Global Epidemiology of Acute Viral Hepatitis A–E

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Hubert E. Blum

1.1 Introduction

Worldwide, the hepatotropic viruses A–E are the major causes of acute and/or chronic liver diseases (Fig. 1.1). They can present with a broad spectrum of clinical signs and symptoms, ranging from an asymptomatic carrier state to acute/fulminant hepatitis or chronic liver disease with progression to liver cirrhosis and its sequelae, including hepatocellular carcinoma (HCC). Thus, viral hepatitis can be associated with significant morbidity and mortality and represents a global healthcare problem. In the following, the history, epidemiology, and global burden of disease (GBD) as well as the clinical presentation of acute hepatitis A–E are addressed.

In the 1940s, two distinct clinical forms of hepatitis were recognized: epidemic or infectious hepatitis, after the discovery of **hepatitis A virus (HAV**) in 1973 by R. H. Purcell and collaborators, designated as hepatitis A [1, 2], and serum hepatitis, after the discovery of **hepatitis B virus (HBV)** in 1960s by B. Blumberg and collaborators [3, 4] and by A. M. Prince [5, 6], designated as hepatitis B. With the specific serological identification of HAV and HBV infection [7, 8], the cause of the so-called post-transfusion non-A/non-B hepatitis [9] was discovered in 1989 by M. Houghton and collaborators as **hepatitis C virus (HCV)** [10], followed by the rapid development of HCV-specific serological and molecular diagnostic assay systems, including HCV genotyping [11–15]. In 1977 M. Rizzetto and collaborators discovered a novel antigen-antibody system that only occurs in association with hepatitis B [16]. This was later shown to be associated with a particle containing a low-molecular-weight RNA genome encapsidated by HBV envelope proteins and designated as **hepatitis delta virus (HDV)** [17]. Further, in 1955 an enterically transmitted acute viral hepatitis was

H. E. Blum (✉)
University Hospital Freiburg, Freiburg im Breisgau, Germany
e-mail: hubert.blum@uniklinik-freiburg.de

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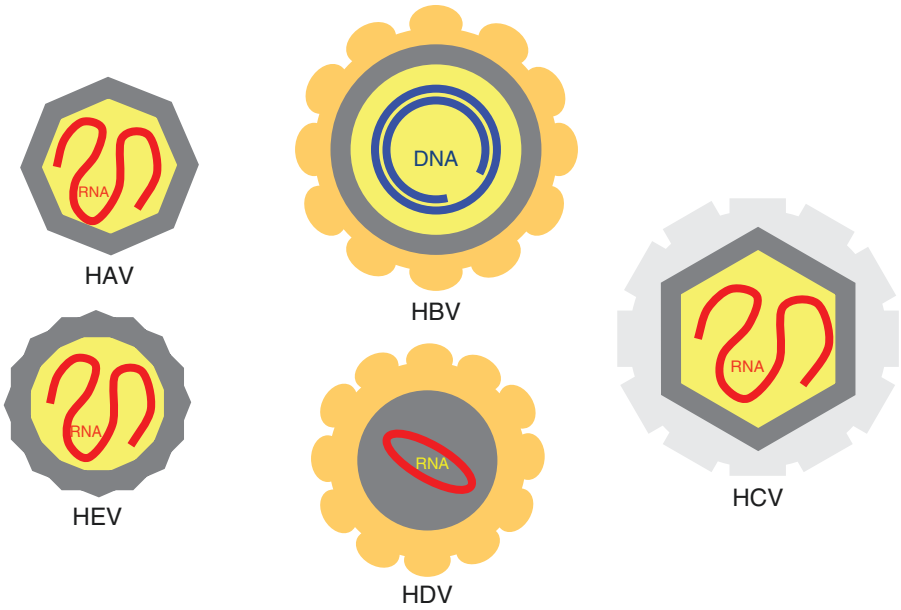

Fig. 1.1 Basic characteristics of hepatitis viruses A–E

Table 1.1 History of the discovery of hepatitis viruses A–E

Year	Virus	Methodology	References
1963/1968	HBV	Serology	[3, 5]
1973	HAV	IEM[a] (stool)	[1]
1977	HDV	Serology, IF[a] (liver)	[16]
1983	HEV	Serology, IEM[a] (stool)	[19]
1989	HCV	Cloning (liver)	[10]

[a]*IEM* immune electron microscopy, *IF* immunofluorescence

identified during an outbreak in New Delhi [18], initially termed epidemic non-A, non-B hepatitis, and later **hepatitis E virus (HEV)** infection [19–23]. The history of the discovery of the five hepatitis viruses A–E is summarized in Table 1.1.

1.2 Epidemiology of Viral Hepatitis A–E

Based on the specific and sensitive detection of hepatitis A–E infections, their epidemiology and global burden as well as their natural course could be studied in great detail. At the same time therapeutic and preventive strategies have been developed that should contribute to a reduced prevalence of these infections and their eventual elimination.

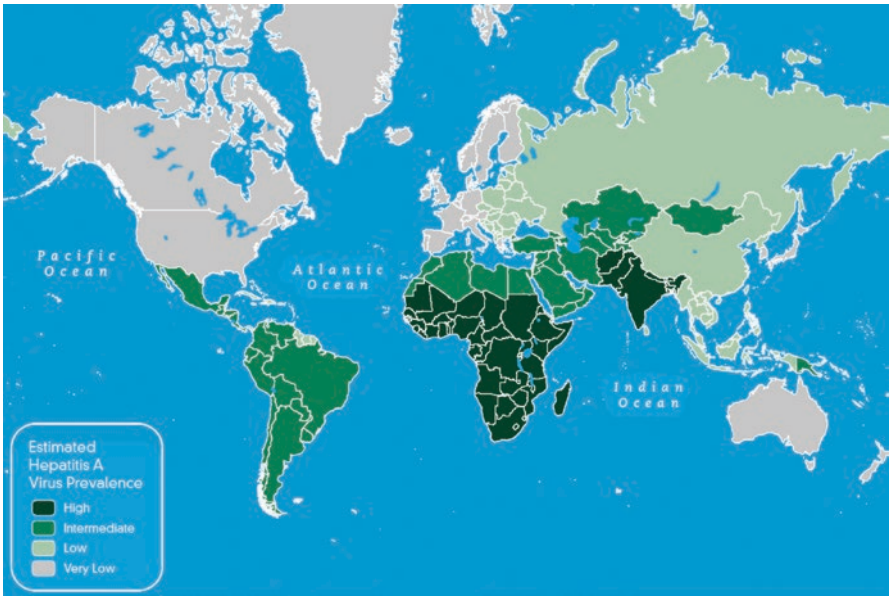

Fig. 1.2 Worldwide prevalence of HAV infection in 2005 [24]

1.2.1 HAV Infection

HAV infection occurs worldwide and shows a distinct geographic distribution with a high prevalence in sub-Saharan Africa, India, Pakistan, and Afghanistan; an intermediate prevalence in Middle and South America, Northern Africa, the Middle East, Turkey, Iran, Kazakhstan, and Mongolia; a low prevalence in Eastern Europe, Russia, China, and Oceania; and a very low prevalence in Western Europe, Scandinavia, North America, and Australia (Fig. 1.2) [24]. Tens of millions of individuals worldwide become annually infected with HAV. The incidence strongly correlates with the socioeconomic indicators and with access to safe drinking water. Universal vaccination of children has been shown to significantly reduce the hepatitis A incidence rates [25] with an increasing anti-HAV seroprevalence between 1990 and 2005 in all age groups and geographic regions [24].

In the USA, HAV infection has declined substantially since 1996 when vaccination has been recommended for individuals at risk [26–30]. In this context, acute hepatitis A has declined in the USA by 92% between 1995 and 2007 from 12 cases to 1 case per 100,000 population [27, 29]. The major risk factor in the USA now is international travel, mainly to Mexico and Central as well as South America.

1.2.2 HBV Infection

HBV infection is a serious global public health problem with about 250 million people chronically infected [31]. It accounts for 500,000–1.2 million deaths per year and is the tenth leading cause of death worldwide. The prevalence of HBV infection

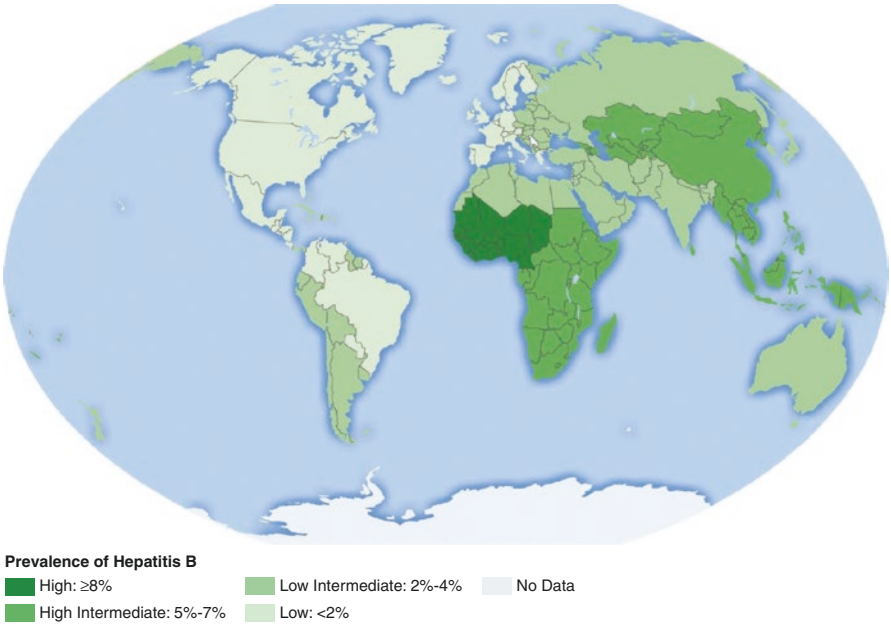

Fig. 1.3 Worldwide prevalence of HBV infection in adults in 2005 [32]

varies markedly in different geographic and in different population subgroups. The area with the highest hepatitis B surface antigen (HBsAg) prevalence of >8% is Western sub-Saharan Africa, followed by Eastern sub-Saharan Africa, Central Asia, Southeast Asia, China, and Oceania with a high intermediate prevalence of 5–7%; Latin America, Eastern Europe, North Africa, the Middle East, Turkey, Afghanistan, Pakistan, India, and Australia with a low intermediate prevalence of 2–4%; and the USA and Canada, Central America, Brazil, and Western Europe with a low prevalence of <2% (Fig. 1.3) [32]. From 1990 to 2005 the prevalence of chronic HBV infection decreased in most regions. This was most evident for Central sub-Saharan Africa, Tropical and Central Latin America, Southeast Asia, and Central Europe. Despite the decreasing prevalence, the absolute number of HBsAg-positive individuals increased from 223 million in 1990 to 240 million in 2005. The decline of HBV infection prevalence may be at least in part related to expanded immunization, suggested by the strongest decline found in Southeast Asian children [32]. In the USA, the HBsAg or anti-HBc prevalence in adults changed little during the period of 1999–2006 compared to 1988–1994 while it significantly decreased in children, reflecting the impact of global and domestic vaccination [33].

In the USA, acute HBV infection has declined by 82% from 8.5 cases per 100,000 population in 1990 to 1.5 cases per 100,000 population in 2007, especially in children and adolescents [28, 29]. Sexual exposure and injection drug are considered the major risk factors.

Different from HCV [9] infection (see below), the annual mortality rate from HBV infection in the USA did not change significantly between 1999 and 2007 with major risk factors being chronic liver diseases, coinfection with HCV, or human immunodeficiency virus (HIV) as well as alcohol-related conditions [34].

Universal vaccination against HBV infection was shown to be cost-saving in countries with high and intermediate endemicity. Apart from exposure prophylaxis through personal protection measures, HBV vaccination should be administered to all unvaccinated individuals traveling to areas with high or intermediate HBsAg prevalence [35].

1.2.3 HCV Infection

HCV infection is endemic worldwide with about 185 million infected people. It shows a significant geographic variability with the highest prevalence rates, based on anti-HCV positivity, in North Africa, the Middle East, as well as Central and East Asia (>3.5%). Intermediate prevalences (1.5–3.5%) are found in Central and Southern Latin America; the Caribbean; Central, Eastern, and Western Europe; sub-Saharan Africa; South and Southeast Asia; as well as Australia. A low prevalence of HCV infection (<1.5%) has been documented in North America, Tropical Latin America, and the Asia Pacific region (Fig. 1.4) [36].

Currently, the published data are inadequate to describe the true disease burden. Nevertheless, it appears that HCV infection is the most common form of viral hepatitis in the European Union. The HCV-related mortality in the USA has significantly increased between 1999 and 2007 from about 3 to about 5 per 100,000 population

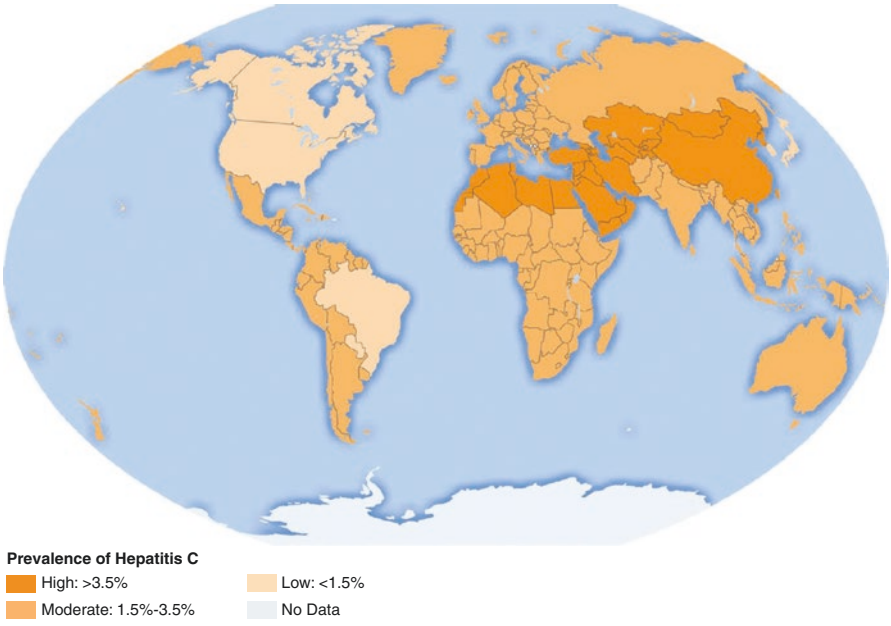

Fig. 1.4 Worldwide prevalence of HCV infection in 2005 [36]

with major risk factors being chronic liver diseases, coinfection with HBV or HIV, as well as alcohol-related conditions [34].

While the currently evolving therapeutic options, especially based on the direct antiviral agents (DAAs), have revolutionized the treatment of patients with chronic hepatitis C of any genotype, unfortunately, there is no vaccine available to date.

1.2.4 HDV Infection

HDV infection is traditionally endemic in central Africa, the Amazon basin, Eastern and Mediterranean Europe, the Middle East, and parts of Asia. It occurs only in association with HBV. Data regarding the global burden of HDV infection are somewhat limited, however [37]. There are eight HDV genotypes; their geographic distribution and the worldwide prevalence of HDV infection are shown in Fig. 1.5 [38]. Longitudinal studies have shown a decrease in HDV prevalence in some endemic regions, such as Italy where in HBV-infected individuals the prevalence of HDV infection has decreased from about 25% in 1983 to 8% in 1997 [39]. Similar trends were observed in Spain, Turkey, and Taiwan, for example. On the other hand, epidemiological studies showed that HDV prevalence in HBV-infected individuals remains in general <10% but is as high as 70% in some developing countries/areas such as Nigeria, Gabon, Iran, Pakistan, India, Tajikistan, and Mongolia as well as the western Brazilian Amazon [38]. Further, in northern Europe and the USA HDV infection still is a healthcare problem. While HDV prevalence is stable in France, it increased in London/England from about 3% in the 1980s to about 9% in 2005 [40]. Also in Germany, after a decrease of anti-HDV prevalence from about 19% in 1992 to about 7% in 1997, since 1999 an increase to about 14% has been documented [41]. This increase is in part caused by migrants from regions with a high HDV prevalence or by still occurring clustered outbreaks, e.g., in Greenland [42] or Mongolia [43].

The treatment of chronic HDV infection remains one of the major challenges in the field of viral hepatitis [38], awaiting the development and implementation of novel therapeutic concepts. Since HDV infection depends on the coexistence of HBV, the well-established HBV vaccination strategies also prevent HDV infection.

1.2.5 HEV Infection

The epidemiology of HEV infection, previously known as waterborne or enterically transmitted non-A, non-B hepatitis, is similar to that of HAV infection. The highest incidence of waterborne human HEV infection (genotypes 1–2) is found in Asia, Africa, the Middle East, and Central America [44]. Waterborne outbreaks have occurred among others in South and Central Asia, tropical East Asia, Africa, and Central America (Fig. 1.6) (http://www.cdc.gov/travel-static/yellowbook/2016/map3-06.pdf).

Apart from fecally contaminated water, sporadic transmission of zoonotic HEV infection (HEV genotypes 3–4) has been demonstrated by consumption of certain

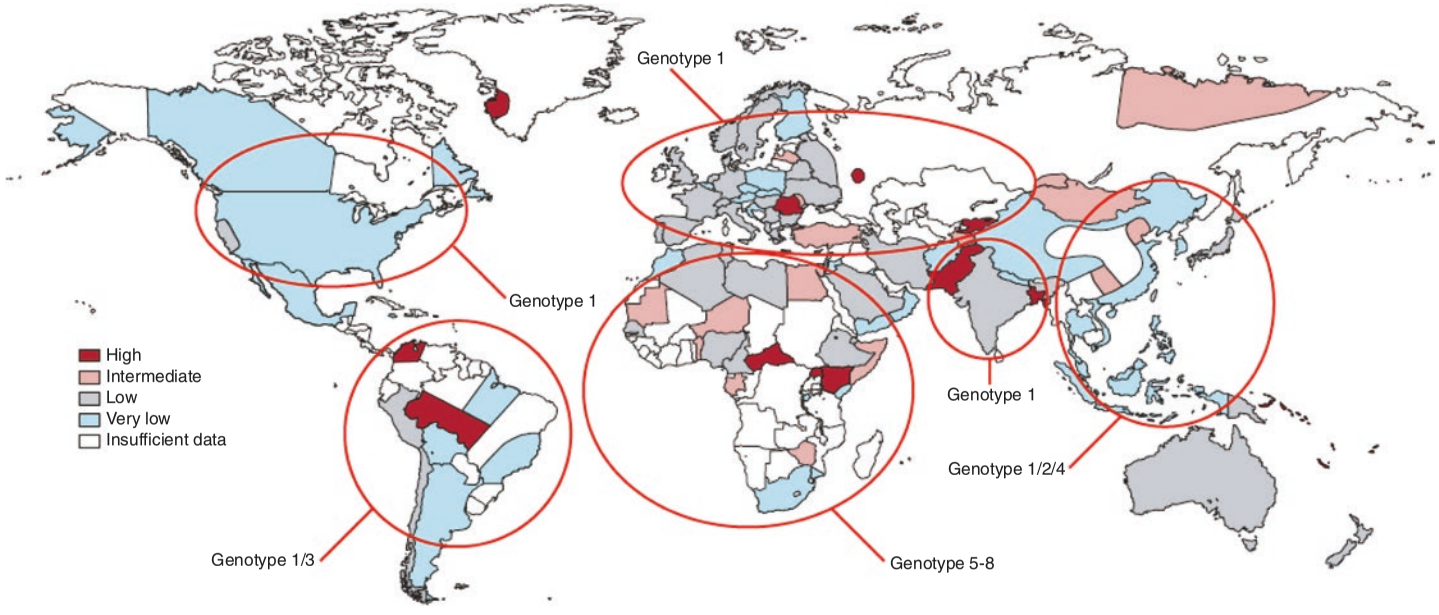

Fig. 1.5 Worldwide prevalence of HDV infection and the geographic distribution of its genotypes [38]

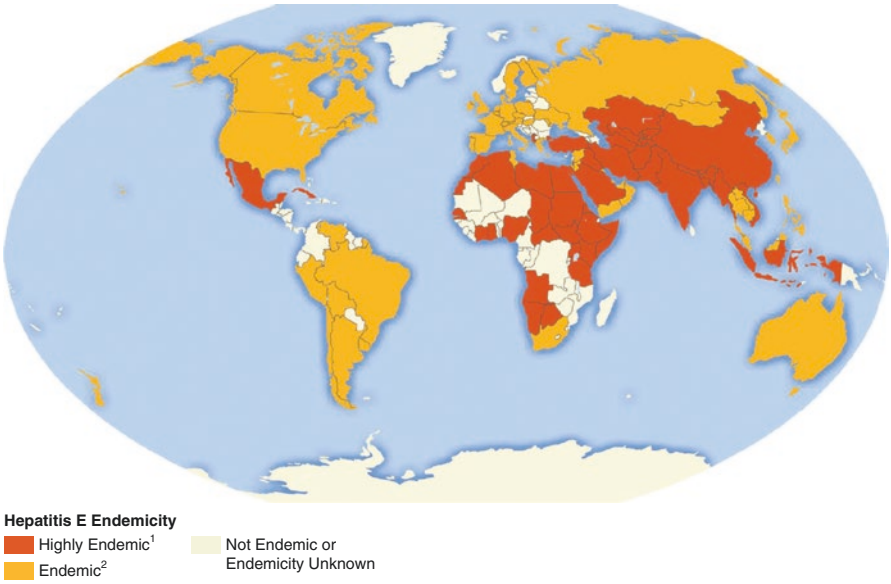

Fig. 1.6 Worldwide distribution of HEV infection (http://cdc.gov/travel-static/yellowbook/2016/map 3-06.pdf)

meats (deer, wild boar, undercooked pig liver), blood transfusions [45], and solid-organ transplantation [22, 23], termed "autochthonous" HEV infection (Fig. 1.7).

The burden of HEV infection in a given population is difficult to estimate. Rates of anti-HEV antibody positivity in the general population are lower in Europe and the USA than in Africa and Asia (30–80%). Nevertheless, in a 1988–1994 survey of adult US citizens [46] anti-HEV prevalence was 21%, lower than anti-HAV (38%) but higher than anti-HBs (8.7%) or anti-HCV (2.0%). While the rates of HEV exposure in the USA appear to be declining [47], a surveillance analysis showed an increase of confirmed HEV cases in Europe between 2005 and 2015 (https://ecdc.europa.eu/en/publications-data/hepatitis-e-eueea-2005-2015).

Overall, the epidemiology of hepatitis E in developed countries is incompletely understood, as is its mechanism of replication, its species or cell specificity, as well as its effective therapy and prevention. Two vaccines with long-term efficacy against HEV genotype 1 and 4 of >95% have been developed and evaluated in Nepal and China [48, 49].

1.3 Clinical Presentation and Management of Acute Viral Hepatitis

1.3.1 HAV Infection

Acute HAV infection (World Health Organization. Global Alert and Response (GAR) Hepatitis A. http://www.who.int/csr/disease/hepatitis/whocdscsredc2007/en/index4.html#estimated) is usually a self-limited disease. After an incubation

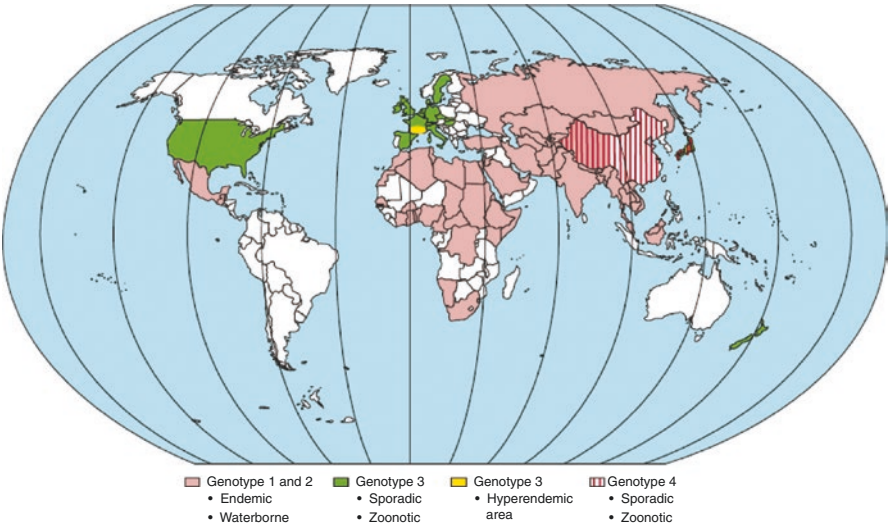

Fig. 1.7 Worldwide distribution of HEV genotypes [22]

period of 15–50 days more than 70% of patients complain of nausea, vomiting, anorexia, fever, and abdominal pain, followed by jaundice and pruritus. Laboratory abnormalities include elevations of serum aminotransferases and bilirubin. Full clinical and biochemical recovery is observed within 2–3 months in 85% of patients and within 6 months in nearly all patients. Extrahepatic manifestations, such as arthralgia, leukocytoclastic vasculitis, glomerulonephritis, and others, can be associated with acute hepatitis A.

Cholestatic and relapsing hepatitis are special clinical presentations of acute hepatitis A (5–10%) that also resolve spontaneously. Rarely, hepatitis A may take a fulminant course or trigger the development of autoimmune hepatitis.

Diagnosis of acute hepatitis A is established by the detection of serum anti-HAV IgM that is followed by anti-HAV IgG that is associated with recovery and immunity against reinfection. Treatment consists of supportive care.

1.3.2 HBV Infection

The incubation period of HBV infection is 45–150 days. The diagnosis of acute HBV infection is based on the detection of HBsAg and IgM antibody to hepatitis B core antigen (anti-HBc) in serum. Treatment depends on the clinical setting [50]. In immunocompetent adults more than 95% will show a spontaneous resolution of HBV infection with seroconversion from HBsAg to anti-HBs and development of IgG anti-HBc. The likelihood of liver failure is <1%. In newborns and children HBsAg will persist in about 90–95% and will be in the vast majority asymptomatic (so-called healthy carrier state). The treatment is mainly supportive. Antiviral treatment (tenofovir, entecavir, or lamivudine) may be considered in patients with a

severe or protracted course of acute hepatitis B until HBsAg has cleared. Importantly, appropriate measures should be taken to prevent infection in all exposed contacts (hepatitis B immunoglobulin, HBsAg vaccine).

1.3.3 HCV Infection

Acute HCV infection is in most cases asymptomatic, very rarely causes liver failure, and usually takes a chronic course. Chronic infection often follows a progressive course over many years or decades and can ultimately result in liver cirrhosis with its complications, including HCC.

1.3.4 HDV Infection

HDV infection is caused by a defective RNA virus and is always associated with HBV infection either as HBV-HDV coinfection or as HDV superinfection of patients with preexisting HBV infection. Acute HBV-HDV coinfection is indistinguishable from classical acute HBV infection and is usually transient and self-limited. Among injection drug users, however, a high incidence of liver failure has been reported. HDV superinfection of chronically HBV-infected individuals may present as severe acute hepatitis in a previously unrecognized HBV carrier or as an exacerbation of a known chronic hepatitis B. HDV infection persists in almost all patients with suppression of HBV infection. The pathogenesis of HDV infection depends on HDV-associated factors, such as HDV genotype and expression of specific HDAg species, on HBV-associated factors, such as HBV genotype and levels of HBV replication, as well as on host factors, such as the host immune response.

1.3.5 HEV Infection

Today, HEV infection is one of the most common yet least diagnosed etiologies of acute viral hepatitis, with distinct differences in transmission and outcomes in resource-rich and resource-limited areas. HEV usually causes a self-limited acute infection with acute hepatic failure developing in only a small proportion of patients. The incubation period ranges from 15 to 60 days. In the vast majority of patients the natural course is asymptomatic or mildly symptomatic. In symptomatic patients jaundice is accompanied with malaise, anorexia, nausea, vomiting, abdominal pain, fever, and hepatomegaly. Less common symptoms are diarrhea, arthralgia, pruritus, and a urticarial rash. Extrahepatic findings may include hematological abnormalities, acute thyroiditis, glomerulonephritis, and a broad spectrum of neurological abnormalities, such as aseptic meningitis, Guillain-Barre syndrome, or peripheral neuropathy. Laboratory findings are elevated serum aminotransferases and bilirubin that normalize usually within 1–6 weeks after the onset of illness.

While the majority of patients clear HEV spontaneously some patients may develop a complicated course, such as acute liver failure, cholestatic hepatitis, or

chronic HEV infection. About 0.5–4% of patients with acute HEV infection develop acute hepatic failure, especially in pregnant women and malnourished individuals or patients with preexisting liver disease, such as HCV-associated liver fibrosis/cirrhosis. Acute hepatic failure carries a high mortality if intensive care and liver transplantation are not available. Cholestatic hepatitis E is characterized by prolonged jaundice (>3 months) that resolves spontaneously with viral clearance and a decrease of anti-HEV IgM and an increase of anti-HEV IgG. Chronic HEV infection is empirically defined as detection of HEV RNA in serum or stool for longer than 6 months. It occurs almost exclusively in immunosuppressed patients (patients with HIV infection and patients after solid-organ or bone marrow transplantation), infected with HEV genotype 3. For most immunocompetent patients the management is supportive while immunocompromised patients may benefit from ribavirin monotherapy [22, 51].

1.4 Global Burden of Acute Viral Hepatitis

Viral hepatitides A–E are associated with significant morbidity and mortality, depending on the global, regional, and national prevalence of these infections and the incidence of the associated liver diseases. In seminal studies, the global burden of disease (GBD) was determined by the systematic analysis of global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010 [52] as well as of disability-adjusted life years (DALYs) in patients with 291 diseases and injuries in 21 geographic regions in 1990, 2005, and 2010 [53]. In these studies deaths from acute hepatitis A, B, C, and E were considered. Recently, the GBD study 2013 (GBD 2013) presented its findings in individuals with disability from 301 acute and chronic diseases and injuries in 188 countries between 1990 and 2013, including hepatitis A, B, C, and E as well as liver cirrhosis and HCC [54].

The global and regional mortality from acute hepatitis A, B, C, and E, as well as from HBV- and HCV-related liver cirrhosis and HCC showed a significant overall increase between 1990 und 2010 (Table 1.2) [52]. By comparison, the age-standardized death rates per 100,000 population decreased for acute hepatitis A but increased for acute hepatitis B, C, and E. During the same time, the deaths from hepatitis B- or C-related liver cirrhosis decreased while deaths from HCC were stable. In a recent follow-up study covering the years 1980–2016 [55] it is apparent that the age-standardized death rate significantly decreased between 2006 and 2016 (Table 1.3).

Table 1.2 Global burden of selected liver diseases: deaths in 1990 and 2010 (modified from [52])

	Deaths (× 1000)			
			Change (%)	
	1990	2010	Total	Std./100,000
Liver disease				
Acute hepatitis A	99	103	4	−25
Acute hepatitis B	69	132	93	29
Acute hepatitis C	8	16	97	26
Acute hepatitis E	35	57	64	36

Table 1.3 Cause-specific deaths and years of life lost [55]

	Deaths (× 1000)		YLL[a] (× 1000)	
		Change (%)		Change (%)
	2016	2006–2016	2016	2006–2016
Liver disease				
Hepatitis	134	−13.3	5497.9	−25.3
Acute hepatitis A	5.2	−45.4	378.9	−49.4
Hepatitis B	100.3	−4.5	3658.4	−12.4
Hepatitis C	2.5	−0.7	77.2	−8.8
Acute hepatitis E	26.1	−30.5	1383.4	−41.3

[a]Years lost to life

Table 1.4 Global burden of selected liver diseases: disability-adjusted life years (DALYs) in 1990 and 2010 (adapted from [53])

	DALYs (× 1000)			
			Change (%)	
	1990	2010	Total	Std./ 100,000
Liver disease				
Acute hepatitis A	4945	4351	−12	−32
Acute hepatitis B	2877	4674	63	25
Acute hepatitis C	276	518	88	44
Acute hepatitis E	2349	3715	58	22

Table 1.5 Disability-adjusted life years (DALYs) and healthy life expectancy (HALE) [56]

	DALYs (× 1000)				
				Change (%)	
	1990	2006	2016	1990–2016	2006–2016
Liver disease					
Hepatitis	9017	7719	5778	−35.9	−25.1
Hepatitis B	4656	4373	3824	−17.9	−12.6
Hepatitis C	88	91	84	−5.3	−7.9
Acute hepatitis E	3000	2405	1420	−52.7	−41.0
Acute hepatitis A	1272	849	451	−64.4	−46.9

The study of Murray et al. [53] analyzed the GBD based on the DALYs. The data show that GBD shifted away from communicable to noncommunicable diseases and from premature death to years lived with disability, except for sub-Saharan Africa where communicable, maternal, neonatal, and nutritional disorders remain the major causes of diseases. While DALYs due to HBV- and HCV-associated liver cirrhosis remained constant between 1990 and 2010, there was an increase in HCC-related DALYs (Table 1.4). In a recent follow-up study DALYs and healthy life expectancy (HALE) [56] show a clear improvement, however (Table 1.5).

The GBD study 2013 [54] shows a clear trend towards a reduction of the prevalence of hepatitis A, B, C, and E, and a reduction or stabilization of the incidence of

Table 1.6 Global burden of selected liver diseases: prevalence between 1990 and 2013 (adapted from [54])

	Prevalent cases (× 1000)	
	2013	Change 1990–2013 (%)
Liver disease		
Hepatitis A	7824	12
Hepatitis B	331,037	−6
Hepatitis C	147,826	16
Hepatitis E	2188	18

HBV- or HCV-related liver cirrhosis between 1990 and 2013. During the same period of time, there was a major increase of HCV-associated HCC, most likely due to the lack of efficient therapeutic strategies for patients with advanced liver fibrosis/cirrhosis in the era of interferon-based treatment regimens (Table 1.6). It is to be expected that the novel, interferon-free therapeutic regimens with DAAs will effectively reduce the incidence of HCV-associated HCCs.

1.5 Summary and Perspectives

Acute viral hepatitis can be caused by the five hepatotropic viruses A–E. These viral infections can be detected by specific serological tests that can be complemented by the identification of the viral DNA or RNA genome in serum. The natural course of acute hepatitis A–E is well characterized and is in the majority of patients self-limited and is managed by supportive care. Exceptions are HDV superinfection of chronically HBV-infected patients as well as HCV infection that usually take a chronic course. In a minority of patients, acute viral hepatitis can result in acute liver failure or a protracted course.

Recent seminal studies showed that the global burden of hepatitis A–E is decreasing worldwide. The coming years are expected to further improve our ability to prevent and to effectively manage patients with acute viral hepatitis A–E, resulting in the control of these global infections and the elimination of their associated morbidities and mortalities.

References

1. Feinstone SM, Kapikian AZ, Purceli RH. Hepatitis A: detection by immune electron microscopy of a viruslike antigen associated with acute illness. Science. 1973;182:1026–8.
2. Martin A, Lemon SM. Hepatitis A virus: from discovery to vaccines. Hepatology. 2006;43:S164–72.
3. Blumberg BS, Alter HJ, Visnich S. A "New" Antigen in Leukemia Sera. JAMA. 1965;191:541–6.
4. Blumberg BS, Gerstley BJ, Hungerford DA, London WT, Sutnick AI. A serum antigen (Australia antigen) in Down's syndrome, leukemia, and hepatitis. Ann Intern Med. 1967;66:924–31.

5. Prince AM. An antigen detected in the blood during the incubation period of serum hepatitis. Proc Natl Acad Sci U S A. 1968;60:814–21.
6. Prince AM. Relation of Australia and SH antigens. Lancet. 1968;2:462–3.
7. Prince AM, Hargrove RL, Szmuness W, Cherubin CE, Fontana VJ, Jeffries GH. Immunologic distinction between infectious and serum hepatitis. N Engl J Med. 1970;282:987–91.
8. Krugman S, Giles JP. Viral hepatitis. New light on an old disease. JAMA. 1970;212:1019–29.
9. Bukh J, Purcell RH, Miller RH. Sequence analysis of the core gene of 14 hepatitis C virus genotypes. Proc Natl Acad Sci U S A. 1994;91:8239–43.
10. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989;244:359–62.
11. Kuo G, Choo QL, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, Miyamura T, et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. Science. 1989;244:362–4.
12. Alter HJ, Purcell RH, Shih JW, Melpolder JC, Houghton M, Choo QL, Kuo G. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. N Engl J Med. 1989;321:1494–500.
13. Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver D. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49:1335–74.
14. Centers for Disease C, Prevention. Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep. 2013;62:362–5.
15. Webster DP, Klenerman P, Dusheiko GM. Hepatitis C. Lancet. 2015;385:1124–35.
16. Rizzetto M, Canese MG, Arico S, Crivelli O, Trepo C, Bonino F, Verme G. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. Gut. 1977;18:997–1003.
17. Rizzetto M, Hoyer B, Canese MG, Shih JW, Purcell RH, Gerin JL. Delta agent: association of delta antigen with hepatitis B surface antigen and RNA in serum of delta-infected chimpanzees. Proc Natl Acad Sci U S A. 1980;77:6124–8.
18. Gupta DN, Smetana HF. The histopathology of viral hepatitis as seen in the Delhi epidemic (1955–56). Indian J Med Res. 1957;45:101–13.
19. Balayan MS, Andjaparidze AG, Savinskaya SS, Ketiladze ES, Braginsky DM, Savinov AP, Poleschuk VF. Evidence for a virus in non-A, non-B hepatitis transmitted via the fecal-oral route. Intervirology. 1983;20:23–31.
20. Kane MA, Bradley DW, Shrestha SM, Maynard JE, Cook EH, Mishra RP, Joshi DD. Epidemic non-A, non-B hepatitis in Nepal. Recovery of a possible etiologic agent and transmission studies in marmosets. JAMA. 1984;252:3140–5.
21. Krawczynski K, Bradley DW. Enterically transmitted non-A, non-B hepatitis: identification of virus-associated antigen in experimentally infected cynomolgus macaques. J Infect Dis. 1989;159:1042–9.
22. Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. N Engl J Med. 2012;367:1237–44.
23. Kamar N, Bendall R, Legrand-Abravanel F, Xia NS, Ijaz S, Izopet J, Dalton HR. Hepatitis E. Lancet. 2012;379:2477–88.
24. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine. 2010;28:6653–7.
25. Wasley A, Fiore A, Bell BP. Hepatitis A in the era of vaccination. Epidemiol Rev. 2006;28:101–11.
26. Wasley A, Samandari T, Bell BP. Incidence of hepatitis A in the United States in the era of vaccination. JAMA. 2005;294:194–201.
27. Advisory Committee on Immunization P, Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep. 2006;55:1–23.
28. Wasley A, Grytdal S, Gallagher K. Centers for disease C, prevention. Surveillance for acute viral hepatitis—United States, 2006. MMWR Surveill Summ. 2008;57:1–24.

29. Daniels D, Grytdal S, Wasley A, Centers for Disease C, Prevention. Surveillance for acute viral hepatitis—United States, 2007. MMWR Surveill Summ. 2009;58:1–27.
30. Klevens RM, Miller JT, Iqbal K, Thomas A, Rizzo EM, Hanson H, Sweet K, et al. The evolving epidemiology of hepatitis a in the United States: incidence and molecular epidemiology from population-based surveillance, 2005–2007. Arch Intern Med. 2010;170:1811–8.
31. Ganem D, Prince AM. Hepatitis B virus infection—natural history and clinical consequences. N Engl J Med. 2004;350:1118–29.
32. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30:2212–9.
33. Wasley A, Kruszon-Moran D, Kuhnert W, Simard EP, Finelli L, McQuillan G, Bell B. The prevalence of hepatitis B virus infection in the United States in the era of vaccination. J Infect Dis. 2010;202:192–201.
34. Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med. 2012;156:271–8.
35. Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, Rodewald LE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the advisory committee on immunization practices (ACIP) part II: immunization of adults. MMWR Recomm Rep. 2006;55:1–33; quiz CE31–34.
36. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013;57:1333–42.
37. Rizzetto M, Ponzetto A, Forzani I. Hepatitis delta virus as a global health problem. Vaccine. 1990;8(Suppl):S10–4; discussion S21–13.
38. Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. Lancet. 2011;378:73–85.
39. Gaeta GB, Stroffolini T, Chiaramonte M, Ascione T, Stornaiuolo G, Lobello S, Sagnelli E, et al. Chronic hepatitis D: a vanishing disease? An Italian multicenter study. Hepatology. 2000;32:824–7.
40. Cross TJ, Rizzi P, Horner M, Jolly A, Hussain MJ, Smith HM, Vergani D, et al. The increasing prevalence of hepatitis delta virus (HDV) infection in South London. J Med Virol. 2008;80:277–82.
41. Wedemeyer H, Heidrich B, Manns MP. Hepatitis D virus infection—not a vanishing disease in Europe! Hepatology. 2007;45:1331–2; author reply 1332–1333
42. Borresen ML, Olsen OR, Ladefoged K, McMahon BJ, Hjuler T, Panum I, Simonetti J, et al. Hepatitis D outbreak among children in a hepatitis B hyper-endemic settlement in Greenland. J Viral Hepat. 2010;17:162–70.
43. Tsatsralt-Od B, Takahashi M, Endo K, Buyankhuu O, Baatarkhuu O, Nishizawa T, Okamoto H. Infection with hepatitis A, B, C, and delta viruses among patients with acute hepatitis in Mongolia. J Med Virol. 2006;78:542–50.
44. Emerson SU, Purcell RH. Running like water—the omnipresence of hepatitis E. N Engl J Med. 2004;351:2367–8.
45. Stramer SL, Moritz ED, Foster GA, Ong E, Linnen JM, Hogema BM, Mak M, et al. Hepatitis E virus: seroprevalence and frequency of viral RNA detection among US blood donors. Transfusion. 2016;56:481–8.
46. Kuniholm MH, Purcell RH, McQuillan GM, Engle RE, Wasley A, Nelson KE. Epidemiology of hepatitis E virus in the United States: results from the third national health and nutrition examination survey, 1988–1994. J Infect Dis. 2009;200:48–56.
47. Teshale EH, Denniston MM, Drobeniuc J, Kamili S, Teo CG, Holmberg SD. Decline in hepatitis E virus antibody prevalence in the United States from 1988–1994 to 2009–2010. J Infect Dis. 2015;211:366–73.
48. Shrestha MP, Scott RM, Joshi DM, Mammen MP Jr, Thapa GB, Thapa N, Myint KS, et al. Safety and efficacy of a recombinant hepatitis E vaccine. N Engl J Med. 2007;356:895–903.

49. Zhu FC, Zhang J, Zhang XF, Zhou C, Wang ZZ, Huang SJ, Wang H, et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. Lancet. 2010;376:895–902.
50. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10:1–98.
51. Peron JM, Abravanel F, Guillaume M, Gerolami R, Nana J, Anty R, Pariente A, et al. Treatment of autochthonous acute hepatitis E with short-term ribavirin: a multicenter retrospective study. Liver Int. 2016;36:328–33.
52. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. Lancet. 2012;380:2095–128.
53. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the global burden of disease study 2010. Lancet. 2012;380:2197–223.
54. Global Burden of Disease Study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the global burden of disease study 2013. Lancet:2015.
55. Collaborators GBDCoD. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the global burden of disease study 2016. Lancet. 2017;390:1151–210.
56. DALYs GBD, Collaborators H. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet. 2017;390:1260–344.