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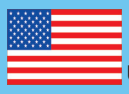

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TOPIC HIGHLIGHT

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Hepatitis E: Epidemiology and prevention

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Abstract

Hepatitis E is caused by the hepatitis E virus (HEV), the major etiologic agent of enterically transmitted non-A hepatitis worldwide. HEV is responsible for major outbreaks of acute hepatitis in developing countries, especially in many parts of Africa and Asia. The HEV is a spherical, non-enveloped, single-stranded, positive sense RNA virus that is approximately 32 nm to 34 nm in diameter and is the only member in the family Hepeviridae and genus *Hepevirus*. There are four distinct genotypes of HEV (genotypes 1-4). While genotype 1 is predominantly associated with large epidemics in developing countries, genotype 3 has recently emerged as a significant pathogen in developed countries. The clinical manifestations and the laboratory abnormalities of hepatitis E are not distinguishable from that caused by other hepatitis viruses. However, high mortality among pregnant women particularly during the third trimester distinguishes HEV from other causes of acute viral hepatitis. Specific etiologic diagnosis among infected cases can be made by serological testing or detection of viral nucleic acid by reverse transcription polymerase chain reaction. Although there are vaccine candidates that had been shown to be safe and efficacious in clinical trials, none are approved currently for use. There is no specific therapy for acute hepatitis E as treatment remains supportive.

Key words: Hepatitis E virus; Acute viral hepatitis; Outbreak; Epidemiology; Serology; Prevention

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INTRODUCTION

Hepatitis E virus (HEV) is a significant international public health problem and it is estimated that 2.3 billion people are infected globally[1]. HEV is the leading cause of acute viral hepatitis in the world, especially in developing countries. The first retrospectively confirmed outbreak of hepatitis E occurred in 1955-1956 in New Delhi, India and resulted in more than 29 000 symptomatic jaundiced persons[2]. Since that time, many large outbreaks have occurred in Asia, Africa and Mexico[3,4]. In addition, sporadic hepatitis E outbreaks commonly occur in developing countries of Asia and Africa as well as in industrialized countries[5,6]. Although there is a distinct epidemiologic picture of HEV infection in North America, Europe, and Japan, this review article will summarize the current epidemiology of HEV infection in the developing world.

HEV

The discovery of HEV followed the development of serological tests for hepatitis A virus (HAV) and hepatitis

B virus (HBV) infections in the mid 1970s. With the ability to diagnose HAV and HBV infections and after ruling out HAV as the cause of the large 1955-1956 jaundice epidemic in New Delhi, the search for the causative agent of the enterically transmitted non-A non-B hepatitis intensified. In 1983, virus-like particles were observed, using immune electron microscopy, in the stool of a human volunteer experimentally infected with what eventually became to be recognized as the HEV[7]. The HEV genome was first cloned in 1990.

HEV is a spherical, non-enveloped, single-stranded, positive-sense RNA virus that is approximately 32 nm to 34 nm in diameter[8]. The organization of the HEV genome is substantially different from other viruses and it has its own family, the hepeviridae, genus *hepevirus*, species *HEV*[9,10]. The HEV genome is arranged in three overlapping open reading frames (ORF). The three coding frames are used to express different proteins. ORF1 encodes a polyprotein of about 1690 amino acids that undergoes post-translational cleavage into multiple non-structural proteins required for virus replication, including a methyltransferase, a putative papain-like cystein protease, an RNA helicase and an RNA-dependent RNA polymerase. ORF2 does not overlap with ORF1; it is located at the 3'-end of the genome and encodes the principal structural protein, the capsid protein of 660 amino acids. ORF3 begins with the last nucleotide of ORF1; it overlaps with ORF2 and encodes for a small immunogenic 123 amino acid phosphoprotein which associates with the cytoskeleton, suggesting its possible role in the assembly of virus particles[11]. The organization of the ORF differs slightly according to genotype however the function remains the same. Compared to the HAV, the HEV is less resistant to environmental conditions such as temperature.

EPIDEMIOLOGY

HEV is classified into at least four major genotypes 1-4 and 24 sub-types[8]. However, HEV has only one serotype. Genotype 1 is the most frequent cause of epidemic and sporadic hepatitis E in the developing world. HEV genotype 2 was first identified from the 1986 epidemic in Mexico and subsequently from Chad and Nigeria[4]. Meng *et al*[12] first described an HEV isolate which was genetically divergent from Burmese and Mexican strains and that was highly prevalent in the swine population. This strain was eventually isolated from a case in the United States that occurred in a person for whom no clear risk factor for infection was identified[13]. HEV genotype 3 is prevalent globally in the swine population and is now being increasingly identified in human cases in the developed world[14]. Genotype 4 was first described in Taiwan and subsequently found in China, Japan and India. Genotypes 3 and 4 also have been isolated from swine in the United States, Africa and Asia. There are clear differences in the epidemic potential of the various genotypes and epidemics occur exclusively in developing countries where the predominant circulating human strain is HEV genotype 1. The geographic distribution, the virulence, the nature of reservoirs and the epidemic potential of the four genotypes that are associated with human disease is shown in Table 1.

The epidemiologic characteristics of epidemic hepatitis E have remained consistent since the first described outbreak in New Delhi with the highest attack rates among young adults and a high mortality among women in the third trimester of pregnancy[2,3]. This latter characteristic has remained to be the hallmark of HEV associated acute viral hepatitis that leads to the initial suspicion of an epidemic in the absence of capacity for serological diagnosis.

To date, few studies have attempted to quantify the incidence of hepatitis E in the general population. Labrique *et al*[15] followed a randomly selected cohort of 1134 subjects from rural southern Bangladesh where the baseline prevalence of antibodies against HEV was 22.5% and found serological incidence of 60.3 per 1000 person-years during the first 12 mo of follow up. Conversely, there are several studies that have examined the prevalence of antibodies against HEV in different population groups. However, the interpretation of these seroprevalence data is immensely challenging. Challenges include the inconsistency of results due to lack of standard tests with comparable sensitivity and specificity, the high seroprevalence in populations where disease rarely occurs or is virtually absent, the presence of multiple genotypes with different disease patterns and the failure of serological tests to distinguish between genotypes.

The prevalence of markers of infection with HEV is much lower in children than for comparable markers of HAV infection in countries endemic for both infections. In a study in Pune, India, researchers found that the prevalence of anti-HAV increased rapidly and reached a peak of around 90% by age 10 years. However, the prevalence of anti-HEV remained low until age 15 at which point it started to increase and peaked at around only 50%[16]. There is no clear explanation for the relatively low prevalence of immunoglobulin G (IgG) antibodies against HEV but it may be due to a rapid loss of serological evidence following natural infection.

In epidemic conditions, HEV is transmitted mainly by drinking fecally contaminated water. In Southeast Asia, outbreaks have usually occurred during the rainy season when flooding can contaminate drinking water supplies[2]. However, many outbreaks also have occurred during the dry season or in conditions where there was no clear flooding or contamination of the drinking water supplies. Recent evidence suggests significant person-to-person transmission in outbreak situations although it is not clear whether this mode of transmission is of comparable magnitude to the person-to-person transmission of HAV infection[17]. There have been reports of transfusion-related transmission and nosocomial transmission of isolated cases of HEV infection[18,19]. Vertical transmission of HEV from a pregnant woman to her unborn fetus is

Table 1 Comparison of the four hepatitis E virus genotypes by select characteristics

Characterstics	Genotype 1	Genotype 2	Genotype3	Genotype 4
Viral discovery	1983	1986	1995	2003
Geographic distribution	Developing countries	Mexico, West Africa	Developed countries	China, Taiwan, Japan
Food-borne transmission	No	No	Yes	Yes
Fecal-oral transmission	Yes	Yes	?	No
Water-borne transmission	Yes	Yes	?	No
Person-to-person transmission	Yes	Unknown	Yes	Unknown
Zoonotic transmission	No	No	Yes	Yes
Occurrence of epidemics	Common	Smaller scale epidemics	No epidemics	Uncommon
Highest attack rate	Young adults	Young adults	Persons ⩾ 40 yr of age	Young adults
Gender	Male preponderance	Not discriminatory	Mostly male	Not discriminatory
Mortality rate	0.5%-3%	0.5%-3%	Not determined	0.5%-3%
Mortality among pregnant women	High	High	Not determined	High
Chronic infection	None	None	Yes	None
Severe disease among immuno-compromised	Not reported	Not reported	Yes	Not reported
Interspecies transmission	Only humans and non-human primates	Only humans and non-human primates	Humans Pigs	Humans Pigs
Subtypes	5	2	10	7

very well documented. Khuroo *et al*[20] investigated fetal outcomes of HEV infection in pregnant women and found in utero transmission with fetal outcomes ranging from intrauterine fetal death to symptomatic and asymptomatic neonatal liver infection. To date, there has been no evidence for sexual transmission of HEV.

Sporadic hepatitis E is also common in countries where epidemic hepatitis E occurs. The mode of transmission or risk factors for sporadic HEV transmission is not known. There are data that show that a significant proportion of acute viral hepatitis in epidemic prone countries is caused by HEV[3,5,6]. The global burden of HEV infection is due much more to the contribution of sporadically transmitted hepatitis E cases than to cases consequent to epidemic hepatitis E. In India alone, it is estimated that 2 million cases of hepatitis E occur annually compared to an estimated 1.4 million cases of hepatitis A[3,6].

In parts of Africa (Sudan, Chad, Uganda, Kenya, and Somalia) a number of large hepatitis E outbreaks have occurred among persons living in refugee camps or internally displaced persons camps[21]. Persons living in such camps may not have adequate access to clean water and sanitary conditions. Furthermore, such populations may be vulnerable to infectious diseases because of crowded living and poor nutrition, leading to higher risk of exposure to infectious agents and poor immune response during infectious exposures. Available medical care services may not be optimal and thus mortality from serious complications of infection may be high. This may explain in part the observed high mortality during hepatitis E outbreaks in Africa[22]. Outbreaks have been reported among migrant workers who move to cities and reside in crowded urban slums[23].

The clinical presentation and sero-epidemiology of hepatitis E (caused by HEV genotype 1) is not consistent globally. Serological data from Egypt have shown that the seroprevalence of anti-HEV can reach close to 100% in a population; similar to that seen with the seroprevalence of anti-HAV. Studies among pregnant women in the Nile Delta have found very high seroprevalence rates without any clinical consequence[24]. Furthermore, a high clinically manifest infection rate has been recorded in young children in the same region[25]. The HEV strain circulating in Egypt is HEV genotype 1 subtype 3. On the basis of this finding some researchers have suggested that HEV genotype 1 subtype 3 may be less virulent but highly contagious.

The persistence of IgG anti-HEV following natural infection has been one area of interest for researchers. In Kashmir, researchers conducted serological follow up of 320 persons who were known to have hepatitis E during the 1978 HEV outbreak. In 50% of the cases there was detectable IgG anti-HEV 14 years after infection[26]. In another short term follow-up study, researchers found that 100% of persons maintained evidence of past infection 3 years later[27]. However, the implication of the persistence of antibodies is not clear. The fact that the prevalence of anti-HEV in the population does not reach the same levels as HAV and that attack rates are higher among young to middle aged adults suggests that infections may not confer lifetime protection. This intriguing finding is also complicated by the recurrence of outbreaks in countries where one would surmise that following past epidemics the population would have developed immunity to prevent future outbreaks. The question of how long anti-HEV IgG remains present following natural infection and the protective efficacy of naturally acquired anti-HEV antibodies is important because of its implications for vaccine development.

Prolonged excretion of HEV in stool following symptomatic/asymptomatic infection is rare. While in HAV it is known that neonates and young children can shed virus for long periods of time, such associations have not been established for HEV. Researchers have however found that HEV RNA from human or animal

(pig) waste can contaminate drinking water, survive and remain infectious for long periods[28]. In genotype 3-associated food borne outbreaks, there has been a clear link between consumption of pig or wild boar liver and development of disease[29,30]. US researchers have isolated HEV RNA from pig livers in grocery stores[31]. In Egypt, consumption of unwashed produce was associated with higher prevalence of anti-HEV IgG, suggesting that produce could be contaminated by human or animal waste before harvest[24]. The reservoir of HEV during inter-epidemic periods is not clearly understood. There are many animal species including rats, cattle, deer and wild boar from whom anti-HEV antibodies or HEV RNA have been isolated. Kuniholm *et al*[32] have shown that having a pet dog was associated with HEV seropositivity, based on the National Health and Nutrition Survey conducted between 1988 and 1994 in the United States.

CLINICAL PRESENTATION, DIAGNOSIS AND TREATMENT

The incubation period of HEV infection ranges from 15 d to 60 d (mean 40 d). Research among non-human primates showed a direct association between infective dose and severity of disease with an inverse relation to the incubation period[33]. HEV causes a range of clinical manifestations including asymptomatic infection, unapparent infection, and icteric hepatitis. The clinical presentation of acute hepatitis E is indistinguishable from other acute viral hepatitis. Hepatitis E is an acute disease with abrupt onset of non specific symptoms followed by right upper quadrant pain, jaundice, anorexia, malaise, nausea and vomiting. Asymptomatic infections occur more often among children than adults. In a study by Khuroo *et al*[3] the symptomatic to asymptomatic ratio for children was 1:12 while for adults it was only 1:3. The symptomatic hepatitis E attack rate during an outbreak can reach up to 15%. The attack rate is always higher among adults even in countries where HEV epidemics have occurred repeatedly. Furthermore, the attack rate varies by gender. In many epidemics men were found to have higher attack rates. However, in a recent HEV outbreak in Uganda, women were more likely to have symptomatic hepatitis E than men and this difference was significant for women aged 15-45 years[21]. Although the outcome of disease is worse in pregnant women, there is no evidence to suggest that they are more susceptible to infection or are at higher risk of infection. HEV infection in pregnant women is typically severe during the third trimester of pregnancy[34,35]. Mortality rates among pregnant women in the third trimester range from 10%-25%. To date, it is not clear what the disproportionately high mortality among pregnant women is due to[36]. The causes of death include fulminant liver failure and obstetric complications including excessive bleeding[37,38]. In contrast, the high mortality observed in many Asian and African countries was not observed among HEV infected pregnant women from Egypt. Stoszek *et al*[24] detected no deaths among more than 2000 pregnant women with serological markers for infection. Other researchers also found very high seroprevalence with little to no symptomatic infections in highly endemic rural Egyptian communities[39]. The commonly circulating HEV isolate in Egypt belongs to genotype 1 subtype 3 and this may explain in part the different morbidity and mortality patterns found there.

Another group prone to develop severe morbidity following HEV infection is persons with pre-existing chronic liver disease. Persons with advanced liver disease including cirrhosis can develop acute hepatic failure when super-infected with HEV[40]. The same phenomenon has been observed with hepatitis A super-infection of persons with chronic liver disease and was the basis for administration of hepatitis A vaccination to persons with chronic liver disease[41]. This will have to be considered when HEV vaccine becomes available.

The frequent occurrence of HEV infection among persons undergoing immunosuppressant therapy for solid organ transplantation in developed countries raises the question of HEV infection among those with AIDS. To date, there are few case reports of acute, chronic or reactivated HEV infection among persons with acquired immune deficiency syndrome (AIDS). However, these reports are from Europe where the causative HEV agent belonged to genotype 3[42]. A few studies have examined anti-HEV seroprevalence among AIDS cases in Africa, but there were no reports of acute or chronic hepatitis caused by HEV. Dalton *et al*[43] found that HEV was the culprit in a number of cases diagnosed as drug-induced liver injury. In developing countries, the high prevalence of HIV/AIDS and drug-induced liver injury should be taken seriously and a systematic search for HEV infection should be part of the management of liver abnormalities in such populations.

The laboratory abnormalities in liver enzymes and liver function tests are similar in HEV to findings with other forms of acute viral hepatitis and include elevated serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, and γ-glutamyltransferase[11,44]. Abnormalities in liver function typically coincide with onset of clinical symptoms. Histopathological changes in the liver during acute infection include focal necrosis and modest inflammation[45]. Cholestatic hepatitis is common and a "pseudoglandular" alteration of hepatocyte plates has been noted. HEV is not thought to be cytopathic and it is possible that disease is due to immunological reactions, although this has not been confirmed. Resolution of biochemical abnormalities generally occurs within 1 wk to 6 wk after onset of illness. Chronic infection with HEV is virtually absent among healthy individuals, and has never been reported from HEV genotype 1 endemic countries[46]. Also, there is no evidence to suggest recurrent HEV infection in endemic countries. However, chronic hepatitis E after infection with HEV genotype 3 has been reported among persons receiving immunosuppressive treatments following organ transplants.

HEV infection elicits both immunoglobulin M (IgM) and IgG antibodies against HEV. The IgM antiHEV response is rapid, occurring about a month after infection and peaking at the time of onset of biochemical abnormalities and/or symptoms[47,48]. HEV RNA can be detected in both blood and stool at the peak of the acute serological response. There are a number of commercial enzyme immunoassays to detect IgM and IgG anti-HEV in serum although there is considerable variability in their sensitivity and specificity, thereby making the diagnosis of HEV infection difficult. Drobeniuc *et al*[49] conducted a pangenotypic validation of six commonly available IgM assays and found that only two of these assays had sensitivity and specificity above 95%. Reverse-transcription polymerase chain reaction can be used to detect HEV RNA in serum and stool but is not available routinely in commercial laboratories. Interpretation of test results can be difficult, and in low endemic regions a definitive diagnosis generally requires use of multiple tests, consideration of risk factors, and exclusion of other causes of acute hepatitis.

The reported mortality rate from hepatitis E during an epidemic has ranged from 0.5%-4%. Two recent investigations have shown that the mortality rate among young children is also high. In Uganda, the mortality rate among children younger than 2 years of age was 8% while in the Kazakhstan the mortality rate among children was 5%[21,50]. Tsega *et al*[51] reported no deaths among more than 400 cases of acute hepatitis E in young soldiers in Ethiopia. Unfortunately, in recent investigations of HEV outbreaks, it has become apparent that HEV is a fatal disease not only of pregnant women or very young children. There is growing evidence that HEV can result in fatal illness in otherwise young and healthy adults. HEV super infection may also increase mortality in otherwise stable individuals with chronic liver disease.

There is no specific therapy for hepatitis E, and treatment currently is supportive. The disease typically resolves within 4-6 wk of the onset of symptoms, usually without any long-term consequences[52]. Patients with severe complications of hepatitis E require hospitalization and it is generally believed that hepatitis E may be more severe than hepatitis A[53]. Vulnerable populations like pregnant women and persons with preexisting chronic liver disease should be identified and be given necessary supportive treatment. To date immune globulin has not been demonstrated to be effective in preventing hepatitis E in HEV-infected persons although there is some evidence to suggest that prior infection protects from disease[54-56].

PREVENTION

In HEV outbreaks, as in other fecal orally transmitted infection outbreaks, the provision of clean drinking water and improving the sanitary disposal of human waste are the two most important preventive approaches. There are challenges in implementing such strategies in a timely manner in areas where such epidemics occur. The outbreak in Uganda resulted in more than 10 000 cases despite attempts to provide clean water and increased access to latrines[21]. The outbreak in Darfur raised questions about the optimal level of chlorination to eliminate HEV from drinking water[57]. In contrast, the lack of specific risk factors for sporadic hepatitis E makes it more difficult to develop prevention strategies.

In Nepal, a phase Ⅱ trial of recombinant HEV vaccine made by expressing the ORF 2 protein in baculovirus has demonstrated that the vaccine is safe and highly efficacious[58]. However, this trial only included men and thus yielded no information on the vaccine's safety and efficacy in women and children. Recently, Zhu *et al*[59] reported a phase Ⅲ trial of another recombinant vaccine expressed in *Escherichia coli*. The trial included almost 110 000 persons randomized to receive vaccine or placebo (hepatitis B vaccine). This trial found a vaccine efficacy of 99%, but did not enroll children and pregnant women. There are other vaccines at different stages of development.

The two vaccine candidates that have undergone phase Ⅱ and phase Ⅲ trials, respectively, are recombinant proteins from truncated ORF 2 of the SAR 55 strain. As HEV has only one serotype, it is expected that these vaccines will be equally protective from infection by any of the four HEV genotypes. Given the experience in Asia that recurrent outbreaks can occur in a population and that the population level prevalence of markers of immunity against HEV are not as high as that against HAV, it seems likely that the vaccine will prove to be the magic bullet for prevention of HEV transmission during outbreaks in these countries. While the results from the recent vaccine trials are promising, many questions remain to be answered before the vaccine can be rolled out for use in the field. The most important question is the safety and efficacy of a vaccine among the most vulnerable populations including pregnant women, young children, and those with pre-existing chronic liver disease. Other questions include the efficacy of a vaccine when used in the immediate post-exposure situation in preventing and controlling transmission during an outbreak, the cost of the vaccine, the length of vaccine induced immunity, and when to vaccinate.

Understanding the global burden of HEV disease will help to develop vaccination policy when vaccines become available. However, there is a lack of epidemiological data from most countries where HEV could be the leading cause of acute viral hepatitis. The available information is mostly limited to data collected during outbreaks or epidemic investigations. To benefit optimally from the vaccine, it will be important for countries to start conducting surveillance for viral hepatitis with emphasis on etiologic rather than syndromic diagnosis. Information on baseline prevalence of markers for past HEV infections also would be useful in informing the target recipients of the vaccine.

CONCLUSION

HEV is the leading cause of non-A, non-B enterically-transmitted acute viral hepatitis in the world. Although HEV has only one serotype, the different genotypes appear to be associated with different epidemiological profiles in the developing world compared to industrialized countries. In most of the developing world, the disease affects mainly young adults and results in very high mortality among very young children and pregnant women. In epidemic settings, the basic premises for prevention of HEV infections are provision of safe drinking water and sanitary disposal of human waste. As the risk factors for transmission in sporadic hepatitis E are not clearly understood, it remains difficult to recommend prevention strategies. However, the same strategy that prevents outbreaks should closely be adhered to, as HEV and other feco-orally transmitted or water-borne infections could be prevented. Specific attention should be given to persons at higher risk of severe illness by giving priority to the prevention of infection in this vulnerable group during outbreaks. Given the huge global burden of epidemic and sporadic hepatitis E, the high mortality among pregnant women and very young children, the severity of autochthonous hepatitis E, and the threat caused by the widespread prevalence of HEV infection in different populations worldwide, expansion of epidemiologic and intervention studies, especially clinical trials of promising hepatitis E vaccine candidates, should be pursued.

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TOPIC HIGHLIGHT

Francesca Cainelli, MD, Professor, *Series Editor*

Management of hepatitis B in developing countries

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Abstract

Hepatitis B is one of the leading causes of chronic hepatitis in developing countries, with 5% to 15% of the population carrying virus. The high prevalence is due to failure to adopt appropriate measure to confine the spread of infection. Most hepatitis B patients present with advanced diseases. Although perinatal transmission is believed to be an important mode, most infections in the developing world occur in childhood and early adulthood. Factors in developing countries associated with the progression of chronic hepatitis B (CHB) include co-infections with human immunodeficiency virus, delta hepatitis virus, hepatitis C virus, alcohol intake and aflatoxin. Treatment protocols extrapolated from developed countries may need modifications according to the resources available. There is some controversy as to when to start treatment, with what medication and for how long? There is now enough evidence to support that hepatitis B patients should be considered for treatment if they show persistently elevated abnormal aminotransferase levels in the last 6 mo, checked on at least three separate occasions, and a serum hepatitis B virus DNA level of > 2000 IU/mL. Therapeutic agents that were approved by Pure Food and Drug Administration are now available in many developing countries. These include standard interferon (INF)-α, pegylated INF-α, lamivudine, adefovir, entecavir and telbivudine. Drug resistance has emerged as a major challenge in the management of patients with CHB. The role of the universal vaccination program for effective control of hepatitis B cannot be emphasized enough.

Key words: Hepatitis B; Management; Developing countries; Hepatitis B surface antigen; Hepatitis B virus DNA; Vaccination

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INTRODUCTION

Hepatitis B is the leading cause of chronic viral hepatitis across the world. More than two billion people worldwide show serological evidence of exposure to this virus, comprising about one third of the global population and approximately 350-400 million carry the chronic infection[1,2]. Chronic hepatitis B (CHB) infection leads to cirrhosis and is still a major cause of hepatocellular carcinoma in many parts of the developing world[3,4]. For children under 1 year, the risk of chronic infection is 90%[5]. About 25% of adults who become chronically infected during childhood die prematurely from liver cancer or cirrhosis, caused by its chronic infection[2]. But if adults are infected by hepatitis B virus (HBV) after childhood, 90% will eventually fully recover. Hepatitis B causes an estimated one million deaths per year worldwide[6].

It is estimated that 5 % to 15% of the population are chronic carriers of hepatitis B in developing countries, whereas in North America and Western Europe only 1% of the population is chronically infected. Chronic HBV infection is highly prevalent in sub-Saharan Africa, Southeast Asia, the Eastern Mediterranean region, the Amazon basin and the Caribbean[7-9]. Hepatocellular carcinoma seems to be more common in Africa and Asia than in other parts of the world due to Hepatitis B infection.

Many developing countries often face significant health and hygiene challenges that predispose to the transmission of hepatitis viruses. Most hepatitis B patients present with advanced disease. Contributing factors leading to late presentation include ignorance, poverty, lack of easy accessibility to healthcare centers, lack of trained personnel and diagnostic facilities, un-affordability of expensive drugs and consultations from quacks and traditional healers that misguide patients.

TRANSMISSION

Perinatal transmission is believed to be the most important mode in regions of developing world with high and intermediate HBV prevalence rates[10]. Transmission occurs from mother to child or from child to child, mainly through cuts, bites, scrapes and scratches. Although most infections in the developing world occur in childhood and early adulthood, a significant proportion of non-immune adults remain at risk to healthcare-acquired infections. HBV remains a major nosocomial pathogen in many hospitals[11]. Transmission may occur due to unsafe injections, blood transfusions and lack of awareness of infection control[12,13]. Healthcare providers may be unaware of the natural history of hepatic cellular cancer (HCC) and the need for continuous lifetime monitoring of HBV infection status[4]. Sexual contact also accounts for some HBV transmission.

Phases of infection

The natural history of CHB has been defined into different phases: the immune tolerant phase, the immune reactive phase and the inactive carrier phase and hepatitis B e antigen (HBeAg) negative disease[14-17]. In the immune tolerant phase, HBeAg is positive, HBV DNA is elevated, abnormal aminotransferase (ALT) is usually normal and liver inflammation is absent or minimal. The immune reactive phase is characterized by ALT elevation, HBV DNA levels > 2000 IU/mL and active liver inflammation and fibrosis of various degrees. A more vigorous cytotoxic T-cell response may occur eventually, resulting in seroconversion from HBeAg to anti-HBe during this phase. After seroconversion, most patients go into the inactive hepatitis B carrier phase characterized by normal ALT levels, low levels of HBV DNA (< 2000 IU copies/mL) and improvement of liver inflammation and fibrosis over time, provided they remain in the inactive hepatitis B phase. These patients may move from the inactive hepatitis phase back to the immune reactive phase, either by experiencing a reversion from anti-HBe to HBeAg or having HBeAg negative CHB with elevated HBV DNA levels > 2000 IU/mL and elevated ALT[18,19]. A small fraction of patients lose surface antigen over years with the disease becoming inactive. Occult infection is associated with negative hepatitis B surface antigen (HBsAg), undetectable HBV DNA in serum which is detectable on liver biopsy as persistent of covalently closed circular DNA (cccDNA) within the nucleus of infected cells[20]. Hepatitis B can reactivate when patient is immunosupressed in such a state[21,22].

There may be some factors operating more in developing countries associated with the progression of CHB, like co-infections with human immunodeficiency virus (HIV), delta hepatitis virus (HDV), hepatitis C virus (HCV), alcohol intake and aflatoxin. Individuals with chronic HBV infection need lifelong monitoring for the development of active chronic hepatitis and HCC.

EVALUATION BEFORE STARTING TREATMENT

Newly diagnosed CHB individuals should be evaluated by relevant history, identifying risk factors and appropriate physical examination[23]. Laboratory tests should include complete blood counts, liver panel, α fetoprotein, HBeAg, anti-HBe antibody status and HBV DNA levels. Every patient should have an ultrasound examination of liver. Other tests that are still not included in the guidelines are quantification of HBsAg and HBV genotype. It is possible to quantify the HBsAg level, which would help improve management and monitoring of hepatitis patients. This test is now becoming available in developing countries and is not very expensive. It reflects transcriptionally active cccDNA while HBV DNA levels reflect active viral replication[24,25]. HBV genotype influences the outcome of the disease as well as outcome of therapy with interferon (INF)[26]. However, in countries like Pakistan where a single genotype predominates, it would be unnecessary to check genotype in every case[27].

Co-infections with other infections should be ruled out by checking HIV, HDV and HCV antibodies. To stage the chronic active disease, liver biopsy is considered to be the gold standard. However, help may also be taken from Fibroscan and non invasive tests. Chen *et al*[28] reported a model to predict compensated cirrhosis due to HBV infection using the findings of ultrasound examination of liver and blood tests.

Screening and vaccination for hepatitis A may not be necessary in areas with high childhood exposure. Screening and vaccination of household/sexual contacts for HBV is recommended.

TREATMENT

Evidence-based guidelines for the treatment of CHB have been developed by three of the world's major liver societies, the American Association for the Study of

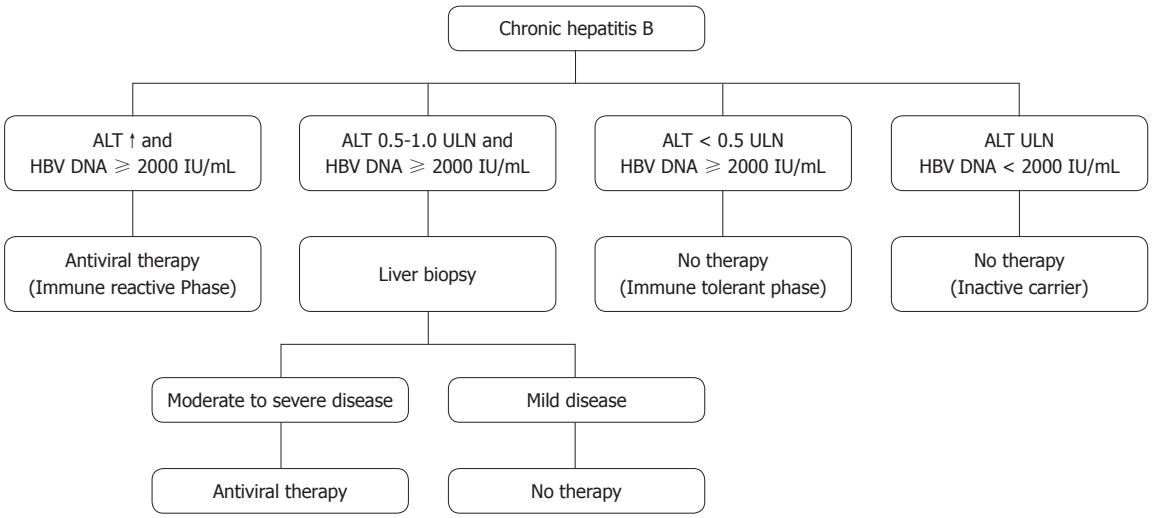

Figure 1 Selecting patients for anti-viral therapy. HBV: Hepatitis B virus; ALT: Abnormal aminotransferase; ULN: Upper limit of normal.

Liver Diseases[29], the European Association for the Study of the Liver[30] and the Asian Pacific Association for the Study of the Liver[31]. These guidelines are reviewed and updated every 2-3 years. National guidelines of local societies from developing countries are also available[32]. Evidence-based guidelines require sufficient evidence to support any recommendations that are made and thus may not cover all situations which a clinician caring for hepatitis B in developing countries may encounter. Treatment can cost thousands of dollars per year and is not available to the majority of patients in these countries.

Who should be treated?

Labeling of HBV infected patients as "inactive carriers" based on ALT alone may be misleading. A fair proportion of patients with CHB and persistently normal ALT have HBV DNA ⩾ 5-log copies/mL and significant histological fibrosis[33]. There have been suggestions for lowering the upper cut off of normal range for ALT to 19 IU/mL for women and 30 IU/mL for men, as higher levels have been shown to be associated with significant liver disease[34,35]. These cut off levels differentiate the really "inactive carriers" from those with active disease with histological damage, who need to be treated. Studies have shown that mildly elevated ALT less than two time upper limit of normal (< 2 ULN) may also be associated with significant underlying liver disease and does not predict a lower risk of long-term complications[36].

HBV DNA detection and quantification form an integral part of disease assessment, disease activity and response to therapy. HBV DNA viremia levels correlate positively with the inflammatory grade and fibrosis stage[37]. Cut off value of HBV DNA of 20000 IU/mL for the initiation of treatment has been challenged. The R.E.V.E.A.L study showed that the value of > 10^4 copies (2000 IU/mL) might be associated with a higher risk for development of cirrhosis and is independent of HBeAg status and serum ALT levels[38]. Three other studies have also suggested that CHB may occur at lower levels of HBV DNA between 10^4 copies/mL and 10^5 copies/mL[39-41]. Moreover, with the single point assessment of HBV DNA level, the accurate differentiation of CHB e-antigen negative infection from inactive carriers is difficult because of wide and frequent HBV-DNA fluctuations. It has been suggested that single-point combined HBsAg and HBV-DNA quantification (HBsAg < 1000 IU/mol and HBV DNA ⩽ 2000 IU/mL) provides the more accurate identification of inactive carriers[42].

Hepatitis B patients should be considered for treatment if they show persistently elevated ALT levels in the last 6 mo, checked on at least three separate occasions, and a serum HBV DNA level of > 2000 IU/mL[30,32]. If ALT fluctuates near the upper limit of normal or remains > 0.5 times ULN all the time with elevated HBV DNA > 2000 IU/mL, liver biopsy is advocated (Figure 1). Patients with HBV DNA positive < 2000 IL/mL and normal ALT levels should be monitored every 3 mo for the first year then every 6 mo thereafter to assess development of active disease. Cirrhotic patients with detectable HBV DNA should be treated irrespective ALT level. Ultrasound examination of liver should be repeated every 6-12 mo.

Therapies for CHB

Two types of agents used for treatment are INF (standard and PEG) and oral nucleosides/nucleotides analogues (NUCs). The former has advantages of having a finite treatment period, no resistance and durable HBeAg seroconversion. While treating with INF, patients infected with genotype A do better than genotype D in Caucasians and genotype B better than genotype C in Asians[26]. INFs cannot be prescribed in cirrhotic patients with decompensated disease. On the other hand, NUCs are easy to administer and monitor, have fewer side effects and can be given in cirrhotics. Therapeutic agents that were approved by Pure Food and Drug Administration include standard INF-α, pegylated INF-α, lamivudine, adefovir, entecavir and telbivudine[16].

Lamivudine is a cheap option in developing countries

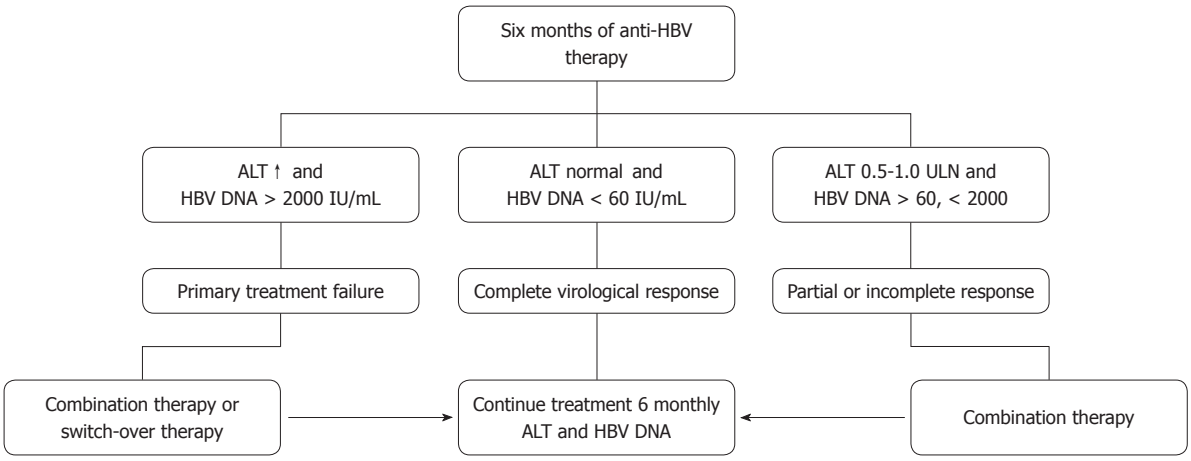

Figure 2 Evaluation of response to therapy at 6 mo (Modified from Keeffe *et al*[33] 2008). HBV: Hepatitis B virus; ALT: Abnormal aminotransferase; ULN: Upper limit of normal.

but is easily susceptible to resistance[43]. The documented figures for lamivudine resistance mutation rises up to 23 %-65% after 1-5 years of treatment[44]. Adefovir dipivoxil is a less effective agent compared to other agents and offers a high chance of resistance, as is telbivudine although it is a more potent drug[45,46]. Entecavir and tenofovir are effective options bearing the least chance of developing resistance with a high potency against the HBV and can be opted as first line option straight away[47]. Tenofovir is a potent inhibitor of HBV viral suppression[48,49]. Emtricitabine (cytosine analog), which is a co inhibitor for both HIV and HBV, is structurally similar to lamivudine with the same resistant mutations and the results are comparable[50].

Thymosin α has been used in Asian countries as an immunomodulatory agent. It has a delayed virological response which is seen after the completion of a year of treatment[51]. Various combination therapies using both INF and NUCs are also used for an additive synergistic effect and greater suppression of virus along with reducing the risks of emergence of resistance[52]. For example, INF and lamivudine when used in combination in wild type virus is more potent than monotherapy with lower rates of resistance to lamivudine[53,54].

Monitoring the response to treatment

Assessment of treatment efficacy can be made by monitoring the parameters during the initial phase, maintenance phase and after completion of treatment. A later sustained response can be established at 6 mo and 1 year after the end of treatment. Figure 2 summarizes the possible scenarios after 6 mo of therapy with NUCs.

In clinical practice, serum HBV DNA and ALT monitoring is the most practical method to detect response and virological breakthrough. It is the key to prevent possible hepatic flares and decompensation[55]. It should be done at 3 mo, 6 m into treatment and thereafter every 6 mo. Serum HBeAg should be checked every 6 mo in patients who are initially HBeAg positive in order to determine the time of e-antigen sero-conversion. Anti-HBe antibody should be checked after HBeAg becomes negative. The quantitative PCR is an expensive test and may not be affordable for many patients from developing countries. In such cases testing at month three may be omitted. In less ideal situations when the test is not available, monitoring with ALT alone every 3 mo would suffice. In patients with virological breakthrough, necessary modifications should be instituted and medication compliance reinforced. Resistance testing (genotyping) should be carried out, where available, in cases of viral breakthrough or suboptimal viral suppression.

There is also a potential role for on-treatment monitoring of serum HBsAg titres to predict virological response during both INF therapy and oral nucleos(t)ide analogue therapy[24]. Good immune control results in dramatic reduction of HBsAg levels. Monitoring HBsAg levels may help to identify patients who would respond to finite therapy and achieve sustained immune control in case of pegylated INF and clear HBsAg in long term treatment with nucleoside analogs[56]. Treatment with pegylated INF may be stopped early in patients who fail to show significant decline in HBsAg levels at week 12 or 24[57].

Drug resistance

Drug resistance, as mentioned above, has emerged as a major challenge in the management of patients with CHB. Emergence of resistant HBV strains leads to virological and biochemical breakthrough, and can further result in histological deterioration during treatment, hepatic decompensation and death. Several factors predispose to development of resistance, including high viral load, resistant variants, slow response, prior therapy with a nucleoside analogue leading to cross resistance, high body mass index, along with patient immune status and compliance, all play a role in the development of resistance to anti viral therapy[58-61].

Entecavir was found to be safe and effective for the treatment of Japanese adults with lamivudine-refractory CHB[62]. *In vitro* studies however, demonstrate that entecavir is less effective against lamivudine-resistant HBV

strains in comparison to wild-type; 20-30-fold higher concentrations are required for polymerase inhibition. This is because lamivudine resistance already preselects two of the three mutations required for entecavir resistance. Virological breakthrough to entecavir requires at least three substitutions. Accumulating evidence from these settings suggests that entecavir switch is not an optimal treatment for patients with lamivudine resistance[63]. Tenofovir may be of value in such cases of baseline lamivudine or adefovir resistance[64]. While dealing with resistance, sequential monotherapy and use of agents with similar cross resistance profiles should be avoided. An add-on approach is preferred. A combination of tenofovir with emtricitabine in one tablet has been licensed for the treatment of HIV infection. This combination, not freely available in developing countries, may be of value in dealing resistant cases of hepatitis B as well.

How long to treat?

The end points of therapy should be normalization of ALT, seroconversion of HBsAg and HBeAg, suppression of HBV DNA and improvement of histological features on liver biopsy to achieve sustained suppression of viral replication and remission of disease[65]. HBsAg seroconversion is difficult to achieve with the current therapy and HBV DNA supression (< 2000 IU/mL) is the primary desirable objective to prevent the progression of active disease[66,67]. Duration of treatment varies from 1 year to 3-5 years or may be for life in some cases. INF-based regimens have a short term period, usually 1 year compared to NUCs.

In patients with HBeAg positive disease, CHB treatment may be stopped after confirmation of undetectable HBV DNA, HBeAg loss and formation of anti-HBe antibodies on two separate occasions 3 mo apart after the consolidation therapy of at least 6 mo[68]. In patients with HBeAg negative disease, the end point of therapy remains undefined. Ideally therapy should be continued until the patient has achieved HBsAg seroconversion, a task difficult to achieve. Treatment discontinuation can be considered if undetectable HBV-DNA has been documented on three separate occasions 6 mo apart[31,32]. However, a risk of relapse remains on stopping treatment.

Special circumstances

There is a risk of up to 50% that individuals with chronic HBV infection will develop an exacerbation of hepatitis during chemotherapy treatment for malignancies. Prophylactic nucleoside analogs are indicated and should be continued for at least 4 mo after completing chemotherapy[68]. Similar risk has been shown in persons treated with tumor necrosis factor α inhibitors for rheumatic disorders or inflammatory bowel disease, and these individuals should also be given lamivudine prophylaxis[69,70]. Decision about starting treatment during pregnancy must weigh pros and cons to both mother and baby. Tenofovir, telbivudine and lamivudine appear to be safe in pregnancy. Treatment of immune reactive mothers may be started during pregnancy[71,72].

HEPATITIS B VACCINATION

The role of the universal vaccination program in effective control of hepatitis B cannot be emphasized enough. The best example is of Taiwan where HBsAg seroprevalence amongst children 1-15 years decreased from 9.8% in 1984 to 0.7%[73]. The vaccine prevents HBV infection in 90%-100% of people who produce sufficient antibody responses[74]. All highly endemic countries included hepatitis B vaccination in their national childhood immunization. All children and adolescents younger than 18 years old and not previously vaccinated should receive the vaccine. World Health Organization recommends that routine infant vaccination against HBV forms part of all national immunization schedules. In countries with high mother-to-child transmission rates, the first dose of HBV vaccine is ideally given within 24 h of birth. A combination of vaccine plus hepatitis B immunoglobulin is superior in decreasing risk of transmission of hepatitis B from a HBsAg positive mother to infant[75]. The Global Alliance for Vaccines and Immunization is supporting hepatitis B vaccination programs in developing countries[76].

Two possible dosing schedules are considered appropriate to prevent mother-to-child HBV infections[77]. Three dose schedule: first dose given at birth, second and third doses given concurrently with the first and third doses of DTP vaccine. Four-dose schedule: first dose given at birth, three doses given concurrently with other Expanded Program on Immunization vaccines. Catch-up campaign strategies may be considered for countries where adult risk factors are associated with acute HBV infection. Targeting adolescents and high-risk adults, such as prisoners or health care workers, can supplement routine infant vaccination[78]. In regions, where there is a high rate of infection, catch-up vaccination is not recommended, as most adults will have already been exposed to the virus. Initial vaccination confers protection against HBV infection even after anti-HBs antibody declines below detectable levels[75]. However, the recommendation of a booster dose after 10-15 years of initial HBV vaccination, although controversial, seems prudent[79,80].

CONCLUSION

There is a high prevalence of hepatitis B in many developing countries due to the failure to adopt appropriate measures to confine the spread of infection. There is a need to define the minimal requirements for delivery of optimal care to hepatitis B patients, establish research institutions and collaborate with international organizations to describe the natural history and response to treatment in the underdeveloped world. Treatment protocols extrapolated from developed countries may need modifications according to the resources available. With recent advances in hepatitis B virology and natural history of the disease, many recommendations are now becoming unresolved issues.

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REVIEW

Hepatic osteodystrophy: An important matter for consideration in chronic liver disease

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Abstract

Hepatic osteodystrophy (HO) is the generic term defining the group of alterations in bone mineral metabolism found in patients with chronic liver disease. This paper is a global review of HO and its main pathophysiological, epidemiological and therapeutic aspects. Studies examining the most relevant information concerning the prevalence, etiological factors, diagnostic and therapeutic aspects involved in HO were identified by a systematic literature search of the PubMed database. HO generically defines overall alterations in bone mineral density (BMD) (osteoporosis or osteopenia) which appear as a possible complication of chronic liver disease. The origin of HO is multifactorial and its etiology and severity vary in accordance with the underlying liver disease. Its exact prevalence is unknown, but different studies estimate that it could affect from 20% to 50% of patients. The reported mean prevalence of osteoporosis ranges from 13%-60% in chronic cholestasis to 20% in chronic viral hepatitis and 55% in viral cirrhosis. Alcoholic liver disease is not always related to osteopenia. HO has been commonly studied in chronic cholestatic disease (primary biliary cirrhosis and primary sclerosing cholangitis). Several risk factors and pathogenic mechanisms have been associated with the loss of BMD in patients with chronic liver disease. However, little information has been discovered in relationship to most of these mechanisms. Screening for osteopenia and osteoporosis is recommended in advanced chronic liver disease. There is a lack of randomized studies assessing specific management for HO.

Key words: Hepatic osteodystrophy; Liver disease; Osteoporosis; Osteopenia

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INTRODUCTION

Hepatic osteodystrophy (HO) is the generic term defining the group of alterations in bone mineral metabolism found in patients with chronic liver disease[1]. These individuals have been described as having a higher rate of osteopenia and osteoporosis and the different studies performed in this connection have shown that the rates vary. HO is therefore a common complication throughout the progression of chronic hepatopathy and involves dete-

rioration in quality of life which affects the patient's long-term prognosis[2]. Consequently, a detailed bone mineral density (BMD) and bone metabolism evaluation should be performed in all patients with chronic liver disease in order to prevent fractures and chronic pain. This article aims to provide a general review of HO.

CHRONIC LIVER DISEASE AND ITS ASSOCIATION WITH OSTEOPENIA AND OSTEOPOROSIS

The prevalence of osteoporosis and fracture risk in patients with chronic liver disease

Metabolic bone disease is a significant disorder which appears in patients with chronic hepatopathy (also known as HO), especially in those affected by chronic cholestasis[3,4]. Its etiology is complex and multifactorial and manifests as osteopenia and osteoporosis. This bone disorder must be evaluated and detected early in all patients with chronic liver disease in order to minimize the risk of fractures and improve their clinical progression and quality of life[5]. Various studies have been conducted on the prevalence of osteoporosis in these patients and in patients with chronic cholestasis (Table 1). In most of this research, bone density is calculated using a bone densitometry. However, the authors use different methods to analyze mineral density in order to select patients and even have different definitions of osteoporosis[6-8].

Patients with chronic liver disease harbor additional risk factors for developing osteoporosis, such as hypogonadism, vitamin D deficiency, alcohol consumption, chronic steroid treatment and a low body mass index[9]. With osteoporosis, the patient is predisposed to suffering bone fractures and increased morbimortality. Vertebral fractures are most frequent in these patients, ranging from 3% to 18%[10,11].

Cirrhosis: Different authors consider that the prevalence of osteoporosis in cirrhotic patients is related to the severity of liver disease expressed by the Child-Pugh index[12,13]. This prevalence ranges from 20% to 56% and inter-individual variations are observed in relationship to bone density. The fracture rate ranges from 5% to 20%[14].

Chronic cholestatic disease: A high prevalence of osteoporosis is associated with both primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). This is one of the most widely studied groups of patients with chronic hepatopathy in terms of bone mineral metabolism pathologies. Its prevalence among different groups is estimated to range from 13% to 60%[15].

PBC

Various studies have been conducted on the BMD of patients with PBC. The predominant alteration in these patients is osteoporosis and osteomalacia is very rare[16]. Reduction in bone density is related to the severity of cholestatic disease, although not all patients with PBC develop osteoporosis and the rate of bone mass loss varies from one individual to another[17,18].

Other factors linked to osteoporosis in PBC are the time to progression of the disease and the degree of cholestasis, as a reflection of the stage of chronic hepatopathy. Post menopause and malabsorption of calcium in the intestine have also been suggested as predisposing factors in these patients[19].

Generally, research on bone pathology in PBC coincides with indicating cholestasis as an independent risk factor for developing osteoporosis. Nevertheless, studies to see if there was an improvement in BMD following treatment with ursodeoxicolic acid did not show significant changes compared to untreated patients. Regarding this aspect, cirrhosis co-existing with advanced cholestatic disease can significantly contribute to alterations in BMD[9,20].

PSC

PSC patients harbor various risk factors for developing osteoporosis: cholestasis, co-existing cirrhosis and corticosteroid treatment in the presence of associated inflammatory bowel disease. Individuals with PSC showed a decrease in the BMD of the lumbar vertebrae compared to healthy controls[10].

Hemochromatosis: Certain studies have described a link between hemochromatosis and low BMD by relating co-existing hypogonadism and iron overload with the development of osteoporosis[21]. The prevalence of the latter is approximately 30%[22].

Alcoholism: Alcoholism is an independent risk factor of the development of osteoporosis and osteoporotic fractures and has been especially studied in male patients. BMD of the lumbar vertebrae in these individuals is lower than in healthy controls[23] and the risk of fractures is independent from existing cirrhosis or associated hypogonadism[24,25]. Alcohol abuse in women who do not have cirrhosis and hypogonadism does not appear to be linked to osteopenia and osteoporosis[26].

Non-cholestatic and non-cirrhotic hepatopathy: The exact prevalence of osteoporosis in patients with chronic hepatopathy but who do not have cirrhosis, cholestasis and hypogonadism is unknown. The approximate prevalence of osteoporosis measured at the lumbar vertebrae in this group of patients ranges from 16% to 50%[27] with a fracture rate ranging from 12% to 18%[28].

PHYSIOPATHOLOGY OF BONE MASS LOSS IN PATIENTS WITH CHRONIC LIVER DISEASE

Bone mass increases from childhood, approximately

reaching maximum levels in one's thirties. From one's forties onwards, it starts to decrease in both genders but with a faster loss in women following the menopause. Peak bone mass is determined by genetic and hormonal factors, type of diet and physical activity. The rate of osteoporosis increases in the elderly as the loss of bone mineral mass is a phenomenon associated with aging.

Bone mass loss occurs as a result of an increase in bone turnover and/or an imbalance in bone remodeling. The latter can be caused by decreased osteogenesis, increased bone resorption or by a combination of both. Certain studies have shown increased bone resorption in the context of chronic liver disease, even in patients without osteoporosis. Other research has shown decreased bone formation[12,29]. A study of bone histomorphometric parameters performed on 50 patients with PBC and PSC showed decreased bone formation (osteoblast dysfunction) in men and women and a significant increase in bone resorption due to osteoclast activation, especially in women. According to the authors, the duration of cholestasis or other associated factors seem to be more important that the severity of the disease itself, expressed by levels of serum bilirubin in the development of osteodystrophy[30].

The risk of osteoporotic fracture is determined not only by BMD but also by trabecular architecture, bone geometry, bone turnover and risk factors which are not associated with the skeleton such as postural instability and the risk of falls.

The main risk factors for developing osteoporosis and, therefore, bone fractures in patients with chronic liver disease include: low body mass index (< 19 kg/m^2), excessive alcohol consumption, prolonged steroid treatment (5 mg/d of prednisolone for over 3 mo), sedentary lifestyle, hip fractures in the mother at a young age (< 60 years), hypogonadism and early menopause (under 45 years)[9].

PATHOGENIC MECHANISMS INVOLVED IN BONE MASS LOSS IN PATIENTS WITH CHRONIC LIVER DISEASE

Genetic factors

Certain genetic polymorphisms have been described which may play a secondary role in the development of osteoporosis in chronic cholestatic hepatopathy. These include the vitamin D receptor gene, the collagen type 1 α 1 gene and insulin-like growth factor (IGF-1) polymorphisms[31].

Anomalies of calcium and vitamin D metabolism

Vitamin D is produced by endogenous synthesis in the skin, aided by sunlight, from which cholecalciferol is synthesized (vitamin D_3). Both cholecalciferol and ergocalciferol or vitamin D_2 can also be obtained from food. Vitamin D undergoes 25-hydroxylation in the liver tissue, a process which is affected by advanced liver disease.

Vitamin D deficiency is associated with secondary hyperparathyroidism, an increase in bone turnover and accelerated loss of bone mass. Various studies have shown low serum 25-hydroxyvitamin D levels in individuals affected by chronic liver disease, which continue decreasing as cirrhosis develops[32-34]. The main factors triggering vitamin D deficiency in chronic hepatopathy are believed to be limited exposure to ultraviolet radiation and nutritional deficiency. Intestinal malabsorption, alterations in the enterohepatic circulation of vitamin D and decreased skin synthesis in individuals with jaundice also contribute to vitamin D deficiency. However, no significant correlation between osteopenia and decreased vitamin D levels has been demonstrated in patients with chronic cholestasis[35].

Vitamin K deficiency

Vitamin K is an essential cofactor for osteoblasts to synthesize osteocalcin - bone matrix protein. Vitamin K deficiency contributes to osteopenia in patients with PBC and supplementing it can prevent them from losing bone mass[36].

IGF-1 deficiency

IGF-1 is involved in osteoblast differentiation and proliferation. Low serum levels of IGF-1 were observed in a study with bile duct-ligated rats, suggesting that cholestasis deeply affects its activity[37]. Therefore, its deficiency observed in cirrhosis and cholestatic hepatopathies may cause osteoblast dysfunction and osteopenia[14,15].

Hyperbilirubinemia

In vitro studies on animal models show that the increase in unconjugated bilirubin impairs osteoblast function in a dose-dependent and reversible effect[38,39]. The results of research on humans are inconsistent. For some authors, osteopenia progresses at the same rate as jaundice does in patients with PBC and PSC[40], while this correlation is insignificant for others[41].

Receptor activator of nuclear factor κB ligand and osteoprotegerin

The receptor activator of nuclear factor κB ligand/osteoprotegerin (RANKL/OPG) system regulates bone metabolism by modulating osteoclast activity, to the extent that OPG is a factor which inhibits that activity while the RANKL ligand activates it. Various research has shown that the OPG/RANKL ratio is high in patients with chronic liver disease compared to control subjects, which shows that there is ligand consumption that activates osteoclastic activity, and an excess OPG as a compensating mechanism which tries to prevent the loss of bone mass[42-44]. Other cytokines involved in the pathogenesis of chronic liver disease such as interleukin (IL)-1, IL-6 and tumor necrosis factor α can activate this system[37]. Additionally, circulating mononuclear cells could have a higher capacity to differentiate into osteoclasts in patients with chronic liver disease and osteopenia[45].

Hypogonadism

Hypogonadism associated with chronic hepatopathy has

Table 1 Prevalence of osteopenia and osteoporosis in chronic liver disease of various etiologies

Ref.	*n*	Etiology	Prevalence of osteopenia/ osteoporosis	Pathogenic mechanisms/ associated factors
Goral *et al*[14], 2010	55	Child A-B-C cirrhosis Mixed etiology	Osteoporosis 37%	Increased TNFα and IL-6 levels Decreased IGF-1 levels
Wariaghli *et al*[53], 2010	64	Cirrhosis Mixed etiology	Osteoporosis 45.3%	Female sex Cholestasis Lower weight and height
Loria *et al*[67], 2010	35	Cirrhosis Viral and alcoholic	Osteoporosis 14% Osteopenia 26%	Not specified
George *et al*[34], 2010	72	Cirrhosis Viral and alcoholic	Low BMD 68%	Low levels of IGF-1
Sokhi *et al*[66], 2004	104	Cirrhosis Mixed etiology	Osteoporosis 11.5% Osteopenia 34.6%	Child B-C stage and female female
Gallego-Rojo *et al*[12], 1998	32	Viral cirrhosis	Osteoporosis 53%	Child stage IGF-1 serum levels
Auletta *et al*[72], 2005	30	Chronic viral hepatitis	Osteoporosis 20% Osteopenia 44%	Chronic hepatopathy per se
Diamond *et al*[11], 1989	22	Hemochromatosis	Osteoporosis 45%	Hypogonadism Low free testosterone levels
Sinigaglia *et al*[22], 1997	32	Hemochromatosis	Osteoporosis 28%	Cirrhosis and iron overload
Mounach *et al*[73], 2008	33	Primary biliary cirrhosis	Osteoporosis 51.5%	Low BMI Menopausal status Duration of liver disease Vitamin D deficiency
Lindor *et al*[20], 1995	88	Primary biliary cirrhosis	Osteoporosis 35%	not specified
Guañabens *et al*[74], 1990	20	Primary biliary cirrhosis	Osteoporosis 35%	Duration of liver disease Post menopause Malabsorption of calcium
Angulo *et al*[10], 1998	81	Primary sclerosing cholangitis	Osteoporosis 17%	Stage of liver disease Associated advanced inflammatory bowel disease
Malik *et al*[23], 2009	57	Alcoholic	Low BMD (z-score ≤ -2.0) 17.5%	25-hydroxy-vitamin D deficiency
Kim *et al*[24], 2003	18	Alcoholic	Osteoporosis 22% Osteopenia 50%	Cumulative alcohol intake
Gonzalez-Calvín *et al*[25], 1993	39	Alcoholic	Osteopenia 23%	Cumulative alcohol intake Impairment of osteoblastic activity by ethanol

BMD: Bone mass density; BMI: Body mass index; IGF-1: Insulin-like growing factor 1; IL-6: Interleukin-6; TNF: Tumoral necrosis factor.

been proposed as a factor which favors the loss of BMD. Low levels of estradiol, luteinizing hormone and follicle-stimulating hormone have been observed in postmenopausal women with cirrhosis, with normal testosterone and sex hormone binding globulin[46]. However, in males with advanced liver disease, there is an increase in the level of estrogen due to peripheral aromatization, which does not seem to protect against bone mass loss in individuals with alcoholic liver disease[47].

Medication

Glucocorticoid-based treatments in autoimmune liver disease and chronic cholestatic liver diseases accelerate the loss of bone mass, although their contribution is difficult to estimate due to the effect of liver disease *per se* on the bone[48]. The adverse effect of cholestyramine on the intestinal absorption of vitamin D has also been reported[15].

Lifestyle

Alcohol consumption and smoking aggravate osteopenia/osteoporosis, together with a sedentary lifestyle, malnutrition and a low body mass index[49].

DIAGNOSTIC AND THERAPEUTIC ASPECTS OF OSTEOPENIA AND OSTEOPOROSIS IN CHRONIC LIVER DISEASE

Diagnosis of osteopenia and osteoporosis

The main objective for assessing and treating HO is to prevent bone fractures. BMD is measured using dual energy X-ray bone absorptiometry performed on the lumbar vertebrae and femoral neck. The results of the measurement are classified on a scale by the World Health Organization, the *t-score* being the basic parameter for diagnosis. Osteoporosis is therefore defined as a BMD of less than 2.5 standard deviation compared to the normal average score for young adults (*t-score* of less than -2.5). Similarly, osteopenia is defined as having a *t-score* of between -1 and -2.5[50]. Prospective studies show how the risk of fractures increases progressively in proportion to the decrease in BMD, with between a two-fold and three-fold increase per standard deviation decrease therein[51].

Assessment of all patients with chronic liver disease and suspected osteoporosis should include a hemogram

and basic biochemistry, including liver function, phosphocalcium metabolism and gonadal and thyroid profile. A simple X-ray of the dorsal and lumbar vertebrae is indicated if there is a clinical suspicion of spinal fracture as this is an indication for treatment, irrespective of bone density.

During the bone remodeling process, enzymes and non-enzymatic peptides reach the bloodstream and/or are eliminated through urine. Their concentration in blood and urine is related to the total bone turnover rate. These products, or bone turnover markers (BTM), are divided into two groups: resorption markers and formation markers. The main osteosynthesis markers are procollagen type 1 carboxyterminal propeptide and procollagen type 1 aminoterminal propeptide, osteocalcin and alkaline phosphatase bone isoenzyme. Noteworthy among the resorption markers are the urinary excretion of deoxypyridinoline, pyridinoline, type 1 collagen amino-terminal telopeptide and hydroxyprolinuria, the latter being less specific. These markers are usually expressed in relationship to the urinary excretion of creatinine.

BTM are higher in patients with osteoporosis and there is an inverse relationship between their levels and BMD. Until now, there has been no particular consensus regarding the most appropriate strategy for their use in clinical practice, although it is thought that they could be useful for monitoring bone mass loss in response to treatment for osteoporosis and for predicting fracture risk. However, this extreme is yet to be verified, because there have been only a few studies with patients suffering from chronic liver disease carried out[52,53]. It would seem that BTM levels are influenced by the extent of hepatic fibrosis and by the intrahepatic metabolism of collagen in these individuals which could make it difficult to interpret the results obtained[9].

Treatment of osteoporosis in chronic liver disease

There are very few randomized-controlled intervention studies on the prevention of osteoporosis and fractures in chronic liver disease. Most of available data relate to studies performed on patients with PBC[6-8] and do not evaluate the effective reduction in fracture rates.

General non-pharmacological measures and specific antiosteoporotic drugs are available to treat HO.

General measures: These include lifestyle and nutritional measures aimed at correcting the reversible risk factors, such as alcohol consumption, smoking and making lifestyle changes by introducing regular moderate physical exercise.

Extensive studies have provided no evidence on the effect of calcium and vitamin D in preventing OP and fractures in these patients. Research has been performed on small groups yielding inconsistent BMD results[16,32,51]. However, it seems reasonable to recommend supplements by taking a daily dose of 800 UI of vitamin D3 and 1 g of calcium[9,54].

Specific drugs in the treatment of HO: Bisphosphonates are powerful anti-resorptive drugs that selectively inhibit osteoclast activity. These agents have been shown to reduce the risk of vertebral and non-vertebral fractures and increase BMD in postmenopausal women with osteoporosis who do not have liver disease[47]. They have also been effective in preventing steroid-induced osteoporosis in patients with PBC[6]. However, there are no long-term controlled studies developed to evaluate the efficiency of bisphosphonates in fracture-prevention in individuals with chronic liver disease. A study with 80 postmenopausal women with osteoporosis and chronic liver disease secondary to hepatitis virus B and C suggests that a cyclic etidronate treatment could be effective to reduce the incidence of bone fracture[55].

Alendronate improves BMD of patients with PBC[56,57], although it should be used with caution because of potential esophageal side effects[9]. Risedronate seems to have a less toxic effect on the esophageal mucosa, which could be useful for treating patients with esophageal varices.

Consequently, bisphosphonates are the main pharmacological agents used in the treatment of HO nowadays, despite the fact that limited data on bisphosphonates-therapy in chronic liver disease are available[38,58,54].

Raloxifene is a selective estrogen receptor modulator. It has positive effects on the lumbar bone mass and femoral neck and reduces vertebral fracture risk in postmenopausal osteoporosis. In a small study of patients with PBC, raloxifene led to significant improvement in lumbar BMD after 1 year of treatment, while no improvement was observed in the femoral neck[59]. Evaluation by a bone disease specialist is recommended before using raloxifene in individuals with hepatic disease[54].

Parathyroid hormone (PTH) is a bone-forming drug that is administered subcutaneously in dosages of 20 to 40 μg per day, achieving an increase in BMD and a decrease in vertebral fracture risk in postmenopausal osteoporosis. Few data are published on its usefulness in osteoporosis secondary to chronic liver disease. A study in rats with induced biliary cirrhosis showed that intermittent administration of human PTH increases BMD and could be effective to prevent loss of bone mass[60].

Treatment of hypogonadism in patients with chronic liver disease and HO remains controversial. Hormone replacement with testosterone in hypogonadic males without chronic liver disease was efficient and increased BMD[61]. Hormone replacement therapy (HRT) with estrogen and progesterone was proposed as a safe treatment for women with chronic hepatopathy, administered either orally or transdermally and sequentially or continuously[62,63]. Following the publication of the HERS Ⅱ[64] and WHI[65] studies questioning the safety of HRT, its use is currently not recommended. The increased risk of hepatocellular carcinoma related to this treatment should be taken into account by weighing up its benefits and risks and it should be better administered transdermally[9,37,59].

Orthotopic liver transplantation and bone metabolism: A high prevalence of low BMD among patients with chronic liver disease just before liver transplantation has been observed. Estimated rates range from 26% to 34% and from 11.5% to 14% for osteopenia and osteoporosis, respectively[66,67].

Immediately after orthotopic liver transplantation (OLT), there is a loss of BMD and fracture risk increases. However, in the long term, osteopenia improves in transplant patients, as shown by a prospective study of patients with PBC and PSC who underwent OLT[68]. Thus, liver transplantation is an efficient long-term treatment for osteoporosis in chronic cholestatic liver disease. Biphosphonates have also shown to be useful to avoid bone loss in transplant patients[69,70] but there is no evidence to consider one single agent among this group of drugs as first line therapy[71].

CONCLUSION

Osteopenia and osteoporosis are important and common complications of chronic liver disease, receiving the generic definition of HO. Their exact prevalence is unknown, ranging between 20% and 50% depending on the series. The development of HO may be due to both increased bone resorption and decreased bone formation. The etiology is multifactorial and can vary in accordance with the origin of the liver disease, having been preferentially studied in chronic cholestatic diseases (PBC and PSC). There are multiple risk factors associated with loss of BMD, the most important being chronic cholestasis and advanced cirrhosis.

Pathogenic mechanisms are diverse and very little is known about some of them: genetic factors, alterations in calcium-vitamin D metabolism, hyperbilirubinemia, vitamin K and IGF-1 deficiency, RANKL-OPG system activity and hypogonadism.

Osteoporosis can result in bone fractures with a harmful effect on morbidity and quality of life. Therefore, an assessment of bone metabolism and risk factors for bone loss and a BMD measurement are recommended in patients with chronic liver disease. An early diagnosis of HO is essential to correct reversible risk factors which predispose to bone mass loss.

Treatment and prevention strategies include general measures, dietary and lifestyle, calcium and vitamin D3 supplementation and bisphosphonates. However, advanced HO is difficult to treat and special care is required to prevent bone loss in individuals with severe hepatic disease. Further research is needed since there are no large randomized controlled trials of intervention in chronic liver disease and osteoporosis. In the same way, there is lack of randomized studies in areas like fracture prevention with available therapeutic agents and potential usefulness of new treatments for osteoporosis.

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AGA Clinical Congress of Gastroenterology and Hepatology: Best Practices in 2011
Miami, FL 33101, United States

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011
San Francisco, CA 94143, United States

January 27-28, 2011
Falk Workshop, Liver and Immunology, Medical University, Franz-Josef-Strauss-Allee 11
Regensburg 93053, Germany

January 28-29, 2011
9. Gastro Forum München
Munich, Germany

February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference
Sydney, NSW, Australia

February 17-20, 2011
APASL 2011-The 21st Conference of the Asian Pacific Association for the Study of the Liver
Bangkok, Thailand

February 22, 2011-March 04, 2011
Canadian Digestive Diseases Week 2011
Vancouver, BC, Canada

February 24-26, 2011
Inflammatory Bowel Diseases 2011-6th Congress of the European Crohn's and Colitis Organisation
Dublin, Ireland

March 3-5, 2011
42nd Annual Topics in Internal Medicine
Gainesville, FL 32614, United States

March 7-11, 2011
Infectious Diseases: Adult Issues in the Outpatient and Inpatient Settings
Sarasota, FL 34234, United States

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011
Birmingham, England, United Kingdom

March 17-20, 2011
Mayo Clinic Gastroenterology & Hepatology 2011
Jacksonville, FL 34234, United States

March 18, 2011
UC Davis Health Informatics: Change Management and Health Informatics, The Keys to Health Reform
Sacramento, CA 94143, United States

March 25-27, 2011
MedicReS IC 2011
Good Medical Research, Istanbul, Turkey

March 26-27, 2011
26th Annual New Treatments in Chronic Liver Disease
San Diego, CA 94143, United States

April 25-27, 2011
The Second International Conference of the Saudi Society of Pediatric Gastroenterology, Hepatology & Nutrition
Riyadh, Saudi Arabia

May 7-10, 2011
Digestive Disease Week
Chicago, IL 60446, United States

May 19-22, 2011
1st World Congress on Controversies in the Management of Viral Hepatitis (C-Hep), Palau de Congressos de Catalunya, Av. Diagonal, 661-671
Barcelona 08028, Spain

May 21-24, 2011
22nd European Society of Gastrointestinal and Abdominal Radiology Annual Meeting and Postgraduate Course
Venise, Italy

May 25-28, 2011
4th Congress of the Gastroenterology Association of Bosnia and Herzegovina with international participation, Hotel Holiday Inn, Sarajevo, Bosnia and Herzegovina

June 11-12, 2011
The International Digestive Disease Forum 2011
Hong Kong, China

June 13-16, 2011
Surgery and Disillusion XXIV
SPIGC, II ESYS
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June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer
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October 19-29, 2011
Cardiology & Gastroenterology Tahiti 10 night CME Cruise
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19th United European Gastroenterology Week
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October 28-November 2, 2011
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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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