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Hepatitis

Alcoholic hepatitis evident by fatty change, cell necrosis, Mallory bodies
Hepatitis (plural hepatitides) is a medical condition defined by the inflammation of the liver and characterized by the presence of inflammatory cells in the tissue of the organ. The name is from the Greek hepar the root being hepat, meaning liver, and suffix -itis, meaning "inflammation" (c. 1727). The condition can be self-limiting (healing on its own) or can progress to fibrosis (scarring) and cirrhosis.

Hepatitis may occur with limited or no symptoms, but often leads to jaundice, anorexia (poor appetite) and malaise. Hepatitis is acute when it lasts less than six months and chronic when it persists longer. A group of viruses known as the hepatitis viruses cause most cases of hepatitis worldwide, but it can also be due to toxins (notably alcohol, certain medications, some industrial organic solvents and plants), other infections and autoimmune diseases.

**Signs and symptoms**

Initial features are of nonspecific flu-like symptoms, common to almost all acute viral infections and may include malaise, muscle and joint aches, fever, nausea or vomiting, diarrhea, and headache. 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 (i.e., jaundice) and abdominal discomfort. Physical findings are usually minimal, apart from jaundice in a third and tender hepatomegaly (swelling of the liver) in about 10%. Some exhibit lymphadenopathy (enlarged lymph nodes, in 5%) or splenomegaly (enlargement of the spleen, in 5%).

Acute viral hepatitis is more likely to be asymptomatic in younger people. Symptomatic individuals may present after convalescent stage of 7 to 10 days, with the total illness lasting 2 to 6 weeks.

A small proportion of people with acute hepatitis progress to acute liver failure, in which the liver is unable to clear harmful substances from the circulation (leading to confusion and coma due to hepatic encephalopathy) and produce blood proteins (leading to peripheral edema and bleeding). This may become life-threatening and occasionally requires a liver transplant.

**Chronic**

Chronic hepatitis often leads to nonspecific symptoms such as malaise, tiredness and weakness, and often leads to no symptoms at all. It is commonly identified on blood tests performed either for screening or to evaluate nonspecific symptoms. The occurrence of jaundice indicates advanced liver damage. On physical examination there may be enlargement of the liver.

Extensive damage and scarring of liver (i.e. cirrhosis) leads to weight loss, easy bruising and bleeding tendencies, peripheral edema (swelling of the legs) and accumulation of ascites (fluid in the abdominal cavity). Eventually, cirrhosis may lead to various complications: esophageal varices (enlarged veins in the wall of the esophagus that can cause life-threatening bleeding) hepatic encephalopathy (confusion and coma) and hepatorenal syndrome (kidney dysfunction).
Acne, abnormal menstruation, lung scarring, inflammation of the thyroid gland and kidneys may be present in women with autoimmune hepatitis.

**Pathology**

The liver, like all organs, responds to injury in a limited number of ways and a number of patterns have been identified. Liver biopsies are rarely performed for acute hepatitis and because of this the histology of chronic hepatitis is better known than that of acute hepatitis.

**Acute**

In acute hepatitis the lesions (areas of abnormal tissue) predominantly contain diffuse sinusoidal and portal mononuclear infiltrates (lymphocytes, plasma cells, Kupffer cells) and swollen hepatocytes. Acidophilic cells (Councilman bodies) are common. Hepatocyte regeneration and cholestasis (canalicular bile plugs) typically are present. Bridging hepatic necrosis (areas of necrosis connecting two or more portal tracts) may also occur. There may be some lobular disarray. Although aggregates of lymphocytes in portal zones may occur these are usually neither common nor prominent. The normal architecture is preserved. There is no evidence of fibrosis or cirrhosis (fibrosis plus regenerative nodules). In severe cases prominent hepatocellular necrosis around the central vein (zone 3) may be seen.

In submassive necrosis – a rare presentation of acute hepatitis – there is widespread hepatocellular necrosis beginning in the centrilobular distribution and progressing towards portal tracts. The degree of parenchymal inflammation is variable and is proportional to duration of disease. Two distinct patterns of necrosis have been recognised: (1) zonal coagulative necrosis or (2) panlobular (nonzonal) necrosis. Numerous macrophages and lymphocytes are present. Necrosis and inflammation of the biliary tree occurs. Hyperplasia of the surviving biliary tract cells may be present. Stromal haemorrhage is common.

The histology may show some correlation with the cause:

- Zone 1 (periportal) occurs in phosphorus poisoning or eclampsia.
- Zone 2 (midzonal) – rare – is seen in yellow fever.
- Zone 3 (centrilobular) occurs with ischemic injury, toxic effects, carbon tetrachloride exposure or chloroform ingestion. Drugs such as acetaminophen may be metabolized in zone 1 to toxic compounds that cause necrosis in zone 3.

Where patients have recovered from this condition, biopsies commonly show multiacininar regenerative nodules (previously known as adenomatous hyperplasia).

Massive hepatic necrosis is also known and is usually rapidly fatal. The pathology resembles that of submassive necrosis but is more marked in both degree and extent.
Chronic

Chronic hepatitis has been better studied and several conditions have been described.

Chronic active hepatitis was the term used to describe cases of hepatitis for more than 6 months with portal based inflammation, fibrosis, disruption of the terminal plate and piecemeal necrosis. This term has now been replaced by the diagnosis of 'chronic hepatitis with piecemeal (periportal) necrosis (or interface hepatitis) with or without fibrosis.'

Chronic persistent hepatitis was the term used to describe chronic hepatitis with no significant periportal necrosis or regeneration with a fairly dense mononuclear portal infiltrate. Councilman bodies are frequently seen within the lobule. This condition is now referred to as 'chronic hepatitis without piecemeal necrosis (or interface hepatitis).'

Chronic lobular hepatitis was the term used to describe chronic hepatitis with persistent parenchymal focal hepatocyte necrosis (apoptosis) with mononuclear sinusoidal infiltrates. This is now referred to as 'chronic hepatitis without piecemeal necrosis (or interface hepatitis).'

These terms have since been deprecated. This was done because it was realised that these conditions could alter over time and what might have been regarded as a relatively benign lesion could still progress to cirrhosis. The simpler term 'chronic hepatitis' is now preferred in association with the causative agent (when known) and a grade based on the degree of inflammation, piecemeal or bridging necrosis (interface hepatitis) and the stage of fibrosis. Several grading systems have been proposed but none have been adopted universally.

Cirrhosis is a diffuse process characterized by regenerative nodules that are separated from one another by bands of fibrosis. It is the end stage for many chronic liver diseases. The pathophysiological process that results in cirrhosis is as follows: hepatocytes are lost through a gradual process of hepatocellular injury and inflammation. This injury stimulates a regenerative response in the remaining hepatocytes. The fibrotic scars limit the extent to which the normal architecture can be reestablished as the scars isolate groups of hepatocytes. This results in nodules formation. Angiogenesis (new vessel formation) accompanies scar production which results in the formation of abnormal channels between the central hepatic veins and the portal vessels. This in turn causes shunting of blood around the regenerating parenchyma. Normal vascular structures including the sinusoidal channels may be obliterated by fibrotic tissue leading to portal hypertension. The overall reduction in hepatocyte mass, in conjunction with the portal blood shunting, prevents the liver from accomplishing its usual functions – the filtering of blood from the gastrointestinal tract and serum protein production. These changes give rise to the clinical manifestations of cirrhosis.
Most of the causes of hepatitis cannot be distinguished on the basis of the pathology but some do have particular features that are suggestive of a particular diagnosis.

The presence of micronodular cirrhosis, Mallory bodies and fatty change within a single biopsy are highly suggestive of alcoholic injury. Perivenular, pericellular fibrosis (known as 'chicken wire fibrosis' because of its appearance on trichrome or van Gieson stains) with partial or complete obliteration of the central vein is also very suggestive of alcohol abuse.

Cardiac, ischemic and venous outflow obstruction all cause similar patterns. The sinusoids are often dilated and filled with erythrocytes. The liver cell plates may be compressed. Coagulative necrosis of the hepatocytes can occur around the central vein. Hemosiderin and lipochrome laden macrophages and inflammatory cells may be found. At the edge of the fibrotic zone cholestasis may be present. The portal tracts are rarely significantly involved until late in the course.

Biliary tract disease including primary biliary cirrhosis, sclerosing cholangitis, inflammatory changes associated with idiopathic inflammatory bowel disease and duct obstruction have similar histology in their early stages. Although these diseases tend to primarily involve the biliary tract they may also be associated with chronic inflammation within the liver and difficult to distinguish on histological grounds alone. The fibrotic changes associated with these disease principally involve the portal tracts with cholangiole proliferation, portal tract inflammation with neutrophils surrounding the cholangioles, disruption of the terminal plate by mononuclear inflammatory cells and occasional hepatocyte necrosis. The central veins are either not involved in the fibrotic process or become involved only late in the course of the disease. Consequently the central–portal relationships are minimally distorted. Where cirrhosis is present it tends to be in the form of a portal–portal bridging fibrosis.

Hepatitis E causes different histological patterns that depend on the host's background. In immunocompetent patients the typical pattern is of severe intralobular necrosis and acute cholangitis in the portal tract with numerous neutrophils. This normally resolves without sequelae. Disease is more severe in those with preexisting liver disease such as cirrhosis. In the immunocompromised patients chronic infection may result with rapid progression to cirrhosis. The histology is similar to that found in hepatitis C virus with dense lymphocytic portal infiltrate, constant peacemeal necrosis and fibrosis.
Alcoholic hepatitis

Ethanol, mostly in alcoholic beverages, is a significant cause of hepatitis. Usually alcoholic hepatitis comes after a period of increased alcohol consumption. Alcoholic hepatitis is characterized by a variable constellation of symptoms, which may include feeling unwell, enlargement of the liver, development of fluid in the abdomen ascites, and modest elevation of liver blood tests. Alcoholic hepatitis can vary from mild with only liver test elevation to severe liver inflammation with development of jaundice, prolonged prothrombin time, and liver failure. Severe cases are characterized by either obtundation (dulled consciousness) or the combination of elevated bilirubin levels and prolonged prothrombin time; the mortality rate in both categories is 50% within 30 days of onset.

Alcoholic hepatitis is distinct from cirrhosis caused by long term alcohol consumption. Alcoholic hepatitis can occur in patients with chronic alcoholic liver disease and alcoholic cirrhosis. Alcoholic hepatitis by itself does not lead to cirrhosis, but cirrhosis is more common in patients with long term alcohol consumption. Patients who drink alcohol to excess are also more often than others found to have hepatitis C. The combination of hepatitis C and alcohol consumption accelerates the development of cirrhosis.
Hepatitis A (formerly known as infectious hepatitis and epidemical virus) is an acute infectious disease of the liver caused by the hepatitis A virus (Hep A), an RNA virus, usually spread the fecal-oral route; transmitted person-to-person by ingestion of contaminated food or water or through direct contact with an infectious person. Tens of millions of individuals worldwide are estimated to become infected with Hep A each year. The time between infection and the appearance of the symptoms (the incubation period) is between two and six weeks and the average incubation period is 28 days.

In developing countries, and in regions with poor hygiene standards, the incidence of infection with this virus is high and the illness is usually contracted in early childhood. As incomes rise and access to clean water increases, the incidence of HAV decreases. Hepatitis A infection causes no clinical signs and symptoms in over 90% of infected children and since the infection confers lifelong immunity, the disease is of no special significance to those infected early in life. In Europe, the United States and other industrialized countries, on the other hand, the infection is contracted primarily by susceptible young adults, most of whom are infected with the virus during trips to countries with a high incidence of the disease or through contact with infectious persons.

HAV infection produces a self-limited disease that does not result in chronic infection or chronic liver disease. However, 10–15% of patients might experience a relapse of symptoms during the 6 months after acute illness. Acute liver failure from Hepatitis A is rare (overall case-fatality rate: 0.5%). The risk for symptomatic infection is directly related to age, with >80% of adults having symptoms compatible with acute viral hepatitis and the majority of children having either asymptomatic or unrecognized infection. Antibody produced in response to HAV infection persists for life and confers protection against reinfection. The disease can be prevented by vaccination, and hepatitis A vaccine has been proven effective in controlling outbreaks worldwide.
Signs and symptoms

Early symptoms of hepatitis A infection can be mistaken for influenza, but some sufferers, especially children, exhibit no symptoms at all. Symptoms typically appear 2 to 6 weeks, (the incubation period), after the initial infection.

Symptoms usually last less than 2 months, although some people can be ill for as long as 6 months.:

- Fatigue
- Fever
- Abdominal pain
- Nausea
- Appetite loss
- Jaundice, a yellowing of the skin or whites of the eyes
- Bile is removed from blood stream and excreted in urine, giving it a dark amber colour
- Clay-coloured feces

There is no apparent virus-mediated cytotoxicity presumably because of the virus' own requirement for an intact eIF4G and liver pathology is likely immune-mediated.

Transmission

The virus spreads by the fecal-oral route and infections often occur in conditions of poor sanitation and overcrowding. Hepatitis A can be transmitted by the parenteral route but very rarely by blood and blood products. Food-borne outbreaks are not uncommon, and ingestion of shellfish cultivated in polluted water is associated with a high risk of infection. Approximately 40% of all acute viral hepatitis is caused by HAV. Infected individuals are infectious prior to onset of symptoms, roughly 10 days following infection. The virus is resistant to detergent, acid (pH 1), solvents (e.g., ether, chloroform), drying, and temperatures up to 60 °C. It can survive for months in fresh and salt water. Common-source (e.g., water, restaurant) outbreaks are typical. Infection is common in children in developing countries, reaching 100% incidence, but following infection there is life-long immunity. HAV can be inactivated by: chlorine treatment (drinking water), formalin (0.35%, 37 °C, 72 hours), peracetic acid (2%, 4 hours), beta-propiolactone (0.25%, 1 hour), and UV radiation (2 μW/cm²/min).
Diagnosis

Serum IgG, IgM and ALT following Hepatitis A virus infection

Although HAV is excreted in the feces towards the end of the incubation period, specific diagnosis is made by the detection of HAV-specific IgM antibodies in the blood. IgM antibody is only present in the blood following an acute hepatitis A infection. It is detectable from one to two weeks after the initial infection and persists for up to 14 weeks. The presence of IgG antibody in the blood means that the acute stage of the illness is past and the person is immune to further infection. IgG antibody to HAV is also found in the blood following vaccination and tests for immunity to the virus are based on the detection of this antibody.

During the acute stage of the infection, the liver enzyme alanine transferase (ALT) is present in the blood at levels much higher than is normal. The enzyme comes from the liver cells that have been damaged by the virus.

Hepatitis A virus is present in the blood, (viremia), and feces of infected people up to two weeks before clinical illness develops.

Prevention

For information about the vaccine, its properties, and its application, see Hepatitis A vaccine.

Hepatitis A can be prevented by vaccination, good hygiene and sanitation.

The vaccine protects against HAV in more than 95% of cases for longer than 20 years. It contains inactivated hepatitis A virus providing active immunity against a future infection. The vaccine was first phased in 1996 for children in high-risk areas, and in 1999 it was spread to areas with elevating levels of infection.

The vaccine is given by injection. An initial dose provides protection starting two to four weeks after vaccination; the second booster dose, given six to twelve months later, provides protection for over twenty years.
The vaccine was introduced in 1992 and was initially recommended for persons at high risk. Since then Bahrain and Israel have embarked on eradication programmes. Australia, China, Byelorussia, Italy, Spain and the United States have started similar programmes. The incidence of Hepatitis A where widespread vaccination has been practised has decreased dramatically. In China and the United States the incidence of Hepatitis A has decreased by 90% since 1990.

**Treatment**

There is no specific treatment for hepatitis A. Sufferers are advised to rest, avoid fatty foods and alcohol (these may be poorly tolerated for some additional months during the recovery phase and cause minor relapses), eat a well-balanced diet, and stay hydrated.

**Hepatitis B**

Hepatitis B is an infectious inflammatory illness of the liver caused by the hepatitis B virus (HBV) that affects hominoidea, including humans. Originally known as "serum hepatitis", the disease has caused epidemics in parts of Asia and Africa, and it is endemic in China. About a third of the world population has been infected at one point in their lives, including 350 million who are chronic carriers.

The virus is transmitted by exposure to infectious blood or body fluids such as semen and vaginal fluids, while viral DNA has been detected in the saliva, tears, and urine of chronic carriers. Perinatal infection is a major route of infection in endemic (mainly developing) countries. Other risk factors for developing HBV infection include working in a healthcare setting, transfusions, and dialysis, acupuncture, tattooing, extended overseas travel and residence in an institution. However, Hepatitis B viruses cannot be spread by holding hands, sharing eating utensils or drinking glasses, kissing, hugging, coughing, sneezing, or breastfeeding.

The acute illness causes liver inflammation, vomiting, jaundice and, rarely, death. Chronic hepatitis B may eventually cause cirrhosis and liver cancer—a disease with poor response to all but a few current therapies. The infection is preventable by vaccination.
Hepatitis B virus is an hepadnavirus—*hepa* from *hepatotropic* (attracted to the liver) and *dna* because it is a DNA virus—and it has a circular genome of partially double-stranded DNA. The viruses replicate through an RNA intermediate form by reverse transcription, which practice relates them to retroviruses. Although replication takes place in the liver, the virus spreads to the blood where viral proteins and antibodies against them are found in infected people.

**Signs and symptoms**

Acute infection with hepatitis B virus is associated with acute viral hepatitis—an illness that begins with general ill-health, loss of appetite, nausea, vomiting, body aches, mild fever, and dark urine, and then progresses to development of jaundice. It has been noted that itchy skin has been an indication as a possible symptom of all hepatitis virus types. The illness lasts for a few weeks and then gradually improves in most affected people. A few people may have more severe liver disease (fulminant hepatic failure), and may die as a result. The infection may be entirely asymptomatic and may go unrecognized.

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 (liver cancer). 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 (MGN).

Symptoms outside of the liver are present in 1–10% of HBV-infected people and include serum-sickness–like syndrome, acute necrotizing vasculitis (polyarteritis nodosa), membranous glomerulonephritis, and papular acrodermatitis of childhood (Gianotti-Crosti syndrome). The serum-sickness–like syndrome occurs in the setting of acute hepatitis B, often preceding the onset of jaundice. 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. About 30–50% of people with acute necrotizing vasculitis (polyarteritis nodosa) are HBV carriers. HBV-associated nephropathy has been described in
adults but is more common in children. Membranous glomerulonephritis is the most common form. Other immune-mediated hematological disorders, such as essential mixed cryoglobulinemia and aplastic anemia.

Transmission of hepatitis B virus results from exposure to infectious blood or body fluids containing blood. Possible forms of transmission include sexual contact, blood transfusions, re-use of contaminated needles & syringes, and vertical transmission from mother to child (MTCT) during childbirth. Without intervention, a mother who is positive for HBsAg confers a 20% risk of passing the infection to her offspring at the time of birth. This risk is as high as 90% if the mother is also positive for HBeAg. HBV can be transmitted between family members within households, possibly by contact of nonintact skin or mucous membrane with secretions or saliva containing HBV. However, at least 30% of reported hepatitis B among adults cannot be associated with an identifiable risk factor. And Shi et al. showed that breastfeeding after proper immunoprophylaxis did not contribute to MTCT of HBV.

**Prevention**

Several vaccines have been developed for the prevention of hepatitis B virus infection. These rely on the use of one of the viral envelope proteins (hepatitis B surface antigen or HBsAg). The vaccine was originally prepared from plasma obtained from people who had long-standing hepatitis B virus infection. However, currently, it is made using a synthetic recombinant DNA technology that does not contain blood products. One cannot be infected with hepatitis B from this vaccine.

The risk of transmission from mother to newborn can be reduced from 20–90% to 5–10% by administering to the newborn hepatitis B vaccine (HBV 1) and hepatitis B immune globulin (HBIG) within 12 hours of birth, followed by a second dose of hepatitis B vaccine (HBV 2) at 1–2 months and a third dose at and no earlier than 6 months (24 weeks). Since 2% of infants vaccinated will not develop immunity after the first three dose series, infants born to hepatitis B-positive mothers are tested at 9 months for hepatitis B surface antigen (HBsAg) and the antibody to the hepatitis B surface antigen (anti-HBs). If post-vaccination test results indicate that the child is still susceptible, a second three dose series at (0, 1 and 6 months) is administered. If the child is still susceptible after the second series, a third series is not recommended.

Following vaccination, hepatitis B surface antigen may be detected in serum for several days; this is known as vaccine antigenaemia. The vaccine is administered in either two-, three-, or four-dose schedules into infants and adults, which provides protection for 85–90% of individuals. Protection has been observed to last 12 years in individuals who show adequate initial response to the primary course of vaccinations, and that immunity is predicted to last at least 25 years.

Unlike hepatitis A, hepatitis B does not generally spread through water and food. Instead, it is transmitted through body fluids; thus, prevention is the avoidance of such transmission: unprotected sexual contact, blood transfusions, re-use of contaminated needles and syringes, and vertical transmission during child birth. Infants may be vaccinated at birth.
Besides the WHO-recommended joint immunoprophylaxis starting from the newborn, multiple injections of small doses of hepatitis B immune globulin, or oral lamivudine in HBV carrier mothers with a high degree of infectiousness (>10^6 copies/ml) in late pregnancy (the last three months of pregnancy), effectively and safely prevent HBV intrauterine transmission, which provide new insight into prevention of HBV at the earliest stage.

Acute hepatitis B infection does not usually require treatment because most adults clear the infection spontaneously. Early antiviral treatment may be required in fewer than 1% of people, whose infection takes a very aggressive course (fulminant hepatitis) or who are immunocompromised. On the other hand, treatment of chronic infection may be necessary to reduce the risk of cirrhosis and liver cancer. Chronically infected individuals with persistently elevated serum alanine aminotransferase, a marker of liver damage, and HBV DNA levels are candidates for therapy. Treatment lasts from six months to a year, depending on medication and genotype.

Although none of the available drugs can clear the infection, they can stop the virus from replicating, thus minimizing liver damage. Currently, there are seven medications licensed for treatment of hepatitis B infection in the United States. These include antiviral drugs lamivudine (Epivir), adefovir (Hepsera), tenofovir (Viread), telbivudine (Tyzeka) and entecavir (Baraclude), and the two immune system modulators interferon alpha-2a and PEGylated interferon alpha-2a (Pegasys). The use of interferon, which requires injections daily or thrice weekly, has been supplanted by long-acting PEGylated interferon, which is injected only once weekly.

However, some individuals are much more likely to respond than others, and this might be because of the genotype of the infecting virus or the person's heredity. The treatment reduces viral replication in the liver, thereby reducing the viral load (the amount of virus particles as measured in the blood). Response to treatment differs between the genotypes. Interferon treatment may produce an e antigen seroconversion rate of 37% in genotype A but only a 6% seroconversion in type D. Genotype B has similar seroconversion rates to type A while type C seroconverts only in 15% of cases. Sustained e antigen loss after treatment is ~45% in types A and B but only 25–30% in types C and D.

Hepatitis B virus infection may be either acute (self-limiting) or chronic (long-standing). Persons with self-limiting infection clear the infection spontaneously within weeks to months.

Children are less likely than adults to clear the infection. More than 95% of people who become infected as adults or older children will stage a full recovery and develop protective immunity to the virus. However, this drops to 30% for younger children, and only 5% of newborns that acquire the infection from their mother at birth will clear the infection. This population has a 40% lifetime risk of death from cirrhosis or hepatocellular carcinoma. Of those infected between the age of one to six, 70% will clear the infection.

Hepatitis D (HDV) can occur only with a concomitant hepatitis B infection, because HDV uses the HBV surface antigen to form a capsid. Co-infection with hepatitis D increases the risk of liver cirrhosis and liver cancer. Polyarteritis nodosa is more common in people with hepatitis B infection.
In 2004, an estimated 350 million individuals were infected worldwide. National and regional prevalence ranges from over 10% in Asia to under 0.5% in the United States and northern Europe. Routes of infection include vertical transmission (such as through childbirth), early life horizontal transmission (bites, lesions, and sanitary habits), and adult horizontal transmission (sexual contact, intravenous drug use). The primary method of transmission reflects the prevalence of chronic HBV infection in a given area. In low prevalence areas such as the continental United States and Western Europe, injection drug abuse and unprotected sex are the primary methods, although other factors may also be important. In moderate prevalence areas, which include Eastern Europe, Russia, and Japan, where 2–7% of the population is chronically infected, the disease is predominantly spread among children. In high-prevalence areas such as China and South East Asia, transmission during childbirth is most common, although in other areas of high endemicity such as Africa, transmission during childhood is a significant factor. The prevalence of chronic HBV infection in areas of high endemicity is at least 8%. As of 2010, China has 120 million infected people, followed by India and Indonesia with 40 million and 12 million, respectively. According to World Health Organization, an estimated 600,000 people die every year related to the infection.

The earliest record of an epidemic caused by hepatitis B virus was made by Lurman in 1885. An outbreak of smallpox occurred in Bremen in 1883 and 1,289 shipyard employees were vaccinated with lymph from other people. After several weeks, and up to eight months later, 191 of the vaccinated workers became ill with jaundice and were diagnosed as suffering from serum hepatitis. Other employees who had been inoculated with different batches of lymph remained healthy. Lurman's paper, now regarded as a classical example of an epidemiological study, proved that contaminated lymph was the source of the outbreak. Later, numerous similar outbreaks were reported following the introduction, in 1909, of hypodermic needles that were used, and, more importantly, reused, for administering Salvarsan for the treatment of syphilis. The virus was not discovered until 1965 when Baruch Blumberg, then working at the National Institutes of Health (NIH), discovered the Australia antigen (later known to be hepatitis B surface antigen, or HBsAg) in the blood of Australian aboriginal people. Although a virus had been suspected since the research published by MacCallum in 1947, D.S. Dane and others discovered the virus particle in 1970 by electron microscopy. By the early 1980s the genome of the virus had been sequenced, and the first vaccines were being tested.
World Hepatitis Day, observed July 28, aims to raise global awareness of hepatitis B and hepatitis C and encourage prevention, diagnosis and treatment. It has been led by the World Hepatitis Alliance since 2007 and on May 2010, it got global endorsement from the World Health Organization.

**Hepatitis C**

Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus (HCV). The infection is often asymptomatic, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years. In some cases, those with cirrhosis will go on to develop liver failure, liver cancer or life-threatening esophageal and gastric varices.

HCV is spread primarily by blood-to-blood contact associated with intravenous drug use, poorly sterilized medical equipment and transfusions. An estimated 130–170 million people worldwide are infected with hepatitis C. The existence of hepatitis C (originally "non-A non-B hepatitis") was postulated in the 1970s and proven in 1989. It is not known to cause disease in other animals.

The virus persists in the liver in about 85% of those infected. This persistent infection can be treated with medication: a combination of peginterferon and ribavirin are the current standard therapy. Overall, 50–80% of people treated are cured. Those who develop cirrhosis or liver cancer may require a liver transplant. Hepatitis C is the leading cause of liver transplantation though the virus usually recurs after transplantation. No vaccine against hepatitis C is currently available.
Acute infection

Hepatitis C infection causes acute symptoms in 15% of cases. Symptoms are generally mild and vague, including a decreased appetite, fatigue, nausea, muscle or joint pains, and weight loss. Most cases of acute infection are not associated with jaundice. The infection resolves spontaneously in 10-50% of cases, which occurs more frequently in individuals who are young and female.

Chronic infection

About 80% of those exposed to the virus develop a chronic infection. Most experience minimal or no symptoms during the initial few decades of the infection, although chronic hepatitis C can be associated with fatigue. Hepatitis C after many years becomes the primary cause of cirrhosis and liver cancer. About 10-30% of people develop cirrhosis over 30 years. Cirrhosis is more common in those co-infected with hepatitis B or HIV, alcoholics, and those of male gender. Those who develop cirrhosis have a 20 fold greater risk of hepatocellular carcinoma, a rate of 1-3% per year, and if this is complicated by excess alcohol the risk becomes 100 fold greater. Hepatitis C is the cause of 27% of cirrhosis cases and 25% of hepatocellular carcinoma worldwide.

Liver cirrhosis may lead to portal hypertension, ascites (accumulation of fluid in the abdomen), easy bruising or bleeding, varices (enlarged veins, especially in the stomach and esophagus), jaundice, and a syndrome of cognitive impairment known as hepatic encephalopathy. It is a common cause for requiring a liver transplant.
The hepatitis C virus (HCV) is a small, enveloped, single-stranded, positive-sense RNA virus. It is a member of the *hepacivirus* genus in the family *Flaviviridae*. There are seven major genotypes of HCV, which are indicated numerically from one to seven. In the United States, about 70% of cases are caused by genotype 1, 20% by genotype 2, and about 1% by each of the other genotypes. Genotype 1 is also the most common in South America and Europe.

**Hepatitis C infection in the United States by source**

The primary methods of transmission in the developed world is intravenous drug use (IDU), while in the developing world the main methods are blood transfusions and unsafe medical procedures. The cause of transmission remains unknown in 20% of cases; however, many of these are believed to be accounted for by IDU.

**Intravenous drug use**

IDU is a major risk factor for hepatitis C in many parts of the world. Of 77 countries reviewed 25 (including the United States) were found to have prevalences of hepatitis C in the intravenous drug user population of between 60% and 80% and China. While twelve countries had rates greater than 80%. It is believed that ten million intravenous drug users are infected with hepatitis C; China (1.6 million), the United States (1.5 million), and Russia (1.3 million) have the highest absolute totals. Occurrence of hepatitis C among prison inmates in the United States are ten to 20 times that of the occurrence observed in the general population; this has been attributed to high-

**Healthcare exposure**

Blood transfusion, transfusion of blood products, or organ transplantation without HCV screening carry significant risks of infection. The United States instituted universal screening in
1992 and the risk subsequently has decreased from one in 10,000 to 10,000,000 per unit of blood down from a risk of one in 200 units of blood. This low risk remains as there is a period of about 11–70 days between the potential blood donor acquiring hepatitis C and their blood testing positive depending on the method. Some countries still do not screen for hepatitis C due to the cost.

Those who have experienced a needle stick injury from someone who was HCV positive have about a 1.8% chance of subsequently contracting the disease themselves. The risk is greater if the needle in question is hollow and the puncture wound is deep. There is a risk from mucosal exposures to blood; but this risk is low, and there is no risk if blood exposure occurs on intact skin.

Hospital equipment has also been documented as a method of transmission of hepatitis C including: reuse of needles and syringes, multiple-use medication vials, infusion bags, and improperly sterilized surgical equipment, among others. Limitations in the implementation and enforcement of stringent standard precautions in public and private medical and dental facilities are known to be the primary cause of the spread of HCV in Egypt, the country with highest rate of infection in the world.

**Sexual intercourse**

Whether hepatitis C can be transmitted through sexual activity is controversial. While there is an association between high-risk sexual activity and hepatitis C, it is not known whether transmission of the disease is due to drug use that has not been admitted to or sex as a risk factor. The majority of evidence supports there being no risk for monogamous heterosexual couples. Sexual practices that involve higher levels of trauma to the anogenital mucosa, such as anal penetrative sex, or that occur when there is a concurrent sexually transmitted infection, including HIV or genital ulceration, do present a risk. The United States government only recommends condom use to prevent hepatitis C transmission in those with multiple partners.

**Body piercings**

Tattooing is associated with two to threefold increased risk of hepatitis C. This can be due to either improperly sterilized equipment or contamination of the dyes being used. Tattoos or piercings performed either before the mid-1980s, "underground," or nonprofessionally are of particular concern, since sterile techniques in such settings may be lacking. The risk also appears to be greater for larger tattoos. It is estimated that nearly half of prison inmates share unsterilized tattooing equipment. It is rare for tattoos in a licensed facility to be directly associated with HCV infection.

**Shared personal care items**

Personal-care items such as razors, toothbrushes, and manicuring or pedicuring equipment can be contaminated with blood. Sharing such items can potentially lead to exposure to HCV. Appropriate caution should be taken regarding any medical condition that results in bleeding,
such as cuts and sores. HCV is not spread through casual contact, such as hugging, kissing, or sharing eating or cooking utensils.

**Vertical transmission**

Vertical transmission of hepatitis C from an infected mother to her child occurs in less than 10% of pregnancies. There are no measures that alter this risk. It is not clear when during pregnancy transmission occurs, but it may occur both during gestation and at delivery. A long labor is associated with a greater risk of transmission. There is no evidence that breast-feeding spreads HCV; however, to be cautious, an infected mother is advised to avoid breastfeeding if her nipples are cracked and bleeding, or her viral loads are high.

As of 2011, no vaccine protects against contracting hepatitis C. However, a number are under development and some have shown encouraging results. A combination of harm reduction strategies, such as the provision of new needles and syringes and treatment of substance use, decrease the risk of hepatitis C in intravenous drug users by about 75% The screening of blood donors is important at a national level, as is adhering to universal precautions within healthcare facilities. In countries where there is an insufficient supply of sterile syringes, medications should be given orally rather than via injection.

HCV induces chronic infection in 50–80% of infected persons. Approximately 40-80% of these clear with treatment. In rare cases, infection can clear without treatment. Those with chronic hepatitis C are advised to avoid alcohol and medications toxic to the liver, and to be vaccinated for hepatitis A and hepatitis B. Ultrasound surveillance for hepatocellular carcinoma is recommended in those with accompanying cirrhosis.
It is estimated that 130–170 million people, or ~3% of the world's population, are living with chronic hepatitis C. About 3–4 million people are infected per year, and more than 350,000 people die yearly from hepatitis C-related diseases. Rates have increased substantially in the 20th century due to a combination of IDU and intravenous medication or poorly sterilized medical equipment.

Among those chronically infected the risk of cirrhosis after 20 years varies between studies but has been estimated at ~10%-15% for men and ~1-5% for women. The reason for this difference is not known. Once cirrhosis is established, the rate of developing hepatocellular carcinoma is ~1%-4% per year.

In the United States, about 2% of people have hepatitis C, with about 35,000 to 185,000 new cases a year. Rates have decreased in the Western world since the 1990s due to improved screening of blood before transfusion. Annual deaths from HCV in the United States range from 8,000 to 10,000; expectations are that this mortality rate will increase, as those infected by transfusion before HCV testing become apparent.

Prevalence is higher in some countries in Africa and Asia. Countries with particularly high rates of infection include Egypt (22%), Pakistan (4.8%) and China (3.2%). It is believed that the high prevalence in Egypt is linked to a now-discontinued mass-treatment campaign for schistosomiasis, using improperly sterilized glass syringes.
Hepatitis D, also referred to as hepatitis D virus (HDV) and classified as *Hepatitis delta virus*, is a disease caused by a small circular enveloped RNA virus. It is one of five known hepatitis viruses: A, B, C, D, and E. HDV is considered to be a subviral satellite because it can propagate only in the presence of the hepatitis B virus (HBV). Transmission of HDV can occur either via simultaneous infection with HBV (coinfection) or superimposed on chronic hepatitis B or hepatitis B carrier state (superinfection).

Both superinfection and coinfection with HDV results in more severe complications compared to infection with HBV alone. These complications include a greater likelihood of experiencing liver failure in acute infections and a rapid progression to liver cirrhosis, with an increased chance of developing liver cancer in chronic infections. In combination with hepatitis B virus, hepatitis D has the highest mortality rate of all the hepatitis infections of 20%.
Hepatitis D virus was first reported in the mid-1977, by an Italian researcher, Mario Rizzetto, as a nuclear antigen in patients infected with HBV who had severe liver disease. This nuclear antigen was then thought to be a hepatitis B antigen and was called the delta antigen. Subsequent experiments in chimpanzees showed that the hepatitis delta antigen (HDAg) was a structural part of a pathogen that required HBV infection to replicate. The entire virus was cloned and sequenced in 1986, and obtained its own genus deltavirus.

![Image of Hepatitis D virus](image)

The routes of transmission of hepatitis D are similar to those for hepatitis B. Infection is largely restricted to persons at high risk of hepatitis B infection, particularly injecting drug users and persons receiving clotting factor concentrates. Worldwide more than 15 million people are co-infected. HDV is rare in most developed countries, and is mostly associated with intravenous drug use. However, HDV is much more common in the immediate Mediterranean region, sub-Saharan Africa, the Middle East, and the northern part of South America. In all, about 20 million people may be infected with HDV.
Hepatitis E

Hepatitis E is a viral hepatitis (liver inflammation) caused by infection with a virus called hepatitis E virus (HEV). HEV is a positive-sense single-stranded RNA icosahedral virus with a 7.5 kilobase genome. HEV has a fecal-oral transmission route. It is one of five known hepatitis viruses: A, B, C, D, and E. Infection with this virus was first documented in 1955 during an outbreak in New Delhi, India.

Although it was originally classified in the Caliciviridae family, the virus has since been classified into the genus Hepevirus, but was not assigned to a viral family. The virus itself is a small non-enveloped particle.

The genome is approximately 7200 bases in length, is a polyadenylated single-strand RNA molecule that contains three discontinuous and partially overlapping open reading frames (ORFs) along with 5' and 3' cis-acting elements, which have important roles in HEV replication and transcription. ORF1 encode a methyltransferase, protease, helicase and replicase; ORF2 encode the capsid protein and ORF3 encodes a protein of undefined function. A three-dimensional, atomic-resolution structure of the capsid protein in the context of a virus-like particle has been described. An in vitro culture system is not yet available.

As of 2009 there are approximately 1,600 sequences of both human and animal isolates of HEV available in open-access sequence databases.

Species of this genus infect humans, pigs, boars, deer, rats, rabbits and birds.

Genotype 1 has been isolated from tropical and several subtropical countries in Asia and Africa. Genotype 2 has been isolated from from Mexico, Nigeria, and Chad. Genotype 3 has been isolated almost worldwide including Asia, Europe, Oceania, North and South America. Genotype 4 appears to be limited exclusively to Asia.
Genotypes 1 and 2 are restricted to humans and often associated with large outbreaks and epidemics in developing countries with poor sanitation conditions. Genotypes 3 and 4 infect humans, pigs and other animal species and have been responsible for sporadic cases of hepatitis E in both developing and industrialized countries.

The incidence of hepatitis E is highest in juveniles and adults between the ages of 15 and 40. Though children often contract this infection as well, they less frequently become symptomatic. Mortality rates are generally low, for hepatitis E is a “self-limiting” disease, in that it usually goes away by itself and the patient recovers. However, during the duration of the infection (usually several weeks), the disease severely impairs a person’s ability to work, care for family members, and obtain food. Hepatitis E occasionally develops into an acute, severe liver disease, and is fatal in about 2% of all cases. Clinically, it is comparable to hepatitis A, but in pregnant women the disease is more often severe and is associated with a clinical syndrome called fulminant hepatic failure. Pregnant women, especially those in the third trimester, suffer an elevated mortality rate from the disease of around 20%.

Differences have been noted between the different genotypes. For genotype 1, the age at which incidence peaks is between 15 and 35 years and mortality is about 1%. Genotype 3 and 4 — the most common in Japan — are more common in people older than 60 years and the mortality is between 5 and 10%. Although prednisolone has been used in the treatment of this condition, because large scale studies have not yet been reported, the role of this drug in treatment is not yet clear.

In immunocompromised subjects - particularly in solid organ transplanted patients - Hepatitis E may cause a chronic infection. Occasionally this may cause liver fibrosis and cirrhosis. The use of low dose ribavirin (600 to 800 milligrams / day) over a three month period has been associated with viral clearance in such cases.

Hepatitis E is prevalent in most developing countries, and common in any country with a hot climate. It is widespread in Southeast Asia, northern and central Africa, India, and Central America. It is spread mainly through fecal contamination of water supplies or food; person-to-person transmission is uncommon. Outbreaks of epidemic hepatitis E most commonly occur after heavy rainfalls and monsoons because of their disruption of water supplies. Major outbreaks have occurred in New Delhi, India (30,000 cases in 1955-1956), Burma (20,000 cases in 1976-1977), Kashmir, India (52,000 cases in 1978), Kanpur, India (79,000 cases in 1991), and China (100,000 cases between 1986 and 1988).

Domestic animals have been reported as a reservoir for the hepatitis E virus, with some surveys showing infection rates exceeding 95% among domestic pigs. Transmission after consumption of wild boar meat and uncooked deer meat has been reported as well. The rate of transmission to humans by this route and the public health importance of this are, however, still unclear.

A number of other small mammals have been identified as potential reservoirs: the lesser bandicoot rat (Bandicota bengalensis), the black rat (Rattus rattus brunneusculus) and the Asian house shrew (Suncus murinus). A new virus designated rat hepatitis E virus has been isolated.
An avian virus has been described that is associated with hepatitis-splenomegaly syndrome in chickens. This virus is genetically and antigenically related to mammalian HEV, and probably represents a new genus in the family.

Replicative virus has been found in the small intestine, lymph nodes, colon and liver of experimentally infected pigs.

In 2004, there were two major outbreaks, both of them in sub-Saharan Africa. There was an outbreak in Chad in which, as of September 27, there were 1,442 reported cases and 46 deaths. The second was in Sudan with, as of September 28, 6,861 cases and 87 deaths. Increasingly, hepatitis E is being seen in developed nations, with reports of cases in the UK, US and Japan. The disease is thought to be a zoonosis in that animals are thought to be the source. Both deer and swine have been implicated.

In 2011, a minor outbreak was reported in Tangail, a neighborhood of Dhaka, Bangladesh.

In June 2011, in Mumbai, six pregnant women died due to hepatitis E.

The most recent common ancestor of Hepatitis E evolved between 536 and 1344 years ago. It diverged into two clades - an anthropotropic and an enzootic form - which subsequently evolved into genotypes 1 and 2 and genotypes 3 and 4 respectively. The divergence dates for the various genotypes are as follows: Genotypes 1/2 367 - 656 years ago; Genotypes 3/4 417 - 679 years ago. For the most recent common ancestor of the various viruses themselves: Genotype 1 between 87 and 199 years ago; Genotype 3 between 265 and 342 years ago; and Genotype 4 between 131 and 266 years ago. The anthropotropic strains (genotype 1 and 2) have evolved more recently than the others suggesting that this virus was originally a zoonosis.

The use of an avian strain confirmed the proposed topology of the genotypes 1-4 and suggested that the genus may have evolved 1.36 million years ago (range 0.23 million years ago to 2.6 million years ago). The use of a rat sequence also confirmed this topology and estimated date of divergence from the swine/human strains was 7.44×10⁴ years ago (range 2.1×10⁴ to 1.4×10⁵ years ago). Since this date is approximately coincident with the advent of agriculture it may be that this virus originally infected rats and subsequently spread to pigs and then to
humans. Additional work is required to support or refute this possibility as very few sequences have been isolated from species other than humans and suids.

Genotypes 1, 3 and 4 all increased their effective population sizes in the 20th century. The population size of genotype 1 increased noticeably in the last 30-35 years. Genotypes 3 and 4 population sizes began to increase in the late 19th century up to 1940-1945. Genotype 3 underwent a subsequent increase in population size until the 1960s. Since 1990 both genotypes' population sizes have been reduced back to levels last seen in the 19th century.

The overall mutation rate for the genome has been estimated at \( \sim 1.4 \times 10^{-3} \) substitutions/site/year.

Improving sanitation is the most important measure, which consists of proper treatment and disposal of human waste, higher standards for public water supplies, improved personal hygiene procedures and sanitary food preparation. Thus, prevention strategies of this disease are similar to those of many others that plague developing nations, and they require large-scale international financing of water supply and water treatment projects. A vaccine based on recombinant viral proteins has been developed and recently tested in a high-risk population (military personnel of a developing country). The vaccine appeared to be effective and safe, but further studies are needed to assess the long-term protection and the cost-effectiveness of hepatitis E vaccination.
**Hepatitis F virus**

Hepatitis F is a hypothetical virus linked to hepatitis. Several hepatitis F candidates emerged in the 1990s; none of these reports have been substantiated.

In 1994, Deka et al. reported that novel viral particles had been discovered in the stool of post-transfusion, non-hepatitis A, non-hepatitis B, non-hepatitis C, non-hepatitis E patients. Injection of these particles into the bloodstream of Indian rhesus monkeys caused hepatitis, and the virus was named hepatitis F or *Toga virus*. Further investigations failed to confirm the existence of the virus, and it was delisted as a cause for infectious hepatitis.

A subsequently-discovered virus thought to cause hepatitis was named Hepatitis G virus, though its role in hepatitis has not been confirmed and it is now considered synonymous with GB virus C and is an "orphan virus" with no causal links to any human disease.
GB virus C

**GB virus C (GBV-C)**, formerly known as **hepatitis G virus (HGV)**, is a virus in the *Flaviviridae* family which has not yet been assigned to a genus, is known to infect humans, but is not known to cause human disease. There have been reports that HIV patients coinfected with GBV-C can survive longer than those without GBV-C, but the patients may be different in other ways. There is current active research into the virus’ effects on the immune system in patients coinfected with GBV-C and HIV.

Hepatitis G virus and GB virus C (GBV-C) are RNA viruses that were independently identified in 1995, and were subsequently found to be two isolates of the same virus. Although GBV-C was initially thought to be associated with chronic hepatitis, extensive investigation failed to identify any association between this virus and any clinical illness. GB Virus C is named after the surgeon, G. Barker, who first fell ill in 1966 with a non-A non-B hepatitis which at the time was thought to have been caused by a new, infectious hepatic virus.

GBV-C is a member of the *Flaviviridae* family and is phylogenetically related to hepatitis C virus but appears to replicate primarily in lymphocytes, and poorly if at all in hepatocytes. GBV-A and GBV-B are probably tamarin viruses, while GBV-C infects humans. The GB viruses have been tentatively assigned to a fourth genus within the *Flaviviridae* named “Pegivirus”, but this has yet to be formally endorsed by The International Committee on Taxonomy of Viruses.

Another member of this clade GBV-D has been isolated from a bat (*Pteropus giganteus*). It appears that GBV-D is ancestral to GBV-A and GBV-C.

The mutation rate of the genome has been estimated at $10^{-2}$ to $10^{-3}$ substitutions/site/year.

GBV-C infection has been found worldwide. High prevalence is observed among subjects with the risk of parenteral exposures including those with exposure to blood and blood products, those on hemodialysis, and intravenous drug users. Sexual contact and vertical transmission may occur. ~10–25% of hepatitis C infected patients and 14–36% of drug users who are seropositive for HIV-1 show the evidence of GBV-C infection.
It has been classified into six genotypes and many subtypes with distinct geographical distributions. A seventh has also been described.

Genotype 1 is predominant in Africa and is divided into five subtypes. Genotype 2 has three subtypes and is found in Europe and America. Genotype 3 is the most common in Asia including Japan and China. Genotype 4 is predominant in Southeast Asia and genotype 5 is only seen in South Africa. Genotype 6 has been described in Indonesia.

It has a single stranded positive RNA genome of about 9.3 kb and contains a single open reading frame (ORF) encoding two structural (E1 and E2) and five non-structural (NS2, NS3, NS4, NS5A, and NS5B) proteins.

The majority of immune-competent individuals appear to clear GBV-C viraemia within the first few years following infection and although the time interval between GBV-C infection and clearance of viraemia (detection of GBV-C RNA in plasma) is not known, infection may persist for decades in some individuals.

Approximately 2% of healthy US blood donors are viraemic with GBV-C, and up to 13% of blood donors have antibodies to E2 protein, indicating prior infection.

Parenteral, sexual and vertical transmission of GBV-C have all been documented, and because of shared modes of transmission, individuals infected with HIV are commonly co-infected with GBV-C. Among people with HIV infection, the prevalence of GBV-C viraemia ranges from 14 to 43%.

Some studies have suggested that co-infection with GBV-C will actually slow the progression of HIV disease.
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