Hepatitis A, B, and C

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Preface

Board certification in gastroenterology and hepatology requires an understanding of all aspects of physiology, diagnosis, and therapy for gastrointestinal tract, liver, and pancreatic disorders. In addition to self-study of this discipline, candidates for board certification must have completed 2 years of fellowship, during which time the practical aspects of the diagnosis and treatment of gastroenterologic and hepatologic complications are learned through hands-on clinical investigation.

The Hospital Physician Gastroenterology Board Review Manual is a study guide intended to help candidates prepare for the written and oral components of this examination. The manual consists of quarterly publications that address the following areas:

- Acid peptic disease
- Acute appendicitis
- Aging and the gastrointestinal tract
- Basic biology
- Chronic cholestatic syndromes
- Cirrhosis and portal hypertension
- Diverticulosis coli
- Drug-induced and alcoholic liver disease
- Endoscopy of upper gastrointestinal hemorrhage
- Esophageal disorders
- Gallstones
- Gastrointestinal manifestations of AIDS
- Inflammatory bowel diseases and other diarrheal diseases
- Intestinal obstruction
- Irritable bowel syndromes
- Ischemic bowel disease
- Liver transplantation
- Malabsorption syndromes
- Nutritional support
- Pancreatic disease
- Small intestinal, colonic, and other tumors
- Viral and chronic hepatitis

Most of these topics are covered in the manual; however, some areas of interest are discussed in greater depth than others.

The manual presents clinical scenarios using a case-based format; questions and answers relating to the clinical presentation are provided. The editors believe that this question-and-answer format is an effective teaching tool and allows for adequate self-assessment. Each quarterly publication addresses only a few of the topics mentioned; board certification candidates should review the entire list of topics to be appropriately prepared for the examination. The Hospital Physician Gastroenterology Board Review Manual is prepared by the Series Editor and contributing authors and not in collaboration with the American Board of Internal Medicine, Gastroenterology/Hepatology.

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INTRODUCTION

The hepatitis A virus (HAV), the hepatitis B virus (HBV), and the hepatitis C virus (HCV) are common causes of viral hepatitis worldwide. When resulting from infection with HAV, viral hepatitis is called hepatitis A. When resulting from infection with HBV, it is called hepatitis B, and it is called hepatitis C when resulting from infection with HCV. Viral hepatitis may be either acute or chronic, although hepatitis A follows only an acute course. The pathologic patterns of acute viral hepatitis are clinically similar regardless of the causative virus. The same is true for chronic viral hepatitis. Jaundice is the most obvious sign of acute viral hepatitis; it may be preceded by influenza-like symptoms, accompanied by nausea and vomiting. Individuals, however, are often asymptomatic or have only mild symptoms. There is no specific treatment for typical acute viral hepatitis. Acute episodes of viral hepatitis usually resolve spontaneously, with full patient recovery often occurring within a few weeks.

Chronic viral hepatitis is defined as evidence of continued or relapsing liver inflammation for more than 6 months owing to infection with a hepatotropic virus. The symptoms of chronic viral hepatitis are usually nothing more than a general feeling of weakness or loss of stamina and abdominal discomfort, though many individuals remain asymptomatic for years. Chronic viral hepatitis is usually discovered only upon a routine medical examination. However, it causes substantial morbidity and mortality worldwide. Effective therapies are being developed to treat those with chronic hepatotropic viral infections and to prevent the long-term sequelae of chronic viral hepatitis. The goal of this manual is to use case-based discussions and a question-and-answer format to describe the diagnosis of, and therapeutic options for, patients with acute hepatitis A and acute and chronic hepatitis B and C.

Hepatitis A

HAV is an enterovirus transmitted by the fecal-oral route, and hepatitis A is highly prevalent in developing countries, where hygiene and sanitation are often poor. In such areas, the infection rate approaches 100%, and it is common for nearly all of the individuals in these countries to go through the process of exposure, infection, and then immunity while in early childhood. In developed countries, successively older age groups have a higher prevalence for the disease. In the United States, the infection rate reaches about 70% in the 50- to 60-year age range. In young children, the disease is often asymptomatic. In adults and older children, the disease tends to be more symptomatic, often presenting with influenza-like symptoms, accompanied by nausea and vomiting. If the patient develops cholestasis, pruritus, jaundice, and choluria will ensue. Hepatitis A does not have a chronic phase, and death from hepatitis A is rare.
HEPATITIS B

HBV is a hepadnavirus (hepatotropic DNA virus), with all regions of the viral genome encoding protein sequences. The vehicles of transmission are blood, blood products, semen, vaginal secretions, urine, and saliva. The mode of transmission is more frequently through contact with infected amounts of these substances than through the fecal-oral route.

In general, the presence of the infection is identified by finding the hepatitis B surface antigen in the blood (HBsAg). The determination of how recent the infection is can be accomplished by identifying the immunoglobulin class of the hepatitis B core antibody (anti-HBc). Anti-HBc of the immunoglobulin M (IgM) class is prevalent in recent infection. Anti-HBc of the immunoglobulin G (IgG) class is prevalent only after approximately 6 months have passed. Anti-HBc of the IgG class is often present following complete resolution of the infection, also. The presence of hepatitis B e antigen (HBeAg) in the serum correlates with the presence of the whole virus in the serum (which can be seen by electron microscopy), the presence of hepatitis B DNA in the serum, virus infectivity, and severe infection. Conversely, hepatitis B e antibody (anti-HBe) correlates with a good prognosis and loss of virus infectivity. The goal of therapy for hepatitis B (chronic disease) is to change the status of patients from being positive for HBeAg in the serum to being negative for HBeAg, with coincident serum positivity for anti-HBe. The hepatitis B surface antibody (anti-HBs) is often found in the serum when there is resolution of infection.

Approximately one third of the world’s population has been exposed to HBV, and globally, there are in excess of 300 million carriers of the virus. These individuals are mostly in developing countries. HBV infection is often chronic in nature, and together with chronic HCV infection, accounts for more than 50% of the causes of chronic liver disease in the United States. In the United States, estimates of the prevalence of chronic hepatitis B are in the range of 1 to 1.25 million individuals. Also, HBV infection often leads to the development of cirrhosis and end-stage liver disease, and patients infected with HBV are at risk of developing hepatocellular carcinoma.

HEPATITIS C

HCV is a single stranded RNA enveloped virus that has been classified in the Flaviviridae family. The 5’ end of the viral genome codes for the structural and envelope proteins, whereas the downstream 3’ end codes for the nonstructural viral proteases and RNA polymerase. It has a high rate of mutation and can be subcategorized into 6 different genotypes based on sequences in the nonstructural-coding region. The high degree of diversity associated with the virus is a major hindrance in developing a vaccine.

Blood, body fluids, and body secretions, such as semen and saliva, are vehicles of transmission. (Semen and saliva transmit HCV much less frequently than HBV, however.) Risk factors for HCV infection include needle-stick accidents in the health care setting, intravenous drug abuse, undergoing tattooing and/or body piercing procedures, and the receipt of blood or blood products by way of transfusion, particularly before 1992. (Since 1992, blood for transfusion has been routinely screened for the virus, making transmission through this means unlikely today.) Estimates of the worldwide prevalence of HCV infection center around 1%, with a much higher value for populations in developing countries. Based on data from the Third National Health and Nutrition Examination, the prevalence of antibody to HCV (or anti-HCV) in the United States is 1.8%, equating to approximately 4 million Americans. In the United States, the prevalence of HCV infection is 4 to 5 times the prevalence of HIV infection.

HCV infection is often chronic in nature, and as previously stated, it, together with HBV infection, accounts for more than 50% of the causes of chronic liver disease in the United States. Not all patients with chronic HCV infection have severe or progressive disease, however. Current estimates project that 20% to 30% of infected patients will be at risk of progression to cirrhosis and/or hepatocellular carcinoma. HCV infection often leads to the development of end-stage liver disease, also. Factors that are associated with more advanced liver disease or cirrhosis are age (correlates with duration of infection), male gender, and concurrent use of alcohol. In the Western world, hepatitis C now ranks as the most common indication for liver transplantation.

CASE 1

INITIAL PRESENTATION

Patient 1 is a 25-year-old woman who urgently presents to the office because of jaundice of her skin. She became ill 1 week ago with chills, fever, and myalgias.
Later, she became severely anorexic, had periodic vomiting, and noted that her urine became dark and her infrequent stool passages light colored. She also developed pruritus. She has been able to maintain her hydration with water and carbonated beverages, but she has eaten little for a week. There is no known exposure to viral hepatitis. She uses cyclic birth control pills. She usually drinks 4 or 5 beers each weekend evening.

**PHYSICAL EXAMINATION**

On physical examination, she is 115 pounds (usually 122) and 65 inches tall. Her skin and sclerae are noticeably icteric. She has moist mucous membranes, and her axillary moisture is normal. Her pulse is 64 bpm. Her temperature is 98.0°F. Her blood pressure is 110/60 mm Hg, with slight orthostatic change. She has no skin rash, and her pharynx is normal. Her liver is slightly tender, below the right costal margin, and 12 cm in span in the midclavicular line (MCL). The spleen is not palpable. Her stool is negative for occult blood.

**QUESTION**

• What is the likely cause of Patient 1’s illness?

**Discussion**

Viral hepatitis A follows an acute course and often presents with influenza-like illness, as Patient 1 has. The choluria, pruritus, and acholic stools are suggestive of cholestasis, which further supports a diagnosis of viral hepatitis A. Although estrogens in birth control pills can produce cholestasis, estrogen cholestasis should not produce all of the clinical symptoms that the patient displayed. Infectious mononucleosis due to Epstein-Barr virus is a possible cause of her illness, but less likely in the absence of pharyngitis or splenomegaly.

**QUESTION**

• Why does cholestasis cause choluria and acholic stools?

**Discussion**

Stool color is predominantly determined by bilirubin and its metabolites. In cholestasis, there is diminished delivery of conjugated bilirubin to the gut. Its absence in the bowel leads to acholic or clay-colored stools. In severe cholestasis, the direct bilirubin is excreted predominantly in the urine, yielding a dark or tea color.

**QUESTION**

• Why does cholestasis cause pruritus?

**Discussion**

Cholestasis can be defined as diminished bile flow. The bulk of bile flow is due to excretion of bile salts. In cholestasis, pruritus is caused by bile salts (or organic anions similar to bile salts) accumulating in the skin. Serum bile salts rise to very high levels in cholestatic syndromes because the liver and bile ducts excrete them incompletely.

**QUESTION**

• Is Patient 1’s liver large?

**Discussion**

Although the liver span in the MCL varies with an individual’s size, it is rarely greater than 12 cm. However, for Patient 1, being a petite woman, 12 cm is clearly enlarged. The liver’s tenderness also points to hepatic disease.

**LABORATORY EVALUATION**

Patient 1’s laboratory work-up shows a serum aspartate aminotransferase (AST) level of 425 U/L (normal, < 40 U/L), alanine aminotransferase (ALT) level of 475 U/L (normal, < 40 U/L), alkaline phosphatase of 800 U/L (normal, < 125 U/L), and serum total bilirubin of 12 mg/dL (normal, < 1.2 mg/dL). She has a normal complete blood count (CBC), and normal results on a urinalysis, except for a positive test result for bilirubin. The prothrombin time is 16 seconds (normal, 10 seconds) with an international normalized ratio (INR) of 1.8. The results from the serologic evaluations and a mononucleosis spot test are pending at this time. Her serum electrolytes, blood urea nitrogen (BUN), and serum glucose are normal.

**QUESTIONS**

• Given the laboratory results, what could a differential diagnosis include?
• Is the diagnosis clearly viral hepatitis A at this point?
• Could Patient 1 have alcoholic steatohepatitis?
Discussion

The abnormal results on her liver test predominantly reflect cholestasis, rather than hepatocellular disease. (The alkaline phosphatase level is very high, and the aminotransferase levels are intermediate.) Although steatohepatitis caused by alcohol is possible, it is unlikely with the patient’s normal alcohol consumption. Infectious mononucleosis and hepatitis A remain in the differential diagnosis, as they can present with cholestasis-predominant hepatitis (cholangiolitic hepatitis). However the cholestatic syndrome requires consideration of other cholestatic illnesses, such as gallstone disease with cholangitis.

**QUESTION**

- Is the prolonged prothrombin time caused by a synthetic defect in Patient 1’s liver or to cholestasis?

**Discussion**

The prolongation of her prothrombin time is probably caused by diminished bile salt delivery to the gut, with consequent vitamin K malabsorption. Fat soluble vitamin absorption is exquisitely sensitive to the presence of bile salts, as the vitamins’ absorption entails solubilization within the core of mixed micelles formed from bile salts. A simple therapeutic test to differentiate a cholestatic defect from a synthetic defect is to administer parenteral vitamin K and remeasure the prothrombin time. Resolution of the abnormal prothrombin time points to cholestasis.

**QUESTION**

- What additional diagnostic work-up is required?

**Discussion**

Ultrasonographic evaluation of the liver and gallbladder is simple to perform and is a highly diagnostic test to rule out other causes of cholestasis such as extrahepatic biliary obstruction. It should be performed while waiting for the results of the viral serologic tests.

**QUESTIONS**

- How should Patient 1 be managed at this point?
- Does she require hospitalization?

**Discussion**

The first decision regarding patient management is to determine whether she requires hospitalization. She does not require intravenous hydration because she has been able to maintain her hydration. Social issues need to be addressed to see if there is someone who can assist her at home until she is feeling better.

**CONTINUED EVALUATION**

The patient lives alone, but has a close boyfriend who can take some time off from work to attend to her at her home. She should be advised to avoid alcoholic beverages, but no other dietary proscriptions are necessary. Her HAV antibody, anti-HAV, (immunoglobulin M [IgM] class) test result is positive. The test for HBsAg has a negative result, as does the test for anti-HCV. The mononucleosis spot test has a negative result, as well. The ultrasonogram shows a common hepatic duct of normal size (4 mm), no gallstones in the gallbladder, and a pancreas that appears normal.

Vitamin K is given parenterally, and her prothrombin time returns to normal. Ten days later, she is able to eat somewhat more easily but has lost an additional 2 pounds. She remains severely pruritic and has excoriations on her back from scratching. Results from liver tests remain about the same. It is now obvious that she has cholestasis, but it is still not known if this cholestasis is associated only with the hepatitis A or also with some other disorder.

**QUESTION**

- Should Patient 1 undergo an endoscopic retrograde cholangiopancreatography (ERCP)?

**Discussion**

The decision tree for cholestatic disorders is to follow the trend of the liver tests in a disease that should resolve spontaneously, perform a liver biopsy when intrinsic liver disease is suspected and the course is not clear, or perform a cholangiographic study when extrahepatic biliary disease becomes more likely. The advent of magnetic resonance imaging cholangiopancreatography (MRCP) has eliminated the need for ERCP in most diagnostic circumstances; if a cholangiographic procedure were needed, MRCP should be used. However the best course for Patient 1’s illness is simply to follow her liver-test trend, because it is known that she has hepatitis A, and hepatitis A usually resolves spontaneously within a few weeks. If the cholestasis is associated only with hepatitis A, as is suspected, it too should resolve accordingly. There is no specific treatment of hepatitis A.

**QUESTION**

- What can be done about the pruritus?
Discussion

Pruritus can be severe in cholestatic syndromes, as is the case with this patient. The use of 4 g of cholestyramine each morning might help so long as some bile salts are reaching the duodenum. Antihistamines are sometimes useful. Rifamycin has been beneficial in some patients. Ultraviolet-B whole body radiation, similar to the treatment given to patients with psoriasis, can be used for the most recalcitrant cases.

TREATMENT AND OUTCOME

The patient is treated with cholestyramine and the pruritus resolves. One week later, her appetite is back to normal and her liver test results begin to improve. The cholestyramine is stopped, and she has no recurrence of the pruritus. Her recovery from acute viral hepatitis is sluggish, but full spontaneous recovery is anticipated.

QUESTION

• Is Patient 1 at risk for developing chronic hepatitis or fulminant hepatitis?

Discussion

Hepatitis A may produce fulminant hepatitis, though this is rare, but it never leads to chronic hepatitis. If chronic hepatitis follows hepatitis A, the clinician should suspect some other cause (eg, autoimmune, coexistent hepatitis B or C, Wilson’s disease).

QUESTION

• Could Patient 1’s disease have been prevented?

Discussion

Although most adults have acquired immunity to hepatitis A (through natural infection), today, many pediatricians include hepatitis A (and hepatitis B) in their vaccine programs.

CASE 2

INITIAL PRESENTATION

Patient 2 is a 22-year-old hemodialysis nurse who is admitted to the emergency room. She became ill 3 days prior to admission with anorexia and nausea. During the ensuing 3 days she gradually ate less, and on the day before admission, she was only able to drink water and juices. She became lethargic and slept most of the time. On the morning of admission, her roommate was barely able to wake her, and she was brought to the emergency room.

On questioning her roommate, it is clear that Patient 2 had been healthy, with no substantial past medical or surgical history. She was generally happy, has a boyfriend, and was planning marriage. She had nothing to suggest depression or a propensity to suicide. Her only medication is birth control pills. She drinks about 4 beers every weekend.

PHYSICAL EXAMINATION

On physical examination, Patient 2 is stuporous and cannot give a coherent history. Her blood pressure is 120/80 mm Hg. Her pulse is 68 bpm and is regular. She is afebrile. Asterixis is present. She is noticeably jaundiced, and her sclerae are icteric. Her heart and lungs are normal. The liver span is 6 cm in the MCL. There is no ascites or splenomegaly. Her stools are negative for occult blood.

LABORATORY EVALUATION

Laboratory investigation shows bilirubin in the patient’s urine. Her CBC and differential count are normal. Her serum electrolytes and BUN are normal. Her blood sugar, at 65 mg/dL, is at the lower end of normal. Her AST level is 2500 U/L, and her ALT level is 4000 U/L. The alkaline phosphatase is 150 U/L; serum albumin, 3.5 g/dL; and total protein, 7.0 g/dL. The prothrombin time is 21 seconds; INR is 2.5.

QUESTIONS

• What is Patient 2’s illness, and what are some of the causes to consider?
• Could her birth control pills or alcohol consumption be responsible?

Discussion

Patient 2 undoubtedly has fulminant hepatic necrosis, manifested by her stupor, extremely high aminotransferase levels and marked prolongation of her prothrombin time. Currently, the most common cause for this is ingestion of acetaminophen in a suicide attempt. Acute hepatitis B, acute hepatitis A, acute infectious mononucleosis, and Wilson’s disease should also be considered. Some patients present with fulminant hepatic necrosis of no discernible cause. Hepatitis C rarely, if ever, presents as fulminant hepatic necrosis. Her small amount of alcohol consumption is inconsequential to her illness.
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QUESTION

• What is the likely cause of the stupor and asterixis?

Discussion

Portosystemic encephalopathy from cirrhosis is secondary to colonic toxins bypassing the liver through portosystemic shunting. The responsible substances produced by the colon include ammonia, mercaptans, medium chain fatty acids, and some biogenic amines (eg, octopamine). However, in fulminant hepatic necrosis, shunting is not responsible. Rather, the liver becomes incapable of metabolizing these potentially toxic substances.

QUESTION

• Is hepatic encephalopathy the only cause of asterixis?

Discussion

Asterixis is also seen in uremia and in chronic obstructive pulmonary disease with CO₂ retention.

QUESTION

• What is the significance of the 6-cm liver span?

Discussion

Although the liver span in the MCL varies with an individual’s size, the 6-cm liver span is rather small and may reflect hepatic necrosis.

QUESTION

• What is the significance of Patient 2’s blood sugar level?

Discussion

Patient 2’s blood sugar level is normal, although on the low side. Hypoglycemia can become a problem in fulminant hepatic necrosis because the liver is partially responsible for maintaining fasting blood sugar levels through glycogen breakdown. It should be noted that not all patients with fulminant hepatic necrosis have hypoglycemia.

QUESTION

• What is the most definitive initial laboratory prognostic indicator?

Discussion

The prothrombin time is a simple, direct, prognostic indicator. A prolonged prothrombin time often becomes the most important laboratory test indicating the need for a transplant. Although Patient 2’s prothrombin time is prolonged, it is not prolonged to a dangerous degree. As long as her condition does not worsen, it is anticipated that she will not require a liver transplantation.

QUESTION

• What additional laboratory studies should be performed at this point?

Discussion

Serologic tests for hepatitis and serum toxicologic evaluations should be performed. Also, serum ceruloplasm and urinary copper levels should be obtained. These tests are used to determine the cause of the fulminant hepatic necrosis.

CLINICAL COURSE

Patient 2 is admitted to an intensive care unit and remains stuporous, but arouseable. Her vital signs remain stable. Pulse oximetry shows normal oxygenation. Her physical examination results remain unchanged. A screen for toxicologic evaluation, involving acetaminophen, shows normal results. Test results for HBsAg are positive. Those for HBeAg are positive, also. Test results for anti-HCV are negative. Test results for Epstein-Barr virus antibody are negative, and those for anti-HAV are negative. On the next day, her aminotransferase levels and prothrombin time are unchanged. Wilson’s disease screening tests are pending during this time. It is clear that the patient has acute viral hepatitis B. The liver transplantation team has been called in consultation.

QUESTION

• Are there any general therapeutic measures useful or needed at this point?

Discussion

Patient 2 should be given intravenous fluid and electrolyte support. Histamine₂ receptor antagonists should be used to decrease the risk of gastrointestinal hemorrhage. Fresh frozen plasma should be used if bleeding ensues. Lactulose via nasoenteral tube or orally, if possible, can diminish encephalopathy. The role of intense nutritional support is controversial, as it has not been shown by controlled studies to be of value. However, if it is used, either parenterally or enterally, a branch-chain-supplemented solution should be used.
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QUESTION

• If Patient 2’s condition were to worsen, are there special monitoring systems available and useful?

Discussion

Some centers have used intracranial monitors for pressure determinations. These are inserted into the subarachnoid space.

QUESTION

• What is the status of artificial hepatic support systems?

Discussion

Standard kidney hemodialysis has not been shown to be beneficial in hepatic encephalopathy. Some physicians have found charcoal hemoperfusion useful, but this is not available in most medical centers. Some newer hepatic support devices and porcine perfusion have been tried experimentally in a few centers. The results are still preliminary.

QUESTIONS

• What should be considered in determining whether Patient 2 should be considered for liver transplantation?

• Does acute hepatitis B preclude her undergoing liver transplantation?

Discussion

The best opportunity for survival in a patient with fulminant hepatic necrosis with stupor or coma who does not improve or continues to worsen is a liver transplantation. However, a patient with acute hepatitis B is perhaps the worst candidate for liver transplantation, as the acute hepatitis B invariably recurs in the transplanted liver, and sometimes has an accelerated course. However, recent modifications of transplantation immunotherapy and treatment with immune globulin and anti-hepatitis chemotherapy have permitted successful liver transplantation in patients with acute hepatitis B.

CONTINUED CLINICAL COURSE: RECOVERY

The patient gradually recovers. Her encephalopathy resolves. She is able to eat, and she is transferred off the intensive care unit. Her aminotransferases fall to about 500 U/L within a week. Her prothrombin time is 15 seconds (INR, 1.3), and she is prepared for discharge. Her boyfriend is taking a 2-week vacation to care for her. Test results for HBsAg and HBeAg remain positive, and those for her anti-HBe are negative. Her hepatitis B DNA titer is 2,400,000 copies/mL.

QUESTION

• What advice should be given to Patient 2 regarding sexual activity?

Discussion

There is a relatively high incidence rate relating to the sexual transmission of hepatitis B. Protected sex should be advised, especially with Patient 2 being positive for HBeAg, and with her high hepatitis B DNA level. Her boyfriend should be assessed for hepatitis B antibodies, and if negative for antigens and antibodies, he should be given hepatitis B vaccine, and probably hepatitis B hyperimmune globulin.

QUESTION

• Should Patient 2 be treated with lamivudine and interferon alfa?

Discussion

Because she is still in the acute stage of her illness, Patient 2 should not be treated with these substances now. If chronicity is established and she has persistently elevated aminotransferase levels, she would be a candidate for hepatitis B chemotherapy.

CONTINUED CLINICAL COURSE: PREGNANCY

Patient 2 gradually improves over the ensuing 3 months, but her aminotransferase levels remain around 200 U/L, and the antigenemia persists. She becomes nauseated in the morning 4 months after her admission, but her liver test results are unchanged. She misses a menstrual period, and this with a positive pregnancy test result confirm that she is pregnant.

QUESTION

• Should Patient 2 be advised to abort the pregnancy?

Discussion

Although there is a slightly higher risk of spontaneous abortion, there is no strong reason to recommend termination of the pregnancy.
QUESTION

• Will Patient 2’s pregnancy have an adverse effect on her health?

Discussion

This young patient, who has survived the acutely fulminant phase of hepatitis B, is now asymptomatic. However, she has persistent infection and will probably develop chronic hepatitis B. However, this does not pose a substantial risk to her health during pregnancy.

QUESTION

• What advice should Patient 2’s pediatrician and obstetrician be given?

Discussion

Assuming the patient remains positive for HBeAg, which is strongly predictive for vertical transmission to her offspring, it is necessary for the newborn to receive hepatitis B immune globulin. Eventually the baby should be immunized against hepatitis B. Hyperimmune globulin has been shown to markedly diminish the vertical transmission of hepatitis B.

CONTINUED CLINICAL COURSE: CHRONIC INFECTION

Patient 2 delivers a healthy 6-pound girl, who is given hepatitis B hyperimmune globulin, and eventually is immunized against hepatitis B. The mother has persistent HBsAg and HBeAg, and her aminotransferase levels remain around 200 U/L.

QUESTION

• Can Patient 2 now be considered a candidate for lamivudine and interferon?

Discussion

The patient is a good candidate for hepatitis B chemotherapy.

QUESTION

• What end points are chosen for treating Patient 2’s chronic hepatitis?

Discussion

The major goals of treatment are to convert her HBeAg to anti-HBe, and to eliminate serum hepatitis B DNA. This will indicate that live virus has been eliminated and that the patient is no longer infectious.

QUESTION

• Should Patient 2 have a liver biopsy?

Discussion

A liver biopsy should precede her therapy, as following the histologic course is also important in judging the efficacy of her therapy.

QUESTION

• What additional testing is necessary in the long-term follow-up of Patient 2?

Discussion

Annual ultrasonographic evaluations of her liver and annual measurements of her α-fetoprotein levels are important for the early identification of hepatoma. Individuals with hepatitis B and a hepatoma and those with hepatitis C and a hepatoma are treated similarly. The treatment options for an individual with hepatitis C and a hepatoma are discussed in Case 3.

CASE 3

INITIAL PRESENTATION AND EVALUATION

Patient 3 is a 46-year-old male accountant who was notified that he was positive for HCV after donating blood. The only notable event in his medical history is a motor vehicle accident that happened 20 years ago, which made it necessary for him to undergo a blood transfusion. He has a history of mild depression and a bleeding peptic ulcer that has now resolved and is currently not on antidepressants. He is asymptomatic for hepatitis C and denies any history of jaundice or decompensated liver disease. The patient reports substantial alcohol consumption during his 20s but has considered himself a social drinker for the past 10 years. The results of his physical examination are normal. His laboratory values are as follows: AST, 86 U/L; ALT, 106 U/L; total bilirubin, 1.0 mg/dL; prothrombin time, 11 seconds; albumin, 4.1 g/dL. He is also anti-HCV positive by third generation enzyme immunoassay (EIA).
QUESTION

• Are most individuals with HCV infection asymptomatic?

Discussion

Most individuals, such as Patient 3, are asymptomatic for HCV infection. This is the case for those with acute and for those with chronic infection. At this point, it cannot be determined if Patient 3 has acute or chronic infection, though his blood transfusion of 20 years ago suggests that he may have chronic infection. Chronic infection is arbitrarily defined as HCV infection of more than 6 months. However, usually producing no symptoms, acute infection often goes undiagnosed, and chronic infection is usually found only upon a routine medical examination.

QUESTION

• What is the role of risk factor analysis for the individual suspected of having HCV infection?

Discussion

For those with possible HCV infection, risk factors should be identified (Table 1) and include parenteral exposure to blood or blood products from other individuals (eg, via blood transfusion before 1992 or intravenous drug abuse [needle sharing]), a history of tattooing and/or body piercing, and sexual contact with an HCV-positive person, which is controversial but thought to occur. (The risk of sexual transmission by sexual secretions is much lower for hepatitis C than for hepatitis B. However, spouses of HCV-positive individuals do show an increased incidence of hepatitis C if followed for 10 years or more.) Despite a thorough review of all risk factors, a source of transmission is usually not defined in at least 20% of patients. Risk factor assessment can also help to determine the duration of infection and the potential for development of cirrhosis.

QUESTION

• Are elevated aminotransferase levels a good indication of possible HCV infection?

Discussion

Although it is already known that Patient 3 has HCV infection, elevation of aminotransferase levels is, in general, the first clue to possible HCV infection, particularly in the asymptomatic patient. The overall range can vary dramatically, but the majority of patients will have aminotransferase levels in the range of 2 to 3 times the upper limit of normal (normal, < 40 U/L). However, approximately 25% of patients will have persistently normal aminotransferases, and the absolute magnitude of elevation does not correlate with the amount of inflammation or rates of progression to fibrosis.

Other causes of elevated aminotransferase levels in patients should be considered in the differential diagnosis of patients with persistently elevated aminotransferases. They include chronic hepatitis B, Wilson’s disease, autoimmune hepatitis, hemochromatosis, and medication- or drug-induced liver toxicity. Rarely, a patient may have another cause superimposed on hepatitis C, both causing an increase in aminotransferase levels.

QUESTION

• What is the role of a history and physical examination in the follow-up evaluation of a patient with elevated aminotransferases and a positive result on an anti-HCV test?

Discussion

The follow-up evaluation of the patient with abnormal results on liver panel tests and a positive anti-HCV test result begins with a meticulous history and physical examination. The history and physical examination can be used to screen for and rule out many of the other previously mentioned causes of elevated aminotransferases. History and physical examination can also determine if there is presence of underlying cirrhosis and hepatic decompensation; extrahepatic manifestations of chronic hepatitis C can also be identified. Also, specific serologic markers are able to indicate the presence of hepatitis A, B, or C. Intravenous drug abuse is a risk factor for HBV and HIV infection (as well as HCV infection). Intravenous drug abusers should be screened for these conditions.

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Table 1. Risk Factors for Hepatitis C

| Chronic hemodialysis       |
| HBV infection             |
| History of tattooing and/or body piercing |
| HIV infection             |
| Intravenous drug abuse    |
| Receipt of blood or blood products via transfusion* |
| Sexual contact with an HCV-positive person |

*Since 1992, the risk of infection via blood transfusion has profoundly declined.

HBV = hepatitis B virus; HCV = hepatitis C virus.
QUESTIONS

• How is a diagnosis of HCV infection normally made?
• How is chronic infection determined?

Discussion

The initial screening test for HCV infection is serologic testing for anti-HCV. This is performed by either a second or third generation EIA. Both have a sensitivity of approximately 95%.

Confirmation of chronic HCV infection was historically made by performing a radioimmunoabsorbent assay (RIBA). This test identified the antigens to which anti-HCV was reacting. In the past, anti-HCV tests were less sensitive and specific and could show falsely elevated results in patients with rheumatologic conditions or other chronic liver diseases. Consequently, follow-up testing with RIBA confirmed the diagnosis by measuring the antigenic determinants against which the EIA was reactive.

Today, a positive result on an EIA, with its improved sensitivity, is followed directly by testing for HCV RNA levels. (The presence of detectable HCV RNA is a sign of chronic HCV infection.) This approach has become the gold standard for detection of chronic HCV infection. HCV RNA is detected by the use of reverse transcriptase polymerase chain reaction.

QUESTION

• When should liver biopsy be considered?

Discussion

Liver biopsy should be considered in patients who have abnormal liver function test results and positive results on HCV RNA tests for chronic HCV infection and who are being considered for therapy. Two critical pieces of information can be obtained from histologic analysis. First, the amount of fibrosis or scar formation can be determined, and secondly, the amount of inflammation can be assessed. These are typically quantified by the pathologist according to a modified hepatic activity index, whereby the amount of inflammation is graded and the amount of fibrosis is graded (Table 2 and Figures 1 to 4). Histologically defined cirrhosis correlates with stage 4 fibrosis although decompensation may not be present.

CLINICAL COURSE

An HCV RNA titer shows 6 million copies/mL. Patient 3 clearly has chronic hepatitis C. He undergoes a liver biopsy which shows stage 2 fibrosis and stage 2 inflammation (Figure 3). Increased amounts of hepatocellular fat are also present, typical of hepatitis C. Risks and benefits of therapy are discussed with the patient.

QUESTION

• Would it be clinically valuable to type the hepatitis C before making a recommendation for therapy for Patient 3?

Discussion

Although the typing of hepatitis C is of interest epidemiologically and investigatively, typing has not been very helpful clinically. It is true that some types yield much more severe disease than others, and unfortunately, the most severe types are less responsive to treatment. However, the liver biopsy and the clinical symptoms usually provide enough information to decide whether to treat or not.

QUESTION

• Does the terminology chronic active hepatitis and chronic persistent hepatitis apply to hepatitis C?

Discussion

Although the liver biopsy findings for Patient 3 appear consistent with chronic active hepatitis, the classification into chronic active and chronic persistent hepatitis is much more useful for autoimmune liver disease than for chronic hepatitis C. This is because the latter often moves from one category to another in time, whereas the histologic nature of disease is more stable through the years for autoimmune disease. The classification into the degree of fibrosis and inflammation at the time of the liver biopsy is a more productive classification for hepatitis C.

QUESTION

• Are there any other tests that would be of value in following patients with chronic hepatitis C?

Discussion

Because hepatocellular carcinoma occurs at a markedly increased incidence in chronic hepatitis C, it is reasonable to measure α-fetoprotein levels and perform a hepatic ultrasonographic examination annually.

QUESTION

• Should Patient 3 be advised to stop drinking alcohol?
Discussion

Although small amounts of alcohol are probably safe with hepatitis C, large amounts clearly accelerate the hepatitis process. It is probably safest to ask the patient to abstain completely.

QUESTION

• Are there any other serologic tests that would be of value in deciding therapy for Patient 3?

Discussion

All patients with chronic hepatitis C should be serologically checked for hepatitis A and B, as it is not uncommon for the patient to develop hepatitis A or B superimposed on hepatitis C, which accelerates the hepatitis process. If the patient is seronegative for hepatitis A or B, hepatitis A and B immunization should ensue.

QUESTION

• Is it necessary for an HCV-positive individual to practice protected sex with his or her spouse?

Discussion

HCV does not appear to be readily transmitted sexually, although there is a statistical increase in spouse anti-HCV after 10 years of disease. No special precautions are therefore necessary with one’s spouse, although protected sex is always the best policy prior to marriage.

QUESTION

• What therapy should Patient 3 undergo?

Discussion

Because Patient 3 has moderately severe disease, it would be reasonable to have him undergo interferon/ribavirin combination therapy. However, the patient’s history of depression is an important consideration because interferon can aggravate or precipitate an underlying depression.

CONTINUED CLINICAL COURSE

Patient 3’s anti-HAV, HBsAg, and anti-HBc test results are negative, and he is started on hepatitis A and B immunization. He is given oral ribavirin and 3 million units intramuscular interferon alfa 3 times weekly. The patient experiences some myalgias and low-grade fever after each intramuscular injection of interferon. On the third week of therapy, the patient feels depressed. Although he is not suicidal, he clearly feels that things are hopeless. He is sleeping poorly, and his ability to perform his work as an accountant is suffering.

QUESTIONS

• What guideposts for therapy should be used?
• How long should therapy be continued?

Discussion

If there is going to be a salutary response to interferon/ribavirin therapy, marked improvement in the aminotransferase levels is usually seen by 3 months. Some physicians discontinue therapy after 3 months if there is no response. For those who have failed to respond to this treatment, alternative treatments include interferon/ursodeoxycholate combination therapy or increases in the dose or duration of interferon alfa. However, it is controversial whether to continue therapy longer or at a higher dose if there is a failure to respond. These alternative treatments are currently under investigation, mostly in clinical trials.

QUESTIONS

• Is the aggravation of Patient 3’s underlying depression a contraindication to further therapy with interferon?

Table 2. Classification of Inflammation and Fibrosis of the Liver

<table>
<thead>
<tr>
<th>Liver Condition</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>1</td>
<td>A few areas of spotty necrosis</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Prominent portal inflammation; slight lobular hepatitis; no piecemeal necrosis</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Prominent portal inflammation; piecemeal necrosis involving up to half of the portal tracts</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Prominent portal and lobular hepatitis; piecemeal necrosis involving all of the portal fields; some areas of collapse (bridging necrosis)</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>1</td>
<td>No substantial fibrosis</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Portal fibrosis; no bridging fibrosis</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Bridging fibrosis</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Regenerating nodules; cirrhosis</td>
</tr>
</tbody>
</table>
If interferon therapy is to be discontinued, what alternative treatment, either currently available or used experimentally, should be considered?

**Discussion**

Most physicians would discontinue therapy with interferon at this point because of the risk of suicide and the severe depressive symptoms. The following are newer therapeutic options for hepatitis C that may be useful in treating those patients for whom interferon therapy is contraindicated or in those who have failed to respond to interferon: phlebotomy in those with normal or increased hepatic iron levels; newer antiviral agents; interleukin-10; and other cytokines. However, as with the other alternative treatments mentioned, these options are currently under investigation, mostly in clinical trials.

**CONTINUED CLINICAL COURSE AND PATIENT OUTCOME**

Although Patient 3 was advised of his risk of worsening depression, he desired to try to work through the depression with his psychiatrist and continue therapy. He was started on sertraline hydrochloride. He visited his psychiatrist twice weekly, and his depressive symptoms resolved. In addition, his myalgias and fever from the interferon therapy improved, and he was
able to continue the therapy. At 3 months, his liver aminotransferase levels returned to normal. It was decided to continue his therapy for a full 6 months, then to discontinue it. At 6 months he no longer had a detectable viral load. (His HCV RNA was no longer present). However, his α-fetoprotein was 50 ng/mL (normal, <12.5 ng/mL), and an ultrasonogram showed a 2-cm irregular hyperechoic lesion in his left hepatic lobe. The possibility of a hepatocellular carcinoma is raised.

**QUESTION**

- What further work-up is required for Patient 3 in light of the hepatic lesion?

**Discussion**

The patient requires a careful computed tomography scan with infusion to further characterize the hepatic lesion. If possible, a specimen of the nodule should be obtained by needle aspiration to characterize the lesion.

**QUESTION**

- Is Patient 3 predisposed to developing hepatocellular carcinoma?

**Discussion**

Both the presence of hepatitis C and the presence of
hepatic regeneration predispose those with chronic hepatitis C to hepatocellular carcinoma.

**QUESTIONS**

- Does Patient 3’s probable hepatoma or his chronic hepatitis C preclude liver transplantation?
- What are his treatment options at this point?

**Discussion**

Liver transplantation provides the most favorable result in a patient with hepatitis C (or hepatitis B) and a hepatoma. If not available, other options include chemoablation of the tumor by interventional radiologists or a segmental resection of the tumor, especially in those who are not cirrhotic. Careful discussion with the patient regarding the risks and benefits of the various treatment options should occur. If the liver transplantation option is adopted, the patient would have to have his listing, ie, his place on the liver transplantation list for available liver donors, augmented, as the usual 2-year wait for a routine liver transplantation would be unsatisfactory.

**QUESTION**

- If Patient 3 does undergo liver transplantation, is it unlikely that his hepatitis C will return since he no longer has detectable hepatitis C RNA?

**Discussion**

His hepatitis C would likely, although not invariably, return following the transplantation, perhaps secondary to the required immunosuppression following the transplantation. Some patients do not have evidence of reinfection.

**REFERENCES**


**SUGGESTED READINGS**