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The Crux

BIMONTHLY FORUM FOR THE LABORATORIANS

CONTENTS

Editorial

Viral hepatitis is liver inflammation due to a viral infection. It may present in acute form as a recent infection with relatively rapid onset, or in chronic form.

The most common causes of viral hepatitis are the five unrelated hepatotropic viruses hepatitis A, B, C, D, and E. Other viruses can also cause liver inflammation, including cytomegalovirus, Epstein-Barr virus, and yellow fever. There also have been scores of recorded cases of viral hepatitis caused by herpes simplex virus.

The most common types of hepatitis can be prevented or treated. Hepatitis A and hepatitis B can be prevented by vaccination. Effective treatments for hepatitis C are available but costly.

In 2013, about 1.5 million people died from viral hepatitis, most commonly due to hepatitis B and C. East Asia, in particular Mongolia, is the region most affected.

The virus first known to cause hepatitis was the yellow fever virus, a mosquito-borne flavivirus. Other viruses than can cause hepatitis include:

- Adenoviruses
- Arenaviruses: Guanarito virus, Junín virus, Lassa fever virus, Lujo virus, Machupo virus, and Sabiá virus
- Bunyaviruses: Crimean-Congo hemorrhagic fever virus, Dobrava virus, Hantaan virus, Puumala virus, Rift Valley fever virus, and Seoul virus
- Coronavirus: severe acute respiratory syndrome virus
- Erythrovirus: Parvovirus B19
- Filoviruses: Ebola virus and Marburg virus
- Flaviviruses: dengue, Kyasanur Forest disease virus, Omsk hemorrhagic fever virus, and yellow fever virus
- Herpesviruses: cytomegalovirus, Epstein–Barr virus, varicella-zoster virus, human herpesvirus 6, human herpesvirus 7, and human herpesvirus 8
- Orthomyxoviruses: influenza
- Picornaviruses: echovirus
- Reovirus: Colorado tick fever virus, reovirus 3

The **"DISEASE DIAGNOSIS"** segment talks all about VIRAL HEPATITIS.

"INTERPRETATION" section highlights Hepatitis Serology Markers in ample detail.

And lastly the**" TROUBLESHOOTING"** part of the communiqué clearly defines the UNIVERSAL GUIDELINES TO BE FOLLOWED DURING AN INFLUENZA LIKE ILLNESS PANDEMIC (like Covid 19) IN RELATION TO DIAGNOSTIC LABS.

Anything missing? Not really. Just peep inside!

DISEASE DIAGNOSIS

VIRAL HEPATITIS

Background

Hepatitis, a general term referring to inflammation of the liver, may result from various causes, both infectious (ie, viral, bacterial, fungal, and parasitic organisms) and noninfectious (eg, alcohol, drugs, autoimmune diseases, and metabolic diseases); this article focuses on viral hepatitis, which accounts for more than 50% of cases of acute hepatitis in the United States, primarily in the emergency department setting. In the United States, viral hepatitis is most commonly caused by hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). These three viruses can all result in acute disease with symptoms of nausea, abdominal pain, fatigue, malaise, and jaundice. Additionally, acute infection with HBV and HCV can lead to chronic infection. Patients who are chronically infected may go on to develop cirrhosis and hepatocellular carcinoma (HCC). Furthermore, chronic hepatitis carriers remain infectious and may transmit the disease for many years.

Other hepatotropic viruses known to cause hepatitis include hepatitis D virus (HDV) and hepatitis E virus (HEV). However, the term hepatotropic is itself a misnomer. Infections with hepatitis viruses, especially HBV and HBC, have been associated with a wide variety of extrahepatic manifestations. Infrequent causes of viral hepatitis include adenovirus, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and, rarely, herpes simplex virus (HSV). Other pathogens (eg, virus SEN-V) may account for additional cases of non-A/non-E hepatitis.

Acute versus chronic viral hepatitis

The term viral hepatitis can describe either a clinical illness or the histologic findings associated with the disease. Acute infection with a hepatitis virus may result in conditions ranging from subclinical disease to self-limited symptomatic disease to fulminant hepatic failure. Adults with acute hepatitis A or B are usually symptomatic. Persons with acute hepatitis C may be either symptomatic or asymptomatic (ie, subclinical). Typical symptoms of acute hepatitis are fatigue, anorexia, nausea, and vomiting. Very high aminotransferase values (>1000 U/L) and hyperbilirubinemia are often observed. Severe cases of acute hepatitis may progress rapidly to acute liver failure, marked by poor hepatic synthetic function. This is often defined as a prothrombin time (PT) of 16 seconds or an international normalized ratio (INR) of 1.5 in the absence of previous liver disease. Fulminant hepatic failure (FHF) is defined as acute liver failure that is complicated by hepatic encephalopathy. In contrast to the encephalopathy associated with cirrhosis, the encephalopathy of FHF is attributed to increased permeability of the blood-brain barrier and to impaired osmoregulation in the brain, which leads to brain-cell swelling. The resulting brain edema is a potentially fatal complication of fulminant hepatic failure. FHF may occur in as many as 1% of cases of acute hepatitis due to hepatitis A or B. Hepatitis E is a common cause in Asia; whether hepatitis C is a cause remains controversial. Although FHF may resolve, more than half of all cases result in death unless liver transplantation is performed in time. Providing that acute viral hepatitis does not progress to FHF, many cases resolve over a period of days, weeks, or months. Acute HBV infection is generally considered resolved once an individual has developed antibodies to the hepatitis B surface antigen (anti-HBs) and has cleared hepatitis B surface antigen (HBsAg) from their serum. Alternatively, acute viral hepatitis may evolve into chronic hepatitis. HBV infection is considered to have progressed to chronic infection when HBsAg, hepatitis B e antigen (HBeAg), and high titers of hepatitis B viral DNA are found to persist in the serum for longer than 6 months. Hepatitis C infection is considered to have progressed to chronic infection when HCV RNA persists in the blood for longer than 6 months. Hepatitis A and hepatitis E never progress to chronic hepatitis, either clinically or histologically. The likelihood of progressing to chronic hepatitis B infection varies with the age at the time of infection. Chronic hepatitis B infection develops in up to 90% of individuals infected as neonates; however only 1-5% of individuals infected with HBV as adults develop chronic hepatitis B infection. Chronic hepatitis C infection develops in 75-85% of patients infected with hepatitis C. Individuals infected with HCV at a younger age are less likely to develop chronic hepatitis C infection. Some patients with chronic hepatitis remain asymptomatic for their entire lives. Other patients report fatigue (ranging from mild to severe) and dyspepsia. Individuals with chronic hepatitis B or hepatitis C infection may go on to develop cirrhosis, with histologic changes of severe fibrosis and nodular regeneration. In their study of serologic markers in patients with cirrhosis and hepatocellular carcinoma, Perz et al estimated that 57% of cirrhosis and 78% of hepatocellular carcinoma worldwide was attributable to chronic infection with either hepatitis B or C. Although some patients with cirrhosis are asymptomatic, others develop life-threatening complications. The clinical illnesses of chronic hepatitis and cirrhosis may take months, years, or decades to evolve.

Pathophysiology

Hepatitis A

The incubation period of hepatitis A virus (HAV) is 15-45 days (average, 4 weeks). The virus is excreted in stool during the first few weeks of infection, before the onset of symptoms. Young children who are infected with HAV usually remain asymptomatic. Acute hepatitis A is more severe and has higher mortality in adults than in children. The explanation for this is unknown. Typical cases of acute HAV infection are marked by several weeks of malaise, anorexia, nausea, vomiting, and elevated aminotransferase levels. Jaundice develops in more severe cases. Some patients experience a cholestatic hepatitis, marked by the development of an elevated alkaline phosphatase (ALP) level, in contrast to the classic picture of elevated aminotransferase levels. Other patients may experience several relapses during the course of a year. Less than 1% of cases result in fulminant hepatic failure (FHF). HAV infection does not persist and does not lead to chronic hepatitis.

Hepatitis B

Hepatitis B virus (HBV) may be directly cytopathic to hepatocytes. However, immune system–mediated cytotoxicity plays a predominant role in causing liver damage. The immune assault is driven by human leukocyte antigen (HLA) class I–restricted CD8 cytotoxic T lymphocytes that recognize hepatitis B core antigen (HBcAg) and hepatitis B e antigen (HBeAg) on the cell membranes of infected hepatocytes.

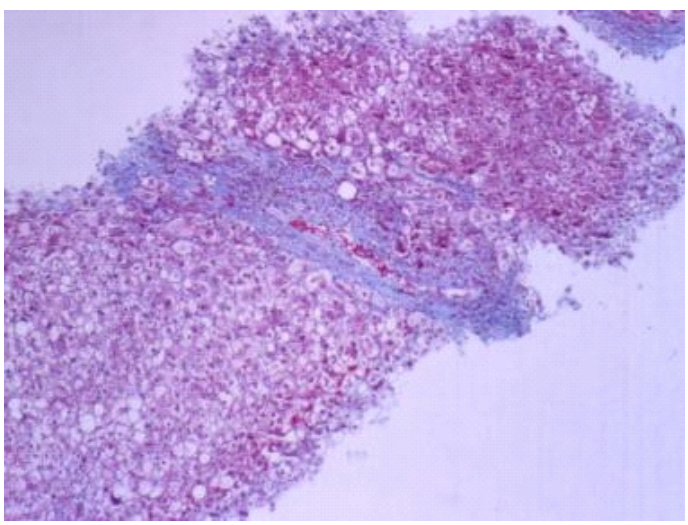
Acute infection

The incubation period of HBV infection is 40-150 days (average, approximately 12 weeks). As with acute HAV infection, the clinical illness associated with acute HBV infection may range from mild disease to a disease as severe as FHF (< 1% of patients). After acute hepatitis resolves, 95% of adult patients and 5-10% of infected infants ultimately develop antibodies against hepatitis B surface antigen (HBsAg)—that is, anti-HBs—clear HBsAg (and HBV virions), and fully recover. About 5% of adult patients, 90% of infected infants, and 30-50% of children infected at age 1-5 years develop chronic infection. Some patients, particularly individuals who are infected as neonates or as young

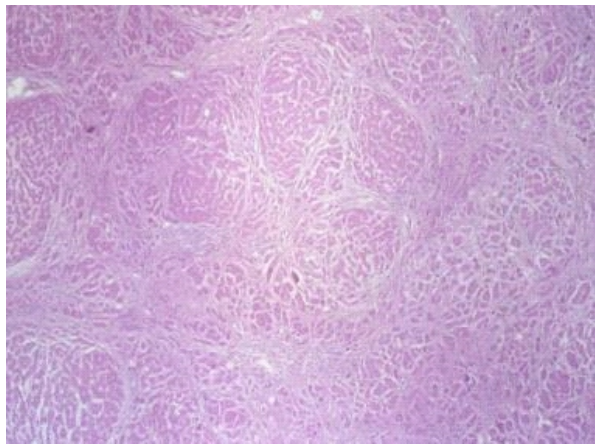
children, have elevated serum levels of HBV DNA and a positive blood test for the presence of HBeAg but have normal alanine aminotransferase (ALT) levels and show minimal histologic evidence of liver damage. These individuals are in the so-called "immune-tolerant phase" of disease. Years later, some but not all of these individuals may enter the "immune-active phase" of disease, in which the HBV DNA may remain elevated as the liver experiences active inflammation and fibrosis. An elevated ALT level is also noted during this period. Typically, the immune-active phase ends with the loss of HBeAg and the development of antibodies to HBeAg (anti-HBe). Individuals who seroconvert from an HBeAg-positive state to an HBeAg-negative state may enter the "inactive carrier state" (previously known as the "healthy carrier state"). Such individuals are asymptomatic, have normal liver chemistry test results, and have normal or minimally abnormal liver biopsy results. Blood test evidence of HBV replication should be nonexistent or minimal, with a serum HBV DNA level in the range of 0 to 2000 IU/mL. Inactive carriers remain infectious to others through parenteral or sexual transmission. Inactive carriers may ultimately develop anti-HBs and clear the virus. However, some inactive carriers develop chronic hepatitis, as determined by liver chemistry results, liver biopsy findings, and HBV DNA levels. Inactive carriers remain at risk for hepatocellular carcinoma (HCC), although the risk is low. At this point, no effective antiviral therapies are available for patients in an inactive carrier state. Other patients who seroconvert may enter the "reactivation phase" of disease. These individuals remain HBeAg-negative but have serum HBV DNA levels higher than 2000 IU/mL and show evidence of active liver inflammation. These patients are said to have HBeAg-negative chronic hepatitis.

Chronic infection

The 10-30% of HBsAg carriers who develop chronic hepatitis are often symptomatic. Fatigue is the most common symptom of chronic hepatitis B. Acute disease flares occasionally occur, with symptoms and signs similar to those of acute hepatitis. Extrahepatic manifestations of the disease (eg, polyarteritis nodosa, cryoglobulinemia, and glomerulonephritis) may develop. Chronic hepatitis B patients have abnormal liver chemistry results, blood test evidence of active HBV replication, and inflammatory or fibrotic activity on liver biopsy specimens (see the images below).



Liver biopsy with trichrome stain showing stage 3 fibrosis in patient with hepatitis B.

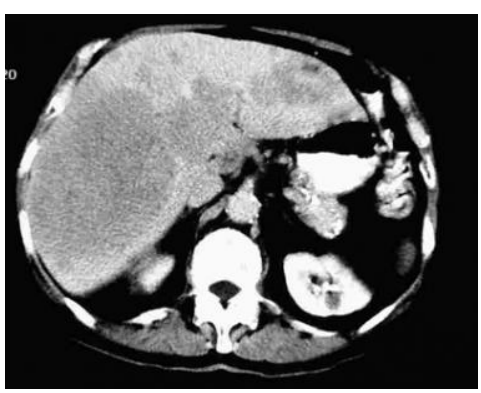


Liver biopsy with hematoxylin stain showing stage 4 fibrosis (ie, cirrhosis) in patient with hepatitis B.

Patients with chronic hepatitis may be considered either HBeAg-positive or HBeAg-negative. In North America and Northern Europe, about 80% of chronic hepatitis B cases are HBeAg positive and 20% HBeAg negative. In Mediterranean countries and in some parts of Asia, 30-50% of cases are HBeAg positive and 50-80% HBeAg negative. Patients with HBeAg-positive chronic hepatitis have signs of active viral replication, with an HBV DNA level greater than 2 × 10 IU/mL. HBV DNA levels may be as high as 10 IU/mL. Patients with HBeAg-negative chronic hepatitis were presumably infected with wild-type virus at some point. Over time, they acquired a mutation in either the precore or the core promoter region of the viral genome. In such patients with a precore mutant state, HBV continues to replicate, but HBeAg is not produced. Patients with a core mutant state appear to have downregulated HBeAg production. The vast majority of patients with HBeAg-negative chronic hepatitis B have a serum HBV DNA level greater than 2000 IU/mL. Typically, HBeAg-negative patients have lower HBV DNA levels than HBeAg-positive patients do. Commonly, the HBV DNA level is no higher than 2 × 10 IU/mL.

HBV and HCC

An approximately 8-20% of untreated adults with chronic hepatitis B go on to develop cirrhosis within 5 years; of these individuals, 20% annually develop hepatic decompensation and 2-5% annually develop HCC (see the image below). Globally, an estimated 30% of cases of cirrhosis and 45% of cases of HCC are attributed to HBV. The incidence of HCC parallels the incidence of HBV infection in various countries around the world. Worldwide, up to 1 million cases of HCC are diagnosed each year. Most appear to be related to HBV infection.

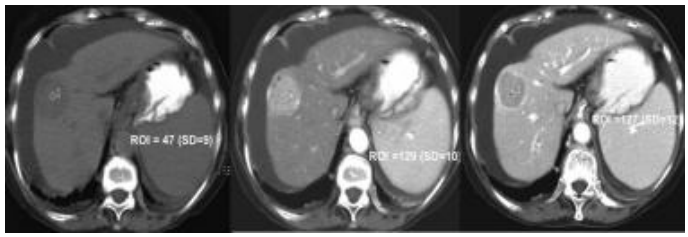


Hepatic carcinoma, primary. Large multifocal hepatocellular carcinoma in 80-year-old man without cirrhosis.

In HBV-induced cirrhosis, as in cirrhosis due to other causes, hepatic inflammation and regeneration appear to stimulate mutational events and carcinogenesis. However, in HBV infection, in contrast to other liver diseases, the presence of cirrhosis is not a prerequisite for the development of HCC. The integration of HBV into the hepatocyte genome may lead to the activation of oncogenes or the inhibition of tumor suppressor genes. As an example, mutations or deletions of the p53 and RB tumor suppressor genes are seen in many cases of HCC. Multiple studies have demonstrated an association between elevated serum HBV DNA levels and an increased risk for the development of HCC. Conversely, successful suppression of HBV infection by antiviral therapy can decrease the risk of developing HCC. HCC is a treatable and potentially curable disease, whether the treatment entails tumor ablation (eg, with percutaneous injection of ethanol into the tumor), liver resection, or liver transplantation. The American Association for the Study of Liver Diseases (AASLD) and the World Health Organization (WHO) recommend screening for HBV-infected individuals who are at high risk for HCC, including men older than 40 years, individuals with HBV-induced cirrhosis, and persons with a family history of HCC. For these patients, ultrasonography of the liver and alpha-fetoprotein (AFP) testing every 6 months are recommended. No specific recommendations have been made for patients at low risk for HCC. Some clinicians recommend that low-risk patients (including inactive carriers) undergo only AFP and liver chemistry testing every 6 months. Other clinicians' practice is to screen all chronic hepatitis B patients with ultrasonography and AFP testing every 6 months, with inactive carriers undergoing liver chemistry and AFP testing every 6 months; however, this is controversial.

Hepatitis C

HCV has a viral incubation period of approximately 8 weeks. Most cases of acute HCV infection are asymptomatic. Even when it is symptomatic, acute HCV infection tends to follow a mild course, with aminotransferase levels rarely higher than 1000 U/L. Whether acute HCV infection is a cause of FHF remains controversial. Approximately 15-45% of patients acutely infected with HCV lose virologic markers for HCV. Thus, about 55-85% of newly infected patients remain viremic and may develop chronic liver disease. In chronic hepatitis C, patients may or may not be symptomatic, with fatigue being the predominant reported symptom. Aminotransferase levels may range from reference values (< 40 U/L) to values as high as 300 U/L. However, no clear-cut association exists between aminotransferase levels and symptoms or risk of disease progression. An estimated 15-30% of patients with chronic hepatitis C experience progression to cirrhosis. This process may take decades. All patients who are newly diagnosed with well-compensated cirrhosis must be counseled regarding their risk of developing symptoms of liver failure (ie, decompensated cirrhosis). Only 30% of patients with well-compensated cirrhosis are anticipated to decompensate over a 10-year follow-up period. Patients with HCV-induced cirrhosis are also at increased risk for the development of HCC (see the image below), especially in the setting of HBV coinfection. In the United States, HCC arises in 1-5% of patients with HCV-induced cirrhosis each year. Accordingly, routine screening (eg, ultrasonography and AFP testing every 6 months) is recommended in patients with HCV-induced cirrhosis to rule out the development of HCC. Nearly 20,000 deaths each year are attributable to HCV as an underlying or contributing cause of death.



Triple-phase CT scan of liver cancer, revealing classic findings of enhancement during arterial phase and delayed hypointensity during portal venous phase.

Hepatitis D

Simultaneous introduction of HBV and HDV into a patient results in the same clinical picture as acute infection with HBV alone. The resulting acute hepatitis may be mild or severe. Similarly, the risk of developing chronic HBV and HDV infection after acute exposure to both viruses is the same as the rate of developing chronic HBV infection after acute exposure to HBV (approximately 5% in adults). However, chronic HBV and HDV disease tends to progress more rapidly to cirrhosis than chronic HBV infection alone does. Introduction of HDV into an individual already infected with HBV may have dramatic consequences. Superinfection may give HBsAg-positive patients the appearance of a sudden worsening or flare of hepatitis B. HDV superinfection may result in FHF.

Hepatitis E

HEV has an incubation period of 2-10 weeks. Acute HEV infection is generally less severe than acute HBV infection and is characterized by fluctuating aminotransferase levels. However, pregnant women, especially when infected during the third trimester, have a greater than 25% risk of mortality associated with acute HEV infection. In a number of cases, FHF caused by HEV has necessitated liver transplantation. Traditionally, HEV was not believed to cause chronic liver disease. However, several reports have described chronic hepatitis due to HEV in organ transplant recipients. Liver histology revealed dense lymphocytic portal infiltrates with interface hepatitis, similar to the findings seen with hepatitis C infection. Some cases have progressed to cirrhosis.

Etiology

Hepatitis viruses A, B, C, D (HAV, HBV, HCV, HDV [which requires coexisting HBV infection]), and E (HEV) cause the majority of clinical cases of viral hepatitis. Whether hepatitis G virus (HGV) is pathogenic in humans remains unclear. HAV, HBV, HCV, and HDV are the only hepatitis viruses endemic to the United States; HAV, HBV, and HCV are responsible for more than 90% of US cases of acute viral hepatitis. Whereas HAV and HBV are the most common causes of acute hepatitis in the United States, HCV is the most common cause of chronic hepatitis.

The following are typical patterns by which hepatitis viruses are transmitted, with + symbols indicating the frequency of transmission (ie, more + symbols indicate increased frequency).

Fecal-oral transmission frequency is as follows:

- HAV (+++)
- HEV (+++)

Parenteral transmission frequency is as follows:

- HBV (+++)
- HCV (+++)
- HDV (++)
- HGV (++)
- HAV (+)

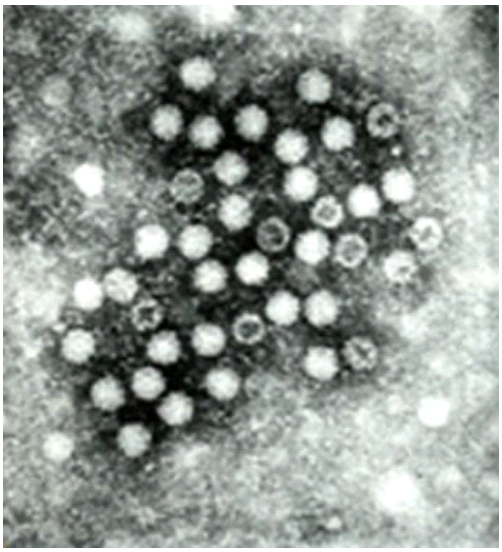
Sexual transmission frequency is as follows:
- HBV (+++)
- HDV (++)
- HCV (+)

Perinatal transmission frequency is as follows:
- HBV (+++)
- HCV (+)
- HDV (+)

Sporadic (unknown) transmission frequency is as follows:
- HBV (+)
- HCV (+)

Hepatitis A

HAV (see the image below), a member of the Picornaviridae family, is an RNA virus with a size of 7.5 kb and a diameter of 27 nm. It has one serotype but multiple genotypes. Classic findings of acute HAV infection include a mononuclear cell infiltrate, interface hepatitis, focal hepatocyte dropout, ballooning degeneration, and acidophilic (Councilman-like) bodies. HAV is present in the highest concentration in the feces of infected individuals; the greatest fecal viral load tends to occur near the end of the HAV incubation period.



Hepatitis A virus as viewed through electron microscopy.

Most commonly, the virus spreads from person to person via the fecal-oral route. Contaminated water and food, including shellfish collected from sewage-contaminated water, have also resulted in epidemics of HAV infection. The virus may also be spread through sexual (anal-oral) contact. Transmission by blood transfusion is rare. Maternal-neonatal transmission has not been established. Although HAV infection occurs throughout the world, the risk is highest in developing countries, areas of low socioeconomic status, and regions without sufficient sanitation. Higher infection rates also exist in settings where fecal-oral spread is likely, such as daycare centers. Other groups at high risk for HAV infection include international travelers, users of injection and noninjection drugs, and men who have sex with men. International travel is the most frequently identified risk factor reported by case patients in the United States. Close contacts of infected individuals are also at risk. The secondary infection rate for hepatitis A virus in household contacts of patients with acute HAV infection is around 20%. Thus, secondary infection plays a significant role in the maintenance of HAV outbreaks.

Hepatitis B

HBV, a member of the Hepadnaviridae family, is a 3.2-kb partially doubled-stranded DNA virus. The positive strand is incomplete. The complete negative strand has four overlapping genes, as follows:
- Gene S codes for hepatitis B surface antigen (HBsAg), a viral surface polypeptide
- Gene C codes for hepatitis B core antigen (HBcAg), the nucleocapsid protein; it also codes for hepatitis B e antigen (HBeAg), whose function is unknown
- Gene P codes for a DNA polymerase that has reverse transcriptase activity
- Gene X codes for the X protein that has transcription-regulating activity

The viral core particle consists of a nucleocapsid, HBcAg, which surrounds HBV DNA, and DNA polymerase. The nucleocapsid is coated with HBsAg. The intact HBV virion is known as the Dane particle. Dane particles and spheres and tubules containing only HBsAg are found in the blood of infected patients. In contrast, HBcAg is not detected in the circulation. It can be identified by immunohistochemical staining of infected liver tissue. HBV is known to have eight genotypic variants (genotypes A-H). Although preliminary studies suggest that particular HBV genotypes may predict the virus's response to therapy or may be associated with more aggressive disease, it would be premature to incorporate HBV genotype testing into clinical practice on a routine basis. HBV is readily detected in serum, and it is seen at very low levels in semen, vaginal mucus, saliva, and tears. The virus is not detected in urine, stool, or sweat. HBV can survive storage at –20°C (–4°F) and heating at 60°C (140°F) for 4 hours. It is inactivated by heating at 100°C (212°F) for 10 minutes or by washing with sodium hypochlorite (bleach).
The major reservoir of HBV in the United States consists of the 850,000 to 2.2 million people with chronic HBV infection. In this group, those with HBeAg in their serum tend to have higher viral titers and thus greater infectivity. HBV is transmitted both parenterally and sexually, most often by mucous membrane exposure or percutaneous exposure to infectious body fluids. Saliva, serum, and semen all have been determined to be infectious. Percutaneous exposures leading to the transmission of HBV include transfusion of blood or blood products, injection drug use with shared needles, hemodialysis, and needlesticks (or other wounds caused by sharp implements) in healthcare workers. Globally and in the United States, perinatal transmission is one of the major modes of HBV transmission. The greatest risk of perinatal transmission occurs in infants of HBeAg-positive women. By age 6 months, these children have a 70-90% risk of infection, and of those who become infected, about 90% will go on to develop chronic infection with HBV. For infants born to HBeAg-negative women, the risk of infection is approximately 10-40%, with a chronic infection rate of 40-70%. Even if transmission does not occur in the perinatal period, these children are still at significant risk for the development of infection during early childhood. Groups at high risk for HBV infection include intravenous (IV) drug users, persons born in endemic areas, and men who have sex with men. Others at risk include healthcare workers exposed to infected blood or bodily fluids, recipients of multiple blood transfusions, patients undergoing hemodialysis, heterosexual persons with multiple partners or a history of sexually transmitted disease, institutionalized persons (eg, prisoners), and household contacts or sexual partners of HBV carriers.

Hepatitis C

HCV, a member of the Flaviviridae family, is a 9.4-kb RNA virus with a diameter of 55 nm. It has one serotype, but at least six major genotypes

and more than 80 subtypes are described, with as little as 55% genetic sequence homology. Genotype 1b is the genotype most commonly seen in the United States, Europe, Japan, and Taiwan. Genotypes 1b and 1a (also common in the United States) are less responsive to interferon (IFN) therapy than other HCV genotypes are. The wide genetic variability of HCV hampers the efforts of scientists to design an effective anti-HCV vaccine. HCV can be transmitted parenterally, perinatally, and sexually. Transmission occurs by percutaneous exposure to infected blood and plasma. The virus is transmitted most reliably through transfusion of infected blood or blood products, transplantation of organs from infected donors, and sharing of contaminated needles among IV drug users. Transmission by sexual activity and household contact occurs less frequently. Perinatal transmission occurs but is uncommon.

Genetic variations and HCV clearance

Genetic polymorphisms involving the IL28B gene have been found to affect the odds that HCV can be cleared in a given patient. The IL28B gene encodes IFN lambda-3. A single nucleotide polymorphism 3 kb upstream of the IL28B gene was associated with patients' ability to clear HCV spontaneously. In a study, about 53% of patients with the favorable C/C genotype and 23% of patients with the less favorable T/T genotype spontaneously cleared the virus. Of the patients who were chronically infected with HCV, those with the C/C genotype were more likely to see viral eradication after treatment with pegylated IFN (Peg-IFN) plus ribavirin. In the same study, the C/C genotype was more common in persons of European ancestry than in those of African ancestry. In contrast, the T/T genotype was more common in persons of African ancestry. These observations may help to explain why black individuals typically exhibit lower sustained virologic response (SVR) rates than white persons when treated with Peg-IFN plus ribavirin.

Hepatitis D

HDV, the single species in the Deltavirus genus, is a 1.7-kb single-stranded RNA virus. The viral particle is 36 nm in diameter and contains hepatitis D antigen (HDAg) and the RNA strand. It uses HBsAg as its envelope protein; thus, HBV coinfection is necessary for the packaging and release of HDV virions from infected hepatocytes. Modes of transmission for HDV are similar to those for HBV. HDV is transmitted by exposure to infected blood and blood products. It can be transmitted percutaneously and sexually. Perinatal transmission is rare.

Hepatitis E

HEV, the single species in the Hepevirus genus, is a 7.5-kb single-stranded RNA virus that is 32-34 nm in diameter. It is transmitted primarily via the fecal-oral route, with fecally contaminated water providing the most common means of transmission. Person-to-person transmission is rare, though maternal-neonatal transmission does occur. Zoonotic spread is possible because some nonhuman primates (cows, pigs and wild boar, sheep, goats, rodents, deer) are susceptible to the disease.

Other viruses

Hepatitis G virus (HGV) (also known as human pegivirus [HPgV]) is similar to viruses in the Flaviviridae family, which includes HCV. (It is an RNA virus within the Pegivirus A species of the Flaviviridae family.) The HGV genome codes for 2900 amino acids. The virus has 95% homology (at the amino acid level) with hepatitis GB virus C (HGBV-C) and 26% homology (at the amino acid level) with HCV. Approximately 750 million people worldwide have HPgV viremia, with an estimated 1.5-2.5 billion people currently infected or with evidence of prior infection. It can be transmitted through blood and blood products. HGV coinfection is observed in 6% of chronic HBV infections and in 10% of chronic HCV infections. About 75% of HPgV infections clear within 2 years of infection, and 25% persist. HGV is associated with acute and chronic liver disease, but it has not been clearly implicated as an etiologic agent of hepatitis. Other known viruses (eg, cytomegalovirus [CMV], Epstein-Barr virus [EBV], herpes simplex virus [HSV], and varicella-zoster virus [VZV]) may also cause inflammation of the liver, but they do not primarily target the liver.

International statistics

Globally, viral hepatitis was the seventh leading cause of death in 2013, up from the 10th leading cause in 1990. Worldwide, HAV is responsible for an estimated 1.4 million infections annually. About 2 billion people in the world have evidence of past or current HBV infection, with 240 million chronic carriers of HBsAg. HBV, along with the associated infection by the hepatitis D virus, is one of the most common pathogens afflicting humans. HBV leads to 650,000 deaths annually as a result of viral hepatitis–induced liver disease. The worldwide annual incidence of acute HCV infection is not easily estimated, because patients are often asymptomatic. An estimated 71 million people are chronically infected with HCV worldwide. About 55-85% of these people infected progress to chronic HCV infection, with a 15-30% risk of developing liver cirrhosis within two decades. China, the United States, and Russia have the largest populations of anti-HCV positive injection drug users (IDUs). It is estimated that 6.4 million IDUs worldwide are positive for antibody to hepatitis B core antigen (HBcAg) (anti-HBc), and 1.2 million are HBsAg-positive.

Hepatitis A virus

HAV is transmitted commonly most via the fecal-oral route. Cases of transfusion-associated HAV or illness caused by inoculation are uncommon. HAV infection is common in the less-developed nations of Africa, Asia, and Central and South America; the Middle East has a particularly high prevalence. Most patients in these regions are infected when they are young children. Uninfected adult travelers who visit these regions are at risk for infection. Epidemics of HAV infection may be explained by person-to-person contact, such as occurs at institutions, or by exposure to a common source, such as consumption of contaminated water or food. As sanitation has improved, the overall prevalence of hepatitis A in the United States and in other parts of the developed world has decreased to less than 50% of the population. Younger individuals in the United States are better protected from hepatitis A because of guidelines adopted in 2006 recommending universal vaccination of children aged 1 year and older. Unfortunately, many older individuals in the United States still remain at risk.

Hepatitis B virus

Infection with HBV is defined by the presence of hepatitis B surface antigen (HBsAg). Approximately 90-95% of neonates with acute HBV infection and 5% of adults with acute infection develop chronic HBV infection. In the remaining patients, the infection clears, and these patients develop a lifelong immunity against repeated infections. Of the approximately 5% of the world's population (ie, 350 million people) that is chronically infected with HBV, about 20% will eventually develop HBV-related cirrhosis or hepatocellular carcinoma (HCC). According to the World Health Organization (WHO), HBV is the 10th leading cause of death worldwide. More than 10% of people living in sub-Saharan Africa and in East Asia are infected with HBV. Maintenance of a high HBsAg

carriage rate in these parts of the world is partially explained by the high prevalence of perinatal transmission and by the low rate of HBV clearance by neonates. In the United States, about 250-350 patients die of HBV-associated fulminant hepatic failure (FHF) each year. A pool of approximately 1.25 million chronic HBV carriers exists in the United States. Of these patients, 4000 die of HBV-induced cirrhosis each year, and 1000 die of HBV-induced HCC.

Perinatal transmission

The vast majority of HBV cases around the world result from perinatal transmission. Infection appears to occur during the intrapartum period or, rarely, in utero. Neonates infected via perinatal infection are usually asymptomatic. Although breast milk can contain HBV virions, the role of breastfeeding in transmission is unclear.

Sexual transmission

HBV is transmitted more easily than human immunodeficiency virus (HIV) or HCV. Infection is associated with vaginal intercourse, genital-rectal intercourse, and oral-genital intercourse. An estimated 30% of sexual partners of patients infected with HBV also contract HBV infection. However, HBV cannot be transmitted through kissing, hugging, or household contact (eg, sharing towels, eating utensils, or food). Sexual activity is estimated to account for as many as 50% of HBV cases in the US.

Parenteral transmission

HBV was once a common cause of posttransfusion hepatitis. Screening of US blood donors for anti-HBc, beginning in the early 1970s, dramatically reduced the rate of HBV infection associated with blood transfusion. According to the National Heart, Lung and Blood Institute, the risk that a blood donation is infected with hepatitis B is 1 in 205,000. Patients with hemophilia, those on renal dialysis, and those who have undergone organ transplantation remain at increased risk of HBV infection. IDU accounts for 20% of US cases of HBV. A history of HBV exposure is identified in approximately 50% of IDUs. The risk of acquiring HBV after a needle stick from an infected patient is estimated to be as high as 5%.

Healthcare associated

Hepatitis B outbreaks have been associated with healthcare settings. Between 2008 and 2015, there were 23 outbreaks and 175 outbreak-associated cases of hepatitis B associated with healthcare settings reported in the United States. Outbreaks were reported in long-term care facilities and outpatient clinic settings. The CDC noted that these numbers likely underestimate the true incidence of healthcare-associated outbreaks because of the asymptomatic course of hepatitis B infection as well as the long incubation period. Additionally, there is no requirement to report these cases to the CDC if they have been investigated by state and local health authorities.

Sporadic cases

In approximately 27% of cases, the cause of HBV infection is unknown. Some of these cases, in fact, may be due to sexual transmission or contact with blood.

Hepatitis C virus

HCV is the most frequent cause of parenteral non-A, non-B (NANB) hepatitis worldwide. Hepatitis C is prevalent in 0.5-2% of populations in nations around the world. The highest rates of disease prevalence are found in patients with hemophilia and in IDUs. In the 1980s, as many as 180,000 new cases of HCV infection were described each year in the United States; by 1995, there were only 28,000 new cases each year. The decreasing incidence of HCV was explained by a decline in the number of cases of transfusion-associated hepatitis (because of improved screening of blood products) and by a decline in the number of cases associated with IDU. New cases of hepatitis C infection tend to occur in individuals who are young and white, with a history of IDU and opioid use.

Transmission via blood transfusion

Screening of the US blood supply has dramatically reduced the incidence of transfusion-associated HCV infection. Before 1990, 37-58% of cases of acute HCV infection (then known as NANB) were attributed to the transfusion of contaminated blood products; at present, only about 4% of acute cases are attributed to transfusions. The risk of having a blood donation infected with hepatitis C is 1 in 2 million. Acute hepatitis C remains an important issue in dialysis units, where patients' risk for HCV infection is about 0.15% per year.

Transmission via intravenous and intranasal drug use

IDU remains an important mode of transmitting HCV. The use of intravenous (IV) drugs and the sharing of paraphernalia used in the intranasal snorting of cocaine and heroin account for approximately 60% of new cases of HCV infection. More than 90% of patients with a history of IDU have been exposed to HCV.

Transmission via occupational exposure

Occupational exposure to HCV accounts for approximately 4% of new infections. On average, the chance of acquiring HCV after a needle-stick injury involving an infected patient is 1.8% (range, 0-7%). Reports of HCV transmission from healthcare workers to patients are extremely uncommon.

Sexual transmission

Approximately 20% of cases of hepatitis C appear to be due to sexual contact. In contrast to hepatitis B, approximately 5% of the sexual partners of those infected with HCV contract hepatitis C. The US Public Health Service (USPHS) recommends that persons infected with HCV be informed of the potential for sexual transmission. Sexual partners should be tested for the presence of antibodies to HCV (anti-HCV). Safe-sex precautions are recommended for patients with multiple sex partners. Current guidelines do not recommend the use of barrier precautions for patients with a steady sexual partner. However, patients should avoid sharing razors and toothbrushes with others. In addition, contact with patients' blood should be avoided.

Perinatal transmission

Perinatal transmission of HCV occurs in 5.8% of infants born to mothers infected with HCV. The risk of perinatal transmission of HCV is higher (about 18%) in children born to mothers coinfected with human immunodeficiency virus (HIV) and HCV. Between 2011 and 2014, the proportion of infants born to HCV-infected mothers increased by 68% nationally, indicating an increase in the number of infants who are at risk for vertical transmission of HCV.

Healthcare associated

Hepatitis C outbreaks have been associated with healthcare settings. Between 2008 and 2015, there were 33 outbreaks and 239 outbreak-associated cases of hepatitis C associated with US healthcare settings reported. Outbreaks occurred in outpatient facilities and hemodialysis settings. The CDC noted that these numbers likely underestimate the true incidence of healthcare-associated outbreaks because of the asymptomatic course of hepatitis C infection and its long incubation period. Additionally, there is no requirement to report these cases to the CDC if they have been investigated by state and local health authorities.

Hepatitis D virus

HDV requires the presence of HBV to replicate; thus, HDV infection develops only in patients who are positive for HBsAg. Patients may

acquire HDV as a coinfection (at the same time that they contract HBV), or the HDV may superinfect patients who are chronic HBV carriers. Hepatitis D is not a reportable disease in the United States, thus, accurate data regarding HDV infections are scarce. However, it is estimated that approximately 4-8% of cases of acute hepatitis B involve coinfection with HDV. HDV is believed to infect approximately 5% of the world's HBsAg carriers (ie, about 15 million with chronic HBV/HDV). The prevalence of HDV infection in South America and Africa is high. Italy and Greece are well-studied areas of intermediate endemicity. Only about 1% of HBV-infected individuals in the United States and Northern Europe are coinfected with HDV. The sharing of contaminated needles in IDU is thought to be the most common means of transmitting HDV. IDUs who are also positive for HBsAg have been found to have HDV prevalence rates ranging from 17% to 90%. Sexual transmission and perinatal transmission are also described. The prevalence of HDV in sex workers in Greece and Taiwan is high.

Hepatitis E virus

HEV is the primary cause of enterally transmitted NANB hepatitis. It is transmitted via the fecal-oral route and appears to be endemic in some parts of less-developed countries, where most outbreaks occur. HEV can also be transmitted vertically to the babies of HEV-infected mothers. It is associated with a high neonatal mortality. In one report, anti-HEV antibodies were found to be present in 29% of urban children and 24% of rural children in northern India. Sporadic infections are observed in persons traveling from Western countries to these regions.

Prognosis

The prognosis of viral hepatitis varies, depending on the causative virus. Hepatitis A virus (HAV) infection usually is mild and self-limited, and infection confers lifelong immunity against the virus. Overall mortality is approximately 0.02%; in general, children younger than 5 years and adults older than 50 years have the highest case-fatality rates. Older patients are at greater risk for severe disease: Whereas icteric disease occurs in fewer than 10% of children younger than 6 years, it occurs in 40-50% of older children and in 70-80% of adults with HAV. Three rare complications are relapsing hepatitis, cholestatic hepatitis, and fulminant hepatitic failure (FHF). The risk of chronic HBV infection in infected older children and adults approaches 5-10%. Patients with such infection are at risk for cirrhosis and hepatocellular (HCC). FHF develops in 0.5-1% of patients infected with HBV; the case-fatality rate in these patients is 80%. Chronic HBV infection is responsible for approximately 5000 deaths per year from chronic liver disease in the United States. Chronic infection develops in 50-60% of patients with hepatitis C. Chronically infected patients are at risk for chronic active hepatitis, cirrhosis, and HCC. In the United States, chronic HCV infection is the leading indication for liver transplantation. In 2014, the number of HCV-related deaths rose to 19,659 from 15,106 in 2007, with over 50% occurring in people aged 55-64 years. Patients with chronic HBV infection who are coinfected with HDV also tend to develop chronic HDV infection. Chronic coinfection with HBV/HDV often leads to rapidly progressive subacute or chronic hepatitis, with as many as 70-80% of these patients eventually developing cirrhosis. HEV infection is usually mild and self-limited. The case-fatality rate reaches 15-20% in pregnant women. HEV infection does not result in chronic disease.

Complications

In general, complications of viral hepatitis may include the following:

- Acute or subacute hepatic necrosis
- Chronic active hepatitis
- Chronic hepatitis
- Cirrhosis
- Hepatic failure
- Hepatocellular carcinoma (HCC) in patients with HBV or HCV infection

Hepatitis B

One of the major complications of hepatitis B is the development of chronic infection. An estimated 240 million people worldwide are chronically infected with HBV. In the United States, 850,000 to 2.2 million people are estimated to have chronic HBV infection. Patients with such infection are at risk for the subsequent development of chronic active hepatitis, cirrhosis of the liver, and eventual HCC. Each year, approximately 650,000 deaths occur worldwide as a result of chronic HBV infection. Patients infected at an early age are at greatest risk for chronic HBV infection: Whereas 90% of those infected at birth and 30-50% of children infected at age 1-5 years develop chronic HBV infection, only 5% of older children or adults go on to develop chronic infection. The risk of chronic infection is also higher in patients who are immunocompromised. Patients with chronic HBV infection are at significantly higher risk for HCC. In fact, HCC is the leading cause of cancer-related deaths in areas where HBV is endemic. Globally, HBV is responsible for 45% of the world's primary liver cancers. Cancer in this setting is postulated to result from repeated bouts of chronic inflammation and cellular regeneration. HCC develops an average of 25-30 years after initial infection. Another major complication of HBV infection is development of FHF. In approximately 0.5-1% of HBV-infected patients, the disease progresses to FHF, with coagulopathy, encephalopathy, and cerebral edema. The case-fatality rate for these patients approaches 80%.

Hepatitis C

Acute infection with HCV may rarely cause FHF. Approximately 75-85% of patients with hepatitis C become chronically infected. About 60-70% of patients will have ongoing chronic liver disease with laboratory evidence of fluctuating or persistently elevated liver enzymes. Of those with chronic infection, 5-20% may go on to develop cirrhosis. The progression from initial infection to the development of cirrhosis may take 20-30 years. Cirrhosis related to chronic HCV infection is also strongly linked to the development of HCC, which usually develops after 30 years in patients who are chronically infected. Of patients with HCV-associated cirrhosis, 20-25% may progress to liver failure and death. As noted earlier, in the United States, cirrhosis associated with chronic hepatitis C is a leading indication for liver transplantation.

Extrahepatic complications of hepatitis C

Patients with chronic hepatitis C are also at risk for extrahepatic complications. In essential mixed cryoglobulinemia, HCV may form immune complexes with anti-HCV immunoglobulin G (IgG) and with rheumatoid factor (RF). The deposition of immune complexes may cause small-vessel damage. Complications of cryoglobulinemia include rash, vasculitis, and glomerulonephritis. Other extrahepatic complications of HCV infection include focal lymphocytic sialadenitis, autoimmune thyroiditis, porphyria cutanea tarda, lichen planus, and Mooren corneal ulcer. Some cases of non-Hodgkin lymphoma can be attributed to HCV infection.

Patient Education

Refer patients with infectious hepatitis to their primary care providers for

further counseling specific to their disease; the precise etiologic virus is unlikely to be known at the time of discharge from the emergency department. Counsel patients regarding the importance of follow-up care to monitor for evidence of disease progression or development of complications. Remind them to exercise meticulous personal hygiene, including thorough hand washing. Instruct them not to share any articles that have the potential for contamination with blood, semen, or saliva, including needles, toothbrushes, or razors. Inform food handlers suspected of having hepatitis A that they should not return to work until their primary care physician can confirm that they are no longer shedding the virus. Instruct patients to refrain from using any hepatotoxins, including ethanol and acetaminophen.

Clinical Presentation

History

The clinical presentation of infectious hepatitis varies with the individual, as well as with the specific causative virus. Some patients may be entirely asymptomatic or only mildly symptomatic at presentation. Others may present with rapid onset of fulminant hepatic failure (FHF). The classic presentation of infectious hepatitis involves four phases, as follows:

- Phase 1 (viral replication phase) – Patients are asymptomatic; laboratory studies demonstrate serologic and enzyme markers of hepatitis
- Phase 2 (prodromal phase) – Patients experience anorexia, nausea, vomiting, alterations in taste, arthralgias, malaise, fatigue, urticaria, and pruritus, and some develop an aversion to cigarette smoke; when seen by a healthcare provider during this phase, patients are often diagnosed as having gastroenteritis or a viral syndrome
- Phase 3 (icteric phase) – Patients may note dark urine, followed by pale-colored stools; in addition to the predominant gastrointestinal (GI) symptoms and malaise, patients become icteric and may develop right upper quadrant pain with hepatomegaly
- Phase 4 (convalescent phase) – Symptoms and icterus resolve, liver enzymes return to normal.

Hepatitis A

The incubation period of hepatitis A virus (HAV) is 2-7 weeks (average, 28 days). Clinical symptoms then develop, often with a presentation similar to that of gastroenteritis or a viral respiratory infection. The most common signs and symptoms include fatigue, nausea, vomiting, fever, hepatomegaly, jaundice, dark urine, anorexia, and rash. HAV infection usually occurs as a mild self-limited disease and confers lifelong immunity to the virus. Chronic HAV infection does not occur.

Hepatitis B

The incubation period for hepatitis B virus (HBV) is 30-180 days (average, approximately 75 days). Patients then enter the prodromal or preicteric phase, characterized by the gradual onset of anorexia, malaise, and fatigue. During this phase, as the liver becomes inflamed, the liver enzymes start to elevate, and the patient may experience right upper quadrant pain. About 15% of patients develop an illness resembling serum sickness. These patients may experience fever, arthritis, arthralgias, or an urticarial rash. As the disease progresses to the icteric phase, the liver becomes tender, and jaundice develops. Patients may note that their urine darkens and their stools lighten in color. Other symptoms in this stage include nausea, vomiting, and pruritus. From this point on, the clinical course may be highly variable. Whereas some patients experience fairly rapid improvements in their symptoms, others go on to experience prolonged disease with slow resolution. Still others may have symptoms that periodically improve, only to worsen later (relapsing hepatitis). Finally, there is an unfortunate subset of patients in whom the disease rapidly progresses to FHF; this may occur over days to weeks.

Hepatitis C

The incubation period for hepatitis C virus (HCV) is 15-150 days, with symptoms developing anywhere from 5-12 weeks after exposure. During acute HCV infection, symptoms may appear similar to those of HBV infection. In up to 80% of cases, however, patients are asymptomatic and do not develop icterus.

Hepatitis D

The incubation period of hepatitis D virus (HDV) is approximately 35 days. Patients simultaneously infected with HBV and HDV often have an acute, self-limited infection. Fewer than 5% of these patients develop chronic HDV infection. Chronic HBV carriers who become superinfected with HDV tend to have a more severe acute hepatitis; 80% of these patients go on to develop chronic HDV infection. Chronic infection with HBV and HDV may lead to fulminant acute hepatitis and severe chronic active hepatitis with progression to cirrhosis. Over the long term, as many as 70-80% of these patients have evidence of chronic liver disease with cirrhosis, compared with only 15-30% of patients with chronic HBV alone.

Hepatitis E

The incubation period of hepatitis E virus (HEV) is 2-9 weeks (average, 45 days). HEV usually causes an acute self-limited disease similar to HAV infection. Fulminant disease does occur in about 10% of cases. In women who are pregnant, HEV infection has a case-fatality rate of 15-20%. No reports exist of chronic infection with HEV.

Physical Examination

Physical findings in patients with hepatitis vary with the type of hepatitis and the time of presentation. Patients often present with low-grade fever. Those experiencing significant vomiting and anorexia may show signs of dehydration, such as tachycardia, dry mucous membranes, loss of skin turgor, and delayed capillary refill. Patients in the icteric phase may have icterus of the sclerae or mucous membranes, or discoloration of the tympanic membranes. The skin may be jaundiced and may reveal macular, papular, or urticarial rashes. In viral hepatitis, the liver may be tender and diffusely enlarged with a firm, sharp, smooth edge. If the patient has a nodular liver or a mass is palpated, clinicians should suspect an abscess or tumor.

Differential Diagnoses

Diagnostic Considerations

In addition to the conditions listed in the differential diagnosis, other problems to be considered in patients with suspected viral hepatitis include the following:

- Liver abscess
- Drug-induced hepatitis
- Autoimmune hepatitis
- Hepatocellular cancer
- Pancreatic cancer

Differential Diagnoses
- Acute Cholangitis
- Acute Cholecystitis and Biliary Colic
- Blunt Abdominal Trauma
- Emergent Management of Pancreatitis
- Emergent Treatment of Gastroenteritis
- Gallstones (Cholelithiasis)
- Intussusception
- Pediatric Gastroenteritis in Emergency Medicine
- Peptic Ulcer Disease
- Small-Bowel Obstruction

Workup

Approach Considerations

A simple screening test for the nonicteric patient with suspected viral hepatitis involves checking the urine for presence of bilirubin. As an alternative, a liver enzyme panel (generally a costly test) could be obtained. Bedside fingerstick glucose testing is important to evaluate for hypoglycemia in patients with an altered or questionable mental status. Total bilirubin levels may be elevated in infectious hepatitis. Bilirubin levels higher than 30 mg/dL indicate more severe disease. Levels of alkaline phosphatase (ALP) are usually in the reference range but may elevate to no higher than twice the normal level. If ALP is elevated significantly, consider liver abscess or biliary obstruction. A prolonged prothrombin time (PT), if present, is a grave finding indicating impaired synthetic function of the liver. Blood urea nitrogen (BUN) and serum creatinine levels should be assessed to look for evidence of renal impairment. Decreased renal function suggests fulminant hepatic disease. Serum ammonia should be measured in patients with altered mental status or other evidence of hepatic encephalopathy. Detection of immunoglobulin M (IgM) for hepatitis A virus (HAV) is the standard for diagnosing acute infection with HAV. Detection of IgM for hepatitis B core antigen (HBcAg) in serum is required to make the diagnosis of acute hepatitis B virus (HBV) infection. Hepatitis B surface antigen (HBsAg) may be present in acute infection or in patients who are chronic carriers. Its presence in patients with symptoms of acute hepatitis strongly suggests acute HBV infection but does not rule out chronic HBV with acute superinfection by another hepatitis virus. The presence of HBsAg in the serum for 6 months or longer indicates chronic infection. Hepatitis C virus (HCV) infection can be confirmed with serologic assays to detect antibody to HCV (anti-HCV) or with molecular tests for the presence of viral particles. Third-generation assays for anti-HCV are sensitive and specific and can detect such antibodies within 4-10 weeks of infection. A rapid antibody test strip is available. Qualitative polymerase chain reaction (PCR) assay for presence of viral particles is the most specific test of HCV infection and may be helpful in diagnosing acute HCV infection before antibodies have developed. Assays to detect IgM antibody to hepatitis D virus (HDV) do not need to be routinely performed in all patients with suspected hepatitis. No specific imaging studies are required to make the diagnosis of hepatitis. However, obtain the appropriate diagnostic imaging studies (eg, ultrasonography or computed tomography [CT]) if the differential diagnosis favors gallbladder disease, biliary obstruction, or liver abscess. Liver biopsy may be recommended for the initial assessment of disease severity in patients with chronic hepatitis B or chronic hepatitis C infection.

Hepatitis A

Acute infection is documented by the presence of immunoglobulin M (IgM) antibody to hepatitis A virus (HAV) (anti-HAV), which disappears several months after the initial infection. The presence of immunoglobulin G (IgG) anti-HAV merely demonstrates that an individual has been infected with HAV at some point in the past, from 2 months ago to decades ago. IgG anti-HAV appears to offer patients lifelong immunity against recurrent HAV infection.

Hepatitis B

Acute self-limited infection

Hepatitis B surface antigen (HBsAg) is the first serum marker seen in persons with acute infection. It represents the presence of hepatitis B virus (HBV) virions (Dane particles) in the blood. Hepatitis B e antigen (HBeAg), a marker of viral replication, is also present. When viral replication slows, HBeAg disappears, and antibody to HBeAg (anti-HBe) is detected. Anti-HBe may persist for years. The first antibody to appear is antibody to hepatitis B core antigen (HBcAg) (anti-HBc). Initially, it is of the immunoglobulin M (IgM) class. Indeed, the presence of IgM anti-HBc is diagnostic for acute HBV infection. Weeks later, IgM anti-HBc disappears, and IgG anti-HBc is detected. Anti-HBc may be present for life. The anti-HBc (total) assay detects both IgM and IgG antibodies. The presence of anti-HBc (total) demonstrates that the patient has had a history of infection with HBV at some point in the past. In patients who clear HBV, HBsAg usually disappears 4-6 months after infection, as titers of antibody to HBsAg (anti-HBs) become detectable. Anti-HBs is believed to be a neutralizing antibody, offering immunity to subsequent exposures to HBV. Anti-HBs may persist for the life of the patient. Several key points should be kept in mind in interpreting serology findings from patients with acute HBV infection. The presence of HBsAg does not indicate whether the infection is acute or chronic. The presence of anti-HBc (IgM) is the sine qua non of acute HBV infection. The presence of anti-HBc (total) indicates that a patient has been infected with HBV at some point. The anti-HBc (total) remains positive both in patients who clear the virus and in patients with persistent infection.

The presence of anti-HBc (total) with a negative HBsAg and a negative anti-HBs indicates one of the following four things:

1. The test result is a false positive
2. The patient is in a window of acute hepatitis between the elimination of HBsAg and the appearance of anti-HBs; this scenario is not observed in patients with chronic HBV infection
3. The patient has cleared HBV but has lost anti-HBs over the years
4. The patient is one of the uncommon individuals with active HBV replication who is negative for HBsAg; this situation is diagnosed when either a positive HBeAg or a positive HBV DNA result is found.

In some clinicians' opinions, the discovery of a lone positive anti-HBc (total) finding in the setting of negative HBsAg and negative anti-HBs findings mandates the performance of a polymerase chain reaction (PCR) assay for HBV DNA.

Chronic infection

HBsAg may remain detectable for life in many patients. Individuals who have positive findings for HBsAg are termed carriers of HBV. They may be inactive carriers or they may have chronic hepatitis. Anti-HBc is present in all patients with chronic HBV infections. HBeAg and HBV DNA may or may not be present. They reflect a state of active viral replication. HBV DNA levels are typically low or absent in inactive carriers. HBV DNA levels are higher in patients with chronic hepatitis B. High HBV DNA levels are associated with increased infectivity. Anti-HBs is usually absent in patients with chronic infection. If anti-HBs is present in a patient who has positive HBsAg findings, it reflects the presence of a low level of antibody that was unsuccessful at inducing viral clearance.

Table 1 (below) summarizes diagnostic tests for HBV.

Table 1. Diagnostic Tests for Hepatitis B (Open Table in a new window)

Test	CHB HBeAg Positive	CHB HBeAg Negative	Inactive Carrier
HBsAg	+	+	+
Anti-HBs	-	-	-
HBeAg	+	-	-
Anti-HBe	-	+	+
Anti-HBc	+	+	+
IgM anti-HBc	-	-	-
HBV DNA	>2 × 10 IU/mL* (>10 copies/mL)	>2 × 10 IU/mL (>10copies/mL)	< 2 × 10 IU/mL (< 10 copies/mL)
ALT level	Elevated	Elevated	Normal

ALT = alanine aminotransferase; anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to HBeAg; anti-HBs = antibody to HBsAg; CHB = chronic hepatitis B; HBV = hepatitis B virus; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; IgM = immunoglobulin M.
*Increasingly, experts in the field use IU/mL rather than copies/mL.

Markers after vaccination for HBV

The HBV vaccine delivers recombinant HBsAg to the patient without HBV DNA or other HBV-associated proteins. More than 90% of recipients develop protective anti-HBs. Vaccine recipients are not positive for anti-HBc unless they were previously infected with HBV.

Hepatitis C

The tests most commonly used in the diagnosis of hepatitis C are liver chemistry, serology, hepatitis C virus (HCV) RNA testing, and liver biopsy. In August 2012, the Centers for Disease Control and Prevention (CDC) expanded their existing, risk-based testing guidelines to recommend a one-time blood test for HCV infection in baby boomers—the generation born between 1945 and 1965, who account for approximately 75% of all chronic HCV infections in the United States—without prior ascertainment of HCV risk (see Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965). One-time HCV testing in this population could identify nearly 808,600 additional people with chronic infection. All individuals identified with HCV should be screened and/or managed for alcohol abuse, followed by referral to preventative and/or treatment services, as appropriate.

Liver chemistry

Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels merely indicate the presence of liver injury. Patients with chronically elevated aminotransferase values should undergo a workup to exclude the possibility of chronic liver disease. Measuring aminotransferase levels is an imperfect test in patients with documented HCV infection. The values do not predict the severity of clinical findings, the degree of histologic abnormalities, the patient's prognosis, or the therapeutic response. Indeed, patients can have HCV-induced cirrhosis while still having normal liver chemistry values. Although increases and decreases in aminotransferase levels do not appear to correlate with clinical changes, normalization of AST and ALT levels after acute infection may signal clearance of HCV. Normalization of AST and ALT levels while a patient is undergoing treatment with interferon predicts a virologic response to treatment. Similarly, an increase in AST and ALT values may signal a relapse after apparently successful drug therapy.

Serology

Structural and nonstructural regions of the HCV genome have been synthesized. These can be recognized by human immunoglobulin G (IgG) antibody to HCV (anti-HCV). Recombinant HCV antigens are used in enzyme-linked immunosorbent assay (ELISA) to detect anti-HCV in patients' sera. Anti-HCV test results remain negative for several months after acute HCV infection. Once anti-HCV appears, it usually remains present for the life of the patient—even in the 15% of cases in which the patient clears the virus and does not develop chronic hepatitis. Anti-HCV is not a protective antibody and does not guard against future exposures to HCV. In 2010, the US Food and Drug Administration (FDA) approved the OraQuick HCV Rapid Antibody Test. It can be used for persons at risk for hepatitis or for those with signs or symptoms of hepatitis. The test strip can be used with a sample collected from oral fluid, whole blood, serum, or plasma. Recombinant immunoblot assays (RIBAs) use recombinant HCV antigens that are fixed to a solid substrate. They are more specific than ELISA testing and have been used to confirm positive ELISA results. However, their use is being abandoned in favor of HCV RNA testing.

A positive HCV result with ELISA or RIBA has one of three potential interpretations, as follows:

1. The test result is a true positive, and the patient is infected with HCV.
2. The test result is a true positive, but the patient is no longer viremic for HCV and does not have chronic hepatitis; the results from neither ELISA nor RIBA distinguish resolved infection from active infection
3. The test result is a false positive

ELISA testing has a positive predictive value (PPV) of more than 95% when used in patients at high risk for hepatitis C (eg, intravenous [IV] drug users and those with abnormal liver chemistry findings. However, its PPV is only 50-61% in patients at low risk for HCV infection. Furthermore, patients with autoimmune hepatitis or hypergammaglobulinemia frequently have false-positive ELISA results. Thus, a positive HCV ELISA or RIBA result does not prove that HCV infection is present. Positive serologic tests require confirmation with HCV RNA testing. Other limitations of ELISA testing are that it fails to detect anti-HCV in 2-5% of infected patients and that it fails to detect anti-HCV in immunosuppressed patients (eg, patients with end-stage renal disease [ESRD], human immunodeficiency virus [HIV] infection, or concomitant immunosuppressant therapy). The possibility of HCV infection in this patient population should prompt HCV RNA testing.

HCV RNA testing

Since the early 1990s, polymerase chain reaction (PCR) assays and branched DNA assays have been used to detect HCV RNA in serum. In contrast to ELISA and RIBA testing, HCV RNA testing can confirm the presence of active HCV infection. HCV RNA testing aids in the diagnosis of early cases of HCV infection (before the development of HCV antibody positivity or an elevated ALT level), seronegative cases (as in the setting of ESRD), and cases of perinatal transmission. It is also useful for confirming false-positive cases (eg, autoimmune hepatitis), assessing the HCV genotype and viral load, predicting the response to interferon therapy, guiding the duration and dose of interferon therapy, and determining the likelihood of relapse after a response to interferon therapy.

Liver biopsy

Liver biopsy is an important diagnostic test in possible cases of chronic hepatitis C. Biopsy results can help confirm the diagnosis, as well as help exclude other diseases that might have an impact on antiviral therapy, such as autoimmune hepatitis or hemochromatosis. Furthermore, liver biopsy offers the most reliable assessment of the severity of the disease. Assessment of the degree of hepatic fibrosis is important for several reasons. The presence of advanced fibrosis (ie, stage 3 or 4) might trigger a decision to initiate screening to rule out the development of hepatocellular carcinoma (HCC) as a complication of advanced liver disease. Patients with previously unsuspected cirrhosis on biopsy should be monitored to ensure they do not develop large esophageal varices. Some clinicians consider that patients with stage 3 fibrosis should be regarded as "cirrhotic until proven otherwise." Knowledge of the severity of histologic changes may influence the patient and the physician to be either more or less aggressive in the pursuit of effective antiviral therapy. The presence of significant fibrosis (ie, stage 2, 3, or 4) might lead to a decision to initiate antiviral therapy in the hope that eradication of HCV would help to improve the patient's long-term outcome. Patients with advanced histologic findings may seek experimental therapies should their condition not respond to standard antiviral therapy. Patients with minimal fibrosis on biopsy (ie, stage 1 disease) might elect either to receive antiviral therapy or to postpone therapy. Indeed, the patient with stage 1 disease might be considered to be at low risk for complications of HCV infection. Furthermore, the risks of therapy might exceed benefits in such a patient (eg, a patient with HCV infection, stage 1 fibrosis and major depression). In some clinicians' practices, before patients with stage 1 fibrosis elect to undergo a course of watchful waiting, they are advised that only virologic eradication of HCV can ensure that none of the extrahepatic complications of hepatitis C will develop. Patients are also advised to return for a repeat biopsy in 3-4 years to rule out progression of liver disease. Liver biopsy has a number of noteworthy limitations. First, as an invasive procedure, it may be accompanied by significant complications (eg, bleeding) in approximately 1 in 1000 patients. Second, a sampling error may occur. Indeed, in some patients, the damage induced by viral infection is not uniform throughout the entire liver. In addition, interobserver variability in the assessment of histologic abnormalities may occur. Finally, as a snapshot in time, liver biopsy findings cannot be used to predict the rate of progression of chronic hepatitis C.

Other tests for estimating fibrosis in chronic hepatitis C

Liver stiffness can be estimated by using a technique known as vibration-controlled transient elastography or Fibroscan. The test is reportedly capable of diagnosing cirrhosis correctly in about 95% of patients; however it is less accurate in assessing patients with lesser degrees of fibrosis. Fibroscan was approved for use in the United States in 2013 and, although it is not a replacement for liver biopsy, it can serve as a useful adjunct to help diagnose or exclude advanced fibrosis and cirrhosis.

Liver fibrosis can also be estimated by means of a number of commercial blood tests, including the following:

- FIBROSpect II uses measurements of hyaluronic acid, tissue inhibitor of metalloproteinase-1 (TIMP-1) and alpha-2 macroglobulin to estimate liver fibrosis
- HepaScore is based on levels of hyaluronic acid, alpha-2 macroglobulin, gamma glutamyl transferase (GGT), and total bilirubin, as well as age and sex
- HCV FibroSURE measures alpha-2 macroglobulin, haptoglobin, GGT, bilirubin, ALT, and apolipoprotein A1.

In general, these tests are considered accurate in determining the presence or absence of early (stage 1) or advanced (stage 4) fibrosis; however, they are considered to be less accurate in differentiating patients with moderate fibrosis. At present, most gastroenterologists do not use serologic fibrosis markers as a substitute for liver biopsy. These tests may be useful for identifying patients at low risk for advanced disease (eg, asymptomatic women with HCV RNA positivity, persistently normal liver chemistry values, and no history of alcohol abuse or HIV infection) or for longitudinal follow-up of patients with minimal disease on biopsy who elect not to undergo antiviral therapy. If future generations of these markers achieve greater accuracy, they may obviate the need for liver biopsy.

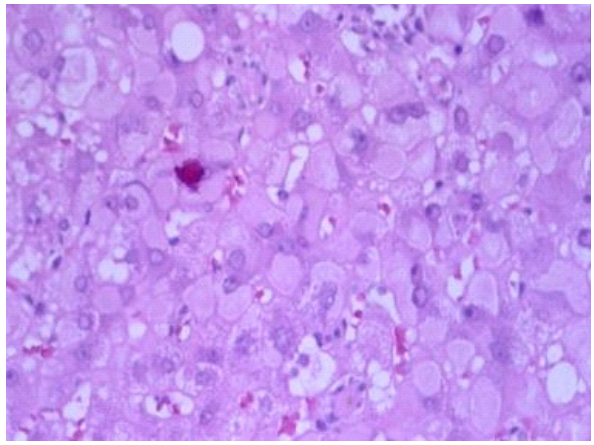
Hepatitis D and E

A serologic diagnosis of hepatitis delta virus (HDV) infection is made by using immunoglobulin M (IgM) antibody to HDV (anti-HDV) and IgG anti-HDV tests. IgM antibody to hepatitis B core antigen (anti-HBc) should be used to help distinguish between coinfection (positive for IgM anti-HBc) and superinfection (negative for IgM anti-HBc). Detecting HDV RNA in serum is also possible. A serologic diagnosis of hepatitis E virus (HEV) infection is made by using IgM antibody to HEV (anti-HEV) and IgG anti-HEV. HEV RNA can be detected in the serum and stool of infected patients.

Histologic Findings

Hepatitis B

Inactive carriers of hepatitis B virus (HBV) have no or minimal histologic abnormalities detected on liver biopsy specimens. Patients with chronic hepatitis B may have a number of classic histologic abnormalities. Inflammatory infiltrates composed of mononuclear cells may either remain contained within the portal areas or disrupt the limiting plates of portal tracts, expanding into the liver lobule (interface hepatitis). Periportal fibrosis or bridging necrosis (between portal tracts) may be present. The presence of bridging necrosis places the patient at increased risk for progression to cirrhosis. Ground-glass cells may be seen (see the image below). This term describes the granular homogeneous eosinophilic staining of cytoplasm caused by the presence of hepatitis B surface antigen (HBsAg). Sanded nuclei reflect the presence of an overload of hepatitis B core antigen (HBcAg). Special immunohistochemical stains may help detect HBsAg and HBcAg.



Liver biopsy specimen showing ground-glass appearance of hepatocytes in patient with hepatitis B.

Hepatitis C

Pathologists who interpret liver biopsy specimens frequently use a histologic scoring system introduced by Batts and Ludwig in 1995 (see Table 2 below) to grade hepatitis C virus (HCV)-induced disease. The METAVIR scoring system developed by the French METAVIR Cooperative Study Group uses similar methodology.

Table 2. Histologic Grading for Hepatitis C–Induced Liver Disease (Open Table in a new window)

Grade	Portal Inflammation	Interface Hepatitis	Lobular Necrosis
1 – Minimal	Mild	Scant	None
2 – Mild	Mild	Mild	Scant
3 – Moderate	Moderate	Moderate	Spotty
4 – Severe	Marked	Marked	Confluent

Histologic staging for hepatitis C–induced liver disease is as follows:

- Stage 1 – Portal fibrosis
- Stage 2 – Periportal fibrosis
- Stage 3 – Septal fibrosis
- Stage 4 – Cirrhosis

Lymphocytic infiltrates, either contained within the portal tract or expanding out of the portal tract into the liver lobule (interface hepatitis), are commonly observed in patients with chronic hepatitis C. Portal and periportal fibrosis may be present. Other classic histologic features of the disease include bile duct damage, lymphoid follicles or aggregates, and macrovesicular steatosis.

Hepatitis D and E

The pathologic abnormalities associated with HBV-HDV coinfection are the same as those observed in patients infected with HBV alone (see above). The classic pathologic findings associated with HEV infection include infiltration of portal tracts by lymphocytes and polymorphonuclear leukocytes, ballooned hepatocytes, acidophilic body formation, and intralobular necrosis of hepatocytes. Submassive and massive hepatic necrosis may be observed in severe cases.

Treatment & Management

Approach Considerations

No specific emergency department (ED) treatment is indicated for viral hepatitis, other than supportive care that includes intravenous (IV) rehydration. A liver abscess calls for IV antibiotic therapy directed toward the most likely pathogens and consultation for possible surgical or percutaneous drainage. Admit patients with hepatitis if they are showing any signs or symptoms suggestive of severe complications. Admit and evaluate for hepatic encephalopathy any patients with altered mental status, agitation, behavior or personality changes, or changes in their sleep-wake cycle. Other admission criteria that are suggestive of severe disease include a prothrombin time (PT) longer than 3 seconds, a bilirubin level greater than 30 mg/dL, and hypoglycemia. Admit any patients with intractable vomiting, significant electrolyte or fluid disturbances, or significant comorbid illness; those who are immunocompromised; and those who are older than 50 years. Certain patients may benefit from pharmacologic therapy. For chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infections in particular, the goals of therapy are to reduce liver inflammation and fibrosis and to prevent progression to cirrhosis and its complications. Because the treatment regimens for hepatitis are being actively researched, medication recommendations, indications, and dosages are all subject to change. Consultations with a gastroenterologist, hepatologist, or general surgeon may be indicated. Most patients with viral hepatitis can be monitored on an outpatient basis. Ensure that patients can maintain adequate hydration, and arrange close follow-up care with primary care physicians. Instruct patients to refrain from using any potential hepatotoxins (eg, ethanol or acetaminophen). Advise patients to avoid prolonged or vigorous physical exertion until their symptoms improve. Patients who are found subsequently to have HBV or HCV should be referred to a gastroenterologist or a hepatologist for further evaluation and treatment.

Acute Hepatitis A

Treatment for acute hepatitis caused by hepatitis A virus (HAV) is necessarily supportive in nature, because no antiviral therapy is available. Hospitalization is warranted for patients whose nausea and vomiting places them at risk for dehydration. Patients with acute liver failure require close monitoring to ensure they do not develop fulminant hepatic failure (FHF), which is defined as acute liver failure that is complicated by hepatic encephalopathy.

Acute Hepatitis B

As is the case for acute hepatitis A virus (HAV) infection, no well-established antiviral therapy is available for acute hepatitis B virus (HBV) infection. Supportive treatment recommendations are the same for acute hepatitis B as for acute hepatitis A. Lamivudine, adefovir dipivoxil, and other antiviral therapies appear to have a positive impact on the natural history of severe cases of acute HBV infection. A study by Schmilovitz-Weiss described a rapid clinical and biochemical response in 13 of 15 patients with severe acute hepatitis B who received lamivudine.

Chronic Hepatitis B

Ideally, treatment of chronic hepatitis B would routinely achieve loss of hepatitis B surface antigen (HBsAg). Indeed, loss of HBsAg is associated with a decreased incidence of hepatocellular carcinoma (HCC) and a decreased incidence of liver-related death in patients with hepatitis B virus (HBV)-induced cirrhosis. However, loss of HBsAg is only achieved in relatively small percentages of patients with chronic hepatitis B, that is, about 3-7% of those treated with pegylated interferon (PEG-IFN) and 0-5% of those treated with oral nucleosides or nucleotides. At present, the key goal of antiviral treatment of HBV is the inhibition of viral replication. This is marked by the loss of hepatitis B e antigen (HBeAg) in patients with HBeAg-positive chronic hepatitis B and by the suppression of HBV DNA levels. Secondary aims are to reduce symptoms, if any, and to prevent or delay the progression of chronic hepatitis to cirrhosis or HCC. Agents currently used to treat hepatitis B include PEG-IFN alfa-2a and the oral nucleoside or nucleotide analogues. Typically, PEG-IFN treatment is continued for 48 weeks for both HBeAg-positive and HBeAg-negative chronic hepatitis. Oral agents may be used for as short as 1-2 years; however, most HBeAg-positive chronic hepatitis patients and almost all HBeAg-negative chronic hepatitis patients require indefinite therapy with these agents. Withdrawal of oral nucleoside/nucleotide analogue therapy in these individuals usually results in virologic relapse.

More detailed information regarding management of chronic hepatitis B is beyond the scope of this emergency medicine topic. The reader is referred to the following references:

- Pyrsopoulos NT, Reddy KR. Hepatitis B. Medscape Drugs & Diseases. Updated: May 26, 2017. Available at:

http://emedicine.medscape.com/article/177632-overview.
- Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016 Jan. 63 (1):261-83.
- World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. 2015 Mar.

Acute Hepatitis C

Acute hepatitis C virus (HCV) infection is detected infrequently. When it is identified, early interferon (IFN) therapy should be considered. In one study, 44 patients with acute hepatitis C were treated with IFN alfa-2b at 5 million U/day subcuteaneously (SC) for 4 weeks and then three times per week for another 20 weeks. About 98% of patients developed a sustained virologic response (SVR), defined as an undetectable level of serum HCV RNA 6 months after completion of antiviral treatment. Most experts now equate achievement of an SVR with viral eradication or cure of HCV infection.

Chronic Hepatitis C

Goals

Antiviral therapy has several major goals, including the following, to:
- Decrease viral replication or eradicate HCV
- Prevent progression of disease
- Reduce the prevalence of cirrhosis
- Decrease the frequency of hepatocellular carcinoma (HCC) as a complication of cirrhosis
- Ameliorate symptoms, such as fatigue and joint pain
- Treat extrahepatic complications of HCV infection, such as cryoglobulinemia or glomerulonephritis

Interferon (IFN) has been the drug of choice for the treatment of hepatitis C for more than two decades. It is often used in combination with another drug, ribavirin. Successful IFN-based therapy, resulting in a sustained virologic response (SVR), can improve the natural history of chronic hepatitis C and may reduce the risk of HCC in patients with HCV-induced cirrhosis. IFN-based therapy appears to reduce the rate of fibrosis progression in patients with HCV infection. One report described regression of cirrhosis in some—but not all—patients who responded well to antiviral therapy. In this study, 96 patients with biopsy-proven HCV-induced cirrhosis were treated with IFN-based therapy. At a median interval of 17 months after the conclusion of antiviral therapy, patients underwent a second biopsy. Overall, 18 patients (19%) had a decrease in fibrosis score on follow-up biopsy, from stage 4 to less than stage 2, and SVR had been achieved in 17 of these 18 patients. With a median follow-up of 118 months, these patients were found to have decreased liver-related morbidity and mortality compared with patients who were not histologic responders. In this study, not all patients who achieved SVR experienced histologic improvements. Thus, it remains important to continue routine surveillance in patients with HCV cirrhosis—even if SVR is achieved through antiviral therapy—in order to rule out the development of HCC as a complication of cirrhosis. Another report retrospectively assessed 920 patients with HCV-induced cirrhosis who underwent IFN therapy in the 1990s. The mean follow-up period was 96 months (range, 6-167 months). Achievement of SVR decreased patients' risk for hepatic decompensation, HCC, and liver-related mortality. When considering treatment of HCV infection, both the clinician and the patient must be clear about the goals of therapy. As an example, in the patient with advanced fibrosis or cirrhosis, the goal of treatment is virologic cure in the hope of preventing progressive liver disease. Unfortunately, SVR cannot be achieved in everyone. Achievement of SVR, although always desirable, is not always necessary to obtain a desired clinical result. Indeed, partial suppression of HCV through antiviral therapy may be all that is needed to stabilize renal function in a patient with HCV-related glomerulonephritis or to prevent the progression of malignancy in a patient with HCV-related non-Hodgkin lymphoma.

Pharmacologic agents

IFNs are a class of naturally occurring compounds that have both antiviral and immunomodulatory effects. They remain the backbone of antiviral strategies used against HCV infection. Agents currently approved by the FDA for the treatment of HCV infection include the following:
- IFN alfa-2b
- IFN alfa-2a
- Ribavirin, which is used in combination with IFN

The addition of a large, inert polyethylene glycol (PEG) molecule to a therapeutic molecule (eg, IFN) can delay the clearance of the therapeutic molecule from the bloodstream. Long-acting PEG-IFN alfa-2b and PEG-IFN alfa-2a are currently the most commonly used medications for hepatitis C therapy in the United States. Other interferons under study include IFN beta, IFN gamma, and natural interferon. Future medications may target the enzymes responsible for HCV replication. Drugs that have activity against viral helicases, proteases, and polymerases are currently under study, as are ribozymes and antisense oligonucleotides.

Factors predictive of an SVR to treatment with PEG-IFN in combination with ribavirin include the following:
- Genotype 2 or 3 status
- Baseline HCV RNA level below 800,000 IU/mL or less than 2 million copies/mL
- Compliance with treatment
- Absence of cirrhosis

However, patients with well-compensated cirrhosis have a reasonable likelihood of achieving viral eradication and should be offered IFN therapy, provided no significant contraindication (eg, severe thrombocytopenia) is present. Ideally, HCV eradication in the cirrhotic patient may prevent or forestall the development of progressive hepatic fibrosis and liver decompensation. Patients treated with IFN may also have a decreased risk of HCC. If a patient ultimately requires liver transplantation for the treatment of complications of cirrhosis, previous eradication of HCV obviates any concerns about potentially severe recurrent hepatitis C after transplantation.

Limitations

Not all patients with chronic hepatitis C are appropriate candidates for therapy with IFN and ribavirin. First, the drugs have well-known adverse effects, which lead to discontinuance in approximately 15% of patients. IFN can induce fatigue, joint pain, emotional irritability, depression, and alopecia. Patients with underlying psychiatric disorders must be carefully screened before they receive a drug that can worsen underlying depression or schizophrenia or that can even induce suicidal ideation. IFN can also induce the development of thyroid disease or exacerbate an underlying immune-mediated disease (eg, psoriasis or sarcoidosis). It has long been recognized that adherence to prescribed doses of PEG-IFN and ribavirin will maximize a patient's ability to achieve an SVR. Missed doses due to lack of patient compliance or to physician-ordered dose reductions (eg, on account of the new onset of anemia or cytopenias) will increase the chance for treatment failure.

Patients invariably need close clinical and laboratory follow-up during treatment. Treatment with PEG-IFN can induce neutropenia. In some patients with IFN-induced neutropenia, granulocyte colony-stimulating factor (G-SCF) must be added to the regimen in order to support a falling white blood cell (WBC) count. Treatment with PEG-IFN can also induce thrombocytopenia. It was once assumed that most patients (typically cirrhotic) with baseline platelet counts lower then 70,000/µL would be unable to tolerate treatment because of the induction of severe thrombocytopenia. Eltrombopag received FDA approval in November 2008 for the treatment of thrombocytopenia in cases of idiopathic thrombocytopenic purpura (ITP). Eltrombopag was studied in patients with HCV-induced cirrhosis and platelet counts lower than 70,000/µL. Treatment with eltrombopag 75 mg orally once daily successfully improved platelet counts in 95% of the patients studied, permitting a majority to undergo IFN treatment. However, eltrombopag use has been associated with both venous thromboembolism and drug-induced liver injury. In the United States, the medication is only available through an FDA-mandated restricted-distribution program. Ribavirin commonly produces rash and hemolytic anemia. Some patients with ribavirin-induced anemia need combination therapy with erythropoietin in order to support a falling hematocrit. Some clinicians believe patients should undergo baseline cardiac stress testing, given the potential for patients to develop severe anemia. Both IFN and ribavirin have been associated with a low risk of inducing retinopathy. Clinicians may wish to consider having patients undergo pretreatment and posttreatment ophthalmologic examinations. The presence of insulin resistance may reduce the chance of achieving viral eradication with PEG-IFN and ribavirin. Excellent control of diabetes is recommended before patients embark on IFN-based therapy. In spite of all of the potential concerns related to combination therapy with PEG-IFN and ribavirin, the vast majority of patients are able to tolerate their recommended 24-week (for genotypes 2 and 3) or 48-week (for genotypes 1 and 4) treatment course.

Treatment of special populations

Chronic renal failure

HCV infection is documented in 10-20% of patients receiving chronic hemodialysis. Anti-HCV therapy is often appropriate for such patients. Attempts to eradicate HCV should be made before renal transplantation is carried out. Indeed, the hepatic histologic abnormalities attributed to HCV infection may worsen dramatically after posttransplant immunosuppressant therapy is started. Reduced doses of PEG-IFN are typically used. Ribavirin should be avoided in all patients with renal insufficiency and in patients receiving hemodialysis because of the increased risk of severe hemolytic anemia.

HIV-HCV coinfection

Approximately 25% of Americans infected with human immunodeficiency virus (HIV) are also coinfected with HCV (10% of HIV-infected people are coinfected with HBV), and 75% of HIV-infected persons who inject drugs have HCV coinfection. Therefore, HIV testing should be routine in patients with diagnosed with HCV infection. HIV-infected individuals appear to have an impaired immune response to HCV infection. This translates into more rapid progression of hepatic fibrosis and higher rates of liver-related death in coinfected patients than in those with only HCV infection. Indeed, HCV-induced cirrhosis is a major cause of death in the HIV-infected population in the United States. Accordingly, physicians are now more aggressive than they once were with respect to diagnosing and treating HCV infection in their HIV-infected patients. It also appears that suppression of HCV by means of IFN therapy may improve a patient's ability to tolerate antiretroviral therapy (ART). Drug-induced hepatotoxicity is common in patients treated with ART. Treatment with PEG-IFN and ribavirin is usually offered to patients with a CD4 cell count higher than 200/µL. CD-4 cell counts lower than 200/µL—and certainly those lower than 100/µL—are associated with a poor response to therapy. In general, HIV-infected patients tolerate treatment well. However, significant neutropenia, thrombocytopenia, and anemia may develop. A few case reports describe mitochondrial toxicity and lactic acidosis when IFN and ribavirin are used in combination with dideoxyinosine, zidovudine, stavudine, and efavirenz. Pancreatitis has been described in patients receiving IFN and dideoxyinosine. Since the introduction of IFN therapy, patients with HIV-HCV coinfection have generally had a diminished rate of hepatitis C SVR in comparison with patients without HIV infection. However, in an early study of coinfected patients who received PEG-IFN alfa-2a 180 µg subcuteaneously (SC) once weekly and ribavirin 800 mg/day orally, patients with genotype 1 had a 29% SVR rate, and those with genotype 2 or 3 had a 62% SVR rate. There are multiple reports of liver transplantation being successfully performed to treat decompensated HCV-induced cirrhosis in coinfected patients. Potential candidates for transplantation include patients who have achieved a negative HIV viral load through ART. Overall, however, 2-year posttransplant survival rates are lower in patients coinfected with HIV/HCV than in patients infected with HCV alone. At present, only a small percentage of the more than 100 transplantation programs in the United States perform liver transplantation in HIV-infected patients.

Newer therapeutic agents

The development of direct-acting antiviral drugs (DAAs) has significantly improved treatment options for patients infected with hepatitis C. These newer agents, which are taken orally for 8-12 weeks, are becoming standard of care for patients with chronic hepatitis C because they have been shown to attain sustained virologic response rates of 90% and greater.

Newer, all-oral, direct-acting antiviral agents :

- Simeprevir and sofosbuvir – approved in 2013. Used in combination with PEG-INF and ribavirin, or as an all-oral combination regimen
- Ledipasvir/sofosbuvir (Harvoni) – approved in 2014
- Ombitasvir, paritaprevir, and ritonavir tabliets; dasabuvir tablets (Viekira Pak) – approved in 2014
- Elbasvir and grazoprevir (Zepatier) – licensed in 2016.

Treatment of Hepatitis D and E

Treatment of patients coinfected with hepatitis B virus (HBV) and hepatitis delta virus (HDV) has not been well studied. The onl effective treatment for HBV/HDV coinfection is pegylated interferon (PEG-IFN); antiviral nucleos(t)ide analogues have limited or no effect on HDV replication. However, multiple small studies have demonstrated that patients with HBV-HDV coinfection are less responsive to IFN therapy than patients with HBV infection alone. Treatment with PEG-IFN alfa-2b produced HDV RNA negativity in only 17-19% of patients. Lamivudine appears to be ineffective against HBV-HDV coinfection. Treatment of patients infected with hepatitis E virus (HEV) infection is supportive in nature.

Prevention

Hepatitis A

Improved sanitation, strict personal hygiene, and hand washing all may help prevent transmission of hepatitis A virus (HAV). The virus is inactivated by household bleach or by heating to 85°C (185°F) for 1

minute. In addition, travelers to endemic areas should not drink untreated water or ingest raw seafood or shellfish. Fruits and vegetables should not be eaten unless they are cooked or can be peeled.

Vaccination

In 1995, the US Food and Drug Administration (FDA) approved the first vaccine for HAV. Beginning in 1996, the Centers for Disease Control and Prevention (CDC) recommended vaccination against HAV for the following individuals:

- People traveling to regions where HAV is endemic
- Men who have sex with men
- Users of illicit drugs

Beginning in 1999, the CDC recommended vaccination for children living in 17 states with consistently elevated rates of HAV infection. Since 2006, the CDC has recommended vaccination for all children at age 1 year as well as encouraged "catchup" vaccination programs for unvaccinated children.

Active immunization with HAV vaccine is also recommended for the following individuals:

- Persons with an occupational risk of infection (eg, persons working with HAV-infected primates)
- Patients who may receive clotting factor concentrates
- "Susceptible persons with chronic liver disease"
- "Susceptible persons who are either awaiting or have received liver transplants"

The third recommendation stemmed from the observation that patients with chronic liver disease, although not at increased risk for exposure to HAV, were at increased risk for fulminant hepatic failure (FHF) if they were infected with the virus. Notably, there are data to suggest that workers exposed to raw sewage do not have a higher prevalence of antibodies to HAV than a comparator population. The inactivated HAV vaccines Havrix and Vaqta are administered as 1-mL (0.5-mL in children) intramuscular (IM) injections given more than 1 month before anticipated travel. This approach results in a better-than-90% likelihood of stimulating production of immunoglobulin G (IgG) antibody to HAV (anti-HAV), with resulting immunity against HAV infection. A booster dose of the vaccine is recommended 6 months after the initial vaccination. Whether HAV vaccine administration should be mandated in children (as HBV vaccination is) remains unclear. An alternative vaccine, containing inactivated HAV and recombinant hepatitis B virus (HBV) vaccines, is Twinrix. This product is immunogenic against both HAV and HBV. The FDA has approved its use in adults. Typical administration involves three injections of 1 mL given IM on a 0-, 1-, and 6-month schedule. Alternatively, a four-dose schedule can be used, with Twinrix administered on days 0, 7, and 21-30, followed by a booster dose at month 12.

Immune globulin

Passive postexposure immunization with hepatitis A immune globulin (HAIG) is an alternative to active immunization with HAV vaccine. Its effectiveness is highest when it is given within 48 hours of exposure, but it may be helpful when given as far as 2 weeks into the incubation period.

Postexposure prophylaxis with HAIG is appropriate for household and intimate contacts of patients with HAV. It is also recommended for contacts at daycare centers and institutions. The typical dosing of HAIG is 0.02 mL/kg IM as a single dose. Postexposure prophylaxis is not recommended for the casual contacts of patients, such as classmates or coworkers. For travelers who anticipate spending less than 3 months in an HAV-endemic region, the dose is 0.02 mL/kg IM. Travelers who are planning to spend more than 3 months in a region where HAV is endemic should receive 0.06 mL/kg IM every 4-6 months.

Hepatitis B

The primary strategies for prevention of hepatitis B are to reduce transmission of the disease and to improve health outcomes for individuals who are already infected with hepatitis B.

Vaccination

Plasma-derived and recombinant HBV vaccines use hepatitis B surface antigen (HBsAg) to stimulate the production of anti-HBs in noninfected individuals. The vaccines are highly effective, with a greater than 95% rate of seroconversion. Vaccine administration is recommended for all infants as part of the usual immunization schedule, as well as for adults at high risk of infection (eg, those receiving dialysis and healthcare workers). Recommendations for hepatitis B vaccination are available from the CDC and the World Health Organization (WHO).

The recommended vaccination schedule for infants consists of an initial vaccination at the time of birth (ie, before hospital discharge), a repeat vaccination at 1-2 months, and another repeat vaccination at 6-18 months. The recommended vaccination schedule for adults consists of an initial vaccination, a repeat vaccination at 1 month, and another repeat vaccination at 6 months. If Twinrix (the combined HAV-HBV vaccine) is used, it is given according to the schedule previously described for hepatitis A. Because of the nonresponse rate, many recommend that healthcare workers undergo postvaccination testing to confirm response within 1-2 months of receiving the vaccine. The duration of immunity conferred by the vaccine is not clearly known. Some clinicians recommend that a booster be given at 5-10 years. Vaccination of children is an effective means of preventing HBV infection and its complications. For example, although HBV infection is endemic in Taiwan, the institution of universal vaccination for neonates in Taiwan in 1984 reduced the HBsAg carrier rate in children from 9.8% to 0.7% over a period of 15 years. There was also a resulting drop in the incidence of HCC in children from 0.54 to 0.20 per 100,000. Follow-up studies are needed to determine whether the overall incidence of HCC in Taiwan decreases as these children enter adulthood. Vaccination is also recommended for older children and adolescents who were not vaccinated as infants; adults with diabetes; and household contacts and intimate partners of individuals with chronic hepatitis B infection.

Prevention of perinatal transmission

Mother-to-child transmission of hepatitis B most commonly occurs at birth, when the neonate is exposed to maternal blood and bodily fluids, or during early childhood. Because acquiring hepatitis B infection early in life poses a high risk of developing chronic infection, strategies to reduce mother-to-child transmission are of vital importance. For such strategies to be effective, it is important that all pregnant women undergo screening for HBV infection so that they and their newborns may be treated appropriately. Administering hepatitis B vaccination within 12 hours of birth to neonates born to mothers with hepatitis B infection is 80-95% effective in preventing transmission of hepatitis B infection. In some cases, depending upon the mother's viral load and human immunodeficiency virus (HIV) status, there may be indications to treat the mother with antiviral agents during pregnancy.

Immune globulin

Hepatitis B immune globulin (HBIG) is derived from plasma. It provides passive immunization for individuals who describe recent exposure to a patient infected with HBV. HBIG is also administered after liver transplantation to persons infected with HBV in order to prevent HBV-induced damage to the liver allograft.

Recommendations for postexposure prophylaxis for contacts of patients positive for HBsAg are as follows:

- Perinatal exposure – HBIG plus HBV vaccine at the time of birth

(90% effective)
- Sexual contact with an acutely infected patient – HBIG plus HBV vaccine
- Sexual contact with a chronic carrier – HBV vaccine
- Household contact with an acutely infected patient – None
- Household contact with an acutely infected person resulting in known exposure – HBIG, with or without HBV vaccine
- Infant (age < 12 months) primarily cared for by an acutely infected patient – HBIG, with or without HBV vaccine
- Inadvertent percutaneous or permucosal exposure – HBIG, with or without HBV vaccine.

Improving health outcomes for those with HBV infection

Improving health outcomes for persons with HBV requires early identification so that they can be made aware of their infection and can receive appropriate treatment and education on risk reduction. To that end, it is recommended that individuals who are at high risk for HBV infection be offered appropriate testing and connection with care.

Hepatitis C

No vaccine against HCV is available, and immune globulin is not proven to prevent transmission. In fact, immune globulin administration has been associated with HCV. At present, the major means of preventing transmission of HCV is to prevent infected blood, organs, and semen from entering the donor pools. The CDC also recommends meticulous infection control practices within healthcare settings.

Additionally, individuals who are at risk for HCV infection should be offered appropriate testing, treatment, and health education to reduce the risk of transmission.

Improving health outcomes for those with HCV infection

With newer treatments that can provide sustained viral response (SVR), health outcomes for individuals with HCV can be improved by linking them to care and providing appropriate treatment. Because many individuals may not be aware that they are infected with HCV, providers should offer testing to individuals at risk to include those with a history of injection drug use, persons infected with HIV, and healthcare workers with blood borne exposures to HCV. Additionally, the CDC recommends one-time screening for all individuals born between 1945 and 1965 because this population is at high risk of HCV infection, and they are at highest risk for morbidity and mortality as a result of HCV infection.

Prevention of perinatal transmission

The finding of HCV among increasing numbers of women of childbearing age raises the concern that more infants will be at risk for HCV as a result of mother-to-child transmission. Providers should screen pregnant women to assess their risks for HCV and offer testing if they are deemed to be at risk; additionally, infants born to infected mothers should be tested for HCV. Women of childbearing age, pregnant women, and infants who test positive for HCV should be referred for care, monitoring, and treatment.

Hepatitis D and E

Because HDV can infect patients only when HBV is present, transmission of hepatitis D can be decreased by effectively immunizing patients against HBV. Unfortunately, at this time, no means of preventing HDV superinfection in patients with chronic HBV is known. No vaccine exists for the prevention of HEV infection. Administration of immune globulin does not prevent the development of clinical disease.

Medication Summary

Certain patients may benefit from pharmacologic therapy. For chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infections in particular, the goals of therapy are to reduce liver inflammation and fibrosis and to prevent progression to cirrhosis and its complications. In addition to the medications listed below (eg, interferons [IFNs], antivirals, and corticosteroids), the nucleoside analogues lamivudine and adefovir have shown promising results in the treatment of patients with chronic hepatitis B. Other antiviral agents that are being studied for treatment of chronic hepatitis B are entecavir and tenofovir. Besides being active against HBV, lamivudine, adefovir, and tenofovir are also active against human immunodeficiency virus (HIV) and thus are potentially useful in the treatment of patients with HBV-HIV coinfection. For patients with chronic HCV infection, one current treatment option is combination therapy with pegylated IFN (PEG-IFN) and the antiviral ribavirin. This regimen may be recommended for a certain subset of patients with moderate or severe inflammation or fibrosis. The combination of the two drugs provides a more sustained clearance of HCV RNA from the serum of infected individuals than monotherapy does. Other therapeutic options are being explored for treatment of chronic HCV with the goals of increasing efficacy and decreasing toxicity. These include protease inhibitors, ribozymes, and viral vaccines.

INTERPRETATION

HEPATITIS MARKERS

Hepatitis Serology Markers

Five forms of viral hepatitis

Hepatitis	A	B	C	D	E
Virus	HAV	HBV	HCV	HDV	HEV
Family	Picornavirus	Hepadnavirus	Flavivirus	Satellite	Calicivirus
Genome	ssRNA	dsDNA	ssRNA	ssRNA	ssRNA
Spread	Fecal-oral	parenteral, sexual, perinatal	parenteral, ?sexual	parenteral, ?sexual	Fecal-oral
Antigens	HAV-Ag	HbsAg, HBcAg, HBeAg	HCV-Ag	HDV-Ag	HEV-Ag
Antibodies	Anti-HAV	Anti-HBs, Anti-HBc, Anti-HBe	Anti-HCV	Anti-HDV	Anti-HEV
Virus markers	HAV RNA	HBV DNA, DNA polymerase	HCV RNA	HDV RNA	virus like partiacles

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Hepatitis A Serology

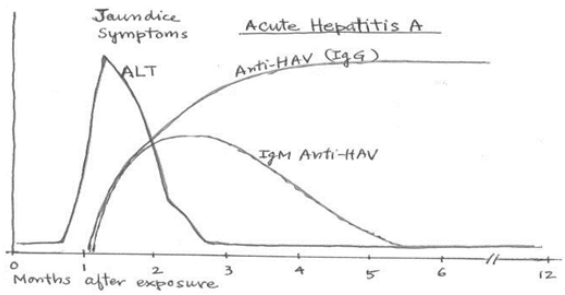
1. anti-HAV (antibody to hepatitis A virus)
   it detects total antibody of both IgG and IgM sublasses of HAV. Its presence indicates either acute or resolved infection.
2. IgM anti-HAV (IgM antibody subclass of anti-HAV, hepatitis A virus)
   it indicates a recent infection with HAV (< 6months). It is used to diagnose acute hepatitis A.

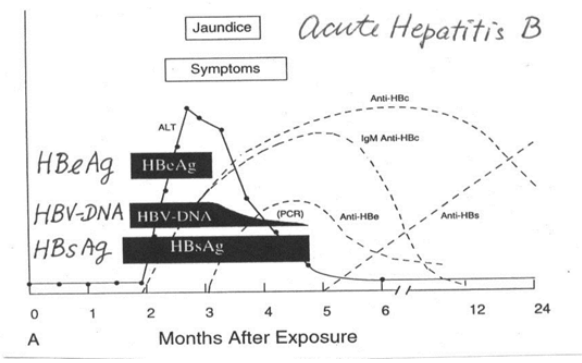
Hepatitis B Serology

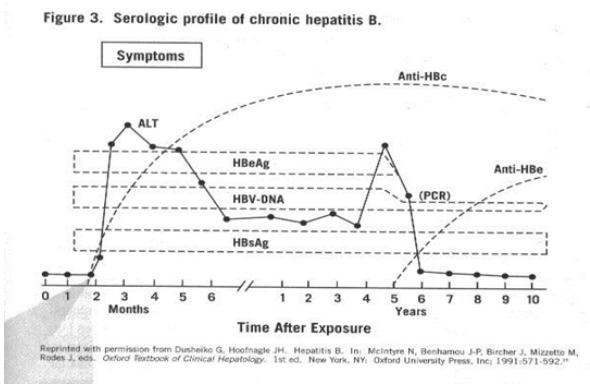
1. HBsAg (Hepatitis B surface antigen)
   it indicates either acute or chronic Hepatitis B virus (HBV) infection.
2. anti-HBs (HBsAb = antibody to hepatitis B surface antigen)
   it is a marker of hepatitis B immunitiy.
3. anti-HBc (HBcAb = antibody to hepatitis B core antigen)
   it is a nonspecific marker of acute, chronic, or resolved HBV infection. It is not a marker of vaccine-induced immunity.
4. IgM anti-HBc (IgM antibody sublass of anti-HBc)
   it indicates recent infection with HBV (<6 months). Its presence indicates acute infection.
5. HBeAg (Hepatitis B "e" antigen)
   it is a marker of a high degree of HBV infectivity, & acorrelates with a high level of HBV replicaiton. It is primarily used to help determine the clinical management of patients with chronic HBV infection.
6. anti-HBe (antibody to hepatitis B "e" antigen)
   it may be presnet in an infected or immune person. In persons with chronic HBV infection, its presence suggests a low viral titer and a low degree of infectivity.
7. HBV-DNA (HBV deoxyribonucleic acid)
   it is a marker of viral replication. It correlates well with infectivity. It is used to assess and monitor the treatment of patients with chronic HBV infection.

Hepatitis C Serology

1. anti-HCV (antibodies to HCV - hepatitis C Virus) by ELISA or RIBA-2 assay
   to detect acute & chronic hepatitis C infection.
2. Serum HCV RNA qualitative & quantitative assay by PCR method
   to establish viremia & is employed in the management of chronic HCV infection.
3. Genotyping of HCV RNA (genotype 1-less Rx responsiveness, or genotype 2 or 3 with better Rx responsivenss)
   The 1998 studies of interferon and ribavirin combination therapy showed important differences in the outcome based on genotype; that is, approximately 30% of patients with genotype 1 and approximately 65% with genotype 2 or 3 had sustained virologic responses. In addition, patients with genotype 1 had higher rates of sustained virologic response with 48 weeks of combination therapy than with 24 weeks of therapy, whereas patients with other genotypes achieved no additional benefit beyond 24 weeks of therapy. These studies have led to the practice of administering therapy for 12 months to patients with genotype 1 but for only 6 months to those with genotype 2 or 3. Factors in addition to genotype are known to predict the likelihood of successful therapy with ribavirin and interferon.







TROUBLESHOOTING

UNIVERSAL GUIDELINES IN AN INFLUENZA LIKE ILLNESS PANDEMIC SCENARIO (like covid 19)

General Guidance

This guidance is to address the general workflow safety concerns of laboratory personnel during the COVID-19 pandemic. All laboratories should perform site- and activity-specific risk assessments to determine the most appropriate safety measures to implement for particular circumstances. In addition, facilities should adhere to local policies and procedures as well as all applicable federal, state, and local regulations and public health guidelines.

Risk assessments should include the following considerations:

- Analyze the number of people that the laboratory space can realistically and safely accommodate while maintaining
- Assess the flow of personnel traffic. Where possible, design one-way paths for staff to walk through the laboratory space.
- Assess procedures for cleaning and sanitizing commonly shared equipment and areas—for example, counters, benchtops, and desks—to ensure clean surfaces and equipment for all users.
- Review emergency communication and operational plans, including how to protect staff at higher risk for severe illness from COVID-19.

Every institution should have a COVID-19 health and safety plan to protect employees. This plan should be shared with all staff. Ideally, this plan would:

- Instruct sick employees to stay home and not return to work until the criteria to discontinue home isolation are met, in consultation with healthcare providers and state and local health departments.
- Provide information on whom employees should contact if they become sick.
- Implement flexible sick leave and supportive policies and practices. If sick leave is not offered to some or all employees, the institution should consider implementing emergency sick leave policies.
- Designate someone to be responsible for responding to employees' COVID-19 concerns. Employees should know who this person is and how to contact this person at all times.
- Provide employees with accurate information about COVID-19, how it spreads, and the risk of exposure.
- Reinforce training on proper handwashing practices and other routine infection control precautions to help prevent the spread of many diseases, including COVID-19.

Ensure that employees have access to personal protective equipment (PPE); disinfectant products that meet EPA's criteria for use against SARS-CoV-2external icon; and soap, clean running water, and drying materials for handwashing, or alcohol-based hand sanitizers that contain at least 60% ethanol or 70% isopropanol.

Social Distancing

To the extent possible, adhere to social distancing recommendations by adjusting staff schedules, adding additional shifts, or implementing non-overlapping teams to minimize personnel contact. Identify laboratory tasks and activities that can be performed with reduced or no face-to-face interactions. Examples include limiting the number of laboratory meetings that occur and, when possible, using remote collaboration tools (such as video and phone conferencing), even for those who work in the same location or building. To the extent possible, reconfigure workspaces and locations of shared equipment to reduce crowding. Create one-directional paths and workflows. Declutter workspaces and dispose of unnecessary items to help with reconfiguration. If reconfiguration is not possible, consider placing barriers (plexiglass, partition, plastic, etc.) between computer workstations, desks, or equipment that position staff six feet apart from each other. Minimize personnel traffic and interactions by limiting visits from vendors and other external partners; engage with them virtually whenever possible.

Face Coverings

To help slow the spread of COVID-19, CDC recommends wearing face coverings in settings where social distancing measures are challenging to maintain, like office spaces, computer workstations, and break rooms. In general, laboratory employees should wear a face covering in laboratory spaces that do not have requirements for respiratory PPE and where other social distancing measures are difficult to maintain. Any face covering that is worn inside a laboratory area where personnel work with potentially infectious material should subsequently not be worn outside of that laboratory area. Laboratory PPE are critical supplies, and employees should refrain from removing them from the laboratory for general use. Site- and activity-specific risk assessments, as well as available resources, should determine where specific facial protection, such as disposable masks, should be used.

These face coverings should not be used in place of recommended personal protective equipment (PPE).

- Face coverings are not intended to protect those who wear them and are not considered PPE.
- All staff should follow established PPE requirements for working in laboratory spaces.

Wash hands before putting on face coverings and minimize the removal while in the laboratory. The guidance below describes how to remove a face covering and replace it with a clean face covering:

- Take off the face covering carefully.
- Be careful not to touch eyes, nose, or mouth when removing a face covering.
- Untie the strings behind the head or stretch the ear loops.
- Handle only by the ear loops or ties.
- Place reusable cloth face coverings in a bag and close the bag until it can be washed.
  1. Cloth face coverings should be washed frequently.
  2. Staff are responsible for maintaining and cleaning their cloth face coverings.
- Wash hands immediately after removing.

Depending on the facility's design or configuration, additional physical barriers, such as a face shield, plexiglass, partition, or plastic barriers, may be needed to achieve social distancing goals.

Personal Hygiene and Disinfection

As more workers return to the laboratory, extra measures may be needed to ensure a clean and appropriate environment. Reevaluate current protocols for cleaning, use of PPE, and handwashing. High-touch locations and equipment with a high frequency of handling and contact present a higher probability of contamination in the work area and should be disinfected frequently. Increasing the number of available cleaning supplies and distributing them throughout the laboratory can encourage staff to more frequently clean surfaces and equipment. Use visual reminders, such as posters displayed throughout the laboratory environment, common areas, and restrooms, to emphasize the importance of hand hygiene and to encourage frequent handwashing. Hands should be washed regularly with soap and water for at least 20 seconds. An alcohol-based hand sanitizer containing at least 60% ethanol or 70% isopropanol can be used when soap and water are not available.

BOUQUET

In Lighter Vein

A very serious fight was going on between Husband and Wife...

Husband said (In anger):
"I resign from the post of your Husband..."

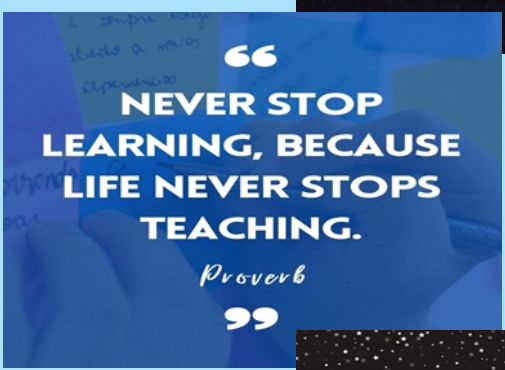
Wife:
"Okay but,
You'll have to stay till
I don't get any other alternative...!"

At late night wife's smartphone beeps. Husband checks her mobile and gets angry.
He wakens his wife.
Husband (angrily): who is this person saying beautiful???
Surprised wife checks her mobile.
Wife (double angrily): heyyy... use your spectacles. It is not beautiful.
It is battery full.

Wife: Our new neighbor always kisses his wife when he goes to work, why don't you do that?
Husband: How can I? I don't even know her.

Wisdom Whispers

"Before you act, listen.
Before you react, think.
Before you spend, earn.
Before you criticize, wait.
Before you pray, forgive.
Before you quit, try."



Brain Teasers

1. **Hepatitis D coexists with ____.**
   A. Hepatitis A
   B. Hepatitis B
   C. Hepatitis C
   D. Hepatitis E.

2. **In hepatitis B infection, which is the first detectable viral marker?**
   A. HbsAg
   B. HbeAg
   C. HBV DNA
   D. None of the above.

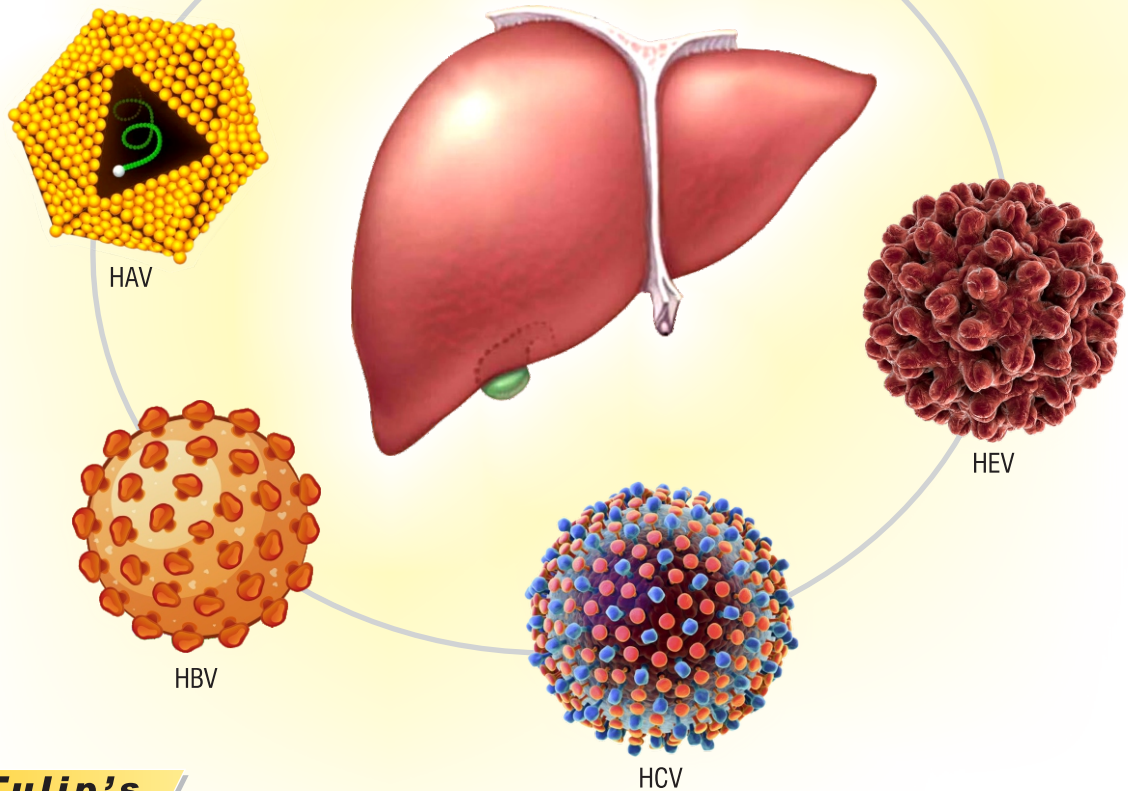
3. **In relation to hepatitis B, the presence of _____indicates recovery and immunity in a previously infected individual.**
   A. Anti-HbsAb
   B. Anti-HbcAb
   C. Both of the above
   D. None of the above.

4. **In relation to hepatitis B, the presence of _____denotes active viral replication.**
   A. HbsAg
   B. HbeAg
   C. HbcAg
   D. HBV DNA

ANSWER: 1.B, 2.A, 3.C, 4.B

DETECT & DIFFERENTIATE

VIRAL HEPATITIS



With Tulip's

COMPLETE DIAGNOSTIC SOLUTIONS

Rapids			Elisa	CLIA
HBV Markers	**HbsAg**	**HCV**	Qualisa - HCV	Electra™ - HCV
Insight - HbsAb	Virucheck	Flaviscreen HCV Plus	Qualisa - HbsAg	Electra™ - HbsAg
Insight - HbeAg	Hepaview		Qualisa - HAV	Electra™ - HAV
Insight - HbeAb	Sensa		Qualisa - HEV	Electra™ - HEV
Insight - HbcAb				
Insight - HAV				
Insight - HEV				

Better Testing System For Better Diagnostics

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