least eight genotypes, four of which (genotypes 5 through 8) seem to be of exclusively African origin. Of the 350 million chronic carriers of HBV worldwide, more than 15 million have serologic evidence of exposure to HDV. Like HBV, HDV is transmitted via the parenteral route through exposure to infected blood or body fluids. Because there is evidence for sexual transmission, people with high-risk sexual activity are at increased risk for infection.

Clinical and Laboratory Manifestations

Acute viral hepatitis typically begins with a prodromal phase lasting several days that is characterized by constitutional and gastrointestinal symptoms including malaise, fatigue, anorexia, nausea, vomiting, myalgia, and headache. A mild fever may be present. Clinical manifestations of hepatitis A depend on the age of the host: fewer than 30% of infected young children showed symptomatic hepatitis, whereas about 80% of infected adults had severe acute hepatitis with remarkably elevated serum aminotransferases. Arthritis and urticaria resembling serum sickness, attributed to immune complex deposition, are present in 5% to 10% of cases of acute hepatitis B and C. Taste and smell alterations may also occur. Jaundice soon appears, with bilirubinuria and acholic (pale) stools, which are often accompanied by an improvement in the patient's sense of well-being. The liver is usually tender and enlarged; splenomegaly is found in about one fifth of patients. Notably, many patients with acute viral hepatitis are asymptomatic or have symptoms without jaundice (anicteric hepatitis). In such instances, medical attention often is not sought.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are released from acutely damaged hepatocytes, and serum levels can rise to 20-fold or more above normal. An elevated serum bilirubin level (>2.5 to 3 mg/dL) results in jaundice and is defined as icteric hepatitis. Values higher than 20 mg/dL are uncommon and correlate in a general way with the severity of disease. Elevations in serum alkaline phosphatase (ALP) are usually limited to 3 times normal levels except in cases of cholestatic hepatitis. A complete blood cell count most commonly shows mild leukopenia with atypical lymphocytes. Anemia and thrombocytopenia may also be present. The icteric phase of acute viral hepatitis may last days to weeks and is followed by gradual resolution of symptoms and laboratory values.

Diagnosis

Acute viral hepatitis can be diagnosed either directly, by detecting the nucleic acids of the infecting virus, or indirectly, by demonstrating an immune response in the host (Tables 41-2 and 41-3). Epstein-Barr virus and cytomegalovirus hepatitis are part of the differential diagnosis and also may be diagnosed by the appearance of specific antibodies of the immunoglobulin M (IgM) class.

In acute hepatitis B, hepatitis B surface antigen (HBsAg) and e antigen (HBeAg) are present in serum. Both are usually cleared within 3 months in acute self-limited infection, but HBsAg may persist in some patients with uncomplicated disease for 6 months to 1 year. Clearance of HBsAg is followed after a variable period by the emergence of antibodies against hepatitis B surface antigen (anti-HBs), which confers long-term immunity. Antibodies against hepatitis B core antigen (anti-HBc) and e antigen (anti-HBe) appear in the acute phase of the illness, but neither provides immunity. Uncommonly, during the serologic window period, anti-HBc IgM, a marker of active viral replication suggesting recent infection, may be the only evidence of HBV infection.

Every patient who is HBsAg positive should be tested for antibodies against HDV (anti-HDV IgG), which persist even after the patient has cleared HDV infection. Active HDV infection is now confirmed by the detection of serum HDV RNA with sensitive real-time polymerase chain reaction (PCR) assays. However, because of the variability of the genome sequence, assays of HDV RNA can produce false-negative results. Testing of anti-HDV IgM antibodies still has a role in patients who test negative for HDV RNA but have clinical features of HDV-related liver disease.

Acute hepatitis C can be detected within 2 weeks after exposure with the use of a sensitive PCR assay for HCV RNA. Serum antibodies to HCV develop within 12 weeks after exposure or

TABLE 41-2 SEROLOGIC MARKERS OF VIRAL HEPATITIS

AGENT	MARKER	DEFINITION	SIGNIFICANCE
HAV	Anti-HAV IgM	IgM antibody to HAV	Marker of acute or recent infection
	Anti-HAV IgG	IgG antibody to HAV	Marker of acute or previous infection; post vaccination; confers protective immunity
HBV	HBsAg	Hepatitis B surface antigen	The presence of HBsAg indicates that the person is infectious.
	HBeAg	Hepatitis B e antigen	Transiently positive in acute infection; may persist in chronic infection; reflection of active viral replication and high infectivity
	Anti-HBs	Antibody to surface antigen	Marker of acute self-limited infection; post vaccination; confers protective immunity
	Anti-HBe	Antibody to e antigen	Transiently positive in convalescence; positive in chronic infection before seroconversion; usually a reflection of low infectivity
	Anti-HBc IgM	IgM antibody to core antigen	Marker of acute or exacerbation of chronic infection
	Anti-HBc IgG	IgG antibody to core antigen	Appears at the onset of symptoms in acute infection and persists for life; not seen in vaccinees without prior infection
HCV	Anti-HCV	Antibody to HCV	Marker of acute and chronic infection; does not provide immunity
HDV	Anti-HDV IgM	IgM antibody to HDV	Positive in acute infection, negative in past infection but persists in a large proportion of patients with chronic infection
	Anti-HDV IgG	IgG antibody to HDV	Positive in all individuals exposed to HDV, and persists long-term, even after viral clearance
HEV	Anti-HEV IgM	IgM antibody to HEV	Marker of acute or recent infection*
	Anti-HEV IgG	IgG antibody to HEV	Marker of chronic or previous infection*

HAV, Hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; IgG, immunoglobulin G; IgM, immunoglobulin M.
*Serologic testing is unreliable, and seroconversion might never occur in immunosuppressed persons.