Viral Hepatitis B: Introduction

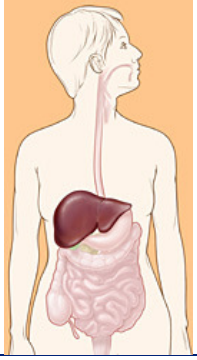

Figure 1. Location of the liver in body.

"Viral hepatitis," refers to infections that affect the liver and are caused by viruses. It is a major public health issue in the United States and worldwide. Not only does viral hepatitis carry a high morbidity, but it also stresses medical resources and can have severe economic consequences. The majority of all viral hepatitis cases are preventable.

Viral hepatitis includes five distinct disease entities, which are caused by at least five different viruses. Hepatitis A and hepatitis B (infectious and serum hepatitis, respectively) are considered separate diseases and both can be diagnosed by a specific serologic test. Hepatitis C and E comprise a third category, each a distinct type, with Hepatitis C parenterally transmitted, and hepatitis E enterically transmitted. Hepatitis D, or delta hepatitis, is another distinct virus that is dependent upon hepatitis B infection. This form of hepatitis may occur as a super-infectionin a hepatitis B carrier or as a co-infection in an individual with acute hepatitis B. Hepatitis viruses most often found in the United States include A, B, C, and D.

Because fatality from hepatitis is relatively low, mortality figures are a poor indicator of the actual incidence of these diseases. The Centers for Disease Control and Prevention estimated that approximately 400,000–600,000 people were infected with viral hepatitis during the decade of the 1990s.

Hepatitis plagued mankind as early as the fifth century BC. It was referenced in early biblical literature and described as occurring in outbreaks, especially during times of war. Toward the end of the nineteenth century, hepatitis was thought to occur as a result of infection of the hepatic parenchyma. The infectious nature of hepatitis was established after World War II. In the mid-1960s, Blumberg and colleagues discovered the surface antigen and antibody of hepatitis B. This Nobel Prize-winning research opened the door to our appreciation of the morphological and immunochemical features of other forms of viral hepatitis.

What is Hepatitis B?

Chronic hepatitis B virus (HBV) is the ninth leading cause of death, with approximately 300 million chronic carriers of HBV worldwide. In the United States there are an estimated 1.2 million chronic carriers, accounting for roughly 17,000 hospitalizations and 5,500 deaths each year. Hepatitis B belongs to the hepadnaviridae class of viruses. It is transmitted by direct percutaneous or permucosal exposure to infected blood. The hepatitis B infection occurs in adolescents and adults and can lead to acute hepatitis, subclinical infection, or the development of chronic infection. The incubation period ranges from 45–160 days, with an average of 75 days, followed by an insidious onset of acute disease (Figure 2).

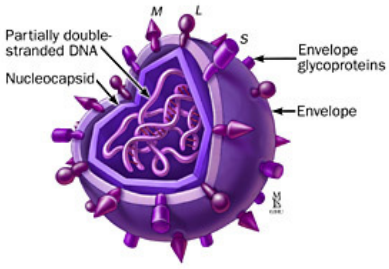

Figure 2. Morphology of hepatitis B virus. M, L, S, envelope proteins.

HBV is a small, partially double-stranded DNA genome (3.2 kb) encoding four genes—HBsAg (surface envelope glycoprotein), HBcAg (viral capsid protein), HBV Pol/RT (polymerase reverse transcriptase), and X gene (transcriptional activator) (Figure 3).

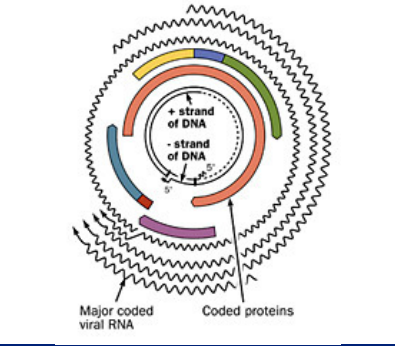

Figure 3. Genomic organization of hepatitis B virus.

There are four major serologic types of hepatitis B virus (adw, ayw, adr, and ayr), with different geographic distributions. The clinical significance of the four types remains unclear. Common to all of these subtypes, however, is an immuno-dominant epitope, the "a" determinant, that is the target of a neutralizing antibody in hepatitis B viral infection (anti-HBsAg). Recently, mutations in the "a" determinant have been reported to be associated with recurrence of hepatitis B viremia in serum despite the presence of protective antibodies (anti-HBsAg).

The life cycle of the hepatitis B virus is depicted in the animation (Figure 4).

The development of clinical hepatitis in HBV-infected individuals is age dependent. Fewer than 10% of infected infants will develop clinical hepatitis compared with 34% of adults 30 years of age or older. About 5–10% of HBV-infected adults will develop a chronic infection with HBV DNA in the liver and antigenemia (having the antigen in the blood). Chronic infection almost always occurs in patients infected in the first few months of life, and may remain for many years—or a lifetime. Individuals with chronic hepatitis B infection are at high risk for serious health complications. Approximately 15–25% of this group will die prematurely from hepatocellular carcinoma or cirrhosis .

Symptoms

Viral hepatitis may develop without clinical signs or symptoms, or with nonspecific symptoms that may appear for a short time with or without jaundice. These symptoms may vary from nonspecific flu-like indications to fatal liver failure. Diagnosis of viral hepatitis often depends on an accumulation of findings considered together (Figure 5).

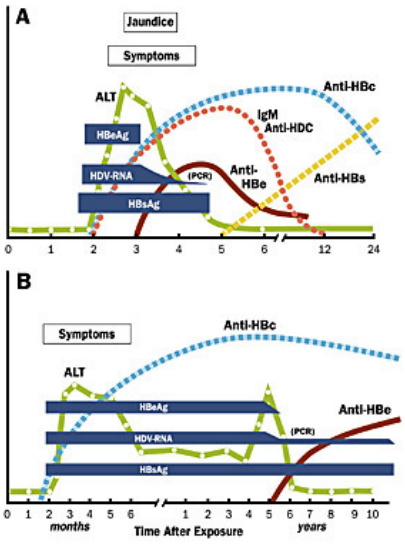

Figure 5. Possible outcomes after hepatitis B infection; A, acute infection; B, chronic infection.

Early in the disease process, generally called the prodromal phase, some patients experience a serum-type sickness that may include fever, arthralgia , arthritis , rash, and angioneurotic edema . These symptoms usually occur 2–3 weeks before jaundice and generally subside before jaundice develops, although they may be concomitant with its appearance.

In the pre-icteric phase, patients may experience respiratory and gastrointestinal tract symptoms, including malaise, fatigue, myalgia, anorexia , nausea, and/or vomiting. They may also experience moderate weight loss, headache, coryza , fever, or pharyngitis and cough. Many patients complain of mid-epigastric pain, right upper quadrant discomfort, or diarrhea. Also characteristic of this phase is the development of dark urine and the lightening of stool color. This duration of this stage of the disease may range from 2–3 days to 2–3 weeks.

The icteric phase is signaled by the development of jaundice. General constitutional symptoms may subside. There may be worsening of anorexia, nausea, and vomiting along with scratching and irritated skin lesions related to pruritis.

Viral Hepatitis B: Anatomy

The liver is located in the right upper quadrant, from the fifth intercostals space in the midclavicular line down to the right costal margin. The liver weighs approximately 1800 g in men and 1400 g in women. The surfaces of the liver are smooth and convex in the superior, anterior, and right lateral regions. Indentations from the colon, right kidney, duodenum, and stomach are apparent on the posterior surface.

The line between the vena cava and gallbladder divides the liver into right and left lobes. Each lobe has an independent vascular and duct supply. The liver is further divided into eight segments, each containing a pedicle of portal vessels, ducts, and hepatic veins (Figure 6).

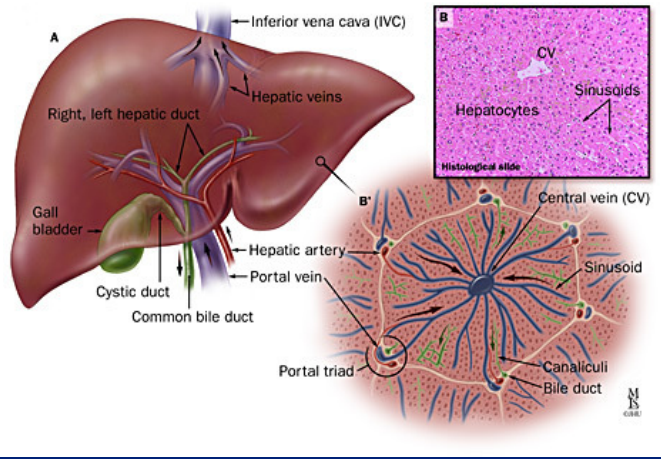

Figure 6. A, Normal gross anatomy of the liver; B, B', histological view.

Viral Hepatitis B: Causes

Overview

Risk factors for hepatitis B include multiple sexual partners, injection drug use, household contact, and health care employment. Infections may be acquired perinatally or during early childhood. Perinatal or early infection have declined as a result of passive immunization with HBV immune globulin in high-risk situations and the initiation of universal HBV vaccination at birth. Infection control practices, changes in blood donation screening, and blood transfusion protocols have also contributed to the decline in the incidence of hepatitis B.

The virus is transmitted parenterally, typically by transfusion of contaminated blood or blood products, or by injection drug use (shared needles). Health care workers who are exposed to blood are at increased risk of infection. In addition, staff in facilities for the developmentally disabled have an increased risk of infection. Non-parenteral spread can also occur between both heterosexual and homosexual partners—with heterosexual activity being the most common risk factor. Many cases of acute hepatitis B occur sporadically without any known source.

In the United States, hepatitis B viral infection occurs primarily in adults and adolescents. In Asian countries, the infection occurs most often during childhood through child-to-child or mother-to-child transmission.

Viral Hepatitis B: Diagnosis

Acute Infection
The incubation period for Hepatitis B—from acute exposure to clinical symptoms—may range from 60–180 days. Clinical presentation may vary from asymptomatic infection of cholestatic hepatitis to fulminant liver failure . Presence of HBV DNA or HBeAg in serum implies active viral replication. These tests may remain positive throughout the prodromal phase and early clinical phases of the illness.

Chronic Infection
Chronic hepatitis B infection is defined as the presence of HBsAg in the serum for more than 6 months. HBsAg is a marker of hepatitis B viral infection, whereas HBeAg and HBV DNA (using a polymerase chain reaction (PCR) assay) are markers of viral replication and infectivity. Chronic infection may lead to serious sequelae, e.g., cirrhosis , liver failure, hepatocellular carcinoma , or death (Figure 7).

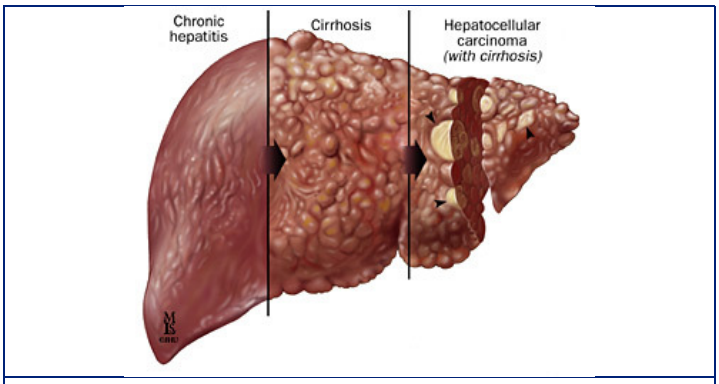

Figure 7. Progression of chronic hepatitis B viral infection.

In a small number of patients, HBV DNA may be present in serum in the absence of HBeAg. These patients have a “precore” mutant, which prevents completion and excretion of the “e” antigen despite active replication of HBV DNA, and is associated with progressive liver disease.

Physical Examination
Physical examination of patients with hepatitis B may reveal posterior cervical lymphadenopathy, splenomegaly, and hepatomegaly . Hepatic enlargement may be minimal, with slight tenderness on palpation or percussion. However, in some patients, the examination may be unremarkable.

Diagnostic Tests

Serum Enzymes
Ornithine, carbamyltransferase, sorbitol dehydrogenase, glutamate dehydrogenase, isocitrate dehydrogenase, malate dehydrogenase, and guanase levels are all helpful in the diagnosis of viral hepatitis. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) remain the most sensitive for establishing a diagnosis of acute viral hepatitis. ALT and AST are the first enzymes to reveal abnormalities during the disease process and the last to normalize. They may reach levels 100 times the upper limits of normal, and ALT is usually more abnormal than AST in the early and late stages of the disease.

Serum Bilirubin
Bilirubin values of 2.5–3.0 mg/dl or greater establish the presence of the icteric phase of hepatitis. Bilirubin levels in excess of 30 mg/dl suggest hemolysis (over production of bilirubin) or renal failure (failure of excretion). Serum bilirubin levels are not always of clinical value.

Hematological Changes
Leukopenia is commonly observed in the presence of viral hepatitis. Anemia and thrombocytopenia are less frequently observed.

Liver Biopsy
Liver biopsy is generally not necessary, but should be considered if the diagnosis is uncertain. Liver biopsy should be performed if there is an atypical clinical course, or the clinical course is prolonged. It should also be undertaken if clues of chronic liver disease are present, or if there are complications such as encephalopathy or fluid retention (Figure 8).

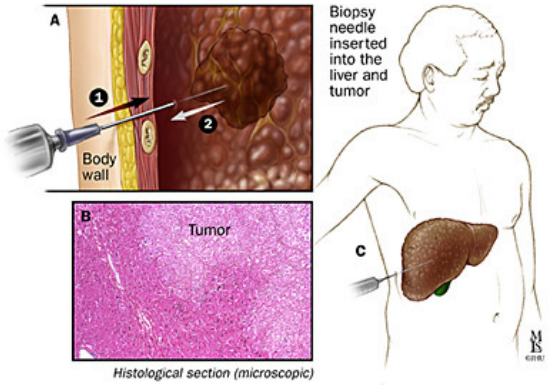

Figure 8. Liver biopsy; A, patient positioning for biopsy; B, histological section of tumor; C, biopsy needle insertion.

Viral Hepatitis B: Therapy

Overview
The treatment goals for chronic hepatitis B infection are: 1) suppression of viral replication, 2) seroconversion to an anti-HBs positive, anti-HBe positive, HBV DNA negative status, 3) improvement in hepatic necroinflammation, and 4) reduction in the likelihood of long-term sequelae of HBV infection, such as cirrhosis and hepatocellular carcinoma .

Medical Therapy
Interferon alfa-2b is the only FDA-approved interferon product for hepatitis B. The recommended dose is 5 million units subcutaneously 5 times per week for 4 months. This has been associated with histological benefit primarily in patients with loss of serum HBeAg. However, most patients do not lose either HBeAg or HBsAg (Figure 9).

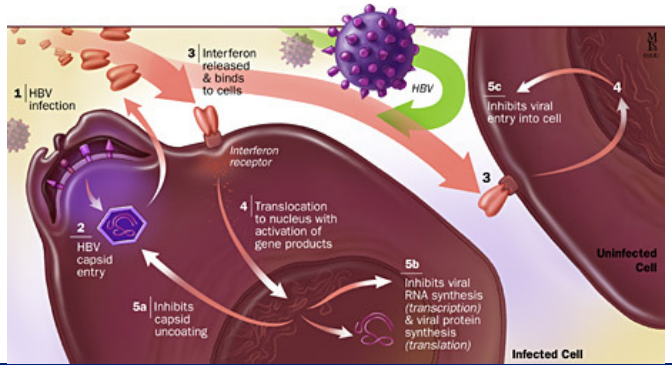

Figure 9. Mechanism of interferon.

Recently, the FDA approved a synthetic nucleoside analog, lamivudine (Epivir-HBV™), for use in patients with chronic hepatitis B viral infection associated with evidence of viral replication and active liver inflammation . Lamivudine inhibits HBV polymerase reverse transcriptase activity resulting in chain termination of nascent HBV DNA strands. It has also been shown to have activity against human immunodeficiency virus (HIV). Preclinical studies demonstrate a satisfactory safety profile with no evidence of mutagenicity, carcinogenicity , or teratogenic potential. Lamivudine (Epivir-HBV™) leads to dose-related reductions in HBV DNA levels after oral absorption, with an equimaximal effect at doses greater than 100 mg/day.

In large placebo-controlled clinical trials, patients treated with lamivudine therapy for 52 weeks produced a significantly greater frequency of histological response (55% vs. 25%, compared with placebo treatment) defined as > 2 point decrease in Hepatic Activity Index (HAI) score. Lamivudine also significantly enhanced the proportion of patients (17% vs. 6% when compared with placebo treatment) undergoing a three-component HBeAg sero-conversion (HBeAg-, HBeAb , HBV DNA-). However, the ideal duration of treatment is not known. Discontinuation of therapy may lead to recurrence of HBV DNA and possibly a “rebound” alanine aminotransferase elevation. In addition, 27% of patients may become resistance to “YMDD” mutations after 52 weeks of therapy. This illustrates the complexity of treatment for chronic hepatitis B infection and demonstrates the need for future treatment regimens that solve these issues. Indeed, combination treatment with lamivudine and interferon appears to improve patient outcomes in preliminary studies.

Finally, a comparison of multiple drug combinations (HBV “cocktails” vs. sequential nucleoside analogs, e.g., adefovir, famciclovir, etc.) is needed to determine the best long-term treatment strategies for chronic hepatitis B infection. Liver transplantation remains an option for those patients who progress to end-stage liver disease. Over time, survival rates have increased and recurrence rates of HBV have declined since the institution of long-term hepatitis B immune globulin after liver transplantation. The availability of nucleoside analogs may further improve outcomes in the post-transplantation period.

Prevention
Two agents are currently available for prophylaxis against hepatitis B viral infection. The first is hepatitis B immune globulin (HBIG), which provides temporary protection from HBV. HBIG is prepared from plasma that contains high titers of anti-HBs. The second is the hepatitis B vaccine, which, to date, has exerted its greatest impact on health care workers (a relatively small subgroup in terms of hepatitis B incidence). Those groups most at risk have not, in most cases, been vaccinated. There are several reasons for this: 1) lack of awareness about hepatitis B and its consequences, 2) lack of public programs, 3) high cost of the vaccine, (4) inability to identify individuals in high risk groups (injection drug users), and (5) disease concentration in people without risk factors.

In an effort to eradicate hepatitis B transmission, the United States has adopted a comprehensive, proactive strategy. Universal HBsAg screening of pregnant women is performed and immunoprophylaxis is given to infants born to potentially infectious mothers to prevent perinatal infection. In addition, hepatitis B vaccination is integrated into current childhood immunization schedules in high-risk populations. This practice provides immunity to teens and adults before they become at risk for hepatitis B infection.

Chronic Active Hepatitis
Chronic active hepatitis is best considered as a group of closely related conditions rather than a specific disease. It is a serious liver disorder that may result in organ failure or cirrhosis (Figure 10). Hepatitis B can cause chronic active hepatitis, as can non-A and non-B viruses and drugs.

About one third of chronic active hepatitis cases follow acute hepatitis, but most develop insidiously. Anorexia , fatigue, and generalized malaise characterize the clinical picture. Jaundice may or may not be present. Immune manifestations, which may include nephritis , acne, arthralgia , ulcerative colitis , amenorrhea , pulmonary fibrosis , and hemolytic anemia , may occur, especially in young women.

Treatment includes the management of complications and cessation of drugs thought to be problematic or causative. Corticosteroids with or without azathioprine may be used to suppress inflammatory responses and may be efficacious in altering the immune response to provocative agents.

The prognosis for chronic active hepatitis is variable. In cases where the etiology is drug related, the disease may completely regress when the offending agent is withdrawn. Idiopathic cases usually improve with treatment. Cases associated with HBsAg tend to prove resistant to therapy. Often, hepatocellular failure or cirrhosis

develops even with adequate therapy.

Fulminant Hepatitis

Fulminant hepatitis is a rare syndrome usually associated with hepatitis B, and is even rarer in hepatitis A or E. It is characterized by rapid clinical deterioration and the onset of hepatic encephalopathy . Coma may develop within hours in some cases. The parenchyma of the liver suffers massive necrosis and there is marked decrease in organ size. Hepatocellular failure and intravascular coagulation may result in bleeding. Functional renal failure may develop.

Viral hepatitis is the leading cause of fulminant hepatic failure throughout the world. Hepatitis A is directly hepatotoxic and, therefore, diminished host defenses and unusually large inoculum may contribute to fulminant hepatic failure. Other factors increasing the likelihood of development of fulminant hepatic failure include hepatitis A viral infection in individuals over 40 years of age, hepatitis A superimposed on pre-existing liver disease, and travel to areas with high endemicity . Hepatitis E is not considered a major cause of fulminant hepatic failure in western countries but should be considered in patients who have returned from endemic regions.

Careful management and painstaking nursing care of specific complications provides the best hope for recovery. Infection control and, in some instances, reverse isolation should be included in the general management of patients with fulminant hepatic failure.

Regular monitoring of blood glucose levels with constant glucose infusion is essential in these patients since hypoglycemia is a constant threat. Monitoring of weight and serum electrolytes is crucial because of the reduction in sodium and free water clearance. Early in the course of fulminant hepatic failure, potassium supplementation is usually required. Hemoperfusion or hemodiafiltration is required when there is significant renal dysfunction.

The degree of hepatic encephalopathy (grade) is a reasonable indicator of prognosis. However, encephalopathy alone is not a threat to the patient. Administration of lactulose may be useful in improving hepatic encephalopathy, but should be administered with care since it may cause electrolyte abnormalities.

Intracranial pressure (ICP) monitoring is essential in fulminant hepatic failure. As the grade of encephalopathy increases (Grade III–IV), intracranial hypertension becomes a serious problem. The risk of brain damage begins when ICP reaches 25 mm Hg. In addition, cerebral perfusion pressure should be maintained above 50 mm Hg to assure adequate perfusion to the brain. Recent studies have shown that monitoring of intracranial pressure has resulted in interventions to lower ICP. These interventions resulted in longer survival and also allowed additional time for spontaneous recovery in a small group of patients. In many cases this improved survival proved essential in the context of liver transplantation.

Intracranial hypertension management should include head elevation, hyperventilation , diuresis , and drug-induced coma. Head elevation above 20 degrees is not recommended as it has been shown to cause a drop in cerebral perfusion pressure and a rise in ICP. Hyperventilation is a common therapy and may be useful in short-term treatment. Maintenance of the pCO2 above 24 mm Hg is recommended, as cerebral vasoconstriction is associated with lower levels. Loop diuretics and osmotic agents (such as furosemide and mannitol) are used to treat elevated intracranial pressures or the clinical signs of cerebral edema . Mannitol is the preferred drug and should be administered in a dose of 0.5–1 g/kg over 5 minutes. Thiopental or pentobarbital may be used to treat unresponsive intracranial hypertension. These agents are initially administered as a bolus and followed by continuous infusion.

Hypotension is a frequent problem in the management of patients with fulminant hepatic failure. Hemodynamic monitoring is essential to maintain cerebral perfusion pressure above 50 mm Hg and to optimize cardiovascular function (including cardiac index > 4.5 L/min/m2, oxygen delivery > 800 L/min/m2, and oxygen consumption > 150 L/min/m2). Epinephrine and norepinephrine are the vasopressors of choice, as they increase both vasopressors and cardiac output. However, these agents may worsen tissue hypoxia . N-acetylcysteine and/or prostacyclin provide blood pressure support (although they are not currently available in the United States). In the absence of these agents, blood pressure support must take precedence in the hierarchy of management of patients with fulminant hepatic failure. Cardiovascular management includes maintenance of renal perfusion, which may be achieved with low-dose dopamine (2–4 mg/kg/h), though dopamine will not prevent a renal shutdown. Renal support should be introduced if volume or electrolyte management dictates. Continuous arteriovenous hemoperfusion or veno-venous hemoperfusion and hemodiafiltration are the preferred methods of providing renal support. anticoagulation of the patient with heparin (to assure an activated clotting time of 200–250 sec) is recommended.

Liver transplantation has become the standard of care in many institutions. Given the reliability of prognostic indicators, and the high mortality in patients with fulminant hepatic failure, orthotopic liver transplantation offers a survival rate of close to 90% with stringent selection criteria.