An Overview of Viral Hepatitis

**Background and Epidemiology**

Viral hepatitis is a global health problem that affects hundreds of millions of children and adults (Table 1). Although multiple viral pathogens have been associated with hepatitis, three in particular — hepatitis A, B, and C — are responsible for the majority of virally-linked hepatitis cases. Hepatitis D and E infections are also important, although not as commonly diagnosed.

According to the World Health Organization (WHO), 2 billion people have been infected with the hepatitis B virus (HBV), and more than 350 million have a chronic HBV infection. In addition, it has been estimated that up to 3% of the world’s population has been infected with hepatitis C virus (HCV), of which 170 million people are chronically infected, and an additional 3 to 4 million people are infected each year. Infections of HBV and HCV are by far the most prevalent, and their consequences can be serious. Long-term chronic infection with one or both of these viruses is the most common cause of liver fibrosis and cirrhosis, leading to liver failure and hepatocellular carcinoma (HCC).

Hepatitis D virus (HDV) is a subviral satellite that requires the presence of another virus to replicate. Commonly, HDV infection will occur with HBV, either as a simultaneous coinfection or as a superinfection in a previously HBV-infected individual. HDV coinfection with HBV can result in more serious complications, including a greater likelihood of liver failure and a mortality rate as high as 20%. HDV is rare in most developed countries and often associated with intravenous (IV) drug abuse or male-to-male sex. Approximately 5% of HBV carriers are coinfected with HDV, leading to conservative estimates that 10 to 15 million people are infected worldwide.

Hepatitis E virus (HEV) is found predominantly in regions with poor sanitation. It does not cause serious or chronic disease in the general population. In pregnant women, however, HEV has been associated with a substantially increased risk of maternal, fetal, and neonatal death.

**Transmission and Prevention**

Viral hepatitis can be transmitted vertically (from mother to child) and horizontally (person to person) via several routes (Table 2). High levels of viral replication can increase the risk of vertical transmission. Prevention varies with the viral pathogen but may include vaccination, immune prophylaxis, and limited sharing of personal items.

### Table 1. Estimated hepatitis burden worldwide

<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
<th>HEV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Infected</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worldwide</td>
<td>1.4 million</td>
<td>2 billion</td>
<td>~250–300 million</td>
<td>10–15 million</td>
<td>1.5%–26% Antibody prevalence</td>
</tr>
<tr>
<td>US</td>
<td>3,579 (reported)</td>
<td>1.45 million</td>
<td>4 million</td>
<td>NA</td>
<td>1.5%–3% Antibody prevalence</td>
</tr>
<tr>
<td><strong>Chronic Infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worldwide</td>
<td>NA</td>
<td>350 million</td>
<td>170–200 million</td>
<td>200,000–300,000</td>
<td>1–1.5 million</td>
</tr>
<tr>
<td>US</td>
<td>NA</td>
<td>800,000–1.4 million</td>
<td>3.2 million</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Newly Infected / Year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worldwide</td>
<td>1.4 million</td>
<td>NA</td>
<td>3–4 million</td>
<td>NA</td>
<td>&gt;50% of reported acute cases of hepatitis</td>
</tr>
<tr>
<td>US</td>
<td>32,000 (estimated total)</td>
<td>46,000</td>
<td>19,000</td>
<td>NA</td>
<td>Usually travel related</td>
</tr>
<tr>
<td><strong>Deaths / Year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worldwide</td>
<td>0.1% &lt;14 yrs</td>
<td>0.3% 15–39 yrs</td>
<td>2.1% 40 yrs</td>
<td>600,000</td>
<td>1.6%–2.5% of the carrier population</td>
</tr>
<tr>
<td>US</td>
<td>5 (reported)</td>
<td>5,000</td>
<td>8,000–10,000</td>
<td>&gt;1,000</td>
<td>0.5%–4.0% 20 pregnant women in 3rd trimester</td>
</tr>
</tbody>
</table>

*a* Extrapolated from total chronic and new infections

*b* If coinfected

*c* If superinfected

*d* Depending on strain

References:

Symptoms and Diagnosis

The symptoms for all forms of acute viral hepatitis are very similar (Table 3). Over 65% of infected individuals may be asymptomatic, and others may have mild symptoms frequently mistaken for the flu. Unlike the flu, symptoms of acute hepatitis may continue for several weeks or, rarely, months. Acute hepatitis may never be diagnosed and chronic hepatitis is frequently undiagnosed for several years or even decades after the initial infection.1–3,12

Because hepatitis symptoms are so nonspecific, diagnosis cannot be achieved through history and physical exam alone. Serological tests are used to identify the causative agent and liver biopsy can be performed to assess the stage of liver damage.1,2,12 Patients presenting with clinical signs and symptoms of hepatitis are typically tested with an acute panel that detects hepatitis B surface antigen (HBsAg), hepatitis B core immunoglobulin M (HBC IgM), antibody to HCV (aHCV), and hepatitis A immunoglobulin M (HAV IgM) to rule out or rule in acute viral hepatitis. Molecular tests to determine viral load may be used to monitor infectiousness and treatment efficacy for HBV and HCV, while determination of genotype (for HBV or HCV) can be instrumental in deciding the appropriate type and duration of antiviral therapy.1–3,12

Conclusion

Viral hepatitis remains a leading cause of virus-associated morbidity and mortality, affecting millions of individuals worldwide. Screening and diagnosis of chronic or acute viral hepatitis, and effective patient care, involve an increasingly complex range of laboratory technologies. Serology markers (individual assays and panels) and molecular tests are utilized for the diagnosis of viral hepatitis as well as for patient monitoring and treatment management. The following sections discuss the more common forms of viral hepatitis (A, B, and C) in greater detail, focusing on both disease and relevant testing modalities.

### Table 2. Important characteristics of common hepatitis viral infections.1–5,7,9,11,12,15,16

<table>
<thead>
<tr>
<th>Source of Virus</th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
<th>HEV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feces</td>
<td>Blood / some body fluids</td>
<td>Blood / some body fluids</td>
<td>Blood / some body fluids</td>
<td>Feces</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Route of Transmission</th>
<th>Fecal–oral</th>
<th>Percutaneous or permucosal</th>
<th>Percutaneous or permucosal</th>
<th>Yes</th>
<th>Fecal–oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Prevention</td>
<td>- Pre / post exposure immunization</td>
<td>- Pre / post exposure immunization</td>
<td>- Risk behavior modification</td>
<td>- Risk behavior modification</td>
<td>- Access to clean drinking water</td>
</tr>
<tr>
<td></td>
<td>- Hand hygiene</td>
<td>- HB Ig</td>
<td>- Risk behavior modification</td>
<td>- Risk behavior modification</td>
<td>- Hand hygiene</td>
</tr>
</tbody>
</table>

Vaccine Yes Yes No No No

| Table 3. Hepatitis symptoms.1–3,5–7,9,11,12,15 |

<table>
<thead>
<tr>
<th>Flulike Symptoms</th>
<th>Other Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fever</td>
<td>• Dark urine</td>
</tr>
<tr>
<td>• Fatigue</td>
<td>• Clay-colored stool</td>
</tr>
<tr>
<td>• Nausea</td>
<td>• Abdominal pain</td>
</tr>
<tr>
<td>• Vomiting</td>
<td>• Jaundice</td>
</tr>
</tbody>
</table>
| • Loss of appetite | • 
| • Joint pain     |               |

### References

Hepatitis A

Background and Epidemiology

Hepatitis A is caused by the hepatitis A virus (HAV), an enterovirus in the Picornaviridae family, and is phylogenetically unrelated to either the hepatitis B or C virus. Infection results in acute hepatitis, with or without symptoms, but does not convert to a chronic infection. After an acute infection resolves, individuals are generally immune to future infection.

With the exception of the rare case of fulminant hepatitis, HAV does not cause lasting liver damage or cirrhosis, and has not been linked to hepatocellular carcinoma (HCC). It is considered to be the least pathogenic of the most common hepatitis viruses (A, B, and C). Fulminant liver disease from HAV infection resulting in liver failure occurs in approximately 0.3% to 0.6% of cases. The greatest mortality (~1.8%) generally occurs in people older than 50 years. Patients with preexisting chronic liver disease are at higher risk for liver failure.

Hepatitis A is most commonly transmitted by the fecal–oral route, often via contaminated water or food, or in areas of poor sanitation or overcrowding. Outbreaks are often associated with poor hygiene of food handlers and via person-to-person contact. Prior to the availability of an effective vaccine, infection occurred primarily in childhood. In developed countries with high childhood vaccination coverage, infections are often associated with travel and may occur in older individuals. For this reason, HAV vaccination is recommended for adults traveling to regions of high endemicity if immunity is unknown.

Despite an effective vaccine, HAV is still prevalent in many geographic regions (Figure 1). Approximately 1.4 million cases of hepatitis A are documented globally every year, although the actual incidence is likely to be 3 to 10 times higher when unreported and asymptomatic cases are taken into account. In some developing countries, nearly 100% of children become infected before the age of nine. Prevalence in the US, Europe, and many other developed countries is low due to effective vaccination programs.

Symptoms

Hepatitis A symptoms generally appear within a month of the onset of infection. Patients are most contagious about a week before symptoms develop (if symptomatic), but may remain infectious for several weeks. As many as 75% of children with HAV have no, or only mild, symptoms, whereas as many as 85% of adults are
symptomatic. Hepatitis A infection can present with flu-like symptoms (nausea, fatigue, myalgia); a mild fever is common, though seldom higher than 101 F (38.3˚C). Patients who drink coffee or smoke cigarettes may temporarily lose their taste for these items. Jaundice, if present, typically lasts 7 to 10 days. Adults are more likely to have severe symptoms, including jaundice and abdominal pain. Most patients completely recover within 4 to 8 weeks. HAV infection in those over the age of 50 years is often more serious, and may, rarely, result in prolonged jaundice or liver failure. It is thought that lifelong immunity occurs once infection is resolved.

Testing

Acute infection is confirmed by testing for immunoglobulin M (IgM) antibodies to HAV (aHAV IgM). Resolved infection or vaccination is indicated by the presence of immunoglobulin G (IgG) in the absence of IgM, and is detected using an assay for total antibody (IgG and IgM [aHAVT]). IgM antibodies are generally present for 3 to 6 months after the onset of active infection, but may show an extended presence in up to 25% of patients (Table 1). In general, testing is limited to patients who are suspected of having acute infection. Prevaccination screening may be advocated for some high-risk populations. In particular, screening for individuals with other chronic liver diseases, such as hepatitis B or C, can be useful at the time of diagnosis, as concomitant infection with HAV can exacerbate liver injury. In addition, postvaccination testing may be of importance in those with decompensated or end-stage liver failure, as vaccination in these patients is less likely to result in seroconversion.

Vaccination

Since the development of the HAV vaccine, hepatitis A is more easily prevented. Vaccination is often recommended for all children aged 12 months to 18 years. In addition, several high-risk groups have been identified and stand to benefit from immunization:

- Travelers to countries with high or intermediate endemicity of HAV infection
- Men who have sex with men
- Users of injected and noninjected illegal drugs
- Persons with clotting factor disorders
- Persons working with nonhuman primates susceptible to HAV infection
- Persons living in close contact or having sexual relations with those diagnosed with HAV infection
- Daycare workers

Studies in the UK and Israel have demonstrated that testing for existing immunity before vaccination can be cost effective, especially for travelers to regions of high endemicity and for those over the age of 40 years.

Who Should Be Tested

In general, testing is limited to patients who are suspected of having acute infection. Prevaccination screening may be advocated for some high-risk populations. In particular, screening for individuals with other chronic liver diseases, such as hepatitis B or C, can be useful at the time of diagnosis, as concomitant infection with HAV can exacerbate liver injury. In addition, postvaccination testing may be of importance in those with decompensated or end-stage liver failure, as vaccination in these patients is less likely to result in seroconversion.

Conclusion

Infection with hepatitis A virus is a common cause of viral illness in many countries. Widespread vaccination significantly reduces disease and the increased morbidity associated with infection acquired at a later age. Serology tests can distinguish an acute from a resolved infection, guiding the physician in patient care. Improved vaccination coverage, coupled with immunity screening for travelers to endemic areas (if vaccination status is unknown), confers a significant level of protection and limits the spread of contagion.

References

Hepatitis B

Background and Epidemiology

Hepatitis B is caused by infection with the hepatitis B virus (HBV), a member of the Hepadnaviridae family. Infection with HBV is the leading cause of significant liver damage worldwide. Damage can occur silently over several decades before infection is diagnosed. Viral transmission is through blood and other body fluids.

The main routes of infection are:
- Sexual contact
- Contaminated injections and transfusions
- Perinatal transmission
- Child-to-child transmission (horizontal in geographical regions of high endemicity)

Acute (primary) HBV infection is frequently unrecognized: approximately 30% of infected individuals experience mild symptoms lasting a few weeks which are commonly mistaken for the flu or other mild viral infections. Fulminant hepatitis occurs in less than 2% of infected individuals. Chronic infection can lead to liver damage (inflammation, fibrosis, and cirrhosis), and can ultimately result in liver failure or hepatocellular carcinoma (HCC). Between 15% to 40% of chronically infected individuals will suffer significant symptoms in their lifetime, and up to 25% will die from directly related causes. In some Asian populations, liver cancer is the second leading cause of cancer-related deaths in men. Development of chronicity is directly related to the age at which infection is acquired (Table 1).

Figure 1. Worldwide prevalence of HBV, 2006.³
Intermediate prevalence rates for HBV, including immigrants and adopted children. Relevant areas include:

- South Asia (except Sri Lanka)
- Africa
- South Pacific Islands
- Middle East (except Cyprus)
- European Mediterranean: Greece, Italy, Malta, Portugal, and Spain
- The Arctic (indigenous populations)
- South America: Argentina, Bolivia, Brazil, Ecuador, Guyana, Suriname, Venezuela, and the Amazon region of Colombia and Peru
- Independent states of the former Soviet Union
- Eastern Europe, including Russia, except Hungary
- Caribbean: Antigua and Barbuda, Dominica, Dominican Republic, Granada, Haiti, Jamaica, Puerto Rico, St. Kitts and Nevis, St. Lucia, St. Vincent and the Grenadines, Trinidad and Tobago, and Turks and Caicos

Other groups recommended for screening include:

- Men who have sex with men
- Inmates of correctional facilities
- Individuals with chronically elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST)
- Individuals infected with hepatitis C virus (HCV) or human immunodeficiency virus (HIV)
- Patients undergoing renal dialysis
- All pregnant women
- Healthcare and public safety workers at risk for occupational exposure to blood or other body fluids
- Residents and staff of facilities for developmentally disabled individuals
- Travelers to countries with intermediate or high prevalence of HBV infection

Seronegative individuals in the above groups should receive the HBV vaccine. Pregnant women, however, should not receive the vaccine.

Testing Is Key to Diagnosis and Patient Care

Several serologic and molecular tests are available for identifying and classifying HBV infection. Serologic tests are available that detect either antibody or antigen. Molecular tests are used to quantitate viral load and determine genotype.

Table 1. The relationship between age at infection and HBV chronicity. 2,3

<table>
<thead>
<tr>
<th>Age at Infection</th>
<th>Chronicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 months</td>
<td>90–95</td>
</tr>
<tr>
<td>6 months</td>
<td>80</td>
</tr>
<tr>
<td>1–4 years</td>
<td>30–50</td>
</tr>
<tr>
<td>&gt;4 years</td>
<td>5–10</td>
</tr>
</tbody>
</table>

Prevalence of HBV infection is highest in the developing world (Figure 1). In highly and moderately endemic regions, infection commonly occurs perinatally or in early childhood (~2%–20%). Overall, approximately 350 million people are chronically infected worldwide. 4 Approximately 800,000 to 1.4 million of these individuals reside in the US. 4 The highest prevalence exists within the Asian American and Pacific Islander American populations, where incidence can be 100 times greater than in the general population. 7

Screening Recommendations

Maternal screening is of particular importance because it can identify HBV-positive women. Children born to HBV-infected mothers can be vaccinated and treated with hepatitis B immunoglobulin (HBIG), which can significantly reduce their potential for chronic infection. Family members of seropositive individuals should also be tested. Screening of high-risk and other groups has been endorsed by various organizations 5–7 and is recommended for individuals born in areas of high and
Hepatitis B (continued)

Serology

Six serologic tests are used in the diagnosis and management of HBV infection (Table 2). Primary screening usually includes testing for the presence of HBsAg and antibodies to HBsAg (aHBs). Some clinicians still prefer to test for total antibodies to core antigen (aHBcT). If aHBcT is used, a positive result requires additional follow-up to confirm infectious status. A reactive aHBcT indicates infection with the hepatitis B virus (the core antigen epitope is not a part of the vaccine). Patients should be assessed to see if the infection is acute, resolved, or chronic, and to determine if therapeutic intervention is indicated.4 HBsAg-positive individuals may require additional testing to determine HBV status. If testing suggests an acute infection, the patient should be retested in 6 months. Patients who have not seroconverted to become HBsAg-negative by 6 months after primary infection are considered chronic.2 Hepatitis B e antigen (HBeAg) and the antibody to HBe (aHBe) are also used to assess viral replication. Table 3 explains the typical interpretation of HBV test results using available serologic markers for HBV antigen and antibody.2,8,9

Molecular Testing: Viral Load

Molecular testing for HBV deoxyribonucleic acid (DNA) can establish the patient’s level of viremia and contagion. In chronic disease, high viral load is associated with active liver disease and is a risk factor for cirrhosis, hepatic decompensation, and HCC (Figure 2). Viral load can also be used to guide treatment options and can be predictive of therapeutic response.10–12 Better patient outcomes have been associated with low or nondetectable viral load.13,14

Figure 2. Increased viral load is associated with increased risk for developing HCC.15

Table 2. Serologic testing for HBV.

<table>
<thead>
<tr>
<th>Antigen Assays</th>
<th>Analyte</th>
<th>Reactivity Suggests</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg*</td>
<td>Main antigenic protein expressed on the viral membrane</td>
<td>Active infection</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Component of the viral nucleocapsid released in serum</td>
<td>Ongoing DNA replication; infectious</td>
</tr>
</tbody>
</table>

Table 3. Interpretation of HBV serologic tests.

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBSAg</td>
<td>aHBcT</td>
</tr>
<tr>
<td>Uninfected, unvaccinated</td>
<td>–</td>
</tr>
<tr>
<td>Vaccinated (immune)</td>
<td>–</td>
</tr>
<tr>
<td>Acute infection</td>
<td>+</td>
</tr>
<tr>
<td>Active infection: recovering</td>
<td>–</td>
</tr>
<tr>
<td>Recovered (immune)</td>
<td>–</td>
</tr>
<tr>
<td>Chronic replicative infection</td>
<td>+</td>
</tr>
<tr>
<td>Chronic nonreplicative infection</td>
<td>–</td>
</tr>
</tbody>
</table>

*An initially reactive HBsAg test is generally confirmed by repeating the test in duplicate. If both repeats are nonreactive, a negative result can be reported. If one or both of the repeats is reactive, a neutralization test is usually done to confirm the presence of HBsAg. Some commercial assays have automated this procedure or introduced algorithms that substantially reduce the turnaround time for HBsAg confirmation results.

b Reactivity results only from infection, not from vaccination. Reactivity for aHBs but not aHBcT is consistent with vaccination.

c Immunoglobulin G and M

Figure 2. Increased viral load is associated with increased risk for developing HCC.15

HCC Incidence per 100,000

Viral Load (copies/mL)
**Genotyping**

HBV has eight known genotypes, which tend to cluster geographically. Genotypes are differentiated as having a sequence divergence of greater than 8%. Different genotypes have been associated with varied outcomes and responsiveness to therapy (Table 4). In addition to the primary genotypes discussed in Table 4, subtypes and coinfections have been identified and should be taken into account when considering treatment options and monitoring patient response.

<table>
<thead>
<tr>
<th>Genotype / Predominant Transmission</th>
<th>Predominance by Geographic Region</th>
<th>Possible Significance for Patient</th>
</tr>
</thead>
</table>
| **A** Horizontal                    | Africa, USA, Western Europe, Middle East, Mediterranean, India | • Lamivudine resistance more common than in chronic D infection  
• Higher level of childhood viremia  
• HBeAg production may be of reduced duration  
• Higher viral load than in B or C infection  
• Greater risk for developing chronic infection than with B, C, or D  
• Associated with higher rate of spontaneous clearance than D or F  
• Associated with higher rate of sustained remission after HBeAg seroconversion than in patients chronically infected with D or F  
• Associated with HIV coinfection |
| **B** Vertical                      | Asia                             | • Apparent faster clearance of HBeAg than with C  
• Higher response to interferon alpha than C or D genotype or mixed genotypes  
• Higher incidence in young patients with HCC in Taiwan and China, and with older patients in Japan  
• Progression to liver fibrosis and HCC may be slower than with C, but carries the same lifelong risk |
| **C** Vertical                      | Asia                             | • Considered to be more virulent and aggressive with worse outcomes than other genotypes  
• Higher HBeAg-positive rate and a faster progression to liver fibrosis and HCC than in A or B infection  
• Lower response rate to interferon alpha than those infected with A or B  
• Higher rate of cirrhosis without HCC |
| **D** Horizontal                    | Africa, USA, Western Europe, Middle East, Mediterranean, India | • Lower response rate to interferon alpha than those infected with A or B  
• Better virologic response with adefovir in lamivudine-resistant cases  
• Higher level of childhood viremia  
• HBeAg production may be of reduced duration  
• More likely to maintain replicative state even after HBeAg seroconversion (higher prevalence of aHBe+ chronic state)  
• Higher viral load than in B or C infection  
• Higher HBeAg-positive rate and a faster progression to liver fibrosis and HCC than in A or B infection |
| **E** Horizontal                    | Africa                           | • Higher level of childhood viremia  
• May be associated with greater occurrence of HBsAg escape mutants  
• Associated with breakthrough infection in vaccinated and aHBs-positive individuals |
| **F** Horizontal                    | Central America, South America, Alaska (Native Amerindians) | • Associated with greater risk of HCC than in A, C, or D infection  
• Median age at HCC diagnosis is lower than for patients with other genotypes (22.5 yr vs. 60 yr)  
• Lower rate of remission and HBsAg clearance than with A or D  
• F1 subtype might be associated with precore stop mutants |
| **G** Horizontal                    | Western Europe, Eastern Europe, North America, Central America | • Primarily exists as coinfection with genotypes A or H  
• Variant cannot make HBeAg (HBeAg is derived from coinfection with A or H)  
• Increased risk factor for liver fibrosis in HIV-coinfected patients |
| **H** Horizontal                    | Central America, South America | • Variant of genotype F  
• Significance unknown |

*Generally found worldwide, but is the most prevalent variant in the regions cited*
Hepatitis B (continued)

Coinfection with Other Viruses
Coinfection with other hepatitis viruses and/or HIV can occur in patients with chronic HBV, most often through high-risk horizontal modes of transmission. Coinfection rates and characteristics are outlined in Table 5.

HBV Mutants: Clinical Relevance
Although rare, HBV mutants have been identified that may impact diagnosis and/or patient care (Table 6). Mutations are most commonly found in regions of high endemicity.

Treatment
The treatment goal for chronic HBV is to reduce the viral load and drive seroconversion to HBeAg-negative status. This, in turn, reduces the immunologic response to HBV, which is the primary cause of liver damage. Standard care includes treatment with antiviral drugs.

Table 5. The effect of copathogens in HBV infection.

<table>
<thead>
<tr>
<th>Copathogen</th>
<th>Coinfected Patients</th>
<th>Clinical Characteristics</th>
</tr>
</thead>
</table>
| HIV²⁷,²⁸ | 5%–10%ᵃ | • More rapid progression of liver disease  
• Higher level of viremia  
• Seroconversion to HBsAg⁻ and HBeAg⁻ occurs only rarely  
• Higher prevalence of HBeAg+ chronic infection  
• Increased risk of hepatotoxicity with highly active antiretroviral therapy (HAART)  
• High rate of lamivudine resistance because of previous antiretroviral therapy |
| HCV²⁹ | 9%–30%ᵇ | • Increased risk for development of HCC  
• More severe liver disease  
• May suppress HBV replicative activity, which can affect diagnosis and/or monitoring  
• Higher rate of severe, fulminant hepatitis in chronic HBV with HCV superinfection |
| HDV³⁰,ᶜ | 5% | • Requires HBV for infection  
• Higher incidence of hepatic failure in acute hepatitis with D superinfection  
• Faster progression to cirrhosis in D superinfection  
• Higher risk of developing end-stage liver disease  
• Greatest prevalence in the Middle East, Italy, some parts of eastern Europe, the Amazon basin, Venezuela, Columbia, some Pacific islands, Pakistan, Japan, northern India, southern Albania, and western Asia  
• Therapy of choice is interferon alpha. Requires higher dose for longer duration than for HBV infection alone |

Table 6. HBV mutant types.³¹

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Effect</th>
</tr>
</thead>
</table>
| Precore and core | • Reduces or eliminates expression of HBeAg  
• May be found in aHBe-positive chronically infected patients previously in a nonreplicative state  
• Routine monitoring for HBe seroconversion to evaluate therapeutic effectiveness may be compromised |
| PreS and S | • May affect immune response to HBsAg  
• May compromise immunity in vaccinated individuals (vaccine escape) |
| Polymerase gene | • Tyrosine-methionine-aspartic acid-aspartic acid (YMDD) mutation is commonly associated with resistance to lamivudine  
• Less likely to be resistant to adefovir and entecavir |
| X gene | • May be involved in suppression of HBV protein secretions, although the clinical impact is unclear |

ᵃCoinfection may approach 20% in Southeast Asia and 5% in North America and western Europe.  
ᵇRegion-dependent  
ᶜHDV: hepatitis D virus
Vaccination

Vaccination against HBV is up to 95% effective in preventing infection; best results occur with administration of the full three-dose regimen. Vaccination in the neonatal period is most effective in preventing HBV transmission from an HBsAg-positive–HBeAg-negative mother to her infant, but less effective if the mother is positive for both HBsAg and HBeAg.

The standard vaccination protocol for children and adults is:
- First injection at any time
- Second injection at least 1 month after the first dose
- Third injection 6 months after the first dose

For infants born to mothers positive for HBsAg, the first dose of vaccine should be given within 12 hours of birth along with administration of HBlg. The second dose should be given at 1 to 2 months of age, and the third dose at 6 months of age. Vaccination is thought to confer lifelong immunity.

Successful immunization is generally indicated by a high titer of antibody to HBsAg (> 10 IU/mL), although antibody titer can decrease over time. Recent data suggests that an initial successful seroconversion with vaccination still confers immunity even if antibody titer is reduced. This is likely due to the presence of HBsAg memory B cells. The Centers for Disease Control and Prevention (CDC) recommends vaccination of everyone up to 18 years of age\(^\text{32}\) and for adults\(^\text{33}\) who are at risk for HBV infection:
- Household contacts and sexual partners of HBsAg-positive individuals
- Injection drug users
- Sexually active individuals not in a long-term, mutually monogamous relationship
- Men who have sex with men
- Individuals with HIV

• Individuals seeking evaluation or treatment for an STD
• Patients receiving hemodialysis and patients with renal disease that may result in dialysis
• Healthcare personnel and public safety workers who are exposed to blood
• Residents and staff of facilities for developmentally disabled individuals
• Inmates of long-term correctional facilities
• International travelers to regions of high prevalence of HBV infection
• Individuals with chronic liver disease

References

Conclusion

Chronic hepatitis B infection continues to challenge public health efforts worldwide. Addressing the disease burden associated with chronic infection is complicated by the lack of a generally effective cure. Disease management is often lifelong, with many cases leading to liver disease, liver failure, or cancer. Prenatal screening can significantly reduce the risk of vertical transmission by identifying neonates in need of vaccination and immune therapy. Screening and patient care can benefit from a range of testing modalities that utilize both serologic and molecular tests.
Hepatitis C

Background and Epidemiology

Hepatitis C virus (HCV) belongs to the family Flaviviridae, and is a common cause of liver disease worldwide. Globally, it is second only to hepatitis B as a leading source of chronic liver disease. The World Health Organization (WHO) estimates that up to 3% of the world’s population is infected with HCV, making it a global public health problem. An estimated 170 million to 200 million chronic HCV infections exist worldwide. Prevalence varies with geographic region (Figure 1). The majority of chronic infections occur in Southeast Asia, Africa, and western Pacific and eastern Mediterranean countries. About 5% to 7% of chronically infected patients will ultimately die from HCV-related causes.

Figure 1. Worldwide prevalence of HCV, 2007.

Approximately 4 million Americans have been infected with HCV, making it four times more common in the US than current estimates for human immunodeficiency virus (HIV) infection. Of these, an estimated 3.2 million are chronically infected, and 10,000 to 12,000 people die each year due to HCV-related disease. Currently, there is no vaccine for hepatitis C.

HCV infection is often a silent disease as the majority of infections lack signs or symptoms in the early stages. Long-term complications of HCV infection can take 20 to 30 years to develop and may be severe by the time a diagnosis is made. Many patients are unaware of their infection status prior to the onset of significant liver damage. Comorbidities, coinfections, and nutritional status may affect disease progression.

While acute cases of HCV are declining in the US, the hepatitis C-related death rate continues to rise. Infection is most prevalent among those born between 1945 and 1965, with the highest prevalence among intravenous drug users who injected in the 1970s and 1980s before risk factors were identified.

Clinical Course

Only about 20% of acutely infected patients will experience symptoms (which can include fatigue, abdominal pain, poor appetite, and jaundice), and the nonspecific nature of symptoms can make infection difficult to diagnose. HCV infection is not commonly identified in the acute phase unless a known exposure is established.

Chronic infection occurs in a high percentage of patients (~75%), and of those, an estimated 20% go on to develop cirrhosis. A low percentage of patients (1%–2%) with chronic infection develop extrahepatic manifestations of the disease (Table 1).

Although elevated alanine aminotransferase (ALT) levels can indicate liver damage, it is not uncommon for levels to fluctuate in patients with chronic HCV infections. Liver enzyme levels can remain normal for over a year despite established chronic liver disease.

Death occurs in 1% to 5% of infections from chronic liver disease, including both liver failure and hepatocellular carcinoma (HCC). Coinfection with HIV is thought to exacerbate HCV disease progression.

HCV-infected patients should be counseled against alcohol consumption as even small amounts have been associated with an increased risk of cirrhosis. Because some medications and over-the-counter drugs (such as nonaspirin pain relievers) can cause liver damage, patients should be
Hepatitis C

HCV Transmission

HCV is transmitted primarily by blood-to-blood contact. Injection drug use is a leading risk factor (Figure 2). The risk of HCV infection from blood transfusion decreased significantly in the US and many countries because of the implementation of rigorous screening for all blood products. HCV can be transmitted through high-risk sexual activity, such as unprotected sex with a large number of partners or sexual practices that can damage mucosal linings.2,12

Vertical transmission (mother to child) occurs in less than 5% of births. Transmission occurs during birth and currently no prophylaxis is available. High levels of viremia at delivery increase transmission risk. Coinfection with HIV can raise the rate of perinatal transmission.13

Other risk factors for contracting HCV are listed in Table 2.

Risk-minimization behaviors include
- Not sharing toothbrushes, razors, and nail-grooming equipment
- Using sterile equipment for tattooing or body piercing
- Using a condom if having sex with multiple partners

Table 1. Extrahepatic manifestations of HCV infection.9

<table>
<thead>
<tr>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoglobulinemia*</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td>Leukocytoclastic vasculitis</td>
</tr>
<tr>
<td>Sicca syndrome</td>
</tr>
<tr>
<td>Seronegative arthritis</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Lichen planus</td>
</tr>
<tr>
<td>Aplastic anemia</td>
</tr>
<tr>
<td>Overt B-cell lymphomas</td>
</tr>
<tr>
<td>Osteosclerosis</td>
</tr>
</tbody>
</table>

*The most common extrahepatic manifestation. It is often marked with one or more of the following: skin rashes, joint and muscle aches, kidney disease, or neuropathy.

Table 2. Other risk factors for HCV.8

- Injection drug use (current or previous)
- Intranasal cocaine use with contaminated implements
- Receipt of unscreened blood, blood products, tissue, or organs
- Tattooing or body piercing under nonsterile conditions
- Children born to an HCV-positive mother
- Promiscuous sex
- Occupational exposure to infected blood
- Persistently elevated ALT
- Infection with HIV
- Healthcare workers after known HCV exposure (eg, needle sticks, eye splash)
- Long-term hemodialysis

*Rare after 1992, when blood screening became available in the US.
Hepatitis C (continued)

HCV Screening / Testing
Screening is recommended for those at increased risk, as well as for patients where the clinical suspicion for hepatitis is high. A serology test for the detection of antibody to HCV is used for the initial screen. Greater than 97% of infected individuals seroconvert to HCV antibody within 6 months, although antibody can often be detected as early as 4 to 10 weeks after infection.8 A reactive test indicates exposure to HCV, but cannot determine if the infection is acute, resolved, or chronic. False-positive results are relatively uncommon. Reactive results are usually followed up with supplemental tests such as a recombinant immunoblot assay (RIBA) or a molecular test for HCV ribonucleic acid (RNA). Table 3 summarizes the CDC-recommended interpretation of HCV test results.15 While a positive RNA test confirms the presence of the virus and indicates active infection, a negative result cannot exclude infection, as the virus may be present at a low viral load, or the patient may have spontaneously cleared the infection.8,13,16

The CDC guidelines suggest that a reactive antibody test followed by a negative RNA test should reflex to RIBA before reporting a result (Figure 3).17 If there is an indeterminate RIBA result, testing at a later date (>1 month) is useful for ruling out early seroconversion.18

Some HCV screening assays have a signal-to-cutoff ratio (S/CO) or index value, in line with CDC recommendations, which can minimize the need for confirmatory testing prior to releasing a result. Both second- and third-generation antibody tests are available, with third-generation tests exhibiting increased sensitivity.

In children born to HCV-positive mothers, serologic testing for HCV should be delayed until the age of 18 months to allow clearance of maternal antibodies that may have transferred from mother to child. RNA testing can be performed at 1 to 2 months of age; however, testing should be repeated at subsequent intervals independent of the initial results because children can spontaneously clear the virus within the first year of life.

Table 3. CDC reference guide for interpretation of HCV test result.15

<table>
<thead>
<tr>
<th>If Your HCV Test Result Is</th>
<th>Interpretation</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HCV Screening Testa</td>
<td>Anti-HCV Supplemental Test</td>
<td>Anti-HCV</td>
</tr>
<tr>
<td>Negative</td>
<td>RIBAb HCV RNA</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>Not Done Not Done</td>
<td>Not Known</td>
</tr>
<tr>
<td>Positive</td>
<td>Not Done</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive (high S/CO ratio)d</td>
<td>Not Done Not Done</td>
<td>Positive Past / Current</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative Not Needed</td>
<td>Negative None</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive Not Done</td>
<td>Positive Past / Current</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive Negative</td>
<td>Positive Past / Current</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive / Not Done Positive</td>
<td>Positive Current</td>
</tr>
<tr>
<td>Positive</td>
<td>Indeterminate Not Done</td>
<td>Indeterminate Not Known</td>
</tr>
<tr>
<td>Positive</td>
<td>Indeterminate Positive</td>
<td>Positive Current</td>
</tr>
</tbody>
</table>

*EIA (enzyme immunoassay) or CIA (enhanced chemiluminescence immunoassay)
*RIBA (recombinant immunoblot assay), a more specific anti-HCV assay
*Single negative HCV RNA result cannot determine infection status, as persons might have intermittent viremia.
*Samples with high signal-to-cutoff ratios usually (>95%) confirm positive, but supplemental serologic testing was not performed.
Less than 5% might represent false positives; more specific testing should be requested, if indicated.

Anti-HCV: antibody to HCV; S/CO: signal-to-cutoff ratio
HCV Therapy

Once a diagnosis of chronic hepatitis C has been confirmed, it is important to determine the patient’s viral genotype if a decision is made to initiate therapy. Genotype is a key predictor of treatment response and can dictate the length of therapy.¹³,¹⁶

HCV has at least 6 genotypes and more than 50 subtypes.¹⁵ Genotypes vary by geographic region and can be associated with patterns of immigration. HCV genotypes 1 to 4 are the predominant genotypes circulating in western countries. In North America, Japan, and western Europe, genotype 1 is, by far, the predominant genotype.²⁰ In the US, genotype 1, 2, and 3 infections are the most common.²⁰ Genotype 4 is the most common variant in the Middle East and Africa, particularly in Egypt where it is responsible for more than 90% of infections.²¹ Patients can be infected with more than one genotype. Further testing should include viral load and tests to assess the patient’s current hepatic function and ability to tolerate therapy (Table 4).¹³,¹⁶

Contemporary treatment utilizes a combination of pegylated interferon (PEG-IFN) alpha-2a or alpha-2b with ribavirin.¹⁹ The goal of therapy is a sustained virologic response (SVR), which is defined as an absence of detectable viral RNA six months after completion of the antiviral therapy.⁸

Table 4. Additional tests for confirmed chronic HCV infection.¹³,¹⁶

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count with differential and platelet counts</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>Bilirubin</td>
</tr>
<tr>
<td>Albumin</td>
</tr>
<tr>
<td>International normalized ratio</td>
</tr>
<tr>
<td>Baseline liver biopsy*</td>
</tr>
</tbody>
</table>

* A liver biopsy may be useful to guide treatment decisions but is associated with both risk and sampling errors.
Impact of Genotypes and Viral Load on HCV Therapy

Patients with genotype 2 or 3 infection generally require shorter treatment regimens than those infected with genotype 1. Trials have demonstrated SVR response rates that ranged from 76% to 82% in patients with genotype 2 or 3, and 42% to 46% in patients with genotype 1. Although there is less data published on genotypes 4 to 6, studies suggest they may also exhibit different clinical courses and treatment outcomes. SVR may improve in patients with genotype 1 if ribavirin dosing is based on weight.

Viral kinetics play an important role in the response to therapy. The early virologic response (EVR) is an important predictor of therapeutic success. EVR is defined as a minimum 2 log₁₀ decrease in viral load during the first 12 weeks of treatment. Therefore, it is important to determine both viral load and genotype prior to the initiation of treatment.

Studies have shown that the inability to achieve an EVR is a strong predictor of treatment failure. Fewer than 3% of patients failing to achieve an EVR will have an SVR after completion of the treatment regimen. Patients failing to show an EVR should be considered for discontinuation of therapy.

The National Institutes of Health (NIH) recommends that patients with an EVR continue therapy for either 24 weeks or 48 weeks, depending on the viral genotype, to maximize the potential for an SVR (Figure 4). At the end of therapy, patients should be tested with an assay sensitive for HCV RNA. If the patient has responded initially, retesting should be done at 6 months to assess SVR and therapy success.

Table 5. Common side effects of therapy.

<table>
<thead>
<tr>
<th>PEG-IFN</th>
<th>Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Pruritus</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Gout</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric disorders</td>
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</tr>
</tbody>
</table>

Side effects of therapy (Table 5) can be severe enough to require a dose reduction or even treatment cessation. Treatment can also be contraindicated in certain patient groups, such as pregnant women, and patients with autoimmune, cardiac, pulmonary, or significant liver disease.

More recent data has suggested a role for a rapid virologic response (RVR). RVR is defined as a detectable drop in RNA within the first weeks of therapy. Studies suggest that an RVR with nondetectable HCV RNA at 4 weeks correlates with an increased probability of an SVR upon therapy completion, and that detectable drops early in therapy are predictive of an increased probability of success.

Figure 4. Treatment algorithm for HCV.
Is a Complete Cure Possible?

Recent research suggests complete cures in many treated patients (based on the ongoing lack of any detectable viral RNA and stable liver function), although occult infection remains a possibility. While nondetectable RNA can be consistent with a cure, patients can relapse months, or even years, after therapy cessation. Patients should be counseled about the potential for recurrence.9,13

Coinfection with HIV

In the US and Europe, up to 30% of patients infected with HCV are coinfected with HIV, which can negatively impact outcomes of HCV treatment.29 HIV coinfection can accelerate liver disease progression, suggesting a need for early diagnosis. RVR at week 4 predicts an SVR in coinfected patients as it does in patients with HCV monoinfection.30 Because coinfected patients with late-stage HIV disease can exhibit abnormal hepatitis C serologic profiles, antibody tests should be interpreted with caution in this patient population. Successful outcomes of HCV therapy are reduced in the setting of HIV coinfection, with the reduction appearing to affect all genotypes.30 Recently updated guidelines for the management of HIV–HCV coinfected patients have been published.30

Conclusion

The lack of an effective vaccine for HCV infection, coupled with the high percentage of acute infections that become chronic, continues to present a clinical challenge. Serology testing is important for identifying potentially chronic infections, which generally are asymptomatic until the late stage of disease. In current treatment algorithms, molecular testing plays a key role in therapy administration and in the assessment of therapy success.

References