Hepatitis B and C

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KEYWORDS

• Hepatitis B • Hepatitis C • Elderly • Antiviral therapy • Interferon

KEY POINTS

- Hepatitis B and hepatitis C are common infections, which can lead to chronic liver disease, cirrhosis, and hepatocellular cancer; end-stage disease can be treated with liver transplantation.
- Significant progress in the evaluation and treatment of both diseases has been made in the past 20 years. Hepatitis B, although not curable, is suppressible with antiviral therapy, which has been shown to decrease liver disease morbidity and mortality.
- Elderly patients should be evaluated and treated for hepatitis in the same fashion as younger patients.
- Hepatitis C remains a major public health concern. Recent recommendations for birth cohort screening of all people in the United States born between 1945 and 1965 will increase the number of patients diagnosed with hepatitis C, especially among the elderly.
- A better understanding of the natural history of hepatitis C is needed. New methods of staging the disease will allow for noninvasive determination of fibrosis and allow more people to be adequately assessed for the disease.
- Newer, more efficacious therapies with fewer side effects and shorter durations of therapy should allow for more patients with hepatitis C to be treated, including the elderly, who remain an understudied and undertreated difficult-to-treat population with hepatitis C infection.

HEPATITIS B

Introduction

Hepatitis B virus (HBV) is a double-stranded DNA virus belonging to the family of hepadnaviruses and is classified into 8 genotypes (A–H). The prevalence of specific genotypes varies geographically. Perinatal and horizontal transmission early in life are most common in high-prevalence areas such as Southeast Asia and China, whereas sexual contact and percutaneous transmission (eg, intravenous drug use) are most common in the United States, Canada, and Western Europe.

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HBV infection is a global public health problem. It is estimated that there are more than 350 million HBV carriers in the world,[1] of whom approximately 500,000 die annually from HBV-related liver disease.

Serologic Assays

The diagnosis of HBV was revolutionized by the discovery of the Australia antigen now called hepatitis B surface antigen (HBsAg) more than 4 decades ago. Since then, serologic assays have been established for HBV antigens and antibodies as well as polymerase chain reaction (PCR) assays for determination of viral load. HBV DNA viral testing is used to assess HBV replication and determine the indication for and response to antiviral therapy.

HBsAg is the serologic hallmark for infection. In the case of an acute exposure to HBV, the antigen is detectable 1 to 10 weeks after exposure, before any symptoms or increase in alanine transaminase (ALT) levels. When the antigen has been present for more than 6 months, the patient has a chronic infection.

The anti–hepatitis B core antibody (anti-HBc) assay is used to detect antibodies to the hepatitis B core antigen, an intracellular antigen expressed in infected hepatocytes that cannot be detected in serum. During acute infection, the anti-HBc is mainly IgM class and can be detectable for up to 2 years after the infection. After resolution of acute infection or progression to chronic infection, the anti-HBc is mainly IgG class.

The hepatitis B e antigen (HBeAg) is a marker of HBV replication and infectivity and is associated with high levels of DNA in serum and higher rates of disease transmission. Conversion of HBeAg to anti–hepatitis B e antibody (anti-HBe) occurs early during acute infection but later in chronic infection. HbeAg-positive patients with infection acquired perinatally can have a normal ALT level and minimal inflammation in the liver.[1,2] Seroconversion from HBeAg to anti-HBe usually leads to decreased HBV DNA levels as well as remission of activity at the hepatocyte level.[3,4]

Serologic markers are used to determine the clinical phase of an acute or chronic infection as well as identify patients in need of immunization (**Table 1**).

Screening

Risk factors for HBV have been determined and should be used to identify patients with possible hepatitis B infection (**Box 1**).[1] Initial testing should include HBsAg, anti-HBc, and anti-HBs. Patients who are negative for these markers should be vaccinated. HBsAg-positive pregnant women should inform their providers so that their infants can receive hepatitis B immune globulin and vaccine immediately after delivery.

Carriers of HBV should be counseled regarding the risk of transmission to others and have a complete evaluation, including evaluation for other causes of liver disease and screening for hepatocellular carcinoma (HCC).

Acute Hepatitis B

Acute hepatitis B manifestations range from subclinical hepatitis in approximately 70% of patients to icteric hepatitis in 30% and fulminant hepatitis in 0.1% to 0.5% of patients. The incubation period is 1 to 4 months. Patients may develop a serum sicknesslike syndrome during the prodromal period followed by anorexia, nausea, jaundice, and right upper quadrant pain. The symptoms usually resolve within 3 months, but some patients have prolonged fatigue. Laboratory testing during this period shows increased aspartate transaminase and ALT levels, with possible increase of bilirubin levels as well. The prothrombin time is the best indicator of prognosis.

Table 1
Hepatitis B serologic panel interpretation

Tests	Results	Interpretation
HBsAg Anti-HBc Anti-HBs	Negative Negative Negative	Susceptible and should be immunized
HBsAg Anti-HBc Anti-HBs	Negative Positive Positive	Immune because of previous exposure
HBsAg Anti-HBc Anti-HBs	Negative Negative Positive	Immune because of vaccination
HBsAg Anti-HBc Anti-HBs IgM anti-HBc	Positive Positive Negative Positive	Acute or reactivation infection
HBsAg Anti-HBc Anti-HBs IgM anti-HBc	Positive Positive or negative Positive or negative Negative	Chronic infection
HBsAg Anti-HBc Anti-HBs	Negative Positive Negative	False positive anti-HBc, distantly immune, recovery phase of acute infection or very low levels of HBsAg which would mean chronic infection

The rate of progression from acute to chronic disease is determined by initial age at infection. For perinatal infections, the rate to development of chronic hepatitis B is 90%, 20% to 50% for age 1 to 5 years, and less than 5% for adult acquired infection.[5]

Treatment of acute hepatitis B is mainly supportive and should include appropriate measures to prevent infection in exposed contacts. Patients with coagulopathy, jaundice, or encephalopathy should be considered for more intensive follow-up, which may include hospitalization or the initiation of antiviral therapy. Older patients, those with significant comorbidities, or those who cannot tolerate oral intake should be hospitalized.

The overall recommendation for supportive care rather than treatment with antiviral therapy has been supported by Kumar and colleagues,[6] who showed that patients

Box 1
Risk factors for hepatitis B

People born in Asia, Africa, Middle East, South Pacific Islands, South America, Eastern Europe, Mediterranean

US-born persons not vaccinated as infants whose parents were born in high-risk regions

Household and sexual contacts of HBsAg-positive persons

Men who have sex with men

Intravenous drug use

Multiple sexual partners

Inmates of correctional facilities

Renal dialysis

receiving lamivudine for acute hepatitis B had no biochemical or clinical benefit compared with the placebo group. However, the role of antiviral therapy in patients with severe or protracted acute infection was not adequately addressed nor was the current standard of care therapies for chronic hepatitis B evaluated.

Current recommendations from the American Association for the Study of Liver Disease (AASLD) are to treat patients with acute hepatitis B with antiviral therapy if a severe or protracted course is present for more than 4 weeks or if the patient is immunocompromised, elderly, or has preexisting liver disease.[1] Telbivudine, lamivudine, tenofovir, or entecavir are all acceptable options, given as monotherapy, because the duration of treatment should be short. Treatment can be stopped after confirmation (2 consecutive tests 4 weeks apart) that the patient has cleared HBsAg. Interferon should be avoided in the acute setting, because of the risk of exacerbating the acute inflammatory response as a result of the possible ALT flare seen with interferon therapy.

Chronic Hepatitis B

Most patients with chronic hepatitis B are asymptomatic unless they have decompensated cirrhosis or extrahepatic manifestations. In decompensated cirrhosis, jaundice, coagulopathy, ascites, and encephalopathy can be present. Extrahepatic manifestations occur in about 10% to 20% of chronic infections and are believed to be mediated by circulating immune complexes. The 2 major complications seen are polyarteritis nodosa, which responds to antiviral therapy, and glomerular disease, which mainly occurs in children.

Phases of infection

Chronic HBV infection generally consists of 2 phases: an early replicative phase, with active liver disease, and a later phase, with low replication and remission of liver disease.[1,3,4] In patients with perinatally acquired HBV infection, there is an additional immune tolerance phase, in which virus replication is not accompanied by active liver disease.[7]

Replicative phase: immune tolerance In patients with perinatally acquired HBV infection, the initial phase is characterized by high levels of HBV replication but no evidence of active liver disease, with normal serum ALT concentrations and minimal changes on liver biopsy.[1,2] One study also showed that fibrosis scores on repeat biopsies were unchanged after 5 years among patients who remained in the immune-tolerant phase.[8] The lack of liver disease despite high levels of HBV replication is believed to be caused by immune tolerance to HBV, but the mechanism is unknown.[9] This is also believed to be the major reason for the poor response to interferon therapy in HBeAg-positive Asian patients who have normal serum ALT concentrations.

This phase can last up to 30 years, during which there is a very low rate of spontaneous HBeAg clearance.[10,11] The cumulative rate of spontaneous HBeAg clearance is approximately 2% during the first 3 years and 15% after 20 years of infection.[11]

Replicative phase: immune clearance During the immune clearance phase, spontaneous HBeAg clearance increases to 10% to 20% per year. Several studies from Asia have found that patients with genotype B infection undergo HBeAg seroconversion at an earlier age than those with genotype C infection.[10,11]

HBeAg seroconversion is frequently accompanied by increases in ALT levels and an increase in serum HBV DNA, but generally, patients remain asymptomatic. For unclear reasons, reactivation is more commonly observed in men more than in women.[12,13] Patients with severe reactivation should be referred to specialized centers for liver

transplantation or oral antiviral treatment. Interferon should be avoided in this scenario, because it can worsen the disease state.

Some patients, despite reactivation, do not have seroconversion and clearance of HBV DNA from the serum and remain with chronic disease. Multiple reactivations is associated with an increased risk of developing cirrhosis and HCC.

Low or nonreplication phase/inactive carrier state Previously termed healthy carriers, these patients are characterized by a pattern of being HBeAg negative and anti-HBe positive, with low HBV viral loads and liver disease that is in remission. However, studies have shown that significant liver disease can be found in patients with HBeAg-negative chronic HBV, but this is rare in those with persistently normal ALT levels and HBV DNA levels less than 2000 IU/mL.[14–16] For these reasons, the terminology of healthy carrier should be abandoned.

Because of the fluctuating nature of chronic HBV infection, patients should not be categorized as inactive carriers unless they have at least 3 ALT levels and 2 to 3 HBV DNA levels that meet the criteria listed earlier over a 12-month period of observation.

Some patients who are HBeAg negative can have moderate levels of HBV replication and active liver disease and are believed to have a residual wild-type virus or HBV variants that cannot produce HBeAg because of precore or core promoter genetic variations.[17,18] These patients tend to be older and have more advanced liver disease.

Resolution of chronic HBV infection

The annual rate of delayed clearance of HBsAg is 0.5% to 2% in Western countries compared with 0.1% to 0.8% in Asian countries.[19,20] Despite a generally favorable prognosis, clearance of HBsAg does not preclude the development of cirrhosis or HCC.[21,22] In 1 report, the likelihood of developing HCC was greater in those who cleared HBsAg when older than 50 years.[23] Furthermore, some of the patients may have had undocumented cirrhosis or irreversible liver damage before seroconversion.

Many patients who clear HBsAg remain HBV DNA positive when tested by PCR assays, particularly during the first 10 years after HBsAg clearance.[23] A reactivation of HBV replication with reappearance of HBeAg and HBV DNA (by hybridization assays) in serum and recrudescence of liver disease may occur when these patients are immunosuppressed or receive systemic cancer chemotherapy, systemic corticosteroids, or biological agents. The disease reactivation can vary in severity from mild and asymptomatic to severe with possible fulminant hepatic failure, resulting in the need for liver transplantation or death.

Prognosis with chronic infection

The estimated 5-year rates of progression from chronic hepatitis to cirrhosis is 12% to 20%; compensated cirrhosis to hepatic decompensation, 20% to 23%; and compensated cirrhosis to HCC, 6% to 15%.[24] The risk of progression seems to be greatest in patients who remain in the immune clearance phase, in patients who have delayed HBeAg seroconversion, and in patients who have had a reactivation of HBV replication after HBeAg seroconversion.[25,26]

However, these rates of progression were based on data in the preoral antiviral treatment era, and these treatments have changed the disease course in many treated patients.

HBV DNA levels correlate with progression to cirrhosis, as seen in the REVEAL HBV (Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer–Hepatitis B Virus) study,[27] which reported that over an 11-year period, the incidence of cirrhosis in patients with a viral load less than 300 copies/mL was 4.5% compared with 36% in

patients with viral load greater than 10^6 copies/mL. The HBV DNA level remained an independent predictor of the development of cirrhosis after adjusting for HBeAg status, age, sex, ALT level, cigarette smoking, and alcohol consumption. High serum HBV DNA (>10^6 copies/mL) was also an independent predictor of the development of HCC.[28]

In patients with HbeAg-negative chronic HBV with a low HBV viral load, HBsAg levels greater than 1000 UI/mL have been associated with an increased risk of disease progression and the development of HCC.[29]

Confection with Hepatitis C Virus or Hepatitis D Virus

Coexistent hepatitis C virus (HCV) infection has been estimated to be present in 10% to 15% of patients with HBV.[30] HCV superinfection in HBsAg carriers seems to reduce HBV DNA levels and increase the rate of HBsAg seroconversion.[31,32] Most patients with HBV/HCV coinfection have detectable serum HCV RNA but undetectable or low HBV DNA levels, indicating that HCV is the predominant cause of liver disease in these patients. Liver disease is usually more severe than in patients infected by HBV alone.[33]

For hepatitis D virus (HDV) infection, the presence of HBV is required for the HDV to replicate. HDV is endemic, particularly in Eastern Europe, Mediterranean countries, and the Amazon basin. It is uncommon in the United States. Acute HBV and HDV coinfection tends to be more severe than acute HBV infection alone and is more likely to result in fulminant hepatitis.[34] HDV superinfection in patients with chronic HBV infection is usually accompanied by a suppression of HBV replication, which is not well understood.[35] HDV superinfection has been associated with more advanced liver disease and accelerated progression to cirrhosis.[36,37]

Treatment of HBV

Given the risk of progressive liver disease, patients who meet the criteria should be considered for treatment.

Patients with compensated cirrhosis and HBV DNA levels of greater than 2000 IU/mL and those with decompensated cirrhosis and detectable HBV DNA by PCR assay should be considered for antiviral therapy, regardless of the serum ALT level.

AASLD recommendations for the treatment of chronic hepatitis C are shown in **Fig. 1**.[1] Recommendations from the European Association for the Study of the Liver, which were updated in 2012, suggest that patients be considered for treatment when they have HBV DNA levels greater than 2000 IU/mL, have serum ALT levels higher than the upper limit of normal, and have evidence of moderate to severe necroinflammation or at least moderate fibrosis on liver biopsy (or assessed using a validated noninvasive marker).[38]

HBeAg-positive patients

Treatment is recommended for those patients with HBV DNA levels greater than 20,000 IU/mL and ALT levels greater than 2 times the upper limit of normal in patients without cirrhosis. Treatment should be delayed for 3 to 6 months in newly diagnosed HbeAg-positive patients with compensated liver disease to determine whether spontaneous HBeAg seroconversion will occur. However, if the patient has recurrent hepatitis flares that fail to clear HBeAg, or active or advanced histologic findings or is older than 40 years, treatment should be considered.[1]

HBeAg-negative patients

Treatment is recommended for patients whose ALT is greater than 2 times the upper limit of normal and HBV DNA levels are greater than 2000 IU/mL. Liver biopsy should

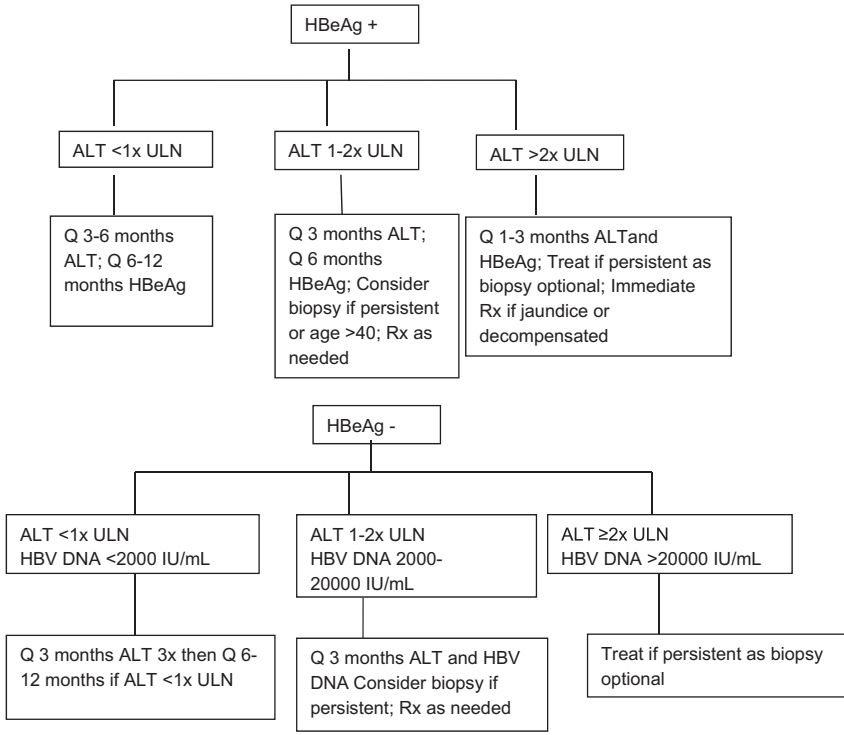

Fig. 1. Management of HBV (AASLD guidelines).

be considered in HbeAg-negative patients who have serum HBV DNA levels of greater than 2000 IU/mL and normal or mildly increased ALT levels to determine if treatment is warranted.

Treatment options

Interferon Interferon α, an injectable medication, may be administered at a dose of 5 million units daily, 10 million units 3 times a week, or as a once-weekly injection for a duration of 16 to 24 weeks in HbeAg- positive patients and at least 12 months in HbeAg-negative patients. Interferon therapy results in a 60% to 70% loss of HBV DNA, 60% to 70% normalization of ALT levels, and a 10% to 20% durability of response.[1] Pegylated interferon is associated with a 48% improvement in liver histology.[1] The advantage of interferon is the finite duration of treatment compared with other treatments. There is also the absence of selection of resistant mutants and a more durable response. There are several disadvantages to interferon use. The side effects of interferon are significant for many patients, especially the elderly, and the need for multiple injections compared with other all-oral therapies may lead to less patient acceptance of this therapy. Furthermore, interferon cannot be used in patients with cirrhosis, decompensated disease, or active or reactivation disease.

Lamivudine Lamivudine was the first oral agent approved for use in chronic hepatitis B infection. Lamivudine therapy results in a 60% to 73% loss of HBV DNA, 60% to 79% normalization of ALT levels, 60% to 66% improvement in liver histology, and a less than 10% durability of response.[1] Its main advantages are low cost and the

many years of experience confirming its safety, including its use during pregnancy. However, there is a high rate of drug resistance, 70% at 4 years, which severely limits its long-term use.[38] The role of lamivudine in the care of HBV is diminishing with the availability of new therapies, which are associated with lower rates of drug resistance.

Adefovir Adefovir was mainly used for lamivudine-resistant HBV, because it has a lower rate of drug resistance compared with lamivudine. Adefovir therapy results in a 51% loss of HBV DNA, 72% normalization of ALT levels, 64% improvement in liver histology, and a less than 5% durability of response.[1] At high doses, adefovir has been associated with nephrotoxicity. The rate of drug resistance has been reported to be as high as 29% after 5 years of treatment.[38]

Telbivudine Telbivudine therapy results in an 88% loss of HBV DNA, 74% normalization of ALT levels, and a 67% improvement in liver histology.[1] Telbivudine has a high rate of resistant mutation development at 2 years therapy (17%).[38] Its role as primary therapy is limited. Myopathy has been reported with telbivudine use.[38]

Entecavir Entecavir therapy results in a 90% loss of HBV DNA, 78% normalization of ALT levels, and 70% improvement in liver histology.[1] The main advantages of entecavir are its potent antiviral activity and a low rate of drug resistance (<1%).[1]

Tenofovir Tenofovir therapy results in a 93% loss of HBV DNA, 76% normalization of ALT levels, and 72% improvement in liver histology.[1] The main advantages of tenofovir are its potent antiviral effects and lack of reported drug resistance.[38]

Treatment End Points

The optimal duration of therapy for the oral drugs is not well established. Most patients require at least 4 to 5 years of treatment, and some may require indefinite treatment. In patients who are HBeAg positive, the end point after 1 year is HBeAg seroconversion and undetectable HBV DNA. If therapy is discontinued, patients should be closely monitored after discontinuation of treatment of viral relapse. In patients who are HBeAg negative, there is no defined end point. Treatment may be discontinued in patients who have confirmed loss of HBsAg and HBsAb seroconversion, but this is uncommon, occurring in less than 5% of patients after 5 years of continued therapy.[1,38]

In patients with compensated cirrhosis, lifelong treatment is recommended to prevent HCC and decompensation, but discontinuing treatment can be considered if the patient has a hepatitis B surface antibody seroconversion.[1,38] For decompensated cirrhosis, lifelong treatment is recommended.[1,38]

Hepatitis B in the Elderly: Special Considerations

The prevalence of hepatitis B among people older than 50 years in the United States is significantly greater than in those younger than 50 years.[39] Clinical manifestations of chronic hepatitis B in the elderly are similar to those of a younger population, but the manifestations of acute disease differ with more presentations of asymptomatic acute disease and fewer episodes of jaundice and fulminant disease. Patients acutely infected with hepatitis B older than 65 years are less likely to clear infection and more likely to develop chronic disease, at a rate of 59%.[40] Chronically infected individuals aged 60 years or older are more likely to spontaneously clear HBsAg than younger patients.[20] Adults older than 60 years are 4 times more likely to be HBeAg positive than those younger than 40 years.[41]

Treatment of hepatitis B is not dependent on age, and the elderly should be treated if appropriate treatment criteria are met. Interferon, with its side effect profile, may best be

avoided in the elderly. Entecavir and tenofovir, which are the recommended agents of choice for the treatment of chronic hepatitis B,[1,38] should be used with caution in the elderly. These agents are excreted by the kidney and must be dose reduced for a creatinine clearance less than 50. Elderly patients on these therapies should have their creatinine clearance and serum phosphate levels monitored during therapy at initial intervals of every 3 months for 1 year and then every 6 months for the duration of therapy.[38]

Elderly patients receiving chemotherapy, systemic corticosteroids, biological response modifiers, and other forms of immunosuppression should be checked for the presence of hepatitis B before initiation of these therapies, because these agents may be associated with disease reactivation. **Screening for hepatitis B in this population should include HBsAg and anti-HBc, and those who are positive should be tested for the presence of HBV DNA**. Certain patients may require prophylaxis before initiation of these therapies. If prophylaxis is required, current recommendations are for lamivudine or telbivudine if the anticipated duration is less than 12 months and tenofovir or entecavir if longer treatment is anticipated.[1,38]

Nursing home residents have an increased risk of hepatitis B acquisition, and the prevalence of hepatitis B infection has been found to be higher in nursing home residents than in noninstitutionalized residents of similar age.[42] Because of this situation, it is recommended that all nursing home residents and their health care providers be vaccinated against hepatitis B.

HEPATITIS C

Introduction

HCV can cause both acute and chronic hepatitis. The acute process is self-limited, rarely causes hepatic failure, and leads to chronic infection in 60% to 80% patients. Chronic HCV infection often follows a progressive course over many years and can result in cirrhosis, HCC, and the need for liver transplantation. In the United States, chronic HCV is the most common cause of chronic viral liver disease and the most frequent indication for liver transplantation.[43]

Because of the long course of the disease, it is difficult to define the natural history. A review of 111 studies evaluating the natural history estimated that the prevalence of cirrhosis was 16% after 20 years.[44] However, not all patients have progressive disease, and mortality is not always related to liver disease. Cirrhosis occurs in about half the chronically infected patients.[45,46] Once advanced fibrosis has occurred, the risk of progressing to cirrhosis is 10% a year. The risk of decompensation is approximately 3.9% a year.[47]

The hallmark of decompensated disease is the appearance of ascites, variceal bleeding, encephalopathy jaundice, or HCC. Hepatitis C also accounts for a third of the HCC cases in the United States. However, deaths associated with HCV in the United States are more likely caused by end-stage liver disease than HCC.[47] The risk of developing HCC is estimated to be approximately 3% a year.[47] It also seems to be greater in patients with genotype 1b than in those with genotype 2a/c.[48]

The reason for the differences in susceptibility among individual patients is not clear, but host and viral factors may play a role. Host factors that have been studied include high BMI, hepatic steatosis, insulin resistance, alcohol intake, and marijuana use. The effect of viral factors such as viral load and genotype on progression is less certain.

Screening for Hepatitis C

Screening for hepatitis C is initially performed through serologic assays that detect antibodies to hepatitis C, followed by confirmatory molecular assays that detect and

quantify HCV RNA in those patients with positive hepatitis C antibody. Historically, patients chosen for hepatitis C testing were those found to have increased liver enzyme levels or those who had 1 or more risk factors for the disease (**Box 2**). However, in August, 2012, the US Centers for Disease Control (CDC) recommended that all people born between 1945 and 1965 be tested once for hepatitis C, including those without identifiable HCV risk factors.[49] The United States Preventative Services Task Force endorsed this recommendation in 2013.[50]

Management of Hepatitis C

Management focuses not only on antiviral therapy but also on psychological counseling and symptom management, as well as screening for complications of cirrhosis. Because of common modes of transmission, patients should be screened for HIV and hepatitis B as well. In addition, patients should be tested for hepatitis A to determine if vaccination is required to prevent the acquisition of hepatitis A or B.

Counseling

Although most patients are asymptomatic, the diagnosis can have important emotional and physical consequences. Patients should be offered counseling and screening for depression, and may benefit from participation in a support group. Education should be provided about the routes of HCV transmission as well as factors that promote hepatic fibrosis, such as alcohol and obesity.

Symptom management

Many patients with HCV who are otherwise asymptomatic complain of fatigue even before the diagnosis. The cause of the fatigue is uncertain and may improve after hepatitis C treatment. One large study of 431 patients who underwent treatment of HCV reported that fatigue improved significantly more often in responders than in nonresponders (35 vs 22%) to antiviral therapy.[51] Ondansetron (a 5-HT3 receptor antagonist) was found to significantly improve fatigue in a placebo-controlled trial of 36 patients.[52] Long-term efficacy of ondansetron is unclear, and adverse effects include constipation and cardiac arrhythmias.

Patients can also present with extrahepatic manifestations of chronic hepatitis C, which seem to be directly related to the viral infection. In 1 study of 321 patients,

Box 2
Risk factors for hepatitis C

- Illicit injection drug use
- Intranasal cocaine use
- Received clotting factors made before 1987
- Receiving a blood transfusion or organ transplant before July, 1992
- Long-term hemodialysis
- Needlestick exposure
- Children born to hepatitis C virus–positive mothers
- Human immunodeficiency virus coinfection
- History of incarceration
- Sexual partner with hepatitis C virus
- Unregulated tattoo

38% patients had at least 1 extrahepatic manifestation (Table 2).[53] Certain extrahepatic manifestations, such as cryoglobulinemia, porphyria cutanea tarda, leukocytoclastic vasculitis, necrolytic acral erythema, and glomerulonephritis, respond to HCV treatment.

Cirrhosis can lead to esophageal variceal bleeding as well as HCC. Patients with cirrhosis should be screened for the presence of esophageal varices with upper endoscopy and undergo surveillance for HCC with imaging twice a year.

Antiviral Therapy

The goal of therapy is to eradicate HCV RNA and have a sustained virologic response (SVR). SVR is associated with a 97% to 100% chance of being HCV RNA negative during long-term follow-up and has been associated with a decrease in all-cause mortality, liver-related death, the need for liver transplantation, HCC, and liver-related complications, even in those patients with advanced liver fibrosis.[54–57]

Patients must be carefully selected for current HCV therapy. The decision to treat is based on multiple factors, including genotype, fibrosis stage, patient motivation, and the efficacy and adverse effects related to therapy. Genotype testing helps determine the choice of therapy and the duration of therapy and predicts the likelihood of obtaining an SVR.

Table 2
Extrahepatic manifestations of HCV infection

Skin	**%**
Purpura	7
Raynaud phenomenon	7
Cutaneous vasculitis	6
Pruritus	6
Psoriasis	20
Porphyria cutanea tarda	1
Lichen planus	1
At least 1 skin manifestation	17
Rheumatologic	
Arthralgia	19
Arthritis	2
Myalgia	2
Neurologic	
Sensory neuropathy	9
Motor neuropathy	5
Miscellaneous	
Sicca syndrome (eye)	10
Sicca syndrome (mouth)	12
Hypertension	10
Uveitis	1
At least 1 extrahepatic clinical manifestation	38

Data from Cacoub P, Renou C, Rosenthal E, et al. Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. The GERMIVIC. Groupe d'Etude et de Recherche en Medecine Interne et Maladies Infectieuses sur le Virus de l'Hepatitis C. Medicine (Baltimore) 2000;79:47.

Fibrosis

Hepatic fibrosis occurs in response to chronic liver injury, regardless of the cause. It is a dynamic process, with potential for reversal and resolution. Determining fibrosis is critical in the management of patients with hepatitis C. Patients with advanced fibrosis tend to have a lower response to treatment. Treatment may be delayed or deferred if minimal fibrosis is present.

Liver biopsy is considered to be the gold standard for the staging of hepatic fibrosis. Liver biopsy may also help exclude other liver diseases, such as autoimmune hepatitis or iron overload.

In recent years, noninvasive serologic tests and transient elastography have been developed as an alternative to liver biopsy to assess hepatic fibrosis. Serologic testing is more readily available, because transient elastography has only recently been approved in the United States. Serologic tests can differentiate patients with significant fibrosis (F2–F4) from minimal fibrosis (F0–F1). Serologic testing does not reliably differentiate between moderate and severe fibrosis.[58]

Ultrasound-based transient elastography was approved for use in the United States in 2013. This technology measures liver stiffness using a section of liver that is approximately 1 cm by 5 cm, an area that is approximately 100 times larger than a liver biopsy and therefore more representative of the hepatic parenchyma.[58] A meta-analysis of 9 studies[59] showed that transient elastography had an 87% sensitivity and 91% specificity for diagnosing cirrhosis and a 70% sensitivity and 84% specificity for diagnosing significant fibrosis. Factors that reduce the accuracy of transient elastography include ascites, increased central venous pressure (heart failure), and obesity.

In the future, it may be feasible to use a combination of tests, such as a serologic panel and transient elastography, to better assess underlying liver fibrosis in a highly accurate and noninvasive fashion and without needing a liver biopsy to garner this important clinical information.

Treatment options

The current standard of care is to treat patients with genotype 1 with pegylated interferon, ribavirin, and a protease inhibitor, either telaprevir or boceprevir, which are considered direct-acting antiviral therapy. Patients with other genotypes are currently treated with pegylated interferon and ribavirin.[43] Treatment is generally indicated in patients with a detectable viral load, fibrosis, and without contraindications to treatment. Changes in viral load during therapy are used to determine if a patient is responding to treatment and to predict whether the patient is likely to eradicate the virus. The earlier the HCV RNA becomes undetectable during treatment, the more likely a patient is to eradicate the virus and develop an SVR. Response-guided therapy, in which the length of treatment is determined by virologic response, has become the standard method of determining treatment duration.[60] Patients with cirrhosis are not eligible for response-guided therapy and are treated for 48 weeks with telaprevir-based or boceprevir-based regimens.[60]

For patients with genotype 1, protease inhibitor–based therapy leads to SVR rates of 70% to 80%.[61] Patients with genotype 2 and 3 treated with pegylated interferon and ribavirin have SVR rates of 70% to 80%.[61]

Contraindications for interferon-based therapy include active major depression, autoimmune disorders, and pregnancy. A more comprehensive list of adverse events is listed in **Table 3**.[60]

Patients receiving telaprevir or boceprevir are at increased risk for developing anemia. Telaprevir is frequently associated with rashes.[60] Care of patients with chronic hepatitis C depends on recognition of those at increased risk for side effects,

Table 3
Adverse effects of peginterferon, ribavirin, and protease inhibitors

Medication	Side Effect
Peginterferon	Flulike symptoms Anemia Neutropenia Thrombocytopenia Rashes Hair loss Thyroid dysfunction Depression Fatigue Irritability and mania Nonproductive cough Dyspnea Ophthalmologic disorders such as retinal hemorrhages Teratogenicity Exacerbations of autoimmune diseases
Ribavirin	Hemolytic anemia Rash Nonproductive cough
Telaprevir	Rash Pruritus Anemia Nausea Hemorrhoids Anorectal discomfort Diarrhea Dysgeusia Fatigue Vomiting Anal pruritus
Boceprevir	Fatigue Anemia Nausea Headache Dysgeusia Dry mouth Vomiting Diarrhea

anticipation (and prevention) of side effects, and appropriate intervention when adverse events occur. The ability to achieve an SVR is dependent on the degree of compliance with therapy.[60]

Future Directions in Hepatitis C Therapy

The treatment of hepatitis C is undergoing a rapid change, with many new, potentially more efficacious, and better tolerated therapies on the horizon. Newer, all-oral therapies for genotype 2 and 3 are likely to be approved before newer all-oral regimens are available for genotypes 1, 4, and 5. Newer regimens for the treatment of genotypes 1, 4, and 5 combining pegylated interferon, ribavirin, and other classes of direct-acting antiviral therapies such as newer protease inhibitors, polymerase inhibitors, NS5A inhibitors, and NS5B inhibitors are likely to become available in the near future. These

therapies seem to be more efficacious, better tolerated, and of shorter duration than currently available treatment options and offer hope that most patients with hepatitis C can be treated and cured.[62–65]

Hepatitis C in the Elderly: Special Considerations

Although the prevalence of hepatitis C is estimated to be about 3% of the global population,[66] the estimated prevalence of hepatitis C in the elderly population is significantly higher. Cainelli[67] estimated the prevalence of hepatitis C infection in individuals in Italy older than 60 years to be approximately 40%. Other prevalence studies[68–72] have described a prevalence of 1% to 11% in people older than 60 years. Risk factor specific screening yielded a prevalence of HCV infection of 87% in elderly individuals with a history of abnormal ALT levels or blood transfusions before 1992.[69] With the adoption of the CDC and US Services Preventive Task Force recommendation for cohort screening of all individuals born between 1945 and 1965, the number of elderly patients diagnosed with hepatitis C in the United States is likely to increase significantly. In addition to common risk factors for hepatitis C infection, older individuals are more likely to have received blood transfusions before 1992 or served in the military as a young adult, another potential risk factor for hepatitis C.

The natural history of hepatitis C in the elderly is unclear, although older individuals are more likely to present with more advanced disease, including cirrhosis and HCC.[73] Older, newly infected individuals progress more rapidly to advanced disease than younger newly infected individuals, with the mean time to cirrhosis described as 16 years in the older group compared with 33 years in the younger group.[74,75] Several investigators have concluded that the time to the development of cirrhosis and HCC in individuals who were infected with HCV after blood transfusions after the age of 50 years is more rapid than in younger patients.[45,76]

Elderly individuals with hepatitis C are more likely to have a normal ALT level than younger counterparts. Because the elderly population is less likely to undergo liver biopsy for disease staging, the value of using noninvasive markers of fibrosis and transient elastography, despite their shortcomings, becomes heightened.

Few studies have examined the treatment of older adults with hepatitis C. Most clinical treatment trials have excluded subjects older than 70 years. Elderly patients are less likely in clinical practice to be offered current antiviral therapy because of concerns regarding medication adverse events and comorbid illnesses, especially heart, pulmonary, and hematologic diseases and depression. These factors led the National Institutes of Health Consensus Conference to identify elderly patients as a difficult-to-treat group.[77] One small study of 33 patients suggested a lower SVR rate (46%) in elderly patients with a mean age of 70.2 years when compared with younger patients (69%) when treated with pegylated interferon and ribavirin.[78] No data are available to assess the efficacy and adverse event profile of the protease inhibitors telaprevir and boceprevir in the treatment of elderly patients. The hope for the treatment of elderly patients with chronic hepatitis C is that the new pipeline of medications, which are more efficacious, have fewer adverse events, have shorter treatment durations and are all oral, will allow this difficult-to-treat patient group to be safely treated.

SUMMARY

Hepatitis B and hepatitis C are common infections, which can lead to chronic liver disease, cirrhosis, hepatocellular cancer; end-stage disease can be treated with liver transplantation. Significant progress in the evaluation and treatment of both diseases has been made in the past 20 years. Hepatitis B, although not curable, is suppressible

with antiviral therapy, which has been shown to decrease liver disease morbidity and mortality. Elderly patients should be evaluated and treated for hepatitis in the same fashion as those of younger ages.

Hepatitis C remains a major public health concern. Recent recommendations for birth cohort screening of all people in the United States born between 1945 and 1965 will increase the number of patients diagnosed with hepatitis C, especially among the elderly. A better understanding of the natural history of hepatitis C is needed. New methods of staging the disease will allow for noninvasive determination of fibrosis and allow more people to be adequately assessed for the disease. Newer, more efficacious therapies with fewer side effects and shorter durations of therapy should allow for more patients with hepatitis C to be treated, including the elderly, who remain an understudied and undertreated difficult-to-treat population with hepatitis C infection.

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