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Chapter 9

Hepatitis E

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Additional information is available at the end of the chapter

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1. Introduction

Hepatitis E virus (HEV) represents the major aetiological agent of enteric non-A hepatitis and it is the only member of a new virus, *Hepevirus*, belonging to the family of *Hepeviridae* [1-2]. HEV is often responsible of acute clinical hepatitis in developing world, specifically the Indian subcontinent and Southeast Asia, the Middle East and North Africa [3-5], where it is a common cause of sporadic and epidemic waterborne outbreaks and determines an important rate of morbidity and mortality, especially in pregnant women. In these countries, where the disease is endemic, antibodies HEV-IgG, which are indicative of past infections, have been detected in 5-60% of the general population. Once thought as an infection confined to developing countries, it is now recognized as a disease with a widespread geographic distribution. In industrialized countries this infection occurs sporadically; most cases are diagnosed in individuals who travel to regions where HEV is endemic [6], even though a growing number of infections have been identified also in patients with no history of recent travels to endemic countries [7-8]. However, in the last years, it has been shown that the host range, geographical distribution and ways of transmission of HEV and clinical features of this infection are much broader than it was previously believed.

2. The history

The existence of a different enteric transmitted hepatitis virus was suspected from epidemiological evidences already many years before the discovery of HEV. However, HEV Infection was first documented in 1955 during an outbreak in New Delhi and only two decades later some researchers have demonstrated the existence of a new non-A virus [3]. During the winter of 1955-56, a significant monsoon flooding in New Delhi caused the Jamuna River to change its direction. The waters ran through the city sewage and then into uptake pipes feeding a

treatment plant that supplied water to most of New Delhi. The treatment facility broke down and contaminated water ran through the city's water supply. Over 30,000 cases of hepatitis were reported, representing 2.3% of the population residing in the affected areas. The epidemic peak was reached in 2 weeks and was reduced in about 7 weeks. The incidence of HEV infection is highest in young adults. Acute hepatitis is preceded by a brief prodromal period. The disease generally had a self-limited course, but pregnant women often had *fulminant hepatic failure* (FHF) with a high mortality rate [2]. It has been hypothesized this epidemic so great could be caused by the same old enteric hepatitis, as hepatitis A virus (HAV), overwhelming any previous immunity of individuals to this infection [3, 9-10]. In the early 1970s, with electron microscopy, were identified the hepatitis A virus and, the hepatitis B virus [11]. This led to the discovery of the serological tests for hepatitis A and B and to the recognition that many cases of post-transfusion hepatitis were not related to either of these agents; such cases were provisionally labeled as non-A, non-B post-transfusion hepatitis [3,5]. During an outbreak of acute viral hepatitis in the Kashmir Valley, India, in 1980, Khuroo was the first to suspect an enterically transmitted non-A, non-B hepatitis virus [12]. Among 16,620 inhabitants of the affected areas, there were 275 clinical cases; most of them were 11–40 years old, and occurred in villages with a common water source. Of the patients, 12 (4.4%) had fulminant hepatic failure, and 10 died; the outbreak was characterized by a high disease attack rate and mortality among pregnant women. With the availability of serological tests for hepatitis A and B, 31 patients were tested for these viruses; only one presented immunoglobulin M (IgM) anti-HAV antibodies and none had hepatitis B surface antigen (HBsAg); in fact, most subjects had evidence of prior immunity against HAV infection (IgG) [12]. After some months, *Wong et al* reported the results of retrospective serological testing on sample sera which had been collected and stored from the 1955–56 hepatitis outbreak in New Delhi; they proved that the outbreak victims at the time had not been infected with hepatitis A or B. Specimens from none of the outbreaks showed evidence of acute hepatitis A and only a few had markers of acute hepatitis B [3]. These findings suggested the existence of a water-transmissible agent distinct from HAV and HBV, and clearly a new virus was responsible for the outbreak. The name "enterically transmitted non-A, non-B hepatitis virus" was coined for this virus.

During the Soviet occupation of Afghanistan in the 1980s, after an outbreak of unexplained hepatitis at a military camp, a pooled aqueous faecal extract of faecal matter from nine patients with epidemic non-A, non-B hepatitis, was ingested by a member of the research team (*Dr. Balayan*), who was immune to HAV. The volunteer developed, on day 36, typical acute hepatitis, which lasted for about 3 weeks. Stool specimens were collected on days 28–45 and showed 27- to 30-nm spherical virus-like particles (VLPs); these VLPs presented aggregation with convalescent sera of patients with enteric non-A, non-B hepatitis, but not with those from patients with HAV virus hepatitis, hepatitis B or post transfusion non-A, non-B hepatitis. The volunteer showed seroconversion against VLPs, but no detectable HBsAg or boosting of anti-HAV antibodies [13].

About ten years after the discovery of a new virus, *Reyes et al.* isolated, from bile obtained from an experimentally-infected animal, a nucleic acid clone representing a part of its genome. They also identified similar genomic sequences in clinical specimens obtained from

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several geographical regions at different time-points; the agent was christened as hepatitis E virus (HEV) [14]

The appearance of IgM anti- HEV antibodies was associated with the beginning of HEV virus hepatitis in most patients, while the IgG anti-HEV are detected shortly thereafter. The new-found molecular and serological tests for the diagnosis of HEV infection are actually used in different geographical areas to determine the frequency of HEV infection in patients with epidemic and sporadic hepatitis, and in different population groups. [15]

3. The virus

HEV is the single virus that belongs to the genus *Hepevirus* in the *Hepeviridae* family [1,2]. It can infect human and animal beings, as domestic pigs, wild boars, deer, rodents [2, 16-17]. The HEV virions are small, icosahedral, non-enveloped, spherical particles of 27-34 nm, with a single capsid protein and a linear, positive-sense RNA genome of approximately 7.2 kb [18]. The HEV genome contains three open reading frames (ORF). ORF1 non-structural polyprotein encodes a protein of 1693 amino acids, and contains domains with methyl-transferase, putative papain-like cysteine protease, RNA helicase, and RNA-dependent RNA polymerase activities, which are important for viral replication [19-20]. The ORF2 encodes the viral capsid protein of 660 amino acids protein, consists of three linear domains and is responsible for virion assembly, interaction with target cells, and immunogenicity [21-22]. ORF3, which overlaps with ORF2 and encodes a small protein of 114 amino acids, is required for HEV replication in the host; moreover, it has pleiotropic effects on host cell pathways and plays a role in viral egress from infected cells [23-24]. In HEV capsid organisation, three domains have been defined: the shell domain (S; amino acids 129–319), the middle domain (M; amino acids 320–455), and the protruding domain (P; amino acids 456–606). These studies placed the neutralising epitope(s) in the P domain of ORF2 [25-26]. At present, are recognized four different HEV genotypes, whose genotype 1-2 are found in human species [19, 27], genotype 1 and 2 strains are transmitted via contaminated water in developing countries, HEV1 occurs mainly in Asia [28-29], and HEV2 in Africa [30] and Mexico [31]. Genotypes 3 and 4 have a broader host range and are also *zoonotic* viruses; in fact they infect human beings, pigs, and other mammalian species and are responsible for sporadic cases of autochthonous hepatitis E in both developing and developed countries [2,16]. Interspecies transmission has been demonstrated for HEV genotypes 3 and 4. HEV3 has a worldwide distribution [32-33]; by contrast, HEV4 mostly occurs in southeast Asia [28-29], but has recently been isolated also in European pigs [33]. On the basis of full-length genome-sequence analyses, HEV genotypes have recently been characterized in rats in Germany [34], wild boars in Japan [35], and farmed rabbits in China [36]. HEV1 can be classified into five sub-genotypes, HEV2 into two, HEV3 into three, and HEV4 into seven. *Phylogenetic analyses show that HEV sub-genotypes, circulating in human beings and animals in the same area are closely related, supporting zoonotic transmission* [27].

The cellular receptor and the mode of entry of HEV into the cell are not known, but heparin sulphate proteoglycans are required for HEV attachment and infection of target cells [37].

It appears that HEV is not directly cytopathic, and liver injury results from the host immune response; this response is marked by an initial increase in anti-HEV immunoglobulin (Ig)M, followed closely by an IgG response; whereas IgM titers wane off in 4- 6 months, IgG persists for longer periods. [38]. Viremia begins 1-2 weeks before and last 2-4 weeks after the onset of symptoms. In experimentally infected nonhuman primates, HEV RNA is observed in serum, bile, and faeces before the elevation of aminotransferases [28]. The HEV antigens first appear in hepatocytes about 7 days post-infection, followed by rapid spread to 70%-90% of hepatocytes [39].

4. The epidemiology

HEV infection can cause both epidemic and acute sporadic hepatitis in developing world. However, the true incidence of this infection is unknown because it is most often a self-limited hepatitis, except for HEV infection during in pregnancy characterized by high mortality, and often for the lack of available serological tests in these areas of the world. Seroprevalence studies have led to establish that HEV can infect about one-third of worldwide population [40].

Anti-HEV IgG antibodies represent evidence of past exposure to HEV; furthermore, the duration of persistence of circulating IgG anti-HEV antibodies remains unclear, varying from some months to several years after acute disease, though its titers declined over time. Anti-HEV antibodies have been found worldwide also in healthy subjects; prevalence rates are higher in developing countries where HEV hepatitis is common, than in countries where clinical cases due to hepatitis E are sporadic [32].

The mode of transmission or risk factors for sporadic HEV transmission is not yet understood. HEV infection is mainly transmitted through contaminated water, perhaps during outbreaks [41], that can last from a few-week to prolonged time, [42]. Other routes of transmission are possible: food-borne, zoonotic, infected-blood products, needle sharing, and vertical (materno-fetal) transmission [9, 11]. Person-to-person spread occurs in only 0.7% to 2.2% of cases compared to 50% to 75% for hepatitis A; even when multiple cases occur in a family, the time interval between cases is usually short, indicating a shared primary water-borne infection rather than person-to-person spread [43-44]. However, person-to person transmission could become efficient perhaps in a peak of HEV infection and, in addition, promiscuity and poor hygienic practices could contribute to HEV infection in households [45]. It is not yet clear if protracted viremia or prolonged fecal shedding of HEV, with endless pollution of sewage, could be the reservoir of HEV, responsible for maintaining the infection in hyperendemic populations. Persons affected with subclinical infection could contribute to maintain HEV infection through fecal dissemination of the virus contaminating water supplies [28,46].

The existence of an animal reservoir in hyper-endemic regions is suggested by the high prevalence of anti-HEV antibodies in several animal species, and by the isolation of HEV genomic sequences from pigs in these regions. above all in genotype 4 [47-48]. On the contrary, genotype 1 has never been isolated from pigs and other domestic and wild animals [49] and so it is not responsible of zoonotic transmission. The way of transmission of HEV infection not

always can be identified, especially in low-endemic regions and sporadic cases in highly endemic areas.

In epidemics, the incubation period varied from 2 to 10 (with an average of 6-7) weeks. Two distinct epidemiological patterns have been observed: endemic and non-endemic, characterized by different routes of transmission and the disease characteristics [4,32].

In high-endemic areas, a large proportion of HEV infections manifest itself as acute sporadic hepatitis in all age groups; the clinical characteristics of these patients are similar to those of epidemic hepatitis E. Main routes of transmission might be the contamination of water or food and this is confirmed by the identification of the HEV genomic sequences in sewage from high-endemic regions [34]. Route of transmission is unclear in such patients, but is likely to be through contamination of water or food; identification of the HEV genomic sequences in sewage from high-endemic regions around the year suggests nearly ubiquitous circulation of HEV in these populations; this could act as a reservoir of infection responsible for sporadic cases [34].

4.1. Epidemiology of hepatitis E in developing countries

The first, retrospectively identified outbreak of hepatitis E caused about 30,000 cases in India in 1955–56 [3]. Other large outbreaks of this disease, subsequently, have been reported frequently in the Indian subcontinent [12], China [5], Southeast and Central Asia [52], the Middle East, and northern and western parts of Africa (Somalia, Uganda) [53-54], affecting up from several hundred to several thousand people. Two small outbreaks occurred in North America (Mexico) during 1986–1987, but none has been reported thereafter [31]. Epidemics of hepatitis E occur periodically throughout the developing world, and are mainly caused by HEV genotype 1 in Asia and HEV genotype 2 in Africa [53] and Mexico [31]. Most infections are due to HEV1 but also to HEV4, although HEV3 has recently been isolated in endemic regions. In the last years, hepatitis E in China has occurred mainly as sporadic cases and occasional food-borne outbreaks. The predominant circulating genotype is HEV4, with only occasional HEV1 cases; this might reflect improvements in water supply and in the sanitary infrastructure in China over the past few decades, allowing zoonotically transmitted HEV4 to predominate in the human population [27]. Sporadic HEV4 cases are more common in elderly men.

Seroprevalence studies conducted in various endemic countries have demonstrated that the rate of HEV seropositivity seldom exceeds 40% of population, and in some countries, such as India, Algeria, and in some parts of China, there is a higher prevalence of anti-HEV [50]. A study in rural areas of southern China demonstrated a prevalence of anti-HEV that ranged from 25% to 63%, particularly in young males [51]. Moreover, a higher incidence of hepatitis E outbreaks occurs during pregnancy, especially, greater incidence is often associated with prematurity, low birth weight and a major risk of perinatal mortality.

Instead, children have lower HEV infection rates, probably because in children there are frequently asymptomatic infections.

In fact in the children, asymptomatic infections are usually more frequent by two to four times in waterborne outbreaks and sporadic cases.

Mortality rates of HEV infection in epidemics range from 0.2% to 4.0% and they are higher in infants under 2 years of age and in pregnant women (10% to 25% of cases).

Mortality in pregnancy occurs largely in the third trimester, and is caused by *fulminant hepatic failure* and obstetric complications such as eclampsia or hemorrhage. [55] Moreover, pregnant cases more often (22.2%) developed FHF than the cases who were non-pregnant women (0%) or men (2.8%). These associations were first noted during the Kashmir and the Delhi outbreaks. The exact cause of this specific predilection for occurrence of the worsening of the disease among pregnant women remains unknown; immunological or hormonal factors have been suspected [56].

4.2. Epidemiology of hepatitis E in developed countries

Previous seroprevalence studies in industrialized countries reported the discovery of locally-acquired cases of HEV hepatitis, determining a substantial change in epidemiological pattern of this infection in regions where HEV is infrequent. Variable rates of anti-HEV antibodies were observed in healthy populations: 2.5% in the USA [57] and 0.4-3% in Western Europe, mainly in Mediterranean European Countries [58-60] (Italy, Spain, France and Greece), where there is a high prevalence of immigrants. However also in other developed countries (Japan, Denmark), high anti-HEV antibodies prevalence (up to above 20%) have been reported; these appear to be markedly higher than those expected from the low rate of hepatitis E disease diagnosed in these areas [61-62]. In the last years, isolated cases or small case series related to autochthonous (locally-acquired) acute hepatitis E have been described in the US, Europe, and in developed countries of Asia-Pacific (Japan, Taiwan, Hong Kong, Australia)). In a recent Italian long-term prospective study, the prevalence of acute hepatitis E was 20.6% in a cohort of 651 patients with acute viral non A-non C hepatitis [69]. A prospective study (unpublished data) was conducted by our group in Southern Italy, in 2010-2011, to evaluate the seroprevalence of HEV in a cohort of 1,217 subjects, 412(34%) of whom were immigrants who had recently arrived in Italy, and 805 were from four different Italian populations (blood donors, general population, HIV-positive patients, haemodialysis patients). A total of 107 (8.8%) of the 1,217 serum samples examined were reactive to anti-HEV IgG and confirmed by Western Blot. The prevalence in immigrants was 19.7%, in Italians was 3.9% (blood donors 1.3%, general population 2.7%, HIV-positive patients 2.0%, haemodialysis patients 9.6%). In our study, we found 38/107 (35.5%) patients with anti-HEV IgM positive. Most of them (34 cases) were immigrants. Several of these cases can be traced to traveling to developing countries and/or immigration, but others occurred among autochthonous individuals reporting no trips abroad or at-risk contacts (travelers and/or immigrants). While the HEV genotypes in immigrant and/or travelers are mainly 1-2, autochthonous acute hepatitis E was determined by genotypes 3-4 [63].The reason for this high anti-HEV seroprevalence is unclair, and might reflect past subclinical HEV infection due to travel in endemic countries or a cohort effect due to recent past HEV infections imported by immigrants. Sporadic cases of the infection are owed to faecal contamination of drinking water. Autochthonous HEV, in industrialized countries, is due

mainly exposure to animals; people with occupational exposure to swine or wild animals in these regions often show a high seroprevalence of anti-HEV antibodies. The genotypes (3-4) also widely circulate in swine populations; these findings reinforce that some cases of autochthonous hepatitis E in developed countries could strengthen zoonotic transmission. Inadequately-cooked deer meat could represent a possible source of HEV infection, as it has been reported in some Japanese cases. The genomic sequences of HEV isolated from these cases were identical to those from the left-over frozen meat, establishing food-borne transmission. A proportion of commercial packets of pig liver sold in Japanese and US grocery stores have been shown to contain genotype 3 or 4 HEV [64]. Contaminated shellfish has also been proposed as a potential vehicle in developed countries. To-day this finding suggests that at least some autochthonous cases are related to consumption of contaminated foods, but the extent of zoonotic transmission is not fully understood. Other routes of transmission, in developed countries, were described:

1. Higher rates of hepatitis E antibodies were found in drug users in Denmark [62] and Sweden [65]: this might indicate parenteral transmission by needle sharing within the group.

2. Furthermore, HEV was found in sewage samples collected in some western countries (France, Spain, USA), with evidence of autochthonous HEV infection in these areas; in southwest France, HEV is hyper-endemic [66].

3. Moreover, several studies unexpectedly showed a high prevalence of antibodies to HEV in haemodialysis patients, and blood donors in developed countries; the mode of exposure and clinical significance of these infections are not well understood [67-68].

Acute HEV-3 and HEV-4 infections in developed countries are usually self-limiting illnesses that last 4–6 weeks; symptomatic HEV infection is much more common in middle-aged and elderly men. The high pregnancy-associated mortality in HEV-1 has not been reported with HEV-3 or HEV-4. In developed countries the mortality rates can to be up to 10%, especially in individuals with several comorbidities in symptomatic cases of HEV infection [8, 33]. Excessive alcohol consumption could contribute to the onset of HEV infection, because these individuals are characterized by major risk of hepatic steatosis or hepatic fibrosis and so by a more severe host response to HEV infection [70-71].

4.3. Epidemiology in travelers

The incidence of HEV in travelers is not well known, but it is very low, on the order of *1 case per 1 million travelers* [6]. This supports the hypothesis that the fecal–oral route is the most important transmission route of HEV infection and it is highly endemic in several countries, particularly the Indian subcontinent, which is a popular travel destination of over 4 million people traveling annually, as reported by World Tourism Organization, and Southeast Asia. Despite the low number of reported HEV cases in travelers, many cases of HEV in travelers are underdiagnosed, perhaps because of the lack of awareness of HEV infection among physicians and the lack of commercial diagnostic tools preventing the confirmation of HEV infection diagnosis in many industrialized countries. Moreover, travelers are not immune to

the disease. A thorough review of the literature from 1989 to 1999 identified 161 reported cases of acute HEV in travelers and military personnel coming mainly from the Indian subcontinent and Southeast Asia [6]. Recent Geo-Sentinel surveillance data from returning travelers during the period 1999-2005 report 33 cases of acute HEV [72]; almost all of these cases were in travelers visiting the Indian subcontinent. Between 1994 and 2003, there were 30 cases of documented Hepatitis E among travelers, expatriates, and Peace Corps volunteers in Nepal who asked for medical treatment at three local clinics in Kathmandu (unpublished data). During a world cruise in 2008, seven UK citizens contracted acute HEV infection during their 12-week voyage, which included visiting several Asian port cities [73]. In a recent long-term prospective study in Italy, a total of 134 out of 651 patients tested had acute hepatitis E, and 109 (81.3%) of them developed hepatitis E traveling to endemic areas [69].

Seroconversion studies among travelers might help to sustain the evidence of HEV risk to travelers from a low to a highly endemic region of the world, but only few data of HEV antibody seroconversion in travelers have been reported. A prospective seroconversion study was conducted in 1993 among 356 American short-term travelers to developing countries: of the 236 initially seronegative patients, 4 (1.7%) seroconverted to HEV IgG positive after 6 months; all were asymptomatic [74]. A 1995 retrospective study of 328 North American missionaries serving in Africa, Asia, and Central and South America between 1967 and 1984 showed no seroconversion [75]. Another seroconversion study was conducted in Nepal from June 1997 to December 1998 and it showed the seroprevalence of anti-HEV among foreigners living in Nepal and it has determined seroconversion rates over a 12-month period. This study conclused that among the 373 persons seronegative for anti-HEV, there was one case of acute HEV infection, for a seroconversion rate of 0.3%; there were no cases of asymptomatic seroconversion.

According to these seroconversion studies, a HEV infection is not widespread among travelers [76]. The acute HEV infection associated with travel is observed mainly in patients of mean age 30 (range 6–65) and 52% female. Most of these individuals (53/69-77%) had traveled to the Indian subcontinent (India, Nepal, Pakistan, and Sri Lanka). The mean duration of travel was about 3 months, but there was a report of HEV infection after only 1 day in an endemic area (range 1 day to 12 months) [77].

5. Clinical course

After the infection there is an incubation period of 15 to 60 days, with an average of 40 days, then the infected patients develop symptoms and clinical signs similar to those of other forms of acute viral hepatitis. The most prominent feature is jaundice accompanied by malaise, anorexia, abdominal pain, nausea, vomiting, fever and hepatomegaly; diarrhea, pruritus, arthralgia and rash can also be present. Serum levels of liver enzymes (AST-ALT) can be elevated and there can be bilirubinemia. These markers usually return to normal values within 6 weeks of onset. Hepatitis E is typically a self-limited disease, lasting 1–4 weeks; most patients recover completely within a few months. However, in about half the cases, HEV infection may occur with protracted coagulopathy and cholestasis in more than half of patients [78].

Liver histology in a study of eleven patients with sporadic acute hepatitis E showed acute lesions in all cases: necro-inflammatory activity and confluent necrosis in nine and five samples, respectively. Moreover, there were also siderosis and cholestasis in eleven and nine patients, respectively [79]. The clinical significance of the genotypes in determining the severity of the diseases is still unknown; a study from Japan compared the clinical features of patients infected with genotypes 3 and 4 and showed that genotype 4 tends to have more severe clinical manifestations than genotype 3 with a significantly higher ALT peak levels and a lower trough prothrombin time [80]. The severity of infections can range from subclinical disease to fulminant hepatitis. Overall mortality ranges from 0.1% to 4%. The mortality rate among pregnant women infected with HEV during their third trimester is as high as 25%. Pathogenetic events leading to increased mortality after HEV infection during pregnancy are not fully understood; endotoxin-mediated hepatocyte injury and elevated T-helper type 2 responses may have some role [81].

Fulminant hepatitis is often associated with patients with chronic liver disease; some patients, however, progress to fulminant hepatitis without any apparent precipitating factors [82]. In 2004 in Dhaka, 23 patients, without other diseases, presented fulminant hepatitis, more than half (13/23) of those were HEV IgM positive; the mortality rate was 87% [83].

The seroepidemiology of hepatitis E suggests a long-term post-infection immunity against subsequent HEV infections during epidemics of the diseases, but lifelong immunity has not been confirmed.

5.1. Clinical course in developing countries

In these regions the disease usually lasts for a few weeks and improves spontaneously; only a few patients have a prolonged illness with cholestatic manifestations, though the outcome is usually good. Some patients, as above said, have a particularly severe illness, presenting as FHF, particularly common in pregnant women. During hepatitis E outbreaks, some patients presented anicteric hepatitis (elevated liver enzymes with normal serum bilirubin) and HEV infection (HEV viremia and seroconversion), and later only the detection of anti-HEV antibodies indicate a prior acute hepatitis [78,82].

In these areas, HEV super-infection can occur in patients with pre-existing chronic liver disease of viral or non-viral etiology, leading to superimposed acute liver injury and clinical presentation with acute on chronic liver disease, determining a higher risk of a poor outcome. In some patients, chronic liver disease had been clinically silent till the time of HEV super-infection [84]. Case-fatality rates of hepatitis E have been reported as 0.5% to 4%. For unknown reasons, mortality is higher in infants <2 years of age, and in pregnant women [54, 85]. However, these data derive from hospitalized cases with more severe disease. In population surveys at the time of disease outbreaks, much lower mortality rates of 0.07% to 0.6% have been observed [3]. The highest rates of mortality are reported in patients affected with acute HEV infection and other chronic liver diseases; studies from the Indian subcontinent showed a 12-month mortality up to 70% in patients with HEV genotype 1 and prior chronic liver disease [86].

5.2. Clinical course in developed countries

Hepatitis E is a neglected disease in Western countries, and many physicians do not consider the diagnosis when there is no history of travel to endemic countries. In these areas the diagnosis is most often recognized when all the markers for other hepatitis are negative and HEV test is undertaken in patients with unexplained liver injury; several studies report anti-HEV seroprevalence rates of less than 5% [87-88]. Clinical features in these patients are generally similar to those in high-endemic regions, except that most patients are *middle aged or elderly men* and often have another coexistent disease, thus patients in developed countries have a more severe disease than those in high-endemic areas [33, 40]. Moreover, some cases were initially suspected to have drug-induced liver injury.

The very high fatality rate among pregnant women in endemic areas cannot be evaluated in the traveler population or in industrialized countries because cases are very rare. Reports of "severe hepatitis" in two pregnant women from the UK in their third trimesters were noted [6]. Another case of liver transplantation due to fulminant HEV occurred in an Israeli woman a few days after an uneventful delivery, and she had no history of travel [83].

Most deaths from HEV genotype 3 is determined by acute or subacute liver failure in patients with prior hepatic disease. Indeed, the mortality and morbidity of this disease in patients in developed countries with pre-existing liver disease is not well-established, since these patients are not routinely tested for HEV infection. Two studies have shown an association between pork consumption (HEV genotype 3 has been detected in pork destined for human food in several countries) and mortality from chronic liver disease [88-90].

5.3. Clinical course in travelers

The incubation period and clinical course in travelers are identical to those observed in inhabitants of HEV-endemic areas affected from acute HEV hepatitis. A study on travelers with HEV infection showed that 96% (155/161) completely recovered without sequelae; only 2.5% (4/161) developed fulminant hepatitis and two of them died [6]. One of these was a 65-year-old man with chronic hepatitis C and the other was a woman with no reported underlying liver disease. The case fatality in this review was 1.2% (2/161), similar to the value of those with autochthonous hepatitis.

In the already mentioned Italian study, in all 109 patients who developed hepatitis E traveling to endemic areas, the acute disease had a self-limited course with ALT normalization within 3-6 weeks. Phylogenetic analysis on 39/109 isolated patients showed that they belonged to genotype 1 [69]. Also our study on patients with a travel-related disease presented similar results both in regards to the genotype of virus and the outcome of the disease.

5.4. Clinical extra-hepatic manifestations

In the last years some reports described HEV-associated neurological syndromes, mainly in developing countries; most cases originate from the Indian subcontinent and the cause is HEV genotype 1. These complications include Guillain-Barre syndrome [91], Bell's palsy [92],

neuralgic amyotrophy [93], and acute meningo-encephalitis [94], and seem to be related to the viral load of HEV. The diagnosis is not sure, it is only serologic, because most of these studies did not use molecular techniques to confirm the presence of the virus and/or the genotype.

Recently, neurological complications were described in seven (6%) of 126 patients with acute and chronic HEV genotype 3 infection; HEV RNA was detected in the in the cerebrospinal fluid (CSF) of all four patients with chronic HEV infection. A complete resolution of neurological symptoms or a significant improvement was observed in patients who achieved viral clearance [95]. Two further cases of HEV-associated Guillain-Barre syndrome (presence of anti-ganglioside GM1 antibodies) and one case of meningoencephalitis have been described in Belgium [96] and France [97]. The patients with Guillain-Barre syndrome responded well to treatment with intravenous immunoglobulin [96].

Other extra-hepatic HEV-related manifestations can be represented by membrano-proliferative glomerulonephritis and membranous glomerulonephritis; some cases have been reported in India in patients with acute HEV genotype 1 infection [97], and in France in patients with chronic HEV genotype 3 infection [98]. Further complications were observed during acute HEV infection as acute pancreatitis [99] and severe thrombocitemia [100].

5.5. Chronic HEV infection

Hepatitis E is considered a self-limited disease, evolving rarely into chronic disease. However, some patients, undergoing organ transplants and subsequent immunosuppressive therapy, may have developed chronic HEV infection. HEV chronic infection is defined by persisting HEV RNA in serum or stools for 6 months or more, in immunosuppressed patients. For the first time in 2008, a French study described a group of 14 solid-organ transplant recipients (liver, kidney, and pancreas) that were diagnosed with acute HEV, who were receiving immunosuppressive drugs. Consumption of game meat, pork products and mussels were associated with viral infections in these patients. About 60% (8 patients) of organ-transplants recipients failed to clear the virus and developed chronic hepatitis, as confirmed by a recent onset, the persistently presence of transaminase elevation (7 asymptomatic, 7 with non-specific symptoms), and persistent HEV viremia. All patients had genotype 3 HEV [101]. Sequential liver biopsies in some of the patients with chronic HEV infection showed portal hepatitis with dense lymphocytic infiltrate, and variable degrees of piecemeal necrosis, with rapid progression in fibrosis, and 10% of patients showed progress to cirrhosis. In this study no correlation between serum HEV RNA load and liver fibrosis progression has been reported [102]. Death occurred in few of these patients due to decompensated chronic liver disease. The patients with persistent infection had a significantly shorter time from organ transplantation to the development of HEV infection, and thus had lower total, and CD2, CD3, and CD4 lymphocyte counts than those with resolving HEV infection [81]. Another study reported two cases of chronic HEV infection in liver transplant recipients leading to cirrhosis and graft-failure. The same study found a prevalence of HEV infection acquired after liver transplantation in only 1% of 274 patients. [103]. Chronic HEV hepatitis was later reported also in HIV positive patients and in immunosuppressed patients for chemotherapy or hematological diseases [82].

The most of chronic hepatitis E cases have been reported among immunosuppressed subjects with genotype 3.

6. Diagnosis

For the diagnosis of acute hepatitis E, the detection of antibodies to HEV or detection of HEV RNA in serum or faeces are essential tests.

6.1. Serology

After the incubation period, the immune response to HEV follows the usual pattern: an initial specific IgM response that remains positive for months followed by IgG antibodies that can be detectable as early as in the second week of clinical symptoms [104]. In the beginning we notice the presence of the low avidity IgG antibodies, and when response matures they are replaced by antibodies with higher avidity [105]. Although four genotypes of HEV are recognized, they elicit very similar antibody responses and appear to represent a single serotype [106]. Confirmation of HEV acute hepatitis diagnosed in this way is either by molecular techniques, detecting rising reactivity in a specific IgG assay, or by positivity in immunoblot IgM assays [107]. The determination of immunity or previous exposure to HEV infection, by serological diagnosis, would be very important but it is difficult because available enzyme immunoassays use different antigens and present various effectiveness. A concentration of anti-HEV antibodies that reliably prevent infection has not been defined, but a vaccine study suggests that antibodies concentrations of 20 Walter Reed units/mL (2,5 WHO units/mL) are protective [104].

Commercial ELISA tests for antibody detection are available in Europe, Canada, and parts of Asia. In the USA, however, these tests are not commercially available. In research settings, there are tests for detecting hepatitis E virus antigen (HEVAg) in the serum. Diagnosing HEV remains a challenge given the lack of available diagnostic methods. PCR is not available in many areas of the world and serology cannot be relied upon.

6.2. Molecular techniques

HEV RNA detection using amplification techniques is a key test for the diagnosis, confirmation, and monitoring of HEV infections. In addition, recently, emerging data on the use of antiviral treatment in patients with chronic hepatitis E have emphasized the role for HEV RNA detection and quantification for monitoring therapeutic responses [100-1071].

In patients with an acute HEV infection, viral RNA occurs during the incubation period and the early phase of disease, it can be detected just before the onset of clinical symptoms in both blood and stool samples. HEV RNA usually becomes undetectable in blood and stool within one to six weeks after the onset of symptoms [108]. The window of detectable RNA is close and so if the detection has been searched later, an undetectable HEV RNA result does not exclude a recent infection. Detection of HEV RNA is very important in the diagnosis of patients

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with chronic HEV infection because, in immunosuppressed individuals, a specific serological response (IgM-IgG) might be absent and there are no markers for HEV infection [78].

7. HEV prevention

Currently, there are two strategies preventing HEV infections in healthy population: decreasing exposure to the virus and inducing immunity through vaccination. Individuals with prior exposure to HEV, demonstrated by pre-existing anti-HEV antibodies, appear to be protected when subsequently exposed to the virus [109]. The reduction of exposure to HEV, in developing countries, is obtained by the provision of safe drinking water, by improving the sanitary infrastructure, and by education about personal hygiene. In developed countries, prevention is more complicated for many transmission routes of infection. Sanitary handling, proper cooking of pork meat and ensuring the proper disposal of pig faeces is recommended in areas with zoonotic transmission.

The use of immune-globulins prepared in HEV-endemic regions of the world does not appear to provide significant protection. This may be because there are relatively low titers of anti-HEV antibody in the general population. There have, however, been studies of the protective efficacy of anti- HEV when immuno-globulins from patients in the convalescent period of natural infection are pooled [110].

Vaccination is, at present, the most important way to prevent HEV infection, two hepatitis E vaccines have undergone clinical testing. The first, a recombinant HEV vaccine, has been developed and a phase 2/phase 3 trial of the vaccine was carried out in seronegative members in the Nepalese army. The soldiers were randomized in two groups to receive either three doses of vaccine (898 participants) or placebo (896 participants) at 0, 1, and 6 months, and were followed for an average of 804 days. The vaccine was well tolerated and was proven highly efficacious, with protective rates of 95.5% in subjects who received all three doses. Administration of two doses was associated with a somewhat lower efficacy rate of 86%. The duration of protection is not known, but the vaccine appeared to render significant protection for at least 2 years after vaccination. The vaccine's safety and efficacy in women has not been established [111]. The second vaccine consisted of a truncated ORF2 protein, p239, which is expressed in Escherichia Coli and occurs as virus-like particles, 23 nm in diameter. In phase 3, in a large clinical trial, in 11 townships in south-eastern China, participants were randomly assigned to receive either three doses of vaccine at 0, 1, and 6 months (56,302 participants) or hepatitis B vaccine as a placebo (56,302 participants), and were followed for a 13-month period. This study enrolled participants aged 16-65 and from both genders, irrespective of their anti-HEV antibody status. The vaccine was well tolerated and showed a protective efficacy of 100% during the following one year; even after two doses of vaccine, 100% protection was noted, though these data are more limited [112]. This vaccine has recently been licensed in China, but it is uncertain whether and when it will be licensed for marketing in other developing and developed countries, possibly because the industry is not assured of a sufficient market. But, due to the zoonotic factor in transmission, there may be an overall increase in HEV infection

worldwide; therefore, in developed countries vaccination might be useful in immune-suppressed patients, in those with a chronic liver disease, and in travelers to endemic areas. However, the studied vaccine regimens of three doses is difficult for travelers, but the need for HEV vaccine remains uncertain in that the attack rate in travelers remains low. On the other hand, with very effective vaccines now available for both hepatitis A and hepatitis B virus, the prevalence of these viruses may decline significantly and HEV may become the dominant hepatitis among travelers.

There are still no comparative data on the safety and immunogenicity of the two vaccines. The results of vaccinations are very promising but many questions about vaccines are still unanswered: 1) whether these vaccines can reduce transmission of infection in community; 2) the duration of protection determined by the vaccines; 3) the protective efficacy when the vaccines are administered post-exposure; 4) whether the vaccines can prevent asymptomatic HEV infection (important reservoir of HEV); 5) if the vaccines could also bring benefits to people at high risk of severe complications following HEV infection; 6) whether the vaccines may reduce the incidence of hepatitis E outbreaks in high endemic areas.

Only when we will obtain the response to these questions, there will be a complete knowledge of these vaccines, thus the exact role for HEV vaccines currently remains unclear. As said above, no vaccine has reached the market at the time of writing this chapter.

8. Treatment of HEV infection

8.1. Acute HEV

Currently, there is not a specific treatment for hepatitis E infection and often some specific interventions are not required. Physician can only monitor this disease, that, in most cases, is self-limiting and is followed by complete recovery, without chronic sequelae. However, patients with acute severe HEV genotype 3 infection have been treated successfully with ribavirin monotherapy [113-114]. Patients with hepatic failure should be transferred to a centre capable of performing liver transplants. In developing countries, the treatment of pregnant women with HEV genotype 1 infection would be necessary, but teratogenicity of ribavirin may pose a problem for use during pregnancy. Taking into account the rapid downhill course of such patients and the high risk of untreated HEV to the mother and foetus, in some cases it is needed to start the treatment with ribavirin, because the temporal window of opportunity for the drug to act and alter the outcome of disease in such patients may also be limited.

8.2. Chronic HEV

In organ-transplant recipients in immunosuppressive treatment, who are affected by chronic HEV infection, viral clearance is needed to avoid the risk of rapid progressive liver injury. Withdrawal or reduction in dose of immunosuppressive therapy (especially drugs that target T cells), if possible, should be tried before considering antiviral treatment. Reduction of immunosuppression results in viral clearance in 30% of patients [116]. Antiviral therapy is

needed for patients for whom it is impossible to reduce immunosuppressive treatment and for those without clearance of HEV RNA after reducing immunosuppression. Pegylated interferon [117] and ribavirin [116] as mono-therapy or in combination for 3-12 months have been tried in subjects with chronic HEV infection, with moderate success in achieving an absence of detectable serum HEV RNA for 3-6 months after stopping the administration of drugs [116,117]. In kidney-transplant recipients it is better not to use the interferon-α, because it increases the risk of acute rejection. HEV infection seems, in these patients, to respond to ribavirin monotherapy, achieving viral clearance within a few weeks. This treatment (duration of 3 months) is now the antiviral agent of choice in kidney-transplants recipients.

In other immunosuppressed patients, treatment options are less well established. Ribavirin and interferon-α have been successfully used in monotherapy and in combination only in a short case series and controlled trials with longer follow-ups are needed [118-119].

9. Concluding remarks

In the last 30 years the landscape of hepatitis HEV has changed enormously. Once thought as an infection confined to developing countries, deriving from a waterborn infection, it is now recognized as a widespread geographic distribution disease, with different ways of transmission, causing an acute and/or chronic hepatic disease. This new knowledge has led to an increasing research activity to better understand the virology and the clinical features of HEV infection. Recent studies deal the treatment and the prevention: the therapy of the chronic disease, at the moment, is represented mainly by ribavirin; the only prevention possible is the use of HEV vaccines, particularly in some high-risk groups or certain situations (e.g. populations displaced due to floods, war or conflicts). At the moment HEV infection is not a major problem in Western European countries, but the increasing number of travelers to endemic regions for HEV, the high number of immigrants arriving in Italy and the new zoonotic aspect of the infection could change this epidemiologic situation in the future. The new epidemiological spreading of HEV infection and the emerging clinical features of the disease require constant surveillance for a better control and prevention of this disease.

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