

HEPATITIS B AND C: A TWIN SILENT KILLER

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ABSTRACT

Hepatitis B and C have been dubbed “Silent killer” because chronic hepatitis B and C are asymptomatic, but can cause considerable liver damage before its recognition. People know very little about hepatitis B and C, an insidious and enigmatic disease of the liver caused by viral agents of at least five major different viruses and non-viral agents: toxic and drug induced, alcoholic, autoimmune, fatty liver and metabolic disorders. Viral hepatitis is the seventh major leading cause of death worldwide. Hepatitis B and C combined caused approximately 80% of all liver cancer deaths and resulted in the death of close to 1.4 million people every year, more than HIV or tuberculosis. Despite this colossal harm and grim statistics most of the 400 million people with chronic hepatitis B and C, the most serious form of hepatitis don't know that they are infected. This enables the infection to go unnoticed and undiagnosed, until the virus has caused serious liver damage. Hepatitis is a global health challenge, its impact under-estimated, services under-resourced, and receive minimal no or political attention.

KEYWORDS: Hepatitis B, Hepatitis C, Silent killer, signs and symptoms, mechanisms, diagnosis, Prevention, treatment.

1.0 INTRODUCTION

Hepatitis is an inflammation of the liver.^[1] The condition can be self-limiting (healing on its own) or can progress to fibrosis (scarring), cirrhosis or hepatocellular carcinoma. Hepatitis may occur with limited or no symptoms, but often leads to jaundice, poor appetite and malaise. Hepatitis is acute when it lasts less than six months and chronic when it persists longer. Juxtaposition of hepatitis and HIV/Aids prevalence shows that hepatitis has an astronomical prevalence compare to HIV/AIDS. Hepatitis is caused by different hepatic viruses and it leads to liver related morbidity.^[2,3,4] Pathogenic agents like infections, toxic substances (e.g. alcohol, certain drugs), fatty liver, metabolic disorders and autoimmune diseases can also cause hepatitis-non-viral agents. Less commonly some bacterial, parasitic, fungal, mycobacterial and protozoal infections can cause hepatitis. Additionally, certain complications of pregnancy and decreased blood flow to the liver can induce hepatitis. Cholestasis due to hepatocellular dysfunction, biliary tract obstruction, or biliary atresia

can result in liver damage and hepatitis. HBV infection is the most common form of chronic hepatitis worldwide and a potentially preventable global health problem. The World Health Organization (WHO) estimates that more than 2 billion people have been infected with HBV, 360 million people are chronically infected and 600 000 people die annually from complications of HBV-related liver disease.^[5,6] The prevalence of chronic HBV infection is >8% among people in sub-Saharan Africa, Asia, and the Amazon Basin; 2%–8% in the Middle East, Eastern Europe, and the Indian subcontinent; and <2% in Western Europe, Australia, and most of the Americas.^[6,7] In the same vein Hepatitis C virus (HCV) is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma, as well as the most common indication for liver transplantation in many countries with an estimated 180m people infected worldwide and up to 80% progress to chronicity. An important therapeutic milestone was achieved with the recent discovery of potent direct acting anti-viral agents (DAAs) against HCV.^[8,9] The majority of persons

chronically infected (i.e. 65%–75% of the infected) are not aware of their infection status until symptoms of advanced liver disease and failure, cirrhosis and HCC appear.^[10] HBV/HIV and HCV/HIV co-infections are an increasing problem in countries with HIV epidemics and among injecting drug users. Despite their high prevalence and infectious state, awareness by people is still very low. This review is therefore aimed to sensitize people on the signs and symptoms, mechanism, diagnosis, prevention and treatment of the twin killer.

2.0 Signs and Symptoms

2.1 Hepatitis B

Many people have no symptoms during the initial infection. Symptoms appear quickly in adults. Infants infected at birth rarely develop only acute hepatitis B. Some develop a rapid onset of sickness with vomiting, yellowish skin, tiredness, dark urine and abdominal pain.^[12] Nearly all hepatitis B infections in infants go on to become chronic. Most of those with chronic disease have no symptoms; however, cirrhosis and cancer may eventually develop.^[13] More specific symptoms, which can be present in acute hepatitis from any cause, are: Profound loss of appetite, aversion to smoking among smokers, dark urine, yellowing of the eyes and skin and abdominal discomfort. Physical findings are usually minimal, apart from jaundice, tender enlargement of the liver, enlarged lymph nodes in 5%, and enlargement of the spleen. Acute viral hepatitis is more likely to be asymptomatic in children. Symptomatic individuals may present after a convalescent stage of 7 to 10 days, with the total illness lasting weeks. Both drug induced hepatitis and autoimmune hepatitis can present very similarly to acute viral hepatitis, with slight variations in symptoms depending on the cause.^[14,15] Cases of drug-induced hepatitis can manifest with systemic signs of an allergic reaction including rash, fever, serositis (inflammation of membranes lining certain organs), elevated eosinophilia, and suppression of bone marrow activities. The transition from acute to chronic infection appears to represent a failure of immune clearance of virus-infected cells and is marked by persistence of high levels of HBV DNA and HBeAg in serum. Chronic infection with hepatitis B virus either may be asymptomatic or may be associated with a chronic inflammation of the liver (chronic hepatitis), leading to cirrhosis over a period of several years. This type of infection dramatically increases the incidence of hepatocellular carcinoma (HCC; liver cancer). Across Europe, hepatitis B and C cause approximately 50% of hepatocellular carcinomas,^[16,17] chronic carriers are encouraged to avoid consuming alcohol as it increases their risk for cirrhosis and liver cancer. Hepatitis B virus has been linked to the development of membranous glomerulonephritis.^[18]

Symptoms outside of the liver are present in 1–10% of HBV-infected people and include serum sickness like syndrome, acute necrotizing vasculitis, membranous glomerulonephritis, and papular acrodermatitis of

childhood (Gianotti-Crosti syndrome).^[19,20] The serum-sickness-like syndrome occurs in the setting of acute hepatitis B, often preceding the onset of jaundice.^[21] The clinical features are fever, skin rash and polyarteritis. The symptoms often subside shortly after the onset of jaundice but can persist throughout the duration of acute hepatitis B.^[22]

2.2 Hepatitis C

According to the Centers of Disease Control and Prevention (CDC), up to 80 percent of those with acute hepatitis C will not experience symptoms. In some cases, people will experience symptoms not long after the virus has infected them. HCV has deteriorating effect on whole body systems which produce exacerbating and excruciating symptoms mostly include fatigue, fever, epigastric pain, burning urination, heart burn, burning palm and sole, chills, fluid retention and muscle pain.^[23] There is also involvement of systemic (gastrointestinal), cognitive, mood and nervous systems in this disease to display the relative intensity of symptoms. It may also include hypoglycemia, hyperglycemia, chest pain, menstrual changes, palpitations and also sexual anomalies whereas in other people early signs and symptoms would be most likely to occur around six or seven weeks after exposure to the hepatitis C virus. Such signs and symptoms may include: nausea or vomiting, pain in the stomach, joint or muscle pain, abnormalities in urine or bowel movements, a yellowing in your eyes or skin. While some people may develop hepatitis C symptoms within two weeks of infection, others might experience a much longer delay before noticing any symptoms. It could take anywhere from six months to 10 years or more before someone with the virus becomes aware of any symptoms, according to the National Digestive Diseases Information Clearing house (NDDIC). This is because it can take years for the virus to lead to liver damage. Long-term infection with the hepatitis C virus (HCV) is known as chronic hepatitis C. Chronic hepatitis C is usually a "silent" infection for many years, until the virus damages the liver enough to cause the signs and symptoms of liver disease. Among these signs and symptoms are: Bleeding, Bruising easily, Fatigue, Poor appetite, Yellow discoloration of the skin and eyes (jaundice), dark-colored urine, Itchy skin, Fluid buildup in the abdomen (ascites) Swelling of the legs, Weight loss, Confusion, drowsiness and slurred speech (hepatic encephalopathy), spider-like blood vessels on your skin (spider angiomas).

3.0 Mechanisms

3.1 Hepatitis B

There is considerable interest and research activities now centered about the idea that the mechanisms actually responsible for tissue injury in HBV infection are immunologic in nature and are initiated by a latent viral infection. The possibilities are complex. The specific mechanism varies and depends on the underlying cause of the hepatitis. Hepatitis B virus primarily interferes with the functions of the liver by replicating in

hepatocytes. A functional receptor is NTCP.^[24] There is evidence that the receptor in the closely related duck hepatitis B is carboxypeptidase D.^[25,26] Generally, there is an initial insult that causes liver injury and activation of an inflammatory response, which can become chronic, leading to progressive fibrosis and cirrhosis.^[27] The pathway by which hepatic viruses cause viral hepatitis is best understood in the case of hepatitis B and C. In several models of HBV infection, it has been observed that the liver injuries in chronic infection are considered to be associated with the activity of HBV specific T cells.

However, few reports suggest that certain chemokine mediated neutrophils infiltration, natural killer cells and lymphocytes also played role in HBV-related liver damage.^[28] The viruses do not directly cause apoptosis (cell death).^[29] Rather, infection of liver cells activates the innate and adaptive arms of the immune system leading to an inflammatory response which causes cellular damage and death. Depending on the strength of the immune response, the types of immune cells involved and the ability of the virus to evade the body's defense, infection can either lead to clearance (acute disease) or persistence (chronic disease) of the virus. The virus elimination may be hindered due to imbalances in cytokine production. Viral infection usually causes inflammatory reaction characterized by release of cytokines and chemokines which may lead to cancer development.^[30] It has been observed that molecular and cellular changes of host gene expression are being supported by the virus replication that protect virally infected hepatocytes from immune-mediated destruction and facilitate tumorigenesis. The oxidative stress induced by Inflammation incurs Kupffer cells to promote stellate cells activation via NF- κ B.^[31] The persistent activation of these genes leads to cirrhosis, fibrosis and severe liver damage leading to the development of HCC.^[32] It has been reported that cirrhosis increases the risk for HCC about 300% in the patients with chronic infection.^[33-36] Individuals with an impaired immune response are at greater risk of developing chronic infection. Natural killer cells are the primary drivers of the initial innate response and create a cytokine environment that results in the recruitment of CD4 T-helper and CD8 cytotoxic T-cells. Type 1 interferon is the cytokines that drive the antiviral response. In chronic Hepatitis B and C, natural killer cell function is impaired. In liver inflammatory lesions, lymphocytes which are virus-specific can be detectable spontaneously but they are not capable to remove active virus infection.^[37] HBV can cause chronic inflammation that leads to the development of cirrhosis and HCC.^[38] It has also been observed that HBsAg could inhibit the production of interferon (IFN) in chronic HBV infection. On the other hand, interferon has been used in the treatment of chronic hepatitis B. A recent study indicates that IFN prevented or delayed the progress of HCC and liver cirrhosis in chronic HBV individuals.^[39]

3.2 Hepatitis C

Host surface molecules required for virus entry are classified as either receptors or co-receptors. Several viruses utilize only one molecule as a receptor for entry into host cells, while many viruses require a co-receptor that localizes near the receptors for their entry. Receptors are primarily involved in the attachment of virus to specific host cells and, in some cases, in viral entry. Affinity for a particular receptor may restrict host range, tropism and pathogenicity, although different viruses that have different or partially crossed pathogenicity may utilize the same receptor. Receptors need not be membrane proteins, as carbohydrates and lipids have been identified as receptors for different viruses. For HCV, several molecules have been reported to be candidates for receptor or co-receptor for viral entry. However, the critical determination of receptor or coreceptor requirements for HCV is quite difficult because a reliable in vitro cell culture system and a sufficient amount of viral particles are not currently available. HCV particles are trapped by glycosaminoglycans and then transferred to a cell surface receptor and/or co-receptor and internalized into cells through endocytosis. After uncoating, viral RNA is translated into a precursor polyprotein that is processed into each viral protein by cellular and viral proteases. Viral replication utilizes the viral polymerase complex and takes place on the ER membrane. Core protein bind to the viral sense RNA^[40] and it was suggested that it also forms the nucleocapsid. HCV particles seem to bud into the ER lumen after interaction of the nucleocapsid with E1 and E2 proteins. It has been suggested that the small hydrophobic peptide p7 forms an ion channel^[41-43] based on the observation that p7 of pestivirus was shown to be essential for virus budding.^[44] NS2 is a membrane-spanning protein with four transmembrane regions.^[45] No functional role for NS2 has yet been described, except for its autoprotease activity cleaving between the junction of NS2 and NS3. NS3 forms a complex with NS4A on the ER membrane. This interaction stabilizes NS3 and retains it on the ER. NS3 has serine protease and RNA helicase activities assigned to the N-terminal one-third and remaining two-thirds of the protein, respectively. Cleavage sites downstream of NS3 are processed by NS3 to yield mature nonstructural proteins. NS4B is localized to the ER and was reported to induce membranous web formation together with other non-structural proteins.^[46] Although mutation of NS4B affected the hyperphosphorylation of NS5A, the function of NS4B in terms of viral replication remains to be defined. NS5A is anchored on the ER through its N terminal 30 amino acids. NS5A was found to be a highly phosphorylated polypeptide that may be involved in resistance to the antiviral effects of interferon (IFN) alpha. NS5A plays an important role in viral replication, because mutation of the phosphorylation sites of NS5A results in enhanced replication of the HCV replicon in the Huh-7.5 cell line. NS5B is also anchored in the ER through a C-terminal hydrophobic region, and the main

body of the replication complex serves as an RNA-dependent RNA polymerase.^[47]

4.0 Diagnosis

4.1 Hepatitis B

Hepatitis B is usually diagnosed on the basis of some or all of the following: a patient's signs and symptoms, medical history including sexual and substance use history, blood tests, imaging, and liver biopsy.^[48] The diagnosis of HBV infection requires the evaluation of the patient's Serological markers for HBV infection consist of HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc IgM and IgG. The identification of serological markers allows: to identify patients with HBV infection; to elucidate the natural course of chronic hepatitis B (CHB); to assess the clinical phases of infection; and to monitor antiviral therapy.^[49]

In general, for viral hepatitis and other acute causes of hepatitis, the patient's blood tests and clinical picture are sufficient for diagnosis.^[50] For other causes of hepatitis, especially chronic causes, blood tests may not be useful. In this case, liver biopsy is the gold standard for establishing the diagnosis as histopathologic analysis is able to reveal the precise extent and pattern of inflammation and fibrosis. However, liver biopsy is typically not the initial diagnostic test because it is invasive and is associated with a small but significant risk of bleeding that is increased in patients with liver injury and cirrhosis.^[51] Although genotyping does not predict the outcome of infection,^[52,53,54] it is useful in predicting the likelihood of treatment response and determines the duration of treatment in many cases.

Blood testing includes liver enzymes, serology (i.e. for autoantibodies), nucleic acid testing (i.e. for hepatitis virus DNA/RNA), blood chemistry, and complete blood count. Characteristic patterns of liver enzyme abnormalities can point to certain causes or stages of hepatitis. Generally, AST and ALT are elevated in most cases of hepatitis regardless of whether the patient shows any symptoms. However, the degree of elevation (i.e. levels in the hundreds vs. in the thousands), the predominance for AST vs. ALT elevation, and the ratio between AST and ALT are informative of the diagnosis.

4.2 Hepatitis C

Health officials recommend that anyone at high risk of exposure to HCV get a blood test to screen for hepatitis C infection. People who may want to talk to their doctors about screening for hepatitis C include: Anyone who has ever injected or inhaled illicit drugs, one who has abnormal liver function test results with no identified cause, Babies born to mothers with hepatitis C, health care and emergency workers who have been exposed to blood or accidental needle sticks, people with hemophilia who were treated with clotting factors before 1987, people who have ever undergone long-term hemodialysis treatments, people who received blood transfusions or organ transplants before 199, sexual partners of anyone

diagnosed with hepatitis C infection, people with HIV infection, anyone born from 1945 to 1965, anyone who has been in prison. Initial testing for the diagnosis of hepatitis C infection uses serologic assays that detect human antibodies generated as a response to hepatitis C virus (HCV) infection. A positive HCV antibody test indicates HCV infection at some point in time, but it does not differentiate whether the person has resolved or current HCV infection. An anti-HCV antibody test is recommended to screen for HCV infection (sensitivity of 95%, specificity of 99%, positive likelihood ratio of 95, and negative likelihood ratio of 0.05). If the anti-HCV antibody test result is positive, current infection should be confirmed with a qualitative measurement of HCV RNA. If the anti-HCV antibody test result is negative in a patient who may have been exposed to HCV within the previous six months, HCV RNA should be measured every four to eight weeks for at least six months or follow-up anti-HCV antibody testing should be performed in 12 weeks. Patients with a positive anti-HCV antibody test result but a negative HCV RNA test result are not considered to have HCV infection. Quantitative HCV RNA testing is recommended before initiating therapy to determine the baseline viral load, and testing for HCV genotype is recommended to help guide treatment decisions.

5.0 Prevention

5.1 Hepatitis B (HBV)

HBV transmission can be prevented by screening of donated blood, plasma, organ tissue and semen, by virus inactivation in plasma-derived products, by risk-reduction counseling and by implementation of infection control practices. The first vaccines were plasma derived; however, these have been replaced over the years by vaccines manufactured in yeast or mammalian cells using recombinant DNA technology.^[55,56] Safe and effective hepatitis B vaccines containing inactivated HBsAg have been available since the early 1980s. Immunization should also be offered to high-risk individuals including healthcare workers, persons with multiple sex partners, intravenous drug users, patients with chronic diseases who are likely to undergo multiple percutaneous procedures and contacts of HBV-infected persons. Babies born to HBsAg carrier mothers should be protected against perinatal transmission by administration of hepatitis B immunoglobulin and HBV vaccine.^[57] In general, the hepatitis B vaccine is administered in a three-dose series: two priming doses administered 1 month apart and a third dose administered 6 months after the second.^[58] Alternative schedules have been used successfully. Administration of the three-dose series results in protective concentrations of anti-HBs in more than 95% of healthy infants, children, and adolescents and in more than 90% of healthy adults aged 40 years old and younger. Immunogenicity drops below 90% in adults over the age of 40 years. The hepatitis B vaccine has a pre-exposure efficacy of 80–100% and a postexposure efficacy of 70–95%, depending on whether hepatitis B immune globulin (HBIG) is given with the

vaccine. The duration of immunity appears to be long-lasting, and booster doses of the vaccine are not routinely recommended.

5.2 Hepatitis C (HBC)

Currently there is no vaccine against the hepatitis C virus. So, to avoid the spread of the disease and other blood borne illnesses, people should engage in personal hygiene like: Cover cuts and scratches with appropriate dressings, hygienically dispose of blood stained items such as bandages and sanitary napkins, avoid sharing personal items which may be contaminated with blood (such as toothbrushes and razors, avoid sharing drug injecting equipment, avoid tattooing, acupuncture or ear piercing where the equipment is not known to be adequately sterilized, Practice safe sex, People with the hepatitis C virus should inform their dentist or any other health professional that they are carriers of the virus.

Primary prevention activities include: screening and testing of blood, plasma, tissue, organ and semen donors; virus inactivation of plasma derived products; risk reduction counseling services and implementation of infection-control practices. Secondary prevention activities include identification and testing of persons at risk and management of infected persons.^[59] Recognition and prompt treatment of infected individuals (especially mothers) can prevent the transmission of HCV to young infants. Recently, the Centers for Disease Control and Prevention advocated screening all individuals born between 1945 and 1965, regardless of the absence of risk factors.^[60] Patients with ongoing risk should be screened annually with an antibody test (anti-HCV) and if positive, with confirmatory testing with a quantitative RNA viral load.

When HCV is detected, genotype screening is important because therapy can be optimized, if indicated. At this time there is no vaccine against HCV. Furthermore, because perinatal interventions such as elective cesarean section or abstaining from breastfeeding do not appear to diminish vertical transmission and because vertical transmission is most likely to occur in the presence of maternal viremia, infection appears to occur in utero. Nevertheless, mothers should be advised to forgo breastfeeding if their nipples are cracked or bleeding.^[61]

6.0 Treatment

6.1 Acute Hepatitis B

Acute infections can be managed supportively. Most patients with symptomatic, acute hepatitis B recover, and antiviral therapy is usually neither recommended nor needed. Certain patients warrant hospitalization, especially those who present with clinical signs of ascites, peripheral edema, and hepatic encephalopathy, and laboratory signs of hypoglycemia, prolonged prothrombin time, low serum albumin, and very high serum bilirubin. Age and comorbid conditions can result in a more prolonged and severe illness. In these rare, more severe acute cases, patients have been successfully

treated with antiviral therapy similar to that used in cases of chronic hepatitis B, with nucleoside analogues such as entecavir or tenofovir. As there is a dearth of clinical trial data and the drugs used to treat are prone to developing resistance, experts recommend reserving treatment for severe acute cases, not mild to moderate.^[62] The serious nature of acute liver failure and the safety of nucleoside analogue therapy support its use in patients at the first sign of severe injury or impending liver failure (prolongation of prothrombin time or hepatic encephalopathy), particularly since a proportion of patients will be referred for emergency liver transplantation and require prophylaxis against recurrence, which usually includes nucleoside analogue therapy.^[63,64]

6.2 Chronic Hepatitis B

The course of chronic hepatitis B is typically silent and associated with few signs or symptoms of disease until cirrhosis and/or HCC arise. Therefore the main goal of treatment of chronic hepatitis B is to suppress HBV replication and to induce remission of liver disease before development of cirrhosis and hepatocellular carcinoma. Chronic hepatitis B management aims to control viral replication, which is correlated with progression of disease.^[65] Monotherapy for Hepatitis B of Six antiviral agents (standard interferon, peginterferon, lamivudine, telbivudine, adefovir dipivoxil, and entecavir) have been approved for use in chronic hepatitis B and at least three others (emtricitabine, clevudine, tenofovir disoproxil fumarate) are being evaluated and may be approved in the near future. These nucleosides and nucleotides work by suppressing viral replication through inhibition of HBV viral polymerase while interferon therapy works by enhancing the host immune response. The two main treatment strategies are finite therapy with interferon or NUC therapy (for those who maintain an SVR off treatment), or long-term therapy with one or more NUCs, for those with cirrhosis or who do not maintain an SVR.^[66] Injectable interferon alpha was the first therapy approved for chronic hepatitis B. It has several side effects, most of which are reversible with removal of therapy, but it has been supplanted by newer treatments for this indication. The advantages of interferon therapy are the absence of viral resistance, the finite course of treatment (normally 48 weeks) and an increased chance of SVR and HBeAg and HBsAg clearance compared with those taking NUC therapy.^[67] Long-term studies have demonstrated that interferon treatment is associated with a significant reduction in the risk of cirrhosis and HCC, even in those who fail to clear HBeAg.^[68] However, interferon has a poor side-effect profile (including persistent flu-like symptoms and psychiatric complications) compared with NUC therapy, requires subcutaneous injection and is not recommended for patients with decompensated cirrhosis. The use of interferon is therefore restricted to patients who are most likely to benefit; in particular, younger patients who have more potential years in which to develop complications

from their CHB and thus have more to gain from achieving an SVR.^[69,70] The potential merits of combination therapy of hepatitis B include greater antiviral activity and lower rates of resistance to the individual agents used. Unfortunately, there have been few properly controlled trials comparing combination therapy with each of the agents alone. In the few studies that have been done, combination therapy was no more effective than monotherapy.

6.3 Acute Hepatitis C

Acute hepatitis C can be treated. Treatment reduces the risk that the disease will progress to the chronic form. The infection will resolve on its own without treatment in 25-50% percent of HCV-positive people. An optimal treatment regimen for acute hepatitis C has not yet been established although some people may need treatment with prescription medicine. Doctors usually prescribe the same medications to treat both acute and chronic hepatitis C. Genotype and HCV RNA levels do not seem to play a role in determining treatment outcomes.^[71] Because acute HCV is self-limiting up to 50% of patients with acute HCV spontaneously clear the virus.^[72] Hence, a delay of treatment for 8–12 weeks after the onset of acute hepatitis C has been suggested. A recent trial demonstrated >90% SVR rates in individuals with acute HCV when treatment with peginterferon was started within 12 weeks after onset of disease. Both IFN and peginterferon with or without the combination of ribavirin have been used in various studies with promising results. Studies with IFN- α have reported SVR rates of as high as 95% when patients are treated for 24 weeks.^[73] Similarly, studies of peginterferon with or without ribavirin have reported SVR rates of 80–89% with 24 weeks of treatment.^[74,75]

6.4 Chronic Hepatitis C

The main goal of therapy for chronic hepatitis C is eradication of the virus, which should limit or prevent the development of complications. The end point of successful therapy is a sustained virologic response, defined as undetectable HCV RNA in serum 24 weeks after treatment has been stopped.^[76] Treatment of chronic hepatitis C in adults is recommended for those who have detectable HCV RNA levels, elevated aminotransferase (ALT) levels, liver biopsy findings suggestive of progressive liver disease and the absence of any serious co-morbid conditions or contraindications.^[77,78] ALT levels however, do not always correlate with disease severity and hence, treatment should not be denied in those with normal ALT levels.^[79] The therapy of hepatitis C has improved substantially over the years. The current recommended treatment of chronic HCV is the combination of peginterferon and ribavirin. α -Interferon was first shown to have a benefit in chronic hepatitis C infection in 1986.^[80] Five to fifteen percent of patients achieved SVR after a 6-to12-month course of IFN- α . The overall response rates were substantially increased by the addition of the oral nucleoside analog ribavirin. IFN- α , by activating a variety of antiviral

pathways, is active against many RNA viruses including HCV. The mechanism of action of ribavirin is not well understood. It has no direct antiviral activity and appears to enhance the antiviral effect of IFN- α in the treatment of hepatitis C, possible by a combination of mechanisms.^[81] Another significant advance in HCV therapy came with the development of long-acting pegylated interferon (peginterferon). A polyethylene glycol moiety is covalently attached to the IFN- α molecule resulting in a product that is still biologically active, but has a larger molecular mass, improved distribution and increased half-life. The combination of peginterferon and ribavirin has been shown to yield the highest response rates in three pivotal trials.^[82,83,84] With peginterferon and ribavirin, 70–80% of patients with genotype 2 or 3 infection and 42–45% of those with genotype 1 infection can achieve a SVR. These results were significantly better than those achieved with standard combination therapy or peginterferon monotherapy. There is no current established treatment for patients with genotype 4, 5 or 6. These patients are usually treated with the same regimen used for genotype 1 patients.^[85]

CONCLUSIONS

Hepatitis B and C still remain a “Silent killer” for now because of the asymptomatic and chronic nature of these insidious killers and more so that People know very little about them. Hepatitis B and C are asymptomatic, but can cause considerable liver damage before its recognition. In spite of the availability of effective vaccine for hepatitis B, at least about 240 million people are chronically infected worldwide, and are at risk of developing liver cirrhosis and hepatocellular carcinoma. In the same vein, people that are chronically infected worldwide with Hepatitis C virus and are also at risk of developing liver cirrhosis and hepatocellular carcinoma (a rich sources of a twin carcinogenesis) and on the other hand in spite of considerable efforts there is still no vaccine available that can protect against hepatitis C. The high tissue and species specificity, as well as a unique genomic organization and replication strategies adopted by HBV and viral protein production appear to contribute to infection persistence by limiting the effectiveness of innate responses coupled with the fact that HCV also has a very high degree of genetic variability and constant mutation of viral genome due to high error rate of viral polymerase resulting in a multigeneous population of the virus quasispecies in infected persons.

However, all hope is not lost as the availability of improved experimental systems and molecular techniques have started to provide new information about the complex network of interactions that establishes within the hepatocyte and that may contribute to disease progression and tumor development and how to counteract it. Also antiviral agents for the treatment of both hepatitis B and C are now readily available though not without its high cost and significant toxicity.

Vaccines for hepatitis B virus is now readily available despite the fact that no single vaccine has been approved or licensed for hepatitis C virus, researches on developing a preventive and therapeutic safe vaccine, are evolving and ongoing.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. "Hepatitis" NIAID, Retrieved 2 November, 2016.
2. World Health Organization, Hepatitis B Factsheet no, 2000; 204. (<http://who.int/mediacentre/factsheets/fs204/en>) Google Scholar.
3. Khokhar N, Gill ML, Malik GJ, General seroprevalence of hepatitis C and hepatitis B virus infections in population. *J Coll Physicians Surg Pak*, 2004; 14: 534-6. PubMedGoogle Scholar.
4. Gaeta GB, Rapicetta M, Sardaro C, Spadaro A, Chionne F, Freni AM, Prevalence of anti-HCV antibodies in patients with chronic liver disease and its relationship to HBV and HDV infections. *Infection*, 1990; 18: 277-9. 10.1007/BF01647003 View ArticlePubMedGoogle Scholar.
5. WHO.HepatitisB(2014)Availableat: <http://www.who.int/mediacentre/factsheets/fs204/e> Accessed June 22.
6. WHO position paper on hepatitis B vaccines, *Wkly Epidemiol Rec*, 2009; 84: 405–20.
7. Franco E, Bagnato B, Marino MG, Hepatitis B: epidemiology and prevention in developing countries. *World J Hepatol*, 2012; 4: 74–80. (PMC free article) (PubMed).
8. Casey LC, Lee WM, Hepatitis C virus therapy update. *Curr Opin Gastroenterol*, 2013; 29: 243–249.
9. Au JS, Pockros PJ, Novel therapeutic approaches for hepatitis C. *Clin Pharmacol Ther*, 2014; 95: 78–88.
10. Ait-Goughoulte M, Kanda T, Meyer K, Ryerse JS, Ray RB, Ray R. Hepatitis C virus genotype 1a growth and induction of autophagy. *J Virol*, 2008; 82: 2241–2249.
11. Colvin HM, Mitchell AE, Editors; Committee on the prevention and control of viral hepatitis infections; Institute of Medicine. *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C*. Washington, DC: The National Academies Press, 2010.
12. "Hepatitis B Fact sheet N^o204" (2014) WHO. Int. July 2014.
13. Chang MH, "Hepatitis B virus infection". *Semin Fetal Neonatal Med*, 2007; 12(3): 160–167.
14. Fontana, Robert; Hayashi, Paul, "Clinical Features, Diagnosis, and Natural History of Drug- Induced Liver Injury". *Seminars in Liver Disease*, 2014; 34(02): 134–144. doi: 10.1055/s-0034-1375955.
15. Manns, Michael P.; Lohse, Ansgar W.; Vergani, Diego, "Autoimmune hepatitis-Update. *Journal of Hepatology*, 2015; 62(1): S100–S111. doi: 10.1016/j.jhep.2015.03.005.
16. El-Serag HB, Rudolph KL. "Hepatocellular carcinoma: epidemiology and molecular carcinogenesis". *Gastroenterology*, 2007; 132(7): 2557–76. PMID 17570226 doi: 10.1053/j.gastro.
17. El-Serag HB. "Hepatocellular carcinoma". *New England Journal of Medicine*, 22 September 2011; 365 (12): 1118–27. PMID 12992124 doi: 10.1056/NEJMar1001683.
18. Gan SI, Devlin SM, Scott-Douglas NW, Burak KW, "Lamivudine for the treatment of membranous glomerulopathy secondary to chronic hepatitis B infection". *Canadian journal of gastroenterology = Journal canadien de gastroenterology*, 2005; 19(10): 625–9. PMID 16247526.
19. Dienstag JL, "Hepatitis B as an immune complex disease". *Seminars in Liver Disease*, 1981; 1(1): 45–57. PMID 6126007. doi: 10.1055/s-2008-1063929.
20. Trepo C, Guillevin L, "Polyarteritis nodosa and extrahepatic manifestations of HBV infection: the case against autoimmune intervention in pathogenesis". *Journal of Autoimmunity*, 2001; 16(3): 269–74. PMID 11334492. Doi: 10.1006/jant.2000.0502.
21. Alpert E, Isselbacher KJ, Schur PH, "The pathogenesis of arthritis associated with viral hepatitis. Complement-component studies". *The New England Journal of Medicine*, 1971; 285(4): 185–9. PMID 4996611. Doi: 10.1056/NEJ197107222850401.
22. Liang TJ, "Hepatitis B: the virus and disease". *Hepatology (Baltimore, Md.)*, 2009; 49(5 Suppl): S13–21. PMC 2809016.
23. St John Tina, Signs and symptoms that may be associated with hepatitis C. *Caring AmbassadHepat C Choices Inc*, 2008; 43-47.
24. Yan H, Zhong G, Xu G, He W, Jing Z, Gao Z, Huang Y, Qi Y, Peng B, Wang H, Fu L, Song M, Chen P, Gao W, Ren B, Sun Y, Cai T, Feng X, Sui J, Li W. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus", 2012.
25. Tong S, Li J, Wands JR "Carboxypeptidase D is an avian hepatitis B virus receptor". *Journal of Virology*, 1999; 73(10): 8696-8702. PMC 112890. PMID10482623
26. Glebe D, Urban S., "Viral and cellular determinants involved in hepadnaviral entry". *World J. Gastroenterol*, 2007; 13(1): 22–38. PMC 4065874. PMID 17206752. doi: 10.3748/wjg.v13.il.22.

27. Dienstag, JL "Chapter 360: Acute Viral Hepatitis". In Kasper, D; Fauci, A; Hauser, S; Longo, D; Jameson, J; Loscalzo, J. *Harrison's Principles of Internal Medicine*, 19e. New York, NY: McGraw-Hill, 2015.
28. Edmunds WJ, Medley GF, Nokes DJ, Hall AJ, Whittle HC, The influence of age on the development of the hepatitis B carrier state. *Proc Biol Sci*, 1993; 253: 197–201.
29. Wong, Grace Lai-Hung. "Prediction of fibrosis progression in chronic viral hepatitis" "Clinical and Molecular Hepatology, 2014-09-01; 20(3): 228–236.
30. Balkwill F, Mantovani A, Inflammation and cancer: back to Virchow? *Lancet*, 2001; 357: 539–545.
31. Fattovich G, Stroffolini T, Zagni I, Donato F, Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*, 2004; 127: S35–S50.
32. Ganem D, Prince AM, Hepatitis B virus infection--natural history and clinical consequences. *N Engl J Med*, 2004; 350: 1118–1129.
33. Villa E, Grottola A, Buttafoco P, Trande P, Merighi A, Fratti N, Seium Y, Cioni G, Manenti F. Evidence for hepatitis B virus infection in patients with chronic hepatitis C with and without serological markers of hepatitis B. *Dig Dis Sci*, 1995; 40: 8–13.
34. 36. Berasain C, Betés M, Panizo A, Ruiz J, Herrero JI, Civeira MP, Prieto J Pathological and virological findings in patients with persistent hypertransaminasaemia of unknown aetiology. *Gut*, 2000; 47: 429–435.
35. Chemin I, Zoulim F, Merle P, Arkhis A, Chevallier M, Kay A, Cova L, Chevallier P, Mandrand B, Trépo C High incidence of hepatitis B infections among chronic hepatitis cases of unknown aetiology. *J Hepatol*, 2001; 34: 447–454.
36. Borzio M, Trerè D, Borzio F, Ferrari AR, Bruno S, Roncalli M, Colloredo G, Leandro G, Oliveri F, Derenzini M, Hepatocyte proliferation rate is a powerful parameter for predicting hepatocellular carcinoma development in liver cirrhosis. *Mol Pathol*, 1998; 51: 96–101.
37. Guidotti LG, Ishikawa T, Hobbs MV, Matzke B, Schreiber R, Chisari FV, Intracellular inactivation of the hepatitis B virus by cytotoxic T lymphocytes. *Immunity*, 1996; 25–36.
38. Rehermann B, Nascimbeni M. Immunology of hepatitis B virus and hepatitis C virus infection, *Nat Rev Immunol*, 2005; 5: 215–229. [PMID: 15738952 DOI: 10.1038/nri1573.
39. Yang YF, Zhao W, Zhong YD, Xia HM, Shen L, Zhang N, Interferon therapy in chronic hepatitis B reduces progression to cirrhosis and hepatocellular carcinoma: a meta-analysis. *J Viral Hepat*, 2009; 16: 265–271. [PMID: 19220736 DOI: 10.1111/ j.1365-2893.2009.01070.
40. Shimoike, T., Mimori, S., Tani, H., Matsuura, Y., and Miyamura, T. Interaction of hepatitis C virus core protein with viral sense RNA and suppression of its translation. *J. Virol*, 1999; 73: 9718–9725.
41. Carrere-Kremer S, Montpellier-Pala C, Cocquerel L, Wychowski C, Penin F & Dubuisson J, Subcellular localization and topology of the p7 polypeptide of hepatitis C virus. *Journal of Virology*, 2002; 76: 3720–3730.
42. Griffin SD, Beales LP, Clarke DS, Worsfold O, Evans SD, Jaeger J, Harris MP & Rowlands DJ, The p7 protein of hepatitis C virus forms an ion channel that is blocked by the antiviral drug, Amantadine. *FEBS Letter*, 2003; 535: 34–38.
43. Pavlovic D, Neville DC, Argaud O, Blumberg B, Dwek RA, Fischer WB & Zitzmann N., The hepatitis C virus p7 protein forms an ion channel that is inhibited by long-alkyl-chain iminosugar derivatives. *Proceedings of the National Academy of Sciences, USA*, 2003; 100: 6104–6108.
44. Harada T, Tautz N & Thiel HJ, E2-p7 region of the bovine viral diarrhoea virus polyprotein: processing and functional studies. *Journal of Virology*, 2000; 74: 9498–9506.
45. Yamaga AK & Ou JH, Membrane topology of the hepatitis C virus NS2 protein. *Journal of Biological Chemistry*, 2002; 277: 33228–33234.
46. Egger D, Wolk B, Gosert R, Bianchi L, Blum HE, Moradpour D & Bienz K, Expression of hepatitis C virus proteins induces distinct membrane alterations including a candidate viral replication complex. *Journal of Virology*, 2002; 76: 5974–5984.
47. Schmidt-Mende J, Bieck E, Hogle T, Penin F, Rice CM, Blum HE & Moradpour D, Determinants for membrane association of the hepatitis C virus RNA-dependent RNA polymerase. *Journal of Biological Chemistry*, 2001; 276: 44052–44063.
48. Kleiner DE, The pathology of drug induced liver injury. *Semin Liver Dis*, 2009; 29: 364–72.
49. Control CfD, Prevention. *Epidemiology and prevention of vaccine-preventable diseases*. Washington DC: Public Health Foundation, 2011; 12.
50. Friedman, Lawrence S. "Chapter 16: Liver, Biliary Tract, & Pancreas Disorders". In Papadakis, M; McPhee, SJ; Rabow, MW. *Current Medical Diagnosis & Treatment*, 2015; 2016: 55e. McGraw Hill.
51. Grant, A; Neuberger J, Guidelines on the use of liver biopsy in clinical practice". *Gut*, 1999; 45(Suppl 4).
52. Friedrich-Rust M, Zeuzem S, Sarrazin C, Current therapy for hepatitis C. *Int J Colorectal Dis*, 2007; 22(4): 341–9 .
53. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar, Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*, 2001; 22: 358(9286): 958–65.
54. Hu KQ, Tong MJ, The long-term outcomes of patients with compensated hepatitis C virus- related cirrhosis and history of parenteral exposure in the United States. *Hepatology*, 1999; 29: 1311?

55. Shouval D, Hepatitis B vaccines. *J Hepatol*, 2003; 39: S70–S76.
56. World Health Organisation, Hepatitis B vaccines: WHO position paper. *Wkly Epidemiol Rec*, 2009; 84: 405–419.
57. Kane MA, Global status of hepatitis B immunization. *Lancet*, 1996; 348: 696.
58. Mast, E. E., and J. W. Ward, Chapter 13. Hepatitis B vaccines. In *Vaccines*. 5th ed, edited by S. A. Plotkin, editor; W. A. Orenstein, editor; and P. A. Offit, editor. : Elsevier Health Sciences, 2008.
59. National Institutes of Health Consensus Development Conference Panel Statement, Management of Hepatitis C. National Institutes of Health Washington, 1997.
60. Centers for Disease Control and Prevention (CDC), Progress toward prevention and control of hepatitis C virus infection--Egypt, 2001-2012. *MMWR Morb Mortal Wkly Rep*, 2012; 61(29): 545–549.
61. Bansal S, Singal AK, McGuire BM, Anand B, Impact of all oral anti-hepatitis C virus therapy: A meta-analysis. *World J Hepatol*, 2015; 7(5): 806–813.
62. Dienstag, JL, Acute Viral Hepatitis". In Kasper, D; Fauci, A; Hauser, S; Longo, D; Jameson, J; Loscalzo, J. *Harrison's Principles of Internal Medicine*, 19e. New York, NY: McGraw-Hill, 2015.
63. Sharma P, Lok A, Viral hepatitis and liver transplantation. *Semin Liver Dis*, 2006; 26: 285-297.
64. Terrault N, Roche B, Samuel D, Management of the hepatitis B virus in liver transplantation setting: a European and an American Perspective. *Liver Transpl*, 2005; 11: 716-732.
65. Dienstag, JL, Chronic Hepatitis". In Kasper, D; Fauci, A; Hauser, S; Longo, D; Jameson, J; Loscalzo, J. *Harrison's Principles of Internal Medicine*, 19e. New York, NY: McGraw-Hill, 2015.
66. Di Marco V, Craxi A, Chronic hepatitis B: who to treat and which choice of treatment? *Expert Rev Anti Infect Ther*, 2009; 7: 281–291.
67. Carey I, Harrison PM, Monotherapy versus combination therapy for the treatment of chronic hepatitis B. *Expert Opin Investig Drugs*, 2009; 18: 1655–1666.
68. Liaw YF, Natural history of chronic hepatitis B virus infection and long-term outcome under treatment. *Liver Int*, 2009; 29: S100–S107.
69. Kao HJ, Diagnosis of hepatitis B virus infection through serological and virological markers. *Expert Rev Gastroenterol Hepatol*, 2008; 2: 553–562.
70. Liaw YF, Chu CM, Hepatitis B virus infection. *Lancet*, 2009; 373: 582–592.
71. Alberti A, Boccato S, Vario A, Benvegnu L, Therapy of acute hepatitis C. *Hepatology*, 2002; 36(5 Suppl1): S195–S200. [PubMed: 12407594]
72. Gerlach JT, Diepolder HM, Zachoval, Acute hepatitis C: high rate of both Spontaneous and treatment-induced viral clearance. *Gastroenterology*, 2003; 125: 80–88. [PubMed: 12851873].
73. Kamal SM, Fouly AE, Kamel RR, Peginterferon alfa-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. *Gastroenterology*, 2006; 130: 632– 638. [PubMed: 16530503].
74. Kamal SM, Ismail A, Graham CS, Pegylated interferon alpha therapy in acute hepatitis C: relation to hepatitis C virus-specific T cell response kinetics. *Hepatology*, 2004; 39: 1721–1731. [PubMed:15185314].
75. Wiegand J, Buggisch P, Boecher W, Early monotherapy with pegylated interferon alpha-2b for acute hepatitis C infection: the HEP-NET acute-HCV-II study. *Hepatology*, 2006; 43: 250–256. [PubMed: 16440367].
76. Omata M, Kanda T, Yu ML, APASL consensus statements and management algorithms for hepatitis C virus infection. *Hepatol Int*, 2012; 6: 409–35.
77. Strader DB, Wright T, Thomas DL, See LB, Diagnosis, management, and treatment of hepatitis C. *Hepatology*, 2004; 39: 1147–1171. [PubMed: 15057920].
78. Dienstag JL, McHutchison JG, American Gastroenterological Association technical review on the management of hepatitis C. *Gastroenterology*, 2006; 130: 231–264. quiz 14(17). [PubMed: 16401486].
79. Bacon BR, Treatment of patients with hepatitis C and normal serum aminotransferase levels. *Hepatology*, 2002; 36(5 Suppl 1): S179–S184. [PubMed: 12407592].
80. Di Bisceglie AM, Hoofnagle JH, Optimal therapy of hepatitis C. *Hepatology*, 2002; 36(5 Suppl 1): S121–S127. [PubMed: 12407585].
81. Feld JJ, Hoofnagle JH, Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature*, 2005; 436: 967–972. [PubMed: 16107837].
82. Manns MP, McHutchison JG, Gordon SC, Peginterferon alfa-2b plus ribavirin Compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*, 2001; 358: 958–965. [PubMed: 11583749].
83. Fried MW, Shiffman ML, Reddy KR, Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*, 2002; 347: 975–982. [PubMed:12324553].
84. Hadziyannis SJ, Sette H Jr, Morgan TR, Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med*, 2004; 140: 346–355. [PubMed: 14996676].
85. El-Zayadi AR, Attia M, Barakat EM, Response of hepatitis C genotype-4 naive patients to 24 weeks of Peginterferon-alpha2b/ribavirin or induction-dose interferon-alpha2b/ribavirin/amantadine: a nonrandomized controlled study. *Am J Gastroenterol*, 2005; 100: 2447–2452. [PubMed: 16279899].