy
   d. Magnetic resonance cholangiopancreatography
   e. Paracentesis

Endoscopic retrograde cholangiopancreatography is not indicated because there is no imaging evidence of an obstructive biliary process that would benefit from endoscopic intervention. Further abdominal imaging with CT may be helpful but will not be immediately useful in determining the cause of ascites or the presence of infection. Esophagogastroduodenoscopy could be useful in the work-up of abdominal pain and early satiety to rule out entities such as peptic ulcer disease, but elucidating the etiology of the ascites should take precedence. Magnetic resonance cholangiopancreatography to further characterize the biliary system may be necessary if the diagnosis is still uncertain after initial testing but would not be the best next test in this situation. Diagnostic paracentesis should be performed as soon as possible to rule out spontaneous bacterial peritonitis in patients with suspected cirrhotic ascites. Delayed paracentesis is associated with a 2.7-fold increase in

See end of article for correct answers to questions.

Resident in Internal Medicine, Mayo Clinic School of Graduate Medical Education, Rochester, MN (M.M.P., D.B.S.); Advisor to residents and Consultant in General Internal Medicine, Mayo Clinic, Rochester, MN (C.R.S.).

mortality in hospitalized patients with spontaneous bacterial peritonitis.[1] Ascitic fluid studies will also be helpful in elucidating the underlying cause of the ascites.

A diagnostic and therapeutic paracentesis was performed, with 750 mL of serous fluid removed. Testing revealed 89 total nucleated cells with 2% neutrophils and no bacterial growth. The total protein level was 0.8 g/dL, with a corresponding serum ascites albumin gradient of 2.0, indicating that the patient's ascites was secondary to portal hypertension. The patient reported improvement in her abdominal discomfort following the procedure.

Abdominal CT revealed no hepatosplenomegaly or abnormal contour of the liver surface. Further testing yielded negative results on viral hepatitis serologies and no antimitochondrial and anti–liver/kidney microsomal antibodies. Results of an antinuclear antibody test were positive at 8.1 U (≤1.0 U), and an anti–smooth muscle antibody test yielded positive results with a 1:80 titer.

2. Given the information obtained thus far, which *one* of the following is the *most likely* diagnosis?

a. Primary biliary cholangitis
b. Alcoholic hepatitis
c. Autoimmune hepatitis
d. Wilson disease
e. Ascending cholangitis

Primary biliary cholangitis could present with elevated alkaline phosphatase and γ-glutamyltransferase levels, but hyperbilirubinemia is typically only present in late stages. In addition, the patient lacks a common clinical feature of pruritus. Diagnostic criteria for primary biliary cholangitis include the presence of at least 2 of the following 3 features: alkaline phosphatase 1.5 or more times the upper limit of normal, presence of antimitochondrial antibodies at a titer of 1:40 or higher, and histologic evidence of primary biliary cholangitis (manifested as nonsuppurative destructive cholangitis and destruction of interlobular bile ducts).[2] Alcoholic hepatitis is the most likely diagnosis given the clinical and laboratory findings. Diagnostic criteria for alcoholic hepatitis include the rapid development or worsening of jaundice and liver-related complications, total bilirubin level greater than 3 mg/dL, ALT and AST concentrations elevated to more than 1.5 times the upper limit of normal but less than 400 U/L with the AST:ALT ratio greater than 1.5, persistent heavy alcohol use until 8 weeks before the onset of symptoms, and exclusion of other liver diseases.[3] In addition, up to 80% of patients with severe alcoholic hepatitis will have underlying cirrhosis, although this may not be seen on imaging.[3] Typical cases of autoimmune hepatitis are marked by antinuclear bodies and anti–smooth muscle antibody positivity at titers of greater than 1:80, but these antibodies are nonspecific and can be seen in nonautoimmune liver disease including viral hepatitis and alcoholic hepatitis.[4] A liver biopsy can help distinguish autoimmune from nonautoimmune hepatitis in clinically equivocal cases.[3] Wilson disease could cause acute hepatitis, but it typically presents at a younger age and is associated with neuropsychiatric manifestations. Ascending cholangitis could account for jaundice and right upper quadrant pain, but the absence of fever and biliary duct obstruction on imaging makes it less likely.

In view of the positive autoimmune serologic results, a transjugular liver biopsy was performed, which revealed markedly active steatohepatitis with neutrophilic infiltration, cirrhosis, and mild macrovesicular steatosis with numerous ballooned hepatocytes and abundant Mallory hyaline, consistent with alcoholic hepatitis. No severe cholestasis or plasma cell infiltration was seen.

3. Which *one* of the following is the *best* treatment option for this patient?

a. Pentoxifylline
b. Prednisolone
c. Adequate nutrition and alcohol abstinence
d. *N*-acetylcysteine
e. Etanercept

Mayo Clin Proc. ■ April 2019;94(4):e51-e55 ■ https://doi.org/10.1016/j.mayocp.2018.05.039
www.mayoclinicproceedings.org

Pentoxifylline is no longer recommended for the treatment of alcoholic hepatitis because recent studies have found no survival benefit.[3,5] Prednisolone is the pharmacologic treatment of choice, with guidelines and studies showing some short-term survival benefit in patients with severe alcoholic hepatitis.[3,5] Nevertheless, the best and most important aspect of treatment of alcoholic hepatitis is adequate nutrition and alcohol abstinence. Patients often present with anorexia and malnutrition, and current guidelines recommend a caloric intake of at least 21.5 kcal/kg per day.[3] If this target cannot be met, enteral nutrition should be instituted because lower caloric intake has been associated with increased mortality.[3,6] *N*-acetylcysteine can be used in cases of acetaminophen toxicity but would not be helpful for this patient. Etanercept is an antitumor necrosis factor agent that has been found to increase mortality in alcoholic hepatitis.[7]

The patient's Maddrey discriminant function score on admission was 40, and her Model for End-Stage Liver Disease (MELD) score was 30. This score corresponds to a poor prognosis and approximately 50% 3-month mortality risk, respectively. The patient was unable receive prednisolone because of a concomitant severe *Clostridium difficile* infection. Oliguria developed despite adequate fluid resuscitation with crystalloid and albumin. Her creatinine level increased from 2.1 mg/dL on admission to 3.5 mg/dL. Urine microscopic examination revealed no cells or casts. There was no proteinuria, and her urinary sodium level was less than 10 mmol/L.

4. **Which *one* of the following is the *most likely* cause of this patient's oliguric acute kidney injury?**
   a. Prerenal acute kidney injury
   b. Acute tubular necrosis
   c. Acute interstitial nephritis
   d. Membranoproliferative glomerulonephritis
   e. Hepatorenal syndrome

Prerenal acute kidney injury would be suspected given the patient's poor oral intake and diarrhea, but progressive oliguria and worsening kidney function despite adequate fluid resuscitation and correction of underlying factors makes this diagnosis less likely. Acute tubular necrosis could result from any prolonged ischemic or toxic insult to the kidney, but a low urine sodium concentration in the absence of granular casts and renal tubular epithelial cells on urine microscopic examination makes it less likely. There is no drug exposure that would raise suspicion for acute interstitial nephritis. Membranoproliferative glomerulonephritis and other primary glomerular diseases are unlikely given the absence of proteinuria, dysmorphic red blood cells, and red blood cell casts. Hepatorenal syndrome is the most likely diagnosis given the patient's progressive oliguria and worsening kidney function despite adequate weight-based fluid resuscitation with albumin in the setting of acute liver injury with ascites and underlying cirrhosis.

The patient received continued supportive therapy in an attempt to maintain adequate kidney perfusion including the avoidance of nephrotoxic medications. She was neither uremic nor hyperkalemic.

5. **Given the most likely diagnosis, which *one* of the following would be the *best* next treatment for this patient's acute kidney injury?**
   a. Intravenous furosemide
   b. Albumin and norepinephrine
   c. Albumin, midodrine, and octreotide
   d. Transjugular intrahepatic portosystemic shunt
   e. Renal replacement therapy

Furosemide would only be indicated if the patient's acute kidney injury occurred in the setting of volume overload (ie, cardiorenal syndrome) or if volume overload occurred as a sequelae of the kidney injury itself. Albumin and norepinephrine would be indicated for treatment of hepatorenal syndrome in the intensive care unit setting.[8,9] On a general care ward, the best initial treatment for hepatorenal syndrome is albumin, midodrine, and octreotide.[8,9]

Transjugular intrahepatic portosystemic shunting can be used as a temporizing measure to reduce portal hypertension and concomitant splanchnic vasodilation in patients whose disease is refractory to medical management but is not recommended as a primary treatment modality for hepatorenal syndrome.[8,9] Similarly, renal replacement therapy can be used as a temporizing measure in patients with progressive oliguria or kidney injury despite medical therapy or in those with acute indications for dialysis such as refractory hyperkalemia, acidosis, or uremia.[8,9] Ultimately, liver transplant is required to correct the underlying cause.[10]

Unfortunately, the patient's condition continued to deteriorate, and health care–associated pneumonia developed with a loculated right-sided pleural effusion. In light of this new complication with ongoing liver and kidney failure, a care conference was held. The patient ultimately decided to pursue comfort care. She was discharged to a care facility and died shortly thereafter.

DISCUSSION

Alcoholic hepatitis is a clinical syndrome of jaundice and liver failure that presents after years of excessive alcohol intake. Patients typically have a history of 80 to 100 g of alcohol consumption daily for 5 years, although it is not uncommon for patients to discontinue alcohol use in the weeks before initial presentation.[3] Alcoholic hepatitis is a serious diagnosis, with severe cases carrying a 40% mortality risk at 6 months.[3] The primary clinical sign is the rapid onset of jaundice. Associated signs, symptoms, and laboratory findings include fever, ascites, tender hepatomegaly, leukocytosis, serum transaminase levels more than 1.5 times the upper limit of normal with an AST:ALT ratio of greater than 1.5 and absolute values greater than 400 U/L, hyperbilirubinemia, and elevated INR.[3] In a patient with ascites and a clinical history of excessive alcohol use with the aforementioned laboratory results, alcoholic hepatitis is the most likely diagnosis until proven otherwise.[3]

Several scoring systems exist to predict outcomes in alcoholic hepatitis. Two of the most commonly used are the Maddrey discriminant function score and the MELD score. The Maddrey discriminant function scale utilizes the bilirubin and prothrombin time to determine which patients may benefit from corticosteroids, with current guidelines recommending consideration of corticosteroids for severe alcoholic hepatitis as defined by a score of 32 or higher.[3] The MELD score was originally developed at Mayo Clinic to predict survival in cirrhotic patients undergoing transjugular intrahepatic portosystemic shunting.[11] It uses bilirubin, INR, creatinine, and sodium in its calculation and has been found to be as good as the Maddrey discriminant function scale in predicting 3-month mortality of patients with severe alcoholic hepatitis, with scores of 21 or higher being used to consider treatment with corticosteroids.[12]

Multiple agents have been investigated as potential treatments for alcoholic hepatitis. Corticosteroids have been reported to confer a small mortality benefit at 28 days (13.8% mortality at 28 days compared to 18% in the placebo group), but no long-term benefit has been found.[5] Current guidelines recommend corticosteroid treatment if the Maddrey discriminant function score is 32 or higher, although corticosteroids are contraindicated in the setting of infection, gastrointestinal bleeding, acute pancreatitis, or renal failure.[3] The most common pharmacological treatment regimen is prednisolone, 40 mg daily for 28 days with subsequent taper. Prednisolone is preferred to prednisone because prednisone requires hepatic metabolism to the active metabolite, prednisolone, to achieve its therapeutic effect.[3] Pentoxifylline was previously used but is no longer recommended given that recent studies have found no survival benefit compared to placebo.[3,5] Adequate nutrition and abstinence from alcohol are the most important long-term aspects of alcoholic hepatitis treatment. Patients are often cachectic and malnourished when they present. Current guidelines recommend intake of at least 21.5 kcal/kg per day, with initiation of enteral nutrition if this cannot be achieved orally.[3,6] Lower caloric intake is associated with increased mortality.[3,6]

Mayo Clin Proc. ■ April 2019;94(4):e51-e55 ■ https://doi.org/10.1016/j.mayocp.2018.05.039
www.mayoclinicproceedings.org

Hepatorenal syndrome is a serious complication of cirrhosis and alcoholic hepatitis that portends a very poor prognosis. Multiple diagnostic criteria exist, but the most widely accepted criteria define hepatorenal syndrome as an increase in serum creatinine to more than 1.5 mg/dL in the setting of cirrhosis and ascites with no improvement in creatinine after diuretic withdrawal and volume expansion with albumin.[8] In addition, there must be no other alternative explanation for the kidney injury (shock, ongoing fluid loss, current or recent treatment with nephrotoxic drugs, and lack of evidence of renal parenchymal disease as indicated by bland urinalysis results and no abnormalities on renal ultrasonography).[8] Hepatorenal syndrome is divided into 2 types. Type 1 is typically precipitated by alcoholic hepatitis, infection, or bleeding, has a more acute onset and rapid course, and has a median survival of 2 weeks without treatment.[9] Type 2 is typically associated with refractory ascites, has a more protracted course, and has a median survival of approximately 6 months.[8] Hepatorenal syndrome is thought to be due to renal vasoconstriction that occurs in response to portal hypertension—induced splanchnic vasodilation. As such, vasoconstrictors are recommended for treatment. Current recommendations are to initiate albumin and norepinephrine in patients being treated in an intensive care unit, whereas albumin, midodrine, and octreotide should be used for patients being treated on a general care ward.[8,9] Renal replacement therapy and transjugular intrahepatic portosystemic shunting can be used in medically refractory cases as a bridge to the definitive therapy of liver transplant, although they are not recommended as primary treatment modalities.[8,9] Early transplant before the typical 6-month abstinence period has been reported to improve mortality without significantly increased rates of recidivism in highly selected patients with alcoholic hepatitis, strong psychosocial support, and high motivation for continued abstinence.[12]

CONCLUSION

Alcoholic hepatitis is a clinical syndrome defined by rapid onset of jaundice and liver failure. Severe cases carry a considerable risk of mortality despite treatment with corticosteroids. It can precipitate hepatorenal syndrome, a form of kidney failure also associated with substantial mortality despite treatment with vasoactive medications. Prevention of both is key, making counseling regarding alcohol cessation and abstinence of the utmost importance in general practice.

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Christopher R. Stephenson, MD, Division of General Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (Stephenson.Christopher@mayo.edu).

REFERENCES

1. Kim JJ, Tsukamoto MM, Mathur AK, et al. Delayed paracentesis is associated with increased in-hospital mortality in patients with spontaneous bacterial peritonitis. *Am J Gastroenterol*. 2014; 109(9):1436-1442.
2. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ; American Association for Study of Liver Diseases. Primary biliary cirrhosis. *Hepatology*. 2009; 50(1):291-308.
3. Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH. ACG clinical guideline: alcoholic liver disease. *Am J Gastroenterol*. 2018; 113(2):175-194.
4. Zachou K, Rigopoulou E, Dalekos GN. Autoantibodies and autoantigens in autoimmune hepatitis: important tools in clinical practice and to study pathogenesis of the disease. *J Autoimmune Dis*. 2004;1(1):2.
5. Thursz MR, Richardson P, Allison M, et al; STOPAH Trial. Prednisolone or pentoxifylline for alcoholic hepatitis. *N Engl J Med*. 2015;372(17):1619-1628.
6. Moreno C, Deltenre P, Senterre C, et al. Intensive enteral nutrition is ineffective for patients with severe alcoholic hepatitis treated with corticosteroids. *Gastroenterology*. 2016;150(4): 903-910.
7. Boetticher NC, Peine CJ, Kwo P, et al. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. *Gastroenterology*. 2008; 135(6):1953-1960.
8. Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*. 2007;56(9):1310-1318.
9. Israelsen ME, Gluud LL, Krag A. Acute kidney injury and hepatorenal syndrome in cirrhosis. *J Gastroenterol Hepatol*. 2015; 30(2):236-243.
10. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology*. 2000;31(4):864-871.
11. Dunn W, Jamil LH, Brown LS, et al. MELD accurately predicts mortality in patients with alcoholic hepatitis. *Hepatology*. 2005; 41(2):353-358.
12. Schneekloth TD, Niazi SK, Simonetto DA. Alcoholic hepatitis: appropriate indication for liver transplantation? *Curr Opin Organ Transplant*. 2017;22(6):578-583.

CORRECT ANSWERS: 1. e. 2. b. 3. c. 4. e. 5. c