8.5.21 Hepatitis viruses (excluding hepatitis C vi

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8.5.21 Hepatitis viruses (excluding hepatitis C virus) 889 8.5.21 Hepatitis viruses (excluding hepatitis C virus) Matthew Cramp, Ashwin Dhanda, and
Nikolai V. Naoumov ESSENTIALS The group of hepatitis viruses includes five unrelated human viruses (A to E), which differ in their genome organization, biology, and epidemiology, while being united by their hepatotropism. About 10–15% of cases of viral hepatitis are considered as non-A to E hepatitis, whose aetiology is still unknown, but the search for which has led to the identification of several new viruses (e.g. hepatitis G virus or GB virus-C, TT, and SEN viruses) of uncertain pathogenic significance. Clinical aspects of viral hepatitis are discussed in Chapter 15.22.1. Hepatitis A virus This is a single-stranded RNA virus with four genotypes in humans. Hepatitis A virus replicates primarily in hepatocytes and is excreted via the biliary system into the faeces, where it can be found in high concentrations prior to clinical symptoms. Hepatitis A virus causes acute hepatitis with significant morbidity and occasional mortality. Antihepatitis A virus IgG remains detectable after acute infection and provides protective immunity. Hepatitis B virus Hepatitis B virus is the smallest human DNA virus. Ten genotypes, designated A to J, have been determined, with variable geograph- ical distribution. The virus is noncytopathic, with virus-specific cel- lular immunity being the main determinant for the outcome of infection and in those cases who resolve. An effective immune re- sponse controls hepatitis B virus replication and prevents liver dis- ease developing. The natural evolution of chronic infection includes four consecutive phases: (1) early ‘immunotolerant’ phase—high levels of virus replication and minimal liver inflammation; (2) im- mune reactive phase—significant hepatic inflammation and ele- vated serum aminotransferases without viral clearance; with some patients progressing to (3) ‘nonreplicative’ phase—seroconversion to anti-HBe; undetectable or low level of viraemia (below 2000 IU/ml by polymerase chain reaction-based assays); resolution of hepatic inflammation; and (4) HBeAg-negative chronic hepatitis B—due to the emergence of viral mutations; characterized by fluctuating

serum hepatitis B virus DNA and serum alanine aminotransferase levels, and progressive liver disease. Hepatitis C virus See Chapter 8.5.22. Hepatitis delta virus This is a defective virus with a single-stranded circular RNA genome. Eight genotypes have been determined in humans; genotype 1 is most common in the Western world and genotype 2 is predom- inant in East Asia. Hepatitis delta virus infection is always associ- ated with hepatitis B virus infection, either arising concurrently with hepatitis B virus as coinfection or after hepatitis B virus as super- infection. Clinical manifestations vary from acute to fulminant hepatitis and from an asymptomatic carrier state to progressive chronic liver disease. Diagnosis is based on the detection of serum HDAg and serum hepatitis D virus RNA. The optimal treatment of hepatitis delta virus is uncertain. Prevention is by vaccination against hepatitis B virus. Hepatitis E virus This is a single-stranded RNA virus. Hepatitis E virus is widely dis- tributed and transmitted by the faeco-oral route and may be zoo- notic, with evidence of infection in pigs, cattle, and sheep in endemic regions. It causes acute viral hepatitis which can be fulminant in those who are pregnant, malnourished, or have existing liver dis- ease. Chronic infection has been reported in solid organ transplant recipients, patients with haematological malignancies and HIV. Immunity can be transient and might wane if acquired in childhood. An effective vaccine has been developed but is not yet commercially available. Introduction Viral hepatitis (Fig. 8.5.21.1) is an ancient disease which re- mains a major health problem worldwide. Five viruses have been identified as aetiological agents and named A, B, C, D, and E (Table 8.5.21.1). These unrelated human viruses differ in their genome organization, biology, and epidemiology, while being united by their hepatotropism. Approximately 10–15% of cases with viral hepatitis are considered as non-A to E hepatitis and the aetiology is still unknown. The search for additional hepatitis agents led to the identification of several new viruses, named hepa- titis G virus (HGV or GB virus-C), TT, and SEN viruses. These viruses have been detected in high proportions of the general population and their pathogenic role, if any, remains uncertain. Thus, the search for new hepatitis agents responsible for the small proportion of cases with cryptogenic hepatitis continues. Clinical aspects of viral hepatitis are discussed in Chapter 15.22.1. Fig. 8.5.21.1 Acute viral hepatitis with jaundice and subconjunctival haemorrhages. Copyright D. A. Warrell.

 Hepatitis A virus (HAV) HAV particles were first discovered by immune electron mi- croscopy in 1973 in stool samples of patients with hepatitis A. The virus is classified in the genus Heparnavirus of the family Picornaviridae. The genome of HAV is a single-stranded, linear RNA of approximately 7474 nucleotides (Table 8.5.21.1). This includes a 5′ untranslated region (5′ UTR) of 742 nucleotides, followed by a single, long, open reading frame (ORF, 6681 nu- cleotides) which encodes a polyprotein of 2227 amino acids, and a short 3′ noncoding region (63 nucleotides). After translation, HAV polyprotein undergoes multiple cleavages by a virally- encoded enzyme, 3C protease. The polyprotein contains three functionally separate domains. At the N-terminal end is domain P1 which includes the major structural polypeptides of HAV in Table 8.5.21.1 Main characteristics of hepatitis viruses Virus Family Morphology Genome Proteins Antibodies Pathogenesis Specific features HAV Picornaviridae 27 nm non- enveloped, spherical particles Single-stranded linear RNA, 7474 nt Four capsid proteins, viral polymerase, and proteases Anti-HAV Non- cytopathic virus Immune-mediated acute hepatitis No chronic infection Effective vaccines available HBV Hepadnaviridae 42 nm particle with nucleocapsid (core) and outer envelope (surface) Partially double- stranded, circular DNA, 3200 nt Envelope Major protein (HBsAg) Middle protein (PreS2 + S) Large protein (PreS1 + S2 + S) Nucleocapsid (HBcAg) HBeAg non- structural, soluble protein Anti-HBs Anti-HBc Anti-HBe Non- cytopathic virus Immune-mediated acute and chronic hepatitis Weak T-cell reactivity—a dominant cause for persistent viral replication

In chronic infection spontaneous evolution from HBeAg(+) to anti-HBe(+) phase Mutant strains (surface, precore, polymerase) evolve under selection pressure DNA integration into host genome Transactivation of cellular genes Effective vaccines available 22 nm spherical and filamentous subviral particles Envelope proteins only Anti-HBs HCV Flaviviridae 50–60 nm enveloped spherical particles Single-stranded linear RNA, approx. 9500 nt Structural Envelope 1 (E1) Envelope 2 (E2) Nucleocapsid (core) Anti-E1 Anti-E2 Anti-core Usually non- cytopathic virus Neutralizing antibodies (?) High degree of virus heterogeneity (genotypes and quasi species) High propensity to chronic infection No integration in host genome Six major genotypes Nonstructural NS2 NS3 NS4 NS5 Anti-NS3 Anti-NS4 Anti-NS5 T-cell reactivity— major role for resolution of acute infection HDV Resembles viroids and plant viruses 35–37 nm enveloped particles Single-stranded circular RNA, 1700 nt HD-Ag (nucleocapsid) HBsAg (envelope) Anti-HD Anti-HBs Direct cytopathic and/or immune- mediated liver injury Defective RNA virus Requires help from HBV for providing the envelope HBsAg HEV Caliciviridae 32–34 nm
nonenveloped spherical particles Single-stranded linear RNA, 7500 nt ORF1—
nonstructural proteins ORF2—structural proteins ORF3—unknown function Anti-HEV Probably immune mediated (?) Enterically transmitted hepatitis mainly in Asia, Middle East, and Central America Chronic infection can be seen in immunocompromised HGV/GBV-C Flaviviridae ? Single-stranded linear RNA, 9400 nt Conserved E2 No core protein Anti-E2 Primary site of replication unknown Does not cause hepatitis Can establish chronic infection No clear pathogenic role TTV Circinoviridae (?) ? Single-stranded, circular DNA, approx. 3850 nt ? ? Does not cause hepatitis Can establish chronic infection High degree of virus heterogeneity No clear pathogenic role NS, nonstructural; nt, nucleotides; ORF, open reading frame.

8.5.21 Hepatitis viruses (excluding hepatitis C virus) 891 the following sequence—VP2, VP3, and VP1. A fourth very small polypeptide, VP4, which is presumed to be involved in HAV capsid formation, is located at the extreme N-terminal end of the polyprotein. These four structural polypeptides assemble into a viral capsid containing 60 copies of each. It is not known how the viral RNA is incorporated into the virion, but both empty and RNA-containing capsids have been observed in most virus pre- parations. The other P2 and P3 domains of the viral polyprotein include at least six separate proteins which are involved in viral replication. These include 2B and 2C helicase, 3A and 3B pro- teins, 3C (the viral protease), and 3D (an RNA-dependent RNA polymerase). Hepatocytes are the predominant site of HAV replication in vivo. Recent data indicate that HAV might also replicate within the epithelial cells of the gastrointestinal tract. However, the mechanism by which HAV reaches the liver remains unknown. The maximal HAV replication in hepatocytes occurs before serum aminotransferases rise. The virus is excreted via the biliary system into the faeces where it can be found in high concentrations around 1–2 weeks before the onset of clinical symptoms. Viraemia is pre- sent from the earliest phase of infection and is due to HAV repli- cation within hepatocytes. HAV differs from other picornaviruses because of its noncytolytic replication. Liver injury is immune me- diated by natural killer cells, virus-specific CD8+ cytotoxic T cells, and nonspecific inflammatory cells recruited to the liver. At the onset of clinical symptoms there is a humoral immune response and antibodies to structural HAV proteins (anti-HAV) are detect- able in patients' serum. Initially, these are mainly IgM antibodies (IgM anti-HAV) which usually persist for approximately 6 months. During convalescence, anti-HAV IgG becomes predominant and remains detectable indefinitely, representing protective immunity to HAV. An effective vaccine generating lasting protective im- munity is widely available. Hepatitis B virus (HBV) Two discoveries related to HBV mark the beginning of the under- standing of hepatitis

viruses. In 1965, Baruch Blumberg identified the hepatitis B surface antigen (HBsAg) of HBV, initially termed ‘Australia antigen’, and in 1970 the complete virion (a 42 nm par- ticle) was identified by Dane and colleagues using electron micros- copy. HBV belongs to a virus family named Hepadnaviridae, which includes similar hepatotropic DNA viruses specific for woodchucks, ground squirrels, and Pekin ducks. An estimated 240 million people are chronically infected with HBV globally, mainly in East Asia and sub-Saharan Africa, where up to 10% of the adult population is infected. Genome organization The HBV genome contains only 3200 nucleotides and is the smallest DNA virus (Table 8.5.21.1). One of the DNA strands, known as the ‘minus’ strand, is almost a complete circle and contains four overlapping ORFs encoding enveloped (pre-S/S), core (precore/ core), polymerase and X proteins (Fig. 8.5.21.2). The other (‘plus’) strand is shorter and varies in length. The envelope ORF contains three start codons which separate the pre-S1, pre-S2, and S regions, encoding the large (L), middle (M), and small (S) envelope proteins respectively. The surface gene encodes the major envelope protein (HBsAg), which has 226 amino acids. The translation product of the pre-S2 and S gene is the middle en- velope protein and the product of pre-S1, pre-S2, and S gene is the large envelope protein. In addition to the complete virion, a much greater amount of noninfectious, 22 nm in diameter, spherical, and 1800 1600 1400 1200 1000 800 600 400 200 3182 3000 2800 2600 2400 2200 2000 1814 EcoRI 0 DR 1 Poly A S1P S2P – + Oligoribo- nucleotide 5′ Enh I XP DR 2 Enh II CP Pre-core/core gene Polymerase gene X-gene Surface gene Pre-S2 Pre-S1 Fig. 8.5.21.2 Schematic representation of hepatitis B virus genome. CP, core promoter; DR1, direct repeat 1; DR2, direct repeat 2; EcoRI, restriction site for EcoRI enzyme used as a starting point for numbering; EnhI, enhancer I; EnhII, enhancer II; S1P, pre-S1 promoter; S2P, pre-S2 promoter; XP, X gene promoter.

892 section 8 Infectious diseases filamentous subviral particles are produced in infected hepatocytes. HBsAg and the middle envelope protein are present in all viral and subviral particles, while the large protein is present in the virions and in some subviral filaments. The pre-S1 domain of the large envelope protein is a key determinant for binding and recently the sodium taurocholate cotransporting polypeptide (NTCP), a multiple trans- membrane transporter predominantly expressed in the liver, has been shown to be the receptor on the plasma membrane of hepatocytes. The precore/core ORF has two start codons which encode two closely related proteins. Translation from the preC start codon produces a precursor molecule, designated precore protein. In the endoplasmic reticulum this protein undergoes two proteolytic steps at the N- and at the C-terminal ends, and the resultant polypeptide is secreted from hepatocytes as hepatitis B e- antigen (HBeAg). This is a nonstructural protein, which is not essential for viral replica- tion. Translation from the C start codon results in the nucleocapsid protein (HBcAg), which has 183 amino acids. In the cytoplasm of hepatocytes HBcAg assembles spontaneously into nucleocapsid particles. HBeAg and HBcAg share about 90% of the amino acids but differ substantially in their conformation. The polymerase ORF encodes the HBV polymerase protein with 832 amino acids. It has three functional domains—terminal pro- tein, reverse transcriptase, and RNAse H activity. The X ORF en- codes a protein with 154 amino acids. Recent studies have shown that the X protein is essential for viral replication through degrad- ation of the Smc5/6 restriction factor. Ten genotypes of HBV (designated with the letters A to J) have been determined. The variations involve approximately 10% of the genome. Data on the geographical distribution indicate that geno- type A is predominant in central and northern Europe, genotypes B and C in Asia, genotype D in the Mediterranean basin, and genotype E in Africa. Viral replication Following HBV entry into hepatocytes, the nucleocapsid is trans- ported to the nucleus (Fig. 8.5.21.3). Cellular enzymes

repair the open circular HBV DNA into covalently closed circular DNA (cccDNA), which serves as a template for the synthesis of pregenomic and mes- senger RNAs. Viral DNA does not integrate into the host genome as part of the normal replication cycle. The pregenomic RNA is trans- ported to the cytoplasm and serves as mRNA for translation of new core and polymerase proteins. When these three components (pregenomic RNA, core, and polymerase proteins) reach sufficient quantities, they assemble into nucleocapsid particles, with the polymerase protein being directly involved in the pregenomic RNA encapsidation. Inside the particles the pregenomic RNA is reverse transcribed into DNA 'minus' strand, while the RNA template is simultaneously degraded by RNAse H. Finally, the 'plus' strand is produced which completes a new, partially double-stranded, HBV DNA. Some of the newly synthesized nucleocapsids with HBV DNA are transported back to the nucleus, which maintains a stable pool of cccDNA. Others are enveloped and leave the cell as new virions. cccDNA persists in the nucleus of infected hepatocytes, even after HBsAg and HBeAg loss, and is considered to be the main mechanism of HBV chronicity. The replication strategy used by hepadnaviruses differs from that of retro- viruses in two main aspects: 1) integration into the host genome is not obligatory during replication; 2) functional mRNAs are produced from several internal promoters of the circular DNA genome. Recent progress in the understanding of the mechanisms of viral entry and replication have identified a variety of new targets for drug therapy that are directed towards a functional cure (sustained loss of HBsAg with or without surface antibody seroconversion). These in- clude entry inhibitors, inhibitors of cccDNA formation and transcrip- tion and targeting the X protein and intracellular trafficking. See Lok et al reference in Further Reading for a contemporary detailed review. 3.5 kb RNA pregenome Subgenomic RNAs 2.4 kb 2.1 kb Envelope proteins NUCLEUS ccc DNA Core protein P protein Reverse transcriptase (–) Strand DNA DNA polymerase (+) Strand DNA Endoplasmic reticulum Subviral particles HBV HBV Fig. 8.5.21.3 Replicative cycle of hepatitis B virus.

8.5.21 Hepatitis viruses (excluding hepatitis C virus) 893 Host immune response and pathogenesis HBV is a noncytopathic virus. The virus-specific cellular immune response mainly determines the outcome of infection. Both human leukocyte antigen class I and class II-restricted T-cell responses are strong and directed to multiple viral antigens in patients with acute self-limited hepatitis B. Despite clearance of serum HBsAg, HBV DNA remains detectable by polymerase chain reaction (PCR) in most cases, and HBV-specific CD4+ and CD8+ T-cell reactivity has been demonstrated 10–20 years after the time of acute infection. Cytokines released from these cells, especially interferon-γ, have been shown to exert a noncytolytic inhibition on HBV replication without causing cell death. Thus, eradication of HBV may be rare, but an effective immune response controls HBV DNA expression and there is no liver disease. Patients with chronic HBV infection (defined by detection of HBsAg in serum for longer than 6 months) show weak virus-specific T-cell reactivity, which is the dominant cause for HBV persistence. This ineffective response, together with antigen nonspecific inflammatory cells recruited at the site of in- flammation, is responsible for the progression of liver damage. The humoral immune response involves antibodies directed at different HBV antigens (Table 8.5.21.1). The clinical significance is based on several aspects: (1) diagnosis—the antibody profile in the serum, together with the result of HBsAg and HBeAg, is used to define different phases of HBV infection; (2) prophylaxis—the development and the level of the protective antibody (anti-HBs) is used to monitor the response to vaccination; (3) pathogenesis—the humoral immune response contributes to viral elimination from the circulation by forming immune complexes. In some cases, the tissue deposition of antigen-antibody complexes is responsible for extrahepatic pathology such as glomerulonephritis,

polyarteritis nodosa, arthritis, and skin changes. Evolution of chronic HBV infection HBV-host interactions change over time, typically in four consecu- tive phases, which are characterized by different levels of HBV rep- lication and associated liver disease. The early ‘immunotolerant’ phase with HBeAg positivity, and high levels of viral replication with HBV DNA levels as high as 107 or 108 IU/ml, but normal liver enzymes, usually occurs in infants after vertical or peri-natal transmission and lasts until adolescence. This phase is often short- lived or absent when HBV is contracted during adulthood. It is associated with minimal liver inflammation or fibrosis. However, recent studies have suggested this phase may not be as benign as previously thought; there have been reports of histologically ac- tive chronic hepatitis in ‘immunotolerant’ children and there is an absence of a tolerogenic T-cell pattern. In early adulthood, there is enhanced immune reactivity to the virus, characterized by sig- nificant hepatic inflammation, elevated or fluctuating levels of serum aminotransferases, and rapid progression of hepatic fibrosis. HBeAg remains positive and HBV DNA level is usually lower but still greater than 2000 IU/ml. This immune reactive HBeAg posi- tive phase can last for weeks to years. Currently, antiviral therapy is only recommended during this immune active stage of the in- fection. Some patients will progress spontaneously to the next ‘nonreplicative’ or low-replicative phase, manifested by serocon- version to anti-HBe, undetectable or less than 2000 IU/ml vir- aemia, and resolution of hepatic inflammation. In a proportion of patients, HBeAg loss may be due to the emergence of mutations in the core promoter and/or in the precore region (usually the G1896A stop codon), which prevent the translation of HBeAg. These HBe- minus mutants are replication competent and when viraemia levels are high, they cause HBe-negative chronic hepatitis B. The latter is characterized by fluctuating serum HBV DNA levels, mirrored by serum alanine aminotransferase (ALT) fluctuations, and progres- sive liver disease. Finally, the patient might achieve HBsAg loss to enter an ‘occult’ phase of chronic infection. During this phase anti- HBc antibodies with or without anti-HBs antibodies are detected. There might be low levels of viral replication although HBV DNA is generally undetectable. Replication-competent HBV genomes remain within hepatocytes and immune reactivation can occur in response to immunosuppression. Hepatitis C virus (HCV) (See Chapter 8.5.22.) Hepatitis D virus (HDV) HDV is a defective virus that causes acute and chronic liver disease only in association with hepatitis B virus. This unique pathogen was discovered in 1977 by Mario Rizzetto in liver biopsies from patients with hepatitis B. HDV particles contain the viral RNA nucleocapsid, which is hepatitis delta antigen (HDAg), and an outer envelope (HBsAg), which is provided by the helper virus HBV. The HDV genome is a single-stranded, circular RNA (Table 8.5.21.1), and is the smallest known animal virus genome. Because of a high degree of internal complementarity, 70% of the nucleotides are base-paired. This gives an unusual, rod-like structure of the HDV genome. HDV RNA replicates via RNA-directed RNA synthesis by transcription of genomic RNA to a complementary antigenomic delta RNA. The latter serves as a template for subsequent genomic RNA synthesis. HDV produces a single protein, hepatitis delta antigen (HDAg), which is encoded by the antigenomic RNA. RNA editing of the antigenomic RNA allows the virus to make two forms of HDAg— small (HDAg-S, 195 amino acids) and large (HDAg-L, 214 amino acids). Both forms are present in the virions and have different func- tions in the HDV replicative cycle. HDAg-S facilitates HDV RNA replication, while HDAg-L inhibits replication and is required for assembly of the virion. Although the formation of delta virions re- quires the helper function of HBV, the replication of HDV RNA within the cell can occur without HBV. Global coinfection prevalence is estimated at 5% but this might be an underestimate due to a lack of standardized testing for HDV in HBV-infected patients. Prevalence in some parts of Europe has recently been reported to be increasing, probably due to patterns of immigration from endemic regions, while in other countries, such as Taiwan, it is decreasing due to

an active hepatitis B immunization programme and systematic screening of blood products. Eight phylogenetically distinct HDV genotypes have been identi- fied. The most widespread is genotype 1, identified in Africa, Asia, Europe, and North America, which is associated with a broad spec- trum of chronic liver disease with chronic infection established in 70–90% of patients. Genotype 2 is found only in East Asia and seems to cause mild hepatitis delta. Genotype 3 is found exclusively in nor- thern parts of South America and is associated with particularly severe hepatitis. At least five additional HDV genotypes have been

 described; their clinical features are less well characterized than genotypes 1 to 3. Clinical manifestations vary from acute to fulminant hepatitis and from an asymptomatic carrier state to progressive chronic liver dis- ease. Clinical outcome might be related to different HDV genotypes. Persistent HDV replication is associated with annual rates of devel- opment of cirrhosis and hepatocellular carcinoma of 4% and 2.8%, respectively. Diagnosis is based on the detection of serum HDAg (detectable in acute infection), serum HDV RNA, and anti-HDV antibodies. In practice, HDV RNA is the most reliable and available test since standardized methods to analyse HDAg and anti-HDV antibodies do not exist. The optimal treatment of HDV is uncer- tain. Interferon-α is the only licensed treatment, but responses have been poor. Pegylated interferon might be better, with randomized controlled trials demonstrating a sustained virological response in 17–43% of patients after 6 months of treatment. Addition of nucleo- side analogues does not appear to be beneficial. Prevention of HDV is by vaccination against HBV. Host immune response and pathogenesis HDV can infect a person either simultaneously with HBV (coinfection) or as superinfection of a person with chronic HBV infection. Because HDV requires the helper function of HBV, the duration of delta infection is determined by the duration of HBsAg positivity. Analogous to the antibodies to HBV nucleocapsid (anti- HBc), antibodies to HDAg are not protective. Chronic HDV infec- tion is accompanied by high titres of IgG anti-HD. A high serum level of IgM anti-HD indicates acute delta infection or exacerbation of chronic hepatitis D. The relative role of cellular immune reac- tions to HDAg, HBV antigens, or both in the immunopathogenesis of hepatitis D is not fully understood. The lack of liver pathology in transgenic mice expressing HDV and data from experimental infections suggest that HDV is not cytopathic. This is supported by the experience with patients undergoing liver transplantation for HDV cirrhosis. Although HDV recurs universally in the graft, necroinflammation is absent unless HBV recurs as well. The pres- ence of microvesicular steatosis in severe hepatitis D indicates a possible direct cytopathic effect in some circumstances. Hepatitis E virus (HEV) HEV was first identified in 1983 by immune electron microscopy in the faeces of patients and classified in the genus Hepevirus, family Hepeviridiae. HEV is an icosahedral, nonenveloped single- stranded RNA virus that is 27–34 nm in diameter. The HEV genome is approximately 7500 nucleotides and contains three ORFs (Table 8.5.21.1). ORF1 encodes nonstructural proteins involved in virus replication—helicase and RNA-dependent RNA polymerase. ORF2, comprising approximately 2000 nucleotides, codes for the major structural proteins. ORF3 has 328 nucleotides and also ap- pears to code for a structural protein. The genomic organization of HEV is different from HAV and HCV because the structural and nonstructural proteins are coded by discontinuous, partially overlapping ORFs. HEV is widely distributed with the highest incidence of infection in Asia, Africa, the Middle East, and Central America. In developed countries including the United Kingdom, France, and Japan, acute HEV is more common than HAV. The seroprevalence of HEV was thought to be low at 1–2% but recent epidemiological data using improved assays suggest a wide geographic variation with sero- prevalence ranging from 4.8 to 16% in the United Kingdom, up to 40% in the southwest of France. In developing countries seropreva- lence rates are

around 30% but there is variation depending on the population studied. It is spread by the faeco-oral route in endemic areas. Person-to-person transmission is uncommon. HEV can be transmitted by blood transfusion, particularly in endemic areas. HEV RNA was found in 0.7% of pooled plasma from donors from England and is estimated to be present in 1 in 3200 to 7000 blood donors in Europe. Unlike HAV, HEV infection might be zoonotic. HEV RNA has been found in the faeces of wild pigs and serological evidence of infection was found in pigs, cattle, and sheep in endemic regions. Transmission has been reported in the context of consump- tion of undercooked meat. Four genotypes of HEV have been identified, which show 25% nucleotide variability. Geographically, genotype 1 has been isolated from tropical countries in Asia and Africa and is responsible for large outbreaks and epidemics. Genotype 2 was found in Mexico, whereas genotype 3 has worldwide distribution, including America, Asia, and Europe and is responsible for the nontravel associated sporadic infections seen in these endemic areas. Genotype 4, in con- trast, has been found only in Asia. Genotypes 3 and 4 infect humans as well as pigs and other mammals while genotypes 1 and 2 are found only in humans. Vaccine development has been helped as all HEV strains share at least one major, serologically cross-reactive epitope. HEV usually causes an acute self-limited infection, although ful- minant infection can occur. Fulminant infection is more common in pregnancy, malnutrition, and in those with pre-existing liver dis- ease. In pregnancy, acute HEV genotype 1 and 2 infections are as- sociated with a high maternal mortality of 20–25% due to obstetric complications or fulminant hepatic failure, as well as a high rate of stillbirth. The same obstetric risk is not apparent for HEV genotype 3 and 4 infections, the reasons for which are not clear. Chronic HEV infection, defined as positive HEV RNA for at least 6 months, is well described in solid organ transplant recipients, in immunosuppressed individuals in the context of haematological malignancy or HIV infection. Chronic HEV can result in significant chronic liver disease. Treatment with ribavirin for 3 months can be effective, with a recent retrospective case series reporting a sustained virological response in 78% of cases. The primary site of HEV replication is not fully understood. Following intravenous HEV inoculation in experimental models, serum aminotransferases levels rise after 24–38 days. Expression of HEV antigens has been detected in the cytoplasm of hepato- cytes as early as 7 to 10 days after inoculation. Experimental data indicate that during an initial phase with high HEV replication the virus might be released from hepatocytes into bile, which occurs be- fore the elevation of liver enzymes and morphological changes in the liver. The virus shedding appears to end with the normalization of serum aminotransferases. HEV RNA is detectable in the stool 1 week before the onset of illness and persists for 2 weeks afterwards. HEV RNA is detectable in the serum by real-time PCR of virtu- ally all patients within 2 weeks of the onset of hepatitis. Prolonged periods of viraemia, between 4 to 16 weeks, have also been reported. The detection of anti-HEV by enzyme immunoassays, involving recombinant HEV antigens or synthetic peptides, is the most fre- quently used method for diagnostic purposes and for epidemio- logical studies. However, these tests are unreliable in the diagnosis

 of chronic HEV infection in immunocompromised individuals and HEV RNA testing is recommended. During acute infection, the humoral immune response gradually develops in parallel with the ALT rise. The serum level of anti-HEV IgM reaches a maximal titre around the time of peak ALT levels and is detectable for 5–6 months. Although the IgG anti-HEV response persists for several years after the acute phase, the natural history of protective immunity to HEV is not fully established. In contrast to HAV, hepatitis E shows an unusually high attack rate among adults, suggesting that immunity to HEV, if acquired in childhood, may wane. Vaccines against HEV are being developed and two large ran- domized

controlled trials have shown 96% preventive efficacy in en- demic settings. A vaccine has been licensed in China for use in high risk populations since 2011 but is not yet recommended in a 2015 World Health Organization position paper due to lack of safety and efficacy data in individuals less than 16 or over 65 years old, as well as no long-term efficacy data. There is no evidence for the efficacy of pre- or postexposure prophylaxis with immune globulin for the prevention of HEV. New hepatitis-associated viruses GB virus-C (GBV-C) or hepatitis G virus (HGV) The genome of GBV-C was identified in 1995 by molecular hybrid- ization techniques in the serum of a patient with the initials GB. In parallel, another group of investigators identified the genome of a new RNA virus, named hepatitis G virus. The comparison of HGV and GBV-C genomes revealed very high homology, both at nucleotide (86%) and amino acid level (100%). It is now accepted that they represent two isolates of the same virus. GBV-C/HGV is an RNA virus with a single ORF encoding a polyprotein of ap- proximately 3000 amino acids (Table 8.5.21.1). Together with another two RNA viruses, GBV-A and GBV-B, it belongs to the Flaviviridae and these three viruses show various similarities with HCV. Specific features of the GBV-C/HGV genome include ab- sence of core gene (nucleocapsid); long 5′ and 3′ NTR and lack of poly A tail. Unlike HCV, this virus has a very conserved E2 re- gion. GBV-C has a global distribution with a high prevalence in the North American blood donor population. Longitudinal studies have shown that GBV-C/HGV can establish chronic infection with RNA persistence in serum for up to 15 years. A proportion of pa- tients clear the virus spontaneously and develop anti-E2 reactivity, which is used as a marker of past infection. Anti-E2 also seems to confer protective immunity. A large body of evidence suggests that GBV-C/HGV does not cause liver disease. Evidence suggests a protective effect of GBV-C in patients coinfected with HIV. The protective effect might be related to maintenance of an intact T- helper 1 cytokine profile, induction of HIV-1 inhibitory cytokines and interference with HIV-1 replication; the therapeutic implica- tions of these findings remain unclear. TT virus (TTV) TTV was identified in 1997 by investigators in Japan. By applying the methodology used for the identification of GBV-C, they de- tected the genome of a new DNA virus in the serum of a patient with cryptogenic posttransfusion hepatitis. The patient’s initials (TT) prompted the name of this new virus and a causative role for acute and chronic hepatitis was suggested. TTV and its smaller variant are now spelt as Torque teno virus (TTV) and Torque teno mini virus (TTMV), after the Latin for ‘thin necklace’. The TTV genome is circular, single-stranded DNA of approxi- mately 3850 nucleotides (Table 8.5.21.1). Three partially open reading frames have been predicted, but TTV proteins have not been expressed so far. It is suggested that TTV belongs to the genus Anellovirus in the Circinoviridae family. TTV DNA has been de- tected in nonhuman primates and in farm animals. The primary site of TTV replication and the biological nature of TTV are still unknown. Unlike other DNA viruses, TTV shows remarkable genomic vari- ability. Phylogenetic analyses of TTV isolates have identified at least 20 genotypes, which differ between each other by more than 40% of the DNA sequences. As recombinant viral proteins are not available, the diagnosis of TTV infection is based on the detection of TTV DNA by PCR. TT virus population is very heterogeneous, and fre- quently a mixed infection with 3 to 5 TTV genotypes is present in one patient. TTV infection is ubiquitous in more than 90% of adults world- wide. The virus was initially thought to have mainly a parenteral route of transmission, although the high prevalence of TTV in- fection in the general population indicates the importance of non- parenteral routes as well. The prevalence of TTV infection was shown to increase with age in paediatric and adult groups. The pathogenic role of TTV, if any, is unknown. Analysis of liver histology in patients with TTV infection, longitudinal studies, as well as experimental TTV inoculation in chimpanzees all demon- strate that this virus does not cause hepatitis. Possible associations with other diseases, such as severe idiopathic inflammatory myop- athies, systemic lupus erythematosus, pancreatic cancer, diabetes mellitus, laryngeal cancer, and

periodontal disease have been re- ported. TTV may replicate in the respiratory tract of children and has been implicated in acute respiratory diseases in infants and ex- acerbations of asthma and bronchiectasis. However, TTV remains an example of a human virus with no clear disease association. SEN virus (SEN-V) SEN-V is a recently discovered single-stranded DNA virus, distantly related to TTV, with a worldwide distribution. Eight genotypes of SEN-V, designated A to H, have been identified. SEN-V is trans- mitted via transfusion of blood products and parenteral contact. Interest in SEN-V was triggered by the initial reports that two SEN- V genotypes, SEN-V-D and H, were associated with posttransfusion non-A, non-E hepatitis. No causative agent and no evidence of hepa- titis due to SEN-V infection have yet been established. FURTHER READING Cristina J, Costa-Mattioli M (2007). Genetic variability and molecular evolution of hepatitis A virus. Virus Res, 127, 151–7. Hino S, Miyata H (2007). Torque teno virus (TTV): current status. Rev Med Virol, 17, 45–57. Kamar N, et al. (2014). Ribavirin for chronic hepatitis E virus infection in transplant recipients. N Engl J Med, 370, 2447–8. Kamar N, et al. (2017). Hepatitis E virus infection. Nat Rev Dis Primers, 3, 17086.

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