Viral Hepatitis: Acute Hepatitis

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Joop E. Arends
Editors

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Dr. Resat Ozaras dedicates this book to his deceased mother and father

and

Dr. Joop E. Arends dedicates this book to his loving family.

Foreword

Viral hepatitis is a major public health problem in need of an urgent response. It is estimated that the yearly mortality rate deriving from acute and chronic viral hepatitis exceeds 1.3 million, approaching that of tuberculosis, and increasing. This is in contrast to TB, HIV and malaria, all of which show a steady decrease in mortality. Although two-thirds of deaths are attributable to hepatitis B, 30% are caused by complications of chronic hepatitis C, 3% to hepatitis E, which can be responsible for fulminant hepatitis in pregnant women, and only 0.8% to hepatitis A. The aforementioned scenario has induced WHO to develop a strategical set of recommendations in an effort to achieve elimination in most countries by 2030. These include (1) achieving 90% coverage of three-dose HBV vaccination preventing 90% of mother to child transmission; (2) 100% screened blood donations and 90% implementation of reuse-prevention devices; (3) harm reduction interventions in at-risk populations such as PWID; and (4) high frequency of diagnosis and linkage to care for hepatitis C, to insure a 90% reduction of incidence and 65% drop in mortality rate. These targets are rather ambitious and probably achievable in a minority of virtuous countries that have implemented universal HBV vaccination and access to the highly efficacious direct-acting antivirals for HCV cure, as well as "one health" approaches to limit the risk of HAV and HEV infections. However, HAV has re-emerged as a sexually transmitted pathogen in MSM over the past 3 years, calling for the implementation of capillary vaccination programmes in at-risk communities. Moreover, HDV is also a re-emerging pathogen, having re-appeared together with the dramatic new wave of infections in PWID.

In this setting, the five major hepatitis viruses play different roles, both in terms of potentially severe acute onset and ability to persist in the host for an indefinite period of time. This last property has for long been considered restricted to HBV, HDV and HCV, while it is now clear that certain HEV genotypes can cause chronic liver disease and cirrhosis in immune suppressed patients. Acute presentation of viral hepatitis is slowly decreasing globally and this is further compounded by an underestimation of cases due to the large number of asymptomatic, anicteric forms, particularly for hepatitis C. Nonetheless, the focus of this excellent collection of review articles, contributed by outstanding investigators in the field and edited by Drs. Ozaras and Arends, is both timely and appropriate. The chapters are unique in that they provide updated information for all hepatitis viruses in terms of global epidemiology, pathogenesis, molecular virology and clinical presentation. They will be extremely useful

not only to hepatologists who will enjoy the feature of finding practical reference information on acute hepatitis caused by all major viruses, but also to non-specialists who, I am sure, will appreciate the essentially clear style of the e-book, capable of conveying a flawless message both to sophisticated and basic readers. The editors and authors should be unconditionally praised for their effort.

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Mario U. Mondelli

Preface

Although a jaundice-like clinical disease patron was known already for centuries after its early descriptions by Hippocrates (Trepo et al. Liver Int. 2014 Feb;34 Suppl 1:29–37), its causative agents remained quite a mystery. The infectious origin was recognized through its epidemic form as opposed to the more recent serum origin, which was described by Lührman in 1885 who reported patients developing hepatitis after smallpox vaccination. It was not until the last 50 years that true remarkable discoveries have unraveled most of the mysteries regarding viral hepatitis. It started with the discovery of the Australia antigen in 1963 by Blumberg (Blumberg BS, Alter HJ, Visnich A. A 'new' antigen in leukemia sera. JAMA 1965; 191: 541–6).

We now live in an era in which many viral causes for hepatitis have been identified, visualized, extensively studied, and curative or suppressive through antiviral therapy. Although hepatitis A is known to cause outbreaks, especially in poor hygienic circumstances, vaccines are available and societies know how to react with isolation and hygiene measures once an outbreak has been confirmed. Successful worldwide vaccination campaign after childbirth has resulted in a sharp decline in prevalence among children in many countries. In addition, the antiviral and immunomodulatory drugs are capable of suppressing the virus with subsequent slowing down of fibrosis progression and lowering the chances of developing hepatocellular carcinoma. In conjunction with this, the prevalence and comorbidity of hepatitis D has gone down worldwide as well. For hepatitis C it is a true success story following the development of direct-acting antiviral agents (DAAs) in the past years. Viral clearances rates over 95% after short courses of therapy resulted in numerous countries speculating about hepatitis C elimination. Also, the World Health Organization (WHO) has set ambitious goals to reduce the burden of viral hepatitis worldwide. Finally, for hepatitis E, it remains to be seen what the future holds. On the one hand, the epidemic genotypes 1 and 2 should be regarded as hepatitis A. However, genotype 3 in Western countries is probably highly spread within the food chain and thus putting numerous people at risk of acquiring the disease. This is mostly problematic for immunocompromised patients, due to the extensive growth in immune modulatory agents, in a growing population. With only ribavirin at hand, treatment prospects for these patients are not so good in the near future. In addition, new types of hepatitis E, like the recently described rat-type hepatitis E, have been described to cause disease in humans.

Given all these developments in the world of viral hepatitis, it is important to bundle this knowledge and transfer knowledge for educational purposes. That is precisely the aim of this book on acute viral hepatitis. We have asked experts with an outstanding reputation in the field to write chapters on different aspects of acute hepatitis A through E. We hope you enjoy this book and that it gives you new insights that will help you in giving the best care to patients with an acute viral hepatitis.

Istanbul, Turkey — Resat Ozaras
Utrecht, The Netherlands — Joop E. Arends

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Global Epidemiology of Acute Viral Hepatitis A–E

1

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

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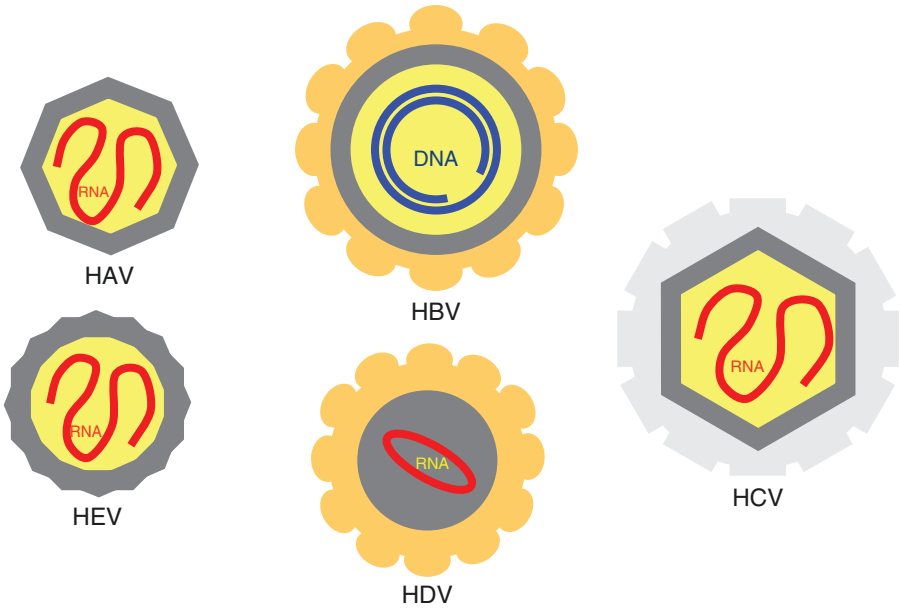

Fig. 1.1 Basic characteristics of hepatitis viruses A–E

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.

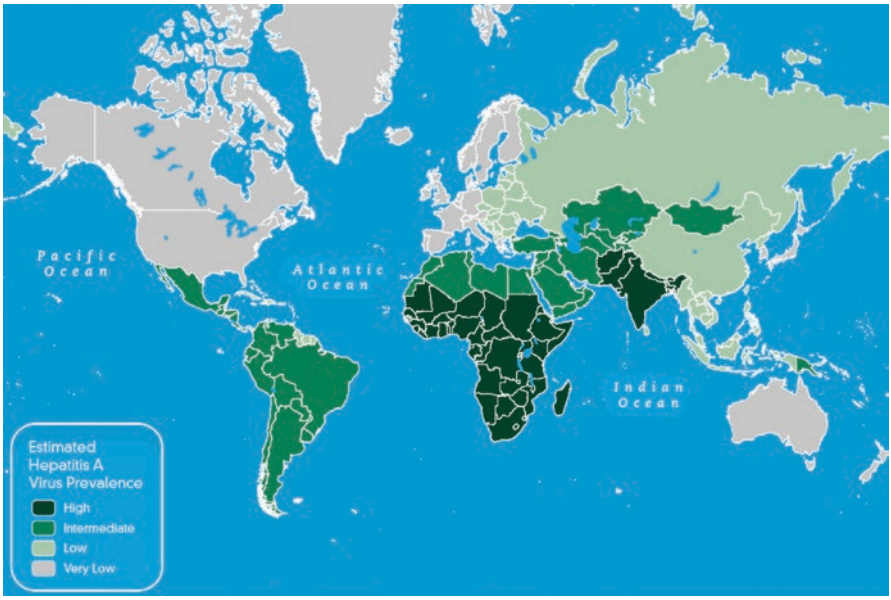

Fig. 1.2 Worldwide prevalence of HAV infection in 2005 [24]

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

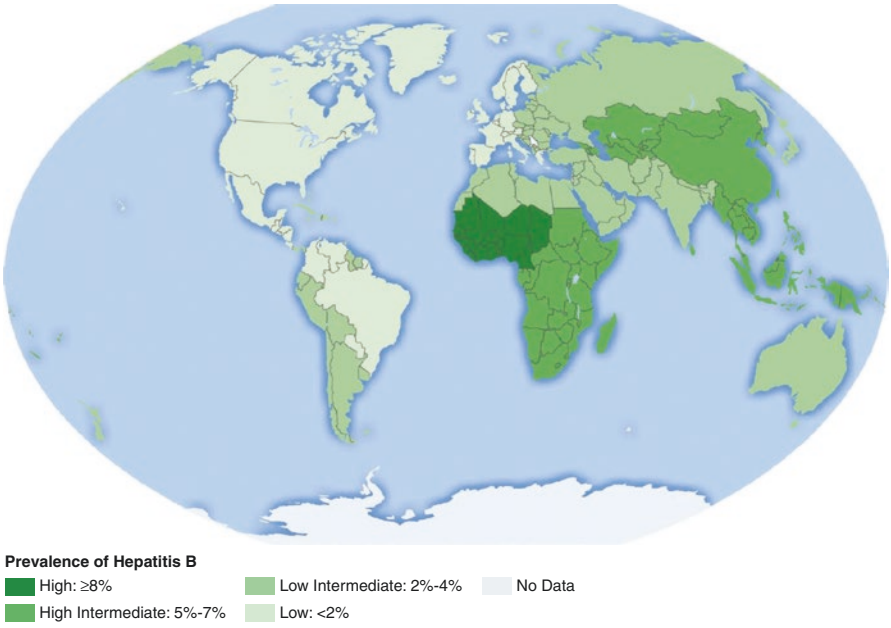

Fig. 1.3 Worldwide prevalence of HBV infection in adults in 2005 [32]

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

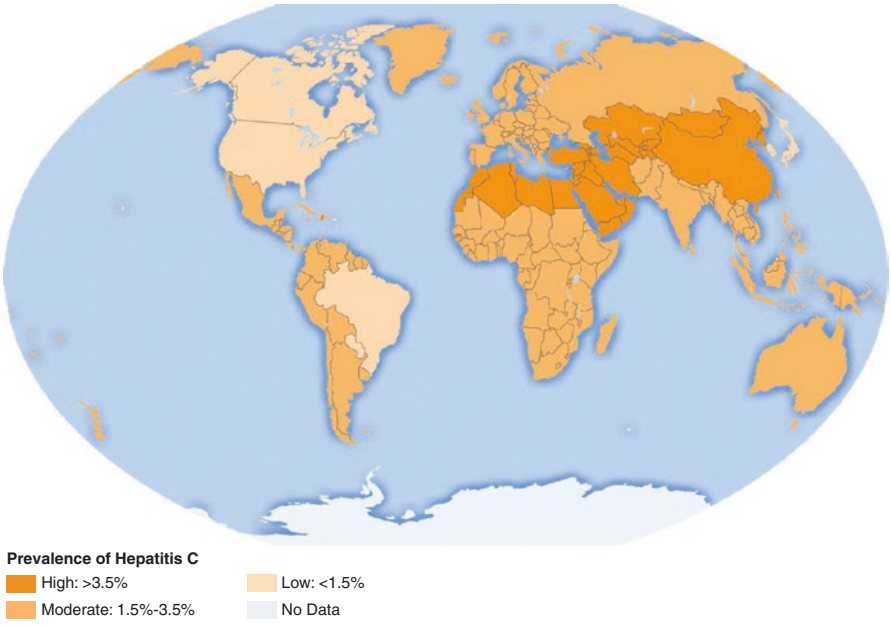

Fig. 1.4 Worldwide prevalence of HCV infection in 2005 [36]

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

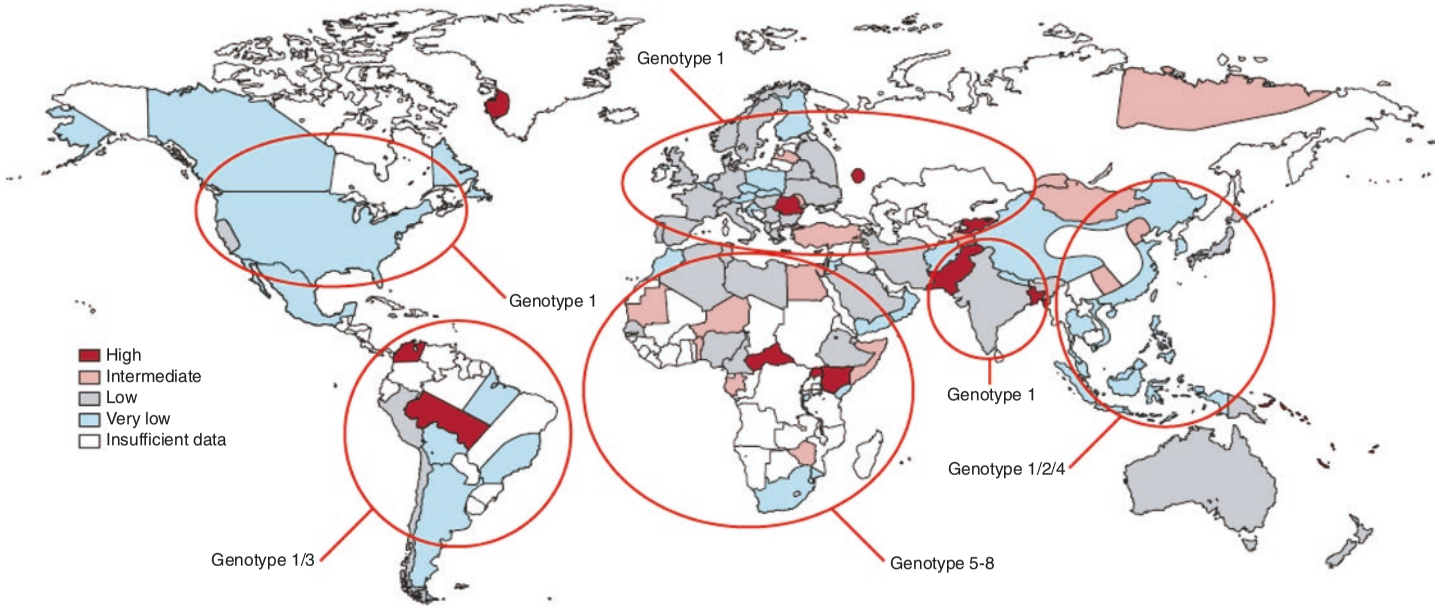

Fig. 1.5 Worldwide prevalence of HDV infection and the geographic distribution of its genotypes [38]

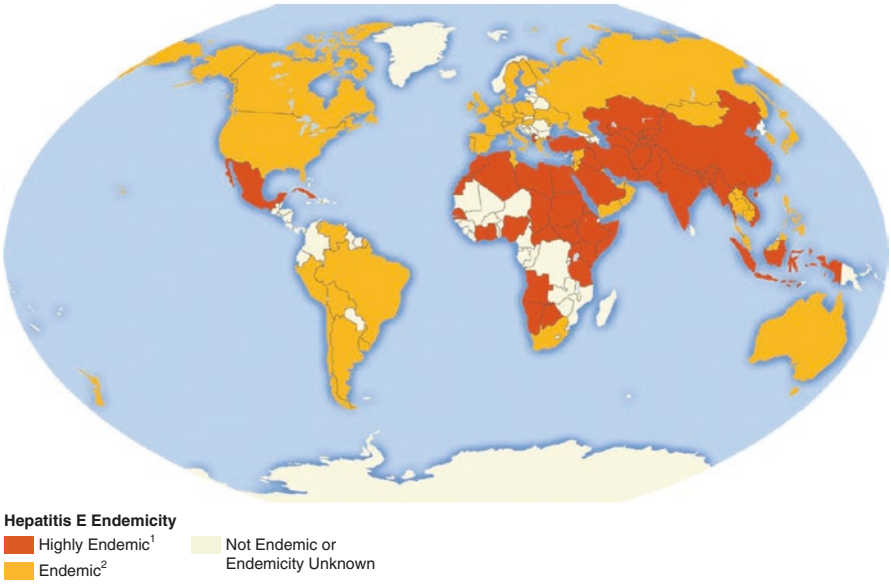

Fig. 1.6 Worldwide distribution of HEV infection (http://cdc.gov/travel-static/yellowbook/2016/map 3-06.pdf)

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

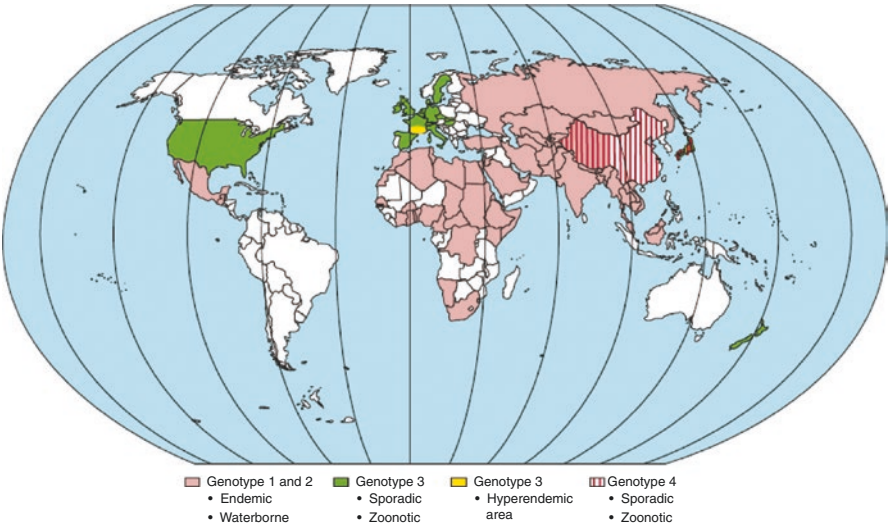

Fig. 1.7 Worldwide distribution of HEV genotypes [22]

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.

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Acute Hepatitis A

2

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2.1 Epidemiology

Hepatitis A virus (HAV) infections occur worldwide and are the most common form of acute viral hepatitis [1]. In 2015 there were 114 million infections [2, 3]. Of those infections approximately 1.4 million were symptomatic and 35,000 of those cases resulted in death—with the majority of infections occurring in low-income societies early in life [2, 3]. In mid- to high-income countries infection typically occurs later in life and is associated with higher rates of morbidity and mortality [4].

The burden of HAV is directly associated with the average age of infection [4]. In communities where HAV infection occurs in early life, infection is often asymptomatic [5, 6]. In communities where there is a lower amount of endemic (proportion of those in the general population with the anti-HAV antibody) incidence, infection is more likely to occur later in life and more likely to cause symptomatic illness [7–9].

2.2 Microbiology

HAV is a non-enveloped single-stranded RNA virus in the family Picornaviridae. Infection occurs via mostly fecal-oral transmission through contaminated water, direct contact (household contact, residential facilities, and daycare centers), and less commonly through sexual contact, IV drug use, and blood transfusions [7, 9–11]. There have not been reports of maternal-fetal transmission. HAV's lack of lipid envelope allows resistance to bile lysis and can survive on human hands and fomites [12]. It can also survive for extended periods of time in fresh and saltwater as well as soil. After being exposed to freezing, detergents, and acids it can remain

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Table 2.1 HAV genotypes and subtypes causing human infection and geographic distributions (Vaughan 2014)

	I	II	III
	— Responsible for most human infections	— Originally identified in France and Sierra Leone but identification of this genotype now rare	— Global distribution but less common than genotype I
A	— Most common in South and North America, Europe, Asia, and Africa	— Believed to have originated in West Africa	— Identified in Asia, Europe, Madagascar, and the USA — More recently IIIA infections reported in Korea, Russia, and Estonia — All reported HAV outbreaks reported in India are IIIA
B	— Most common in the Middle East and South Africa	— Rarely reported	— IIIB circulates mainly in Japan

infectious [13]. HAV is inactivated by chlorine, formalin, and temperatures greater than 85 °C [5].

One serotype and six genotypes of HAV exist. Genotypes I–III infect humans while genotypes IV–VI are found in simians [9]. Genotypes I–III are further divided into subtypes A and B. Most human infectious are caused by IA. Genotype IIIA has been known to cause infections in South Korea and India (see Table 2.1) [9].

Once HAV enters a host it enters the bloodstream through the oropharynx or intestine. Replication then occurs in hepatocytes and GI epithelial cells. Virions arise by surface budding from hepatocytes and are then released in both blood and bile. Virions which are released in the bile are then excreted in feces [14]. HAVCR1, a protein on hepatocyte surface, is the cellular receptor for HAV; 6 amino acid insertion at residue 157 of this protein is associated with more severe disease which allows hepatocytes to bind to HAV more efficiently and increases cytotoxicity of natural killer I cells against HAV cells [9]. Damage to hepatocytes occurs through HAV-specific CD8+ T lymphocytes and natural killer cells and there is no virus-associated cytotoxicity [9]. A brisk host immune response is associated with severe acute hepatitis.

2.3 Clinical Presentation

HAV is a systemic disease leading to a wide variable clinical presentation, especially in different age populations. Symptoms and severity of the disease increase with age. Individuals are infectious 2 weeks prior to most symptom development and remain infectious 1 week after symptoms begin. Nearly all hosts are no longer infectious 2 months after symptoms arise. The disease has an abrupt onset after a

Table 2.2 Clinical presentations and complications in age ranges during infection with acute hepatitis A virus

Age	Clinical presentation	Complications	Fatality
Children	• Asymptomatic, with most having no jaundice (only 7%)	• <10 years of age can require liver transplantation	Fatality 0.3%
Adults	• 70% with jaundice • Prodrome of gastrointestinal symptoms and flu-like symptoms • 80% ill up to 8 weeks	• >40 years of age can require liver transplantation	Fatality 2%
Geriatrics	• Similar to adult presentation with jaundice and prodrome	• >40 years of age can require liver transplantation • >70 years old can develop ascites, prolonged cholestatic features, pancreatitis, and death from hepatic failure	Fatality 2%

15–50-day (28 days average) incubation period where viral excretion is the greatest in feces [5, 11]. No chronic stage of the disease exists.

Younger children are typically asymptomatic with 30% of children under the age of 6 having symptoms and 7% of children under 4 years of age reporting jaundice [15]. However, these children are able to shed the virus for 6 months. In adults, 70% with HAV present with jaundice (Table 2.2). Besides several weeks of jaundice, older adults present with a 1-week prodrome of gastrointestinal and flu-like symptoms and after their several weeks of jaundice undergo a convalescent period lasting for weeks (Table 2.2) [14]. Over 80% of adults are ill for up to 8 weeks. The older the patient at the time of infection the more the risk for acute liver failure.

Symptoms that may be seen include fever, malaise, anorexia, weight loss, arthralgias, headache, pruritus, cough, nausea, vomiting, diarrhea, constipation, abdominal pain, pale clay-colored stools, dark urine, decreased tobacco and/or alcohol use, and in pregnant females preterm labor [5, 6, 16]. Physical examination includes jaundice, posterior cervical lymphadenopathy, bradycardia, hepatomegaly, splenomegaly, abdominal tenderness to palpation, and rarely palpable purpura, encephalopathy, and cardiac rub.

2.4 Evaluation/Diagnosis

The evaluation and diagnosis of acute hepatitis A require both clinical expertise and laboratory data. First, as with any diagnosis a thorough history is needed. This includes determination of any exposure to raw vegetables and fruits such as lettuce, tomatoes, green onions, strawberries, or raspberries that could have possibly caused infection as a host. Further questioning should include possible consumption of undercooked foods as this has caused previous HAV food-borne outbreaks. Inquiring about sanitary water access and recent shellfish consumption is equally important as these are also known as sources of HAV outbreaks. Food-borne or waterborne

outbreaks account for 16% of the cause of HAV cases [16]. Moreover, it is equally important to discuss household or sexual contacts with infected persons or homosexual male activity as 11% and 9.5% of hepatitis A is caused from these [16]. Other high-risk behaviors such as illegal drug use account for 7.3% of infections [16]. Lastly, regarding social history inquiries to determine possible HAV cause through international travel (11%) and daycare center contact is important. Interestingly enough, over 50% of HAV origins cannot be determined [3].

Several differentials exist with the diagnosis of HAV. These include but are not limited to other viral infections such as hepatitis B, C, D, E, and G; human immunodeficiency virus; drugs/medications; toxins; bacterial infections; parasitic infections; autoimmune hepatitis; and systemic lupus erythematosus. Regarding physical examination there are some studies that have suggested that the presence of intra-abdominal lymphadenopathy may predict hepatitis A etiology [11].

Laboratory values will reveal elevated transaminases usually in the thousands (500–5000 U per L) in the acute phase with ALT greater than AST, elevated total and direct bilirubin, and alkaline phosphatase [17]. In HAV, transaminase levels increase prior to elevation of bilirubin. The level of transaminase and bilirubin elevation does not correlate with the severity of disease. Viral serologies for other differentials listed above must also be checked and excluded. For diagnosis of acute HAV, anti-HAV antibody immunoglobulin M in serum should be identified. This has a sensitivity and specificity of over 99% [14]. Liver biopsies are not routinely performed after the 1980s. However, ballooning, focal necrosis, and acidophilic degeneration were much less than liver biopsies from patients with hepatitis B virus yet portal inflammation is similar [14].

2.5 Complications

HAV is self-limiting. Complications are seen usually in adults older than 50 years of age. There is no chronicity of the disease. However, 10–15% of individuals infected with the virus relapse within the first 6 months of infection [7, 18]. Here, liver enzymes return to normal but bilirubin remains elevated in a relapsing or prolonged course. In younger patients, fatality is almost 0% (approximately 0.3%) but increases to 2% in adults over the age of 40 (Table 2.2) [5, 16]. Thus, disease severity is the worst in elderly. In the United States during 2000 HAV led to hospitalization of 31.8% of patients and 15 deaths [16]. Patients who require transplant from acute HAV are at either end of the age spectrum, younger than 10 years of age and older than 40, jaundiced for more than 7 days before onset of encephalopathy, or with increased laboratory markers indicative of synthetic function such as bilirubin or PT/INR (i.e., elevated model for end-stage liver disease labs).

The most severe complication is fulminant hepatic failure which is extremely rare occurring in less than 1% and those who have underlying liver disease. For instance, coinfection of HAV and hepatitis B virus increases one's mortality rate. Yet, fulminant hepatic failure is more likely to be seen with HAV and hepatitis C virus with an estimated fatality of 35% with this coinfection combination [19].

Observed with this is worsening jaundice with encephalopathy. Moreover, another example of coinfection with HAV is increased viral loads in HIV leading to further complications from both viruses [20].

Renal failure has also been documented requiring temporary hemodialysis. This is usually due to acute tubular necrosis which is the most common type of renal injury in HAV [21]. Other rare complications including Guillain-Barre syndrome, autoimmune hemolytic anemia, pericarditis, aplastic anemia, red-cell aphasia, acute pancreatitis, development of diabetes as a long-term complication, cutaneous vasculitis, cryoglobulinemia, myelopathy or transverse myelitis, toxic epidermal necrolysis, mononeuritis, or meningoencephalitis can also occur [11].

Looking at specific populations can also determine complications expected from the virus such as geriatric patients and pregnant patients (Table 2.2). As mentioned above those older than 70 years have increased severity of the disease and fatality. Complications in this population specifically include ascites, prolonged cholestatic features, pancreatitis, and death from fulminant hepatic failure (Table 2.2) [14]. As with any infection during pregnancy complications from HAV can be severe and include premature contractions, placental separation, premature membrane rupture, preterm labor, and increased systemic infection [16]. Patients with autoimmune conditions such as autoimmune hepatitis may be triggered by HAV as well as have decompensation and deterioration of liver histology from the virus [22].

It should be noted that for each case of hepatitis A in a community 11 people are exposed [16]. HAV directly accounts for $433 in pediatric cases and $1817 in adult cases. It costs $1492 for pediatric cases and $2459 in adult indirect costs [23]. Overall, approximately 27 days of work are lost per symptomatic adult with HAV [16].

2.6 Approach to the Patient

First and foremost, sanitary measures must be ensured as the virus is primarily spread fecal-orally. Vaccination, which will be explained in detail in the next section, should be stressed in those traveling and with other liver diseases given the increased risk of exposure, morbidity, and mortality associated with these. For example, in a survey of travelers with destinations to Asia and Latin America in the New York John F Kennedy International Airport only 14% were appropriately vaccinated against HAV [16].

Individuals infected with the virus should be counseled to avoid work, or school until their fever and jaundice resolve. Additionally, they should be told to avoid all alcohol consumption. Most do well with supportive care including rest, nutrition, and avoidance of hepatotoxins (i.e., acetaminophen). Roughly, 30% patients may require hospitalization for dehydration, coagulopathy, encephalopathy, and other signs and symptoms of hepatic decompensation. Unlike hepatitis B and C viruses antivirals are not utilized for acute infection.

2.7 Active Immunization

For many countries, except those with high endemic incidence, HAV vaccine is mandatory if not at least recommended. In 2006 the United States Centers for Disease Control and Prevention recommended mandatory vaccines, two doses 6 months apart, for children aged 12–23 months, allowing avoidance of interference by acquired maternal antibodies, leading to an efficacy of 95% [16]. Additionally, it is recommended to vaccinate any individual who is at increased risk of infection, or increased risks for complications from hepatitis A and anyone wanting immunity towards HAV [10]. Due to high efficacy, there is no recommendation after vaccination to test for response. Since initiating vaccination efforts in the United States there has been an 82% decrease in incidence [1].

Currently several inactive (non-live) vaccines exist include HAVRIX, VAQTA, and TWINRIX (HAV and HBV). These vaccines are given intramuscularly in the deltoid. After both doses most develop 100% lifelong immunity with no need to revaccinate [6, 10]. Individuals who are immunocompromised, such as those with intravenous drug use history, chronic liver disease, or HIV, may have lower likelihood for immunity with vaccination [23]. However, it is still recommended to vaccinate this population. The HAV vaccine is also safe to give with other vaccines including but not limited to yellow fever virus, rabies, cholera, hepatitis B virus, diphtheria, poliovirus, tetanus, and typhoid. In fact, combined hepatitis A and hepatitis B vaccines (i.e., TWINRIX) have superior response rate, easier tolerability rate, safety, and cost compared to monovalent vaccines such as HAVRIX and VAQTA [1]. However, some of these require alternative sites of injection. Side effects of the vaccine include pain, headache, and malaise.

Overall, vaccination should be offered based on risk. For instance, low socioeconomic areas have higher instances of HAV infection in children and thus immunity whereas higher socioeconomic areas have more susceptible adults due to lower rates of childhood infection [4, 10].

2.8 Passive Immunization

Immunity is achieved through immunoglobulin administration which provides transfer of the HAV antibody. This method provides short-term protection for 3–5 months and is not contraindicated in pregnancy of lactation. However, it is not for those individuals with IgA deficiency which it can cause anaphylaxis. This can be used for pre-exposure prophylaxis (PrEP) and some postexposure prophylaxis (PEP).

2.9 Pre-exposure Prophylaxis (PrEP)

As mentioned above all children at the age of 12 months should be vaccinated or at least considered for vaccination against HAV if living in non-endemic countries [4, 9]. Immune globulin (IG) can also be used for pre-exposure prophylaxis. IG or

vaccination should be given to all persons traveling to developing countries that are at high risk for HAV despite where they are staying and the perceived level of sanitation or diligent handwashing methods [23]. Vaccination is usually sufficient if one dose of HAV vaccine is administered prior to travel protecting the individual for up to 2 weeks. In immunocompromised persons such as those with HIV or chronic liver disease immunoglobulin should be co-administered if traveling within 2 weeks. The recommend dosage for immunoglobulin, GamaSTAN S/D, for pre-exposure prophylaxis either as monotherapy or in combination with vaccination is 0.1 mL/kg for 1-month immunity or 0.2 mL/kg for 2-month immunity depending on the length of immunity warranted [15]. This recommendation is about 85% effective for pre-exposure prophylaxis against HAV.

With any vaccination recommendation whether for immunity and pre- or postexposure there needs to be discussion of alternatives for individuals with allergies to the vaccines. For people who are allergic to any component of the HAV vaccine immunoglobulin should be used instead. This is true for infants less than 12 months of age and for individuals who refuse vaccination. This method allows for immunity for up to 2 months—when using 0.2 mL/kg—and can be repeated every 2 months for continued immunity [23].

2.10 Postexposure Prophylaxis

Prophylaxis that is administered after exposure to someone with hepatitis A is known as postexposure prophylaxis (PEP). Either vaccination or immunoglobulin may be used to achieve this. Literature states that HAV vaccines are preferred over IG in immunocompetent individuals as they are cheaper, provide longer protection, and most importantly are equally as effective. Administration of either vaccine or immunoglobulin must occur within 2 weeks of exposure which prevents 70–90% of symptomatic infections [23]. Administration of PEP allows for decreased viral transmission and alleviation of symptoms.

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Acute Hepatitis B

3

Aliye Bastug and Hurrem Bodur

3.1 Historical Background

Hippocrates has described epidemic jaundice in the fourth century. Modern HBV cases emerged after the use of conventional viral vaccines which were containing human serum in 1885 [1]. In the twentieth century, the common use of contaminated insulin needles and syringes by diabetic patients increased the importance of hepatitis [1, 2]. Thereafter, it was considered to be the role of blood and blood products for transmitting HBV. In the year of 1965, Blumberg reported the viral etiology as an Australian antigen which was known as hepatitis B surface antigen (HBsAg), subsequently [3]. In 1971, the complete hepatitis B virion (diameter of 42 nm) termed Dane particle was identified [4]. The complete DNA sequence of HBV was determined after it was molecularly cloned from the sera of the patient in 1979 [5, 6]. Identification of serologic markers also helped to understand the natural course of the infection. Eventually, HBsAg was prepared in quantity and constituted the immunogen in quite effective HBV vaccines.

3.2 Virology and Etiology

HBV is a small (42 nm diameter), double-stranded DNA virus with a circular, 3200 bp sized compact genome which belongs to Hepadnaviridae family. Although HBV is a DNA virus, its replication characteristics are close to retroviruses. It has a RNA intermediate replication with the reverse transcriptase in the cytoplasm. The covalently closed circular DNA (cccDNA) is the stable form of virion which is found in the nucleus and highly resistant to antiviral treatment. The cccDNA

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molecule uses host polymerase II for synthesizing viral transcripts and serves as the substrate for transcription. HBV genome has four overlapping open reading frames (ORFs; S, C, Pol, and X) which encode different antigenic proteins. Viral DNA polymerase (pol) gene covers the big part of the genome sequence. The S gene constitutes with three pieces named as pre-s1, pre-s2, and s, and exists within the pol gene. It is also partially overlapped with C and X genes. S region encodes envelope proteins/surface antigen (HBsAg), C; nucleocapsid hepatitis B core antigen (HBcAg); and hepatitis B "e" antigen (HBeAg) secretory protein, Pol; polymerase gene and X region encodes HBx gene [1]. Three different sized proteins as small (s), middle (pre-s2+ s), and large (pre-s1+ pre-s2 + s) are derived from the envelope gene [7]. HBcAg, a nucleocapsid protein of HBV, has potent immunogenic activity, induces production of anti-HBC when the virus enters the body. HBeAg provides a detectable qualitative indicator for HBV replication and infectivity. The serum containing HBsAg with HBeAg is more infectious than HBeAg-negative or anti-HBe-positive serum and associated with the detectable HBV DNA. It is known that, while the vertical transmission risk from HBsAg- and HBeAg-positive mother is >90%, it is 10–15% from HBeAg negatives [8].

HBV genomic structure has at least 8% genetic diversity for which it was divided into ten genotypes (A–J) [9]. The characteristics of genotype A–D are well known. Geographic distribution of genotypes and subtypes varies; genotype A is predominate in Europe and in some parts of Africa and North America, genotypes B and C in Asia, genotype D in the Middle East and Mediterranean region, etc. [1]. There are also different subgenotypes within the genotypes based on 4% sequence diversity. Genotype C has 16 subgenotypes while genotypes E, G, and H have no subgenotypes [7, 10]. Recombinant virus variants have also been reported as a consequence of dual infections with different HBV genotypes [7, 11]. Some of the clinical characteristics of HBV infections such as rapid progression, severe liver disease, risk of hepatocellular carcinoma (HCC), and/or response to antiviral therapy may be different between genotypes [12, 13]. For example, patients infected with genotypes C and G have higher risk for HCC and severe disease. In addition, pegylated interferon-α (PEG INF-α) treatment is more effective in genotypes A and B than genotype C. Thus, HBeAg seroconversion as a response of PEG INF-α treatment is also slower in genotype C compared with genotypes A and B [13, 14]. Although the geographic distribution varies, genotype D is widespread and causes the majority of acute HBV infection in adults. Genotypes B and C frequently lead to chronic infections after perinatal transmissions in Asia. In addition, HCC and cirrhosis may frequently be seen in infected patients with HBV genotype B since core promoter mutations are mainly seen in this genotype [7]. There are also in vitro studies in the literature that suggest that replicative characteristics and protein expression differ between genotypes. Sozzi et al. identified that genotypes A, C, and D have higher replicative capacity while genotypes B and J have the lowest. They have also reported marked differences in the expression of HBsAg across genotypes which may have an impact on response to the treatment [15].

3.2.1 HBV Genetic Variants

It is important to know the role of genetic variants in disease progression, pathogenesis, and maintenance of infection. Molecular variations occur due to the selected mutations in HBV genome, resulting in unusual serologic profiles among infected patients. One of the important mutations is precore/core promoter mutations which reduce HBeAg expression and augment viral replication. Patients infected with this mutant strain will have a HBeAg-negative phenotype and severe liver disease. Precore mutant HBV infection may also progress more rapidly to acute liver failure, HCC, and/or cirrhosis due to the enhanced viral replication capacity. It is more frequently seen in Asia and in Mediterranean countries.

Escape mutants (named also HBV/α mutant) are the other important variants that occur due to the single-amino acid mutations in envelope gene. This mutation usually exists in "a" determinant of the HB gene. It results in downregulation of HBsAg expression and loss of neutralizing activity by anti-HBs. It may occur after the implementation of hepatitis B immunoglobulin (HBIG) for passive immunization to the transplant patients and newborns of HBV-infected mother. The clinical reflection may be seen as breakthrough infection in transplant patients with escape mutant HBV strain. It is also one of the reasons of intrauterine HBV infection although full immunization schedule was applied properly to the newborn. In addition, serologic diagnosis may become complicated in the existence of infection with HBV/α mutant [7, 8].

3.3 Serologic and Virologic Markers

HBsAg is the first virologic marker, detectable in the serum after HBV exposure within 1–12 weeks (~8–12 weeks). It usually becomes undetectable 4–6 months after the onset of infection. HBeAg occurs concurrently with or soon after HBsAg and reflects the presence of detectable HBV DNA. HBsAg and HBV DNA are the markers of viral replication which are present in serum at the same time as anti-HBc. IgM anti-HBc is the characteristic marker for acute hepatitis B infection which disappears within 6 months after the infection. It may be the only detectable marker in the "window" period of infection. IgG anti-HBc is the other antibody induced against the core antigen which remains lifelong. Anti-HBc can be detectable within the first 1–2 weeks after the appearance of HBsAg. Jaundice and other nonspecific symptoms of acute hepatitis usually resolve after 1–3 months (see Fig. 3.1 for an illustration of a typical course of acute hepatitis B infection with recovery) [1, 16]. Anti-HB positivity occurs by weeks to months in the recovered patients. Disappearance of HBsAg, HBeAg, HBV DNA, and IgM anti-HBc and occurrence of anti-HBe and anti-HBs show immunity. Patients who recovered with enough anti-HB titers usually have lifelong protection against HBV infection unless they have significant immunosuppression.

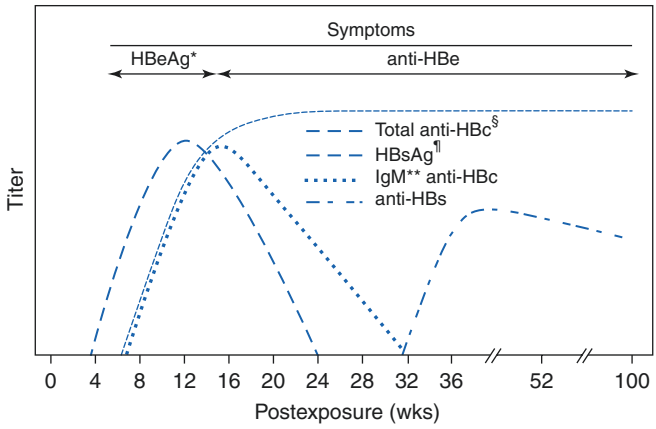

Fig. 3.1 Typical course of acute hepatitis B infection with recovery. § Antibody to hepatitis B core antigen, ¶hepatitis B surface antigen, **immunoglobulin M. *Source*: [16] Centers for Disease Control and Prevention (CDC). Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection. MMWR 2008; 57 (No. RR-8). www.cdc.gov/mmwr

3.4 Epidemiology

HBV infection is a major health problem since more than 2 billion people have been infected with HBV, globally [17]. World Health Organization (WHO) reported that 257 million people have chronic HBV infection (~3,5% of the population) in the world. Most of them are from the areas with high prevalence such as Western Pacific region and Africa. However, the seroprevalence rates are low (<2%) in Western Europe and Central and North America (Fig. 3.2) [18].

The incidence and prevalence of HBV infection and routes of transmission differ due to the local endemicity of the countries. High endemic regions have been defined as the countries where the prevalence of hepatitis B is more than 8%, while low endemic regions have been defined as the areas with the prevalence <2% (Fig. 3.3) [19–21].

According to European Centre for Disease Prevention and Control (ECDC) surveillance data from 24 countries, the incidence rate of acute HBV cases ranged from 0 to 3.2 per 100,000 population in 2014. It was reported as 1.1 cases per 100,000 population from the USA for 2015. It is estimated that the accurate number of acute cases is 6.48 times higher than the reported cases in any year. There have been a significant decrease in the reported number of acute HBV cases in the USA since the early 2000s, which is most probably due to the effect of comprehensive vaccination programs (Fig. 3.4). The incidence rate of acute hepatitis B cases was 2.2 and 1.6 times higher in males according to ECDC and CDC reports, respectively. CDC 2000–2015 surveillance data showed that the incidence rate of reported acute HBV cases was highest among the 30–39-year-old people (2.6 cases/per 100,000 population), while it was lowest among the 0–19-year age group

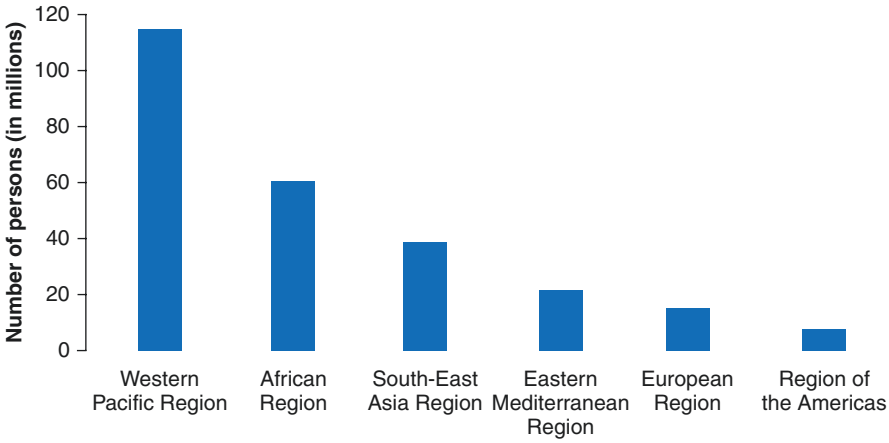

Fig. 3.2 Prevalence of HBV infection globally taken from WHO Global Hepatitis report 2017. Source: WHO Global Hepatitis report, April 2017. http://www.who.int/hepatitis/publications/global -hepatitis-report2017/en/ Accessed November 11, 2017 [18]

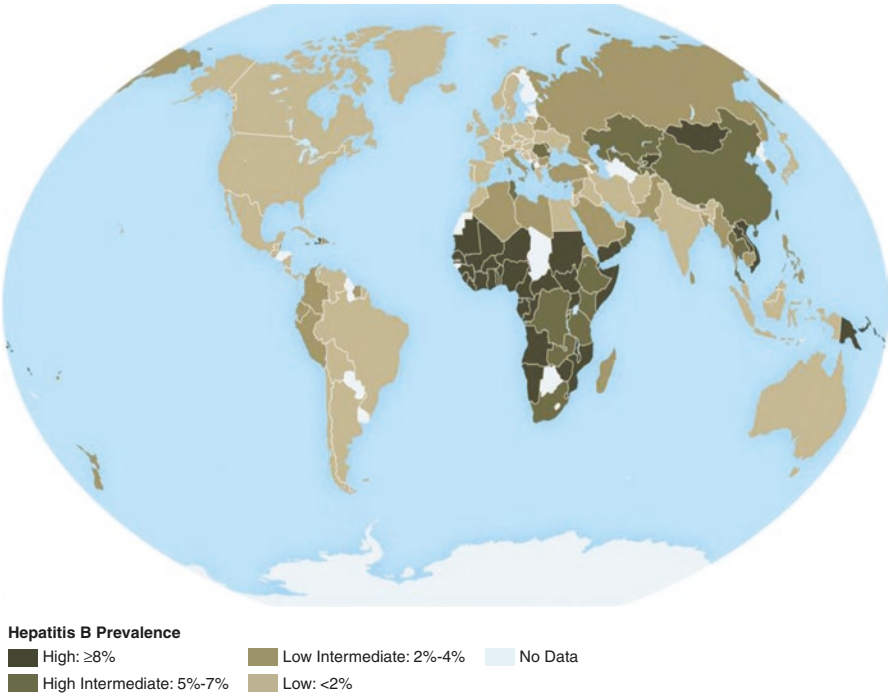

Fig. 3.3 Prevalence of hepatitis B virus infection* [19] (from Centers for Disease Control and Prevention. Infectious Diseases Related to Travel: Hepatitis B. Available at https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/hepatitis-b Accessed November 11, 2017). *Disease data source: [20]. Schweitzer A, Horn J, Mikolajczyk R, Krause G, Ott J. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic rewiev of data published between 1965 and 2013. www.thelancet.com. 2015 Vol 386

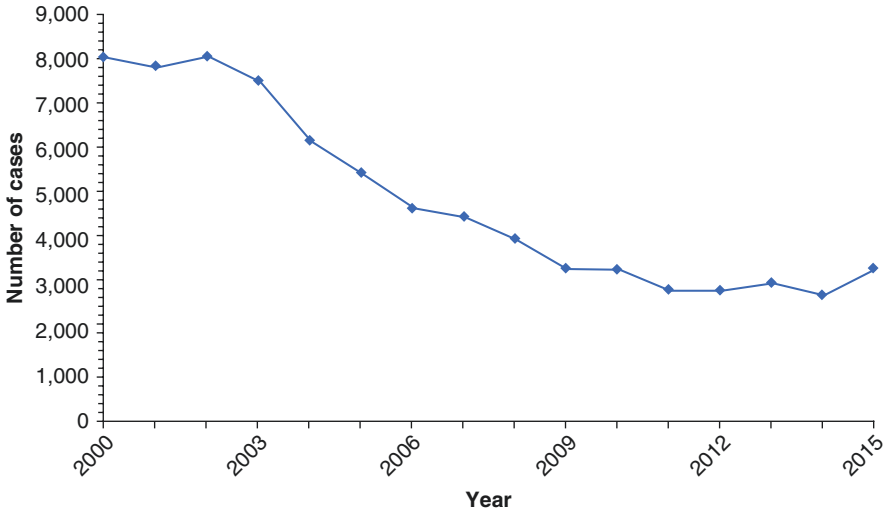

Fig. 3.4 The number of reported acute hepatitis B cases between 2000 and 2015 in the USA. Source: CDC, National Notifiable Diseases Surveillance System https://www.cdc.gov/hepatitis/statistics/2015surveillance/index.htm. Accessed November 15, 2017 [21]

[21, 22]. The new HBV infections in childhood were steadily reduced due to the common use of vaccination programs in infancy, coverage of which reached 84% in 2015, globally [18].

3.5 Transmission Routes

HBV is transmitted by percutaneous or mucosal exposure to infected blood or body fluids (e.g., semen, saliva, vaginal secretions). The transmission risk of HBV is associated with the level of HBVDNA in serum which is much higher in HBeAg-positive patients [23]. Perinatal transmission, unprotected sexual contact with an infected partner, intravenous drug use (due to the use of contaminated needles, syringes, etc.), and sharing contaminated items such as razors or toothbrushes with an infected person are potential routes of HBV transmission. HBV is not found in sweat, urine, and stool [1]. The virus can be viable at contaminated environmental surfaces up to 7 days and is transmissible if the contact occurs with nonintact skin or mucosa [24]. Thus, horizontal transmission may occur with close personal contact probably due to the inapparent contact of infected secretions. The predominant route of transmission varies between regions due to the level of endemicity (Table 3.1). Intravenous drug use and unprotected sexual contact with infected partners are the main transmission routes of infection in low-prevalence areas. Perinatal transmission is the major route of transmission in high-prevalence regions and early childhood infections are common in these areas.

Table 3.1 Global endemicity levels and predominant routes of transmission of HBV

Characteristics	High prevalence	Intermediate	Low prevalence
Carrier rate of HBV	>8%	2–7	<2
Lifetime risk of infection	>60%	20–60%	<20%
Age at infection	Perinatal and early childhood	Childhood	Adult
Predominant route of transmission	Perinatal/maternal	Horizontal	Percutaneous/sexual
Distribution	Sub-Saharan Africa, Southeast Asia, China, Middle East except Israel, Dominican Republic	Southern and eastern Europe, Central Asia, Mediterranean, South and Latin America, Israel	Canada, western Europe, Australia, New Zealand, the USA

3.5.1 People at High Risk for HBV Infections Include

- Infants born from infected mothers
- Household contacts and sexual contacts of HBV-infected persons
- Intravenous drug users, and transgender people
- Homosexual or heterosexual people with multiple partners, and sex workers
- Healthcare workers at risk for occupational exposure to blood or contaminated body fluids
- Hemodialysis patients
- Regular recipients of blood or plasma-derived products (thalassemia, hemophilia, etc.)
- Residents and staff of facilities for disabled people
- Unsafe tattooing, acupuncture, piercing, etc.
- Travelers/migrants to countries with high or intermediate prevalence of HBV infection

The high-risk population should be screened for HBV and vaccinated if they are seronegative. Additionally, all pregnant women should be routinely screened in order to prevent perinatal transmission and new infection, especially in the countries with intermediate or high prevalence [18].

3.6 Pathogenesis and Natural Course of Acute Hepatitis B Virus Infection

Acute hepatitis B is a self-limited infection with the case fatality rate of 0,5–1% [25]. It is characterized with acute inflammation and hepatocellular necrosis. After exposure to the virus, HBV circulates in bloodstream and enters hepatocytes following the binding of pre-S protein of virus to an asialoglycoprotein receptor on the

hepatocyte cells [26]. Following the entrance of virus to hepatocytes and initiation of viral replication, viral proteins are expressed on the hepatocyte which induces immune response. Thus, liver cell injury and rising of the level of HBVDNA in serum occur. Natural killer (NK) cells and $CD4^+$ and $CD8^+$ cytotoxic T lymphocytes (CTL) as components of cellular immunity have an important role to control infection. The clearance of infection is possible with the vigorous $CD4^+$ T cells and CTL response against the antigenic epitopes of HBV, such as anti-HBc. The HBc-specific $CD4^+$ T cells also help in the development of anti-HBs. The noncytopathic response lowers the level of HBV DNA in the early week of infection before the liver damage occurs in self-limiting infections [27, 28].

Following the entrance of the virus, the incubation period of HBV infection ranges from 2 to 24 weeks (60 days on average) due to the viral inoculum size, binding ability of virus to the receptor, and immune response of the patient [23, 29]. The clinical presentation of acute HBV infection varies between infected individuals depending on the viral inoculum, pathogenicity of the strain, age, and immune status of the infected patients [30]. The clinical spectrum of acute HBV infections ranges from asymptomatic infection to symptomatic and fulminant hepatitis. Asymptomatic infection usually occurs in infected infants, children <5 years old, and immunosuppressed adults such as patients with human deficiency virus (HIV), chronic renal failure, and diabetes mellitus. The symptoms of acute hepatitis B infection are usually nonspecific flu-like symptoms such as fatigue, malaise, nausea, vomiting, and right upper quadrant discomfort which may last for 1–5 days [23]. Symptomatic illness is usually seen in adults (30–80%) while the frequency is 10% in infected children <5 years old [1, 31]. It is estimated that only one-third of patients are diagnosed since others have subclinical disease.

3.6.1 The Case Definition of CDC Includes Clinical and Laboratory Criteria as Below (2012 CSTE/CDC Definition) [21]

3.6.1.1 Clinical Criteria

Acute hepatitis is defined as acute disease with:

(a) Onset of nonspecific symptoms such as fever, headache, abdominal pain, nausea, vomiting, diarrhea, malaise, and anorexia in the patients who have negative HBsAg, HBeAg, and/or HBV DNA within 6 months prior to the positive results (acute clinical presentation is not required to meet surveillance criteria)
(b) Icterus or increased serum alanine aminotransferase (ALT) >100 IU/L

3.6.1.2 Laboratory Criteria

- The positive test results for HBsAg and IgM anti-HBc

If the patient is asymptomatic or have mild symptoms, he/she usually will not require medical care. Thus, it will not be possible to detect these cases of acute

hepatitis. After a while, such individuals may be diagnosed as people who have either chronic hepatitis or serologic evidence of HBV exposure (IgG anti-Hbc ± anti-HB positivity).

Acute hepatitis B is characterized by the detection of HBsAg, HBeAg, HBV DNA, and IgM anti-HBc followed by the development of IgG anti-HBc. Patients will not be able to be aware of the illness in the incubation phase after the exposure to the virus. It is possible to detect the HBsAg in the serum during this phase, 2–6 weeks before the occurrence of the symptoms [32]. Viral DNA can also be detectable in this phase, even 1–2 weeks before the appearance of the HBsAg with the highly sensitive molecular assays. Nonspecific symptoms such as fatigue, malaise, nausea, vomiting, flu-like illness, and right upper quadrant discomfort may be seen after the incubation period. After 3–10 days of preicteric phase, icteric period may be seen. However, jaundice has been reported in only about one-third of patients and it usually resolves after 1–3 months. The possibility of the distinguishable jaundice differs according to the age of the patients. It is approximately 10% in <5-year-old children while it may be up to 30–50% in adults. Scleral icterus may be noticeable when the level of bilirubin becomes higher than 2.5–3 mg/dL. Patients with scleral and/or skin icterus and nonspecific symptoms may have a diagnosis of acute hepatitis when they are admitted to the hospital. The darkness in the urine, alcoholic gait, lymphadenopathy, hepatomegaly, and splenomegaly are the other possible detectable symptoms and findings of the disease. In the acute phase of hepatitis B, elevations in the concentrations of serum aminotransferases range from 10× upper limit of normal levels up to 1000–2000 IU/L, occur by 2–6 weeks, and remain high during the symptomatic phase. The level of ALT is typically higher than AST. It is the best indicator for acute liver injury but does not show the severity of the disease. The level of bilirubin varies due to the severity of disease and complications such as cholestasis and hemolysis. A raised prothrombin time and international normalized ratio [INR] are other characteristic findings of severe acute hepatitis B. Resolution of the symptoms and improvement of the value of abnormal laboratory tests vary due to the severity of acute disease. It takes a few days to weeks in the patients with mild clinical presentation. However, it may be longer in patients with severe jaundice who have high level of bilirubin (>10 mg/dL). Among the recovered patients, normalization of serum aminotransferase is usually seen in 1–4 months [1]. Factors influencing the outcome of the acute HBV infection are age, immune status of the patients, and viral characteristics of the virus. There are some other factors which complicated the clinical progress such as coinfection with hepatitis D virus (HDV) or other viral infection, and alcoholic liver disease.

The possible outcomes for the acute HBV infections are the following:

- Recovery from acute infection
- Fulminant hepatitis
- Inactive carriage of HBV
- Chronic HBV infection

Full recovery with the seroconversion to anti-HBs without antiviral treatment is seen in the majority (>95%) of adult patients [33]. Anti-HBs can be detectable after the clearance of HBsAg, HBeAg, IgM anti-HBc, and HBV DNA in the patients who recovered from acute hepatitis B (see Fig. 3.1 and "serologic and virologic markers" for details). If these patients have enough titers of anti-HBs (>10 IU/L) after recovery, they usually have lifelong protection against HBV infection unless they have highly effective immunosuppressive treatment which may lead to reactivation. Fulminant hepatitis is seen in only 0.1–0.5% of HBV-infected patients. HDV coinfection has an impact on fulminant progression of the infection which is detailed separately. The age of the patient who becomes infected also has an important role in the progress of infection. The chronicity risk of the infection is 80–90% when the infection is acquired by perinatal transmission or in infancy (<1 years old) while it is 30–50% in children between 1 and 5 years old. On the contrary, it is only 2–6% for the patients with symptomatic infection [34].

3.7 Different Presentations of Acute HBV Infection

The classic phases of acute HBV include incubation, prodrome, icteric, and resolution phases. However, it may not always present as a typical clinical syndrome. Different clinical presentation may be seen, such as asymptomatic and/or symptomatic icteric acute HBV, coinfection of acute HBV with hepatitis C virus (HCV), HDV or human immunodeficiency virus (HIV), and acute fulminant hepatitis. Anicteric HBV is the most common presentation type and it is more frequently associated with chronicity of infection when it is compared to severe acute icteric hepatitis B. Characteristic findings of severe acute hepatitis B are coagulopathy (high level of prothrombin time and international normalized ratio [INR], >1.5) and/or prolonged disease which was defined as the presence of persistent symptoms or significant jaundice for 4 weeks [33].

3.7.1 Coinfection of Acute HBV with HCV

Coinfection is frequent (high up to 18%) in endemic areas and in intravenous drug users who are in risk of infection for both HBV and HCV [35]. Acute coinfection or superinfection with HCV may result in the suppression of the HBV replication [36]. HBsAg and HBeAg clearance may also be seen in this condition. If both of the viruses continue to replicate, the severity of the infection and the liver damage will be higher than monoinfection [37].

3.7.2 Coinfection of Acute HBV with HDV

HDV is a single-stranded RNA virus in the family of Deltaviridae. It is also named as defective virus since it requires HBsAg to cause an infection. That's why HDV

only has an ability to infect patients who have HBV infection. Coinfection with HDV results in severe acute disease and have low risk for chronicity. HDV superinfection may also have a presentation as acute hepatitis, although it has higher risk for chronicity. In the patients with HDV coinfection, the risk for acute liver failure is 20%, which is higher than monoinfection of acute HBV [38]. It should be thought in the differential diagnosis of severe cases of acute hepatitis B. Additional tests should be applied to have an accurate diagnose. In addition to positivity of IgM anti-HBc, IgM anti-delta (IgM anti-HDV) and IgG anti-HDV may be detected in the majority of acute HBV-HDV-coinfected cases. Hepatitis delta antigen (HDAg) is detectable in only 25% of the serum of these cases. HDV-RNA detection by polymerase chain reaction (PCR) is another test to use for diagnosis [34]. The patients who have HBV-HDV coinfection usually do not need antiviral therapy since the clinical picture is generally self-limited. They should be closely monitored in order to decrease the risk of fulminant hepatitis.

3.7.3 Coinfection of Acute HBV with HIV

The endemicity level of the infection and the presence of similar transmission routes have an impact on the possibility of dual infection. It is estimated that 4–10% of HIV-positive patients have detectable HBsAg level in the USA [38]. Coinfected patients with HBV and HIV have higher risk for cirrhosis and liver-related mortality than monoinfeced ones [39, 40]. HCC risk is also higher in the dual-infected patients with lower CD4 count [41].

3.7.4 Fulminant Hepatitis B

Fulminant HBV infection is a rare clinical syndrome. It is seen in only 0.1–0.5% of HBV-infected patients. It constitutes less than 10% of all caused fulminant hepatitis cases in the USA [42]. Although the pathogenesis of acute liver failure (ALF) is not clear, it is thought that it may be due to the impact of exuberant immune response to the virus. ALF is diagnosed in the patients who had abrupt loss of liver functions and hepatocyte cell necrosis without known liver disease previously. The risk for ALF is higher in older age and in the patients with hepatitis D and/or hepatitis C coinfection. Clinical progress and laboratory deterioration are more rapid in these cases. Coagulopathy and encephalopathy are the main characteristic signs of liver failure. The most frequent reason of ALF is toxicity of medications such as acetaminophen or some other drugs metabolized by liver in the USA [43]. Acute hepatitis B is the second frequent cause of ALF in the 5–10% of the cases. Patients with severe acute hepatitis B should be monitored closely for mental alterations and laboratory parameters such as hemostasis parameters, and level of ammonia, aminotransferases, albumin, and prothrombin time. One of the best indicators for the prognosis is prothrombin time (PT). High levels of PT and clinical/laboratory signs of hepatic encephalopathy indicate fulminant hepatic failure.

Fulminant hepatitis is categorized according to the interval from the beginning of the jaundice to the onset of the hepatic encephalopathy as follows [44]:

1. Hyperacute, <7 days
2. Acute, 7–28 days
3. Subacute, >28 days and <26 weeks

The possible mechanism responsible for the pathogenesis of fulminant hepatitis is vigorous immune response against the virus. In some of the cases of fulminant hepatitis, HBsAg cannot be detected due to the early clearance, whereas IgM anti-HBc and HBV DNA are still positive. Lots of viral and host factors may have a role for fulminant progression such as immunosuppressive treatment and/or conditions, infection with precore mutants of HBV (HBeAg-negative infection), and coinfection with HDV, HCV, HIV, etc.

Thrombocytopenia and hypotension on admission are the poor prognostic factors. The regeneration capacity of the liver correlates with the replication ability of the hepatocytes and it has an important role in the prognosis of fulminant hepatitis. This is why the prognosis is poorer in older age and patients with preexisting liver disease. The mortality risk is extremely high in the patients with ALF, if the liver transplantation is not applied. For this reason, patients in risk of fulminant progression should be sent to liver transplant center as early as possible to evaluate the need of transplantation. The liver transplantation is indicated if the patient has severe hepatic encephalopathy and high level of INR >6.5 or has three of the following criteria:

1. The age of the patient <11 or >40 years old
2. The level of serum bilirubin >300 μmoL/L
3. INR >3.5.
4. The time from the occurrence of the symptoms to the presence of coma >7 days

The indications for liver transplantation should be evaluated carefully to avoid unnecessary transplantation. It is indicated if the patients has the mortality higher than 80% without transplantation. Uncontrolled acquired immunodeficiency syndrome, severe sepsis, and irreversible brain damage are the contraindications for transplantations [30]. As a consequence, clinicians should be aware of the signs of fulminant hepatitis, indications, and contraindications of liver transplantation for managing patients properly in time [1].

3.8 Prevention Measures to Combat the Chronicity of Acute Hepatitis B

Persistent ALT elevation for more than 6 months indicates progression to chronic infection. The risk for chronicity is highest in infants 80–90% while it is <5% in adults [1]. It is possible to prevent infant infections by active–passive vaccination of

newborns and antiviral treatment of the patients with high viral load in the last trimester of pregnancy [30]. The incidence of acute hepatitis B is decreased in most countries, after the implementation of vaccination schedules to the newborns and the individuals with high risk [18].

3.9 Extrahepatic Manifestations of Hepatitis B

Extrahepatic manifestations of HBV occur due to the effect of immunocomplex formation with HBsAg or HBeAg. Serum sickness-like illness, membranous glomerulonephritis (MGN), polyarteritis nodosa (PAN), and Gianotti- Crosti syndrome are some of the examples of these manifestations. Acute hepatitis B patients may be presented with the symptoms of fever, arthralgias, polyarthritis, and skin rash as a serum sickness-like illness. Macular, maculopapular, erythematous, petechial, or urticarial type rash may be seen. PAN is an occasional complication of chronic HBV infection. Glomerular disease and nephrotic syndrome with proteinuria are the rare complications of HBV infection. Current therapy options for dealing with these conditions include antiviral therapy for controlling HBV replication. Intravenous ımmunoglobulin (IVIG) and plasma exchange are other treatment options which may be beneficial [30, 45, 46].

3.10 Diagnosis and Differential Diagnosis

The most frequent symptoms are fatigue, malaise, nausea, vomiting, and abdominal pain in the patients with acute symptomatic hepatitis. Scleral icterus, jaundice of skin, darkening in the color of urine, and clay-colored stool may be present in the complaints of the patients [34]. There are different causes of acute hepatitis such as toxins, medications, and other viruses (hepatitis A, C, D, E; cytomegalovirus; herpes simplex virus; adenovirus; coxsackievirus; etc.). The similar clinical symptoms and findings may be seen in acute flare on chronic liver disease and acute presentation of autoimmune hepatitis, too. As a consequence, acute hepatitis B cannot be diagnosed on the basis of clinical symptoms and findings alone. When the patient is evaluated with the signs and symptoms of acute hepatitis, all possible causes (medications, toxins, risky behaviors, contact exposure to any hepatitis patients, etc.) should be asked to the patient. Then, serologic tests are required for definitive diagnose in addition to biochemical laboratory test. The detection of HBs Ag with IgM anti-HBc in the serum indicates the diagnosis of acute hepatitis. The detectable IgM anti-HBc may be the only marker in the “window” period of infection between the disappearance of HBsAg and the occurrence of anti-HBs. It is important for distinguishing acute infection from chronic HBV, in which IgM anti-HBc is undetectable. However, IgM anti-Hbc may not resolve up to 2 years after acute infections in some cases and also may be detectable during acute-on-chronic HBV infection. HBe Ag and HBV DNA are the other markers detectable in the replicative phase of infection. HBs Ag is the first serologic marker to occur in acute HBV infection which may be

detected by enzyme-linked immunoassay (ELISA) or radioimmunoassay (RIA) methods [1]. The hybridization assays and gene amplification techniques such as branched DNA assay and nucleic acid amplification tests may be used to detect and quantify viral load (HBV DNA). PCR-based amplification assays are commercially available and constitute the most useful tests with high sensitivity (5–10 IU/mL) and large range (10^0–10^9 IU/mL) [8]. Anti-HB positivity occurs by weeks to months in the recovered patients after the disappearance of HBsAg, HBeAg, HBV DNA, and IgM anti-HBc. The presence of anti-HBs in the serum shows immunity which may be due to the vaccination or resolved infection. Differential diagnosis can be made by assessing IgG anti-HBc which is found positive in resolved infection, while it is negative in vaccinated individuals.

3.11 Management of Acute Hepatitis

Since the majority of the adult patients with acute hepatitis B are healing without antiviral treatment, routine antiviral treatment is not suggested in this setting. Supportive therapy is the principle for dealing with the acute hepatitis patient. If the patient is using any medications metabolized by liver, it should be minimalized. Spontaneous seroconversion to anti-HBs is seen in the majority of the adult patients (>95%) with acute hepatitis B. The main indication for antiviral treatment is preventing progression to the fulminant hepatitis in the severe acute hepatitis B cases with increased INR and protracted jaundice >4 weeks. It is also possible to lower the risk of chronicity in these patients with antiviral treatment. Early antiviral treatment with highly potent antivirals, such as tenofovir (TDF) and entecavir (ETV), can prevent the development of acute liver failure and the need for liver transplantation consequently. The use of lamivudine (LAM) treatment is also supported in this indication. The use of antiviral therapy does not increase the possibility of the development of chronic hepatitis. Antiviral treatment in the cases of fulminant hepatitis should be given at least 3 months after the seroconversion of HBsAg to anti-HBs and 12 months after HBeAg seroconversion if HBsAg loss does not occur [33, 47, 48].

3.12 Control Measures and Prophylaxis

The HBV vaccine is safe, immunogenic, and 95% effective in preventing HBV infections. It has been available since 1982. The extensive use of universal vaccination programs is the best way for dealing with HBV infections and its complications such as hepatocellular carcinoma (HCC). WHO reported that 179 of its member states have been using HBV vaccine in their routine infancy immunization schedule by 2011 [49].

In May 2016, the World Health Assembly performed global strategy for eliminating HBV infection by 2030. To achieve this goal, the countries should reduce the incidence of HBV infection by 90% and reduce mortality by 65% in 2030 comparing with the 2015 baseline. The implementation of national vaccination programs in

risk groups of hepatitis B, especially to the newborns of infected mothers, is essential for eliminating this infection.

The following five strategic prevention and treatment interventions were determined in this global HBV elimination program [18]:

(a) Immunization against hepatitis B
(b) Prevention of perinatal transmission by routine screening of all pregnant women for HBsAg and applying postexposure immunoprophylaxis to the infants of women with HBsAg positive or unknown
(c) Developing safe blood and injection interventions
(d) Prevention of transmission of HBV among intravenous drug users
(e) Testing risk groups for HBV and applying efficient treatment

3.12.1 Active Immunization for Preventing HBV Infection

There are both plasma-derived and recombinant types of vaccine available for immunization against HBV. Both of them are safe, effective, and immunogenic. The first developed and the cheaper one is human plasma-derived vaccine which is prepared from the plasmas of HBV-infected patients. Although it is widely used in India and some of Asian countries, it is no longer available in Europe and North America. The recombinant HBV vaccines are used widely in most of the countries. In the recombinant technologies, the gene of HBsAg has been inserted into the mammalian cells or *Saccharomyces cerevisiae* yeast for synthesizing HBsAg used in vaccines [34]. There are many different types of recombinant HBV vaccine available commercially. Single-dose formulations do not contain thiomersal as a preservative. Recombivax-HB (10 μg HBsAg/mL) and Engerix-B (20 μg HBsAg/mL) are widely used in all age groups. There are also combination vaccines such as Twinrix, Pediarix, and Comvax for use to protect against more than one infectious agent. Pediarix and Comvax are the vaccines which should only be utilized in children. The immunization program consists of minimum of three doses of hepatitis B vaccine administered intramuscularly in deltoid muscle at 0 and 1–6 months, for individuals at high risk for transmission.

The four-dose immunization schedule at 0, 1, and 2–12 months is also approved for vaccination with similar response rate to three-dose schedule [50]. The different types of HBV vaccines, recommended dosage, and immunization schedule are summarized in Table 3.2. Adverse reactions such as malaise, headache, myalgia, and low-grade fever are rarely seen (<1%) after immunization. The vaccine is safe and it can also be used during pregnancy.

3.12.2 The Vaccine Efficacy

HBV vaccines do not give rise to HBV infection since it doesn't contain live organism. It is safe, recombinant DNA vaccine, and highly effective to prevent infection.

Table 3.2 Recommended dosages of hepatitis B vaccine according to age, vaccine type, and immune status of the individuals

	Age	Dose/volume	Schedule
Single-dose vaccines[a]			
Recombivax-HB	<20 years	5 μg/0.5 mL	0, 1, 6 months
	>20 years	10 μg/1 mL	0, 1, 6 months
	Diabetes 19–59 years	10 μg/1 mL	0, 1, 6 months
	For dialysis and other immunosuppressed adults	40 μg/1 mL (special formulation)	0, 1, 6 months
Engerix-B	<20 years	10 μg/0.5 mL	0, 1, 6 months
	>20 years	20 μg/1 mL	0, 1, 6 months
	Diabetes 19–59 years	20 μg/1 mL	0, 1, 6 months
	For dialysis and other immunosuppressed adults	2 doses × 20 μg/1 mL (a total of 40 μg)	0, 1, 2, 6 months
Combination vaccines			
Twinrix (contains HAV and HBV)	>18 years	20 μg HBsAg/1 mL	0, 1, 6 months
Pediarix (HBV, diphtheria, tetanus, pertussis, and polio viruses)	6 weeks–6 years	10 μg HBsAg/0.5 mL	2, 4, 6 months
Comvax (HBV and *Haemophilus influenzae* type b)	6wk–4 yr	5 μg HBsAg/0.5 mL	2, 4, 12–15mo

HAV hepatitis A virus, *HBV* hepatitis B virus, *HBsAg* hepatitis B surface antigen
[a]See package insert for available other schedules of single-dose vaccines

After vaccination, a desired and protective level of anti-HBs is defined as ≥10 IU/L. Although the efficacy of the vaccine is >95% in healthy individuals, it is lower in immunosuppressed patients.

3.12.2.1 Suboptimal Response to HBV Vaccination May Be Seen in the Following Groups [51, 52]

- Preterm infants and elderly population
- Obese individuals, smokers, and alcoholics
- Those with diabetes mellitus (DM) and/or cancer
- Patients with ongoing hemodialysis due to the chronic renal failure
- People with chronic hepatitis C infection with or without cirrhosis
- Infected patients with HIV (response rate to vaccination is 40–53%) [53]

The first HBV vaccination dose of preterm infants (<1800 g or <34 weeks of gestational age) of HBsAg-negative mothers is recommended to be postponed by 1 month of age to increase the immunogenicity of vaccine [54]. To improve the efficacy of the HBV vaccine in patients with suboptimal response, increasing vaccine dosage and frequency, improving adjuvants, or applying vaccine by

intradermal route may be thought in the options [55]. Although it is not recommended to test routinely anti-HB level after vaccination, it may be tested in low responders especially with high-risk groups [52]. Testing for anti-HB titers should be performed 1–2 months after the immunization schedule is completed in these individuals. If the immune response is inadequate (anti-HBs <10 IU/L) after primary vaccine series, applying revaccination series with three doses is recommended. If the individual is still a nonresponder after two series of vaccination, he/she should be administered HBIG in any risky exposure to HBV.

3.12.3 Indications for HBV Immunization

3.12.3.1 Pre-exposure Immunization

Pre-exposure immunization should be offered to the patients at high risk who are listed previously in the text. In addition, patients with chronic liver disease (HCV, etc.) and renal failure should also be vaccinated against HBV. Additionally, Advisory Committee on Immunization Practices (ACIP) updated their guidelines in 2011 and recommended that 19–59-year-old patients with diabetes mellitus (DM) should also be vaccinated for HBV if they are nonimmunized. It is also recommended that >60-year-old patients with DM should be thought for HBV vaccination by clinician after evaluating the possibility of response to the vaccine and the patients' risk [56].

3.12.3.2 Postexposure Immunization

Vaccination is recommended as early as possible to the babies of HBV-infected mothers to prevent perinatal transmission. Hepatitis B vaccine should be applied within 12–24 h after delivery and it should be followed by vaccine doses at 1–6 months. In addition to vaccination, hepatitis B immunoglobulin (HBIG) should also be applied a total of 30 IU dose at birth. Although it has no impact on intrauterine transmission risk, these immunization strategies are 90–95% effective in preventing perinatal transmission [57, 58]. It is possible to reduce the transmission risk from 90% to <10% with the implementation of HBIG and HBV vaccine at birth. For reducing vertical transmission risk, giving antiviral prophylaxis to the pregnant women with high viral load (>200,000 IU/mL) during the third trimester is also recommended. Although tenofovir is preferred for antiviral prophylaxis, lamivudine and telbivudine may also be used in this setting [33].

Postexposure prophylaxis is also recommended to the individuals who are exposed to HBsAg-positive blood or body fluid (percutaneous or mucosal exposure); 0.06 mL/kg HBIG should be administered as soon as possible (preferably within 12–24 h) with the full-dose HBV vaccination series. The first dose of vaccine and HBIG should be administered at the same time in a different site. If the individual is a nonresponder to the vaccination, he/she should be administered HBIG and vaccinated whenever the HBV exposure occurs. The implementation of two doses of HBIG 1 month apart is recommended to the individual who had no response although the two series of vaccine was given before [59].

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Acute Hepatitis C

4

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4.1 Epidemiology

4.1.1 Incidence

Hepatitis C virus (HCV) infections remain one of the main causes of chronic liver disease worldwide [1]. According to the last World Health Organization (WHO) Hepatitis Report, in 2015 71 million people worldwide are living with chronic hepatitis C (Fig. 4.1). Although several studies suggest a global decline in the incidence of HCV infections since the second half of the twentieth century, a rise again was noted in the early twenty-first century with still 1.75 million new HCV infections occurring worldwide in 2015 [2]. For example, a decline in acute hepatitis C was described in the USA until the first years of the 2000s [3]. A great contribution to this trend surely came from improvements in injection safety, which has led to a reduction of infections transmitted through unsafe medical procedures [4, 5]. Despite this, during recent years this trend of declining incidence seems to be changing in many countries, related to emerging prevalent routes of transmission (i.e., iv drug use) and improved case detection.

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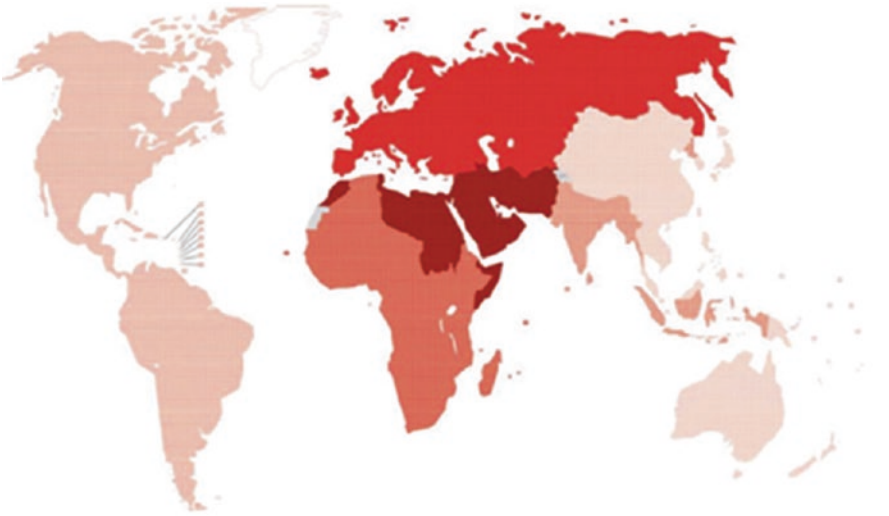

Incidence of HCV infection

		Incidence rate (per 100 000)		Total number (000)	
WHO region	Map key	Best estimate	Uncertainty interval	Best estimate	Uncertainty interval
African Region		31.0	22.5-54.4	309	222–544
Region of the Americas		6.4	5.9–7.0	63	59–69
Eastern Mediterranean Region		62.5	55.6–65.2	409	363–426
European Region		61.8	50.3–66.0	565	460–603
South-East Asia Region		14.8	12.5–26.9	287	243–524
Western Pacific Region		6.0	5.6–6.6	111	104–124
Global		23.7	21.3–28.7	1751	1572–2120

Fig. 4.1 Global incidence and prevalence of hepatitis C. Reproduced with permission of the WHO (Global Hepatitis report 2017)

In the USA 3.5 million people are estimated to be living with hepatitis C. The most common risk factor for transmission, responsible for the majority of infected cases, is injection drug use (IDU). Since the late 1980s, acute hepatitis C incidence has declined because of instituted risk-reduction practices among people who injected drugs (PWIDU) [6]. However, in recent years, from 2010 onwards a 2.9-fold rise in acute HCV infections was noted in the USA which is mainly attributed to an increase in IDU in young people, particular in rural area. For example, a large increase in incidence was observed East of the Mississippi river, especially in Kentucky, Tennessee, Virginia, and West Virginia [7]. A similar situation was reported for Massachusetts, Wisconsin, and New York state. Transmission among men having sex with men (MSM) has also become relevant, especially between those coinfected with HIV [8].

Between 7 and 9 million people live with hepatitis C in Latin America and Caribbean [9]. There is scarce data pertaining to acute hepatitis C infection in South America. A survey conducted in Argentina, Uruguay, and Paraguay found that the most common risk factors for acute hepatitis C were related to nosocomial exposure

[10]. In another survey conducted in Brazil the main risk factors for acute hepatitis C transmission were identified in hospital procedures especially hemodialysis, while it was low intravenous drug users [11].

In **Europe** it is estimated that around 19 million people are living with chronic HCV [12]. Incidence rates fluctuate between 2010 and 2014 but are overall steadily increasing. However, the annual epidemiological report of 2015 by the European Centre of Disease Prevention and Control (ECDC) reports 34,651 new cases in Europe which is a decrease of 4% compared to the previous year. The reason for this is currently not clear but it might be speculated that it is caused by the new direct-acting antiviral agents (DAAs) being used in the treatment of chronic HCV [13]. It is estimated that 1% of all cases are classified as acute infection, mostly due to IDU and health-care-associated transmission. An increase in acute (re)infection is also observed in MSM, coinfected with HIV living in large European cities [14].

Approximately 210,000 people live with chronic HCV infection in **Australia**, with an estimated 80% having acquired their infection through IDU [15]. From 1996 to 2001 a steady increase in new infections was registered with the majority of the cases diagnosed in the age group of 20–39 years old related to injection drug use [16]. Again sexual transmission was found to be relevant among HIV-positive MSM [17].

The estimated prevalence of chronic HCV in the whole **Asian** continent is 2.8%, accounting over 60% of the estimated cases worldwide. In the Asia Pacific region prevalence recently has been scaled down, since better seroprevalence studies demonstrate lower rates of active infection in China than previously believed. There are no firm estimates on the incidence of acute HCV around the Asian continent due to the lack of systematic population-based estimates or national surveillance reporting system. Epidemiology is often described by isolated studies or blood bank data [18]. So available data are mostly about chronic HCV infection. China, a large Asian country, has approximately 25–50 million HCV-infected individuals, accounting for 1.8–3.7% of the overall Chinese population [19]. Blood transfusion and IDU are the main routes of transmission. A similar situation was shown for India where transmission is mainly related to unsafe health-care procedures, although it appears to be highly variable according to the geographical site or the population analyzed (0.09–7.89%) [20]. In Thailand there is no national HCV reporting system. Approximately 759,000 individuals are currently anti-HCV positive and that 357,000 individuals have viremic HCV infection. In Indonesia the prevalence of anti-HCV is estimated to be 0.8% [21] and it is found to be higher in Java than Sumatra which is probably due to the more dense population in Java [22]. Japan, however, is considered to be a low-prevalence country for HCV with also a low incidence, but also here acute cases among MSM HIV-positive patients were recently reported [23]. In Asia, the first study describing a transmission network among HIV-infected MSM was performed in Taiwan, finding an incidence of 9.25 per 1000 PY [24].

In **North Africa**, accurate assessment of the burden of hepatitis C infection is difficult due to the lack of adequate surveillance data and poor resources for proper data collection and management. Despite the geographic proximity of these countries and long-standing interaction between them, the prevalence and complications of HCV greatly differ between them. According to current estimates, the lowest prevalence of HCV is in Libya (0.9–1.6%) whereas the highest is in adjacent Egypt (12.5–26.6%)

[25]. In the latter in 2015, it was estimated that 5.3 million individuals were anti-HCV positive. With this high seroprevalence rate, Egypt ranks among the highest in the world [26]. From 2008 to 2015 a significant reduction in prevalence was observed (from 14.7% to 10.0%) because behavioral changes with respect to promotion and expansion of infection prevention and control programs (including safe injections and blood transfusions) led to a decline in HCV incidence in the younger age groups [27].

Sub-Saharan Africa has a substantial HCV disease burden, but detailed epidemiology is limited due to the scarcity of reliable prevalence data and population-based studies. A meta-analysis published in 2015 suggested an overall HCV seroprevalence of 2.98% [28] with substantial variation between regions, related to the quality of serological tests used in various studies, the variability of populations screened (e.g., blood donors vs. injecting drug users), and the HIV seroprevalence within the countries [29]. Prevalence was found to be the highest in Central African region (4.34%).

4.1.2 Definition of Acute HCV

Acute infection classically refers to the first 6 months after exposure to hepatitis C virus [30], though definition varies, mainly because of the absence of specific markers of acute infection and additionally because most patients experience no symptomatology of an acute infection [31]. As is shown in Fig. 4.2, a diagnosis of acute HCV can also be established by seroconversion to anti-HCV, or with the detection

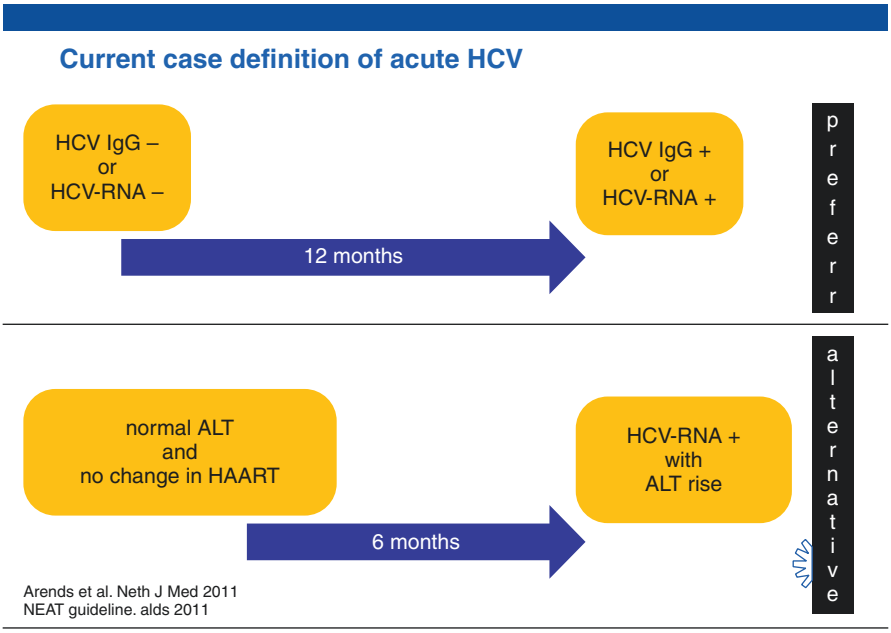

Fig. 4.2 Currently used case definition of acute HCV

of hepatitis C virus nucleic acid (HCV RNA) in serum/plasma in the absence of the specific Ig antibody (anti-HCVIg) [32].

Identification of acute HCV infections is important from an individual patient's point of view since 70–75% of the patients progress to chronic infection with a possible long-term risk of developing cirrhosis, hepatocellular carcinoma, and decompensated liver disease [33]. From a public health point of view, identification of an acute infection is equally important because of the high risk of transmission these patients have in the acute phase of the infection and therefore spreading of the virus among others. Starting therapy during the acute phase is of particular importance since treatment could reduce transmission and could improve clinical outcome and possibly could also be cost effective compared to deferring treatment until the chronic phase of infection [34].

Identifying those who are able to spontaneously clear the infection from those who will develop chronic HCV is important. One proposed way of identification of spontaneous clearance was proposed by Vogel et al. [35] who in an intent-to-treat (ITT) analysis evaluated spontaneous viral clearance rates in 92 HIV-infected patients with acute HCV. Those patients who did not develop a 2log10 drop in HCV-RNA at week 4 after the diagnosis had an 85% chance of becoming chronically infected with HCV. Since this observation has not been firmly established in prospective randomized trials, this 2log drop rule has not been adopted in the clinical management of acute HCV [36].

4.1.3 Routes of Transmission and Related Risk Group

Although the mode of transmission of acute HCV varies among different regions and within countries, injection drug use (IDU) and unsafe health-care practices remain the leading modes of transmission [37]. Areas with high rates of infection related to unsafe health-care transmission are located in the Eastern Mediterranean Region (62.5 per 100,000, usually related to unsafe health-care transmission) [38, 39] and in the European Region (61.8 per 100,000) where IDU accounts for a substantial proportion of the new cases each year [40]. Worldwide, acute HCV infections are more frequent among male young adults, reflecting the demographic profile of injection drug users [41, 42]. According to a study published in 2013, all forms of drug dependence and related disease were highest in men aged 20–29 years and the majority of new infections are related to illicit drug use [43]. The three countries with the largest populations of IDUs living with HCV are China (1.6 million, range 1·1–2·2), Russia (1.3 million, range 0·7–2·3), and the USA (1.5 million, range 1·0–2·2) [44]. In the early 1990s the incidence of HCV was extremely high in people who injected drugs. The implementation of HIV sexual transmission prevention programs, methadone substitution, and needle exchange services reduced transmission rates in many countries [12]. But the rate of new infection remains high or is again raising since iv drug use still remains the primary mode of transmission due to poor health-care services (i.e., Eastern Europe/Russia) or availability of cheap drug (USA) [45].

Transmission related to unsafe medical care practice has diminished over time. Before the advent of blood screening assays before transfusion, in the early 1990s most infections were due to transfusions with infected blood and its derivates or due to unsafe medical and surgical procedures. The introduction of large-scale screening essays reduced the risk to less than 1 per 100,000 units of blood [46]. However, even though there has been a successful implementation of blood screening strategies in a lot of countries worldwide, the situation still remains alarming in some resource-limited settings (Africa and Americas WHO areas). According to the WHO database on blood safety in 2012, 39 countries did not perform routine screening of HCV in blood products and 47% of all worldwide blood (derivate) donations were tested in settings without any quality insurance [47]. However, a significant decrease of HCV infection was observed in hemodialysis patients in the USA and Europe [48]. Transmission related to dialysis depends on reuse of lines, hygiene and sterilization of equipment, patient rotation of machines, and undertaking of rigorous universal precaution rules [49]. In addition to transmission via blood transfusions, unsafe injection using contaminated syringes or needles was the most common way to acquire infection in the past and continues to be responsible for a large amount of nosocomial HCV transmissions, both in developed and developing countries [50]. A case report published in 2016 reported acute hepatitis C infection after accidental needlestick injury with a used blood glucose lancet of a diabetic patient with a chronic hepatitis C infection [51]. Egypt's mass campaigns for schistosomiasis treatment may represent the world's largest iatrogenic transmission of HCV [52]. The parenteral anti-schistosomal therapy with tartar emetic injections was administered in a nationwide campaign during the 1950s until the 1980s. Over the 18 years of treatment, 36 million injections were administered to >6 million people, almost all with unsterilized and shared syringes and needles. This intensive transmission established a large reservoir of chronic HCV infection genotype 4, responsible for the high prevalence of HCV infection and current high rates of transmission [53].

Finally, a far less common but incidentally described way of HCV transmission is between hepatitis C and acupuncture. A modest association has been reported in some countries, stressing the importance of exclusively using disposable acupuncture needles [54]. In addition, investigators have reported methods such as tattooing, piercing, coke straw sharing, and cupping as additional agents for HCV transmission [55, 56].

Another possible way of HCV transmission includes sexual contacts with a person infected with HCV. Sexual transmission was long considered an inefficient mode to spread the infection [57]. Indeed, heterosexual transmission of HCV is estimated to occur at a very low rate of 0–0.6% per year between sero-discordant heterosexual partners [58]. Moreover, a lack of association between specific sexual practices and HCV acquisition was observed. This transmission rate is somewhat higher for heterosexuals with multiple partners or in the context of coexistent STI (0.4–1.8% per year) [59]. For men having sex with men (MSM) however, this is totally different as was learned over the past decade. The first reports of acute infection between MSM mostly associated with sexual and non-IDU behavior date from the beginning of the twenty-first century in London [60, 61] and were soon

thereafter followed by additional cases from other European countries, Australia, the USA, and Asia [14, 62, 63]. In the Swiss Cohort Study, HCV incidence increased 18-fold in MSM between 1998 and 2011, while it declined in PWID and remained <1 per 100 in heterosexuals [64]. A similar increase was reported in MSM for the Netherlands (32–53 corresponding to a 65.6% increase) [65]. Similar situation is described in Australia and Asia. Sexual behavior is also responsible for the increase in acute case in the USA. Several factors have been attributed to this increase like increased cheap air travel, rising popularity of Internet, increase in extreme sexual techniques, and use of drugs and stimulants for sexual pleasure. However, this does not fully explain the finding in a recent meta-analysis that MSM HIV-positive have a higher rate of acute HCV infection than HIV-negative MSM [66]. It has been hypothesized that the destruction of gut-associated lymphoid tissue (GALT) early in an acute HIV infection might be responsible for a lower immunological barrier in the gut during anal intercourse between MSM leading to increased susceptibility for HCV.

Finally, acute hepatitis has been rarely reported during pregnancy [67]. Vertical transmission from mother to child is the primary route of transmission of HCV infection among children. Infection can occur in utero, intrapartum, and postpartum. It is estimated that the prevalence of Ig antibodies to HCV in pregnant women is 0.1–2.4% and the proportion of women with anti-HCV who have active infection with viremia is approximately 70% [68]. A recent meta-analysis by Benova et al. suggested that vertical risk transmission appears to be limited to infants of viremic mothers, ranging from 5.8 to 10.8% depending on their HIV status and HCV viremia [69]. Spontaneous clearance of the HCV virus has been reported in up to 25–30% of HCV-infected children [70]. Diagnosis could be difficult because specific antibodies (not the ones of the mother) appear 12 months after birth [71] and HCV RNA can be detected only 1–2 months after birth and has a low sensitivity [72].

In conclusion, global incidence of HCV infection seems to decrease and the introduction of DAAs could significantly modify the natural history of the disease due to large-scale treatment implementation programs. At this time IDUs and HIV+ MSM share the largest incidence of acute HCV infections. It would be important to identify if screening strategies in particular populations and therapy of acute infection, as was recently suggested in a publication for the Netherlands, could indeed contribute to final stop in spreading of the disease [13].

4.1.4 Spontaneous Clearance and Predictive Factors

Spontaneous viral clearance occurs in about 25% of individuals, generally in the first 3–6 months of infection [73], although cases have been reported after 1 year [74]. A recent study by Ragonnet et al. [75] showed a median spontaneous clearance rate of 184 days after diagnoses.

The outcome of acute HCV is affected by complex interactions between virus and host, which is only partially understood. Diversity of HCV viral quasispecies

and HCV genotype might be linked with clearance. Host factors such as female sex, initial cellular immune response, virus-specific neutralizing antibodies, and host genetics such as polymorphism of interleukin-28 gene (IL28B) have been associated with clearance of acute infection [76]. In particular individuals with a IL28B type CC genotype are more likely to clear the infection spontaneously than those with a type CT or TT. There is evidence to support that spontaneous viral clearance is better for building up immunological memory compared to chemically induced clearance. For the latter strong host innate and adaptive immune responses are necessary. For example, Thimme et al. demonstrated that in patients spontaneously clearing their acute HCV infection, a strong, broadly specific, and sustained adaptive cellular immune response is necessary [77]. Long-term follow-up of patients spontaneously clearing HCV infection showed detectable HCV-specific memory CD4 and CD8 T cells up to 20 years after resolution [78]. Similarly, in chimpanzees, memory CD4 and CD8 T cells were detectable in the peripheral blood and liver 7 years after clearing an acute HCV infection [79]. Upon rechallenge with HCV, chimpanzees demonstrated no sterilizing immunity but were characterized by a shorter duration of viremia and lower viral loads. Further evidence to support partial memory after clearance of acute HCV comes from epidemiological studies in high-risk injecting drug users (PWID). Several studies have shown that in those PWID spontaneously clearing one infection it was less likely for them to become reinfected compared to HCV-naïve individuals in the same high-risk circumstances, although this has not been shown for MSM [80, 81]. In HIV-infected patients with acute HCV chances of spontaneous viral clearance were lower (around 10–15%) before C ART, but also highest within the first 12 weeks after the diagnosis [82].

4.1.5 Reinfection

In the presence of maintained risk behaviors, HCV reinfections have been described in PWID and MSM who cleared the infection spontaneously or were successfully treated with either interferon-based therapy or new direct-acting antivirals [76]. In a recent meta-analysis of 61 studies, the 5-year risk of HCV reinfection in HIV-infected MSM was as high as 15% and higher than in studies on PWID [83]. A large cohort study of HIV-infected MSM conducted in Western Europe demonstrated a high reinfection incidence among this population (7.3/100 py) [84]. It has been suggested in some studies that individuals who spontaneously clear their acute infection may be at lower risk of future HCV reinfection when compared to those who are treated and achieve SVR due to a stronger immunological response [80, 85]. This indicates that a degree of protective immunity may develop for some patients. An effective immune response against HCV through multiple infections has been shown in animal models [86]. However, studies among PWID have failed to consistently demonstrate a protective effect [87]. This is highlighted by the observation that MSM can be repeatedly infected by acute HCV with either the same genotype or a different genotype [84].

Other studies demonstrated no difference in the incidence of HCV infection in individuals with no previous infection and in those with previous HCV clearance [88]. However, it has been shown that the chance of spontaneous clearance of HCV in case of a reinfection is higher. This is possibly due to a lower HCV RNA concentration which is generally more transient, and shorter in duration than during initial infection [89].

HCV reinfection is a critical health concern among HIV MSM and PWID after successful treatment or spontaneous clearance of acute HCV infection. Prevention strategies—both treatment and behavioral—are needed to target high-risk groups to reduce morbidity and treatment costs.

4.2 Diagnostics

4.2.1 Definition

According to the latest EASL guidelines published in 2016, diagnosis of acute infection is based on seroconversion to anti-HCV, or with the detection of hepatitis C virus nucleic acid (HCV RNA) or hepatitis C virus core antigen (HCV-core) in serum/plasma in the absence of the specific antibody (anti-HCV). The incubation period is within 7–21 days after viral transmission and when HCV RNA becomes detectable in serum (Fig. 4.3). Usually, the qualitative detection of HCV RNA confirms the diagnosis [90]. However, the exact time course of virological and immunological markers of HCV infection is not well defined, particularly during the first

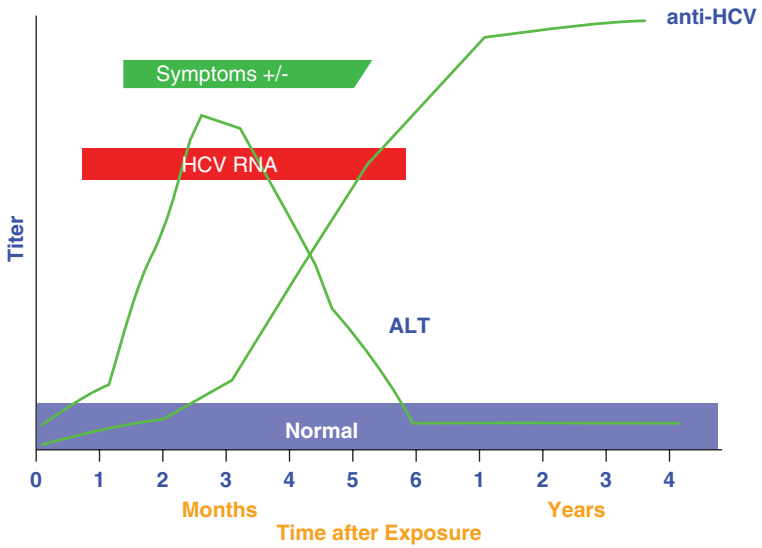

Fig. 4.3 Overview of the serological pattern of an acute HCV infection

months of infection, due to differences in the host immune response, specific properties of the infecting virus, and sensitivity of the assays used to determine the appearance of HCV markers.

Following an initial phase (window period) of 1–2 weeks when no virological or serological markers of infection can be detected, the natural course of HCV infection is characterized by the appearance of HCV RNA and subsequently the HCVcorep22 Antigen (Ag) in the absence of an antibody response (Ab) by the host. Seroconversion is defined by the development of a specific antibody response in a previously seronegative person occurring within 4–10 weeks after infection.

In Western countries, acute hepatitis C is most often diagnosed in the setting of postexposure surveillance, or seroconversion in high-risk individuals (e.g., healthcare professionals or injecting drug users) previously known to be seronegative. Seroconversion is most frequently documented in the setting of needlestick injuries, when the exposed individual is followed prospectively, or during surveillance of high-risk individuals [91].

In HIV-infected people, who are usually followed frequently for HIV, an unusual ALAT elevation is a sign of alert in favor of a recent HCV infection. In the other cases diagnosis could be difficult due to different reasons. Firstly, most of the patients do not exhibit symptoms within the first 6 months [92]. The classic clinical picture of an acute hepatitis with jaundice is observed in only 10–15% of the cases. Less commonly, the presentation of acute infection could include constitutional symptoms like nausea, loss of appetite, fatigue, and abdominal pain [31]. A large increase in alanine aminotransferase (ALT), which often can peak around 1000 UI/ml is usually an indicator of acute hepatic illness, could be observed, but it may frequently be the presentation of another acute process, such as alcohol-induced hepatitis or a second viral infection superimposed upon a chronic HCV infection [93]. It is therefore likely that these symptomatic patients will be diagnosed as having acute HCV. This is opposite to asymptomatic patients. Since the latter also have a much lower probability to clear the infection spontaneously, they most likely will be diagnosed at some point during their chronic infection [23]. Rates of spontaneous clearance are higher in symptomatic patient and occur usually during the first 3 months after the onset of the symptoms [94].

4.2.2 Assays

Assays detecting HCV infection can be broadly divided into molecular tests, which can directly identify the virus or partial sequences, and include qualitative and quantitative determination of HCV RNA or antigen, and in serological tests, which identify antibodies or viral proteins (Table 4.1) [90].

Table 4.1 Virological assays for the diagnosis of acute hepatitis C infection

Assays	Specificity	Sensitivity	Current application	Future application
IGM antibody			Not useful*	
IgG antibody	100%	100%	Diagnosis of acute or chronic infection	
Quantitative HCV RNA	95%	95%	Diagnosis of acute and chronic infection	
Qualitative HCV RNA		Some tests more sensitive than quantitatives because of low level of detection	Detect the presence of HCV RNA	
NAT	98–99%	99%	— Confirm viremia in pts. with reactive serology in short time after exposure (1–2 weeks) — Screening blood donations	
HCV Ag	100%	Less sensitive than NAT	Diagnosis of acute infection in the absence of antibody	— Screening test with antibody — Diagnosis of acute infection in HIV coinfected — Monitor treatment in DAA era

Present in both acute and chronic infection

4.2.2.1 Serological Assays

Serological assays are based on the immunoassay principle, and are available in the form of rapid diagnostic tests (RDTs) or laboratory-based enzyme immunoassays (EIAs), chemoluminescence immunoassays (CLIAs), and electro-chemoluminescence immunoassays (ECLs). Most of these tests have a sensitivity and specificity close to 100% [95]. False-negative results may occur in the setting of severe immunosuppression such as infection with HIV, solid-organ-transplant recipients, hypo- or agammaglobulinemia or in patients on hemodialysis. False-positive results are more likely to occur among populations where the prevalence of hepatitis C is low [96]. Current serological markers cannot reliably distinguish acute hepatitis from an exacerbation of chronic infection [97]. The anti-HCV IgM antibody has not proven useful because they are present in similar level in both acute and chronic diseases [93], even if someone suggested that IgM levels are undetectable or present with low steady level in reactivation of chronic hepatitis

[98]. In recent years much work has been done to develop a test for measuring avidity of the HCV antibody which was proven in other infections to be a more reliable marker for distinction of a recent viral infection. Avidity increases progressively with time after exposure to immunogen due to rapid mutation in the DNA coding for the variable part of the antibody [99]. It was confirmed that IgG anti-HCV avidity increases with time after primary infection [100] and if detected very early after onset of symptoms it could be useful to distinguish acute process from exacerbation of chronic infection [101]. It has been shown that testing for IgG antibody avidity allows diagnosis in up to 90% of acute hepatitis C [100]. These promising assays still require further evaluation and validation in various clinical settings [102].

4.2.2.2 Molecular Assays

Qualitative and quantitative methods for detection of HCV RNA—including reverse transcriptase (RT) PCR, branched DNA (bDNA) assays, and transcription-mediated amplification (TMA)—are the most sensitive means to document viremia [91]. Qualitative assays detect the presence of HCV RNA but they cannot measure HCV viral load. The lower limit of detection varies by the method used. The newer real-time PCR detection assays, such as the Cobas TaqMan assay (Roche Diagnostics) and Abbott Real-Time HCV assay (Abbott Laboratories), have very low limits of detection (15 IU/mL and 10 IU/mL, respectively). The Bayer TMA assay (Bayer Laboratories) can detect HCV at limits of 5 IU/mL.

HCV RNA can be quantified by target amplification techniques (competitive PCR or real-time PCR) or signal amplification techniques (branched DNA (bDNA) assay). Five standardized assays are commercially available. Ranges of quantification of the assays refer to the HCV RNA intervals within which quantification is accurate in the corresponding assay [103]. HCV RNA levels falling above the upper limit of quantification of the assay are underestimated and the samples must be retested after 1/10–1/100 dilution in order to achieve accurate quantification. It is recommended not to take into account HCV RNA load variations of less than threefold (i.e., $\pm 0.5 \log_{10}$), which may be related to the intrinsic variability of the assays. In contrast, variations of more than threefold (i.e., $0.5 \log_{10}$) can reliably be considered to reflect significant differences in HCV RNA load. The newer assays are extremely reliable with a very high sensitivity and specificity (both >95%). However, detecting HCV RNA by PCR is not cost effective in a low-risk population, and is not recommended as a screening test for chronic infection [93].

NAT (nucleic acid amplification technology) test is a molecular technique that detects the presence of viral nucleic acid—DNA or RNA—through targeting a specific segment of the virus, which is then amplified. Amplification step enables the detection of low levels of the virus earlier than the other screening methods, thus narrowing the window period to only 4 days. It is used for screening blood donation to reduce the risk of transfusion-transmitted infections in the recipients [104].

Finally, it has been demonstrated that the HCV core antigen level strongly correlates with the HCV RNA level for various genotypes. Currently, core antigen can be easily detected and quantified by means of a chemiluminescent microparticle immunoassay in the fully automated Architect HCV Core antigen test (Abbott Laboratories) [105]. The Architect HCV Ag assay had a specificity of 100%, with a

lower limit of detection of 3 fmol/L corresponding to approximately 1000 IU/mL of HCV RNA [106]. Although a study conducted in the Netherlands suggested that HCV core antigen assay could also be used in the diagnosis of acute HCV infection among coinfected HIV patients [107], as it is a sensitive and specific test, so far it still has not gained a role in the diagnostics of an acute HCV infection.

4.2.3 Assays in Clinical Practice

Since there is no definite test to prove an acute infection, physicians usually rely on clinical judgments (i.e., the presence of symptoms) in combination with abnormal laboratory results such as elevated aminotransferases, and a positive HCV-RNA or serology in combination with a prior seronegative assay. In specific circumstances, for example in HIV-infected patients with an acute HCV, antibody generation by the host immune response could be initially absent or delayed for months [108]. Also, successful viral clearance may occur in the absence of antibody production or be associated with rapid antibody loss [93]. This suggests that clearance of viremia may be related to both humoral and cellular responses [109]. Among IDUs some studies suggested an average interval from first injection and HCV infection to the development of HCV Ig antibodies of 1 year or even longer. Factors associated with a shorter interval to seroconversion included injecting every day, the shared use of syringes to inject, and the shared use of a cooker or cotton to prepare drugs for injection [110]. In another study conducted on IDUs a delayed and low-titer antibody response was observed during acute hepatitis C [111].

Another pitfall in the diagnosis of acute HCV in high-risk HIV+ MSM is the distinction between relapse of infection after DAA therapy or reinfection. When the same genotype again is present, it still might be a reinfection. Only phylogenetic analysis can firmly distinguish between these two entities [84].

4.2.4 Treatment

In a chapter about treatment of acute HCV, a distinction should be made in the era before and after availability of direct-acting antivirals (DAAs). Similar to chronic HCV, DAAs proved to be highly efficacious in the treatment of patients with acute HCV, leading experts in the field to believe that there is no distinction anymore between acute and chronic HCV. Therefore, current HCV treatment guidelines recommend a treatment with a combination of two DAAs based on genotype for a total duration of 8 weeks. Patients with acute hepatitis C and HIV coinfection and/or a baseline HCV RNA level >1 million IU/l may need to be treated for 12 weeks with the same combination regimens [32]. However, the question remains if this is totally true. There have been several issues in the pre-DAA era which remain intriguing still today, as we mentioned above. It has been common clinical practice to await spontaneous clearance before considering starting therapy. The publication of the landmark study by Jaeckel et al. [112] clearly demonstrated that treatment of patients with an acute HCV mono-infection with at that time standard interferon-alpha (thrice weekly) for

24 weeks resulted in a sustained virological respond (i.e., HCV-RNA negativity 24 weeks after discontinuation of therapy) rate of 98%. Then SVR rates achieved by treating the acute stage of the infection were superior to SVR rates achieved with treatment in the chronic phase. Over time, treatment regimen changed similar to that being administered in chronic HCV. For a long time pegylated interferon-alpha for 24 weeks was the recommended course of therapy for acute HCV mono-infection while ribavirin was added in case of coinfection with HIV [113, 114].

With the availability of DAAs for chronic HCV and its demonstration of high efficacy, it is obvious to use DAAs in cases of acute HCV as well. However, to date none of the currently available DAAs formally registered for the treatment of acute HCV. This is because there is insufficient data about efficacy of particular regimens and treatment durations in acute HCV infection mostly due to the low number of patients per study in the field. An overview of studies regarding treatment of acute hepatitis C is summarized in Table 4.2. The largest study to date in patients with an acute HCV treated with DAAs is running in the Netherlands. An interim analysis showed a SVR of 98% after a short course of 8-week grazoprevir/elbasvir (an NS3/NS5a combination) (personal communication) [115].

Taken together, the use of DAAs in patients with an acute HCV infection seems promising based on a couple of case reports and small cohort studies but clear recommendations regarding optimal regimen and treatment duration are currently unavailable.

4.2.5 Postexposure Prophylaxis

Ever since the notion of blood-borne transmission of viruses through needlestick injuries, HCV (previously called non-A, non-B hepatitis) has been one of the viruses recognized for causing acute hepatitis syndrome. Early on postexposure prophylaxis with then available interferon-based therapies was tried but shown to be unsuccessful in the case of a Japanese health-care worker who was treated with a short course of interferon after a needlestick injury [116].

In the current DAA era there are no data on the efficacy or cost-effectiveness of antiviral therapy for pre-exposure or postexposure prophylaxis of HCV infection.

4.2.6 Prevention of Acute Hepatitis

In the era of highly effective DAAs that promises an individual as well as a collective benefit, the World Health Organization (WHO) launched the first global health strategy on the elimination of viral hepatitis as a public health threat by 2030 [117]. Targets by 2030 are to achieve a 90% reduction of new viral hepatitis infections, a 65% reduction of liver-related deaths, and a 90% diagnosis rate of those being infected. Studies have shown that increased capacity for treatment as well as screening is going to be critical in several countries [118]. However, the former is difficult since the high cost

Table 4.2 Overview of acute HCV studies performed with DAAs

Study author (year)	Country	Number of patients	Therapy	Duration	Genotype	SVR12	HIV	Comorbidities
Naggie S (2017) [125]	USA	17	Sof/RBV	12 ws	1	59%	Positive	
Rockstroh JK (2017) [126]	Germany, UK	26	Led/sof	6 ws	1,4	79%	Positive	
Deterding K (2017) [127]	Germany	20	Led/sof	6 ws	1	100%	Negative	
Boerekamp A. (2016)	The Netherlands, Belgium	49	Grazo/ elbasvir	8 ws	1,4	98%	Positive	
He YL (2018) [128]	China	33	Sof[a]/Dac	24ws	2a,1b	100%	Negative	End-stage renal disease
Brancaccio G (published in 2017) [129]	Italy	6	Led/Sof	8–12ws	1b	66%[b]	Negative	Hematological malignancies

Sof Sofosbuvir, *RBV* Ribavirin, *Led* Ledipasvir, *Grazo* Grazoprevir, *Dac* Daclatasvir, *Ws* weeks

[a]Sofosbuvir used in half dose (200 mg)

[b]Two patients died at week 8 after treatment as a result of recrudescence of hematological disease

of DAAs in many countries continues to lead to prioritization of therapy [120]. In addition, there are several barriers to scaling up of HCV treatment in high-risk populations, especially in PWID [121]. To reduce HCV incidence in PWID, combining universal introduction of DAAs with increased diagnosing rates and enhanced prevention measures such as opioid substitution treatment and needle and syringe exchange programs, provided in multidisciplinary settings, was shown to be crucial [122].

Strategies to control the spreading of infection are needed also among MSM. The ECDC published a document focusing on communication strategies for the prevention of hepatitis and other STI which stressed the importance of counselling information and public awareness of the disease [123]. In Amsterdam a local program (MC Free) organized by the Amsterdam Institute for Global Health and Development (AIGHD) developed online and off-line interventions to increase knowledge and awareness of HCV infection among MSM population by increasing regular HCV testing and earlier diagnosis and to stimulate risk reduction behavior. The early treatment of acute infection also seems to reduce the incidence of hepatitis C in this population [13].

An increase in appropriate prevention measures such as safe medical procedures, safe sexual practices, and prevention of mother-to-child transmission needs to be encouraged [119]. Improving public health surveillance could help state-run and local programs to identify and address HCV-related health disparities by documenting and monitoring the impact of testing, care, and treatment services [124].

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Acute HBV/HDV Infection

5

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In 1977 Rizzetto and his colleagues discovered by immunochemical methods in patients with severe hepatitis B a new antigen–antibody system, which they called delta antigen and delta antibody [1]. The same group then was able to identify that this novel antigen–antibody system was an internal part of a new virus which was then called the delta virus or the hepatitis D virus (HDV) [2]. This HDV virion with a diameter of 36 nm is comprised of an outer layer coat consisting of hepatitis B surface antigen (HBsAg). Inside the virion is a nucleoprotein complex containing a single-stranded HDV RNA of 1679 nucleotides and around 200 molecules of hepatitis D antigen (HDAg) [3–5]. The HDV genome is by far the smallest animal virus but is able to lead to the most severe form of viral hepatitis in humans. Nevertheless HDV is a defective virus which cannot cause disease by itself and needs a helper function provided by the hepatitis B virus (HBV). This helper function consists of and is limited to HBsAg production. HDV also does not replicate through a polymerase of its own but highjacks the RNA polymerase of the human host. These properties of HDV are critical for our understanding of its management and explain to some extent why treatment of HDV infection has not much changed decades after its discovery. The topic of this chapter is acute HBV/HDV infection. Two issues may be underlined here related to this topic. HDV infection represents the rarest form of viral hepatitis in humans and acute infection today represents the very rare form of this rare infection. This should be seen as good news since the management of acute HBV/HDV remains as supportive therapy in contrast to acute hepatitis B or acute hepatitis C where antiviral therapies against the etiologic agents are possible today.

Eight genotypes of HDV have been reported based on a sequence variation of 19–38% [6, 7], and it is worth mentioning them since they may affect disease severity. Genotype 1 has a worldwide distribution and it is in general associated with

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more severe disease compared to infections with HBV and HCV; however their clinical presentation may vary. Genotypes 2 and 4 have been mainly reported from the Far East. Genotype 2 may be associated with a milder form of the disease compared to genotype 1 [8]. In contrast, genotype 3 has been linked to a particular severe from of the disease and is confined to the Amazon basin in the north of South America [9]. Genotypes 5–8 have been reported only from Africa and they may also be associated with a milder clinical presentation [8, 10]. Besides HDV genotypes, HBV genotypes may also affect disease outcomes [8].

5.1 Clinical Forms of Acute HBV/HDV

Infection with HDV can occur as coinfection of HBV and HDV infection or as superinfection of a chronic hepatitis B surface antigen (HBsAg) carrier with HDV. In general terms, coinfection leads to acute disease and superinfection leads to severe chronic hepatitis. Inherent with the latter is the possibility of an acute hepatitis-like exacerbation of the chronic HBV infection, formerly known as "inactive HBsAg carrier" [11]. Finally, a third form of acute HDV hepatitis may occur after liver transplantation [12]:

1. Acute HBV/HDV coinfection: The two viruses present in the inoculum may lead to two ALT peaks; the first peak is in general related to HBV and the second to HDV although the sequence of peaks may be in the reverse order. A monophasic ALT peak is also possible [3, 13]. The clinical presentation varies and will be discussed below.
2. Superinfection of a patient with chronic HBV infection: This form is in general associated with the development of an acute hepatitis episode. In the vast majority of cases (90%) progressive chronic hepatitis will ensue. However, in about 10% of cases, such a presentation can lead to clearance of both HBV and HDV or of HDV only.
3. HDV disease in the liver transplant setting: In a patient transplanted for HDV-induced liver disease hepatitis due to HDV may appear if HBsAg persists after liver transplantation. This form is characterized by HDV infection associated with low levels of HBV viremia and in the early 1990s there was some controversy regarding the possibility of posttransplant HDV in the absence of detectable HBV antigens in the serum or liver [14]. However, a more recent study investigating some of these cases revealed that insensitivity of the assays used was the main reason for the controversy [12].

5.2 Epidemiology

In the last decades HDV infection has decreased in particular in the industrialized world and HDV-induced liver disease has received orphan disease status in the European Union and in the USA. HDV needs the helper function of HBV to

propagate and to cause disease. However, HDV epidemiology does not follow the epidemiology of HBV. Several hot spots of HDV disease have been reported and these include Mongolia and Pakistan and several countries from the former Soviet Union in Asia; Turkey, Albania, and Romania in Europe; the Amazon basin in South America; and countries in sub-Saharan Africa [15]. The decline in HDV has been ascribed to universal HBV vaccination and several other measures including hepatitis virus screening of blood and blood products, more widespread use of disposable syringes, improvement in hygiene, better adherence to infection control precautions, and others. The decline in HDV infection has been shown in several studies from Italy [16], Spain [17], Turkey [18], and Taiwan [19]. Expectedly, the decline in HDV incidence was most pronounced for acute HBV/HDV hepatitis as has been shown in studies from Spain and Italy and even from Mongolia [17, 20, 21]. Despite these declines, HDV continues to be a significant health problem in the abovementioned countries and regions and the decline has not reached the state of disappearance of the disease in Western countries due to migration from HDV endemic countries [22, 23]. In these countries HDV is seen mainly in intravenous drug users and migrants.

5.3 Clinical Presentation

The clinical course of acute HBV/HDV disease is similar to the clinical course of other forms of acute viral hepatitis. Thus the clinical presentation may range from mild hepatitis to fulminant hepatitis which is to be expected in any immune-mediated viral disease reflecting the variable immune response by the host. The helper function of HBV needs special attention as the wider spread of HBV to hepatocytes may lead to more severe coinfection. A restricted expression of HBV may lead to mild disease [13]. HBV and HDV genotypes may also contribute as has been shown in particularly severe cases in South America [9, 24] and also in the setting of chronic delta hepatitis in the Far East [8]. However, in general, a more severe course is reported in the setting of acute HBV/HDV infection. This has been clearly shown in early studies when patients with acute hepatitis B monoinfection were compared to patients with dual-HBV-HDV infection (Table 5.1). In two studies from Europe and the USA, respectively, patients with coinfection more often led to fulminant hepatitis [25, 26]. This high proportion of fulminant hepatitis in patients with acute HBV/HDV is much less encountered today. In a recent study analyzing 115 patients with acute HBV/HDV fulminant hepatitis was observed in only 2 (1.7%) patients [27]. This may suggest that with the slower turnover of HDV in the community, acute fulminant HDV may also be much less frequently encountered.

Table 5.1 Proportion of patients with serologic evidence of delta infection among patients with acute self-limited versus acute fulminant hepatitis B

	Fulminant hepatitis B	Acute hepatitis B	*p*-Value
Europe [25]	43/111 (39%)	101/532 (19%)	<0.000001
USA [26]	24/71 (34%)	5/118 (4%)	0.000016

The incubation period of acute infection is 2–8 weeks. It may depend on the virulence of HBV and is shorter in patients with HDV superinfection [13]. The mono- or biphasic acute hepatitis peaks may depend on the relative HBV and HDV titers. After the incubation period a typical acute hepatitis will ensue with nonspecific symptoms such as anorexia, nausea, and fatigue which then may be followed within days by the appearance of jaundice, dark urine, and pale stool. Symptoms accompany typical hepatitic liver enzyme elevations and increased direct and indirect serum bilirubin levels. In self-limited acute hepatitis the acute hepatitis phase is followed by the convalescence phase where symptoms of anorexia, nausea, fatigue, and jaundice gradually decrease and eventually subside. In the superinfection setting the acute hepatitis leads to active chronic hepatitis in the vast majority of patients (90%). In the rest, depending on the interplay of the two viruses with the immune system, both HBV and HDV or only HDV is cleared. Rarely (in less than 5%), acute HBV/HDV infection may progress to chronic hepatitis.

However, acute hepatitis can often be more severe than encountered with other hepatotrop viral infections and may lead to acute liver failure or in the superinfection scenario it may lead to the clinical picture of acute-on-chronic liver failure (ACLF) [28]. Severe acute hepatitis may convert to fulminant hepatitis with development of symptoms of hepatic encephalopathy. Assessing disease severity is important since patients with severe hepatitis should best be referred to transplantation centers for optimal management including potential liver transplantation [29]. Patients with an INR of >1.5 or patients with hypoglycemia or metabolic acidosis should be considered as having severe hepatitis [29]. Acute liver failure is diagnosed when symptoms of encephalopathy are recognized. Initial symptoms of hepatic encephalopathy include confusion and change in personality. With deepening of encephalopathy a more objective clinical element is the development of asterixis leading to the characteristic flapping tremor. Stupor and coma may follow and such cases may only be rescued through liver transplantation. The potential development of ACLF with HDV superinfection is in the form of type A ACLF as it develops in a patient with background chronic hepatitis rather than cirrhosis [30]. There is no overall agreed definition of ACLF. The World Gastroenterology (WGO) proposed it to be defined as “a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis, characterized by acute hepatic decompensation resulting in liver failure and one or more extrahepatic organ failures associated with increased mortality” [30]. A recent proposal is that the increased mortality should be within a period of 3 months [31].

5.4 Diagnosis of Acute HBV/HDV Hepatitis

Serologic and virologic markers are used for diagnosing HDV infection. They help not only in diagnosis but also in the differentiation of acute HBV/HDV coinfection from superinfection with HDV of a patient with chronic HBV infection. This is crucial since their management differs. During acute HBV/HDV coinfection, the virulence of concomitant HBV infection determines the expression capacity of

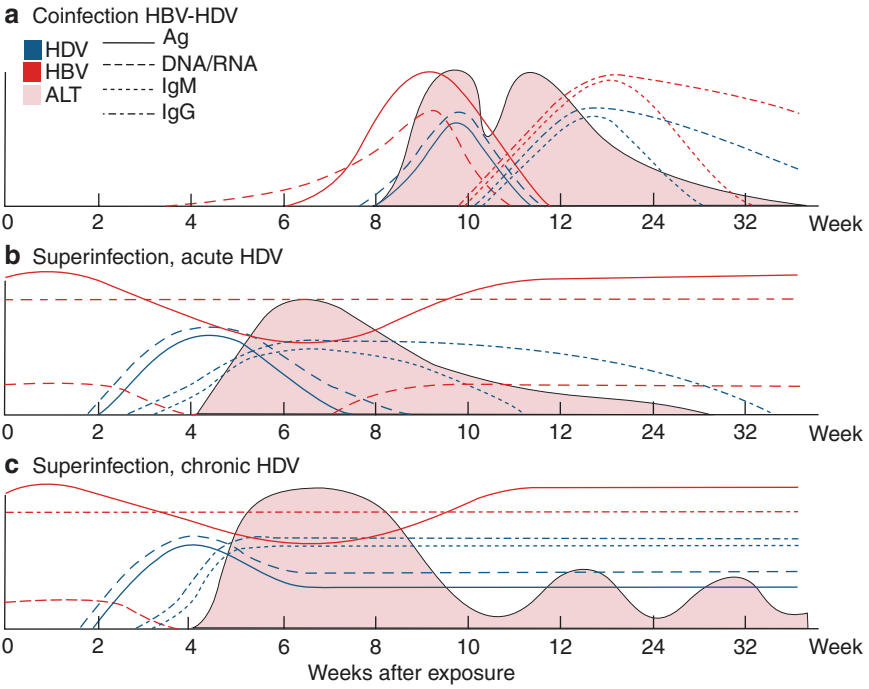

Fig. 5.1 Serologic. Biochemical and virologic evolution in patients with acute HBV/HDV coinfection (**a**), in HDV superinfection of a chronic hepatitis B carrier with resolution of HDV (**b**), and with progression to chronic hepatitis (**c**)

HDV [13, 32]. First markers of the infection are the presence of HBsAg with HBV and HDV viremia [32, 33] (Fig. 5.1). Hepatitis D antigen (HDAg) expression can be observed by immunohistochemical staining in the liver in the nuclei of hepatocytes. Serum HDAg is measured commercially with an enzyme-linked immunosorbent assay (ELISA) or a radioimmunoassay (RIA) and is detectable only for a short period. It has been reported that HDAg may be found detectable in the first 2 weeks of acute HBV/HDV coinfection [34]. With the development of anti-HDV antibodies HDAg becomes part of an antigen–antibody complex and can be detected using an immunoblot assay under denaturating conditions [35] but can no longer be detected by the former methods available routinely. HDAg may however persist to be detectable in immune-compromised patients where the weak immune response prevents the development of a strong anti-HDV response [36]. HDV viremia will disappear after resolution of acute hepatitis.

In acute HBV/HDV infection, anti-HBc IgM becomes present in high titers, is transient, and disappears after infection subsides. In HDV superinfection of an HBsAg carrier, anti-HBcIgM is either not detectable or if present only detectable in low titers. Anti-HDV IgM may develop late in the course of acute infection; hence, there is a need to repeat testing to confirm the diagnosis of HDV. Anti-HDV IgM will gradually disappear after the acute infection. Anti-HDV IgG's appearance in

serum follows anti-HDV IgM but appears somewhat later. However, after the resolution of the infection it will remain detectable in long term. HD viremia will continue to be detectable in the majority of patients who will develop chronic delta hepatitis. However, in the 10% where the acute HDV superinfection of a chronic HBsAg carrier will lead to HDV eradication HDV viremia will cease.

In the current posttransplant setting where patients receive immunoprophylaxis against HBV with hepatitis B immune globulin (HBIG) with nucleo(t)ide analogs, hepatitis B and hepatitis D viremia will disappear within days after transplantation [37]. However, in some patients HDAg is detected as long as 1.5 years after liver transplantation in liver tissue [37]. This raises the theoretical concern of the rescue of HDV by HBV several months after transplantation. This is important since current treatment of HDV consists only of the use of interferons and interferon use in the posttransplant setting is not straightforward. HDV does not need HBV for replication but for propagation. In chimpanzees HDV was rescued by HBV inoculation 7 days after HDV inoculation. This did not happen however after 28 days [12]. In woodchucks HBV inoculation after 33 days was able to rescue HDV infection [38]. It is difficult to give a clear statement with regard to the situation in humans since few studies on immune prophylaxis in patients for delta hepatitis exist. Recently Martini et al. [39] questioned the need for HBIG prophylaxis based on their assessment of existing literature according to which only 1 out of 81 patients (1.2%) developed HDV recurrence after stopping various lengths of HBIG administration. Some caution is needed since in one of the studies, 6 out of 25 (24%) patients became HBsAg positive. It is not reported if they developed HDV disease [40]. In the other relatively large study, actually 2 out of 34 patients developed HBV/HDV recurrence; however one had received a HBsAg (+) graft [41]. Overall, including this patient, the 2 patients with recurrence received a shorter duration of HBIG (median 9 months) than the 32 patients whose disease did not recur (median 28 months). We recently observed a similar patient in the context that he too had received a HBsAg (+) liver. This patient developed posttransplant HDV recurrence and cirrhosis within 1 year (unpublished observation). Although these numbers are small, it nevertheless suggests a cautious approach in the posttransplant setting to avoid posttransplant acute HDV hepatitis. At this point in time, HBIG + NA prophylaxis should probably be continued for a period of at least 1 year posttransplantation after which HBIG may be stopped but NA treatment continued.

5.5 Treatment of Acute HBV/HDV Hepatitis

Management of acute HBV/HDV remains mainly supportive as treatment of proven efficacy does not exist. Interferons which represent the only available treatment for chronic hepatitis D have been used in fulminant hepatitis D with dismal results [42]. No report of interferon use in patients with acute non-fulminant hepatitis exists. Another drug tested in patients with fulminant HBV/HDV was trisodium phosphonoformate (foscarnet). Foscarnet is a DNA polymerase inhibitor and it actually appeared to have some effect in the three patients it was used [43].

However, foscarnet was not further tested due to nephrotoxicity and poor bioavailability when given orally [44]. Further, in vitro data suggest that it actually increases HDV replication [43].

Currently, several new drugs are tested in phase 2 studies in chronic hepatitis D. These include the HBV hepatocyte entry inhibitor Myrcludex B, the prenylation inhibitor lonafarnib, nucleic acid polymers, and interferon lambda [45]. The former three drugs act on various steps of the HDV life cycle while the latter is an immune modulator. Myrcludex B inhibits cell entry of the HBV/HDV virion via interaction with the HBV receptor sodium taurocholate co-transporting polypeptide (NTCP), lonafarnib inhibits virion assembly, and nucleic acid polymers are thought to prevent extrusion of the HDV virion from hepatocytes. First reports of their use in chronic hepatitis D have been recently published or presented [46–49]. All of the three drugs reported better efficacy when combined with pegylated interferon alpha 2a [46, 48, 50] and various doses of Myrcludex B have now been tested [51]. These new drugs could well be tested in the setting of acute HDV/HBV infection and provide hope for the future.

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A Review of Acute Viral Hepatitides Including Hepatitis E

6

Mohammad Sultan Khuroo

6.1 Introduction

Acute viral hepatitis (AVH) is a systemic infection, caused by a group of viruses, which have special affliction and primary site of replication in the liver [1]. As of today, five unelated hepatotropic pathogens have been identified to cause AVH. These include the hepatitis A virus (HAV), the hepatitis B virus (HBV), the hepatitis C virus (HCV), the hepatitis D virus (HDV), and the hepatitis E virus (HEV). However, varying proportion of AVH cases fall in to the non-A-E group and are in search of putative agent/s. This includes 2–30% cases of sporadic AVH [2], 30–55% cases of acute liver failure [3], and most cases of giant-cell hepatitis (postviral hepatitis) aplastic anemia [4]. Over the years, several viruses have been identified and all are in search of disease. Transfusion-transmitted agents, namely human pegivirus (HPgV) (formerly known as GBV-C/HGV), TT virus, and other TTV-related viruses (SANYAN, YONBON, SEN viruses, and TTV-like Mini virus), have been identified but do not cause AVH [5]. There have been new kids on the block of whom we must learn more about in future. Two more novel agents in the pegivirus genera of the family Flaviviridae have been identified and named as human hepegivirus 1 (HHpgV-1) [6] and human pegivirus 2 (HPgV-2) [7]. A number of systemic viral infections that may involve liver and cause hepatitis include Epstein-Barr virus infection, cytomegalovirus infection, herpes simplex virus infection, Varicella-Zoster virus infection, and severe acute respiratory syndrome [8].

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6.2 Overview

AVH is a global health problem and constitutes an important cause of liver-related global disability and deaths [9, 10] (Fig. 6.1)**.** It is estimated that 1.4 million people were infected with HAV in 2005, with 31 million symptomatic illnesses and 34,000 deaths [11]. There were 20 million HEV infections, 3.4 million symptomatic illnesses, 70,000 deaths, and 3000 stillbirths in 2005 [12]. Outbreaks of hepatitis A (foodborne) and E (waterborne) affecting more than 100,000 people and causing significant morbidity, mortality, and disruption of trade and tourism have been documented [13, 14]. It is estimated that more than 2 billion people have been infected with HBV. Of these 240 million are chronically infected and at risk of serious illness and death from cirrhosis and hepatocellular carcinoma. Between 500,000 and 700,000 people die annually because of HBV infection [15]. Around 150 million are chronically infected with HCV. More than 350,000 people are estimated to die from HCV-related liver diseases each year [16]. Thus, around 500 million people are chronically infected with HBV and HCV and over 1 million die each year (2.7% of all deaths) from causes related to viral hepatitis (liver cirrhosis, liver cancer, and acute liver failure). An estimated 57% of cases of liver cirrhosis and 78% of cases of primary liver cancer result from HBV or HCV infection [17]. HDV, the hitherto vanishing disease, has infected 15–30 million people with varying prevalence depending upon the region [18].

6.3 Agents, Epidemiology, and Transmission

The five known hepatitis viruses are unrelated and belong to different viral families. However, all five viruses are hepatotropic and can cause AVH (Table 6.1). These agents are transmitted by several routes which include fecal-oral, parenteral, percutaneous, sexual, vertical, perinatal, and food-borne zoonotic transmission (Fig. 6.2).

6.3.1 Hepatitis A Virus

6.3.1.1 Agent

Hepatitis A virus (HAV) is classified in the *hepatovirus* genus of the *Picornaviridae* family [19, 20]. The virion is an icosahedral, non-enveloped, symmetrical, small 27 nm, spherical particle. HAV capsid is made from 60 densely packed protomers; each consists of three major structural proteins. The HAV genome is about 7.5 kb and is divided into three parts: long UTR at 5′ end which contains a type III internal ribosome entry site (IRES), a single open reading frame, and short UTR at 3′ polyadenylated end. HAV genome is organized into 3 regions, namely P1, P2, and P3, and encodes 11 genes. P1 region encodes four capsid proteins and P2 and P3 regions encode a series of nonstructural proteins [19–21]. HAV exists only as a single serotype, with three genotypes (I–III) that circulate in humans and three additional genotypes (IV–VI) recognized in nonhuman primates [22, 23].

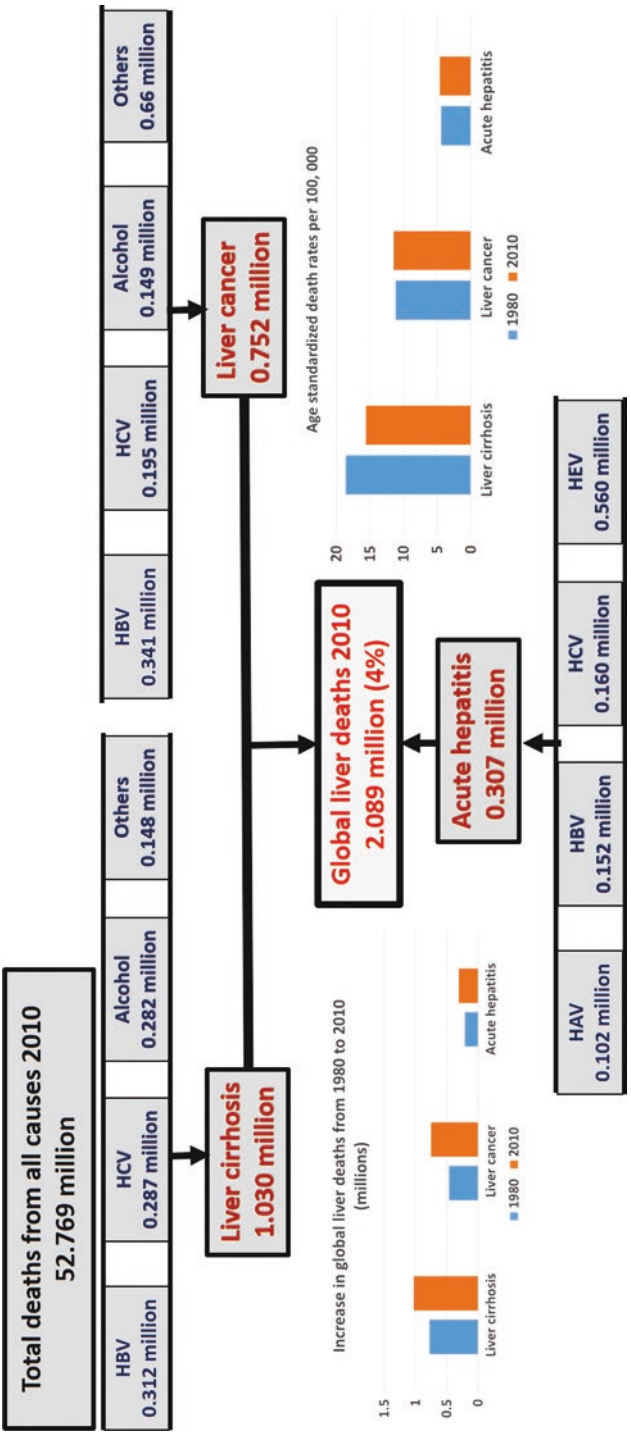

Fig. 6.1 Global disability and deaths caused by liver disease [source of Data Lancet. 2012;380(9859):2095–128] [10]

Table 6.1 The five hepatitis viruses

	HAV	HBV	HCV	HDV	HEV
Family	Picornaviridae	Hepadnaviruses	Flaviviridae	Satellite	Hepeviridae
Genus	*Hepatovirus*	*Hepadnavirus type 1*	*Hepacivirus*	*Deltaviridae*	*Orthohepevirus A*
Virion	27 nm, icosahedral, non-enveloped	42 nm, double-shelled Dane particle, sphere 27 nm, spheres 22 nm	60 nm, enveloped	36 nm, enveloped, hybrid	32 nm, non-enveloped, icosahedral
Genome	7.5 kb, RNA, SS, linear, +	3.2 kb, DNA, circular, SS/DS	9.6 kb, RNA, linear, SS, +	1.7 kb, RNA, circular, SS, –	7.2 kb, RNA, SS, +
ORFs	One (3 regions P1, P2, P3)	Four (S, P, C, and X)	One (one large polyprotein cleaved posttranslational)	Six (only one ORF translated)	Three
Proteins	VP1, VP2, VP3, VP4, 2A, 2B, 2C, 3A, 3B, 3C, 3D	HbsAg, HBcAg, HBeAg, DNA polymerase, HBxAg	C, E1, E2, P7, NS2, NS3 (2 proteins), NS4A, NS4B, NS5A, NS5B	HDAg	ORF1, ORF2, ORF3 proteins
Genotypes	3 human (I–III) and 3 nonhuman primates (IV–VI)	Eight (A–H)	Six (1–6) with over 50 quasispecies	Eight (1–8)	Human (1 and 2); pigs, wild boar, deer (3, 4, 5, and 6), camel (7)
Transmission	Oral-fecal route [person to person, food/waterborne]	Parenteral, percutaneous, sexual, perinatal	Parenteral, percutaneous	Same as HBV	Waterborne, person to person, vertical, zoonotic food-borne, transfusion associated
Incubation period	15–45 days	30–180 days	15–160 days	30–180 days	15–45 days
Epidemics	Yes	No	No	Yes	Yes
Acute hepatitis	Mild disease	Neonate—asymptomatic; children—mild disease; adults—severe disease	Mild disease, 20% only have icterus	Coinfection (mild disease); superinfection (severe disease)	Mild disease

	HAV	HBV	HCV	HDV	HEV
High-risk groups	Severe disease in adults and superinfections	Age of occurrence determines severity of disease and chronicity	Nil	Superinfections present as severe disease	Severe disease in pregnancy and underlying cirrhosis
Chronicity	Nil	98% in neonates; 10% in children; <5% in adults	>75%	Coinfection self-limiting; superinfection—most lead to chronic liver disease	HEV genotype 3 leads to chronic liver disease in immunocompromised patients
Diagnostic test (acute hepatitis)	IgM anti-HAV	HbsAg, IgM anti-HBc	Anti-HCV	IgM anti-HDV	IgM anti-HEV
Nucleic acid testing in clinical practice	Not needed	HBV DNA	HCV RNA	HDV RNA	HEV RNA
Vaccine	Yes, highly effective	Yes, highly effective	No	No	Yes (available in China only)

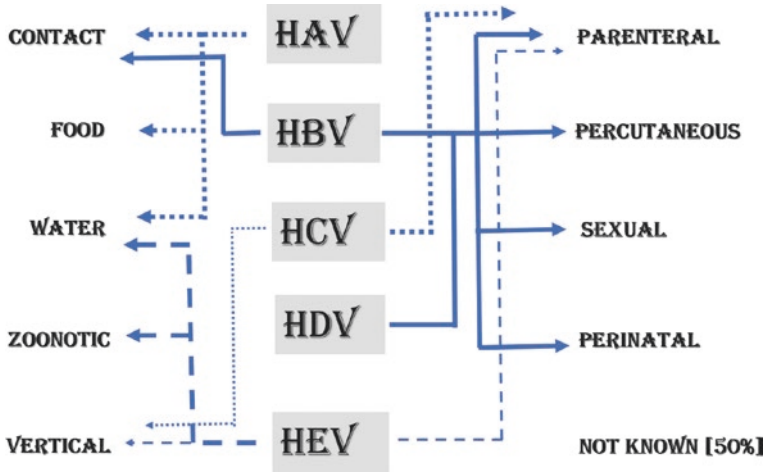

Fig. 6.2 Routes of transmission of hepatitis viruses A–E. Hepatitis viruses are transmitted by several routes which include fecal-oral, parenteral, percutaneous, sexual, vertical, perinatal, and food-borne zoonotic transmission. Fecal-oral route of transmission may occur from person-to-person contact or through ingestion of contaminated food or water. Transfusion of blood and blood products causes parenterally transmitted hepatitis. Accidental needlestick exposure, unsafe medical injections, and injecting drug use are major ways of percutaneous spread of hepatitis viruses. Sexual transmission occurs in men who have sex with men (MSM) and those promiscuous persons with multiple sex partners (MSP). Vertical transmission occurs when virus passes across the placenta to the fetus. Perinatal transmission occurs from mother to baby during or immediately after the birth. Hepatitis viruses can be spread by consumption of animal products infected with hepatitis viruses

6.3.1.2 Epidemiology

HAV has global distribution. Seroprevalence of HAV reveals three zones, namely very high endemic zone, high-to-intermediate endemic zone, and low endemic zone [24] (Table 6.2). Very high endemic zone includes resource-poor countries of Southeast Asia and sub-Saharan Africa. Children are infected with HAV soon after weaning and age at midpoint of the population immunity reaches in childhood around 5 years of age. Majority of these infections are subclinical. HAV infections in adults are reported infrequently in such countries [25]. High-to-intermediate endemic zone for HAV exists in developing countries of Asia, Latin America, Eastern Europe, and Middle East [26–28]. In these countries, there is recent continued improvement in sanitary conditions and access to safe water and reduced exposure of children to HAV infection. Age of midpoint of population immunity (50%) reaches at 5–14 years (high endemic zone) and 15–34 years (intermediate endemic zones). HAV circulation in the community is common. There is exposure to HAV infection in older children and adolescents and most of these infections are symptomatic. Person-to-person and foodborne outbreaks of HAV infection are common. Thus, paradoxically such regions of the world have high occurrence of clinical hepatitis A in young adults. Low endemic zone of

Table 6.2 Global epidemiology of hepatitis A[virus]

Endemicity zones	Very high	High to intermediate	Low
Socioeconomic status	Low resource	Developing	Developed
Countries	Sub-Saharan Africa, Southeast Asia	Asia, Latin America, Eastern Europe, Middle East	Western Europe, Australia, New Zealand, Canada, the USA, Japan, Korea, Singapore
Age at midpoint of population immunity (50%)	<5 years	High—5–14 years; intermediate—15–34 years	>35 years
Ig anti-HAV	>90%	<50%	<50%
Childhood infections	Universal	Uncommon	Nil
Immunity	High	Low	Very low
HAV circulation in community	Very common	Common	Negligible
Adult infections	Not seen	Common (paradoxical)	Not seen
Disease load	Negligible	Adolescents and adults	Special groups (travelers); schools; camps
Outbreaks	Not seen	Person to person, food-borne	Food-borne outbreaks (imported)

HAV spreads over developed world including Western Europe, Australia, New Zealand, Canada, the United States, Japan, Korea, and Singapore. Age at midpoint of population immunity (50%) reaches after 35 years of age. HAV circulation in the community is negligible and there is minimal exposure to the virus in the community. HAV infections are reported in travelers to endemic countries. Outbreaks and large-scale epidemics of HAV have been traced to contaminated foods and fruits, imported from endemic zones [29–32].

6.3.1.3 Transmission

Humans are the only natural host for HAV. The virus is a heat-stable and acid/ether-resistant RNA virus [33]. The infectious period starts 1–3 weeks before and lasts for 1–8 days after onset of jaundice. HAV transmission is predominantly through orofecal route, either by person-to-person contact or through contaminated food and water. The contact transmission is supported by low hygiene, overcrowded families, and close contact and occurs among international travelers, daycare centers, schools, institutions with mentally challenged, prisoners, and military forces. Water and food items like milk, milk products, seafoods, salads, and ice creams can get contaminated and spread HAV infection especially to Western travelers in endemic regions of the world [30, 34]. Western travelers to endemic regions are at high risk of getting infected through contaminated food and water [35]. Infected food handlers may contaminate foodstuffs and beverages and result in outbreaks of HAV [36]. Outbreaks and large-scale epidemics of hepatitis A have been traced to consumption of raw or partially cooked bivalve molluscs including mussels, oysters, and clams

[37, 38]. Bivalve molluscs concentrate HAV over 100-fold from contaminated seawater and the virus stays live inside the organism for up to 7 days [39]. The Shanghai epidemic of 1988, causing more than 300,000 cases, was caused by contaminated clams [40]. Bloodborne transmission of HAV infection is rare [41]. Outbreaks of HAV infection occurring in injecting drug users (IDUs) may be caused by sharing infected needles [42]. HAV infection does also spread among men having sex with men [43].

6.3.2 Hepatitis B Virus

6.3.2.1 Agent

HBV is recognized as a member among the family of animal viruses, hepadnaviruses (hepatotropic DNA viruses), and is classified as hepadnavirus type 1. Three types of viral particles, namely 42 nm Dane particle, 20 nm wide tubular forms of varying length, and 22 nm spherical particles, are visualized under electron microscope [44]. The infectious virion (Dane particle) has double-shelled structure consisting of outer lipid envelope containing hepatitis B surface antigen (HBsAg) and an inner nucleocapsid consisting of hepatitis B core antigen (HBcAg), hepatitis B e antigen (HBeAg), viral DNA genome, and DNA polymerase. HBcAg is the protein product, has no signal peptide, and is not secreted, but assembles into nucleocapsid particles. Hepatitis B e antigen (HBeAg) is a non-particulate soluble nucleocapsid protein and is immunologically distinct from HBcAg. The tubules and the spherical particles consist of HBsAg and lack viral DNA and are thus noninfectious. The HBV genome is about 3.2 kb and has four partially circular overlapping open reading frames (ORF), namely S, P, C, and X ORFs. S ORF comprises pre-S1, pre-S2, and S-regions and code for viral surface proteins, the HBsAg. C ORF consists of core and pre-core regions and codes for HBcAg and HBeAg, respectively. The larger P gene encodes for DNA polymerase. The X gene encodes for HBxAg, a protein whose clinical relevance is not known. HBV has been classified into eight genotypes named as A to H, based on sequence divergence [45].

6.3.2.2 Epidemiology

HBV is a global disease. Based on seroprevalence, world is divided into three zones, namely high, intermediate, and low endemic zones. High endemic zone includes China, Southeast Asia, sub-Saharan Africa, and Alaska, with a HBsAg carrier rate of over 8%. Intermediate zone includes India and Japan, with a HBsAg carrier rate of 3–5%. In low endemic zones such as the United States, Western Europe, and Australia, the carrier rate is 0.1–2% [15]. There is marked epidemiological change in global HBV infection due to impact of immigration and migrants [46]. This change is perceptible in low endemic areas, namely the United States and the Western Europe. Immigrant population in the United States has reached 81 million or 26% of overall population. Around 1 million population has moved out of conflict zone in Syria and nearly half of these are in Germany. In the United States, effective childhood vaccination has reduced childhood infections, but HBV disease

load has not been reduced correspondingly. Most of the disease load is due to high prevalence of HBV infection in foreign-born or locally born to immigrant population.

6.3.2.3 Transmission

The virus has highest titers in serum and blood, followed by saliva, semen, and vaginal fluids and lowest in tears, urine, feces, and breast milk. HBV can spread by a multitude of routes; however, mode of transmission is determined by the endemicity of the disease and healthcare practices in the region. In high endemic zones, perinatal (mother-to-child) transmission is the most important route spread of HBV. The chances of transmission to the baby are around 5–20% if the mother is HBsAg positive and 70–90% if the mother is HBeAg positive. In intermediate zones, HBV is spread at early age through close contact with the infected persons. This horizontal route of transmission occurs in children below 10 years of age possibly through inapparent infected blood or body fluid exposure. In low endemic zones, namely Europe and the United States, transmission occurs in injection drug users (IDUs). The risk of HBV transmission in IDUs is proportional to the prevalence of HBV in community, drug sharing, and preparation practices. Around 70% of IDUs are infected by 5 years and outbreaks of HBV infections linked to tattooing and acupuncture have been reported. Disease load of HBV infections in IDUs is substantially high. Of the total 16 million (range 11–21 million) IDUs globally, around 1.2 million are HBV infected. Another route of transmission in such countries is sexual route of transmission, which occurs in men who have sex with men (MSM) and promiscuous persons with multiple sex partners (MSP). Transfusion-transmitted HBV has nearly been eliminated in developed countries; however, it continues to be a problem in developing countries due to poor health practices. Use of unsafe medical injections (use and reuse of syringes and needles) has caused a huge burden of HIV, HCV, and HBV infections in the developing countries. Over the years, WHO safe injection campaign has caused a significant impact in reducing the infection load in these countries [47].

6.3.3 Hepatitis C Virus

6.3.3.1 Agent

HCV is the sole member of the genus Hepacivirus in the family Flaviviridae. HCV virion is a 60 nm enveloped RNA virus. The HCV genome contains a single large ORF (gene) which encodes for a virus polyprotein of around 3000 amino acids, which is cleaved after translation into 10 proteins by both host and viral proteases. These include three envelope glycoproteins at 5′ end from C, E1, and E2 regions of the genome, an adjacent membrane protein from P7 region, and six nonstructural proteins at 3′ end from NS2, NS3, NS4A, NS4B, NS5A, and NS5B regions of the genome. NS2 codes for a cysteine protease; NS3 codes for a serine protease and an RNA helicase; NS4A, NS4B, NS5A, and NS5B code for RNA-dependent RNA polymerase rate. At least six distinct genotypes with >50 subtypes within the

genotypes have been identified by sequence analysis. Because of high mutation rate, intragenotype differences result in formation of *quasispecies*, which differ in sequence homology by a few percent [48, 49].

6.3.3.2 Epidemiology

HCV is a global disease with consistent prevalence over most of the regions of the world. Around 3% of world population is infected with HCV. The seroprevalence varies from 0.5 to 2.0%. However, few regions of the world, namely Egypt and Japan, have high HCV prevalence. The reasons for such high infection load are related to mass vaccination program against schistosomiasis between 1961 and 1985 in Egypt and use of blood transfusions during the Second World War in Japan. Anti-HCV prevalence is high in IDUs, African-Americans, hemophiliacs, patients on hemodialysis, and lifetime sexual partners [50].

6.3.3.3 Transmission

Blood and blood product transfusions have been the major sources of HCV transmission till 1980. Posttransfusion HCV has been nearly eliminated in developed countries due to routine screening of blood and blood products for anti-HCV. However, transfusion-transmitted HCV continues to be a problem in developing countries. Today, dominant source of HCV transmission occurs percutaneously in IDUs and due to use of unsafe medical injections (use and reuse of syringes and needles). The disease load in IDUs is high and it is estimated that around 10 million IDUs are infected with HCV. Nosocomial HCV infections due to use and reuse of syringes/needles is a major problem in developed countries and causes between 2.3 and 4.7 million new infections per year. Epidemic HCV in Egypt was related to mass injectable treatment of schistosomiasis in 1980s, leading to prevalence of 14% (20–30% in young adults). Vertical transmission from mother to fetus does not occur, except when HCV viral load is high or with concomitant HIV infection. HCV can be transmitted in hemodialysis centers (10–30%); through sexual route; and through breast milk and nonsexual intrafamilial contacts. However, such routes of transmission are not important from public health perspective [51].

6.3.4 Hepatitis D Virus

6.3.4.1 Agent

HDV is a 36 nm defective RNA plant virus which requires the helper function of HBV for replication and expression and can only coinfect with either HBV infection or superinfection on chronic HBV infection. The delta antigen is the inner ribonucleoprotein of the subviral particle enveloped by the HBsAg and consists of small and large delta antigens and a single-stranded circular RNA genome 1.7 kb in length. The genome has extensive self-complementation to form rodlike structures. The HDV genome uses host RNA polymerase II to carry out RNA-directed RNA synthesis [52].

6.3.4.2 Epidemiology

The prevalence of HDV mimics that of HBsAg because HDV is an incomplete virus and can only infect along or over HBV infection. Around 5% carriers of HBsAg are coinfected with HDV infection. However, there are regions of the world with high occurrence of HDV infection, namely Mongolia, southern Mediterranean, Amazon basin, and tropical and subtropical Africa [53]. Previous data showed that there is a decline in prevalence of HDV infection and HDV was nicknamed as a disappearing virus. However, recent data have shown that this is not true anymore [18]. Worldwide 15–20 million people are infected with HDV with wide varying prevalence depending on the region. Recent data show increasing prevalence in low endemic areas (the United States, Australia, and Europe) and very high prevalence in endemic regions (Mediterranean, the Middle East, Amazon, West Africa, northern Asia, and Vietnam) despite implementation of HBV vaccine program. Immigration is a risk for HDV as well. Sexual transmission is an important factor in transmission of HDV, in addition to known risk in IDUs.

6.3.4.3 Transmission

HDV transmission occurs only in the presence of HBV infection. Thus, HDV is transmitted in a similar fashion as HBV infection. Thus, blood and blood products, IDUs, and sexual transmission are major routes of transmission. In endemic zones like Mongolia, Africa, and the Amazon basin, transmission of HDV infection is possibly related to tribal practices or cultural customs exposing individuals to blood percutaneously or through sexual routes [54]. Perinatal transmission of HDV infection is rare.

6.3.5 Hepatitis E Virus

6.3.5.1 Agent

HEV has marked heterogeneity and is widely distributed in animal kingdom [55] (Fig. 6.3). HEV has been classified in the family *Hepeviridae*, with two genera: *Orthohepevirus* with four species A–D and *Piscihepevirus* with one isolate infecting cutthroat trout [56]. *Orthohepevirus A* species comprises seven HEV isolates (genotype HEV-1 to HEV-7). These include two isolates involving human alone (genotypes HEV-1 and HEV-2), two isolates prevalent in pigs, boar, deer, and infecting humans (HEV-3 and HEV-4), two isolates infecting wild boar in Japan (HEV-5 and HEV-6), and one isolate identified in dromedaries from Dubai, which also infected a liver-transplant patient (HEV-7). The genome of the virus is a single-stranded RNA of ~7.2 kb, with7-methylguanine cap (m^7G) at its 5′ end and is polyadenylated at its 3′ end. HEV RNA replicons express genomic RNA and only one bicistronic 2.2 kb subgenomic RNA. The genome has three partially overlapping open reading frames (ORF). ORF1 encodes a nonstructural polyprotein (pORF1), ORF2 encodes the major viral capsid protein (pORF2), and ORF3 encodes a small phosphoprotein (pORF3), which is associated with the cytoskeleton and microtubules. This phosphoprotein is also involved in HEV egress from hepatocytes [57]).

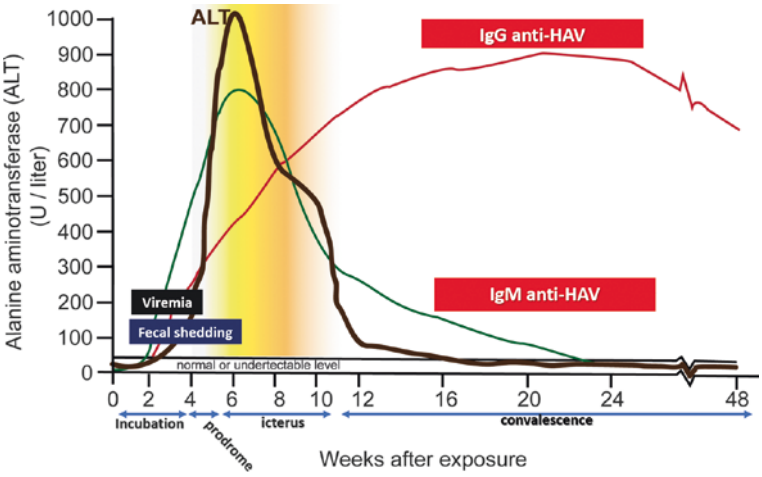

Fig. 6.3 Sequence of events following HAV infection

6.3.5.2 Epidemiology

HEV has a global distribution [14]. There are several global epidemiological disease patterns [58]. Hyperendemic disease caused by HEV-1 occurs in developing countries and presents as massive waterborne outbreaks of hepatitis, which hit such regions on periodic intervals [59]. Around a half of endemic disease in such regions is caused by hepatitis E [60, 61]. HEV-2 has been reported to cause hyperendemic disease in Central America (Mexico) and West Africa. Hepatitis E in endemic zone accounts for nearly one-fourth of sporadic acute viral hepatitis. No epidemic of hepatitis E is reported in these regions. This zone includes several countries in Middle East, southeast Asia, Taiwan, and Central and Eastern China. The disease is etiologically related to HEV-1 in the Middle East, while HEV-4 is the predominant prevalent genotype in Taiwan, China, and Southeast Asia [62, 63]. A distinctive hepatitis E zone is limited to Egypt [64, 65]. Autochthonous sporadic HEV infections in industrialized countries are spread through food-borne zoonotic transmission; however, some cases may be transfusion associated. The disease is caused by HEV-3 in all these countries; however, HEV-4 contributes to disease in Japan and few European countries [66–69].

6.3.5.3 Transmission

Hepatitis E transmission is predominantly waterborne in developing countries and causes large-scale epidemics of jaundice, involving hundreds and thousands of cases [59, 70–72]. Person-to-person transmission has been documented in one epidemic [73] and suspected in another epidemic with multiple epidemic peaks over protracted period [71]. Endemic hepatitis E disease in developing countries is possibly transmitted from one person to another [74–76]. Hepatitis E in industrialized countries is a zoonotic disease [55]. HEV-3 and HEV-4 are ubiquitous in domestic

pigs, wild boar, and sika deer and show cross-transmission of infection from one animal species to another. The common practice of eating of parboiled flesh or liver of game animals can cause autochthonous isolated cases and small outbreaks of hepatitis E ([77] (Fig. 8)). Pig liver in the supermarket and Corsican figatelli sausage in several industrialized countries are infected with live HEV and consumptions of these food items can cause human infections [78–80]. Another risk factor for HEV transmission is vocational exposure of veterinarians and workers to pig farms, pig manure, and pig sewage. Several agricultural products like raspberry, strawberry, and other vegetables can get infected from pig slurry used as a pasture fertilizer and can transmit hepatitis E. Similarly, surface runoff of the pig slurry can contaminate surface water, which in turn can contaminate produces like fruits and vegetables. These runoffs can also contaminate coastal waters, fish, and shellfish, which are risk factors for spread of hepatitis E. Transfusion-associated HEV infections are being recognized as an important mode of transmission [81–88]. In view of published data, there is urgent need to conduct donor-screening program for HEV in many industrialized countries using NAT testing. Vertical transmission from HEV-infected mother to fetus and neonates is known to occur frequently [89]. Intrauterine fetal and neonatal HEV infections cause significant perinatal morbidity and mortality [90]. Occurrence and severity of fetal HEV infections correlate with severity of liver disease in the mother [91]. HEV is known to replicate in many body tissues including placenta and placental infections correlate with fetal and maternal mortality [92]. Colostrum from infected mothers is often positive for HEV RNA [93]. As viral titers are low, breastfeeding is an unlikely route of transmission for neonatal HEV infections. Camelid HEV-7 infection can be transmitted from camel milk as reported in a liver-transplant patient from Dubai [94].

6.4 Clinical Manifestations

6.4.1 Acute Hepatitic Syndrome

Infection with hepatitis viruses presents as a clinical syndrome of acute hepatitis. It is not possible to differentiate one form of hepatitis viral infection from another on clinical manifestations alone. The disease can present as subclinical infection with isolated elevation of aminotransferases to fulminant hepatitis with frank jaundice and rapidly developing liver failure. Overall around 20% of infections present with jaundice. The infection is asymptomatic during incubation period which varies with the type of virus infection. Symptoms start with prodrome lasting for 1 day to 2 weeks. Patient complaints of varying constitutional symptoms including malaise, loss of appetite, nausea, vomiting, and fever. In addition, abdominal discomfort and altered bowel habits may occur. The prodrome is followed by icteric phase. With the appearance of jaundice, there is significant abatement of systemic symptoms. The jaundice quickly deepens and reaches a plateau in few days to weeks, followed by slow recrudescence. The duration of icteric phase varies from few days to few months, but averages 4–6 weeks. During the icteric phase patient

develops features of cholestasis of varying degree and duration. Finally, illness enters a recrudescence with resolution of most of the symptoms. Weight loss of 2–10 kg is not uncommon. Fatigue lasts for 2–6 months. Physical examination reveals icterus of varying degree, itching marks during cholestasis, and tender soft and smooth hepatomegaly. Splenomegaly and cervical lymphadenopathy are detected in 10–20% of patients. Rarely few spider angiomas may appear which disappear during convalescence [95].

6.4.1.1 Acute Hepatitis A

Acute hepatitis A disease passes through four phases including incubation period (15–45 days), prodromal symptoms (1–7 days), icteric period (2–6 weeks), and convalescence (up to 6 weeks) (Fig. 6.3). The clinical outcome is strongly correlated with age. HAV infection in children below 6 years of age is either asymptomatic or subclinical, while older children and adults commonly experience symptomatic disease [96]. A small percentage may present with unusual variant called cholestatic hepatitis A [97]. Patients have protracted clinical course lasting for 12–18 weeks and is dominated by severe cholestasis with deep jaundice, dark urine, clay stools, and severe itching, resembling large bile duct obstruction. All patients show clearance of the virus and clinical recovery. Occasionally, HAV disease relapses in some patients after recovery from the acute illness [98]. Relapse is characterized by reappearance of jaundice and other symptoms of hepatitis with abnormalities of liver tests and fecal viral shedding [99]. All patients eventually recover. Fulminant hepatitis A occurs in 1:1000 cases of acute hepatitis A and may be fatal [100]. The disease can be recognized early on by worsening prothrombin time, significant reduction in liver size (detected on percussion for liver dullness), irritability, and alteration in sleep rhythm. The risk for fulminant hepatitis increases with patients' age and is particularly high in patients above 30 years [101]. HAV superinfection in patients with compensated chronic liver disease is of higher risk for fulminant hepatitis A [102].

Extrahepatic manifestations of acute hepatitis A include joint pains, cutaneous vasculitis, cryoglobulinemia, pancreatitis, myocarditis, atypical pneumonia, aplastic anemia, red cell aplasia, and neurologic syndrome such as Guillain-Barre, myelopathy, mononeuritis, and meningoencephalitis [103, 104]. Rarely autoimmune hepatitis can be triggered by a self-limited acute hepatitis A [105]. HAV infection in patients with glucose-6-phospahtase deficiency or sickle cell anemia can induce acute hemolytic crises leading to extremely high levels of serum bilirubin ($\geq$30 mg/dL). This is not necessarily associated with a poor prognosis.

6.4.1.2 Acute Hepatitis B

The clinical syndromes with acute hepatitis B virus infection are directly related to the age of occurrence of the disease. Acute hepatitis B in neonates (perinatal transmission) is invariably asymptomatic, with normal liver enzymes and liver histology with HBeAg positivity and circulating HBV DNA. Most of these neonates (>98%) fail to clear the virus and become chronic HBV carriers. Children and young adults often get infected through horizontal transmission of HBV infection. Such patients

are HBsAg/HBeAg positive and have detectable circulating HBV DNA. The persons rapidly clear circulating HBV DNA and around 10% become chronic HBV carriers. HBV infection in adults can present with acute hepatitic syndrome of varying severity. Most of such patients clear the virus and become HBsAg negative with detectable antibody to hepatitis B surface antigen (anti-HBs). Less than 5% of such patients become chronic carriers of HBsAg [106].

Around 5–15% of acute hepatitis B develop acute serum sickness-like illness. It presents as low-grade fever, rash, arthralgia, and angioneurotic edema. Another well-described association with acute hepatitis B infection is polyarteritis nodosa. It occurs in around one-third of newly diagnosed cases of HBV infection and results from deposition of antigen-antibody complexes (HBsAg/anti-HBs) in the intima of blood vessels. Patients present with arthralgia, fever, abdominal pain, skin rash, mononeuritis, and renal disease. Another extrahepatic manifestation of HAV, HBV, HCV, and HEV infection is essential mixed cryoglobulinemia. Of the hepatitis viruses, essential mixed cryoglobulinemia is strongly associated with HCV infection. Acute HBV and HCV can cause renal disease. The spectrum of renal disease with acute viral hepatitis varies from mild proteinuria with abnormal urinary sediment to frank glomerulonephritis with renal failure. Histologically, both membranous and membranoproliferative glomerulonephritis have been reported. The disease occurs because of deposition of immune complexes of HBsAg, HBeAg, and HCV on the glomerular basement membrane. Papular acrodermatitis (Gianotti syndrome) has been reported in children of 1–6 years with acute hepatitis B. The syndrome causes self-limiting papular rash on arms, legs, and face with generalized lymphadenopathy [107].

6.4.1.3 Acute Hepatitis C

Acute hepatitis C is generally asymptomatic or presents with nonspecific symptoms such as mild fever, malaise, nausea, anorexia, arthralgia, and vague abdominal discomfort. It accounts for 25% of acute hepatitis in the United States. Acute HCV does not cause fulminant hepatitis unless there is concurrent coinfection with another hepatitis virus such as HBV. Majority of patients with acute HCV progress to chronic HCV infection. Spontaneous recovery with clearance of the virus occurs in a small percentage of patients. HCV infection can cause a wide spectrum of extrahepatic manifestations including essential mixed cryoglobulinemia, glomerulonephritis, leukocytoclastic vasculitis, neuropathy, large B-cell lymphoma, and autoimmune diseases [108].

6.4.1.4 Acute Hepatitis D

Hepatitis D infection can coinfect with acute HBV infection or superinfect chronic hepatitis B carriers. HDV/HBV coinfection causes self-limiting acute hepatitis. Fulminant hepatitis failure has been reported but is rare. Chronic HDV carrier state does not occur as HDV infection cannot persist after clearance of HBV infection. HDV superinfection on chronic hepatitis B carrier can result in severe hepatitis and may result in fulminant hepatitis. Majority of such patients result in chronic hepatitis D infection [109].

6.4.1.5 Acute Hepatitis E

The clinical manifestations of acute hepatitis E include classical acute hepatitic syndrome with incubation period (15–45 days), prodromal symptoms (1–7 days), icteric period (2–6 weeks), and convalescence (up to 6 weeks) [110, 111]. HEV infection can present from subclinical infection to typical acute viral hepatitis, and to acute liver failure [100, 112, 113]. Most of the patients with epidemic or endemic hepatitis E in developing countries are young adults (15–45 years) (Table 6.4). Cholestatic features occur in around 20% of patients and are more pronounced [110]. Disease runs a severe clinical course in pregnant women, with maternal mortality of over 44.4% in third trimester [75, 114]. The clinical profile of acute liver failure during pregnancy is dramatic with severe encephalopathy, gastrointestinal bleeding, cerebral edema, and cerebellar coning developing in a matter of few days. HEV infections can superinfect patients with well-compensated liver cirrhosis and culminate in rapid hepatic decompensation and death [115–118]. HEV superinfection occurs in approximately 21% of cirrhotic patients in India with a rapid worsening in liver synthetic function, causes rapidly progressive liver failure, and culminates in 30-day mortality of 34%. Almost all cases of hepatitis E in developing countries are self-limiting unless patients are immune suppressed. However, there may be relapse of clinical and biochemical disease activity in an occasional patient and a small percentage of patients present with prolonged cholestasis as seen in hepatitis A [119].

Hepatitis E in industrialized countries is seen as an autochthonous infection, caused by HEV-3 and HEV-4 and mostly related to zoonotic food-borne transmission or following blood transfusion [77, 82, 83, 120–122]. Disease occurs in higher age groups and has more severe clinical manifestations than disease in endemic zones. Hepatic and extrahepatic complications are reported in around 15% of such patients and acute liver failure occurs in 8–11% of patients. HEV superinfection in patients with chronic alcoholic with cirrhosis in these countries leads to rapid hepatic decompensation and high mortality. Hepatitis E in such regions does not cause high mortality in pregnant women.

Most HEV infections run a self-limiting course with eventual clinical, biochemical, and virologic recovery. However, a subset of immunocompromised patients with solid-organ transplant, HIV, and hematological neoplasm infected with HEV-3 can cause chronic hepatitis E and cirrhosis [120, 123, 124]. The diagnostic criteria of chronic hepatitis E include persistent viremia using PCR in blood and stool and modest liver abnormalities lasting beyond 3 months. Acute HEV disease usually is asymptomatic with isolated liver enzyme abnormality, resembling drug toxicity. However, a subgroup of patients run a rapid downhill course with progressive liver fibrosis and cirrhosis, culminating in end-stage liver disease in a 2–3 years' period. Use of tacrolimus, low platelet, and low CD4 in HIV-infected patients are of high risk for development of liver fibrosis [125].

Hepatitis E can present with wide range of extrahepatic manifestations, including cryoglobulinemia with skin rashes, glomerulonephritis, autoimmune thyroiditis, thrombocytopenia, aplastic anemia, myositis, and acute pancreatitis [126–131]. A small percentage of infected patients present with broad group of manifestations

involving nervous system. These include Guillain–Barre syndrome, brachial neuropathy, peripheral neuropathy, and Bell's palsy [126, 132–135]. Extrahepatic hepatitis E disease has global distribution, is independent of genotype, and has variable clinical outcome. Pathogenesis of HEV-related manifestations of nervous system may be multifactorial. HEV may trigger immune reactions and induce antiganglioside antibodies through molecular mimicry [136]. Also, HEV replicates in many body tissues and shows significant neurotropism, which may cause disease.

6.4.2 Diagnosis

6.4.2.1 Serum Chemistry

Patients with acute viral hepatitis during incubation period have no abnormality in laboratory tests. Alanine transaminase (ALT) and aspartate transaminase (AST) are elevated during prodromal phase, while serum bilirubin remains within normal limits. The peak levels may vary and can reach from 400 to 4000 IU or more. The serum enzymes show a progressive decline in the convalescence and eventually return to normal. The magnitude of rise in serum enzymes has no prognostic significance. Serum alkaline phosphatase may be normal or show mild elevation. However, patients with cholestatic hepatitis A depict marked elevation of serum alkaline phosphatase and GGT. Serum albumin levels stay unchanged in most patients [137].

Serum bilirubin rises above 2.5 mg/dL during the icteric phase of disease. Serum bilirubin rises to levels ranging from 5 to 20 mg/dL. Hyperbilirubinemia is biphasic, with rise of both conjugated and unconjugated bilirubin. Deep jaundice with serum bilirubin levels of 20 mg/dL is associated with severe disease. Acute viral hepatitis is associated with several abnormalities in blood counts including transient neutropenia and lymphopenia followed by relative lymphocytosis and atypical lymphocytes (2–20%). The INR has prognostic significance and increased values occur in patients with severe hepatic synthetic defect, which signifies extensive hepatocellular necrosis. Hypoglycemia occurs occasionally and is related to inadequate intake with underlying poor hepatic glycogen reserves.

6.4.2.2 Serology

Patients with acute viral hepatitis need to be tested for acute serological markers of hepatitis A (IgM anti-HAV), hepatitis B (HBsAg and IgM anti-HBc), hepatitis C (anti-HCV), and hepatitis E (IgM anti-HEV) [1] (Table 6.3). A diagnosis of acute hepatitis A is made if anti-HAV is positive. IgM anti-HAV is detectable during early clinical disease and stays reactive for 4–6 months and is the gold standard for diagnosis of acute HAV infection [138–140]. IgG anti-HAV is detected during acute phase and persist for life. IgG anti-HAV is used to evaluate seroprevalence of HAV. Stool HAV RNA is rarely employed for diagnosis of acute hepatitis A [141]. The presence of HBsAg along with reactive IgM anti-HBc suggests acute hepatitis B infection. If IgM anti-HBc is not detected in the presence of reactive HBsAg, a diagnosis of chronic hepatitis B is made. Such patients need further testing for HBeAg and anti-HBe to test for relative infectivity. Sometimes HBsAg may be

Table 6.3 Diagnostic approach in patients with acute hepatitis

Tests					
IgM anti-HAV	HbsAg	IgM anti-HBc	Anti-HCV	IgM anti-HEV	Interpretation
+	–	–	–	–	Acute hepatitis A
–	+/–	+	–	–	Acute hepatitis B
–	+	–	–	–	Chronic hepatitis B
–	–	–	+	–	Acute/chronic hepatitis C
–	–	–	–	+	Acute hepatitis E
–	–	–	–	–	Non-A–E hepatitis

1. Patients with dual infections have serological tests positive for more than one hepatitis virus.
2. Anti-HCV may be nonreactive in immunocompromised patients and such patients need HCV RNA testing; HCV serology and/or HCV RNA test cannot differentiate acute from chronic HCV infection.
3. Patients with chronic hepatitis B need tests for HBeAg/anti-HBe and HBV DNA to evaluate chronic HBV infection.
4. IgM anti-HEV may be nonreactive in immunocompromised patients and need tests for HEV RNA (stool/blood).
5. Anti-HDV should be tested in severe and/or fulminant disease hepatitis B, severe chronic hepatitis B, chronic hepatitis B with acute hepatitis exacerbation, and hepatitis B persons from endemic area.
6. Non-A–E hepatitis patients should be tested for infectious mononucleosis, cytomegalovirus, herpes simplex, and toxoplasmosis.

absent in the presence of IgM anti-HBc in acute hepatitis B infection. The presence of anti-HCV suggests diagnosis of acute hepatitis C. Acute hepatitis E is diagnosed if IgM anti-HEV is reactive. Anti-HDV should be tested in patients with acute or chronic hepatitis B under the following circumstances: i. severe and/or fulminant disease, ii. severe chronic hepatitis, iii. chronic hepatitis B with acute hepatitis exacerbation, and iv. persons from endemic area. Family members of hepatitis B need to be assessed for HBsAg, anti-HBc, and anti-HBs to check for immunity and susceptibility to HBV and need for vaccination. Absence of all serological markers suggests diagnosis of non-A–E hepatitis.

6.4.2.3 Nucleic Acid Testing

Occasionally anti-HCV may be nonreactive early during acute hepatitis C infection or in immunosuppressed patients and patients with chronic renal failure. In such circumstances, testing for HCV RNA is confirmatory. Patients suspected of chronic hepatitis B need to be tested for HBV DNA. HEV RNA detection in serum and stools has a role in diagnosing HEV infections in immunocompromised patients, who often show negative IgM anti-HEV test [142, 143]. The test is also useful in the diagnosis of chronic HEV-3 infection. Such patients continue to be viremic and show fecal viral shedding beyond 3 months. Serial HEV RNA testing is essential to document response to antiviral drug therapy [144–146].

6.4.2.4 Testing for Other Viral and Infectious Agents

Patients with acute hepatitis and negative serological tests of HAV, HBV, HCV, and HEV infection may need testing for other viral infections such as infectious mononucleosis, cytomegalovirus, herpes simplex, and toxoplasmosis. Other infections, namely *Leptospira, Candida, Brucella, Mycobacteria* and *pneumocystis*, may cause elevated aminotransferases and need appropriate tests [8].

6.4.2.5 Other Causes of Acute Hepatitis

Acute hepatitis syndrome can occur due to drug toxicity and drug history is important in the evaluation of such patients. Alcoholic hepatitis can cause moderate elevation of aminotransferases and other stigmata of alcoholism. Right ventricular failure with hepatic venous congestion may mimic acute hepatitic syndrome. Patients with severe left ventricular pump failure, severe hypoperfusion, and shock can result in ischemic liver injury and cause acute hepatitic syndrome. Other clinical syndromes such as acute fatty liver of pregnancy, cholestasis of pregnancy, eclampsia, and HELLP (hemolysis, elevated liver tests, and low platelets) need to be considered in patients with unexplained acute hepatitis syndrome [1].

6.4.3 Management

6.4.3.1 General Treatment Measures

Patients with acute viral hepatitis need supportive treatment [137]. During prodromal period, nausea and vomiting need treatment with antiemetic. Few patients require short hospital stay to manage dehydration. Intravenous alimentation is rarely needed in patients who have persistent vomiting and cannot maintain oral intake. Patients often need bed rest with bathroom privileges during prodromal and icteric disease. Later patients should be advised to restrict activity and given no-work advice till disease recovery ensues. Restriction of diet has no proven benefit. A high-calorie diet is advisable. Low-fat, high-carbohydrate diet is often enforced. However, apart from being palatable this regimen has no added advantage. Alcohol and hepatotoxic drugs should be avoided. Acetaminophen may be administered if needed to a maximum dose of 2–4 g/day in adults. Patients with cholestasis may benefit from bile salt sequestering resin cholestyramine and/or ursodeoxycholic acid (UDCA) [147]. Corticosteroid therapy has no role, even in severe cases, unless there is evidence for autoimmune hepatitis. At the outset, it is not possible to predict the course of disease and all patients need to be watched carefully for severe disease and impending acute liver failure. Patients with rapidly shrinking liver size, high INR, rapid rise in serum bilirubin and ascites with confusion, altered sleep pattern, and disorientation should be identified early and admitted to intensive care for management of acute liver failure. Liver transplantation has been done in patients with progressive liver failure [100, 148].

6.4.4 Specific Treatment

6.4.4.1 Acute Hepatitis A

Patients with acute hepatitis A do not benefit from antiviral therapy. Cholestatic hepatitis A has excellent prognosis with eventual recovery. However, a short course of prednisolone 30 mg per day reducing it to zero over 3 weeks may shorten the course of cholestasis.

6.4.4.2 Acute Hepatitis B

Most of the patients with acute hepatitis B do not benefit from antiviral therapy. However, severe acute hepatitis with high INR (>1.5) and early signs of liver failure should be treated with antiviral therapy. The drug of choice in such conditions is entecavir or tenofovir. Recent introduction of tenofovir alafenamide is welcome, as the drug is less nephrotoxic and safer for bones. Patients with acute-on-chronic hepatitis B benefit from antiviral therapy. Patients with HBV reactivation syndrome should receive antiviral therapy [149].

6.4.4.3 Acute Hepatitis C

Patients with clinically evident acute hepatitis C benefit from antiviral therapy. Studies show that 6-week course of IFN-free direct-acting antivirals (DAA) can improve clinical outcome, is highly effective, and can prevent progression to chronic phase of infection [150].

6.4.4.4 Acute Hepatitis E

Patients with acute hepatitis E need supportive care as in any other cause of acute hepatitis. HEV infection in pregnant women needs a careful combined approach between the hepatologist and the obstetrician [75]. Such patients are at high risk of acute liver failure. Patients with impending signs of acute liver failure need intensive care management. Termination of pregnancy and its beneficial effects on liver disease in the mother are debatable [91]. Vertical HEV transmission to fetus causes intrauterine deaths and high perinatal morbidity and mortality [89, 90]. Neonates born to such mothers need neonatal intensive care management. HEV superinfection in compensated chronic liver disease presents as rapid acute-on-chronic hepatic decompensation. Patients need active management of complications of liver failure, namely ascites, encephalopathy, variceal bleed, and renal failure. Such patients and those with chronic hepatitis E may benefit from ribavirin therapy against HEV infection [146, 151–153] (Table 6.4).

6.4.5 Global Control

6.4.5.1 Acute Hepatitis A

Global control of hepatitis A is dependent upon improved socioeconomic status, improvement in living standards, availability of safe potable water, and proper sewage disposal. We need to target personal hygiene practices like regular hand

Table 6.4 Effect of drugs on HEV replication and their use and impact on immunosuppressant therapy during chronic HEV infection in solid-organ-transplant patients

Class	Drug	Effect on HEV replication	Clinical use
Calcineurin inhibitors	Cyclosporine, tacrolimus	Stimulates HEV replication with increase in HEV load and promotes HEV persistence	Reduce dose
mTOR inhibitors	Rapamycin, everolimus	Stimulates HEV replication with increase in HEV load	Reduce dose
Antimetabolite immunosuppressant	Mycophenolate mofetil	Inhibits HEV replication and helps HEV clearance	Continue the drug
Guanosine analog	Ribavirin	Inhibits HEV replication and causes HEV clearance	Primary drug for therapy
Cytokines	PEGylated interferon α	Inhibits HEV replication and causes HEV clearance	Indicated if ribavirin therapy fails
Nucleotide analog	Sofosbuvir	Inhibits HEV replication in vitro	Unclear, clinical trials indicated

washing, especially in schools, offices, homes for mentally challenged, etc., and help to reduce risk of infection. Western tourists should be discouraged from ingestion of uncooked or inadequately cooked foods, salads, untreated tap water, and ice creams.

Both passive and active immunization are playing a major role in global control of hepatitis A [25, 154, 155]. IG, administered 0.02 mL/kg, prevents clinically apparent hepatitis A when administered before exposure as in international travelers or following exposure as in intimate contacts. HAV vaccine is safe, immunogenic, and effective in preventing hepatitis A [156, 157] (Table 6.5). Vaccine is safe above 1 year age and protects 4 weeks after a primary inoculation [158]. Based on the global epidemiology and hepatitis A disease pattern, WHO has put forward recommendations for global pre-exposure prophylaxis. These include the following:

1. HAV vaccination programs are not recommended in very high endemic zones. In such countries, there is universal exposure to HAV infection in children below 5 years of age, and thus the population is protected from HAV infection.
2. Countries with improving socioeconomic status and with high-to-intermediate endemicity have high rate of HAV infection in adults. It is recommended that HAV vaccination program should be incorporated into national immunization schedule for children over 1 year of age. This decision should be individualized for each country based on the incidence of acute infections, magnitude of change from high to intermediate endemicity, and cost considerations. This algorithm causes a striking decrease in the incidence of new and symptomatic HAV infections [159–162].
3. In low endemic zones, HAV circulation is negligible and HAV is rarely reported in adults. Thus, mass vaccination is not recommended. However, most adult population lack anti-HAV and are susceptible to HAV infection. So, targeted

Table 6.5 Hepatitis A vaccines

Vaccine	Age yr.	Dose (mL)	Antigen quantity	Schedule
Monovalent inactivated HAV vaccines				
Havrix (GSK) Junior	2–16	0.5	720 ELISA units inactivated HAV antigen	0. 6–12 months
Havrix (GSK) 1440	>16	1	1440 ELISA units inactivated HAV antigen	0, 6–12 months
Vaqta (Merck) Paed	1–18	0.5	25 units inactivated protein	0, 6–18 months
Vaqta (Merck) Adult	>18	1	50 units inactivated protein	0, 6–18 months
Avaxim (Sanofi)	>2	0.5	160 ELISA units of inactivated HAV antigen	0, 6–12 months
Combined HAV-HBV vaccine				
Twinrix (GSK) Junior	1–16	0.5 l	360 ELISA units HAV and 10 µg recombinant HBsAg protein	0, 1, 6 months
Twinrix (GSK) 720/20	2–16	1	720 ELISA units HAV & 20 µg recombinant HBsAg protein	0, 1, 6 months
Combined HAV-typhoid vaccine				
Vivaxim (Sanofi)	>16	1	160 ELISA units HAV antigen	0, 6–36 months
Live attenuated HAV vaccine (Chinese)				
H2 strain	>1	1	$10^{5.50}$ $TCID_{50}$ given subcutaneously (tissue culture infective dose)	Single dose
L-A-1 strain	>1	1	$10^{5.50}$ $TCID_{50}$ given subcutaneously (tissue culture infective dose)	Single dose

vaccination in selected groups, who are at increased risk of infection, is recommended. These include (i) travelers to intermediate and high endemic zones; (ii) people needing lifelong blood products; (iii) males who have sex with males; (iv) injection drug users; and (v) patients with cirrhosis, as they run a risk of a severe clinical disease course.

4. HAV vaccine is now being recommended for Western travelers to endemic areas and for contacts of patients with acute HAV infection [163].
5. HAV vaccine has been successfully used to control community-wide outbreaks. Vaccination should be initiated early on during the epidemic. Supplemental health education and improved sanitation need to be enforced.

6.4.5.2 Acute Hepatitis B

Universal vaccination program has caused dramatic decline in the incidence of acute HBV infections in the United States. The incidence of acute hepatitis B in children in Taiwan and Alaska dropped to 0/100,000 population. In countries where HBV vaccine is administered at birth, the subsequent prevalence of HBsAg in children will fall below 1% and approach zero in near future. In countries where HBV vaccine is administered after 6 weeks along with other vaccine, the

prevalence of HBsAg does not fall below 1–2%. In countries with high incidence of HCC in children (Taiwan and Thailand), HBV vaccination has dramatically reduced the incidence below 1% in 10 years. In Alaska, no case of HCC has been reported in children since 1990, 15 years after introduction of infant and catchup vaccination. In other countries with age of occurrence of HCC in fourth decade and later, the impact of the vaccine on incidence of HCC shall occur 40 years after introduction of the vaccination program. Hepatitis B prevention strategies including vaccination program in migrant population to the United States and the Western Europe need to be implemented aggressively to decrease disease load in this population [164, 165].

6.4.5.3 Acute Hepatitis C

Hepatitis C vaccine has been evasive over the years and we are unlikely to get a breakthrough to control global hepatitis C load. Fortunately, introduction of direct-acting antivirals (DAA) has been a game changer in fighting global HCV infection. DAA are administered orally, are highly effective, give a cure in over 95% of HCV infections, and show minimal resistance. The drugs are safe and now we have a pangenotypic DAA. Thus, DAA are the way to control and cause global control of HCV infection. Worldwide eradication of hepatitis C virus (HCV) is possible through a combination of prevention education, universal clinical and targeted community screening, effective linkage to care, and treatment with promising new direct-acting antiviral drug regimens [166].

6.4.5.4 Acute Hepatitis E

Control of hepatitis E in developing countries is a challenging task and needs clean drinking water, good sanitation, and proper personal hygiene [167]. Western travelers to such regions should avoid drinking contaminated water or beverages and avoid eating uncooked shellfish [168]. Patients with solid-organ transplant need to eat properly cooked pork and deer meat. Patients should abstain from eating raw or undercooked pork liver from supermarkets. Intake of Corsican figatelli sausage is a high risk for HEV infection and should be avoided [169]. Development of hepatitis E vaccine has been a major breakthrough in the control of hepatitis E [170]. The Chinese vaccine HEV-239 has been derived from a HEV-1 Chinese isolate. It is a particulate vaccine, consists of truncated ORF2 protein (368–606 amino acids), and has been expressed in *Escherichia coli*. The vaccine induces a healthy T-cell-dependent immune response. HEV-239 marketed as Hecolin in China is administered as 30 μg doses at 0, 1, and 6 months. The vaccine is highly immunogenic and efficacious [171, 172]. HEV-239 has been shown to give cross-protective efficacy against HEV-4. It is imperative that hepatitis E vaccine be made available in other countries for trials and use [173]. To do so, we need to extend vaccine safety data in pediatric age group, elderly, and pregnant women. Postmarketing phase IV study needs to be done once vaccine is available globally. Cost-effectiveness of the vaccine program for prevention of hepatitis E needs to be done [174].

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Correction to: Acute Hepatitis C

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The original version of Chapter 4 was inadvertently published with the incorrect Figure 4.1. The correct figure 4.1 has been corrected below:

The updated online version of this chapter can be found at
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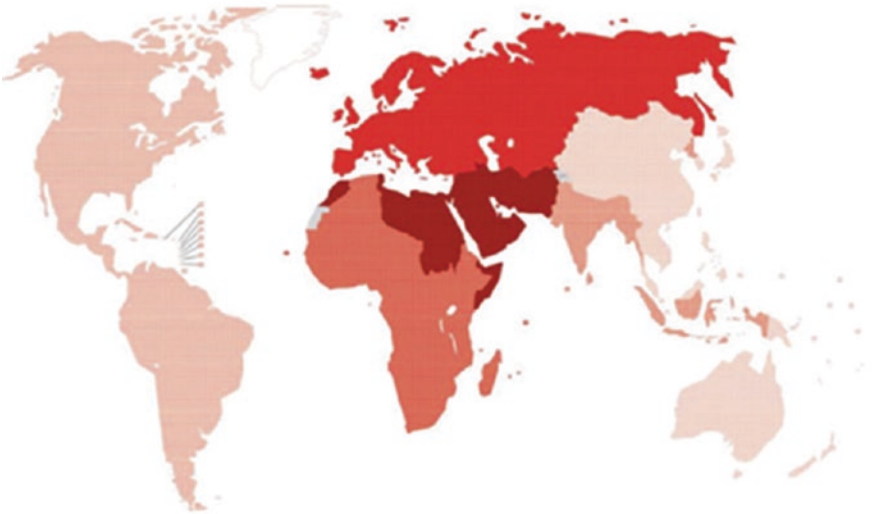

		Incidence of HCV infection			
		Incidence rate (per 100 000)		Total number (000)	
WHO region	Map key	Best estimate	Uncertainty interval	Best estimate	Uncertainty interval
African Region		31.0	22.5-54.4	309	222–544
Region of the Americas		6.4	5.9–7.0	63	59–69
Eastern Mediterranean Region		62.5	55.6–65.2	409	363–426
European Region		61.8	50.3–66.0	565	460–603
South-East Asia Region		14.8	12.5–26.9	287	243–524
Western Pacific Region		6.0	5.6–6.6	111	104–124
Global		23.7	21.3–28.7	1751	1572–2120

Fig. 4.1 Global incidence and prevalence of hepatitis C. Reproduced with permission of the WHO (Global Hepatitis report 2017)