RNA in the serum needs close clinical follow-up. *A feature unique to hepatitis C infection is the association with the metabolic syndrome,* in particular with HCV genotype 3. Apparently, HCV can give rise to insulin resistance and non alcoholic fatty liver disease.

HCV infection is potentially curable. Until recently, treatment has been based on combination of pegylated IFN-α and ribavirin and cure rates depended on the viral genotype; patients with genotype 2 or 3 infection generally have had the best responses. Interestingly, host genotype also influences the response. Certain polymorphism in the IL-28B gene are associated with better response to interferon-alpha and ribavarin. IL-28B encodes interferon lambda, which is involved in resistance to HCV. New drugs targeting viral protease and polymerase have now been approved or are in development. With currently available drugs sustained virologic response (defined as undetectable HCV RNA in the patient's blood 24 weeks after the end of treatment) can be achieved in 50% to 80% of patients. Thus there is every reason to believe that newer regimens, based on principles similar to those used in highly active antiretroviral therapy (HAART) for HIV infection, will change the course of chronic hepatitis C in the coming decade.

Hepatitis D Virus

Also called "the delta agent," hepatitis D virus (HDV) is a unique RNA virus that is dependent for its life cycle on HBV. Infection with HDV arises in the following settings.

- *Co-infection* occurs following exposure to serum containing both HDV and HBV. The HBV must become established first to provide the HBsAg necessary for development of complete HDV virions. Co-infection of HBV and HDV results in acute hepatitis that is indistinguishable from acute hepatitis B. It is self -limited and is usually followed by clearance of both viruses. However, there is a higher rate of acute hepatic failure, in intravenous drug users.
- *Superinfection* occurs when a chronic carrier of HBV is exposed to a new inoculum of HDV. This results in disease 30 to 50 days later presenting either as severe acute hepatitis in a previously unrecognized HBV carrier or as an exacerbation of preexisting chronic hepatitis B infection. Chronic HDV infection occurs in almost all of such patients. The superinfection may have two phases: an acute phase with active HDV replication and suppression of HBV with high transaminase levels, and a chronic phase in which HDV replication decreases, HBV replication increases, transferase levels fluctuate, and the disease progresses to cirrhosis and sometimes hepatocellular carcinoma.

Worldwide, 15 million people are estimated to be infected with HDV (about 5% of 300 million of HBV infected persons). Prevalence varies, being high in the Amazon basin, and in central Africa, the Middle East, and the Mediterranean basin, where 20% to 40% of HbsAg carriers may have anti-HDV antibody; the rate has been declining in recent years. Surprisingly, HDV infection is uncommon in the large population of HBsAg carriers in Southeast Asia and China. In western countries it is largely restricted to intravenous drug abusers and those who have had multiple blood transfusions.

HDV, discovered in 1977, is a 35-nm, double-shelled particle. The external coat antigen of HBsAg surrounds an internal polypeptide assembly, designated delta antigen (HDAg), the only protein produced by the virus. Associated with HDAg is a small circular molecule of single-stranded RNA, whose length is smaller than the genome of any known animal virus. Replication of the virus is through RNA-directed RNA synthesis by host RNA polymerase.

HDV RNA is detectable in the blood and liver just before and in the early days of acute symptomatic disease. IgM anti-HDV antibody is the most reliable indicator of recent HDV exposure, although its appearance is late and frequently short-lived. Nevertheless, acute co-infection by HDV and HBV is best indicated by detection of IgM against both HDAg and HBcAg (denoting new infection with hepatitis B). With chronic delta hepatitis arising from HDV superinfection, HBsAg is present in serum, and anti-HDV antibodies (IgG and IgM) persist for months or longer. Vaccination for HBV also prevents HDV infection.

Hepatitis E Virus

Hepatitis E virus (HEV) is an enterically transmitted, water-borne infection that occurs primarily in young to middle-aged adults. HEV is a zoonotic disease with animal reservoirs, such as monkeys, cats, pigs, and dogs. Epidemics have been reported in Asia and the Indian subcontinent, sub-Saharan Africa, Middle East, China and Mexico, although sporadic cases are seen in industrialized nations, particularly in regions where pig farming is common. Sporadic infection may also occur in travelers to these regions, but, most importantly, HEV infection accounts for more than 30% to 60% of cases of sporadic acute hepatitis in India, exceeding the frequency of HAV. *A characteristic feature of HEV infection is the high mortality rate among pregnant women, approaching 20%.* In most cases the disease is self-limiting; HEV is not associated with chronic liver disease or persistent viremia in immunocompetent patients. Chronic HEV infection does occur in patients with AIDS and immunosuppressed transplant patients. The average incubation period following exposure is 4 to 5 weeks.

Discovered in 1983, HEV is an unenveloped, positive-stranded RNA virus in the *Hepevirus* genus. Viral particles are 32 to 34 nm in diameter, and the RNA genome is approximately 7.3 kb in size. Virions are shed in stool during the acute illness.

Before the onset of clinical illness, HEV RNA and HEV virions can be detected by PCR in stool and serum. The onset of rising serum aminotransferases, clinical illness, and elevated IgM anti-HEV titers are virtually simultaneous. Symptoms resolve in 2 to 4 weeks, during which time the IgM is replaced with a persistent IgG anti-HEV antibodies.

Clinicopathologic Syndromes of Viral Hepatitis

Several clinical syndromes may develop following exposure to hepatitis viruses: (1) acute asymptomatic infection with recovery (serologic evidence only), (2) acute symptomatic hepatitis with recovery, anicteric or icteric, (3) chronic hepatitis, with or without progression to cirrhosis, and (4) acute liver failure with massive to submassive hepatic necrosis. Table 18-3 provides a summary of the salient features of infection by various hepatitis viruses. All of the hepatotropic viruses can cause acute