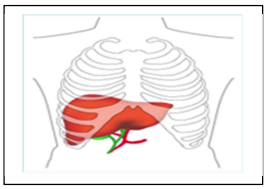
CHAPTER 1



Microbial Pathogenesis of Liver Diseases

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Abstract: Most of the liver disease occurs due to the multifactorial origin and associated with the microbial pathogen, other pathogens and disease states and drug treatments all contributing. Microbial pathogen an important cause of acute-on-chronic liver failure (ACLF). The impact of microbial pathogens on the liver can vary greatly, presenting with a wide variety of manifestations from asymptomatic elevations in aminotransaminases, acute liver failure, hepatic fibrosis, cirrhosis and is accompanied by an increased short-term risk of mortality. The etiology of liver disease can be classified on basis of pathogenesis of microbial agents including viruses, bacteria, fungus and parasites ranging from mild to serious life-threatening infections Pathogenesis of liver illnesses can be caused by a variety of variables such as genetic predisposition, infections, and the environment, necessitating proper diagnosis along with targeted options for treatment. Liver illnesses require substantial research to increase knowledge of disease causes and guide treatment decisions in terms of drug selection and timing.

Key words: Hepatitis, Hepatocellular carcinoma, Liver cirrhosis, steatosis, Acute liver failure, Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Chronic liver disease (CLD), Hepatitis C Virus (HCV) Human Immuno-deficiency Virus (HIV), Epstein Barr Virus (EBV), Herpes Simplex Virus (HSV)

INTRODUCTION: The liver is the largest organ in the body, accounting for around 2% of the body's total weight, which is approximately 1.5 kg in an adult human [1]. The liver is positioned in the right upper quadrant of the abdomen, beneath the right lower rib cage opposite the diaphragm, and projects to a varying extent into the left upper quadrant. Ligamentous attachments to the diaphragm, peritoneum, major arteries, and upper gastrointestinal organs keep the liver in place [2]. It is a cylindrical object with a diameter of 0.8 to 2 millimetres and a length of several millimetres. Between 50,000 and 100,000 separate lobules comprise the human liver. The liver has two main lobes, the right of which is significantly bigger than the left. Further division of these lobes into smaller lobules [1,2].

The liver performs many different functions yet is also a discrete organ, and many of its functions interrelate with one another. This becomes especially evident in abnormalities of the liver, because many of its functions are disturbed simultaneously while there are many causes of liver disease, they generally present clinically in a few distinct patterns, usually classified as hepatocellular, cholestatic (obstructive), or mixed. In hepatocellular diseases such as viral hepatitis or alcoholic liver disease, are the result of liver injury, inflammation, and necrosis predominate [1]. When the liver is exposed to viruses or toxins, it might develop inflammatory

(hepatitis) or fatty (steatosis) alterations, or both (steatohepatitis). The liver disease progresses from acute to chronic at this stage [3].

Liver disease: Acute or chronic diseases that affect the liver are called liver diseases. According to the American Association for the Study of Liver Diseases (AASLD), a patient has acute liver failure (ALF) if they have no history of liver disease, but show signs of blood clotting problems (usually an international normalized ratio above 1.5) and mental changes (encephalopathy) within 26 weeks of getting sick. Some patients, such as those with Wilson's disease, hepatitis B virus from birth, or autoimmune hepatitis, may also have ALF even if they have some scarring of the liver (cirrhosis) as long as their disease has been known for less than 26 weeks [3,5].

(A) Acute liver disease: If something happens to the liver suddenly and Acute liver disease is when a patient has symptoms for less than six months. Usually, the liver cells are inflamed or injured, but they heal without any problems. Sometimes, the injury is very bad and the whole liver stops working. This is called acute liver failure and it can be deadly. Some patients may need a new liver from a donor.

(B) Chronic liver disease: If something is continuing to affect the liver more than six months it is chronic liver disease. It occurs when permanent structural changes within the liver occur secondarily to longstanding hepatocyte damage. The epidemic of chronic liver disease are a major cause of morbidity and mortality and how to combat its complications has been a challenging aspect for many years worldwide [3,4].

Clinical feature of liver diseases: Liver disease can start with inflamation (hepatitis) or fatty (steatosis) in the liver, or both (steatohepatitis). If the liver is not healed, the damage can get worse and cause scarring (fibrosis) and hardening (cirrhosis) of the liver. People with liver disease often feel tired, lose their appetite and weight. They may also have yellow skin and eyes (jaundice), bleeding problems (coagulopathy), confusion (encephalopathy), high blood pressure in the veins of the liver (portal hypertension), swollen veins in the oesophagus or stomach (varices) and fluid in the belly (ascites) [3].

ROLE OF INFECTIOUS AGENT IN LIVER DISEASE:

The liver plays an important role in host defence against invasive microorganisms. Microbial infection is an important cause of acute-on-chronic liver failure (ACLF). The impact of microbial infections on the liver can vary widely, presenting with a wide range of symptoms from asymptomatic aminotransaminase increases to acute liver failure, hepatic fibrosis, and cirrhosis, as well as short-term risk of mortality. Early diagnosis and treatment of microbial infection can significantly lower the mortality rate of ACLF patients [5, 6]. Infectious diseases range from mild to severe infection, including abscesses, parasitic diseases, fungal diseases,

granulomatous diseases, viral hepatitis, and other less common infections. resulting in severe liver dysfunction that can lead to multi-organ failure and death. It can occur in patients without pre-existing liver disease and cause rapid deterioration of liver function within few days [5,6,7].

CLASSIFICATION OF MICROBIAL AGENT CAUSING LIVER DISEASES:

Microbial infections are the most important cause of liver diseases, which progress to acute to chronic stage that results in multi organ dysfunction or failure and is accompanied by an increased short-term risk of mortality. The etiology of liver disease can be classified on basis of pathogenesis of microbial agents including viruses, bacteria, fungus and parasites ranging from mild to serious life-threatening infections [6,7].

PATHOGENESIS OF VIRUSES CAUSING LIVER DISEASES:

Among all the infectious microbial agent viruses are the most common cause of liver diseases in human. Viral infection There are several viruses that can cause hepatitis, fatty liver disease, liver fibrosis, abscess, Malignancy and liver failure.

Hepatitis (A, B, C and E), Cytomegalovirus (CMV), Epstein – Barr Virus (EBV), Herpes virus, Varicella Zoster virus and Parvoviruses are the causative agent of viral hepatitis which as mentioned in table 1.

Virus	Mode of Transmission	Liver Disease	Prophylaxis
Hepatitis A	Ingestion of contaminated food or water (eg, faecal-oral transmission)	Acute liver disease	Vaccination & Immunoglobulin
Hepatitis B	Blood, Sexual, Vertical	cirrhosis and steatosis of the liver and hepatocellular carcinoma	Vaccination, HBIG Interferon & Lamivudine
Hepatitis C	Blood, Sexual, Vertical	cirrhosis and steatosis of the liver and hepatocellular carcinoma (HCC)	Pegylated interferon and ribavirin
Hepatitis D & E	HDV by Blood, Sexual, Vertical and HEV by faecal-oral transmission	HDV cause cirrhosis, HCC and HEV cause Acute liver disease	None
Epstein – Barr virus (EBV)	Oropharyngeal contact	Hepatosplenomegaly	No Vaccination,
Cytomegalovirus (CMV)	Oropharyngeal contact Infected birth canal during delivery	Hepatitis like liver diseases	No-Vaccination, Ganciclovir
Varicella zoster virus	Oropharyngeal contact & Conjunctiva	Hepatitis like liver diseases	Vaccination and Acyclovir
Herpes virus	Abraded skin or Mucosa from any site	Hepatitis like liver diseases	No Vaccination, Acyclovir, Famciclovir
HIV	Blood, Sexual, Vertical	Co infection result in hepatitis, Cirrhosis, hepatomegaly	No vaccination, Anti-retroviral drugs (ART)
Parvoviruses B-19, Adenovirus and Coxsackie B virus	Blood & Vertical	Liver Cirrhosis, hepatomegaly	No vaccination

Table 1. Viral aetiology of liver disease

Viral hepatitis: According to WHO global hepatitis report 2017, Viral hepatitis caused 1.34 million deaths in 2015, a number comparable to deaths caused by tuberculosis and higher than those caused by HIV. However, the number of deaths due to viral hepatitis is increasing over time, while mortality caused by tuberculosis and HIV is declining. Most of the deaths among viral hepatitis in 2015; were due to chronic liver disease (720 000 deaths due to cirrhosis) and primary liver cancer (470 000 deaths due to hepatocellular carcinoma). Globally, in 2015, an estimated 257 million people were living with chronic HBV infection, and 71 million people with chronic HCV infection [8].

1. Hepatitis A: Hepatitis A virus (HAV) is one of the common causes of acute hepatitis and was discovered by Robert H. Purcell in 1973. Humans seem to be the only host for this virus. Hepatitis A viral infection affects about 1.5 million people a year globally especially in low-resource regions. The highest seropositivity (ie, the highest rate of antibody to HAV) is seen in adults in urban Africa, Asia, and South America, where almost everyone has been infected in the past [9, 10].

HAV is a single-stranded, positive-sense, linear RNA enterovirus that belongs to the Picornaviridae family. In humans, viral replication depends on hepatocyte uptake and synthesis, and assembly happens only in the liver cells. The virus is mainly acquired by ingestion (fecal-oral transmission), although rare cases of parenteral transmission have been reported. The incubation period usually lasts 2-6 weeks, and the time to the onset of symptoms may be related to the infective dose. The occurrence and severity of symptoms after HAV infection are directly linked to the patient's age. In developing countries, the age of infection is usually early childhood (before age 2 years). In Western societies, infection is most common in people aged 5 17 years. Within this age range, the illness is more often mild or subclinical; however, severe disease, including acute hepatic failure, does occur at any age. Typical cases of acute HAV infection are marked by several weeks of malaise, anorexia, nausea, vomiting, and elevated transaminases. The period of greatest shedding of HAV is during the anicteric prodrome (14-21 d) of infection and corresponds to the time of transmission is the shown in figure 16.4.1.1.

The primary goal is to control the source of the disease by treating contacts. Long-term secondary goals include immunization, which increases herd immunity and reduces the likelihood of further outbreaks in high-risk communities. Education about transmission and prevention of transmission (eg, hand washing, safe food sources) is also important [9,10].

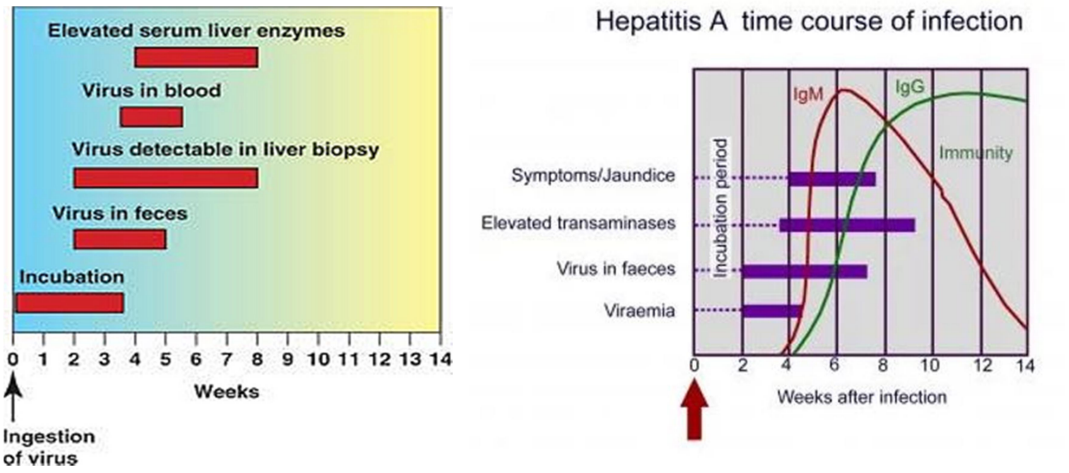

Figure 16.4.1.1 Time course of hepatitis A infection [9, 10]

2. Hepatitis B: HBV is the most common deadly hepatotropic virus worldwide due to its high transmission rate and the potential for progression to a chronic infective carrier state, which can lead to complications such as cirrhosis and hepatocellular carcinoma [11].

WHO estimates that in 2015, 257 million persons and there were 3.5% of population living with chronic HBV infection all over the world, The African and Western Pacific regions accounted for 68% of those infected with HBV [8].

Most HBV infections occur before the age of 5, but the low incidence of chronic HBV infection in children less than 5 years of age can be attributed to the widespread use of the hepatitis B vaccine [8].

HBV is transmitted through exposure to blood or other body fluids of infected persons and sexual intercourse. Vertical transmission is also an important factor in East Asian countries [12, 13].

The pathogenesis of HBV infection in itself does not lead to the death of infected hepatocytes. HBV in a non-cytolytic infection. Among adults with acute HBV infection, up to 65% develop a subclinical infection characterized only by the appearance of one or more viral antibodies in the blood. The remaining 25% develop acute resolving infection, which may or may not include a bout of hepatitis. The remaining 10% of patients develop chronic infection (i.e., the persistence of virus and virus antigens in the blood for more than 6 months). [13].

Persistent HBV infection is characterized by a weak adaptive immune response, which is thought to be due to inefficient CD4+ T cell priming early in the infection and subsequent development of a quantitatively and qualitatively ineffective CD8+ T cell response [12,13].

Further research has shown that CD4+ and CD8+ T cells, natural killer (NK) cells, Fas, various IFNs and corresponding receptors, and the TNF receptor 1 participate in virus clearance. This

contribution of a T cell response appears to clear virus-infected cells by cytolytic mechanisms involving Fas and granzymes. In this context, CD4+ T cells are required to prime CD8+ T cells to facilitate virus elimination in acute infection [15]. When this happens in acute resolving infection, the T cell response to HBV is vigorous, polyclonal and multi-specific. Among those who develop chronic infection, adaptive immunity is relatively weak and narrowly focused. This suggests that clearance of HBV is T cell dependent [15].

Establishment of an effective adaptive antiviral immune response is dependent on CD4+ T cells and their priming early in infection, most likely triggered by the subviral antigens present in the inoculum rather than by the infectious virions. Failure to trigger early CD4+ T cell responses, as occurs in low-dose infections, induces functionally impaired CD8+ T cell responses resulting in the establishment of persistent infection. The inefficient immune response to HBV during chronic HBV infection results in persistent infection, which is characterized by chronic liver cell injury, regeneration, inflammation, widespread DNA damage, and insertional deregulation of cellular growth control genes over long periods of time. Collectively, these lead to fibrosis, cirrhosis and steatosis of the liver and hepatocellular carcinoma [13,14]. HBV can be controlled when properly activated HBV-specific CD8+ T cells enter the liver, recognize antigen, kill infected cells, and secrete IFN-γ which triggers a broad-based cascade that amplifies the inflammatory process and has noncytopathic antiviral activity against HBV sown on figure 1 [13].

Role of HBV proteins:

In the mechanism of pathogenesis, it is also possible that certain HBV proteins hepatitis B surface antigen (HBsAg) HBV precore protein (HBeAg) and HBV X protein may directly participate in chronic liver disease (CLD) development.

HBeAg has been shown to suppress the antibody and T cell response to HBcAg in adult T cell receptor transgenic mice. Thus, HBeAg may suppress immune elimination of infected cells by HBcAg-specific T cells and contribute to viral persistence in chronically infected adults. This is consistent with the clinical observation that viral mutations that preclude the production of HBeAg are often associated with exacerbations of liver disease and sometimes even with viral clearance in chronically infected patients. The hepatitis B surface antigen (HBsAg) might also suppress immune elimination of infected cells by functioning as a high-dose tolerogen since extremely high serum HBsAg titer in the mg/ml range is often seen in chronically infected patients. [13,14].

In addition, HBV X protein, a trans-activation protein of HBV, trans-activates virus gene expression and replication. In human infection, HBx often co-exists with HBe in serum and replication complexes (i.e., with HBcAg) in the liver. Thus, HBx expression is associated with

virus replication. There is evidence to suggest that persistent, high levels of HBV replication correlate with the progression of CLD to HCC [13,14]. Fig. 1

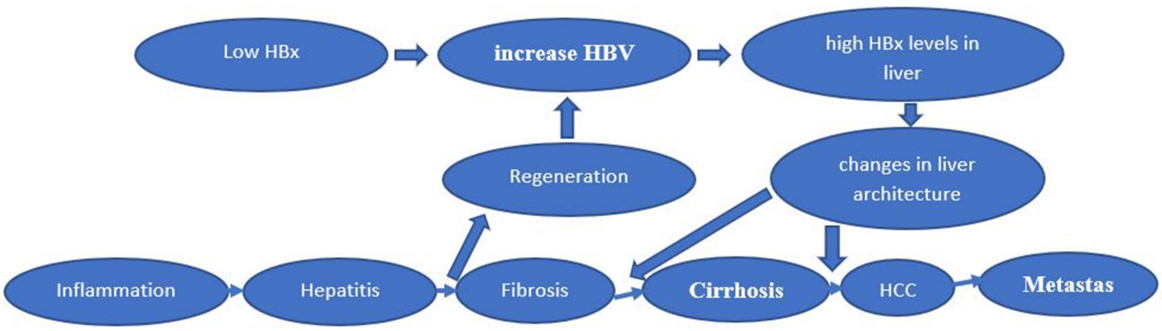

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Figure1: Pathogenesis of Hepatitis B infection in liver disease [53]

3. Hepatitis C: According to the World Health Organization, in 2015 nearly 1% of the world population has been infected with HCV. Therefore, in 2015, 71 million persons were living with chronic HCV infection. Compared with HBV, the prevalence of HCV infection is lower but more heterogeneously distributed. The Eastern Mediterranean Region had the highest prevalence (2.3%), followed by the European Region (1.5%) [8, 16].

HCV is a small enveloped virus that belongs to the Flaviviridae family [8,17]. Its genome is composed of a single-stranded RNA of positive polarity that has two terminal regions, 5'- and 3'untranslated regions, and a single open reading frame that encodes a polyprotein with approximately 3000 amino acids. This polyprotein cleaves at the N-terminal side of three structural proteins, the nucleocapsid (core), envelope 1 (E1) and envelope 2 (E2), which are involved in the architectural organization of HCV. At the carboxyterminal side, the polyprotein cleaves to six non-structural proteins, NS2, NS3, NS4 (NS4A and NS4B), NS5 (NS5A and NS5B) and NS6, which are responsible for the life cycle of the virus. [18].

It is known that the liver is the main site of HCV replication. To enter the host cell, HCV E2 and E1 proteins recognize and bond with the CD81 receptors present on the surface of hepatocytes and lymphocytes [19,20]. After the interaction of the virus envelope with the host cell membrane, HCV enters the cell through endocytosis. In the cytoplasm, messenger RNA undergoes translation, and polyproteins are processed. The HCV RNA then replicates, after which the new viral 'RNA's are packaged and transported to the surface of the host cell so that they can disseminate and complete a new cycle [21]. The HCV replication rate is high,

approximately 1 × 1012 virions per day. Its high mutation rate, estimated at 10-3 nucleotide substitutions per year, leads to great heterogeneity in its presentations, which are known as quasi-species [17]. The selection of host adaptation to HCV quasispecies has given rise to new virus genomic of distinct genotypes [22]. The progression of fibrosis in chronic hepatitis C has been associated with the diversity of HCV quasispecies [23]. The production of new viruses is counterbalanced by the destruction of infected cells through tissue apoptosis or degradation in peripheral blood since the half-life of the virus in peripheral blood is approximately 2.7 hours [7]. Few studies have shown that NS3 and NS5 proteins induce apoptosis in infected hepatocytes [24].

In most cases of human infection, HCV is highly potent and establishes lifelong persistent infection, which progressively leads to chronic hepatitis, liver steatosis, cirrhosis, and hepatocellular carcinoma.

Humoral Immune Response to HCV: Immune response to HCV is responsible for the activation of the hypervariable NS1/E2 region on the surface of the virus, which stimulates B cells to produce high antibody titters of destroying the permanence of the virus [25].

The presence of anti-HCV antibodies is significantly delayed, and antibody detection can first be seen from 7 to 31 weeks after infection [26]. The host applies selective pressure on HCV, and this stimulates high nucleotide variation as well as the appearance of mutations in the envelope proteins, from which the virus selects genomic variants in an attempt to eliminate the site of immune response recognition [27]. The major quantity of HCV quasispecies formed allows the virus to evade the humoral immune response, and the effect of HCV neutralizing antibodies appears to be insufficient to control the infection, which therefore persists [28,29]. The persistence of HCV can be attributed to the large inoculum and the high rate of viral replication, which allow the virus to evade the host immune response resulting in chronic liver damage leading to cirrhosis, hepatic steatosis, and development of hepatocarcinoma. [30,31].

Cell Response to HCV: Since there is a weak humoral immune response to HCV, it is believed that the reactivity of cytotoxic T-lymphocytes (CTLs) or CD8+ T cells is fundamental to viral elimination. CD8+ T cell response to the high viral load that persists in individuals chronically infected with HCV [30, 31]. In addition to CD8+ T cells, CD4+ T cells seem to be involved in the viral damage mediated by the increased expression of MHC class II molecules. Some studies have attributed the vigorous and long-lasting response of CD4+ T cells to the elimination of HCV in the acute form of infection [30,31]. However, the loss of specific CD4+ T cell reactivity to HCV has been associated with the persistence of the virus and the progression of liver damage. The impairment of this reactivity is one of the factors responsible for the chronicity of the infection [26,31,32,67,68]. See fig. 2

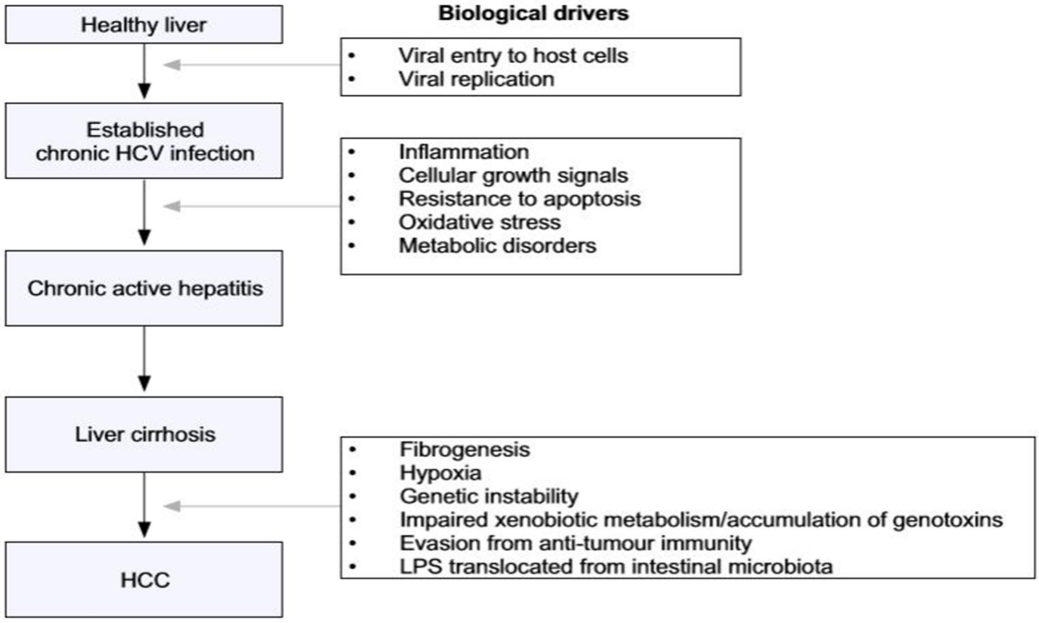

Figure 2 Pathogenesis of Hepatitis C infection in liver disease [33]

There are currently no firm guidelines regarding treatment regimens, treatment duration and timing of its initiation. Monotherapy with high dose interferon α or peg-interferon for 6 months is recommended.

4. Hepatitis D: Hepatitis D virus is caused by an incomplete virus, HDV. It is transmitted mostly through the percutaneous route through contact with infected blood. HDV infects only those persons who already have HBV infection. Infection of an HBV-infected person with HDV (a phenomenon referred to as "superinfection") worsens the outcome of HBV infection. Hence, HDV is a cofactor of chronic liver disease. Most experts estimate that 5% of HBV-infected persons are also coinfected with HDV [34,35]. Vaccination against HBV is also protective against HDV infection [8].

5. Hepatitis E: HEV causes mostly acute hepatitis. It is transmitted via the faecal–oral route, principally via contaminated water. Every year, there are an estimated 20 million HEV infections worldwide, leading to an estimated 3.3 million symptomatic cases of acute hepatitis E [36]. WHO estimates that hepatitis E caused approximately 44,000 deaths in 2015 (accounting for 3.3% of the mortality due to viral hepatitis). Hepatitis E is a usually self-limiting illness, but some patients may progress to acute liver failure. Hepatitis E has a higher case fatality in pregnant women. This leads to devastating maternal mortality. Infection with HEV is reported worldwide, but it is most common in East and South Asia. A vaccine to prevent HEV infection has been developed and is licensed in China but is not yet available in most other countries [8,37].

The virus is most commonly spread by the fecal-oral route through food and/or water contamination, or person-to-person contact, depending on the genotype of the virus,

Pregnant women are at particular risk. This disease is usually self-limiting within two weeks and does not appear to cause chronic infection. The HAV vaccine is also protective against HEV [38,39].

6. Human Immuno-deficiency Virus (HIV): Among 36.7 million persons living with HIV in 2015, an estimated 2.7 million had chronic HBV infection and 2.3 million had been infected with HCV. Liver diseases are a major cause of morbidity and mortality among those living with HIV and coinfected with viral hepatitis [8]. The liver and biliary tracts are frequent sites of involvement during the course of HIV infection [40]. A variety of viral, bacterial, fungal, and other opportunistic infections can manifest with hepatobiliary involvement as either the primary site of infection or secondary to a disseminated process. Coinfection with hepatitis B and C viruses is particularly common due to the shared means of transmission of these viruses with HIV [40]. In HIV infection, AIDS-related liver disease has also been defined as cholangiopathy and cholangitis but not directly demonstrated as causative. Direct involvement by HIV has also been postulated as a possible cause [41]. These people should be diagnosed and provided with appropriate and effective treatment for both HIV and hepatitis as a priority [8].

7. Epstein Barr Virus (EBV): EBV is a member of the herpes virus group and up to 95% of the adult population is seropositive for EBV. The virus typically causes an infectious mononucleosis syndrome (fever, sore throat and lymphadenopathy) in adolescents and young adults who have not had prior exposure. A minority of patients (2–15%) might have gastrointestinal complaints such as nausea and abdominal pain, and less than 5% might have jaundice. On physical examination up to 14% of patients have hepatomegaly and one-half have splenomegaly [6,42,43]. Severe, fulminant hepatitis occurs very rarely and usually in immunosuppressed patients. Despite the infrequency of liver-related complaints and findings observed clinically, most patients with EBV–associated infectious mononucleosis have abnormal liver function tests. Upwards of 90% of patients might have mild elevations of amino transferases (two to three times the upper limit of normal), which typically manifest in the second week of the illness and resolve by six weeks. Mild elevations in alkaline phosphatase (60% of patients) and bilirubin (45%) are also observed, with cholestasis occurring in less than 5% of cases [6,42,43,44,45]. EBV replicates primarily in nasopharyngeal epithelial cells and B lymphocytes. However, infection of hepatocytes by EBV has been demonstrated in patients with post-transplant lymphoproliferative disease [6,46]. The mechanism of liver damage has not been well defined but likely involves the host immune responses to EBV antigens [6].

Treatment for EBV-associated hepatitis is mainly supportive; however, there have been case reports of effective therapy for severe EBV hepatitis in both immunocompetent and post-liver transplant patients [6].

8. Cytomegalovirus: Like EBV, cytomegalovirus (CMV) is a member of the herpes virus family with high (60–100%) seroprevalence rates in adults [6]. CMV also causes an infectious mononucleosis syndrome with concomitant hepatitis. The mononucleosis syndrome caused by CMV in immunocompetent hosts is very similar to EBV-associated illness except splenomegaly is less frequent. Aminotransferase elevations are also common with abnormal AST levels in up to 91% of immunocompetent patients; only 2.8% had a total bilirubin level greater than 2.0 mg/dl [44]. The characteristics of liver biopsies among immunocompetent patients are a sinusoidal and portal lymphocytic infiltrate and granulomas [6,47]. Owl's eye nuclear inclusion bodies may also be found in hepatocytes and bile duct epithelium. [47,48].

The incidence of CMV hepatitis following liver transplantation varies from 2–34% [6,49]. Factors including immunosuppressive regimen, use of antiviral prophylaxis, and donor and recipient serostatus likely contribute to this variability in incidence. A large retrospective study of over 1146 liver transplant recipients between 1988 and 2000 found CMV hepatitis in 24 (2%) patients [6,49].

9. Herpes Simplex Virus (HSV) and other Herpes Viruses: HSV-1 typically causes orolabial infections and HSV-2 causes genital disease among adolescents and young adults [50]. Hepatic involvement with HSV-1 and HSV-2 is rare, and most cases in the medical literature have had acute liver failure. Hence the spectrum of liver involvement during disseminated HSV is not well characterized and may be doubted toward the more severe hepatitis cases. According to a study of the approximately 100 cases described in the literature, less than 10 were described in immunocompetent patients. The risk factor of cases had varying degrees of impaired immunity, including neonates, malnourished children, pregnant women, and patients receiving immunosuppressive medications [51]. Clinical presentation includes fever (82%), severe abdominal pain (33%), concomitant lesions suggestive of HSV (57%), and hepatomegaly (45%). Jaundice was uncommon. The finding of acute liver failure with fever, leukopenia, and thrombocytopenia without jaundice, even in the absence of suspicious mucocutaneous lesions, should arouse suspicion for HSV hepatitis [6,52].

Hepatitis associated with other herpes viruses including HHV-6 and HHV-7 in immunocompromised patients and disseminated varicella-zoster infections have also been reported. Early treatment with acyclovir appears to be associated with improved survival, reinforcing the need to establish the diagnosis promptly [6,52].

10. Yellow Fever: Yellow fever is an arthropod-borne viral haemorrhagic fever syndrome caused by the yellow fever virus. A member of the Flavivirus genus, yellow fever virus is unique among the viral haemorrhagic fevers in its capacity to cause hepatitis and jaundice. The virus is spread by the Aedes species mosquitoes in Africa and the Haemoagogus species in South

America. Person-to-person transmission does not occur. The clinical spectrum of yellow fever ranges from asymptomatic infection (5–50%) to a febrile multisystem haemorrhagic illness. The incubation period is 3–6 days after acquisition of infection [6]. The liver histopathology in YFV infection typically reveals mid-zonal hepatocyte necrosis and injury often with sparing of the central vein and portal tracts, minimal inflammatory cell infiltrates, and preserved reticulin framework. The infected hepatocytes undergo apoptosis with characteristic eosinophilic condensed nuclear chromatin called Councilman bodies [53]. Among patients who develop jaundice, mortality is estimated at 20–50%, usually 7–10 days afterward. The pathogenesis of severe disease is not fully understood. A 17D live-attenuated vaccine is available for the prophylaxis of yellow fever virus infection but is contraindicated in pregnancy and immunosuppressed persons. [6].

11. Dengue Virus: Dengue is an acute, usually self-limited febrile zoonotic illness commonly referred to as "break bone fever." Dengue virus is a flavivirus spread by the mosquito, Aedes aegypti and the disease distribution generally occurs within the vector's distribution largely tropical and subtropical regions of Africa, the Americas, Asia, and Australia. The incubation period ranges from several days to 1–2 weeks. The symptoms and severity of disease vary with age. Classic Dengue presents with fever, severe myalgias, arthralgias, headache, retro-orbital pain, gastrointestinal symptoms and rash. Minor bleeding from mucosal surfaces, hemoptysis and gastrointestinal haemorrhage can occur. In contrast, Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) are characterized by increased vascular permeability, spontaneous haemorrhage, and hypotension. [6,54].

Serum aminotransaminases are increased in the majority of cases (60–80%) and can be accompanied by symptoms of acute hepatitis including right upper quadrant pain, hepatomegaly, and jaundice. Although the presence of hepatic dysfunction generally does not confer a worse prognosis, liver involvement has been reported to be more severe in DHF and DSS and fulminant hepatic failure can occur [6].

Parvovirus B-19, Adenovirus and Coxsackie B virus may also cause a narrow spectrum of liver disease if they persist as primary infection.

B. BACTERIAL INFECTION CAUSING LIVER DISEASE:

Systemic bacterial infections can have an impact on many organs and the liver is one of the most important sites of infection. The bacterial pathogens infecting liver varies according to the site of entry, and could be enteric and usually polymicrobial in nature. The bacterial or pyogenic abscess of liver is thus, classified as per one of the routes of entry such as the biliary tract, portal vein and hepatic artery or by direct extension [55].

The main source of bacterial infection in patients with liver disease is from intestinal bacterial flora. Gram-negative bacteria and Enterococcus are the most common pathogens harbouring liver infection [5]. See table 2

Bacteria	Mode of Transmission	Liver Disease	Lab Diagnosis	Treatment
Gram positive cocci (GPCs)	Ingestion of contaminated food or water Oropharyngeal contact Conjunctiva Abraded skin or Mucosa from any site and fomites	May cause pyogenic liver abscesses in some condition	Gram staining, culture, antibiotic sensitivity testing serology and detection of bacterial nucleic acid by PCR	Vancomycin, linezolid, co trimoxazole, cefdinir and teicoplanin
Enterobacteriaceae	Ingestion of contaminated food or water Oropharyngeal contact Conjunctiva Abraded skin or Mucosa from any site and fomites	May cause pyogenic liver abscesses, liver cirrhosis and Hepatomegaly in some condition	Gram staining, culture, antibiotic sensitivity testing serology and detection of bacterial nucleic acid by PCR	4th generation cephalosporin, Carbapenems, amikacin, tigecycline, Aminoglycosides
***Salmonella enterica* serotype Typhi**	Ingestion of contaminated food or water	Hepatomegaly, splenomegaly	Gram staining, culture, antibiotic sensitivity testing serology and detection of bacterial nucleic acid by PCR	Quinolones, 3th generation cephalosporin,
Helicobacter pylori	Ingestion of contaminated food or water	liver cirrhosis and Hepatocellular carcinoma	Gram staining, culture, antibiotic sensitivity testing serology and detection of bacterial nucleic acid by PCR	Amoxicillin, Clarithromycin and Metronidazole
Brucella species	By ingestion of raw milk or diary product and direct contact with infected animals	Hepatic brucelloma a rare complication	Gram staining, culture, antibiotic sensitivity testing serology and detection of bacterial nucleic acid by PCR	Rifampicin, Streptomycin Doxycycline
Mycobacterium tuberculosis	Air droplet nuclei	Hepatic tuberculosis and Hepatic tuberculous abscesses	Acid fast staining, culture, antibiotic sensitivity testing, detection of bacterial nucleic acid by PCR and GeneXpert	Antituberculosis drugs as per PMDT guidelines
Rickettsia	By arthropod vectors	Bacterial hepatitis	Indirect immunofluorescence assay, PCR and	Penicillin, Doxycycline, Azithromycin, or Ceftriaxone
Spirochaetes	Inhalation of aerosols, sexual contact and Transplacental blood	Involvement of liver may occur in chronic stage of infection cause hepatomegaly and acute liver failure and syphilitic hepatitis'	ELISA Test, RPR, VDRL and PCR for Treponema Pallidum ELISA Western blot and PCR for Borrelia and Leptospira	Penicillin, Doxycycline, Azithromycin, or Ceftriaxone
Pseudomonas aeruginosa	Ingestion of contaminated food or water Oropharyngeal contact Conjunctiva Abraded skin or Mucosa from any site and fomites	May cause pyogenic liver abscesses in some condition	Gram staining, culture, antibiotic sensitivity testing serology and detection of bacterial nucleic acid by PCR	Doxycycline, Penicillin, and 3rd generation Cephalosporin
Yersinia species, Providencia species, Enterobacter species, Citrobacter species, Serratia species	Ingestion of contaminated food or water Oropharyngeal contact Conjunctiva Abraded skin or Mucosa from any site and fomites	May cause Cystic or Mass Lesions of the Liver and also involved in acute hepatitis, Liver abscess, cirrhosis, and hepatomegaly	Gram staining, culture, antibiotic sensitivity testing serology and detection of bacterial nucleic acid by PCR	Doxycycline, 3rd generation cephalosporin and carbapenem

		depends upon the risk factors		

Table 2: Bacterial aetiology of liver disease

a. *Enterobacteriaceae:* *Infections caused by Escherichia coli, Klebsiella pneumoniae, and Proteus vulgaris* that invade the biliary system are the most prevalent cause of liver abscess, hepatomegaly, and progression to ALF. Complicated diverticular disease, appendicitis, peritonitis, and pancreatitis can all induce portal vein pyaemia, which can lead to pyogenic liver abscesses [56]. Symptoms include pyrexia, right upper quadrant discomfort, malaise, and anorexia, as well as painful hepatomegaly in certain instances. Serum biochemistry reveals an increase in bilirubin, alkaline phosphatase, and transaminases. [56,57]. Pyogenic liver abscess is usually polymicrobial because of the ascending route of infection from the gastrointestinal tract [1, 4–6]. Liver abscess caused by *E. coli, Klebsiella pneumoniae, Proteus vulgaris* is a new clinical syndrome that has emerged as an important infectious complication in diabetic patients [58,59].

Escherichia coli and other Enterobacteriaceae are the common bacterium involved in patients in advanced stages of liver cirrhosis and tend to develop bacterial peritonitis without evident source of infection, termed as spontaneous bacterial peritonitis (SBP) [58,60].

Pathogenesis of Microbial Translocation:

Cirrhosis may lead to microbial translocation (MT) via different mechanisms, including small intestinal bacterial overgrowth (SIBO), disturbance of luminal factors, increased permeability of intestinal mucosa, hypochlorhydrias, malnutrition, intestinal and impaired immunity. SIBO has been shown to frequently occur in the setting of chronic liver diseases and to be related to the degree of hepatic dysfunction [61].

The most recent evidence suggests that MT may occur not only in cirrhosis, but also in the early stage of several liver diseases, including hepatopathy and non-alcoholic fatty liver disease.

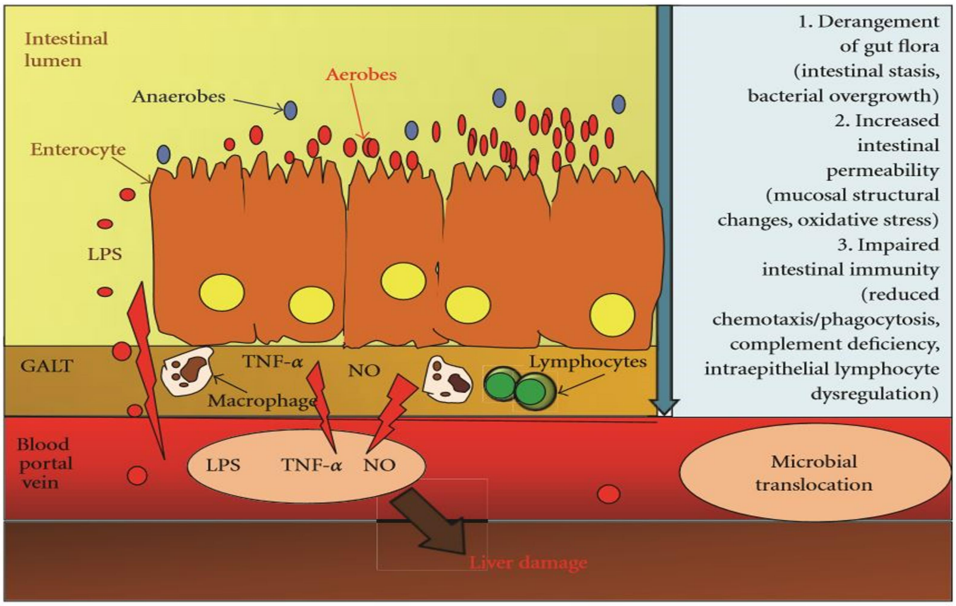

Figure 2: Mechanisms of microbial translocation in chronic liver diseases. LPS: lipopolysaccharide; NO: nitric oxide; GALT: gut-associated lymphatic tissue; TNF-α; tumour necrosis factor. [4]

b. *Salmonella enterica* serotype Typhi: It is the causative agent of typhoid fever, an enteric fever illness that involves an immediate onset of fever and gastrointestinal discomfort. Other clinical signs of typhoid fever, aside from fever and stomach discomfort, are diverse and non-specific, and include headache, relative bradycardia, leukopenia, hepatomegaly, and splenomegaly. Salmonella enters the liver by both hematogenous seeding during bacteraemia and infection of reticuloendothelial system [6].

c. *Helicobacter pylori:* This infection has been linked to a range of human disorders, including liver ailments. The generation of ammonia in intestinal infections caused by *Helicobacter pylori* and portal hypertension-related congestive gastropathy in patients with cirrhotic conditions increases the chance of developing encephalopathy. Helicobacter hepaticus can cause damage to the liver by generating toxins having a granulating impact on liver cell lines, which can then enter the liver in vivo via the portal route and cause hepatocellular damage [61].

d. Brucella species: It causes zoonotic disease in human being called Brucellosis. It is characterized by systemic febrile illness caused by zoonotic infection with Brucella species, which are small, intracellular Gram-negative coccobacilli. The four species responsible for disease in humans and their main domestic animal hosts. The majority of human infections are caused by *B. melitensis*. Exposure to domestic animals is the usual mode of transmission. The hepatitis associated with brucella appears to be mild, with no reports of acute liver failure. In its more severe form, brucella can cause hepatic abscesses, traditionally associated with *B. suis* [6]. Brucelloma is hepatic abscess caused by *Brucella melitensis.* Hepatic brucelloma is a rare complication of brucellosis, causing a range of clinical manifestations [58].

e. *Mycobacterium tuberculosis:* There are a variety of clinical manifestations of hepatic tuberculosis prompting some investigators to further classify the various forms as miliary, granulomatous, and localized hepatic tuberculosis. Miliary or disseminated tuberculosis accounts for 50–80% of cases [62, 63]. The granulomatous disease refers to cases of caseating granulomatous hepatitis and fever that respond to empiric antitubercular therapy. Localized hepatic tuberculosis may occur either with or without biliary involvement. This last form includes hepatic tuberculous abscesses and tuberculomas but occurs in less than 1% of tuberculosis in various case series [6, 64,65].

f. Rickettsia: *Coxiella burnetii* is an intracellular Gram-negative coccobacillus formerly classified as rickettsiae. *Coxiella burnetii* is causative agent of a zoonotic disease known as Q fever worldwide. Many animals are reservoirs of infection with cattle, goats and sheep being the most frequent sources of human infection. Acute Q fever may manifest as a flu–like illness, hepatitis, and pneumonia. Q fever hepatitis is seen in younger patients and may even vary geographically as it appears to be more common among cases reported in southern Europe [6, 63].

g. Spirochaetes: The Leptospira genus of spirochetes causes leptospirosis in humans. It is one of the most widespread zoonotic infections in the world. Human infection is usually acquired through contact with urine from infected animals, most commonly rodents and other small mammals. The involvement of the liver may occur in the chronic stage of infection causing hepatomegaly and acute liver failure [6].

Liver dysfunction in primary or secondary syphilis caused by Treponema pallidum is termed as ‘syphilitic hepatitis’ and is rare. However, this is seen in congenital and tertiary syphilis that typically results from the generalized pathological changes affecting multiple organs. Primary and secondary syphilis are easy to treat with penicillin, doxycycline, azithromycin, or ceftriaxone [58].

Lyme disease caused by Borrelia burgdorferi may also be accompanied by hepatitis, usually manifesting as incidental asymptomatic elevations in aminotransferases but patients presenting with hepatitis as the primary manifestation of Lyme’s disease are extremely rare [6].

h. Others Gram Negative Bacteria causing liver disease: *Pseudomonas aeruginosa, Yersinia species, Providencia species, Enterobacter species, Citrobacter species, Serratia species* etc may cause cystic or mass lesions of the liver and also involved in acute hepatitis, liver abscess, cirrhosis, and hepatomegaly. Most bacterial infections of liver are however, Secondary hepatitis is caused by risk factors such as illness severity, geographical dispersion, immunocompromised status, starvation, and so on [6,7].

i. Gram Positive Bacteria causing liver disease: *Streptococcus* species including *pyogenes* and *pneumoniae, Staphylococcus aureus, Enterococcus species, Listeria monocytogenes* also cause liver disease in some degree of circumstances in humans. They are also common cause of liver abscesses and hepatomegaly. Disseminated Gram positive bacteria in bloodstream may involve in acute liver failure [6,7, 58].

In individuals with liver cirrhosis, the infection incidence for Gram-positive bacteria (mostly Staphylococcus) is growing, as is the development of antibiotic resistance, including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) [5].

C PARASITES CAUSING LIVER DISEASE:

Evaluation of parasitic infections requires a careful clinical history including travel and exposures in order to direct further work-up. Many parasitic infections may cause liver pathology as outlined in **Table 16.5.1** Schistosoma and malaria are two of the most common parasitic infections globally are defined as;

1 *Entamoeba histolytica:* It is endemic worldwide, with an estimated 10% of the world's population being infected. Amoebic liver abscess is the most common extraintestinal complication of amebiasis, occurring in 8.5% of cases. Hepatic infection occurs because colonic trophozoites ascend via the portal vein and invade the parenchyma [67,68]. Patients with amoebic abscess are usually more acutely ill than patients with pyogenic abscess, with high fever and abdominal pain. The amoebicidal therapy is generally highly effective, catheter drainage of amoebic abscess is rarely necessary [7, 67,69].

2. Malaria Parasite (Plasmodium spp.): Malaria is caused by one of four species of the protozoan parasite, Plasmodium: Plasmodium falciparum, Plasmodium vivax, Plasmodium malaria and Plasmodium oval. The WHO estimates that there were 246 million cases of malaria in 2006 which led to close to one million deaths [70]. It is transmitted through the bite of an infected anopheline mosquito. Approximately 60 percent of patients with Plasmodium falciparum or vivax may have hepatomegaly and/or splenomegaly. The reports of jaundice seen with malaria vary greatly, from 2.58–5.3% of patients with falciparum malaria; however, jaundice has been reported in 11–62% of patients during epidemics. The treatment for malaria depends on the species and the prevalence of antimalarial drug resistance in the region malaria was acquired. Chloroquine is the drug of choice for the treatment of malaria [6, 70,71].

3. *Echinococcus granulosus:* *Echinococcus granulosus* is the causative agent of hydatid cyst disease. Humans become infected by ingestion of eggs of the tapeworm E granulosus, either by eating contaminated food or from contact with dogs. The ingested embryos invade the intestinal mucosal wall and proceed to the liver via the portal venous system. Although the liver filters out most of these embryos, those that are not destroyed become hepatic hydatid cysts [7].

Mebendazole therapy, surgical removal and PAIR (puncture, aspiration, injection and re aspiration) are the method of treatment [71].

4. Schistosoma: Schistosoma causes schistosomiasis which remains a significant health risk for travellers to endemic regions. *Schistosoma japonicum, S haematobium, and S mansoni* are the three most important species that infect humans [6]. Hepatic disease is usually caused by S. *mansoni, S japonicum, or S mekongi.* The spectrum and severity of liver disease seen in schistosomiasis varies according to duration of infection and load of the organism. Early in the disease, egg deposition in portal vein tributaries elicits an immune response with granuloma formation, hepatomegaly and splenomegaly. This inflammatory hepatic form of schistosomiasis is usually seen in children. 5 -10% of infected young and middle-aged adults who have been infected for a number of years develop periportal or *Symmers pipestem fibrosis* as a consequence of the chronic inflammation. Hepatic parenchymal perfusion is usually preserved; thus, hepatocyte dysfunction is generally not observed, and lobular architecture remains intact [6,7].

5. Other Parasites: Some other parasites may also cause liver disease in human if not treated at early stage of infection such as *Ascariasis lumbricoides* cause biliary hyperplasia*, Babesia spp.* cause Kupffer cell hyperplasia or infection, *Toxoplasma gondii* cause hepatitis, hepatocyte necrosis**,** *Trypanosoma cruzi* can cause Kupffer cell infection, fatty degeneration and fibrosis, Visceral Leishmania cause Kupffer cell infection, rare noncaseating granulomas, Cryptosporidium spp. cause Biliary strictures, cholangitis, *Fasciola hepatica* cause fibrosis and necrosis, cholangitis, biliary obstruction and biliary cirrhosis, *Strongyloides stercoralis* can cause Periportal inflammation, granulomatous hepatitis and *Toxocara spp.* cause granulomatous hepatitis.

Parasites	**Mode of Transmission**	**Liver disease**	**Lab diagnosis**	**Treatment**
Entamoeba histolytica	Ingestion of contaminated food or water (eg, fecal-oral transmission)	Amoebic liver abscess	Microscopy, Stool culture, ELISA, PCR and Ultrasonography (USG)	Amoebicidal therapy
Malaria Parasite	Transmitted through the bite of an infected anopheline mosquito	Hepatomegaly and splenomegaly	Peripheral blood smear, Rapid Immunochromatographic test, ELISA and PCR	Antimalarial drug however chloroquine is the drug of choice
Echinococcus granulosus	Ingestion of contaminated food of infected dogs contact	Hepatic hydatid cysts disease	Microscopy, ELISA, USG, CT scan, MRI and PCR	Mebendazole Surgical removal and PAIR are the method of treatment
Schistosoma spp	Penetration of skin by larva present in contaminated water	Hepatic disease hepatomegaly	Microscopy, Biopsy, ELISA	Praziquantel
Fasciola	By eating	Liver	Stool microscopy,	Triclabendazole

hepatica	water plant	cirrhosis and liver abscesses	ELISA Western blot technique, PCR, USG and CT scan	and Praziquantel
Others	Ingestion of contaminated food and Transmitted through the bite of an infected vector and Penetration of skin	Fibrosis, Cirrhosis Granulomatous Hepatitis	Stool microscopy, ELISA Western blot technique, PCR, USG and CT scan	Albendazole, Praziquantel

Table 3: Parasitological aetiology of liver diseases

16.7 FUNGI CAUSING LIVER DISEASE:

Fungal infection is a clinical manifestation of disseminated fungal disease in patients with hematologic malignancies or compromise of the immunologic system. The reported prevalence of fungal dissemination in affected patients ranges from 20% to 40%. Few of them often also involve the spleen and, occasionally the kidney. Most hepatic fungal micro abscesses occur in leukaemia patients and are caused by Candida albicans. Other fungus-related diseases include Cryptococcus infection, histoplasmosis, and Mucor mycosis. Sporadic cases of liver infection by Aspergillus species have also been reported [72].

16.7.1 Candida *spp*.: Liver infection with Candida species usually manifests as hepatosplenic candidiasis, a complication of disseminated candida infection that is usually seen among patients with hematologic malignancies who are recovering from a prolonged severe neutropenia. Prior to the more widespread use of antifungal chemoprophylaxis among high-risk patients with hematologic malignancies, the incidence of disseminated hepatosplenic candidiasis in various case series varied from 3–7% [73,74]. The incidence appears to be decreasing with the more widespread use of antifungal prophylaxis among high-risk patients [75,76].

16.7.2 Other fungi causing liver disease: Other fungi may involve the liver and do so in a similar manner to candida, *i.e* during disseminated infection in immunocompromised hosts perhaps accounting for the rarity of hepatic fungal infections in the absence of disseminated disease. Other fungal infections, such as those with endemic mycoses like Histoplasma capsulatum are acquired exogenously and typically disseminate in immunocompromised hosts, most commonly those with AIDS. The disseminated histoplasmosis is a rare event after acute infection, occurring in about 1 in 2000 cases. However, the liver is involved in up to 90% of cases of disseminated histoplasmosis [6,7]. The most common hepatic findings include portal lymphohistiocytotic inflammation and discrete, well-formed granulomas, the latter being seen in approximately 20% of involved livers. In the acute setting, hepatic imaging findings include hepatomegaly and hypoattenuating lymph nodes [6,7]. The pattern of liver involvement is not well characterized and, in one review of 36 cases with hepatic infection, liver involvement was

characterized by hepatomegaly and a more diffuse infiltrative infection; focal lesions were only seen in 17% of cases. When present, the focal lesions were small nodules ranging from 0.2 to 1.0 cm. In this series, the yield of visualizing organisms through special fungal stains, such as methenamine silver staining, was high. Presumably, this occurs through liver seeding during dissemination of infection due to the organisms' affinity for the reticuloendothelial system. The liver biopsy findings are variable and include sinusoidal Kupffer cell hyperplasia and granulomatous changes in 19% of cases [78]. The diagnosis and treatment of disseminated histoplasmosis are reviewed elsewhere [77,78,79]. As hepatic involvement by fungi occurs almost exclusively in the context of disseminated infection in immunocompromised hosts. [6,7].

Summary: Liver disease is one of the most common causes of death worldwide. The increasing trends of microbial liver infection responsible for high morbidity and mortality Liver illnesses can be caused by a variety of causes, including genetic predisposition, infections, and the environment, necessitating proper diagnosis and focused treatment choices. Among others, liver cancer, hepatitis, non-alcoholic fatty liver disease, and end-stage liver disease required substantial research to better our understanding of disease processes and guide treatment decisions in terms of drug selection and timing.

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