MICROBIAL PATHOGENESIS OF LIVER DISEASES IN PRESENT TIME

Abstract

Most of the liver disease occurs due to the multifactorial origin and associated microbial pathogen, some othermicrobial agents and pathophysiological conditions and therapeutics all contributing. Microbialpathogen an important cause of acute-on-chronic liver failure (ACLF). A viral infection is a major cause of acute-on-chronic liver failure (ACLF). The consequences of infectious agents on the liver can vary widely, presenting with an extensive spectrum of manifestations that include asymptomatic increases in aminotransaminases to acute liver failure, hepatic fibrosis, and cirrhosis, as well as a significant short-term risk of death. The aetiology 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.

Keywords: 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)

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I. INTRODUCTION

The liver is the largest vital 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 numerous functions yet is also a distinct organ, and many of its functions are interconnected. This becomes especially noticeable in liver abnormalities because many of its functions are simultaneously disrupted, hepatocellular classified as cholestatic (obstructive), or mixed due to its distinct patterns of liver diseases. In hepatocellular, 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].

II. 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].

1. **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.

2. **Chronic liver disease**: If something is continuing to affect the hepatic cells > 6 considered as chronic liver disease. It happens mostly if the pathophysiological changes persist continuously and degenerating and necrosinghepatocyte. 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 inflammation (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].

III. 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. Infectious diseases range from mild to severe infection [5,6,7].

IV. 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 liver failure subsequently threat to death in a very short time duration. Theetiology 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].

V. 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	Consumption of contaminated water and food (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-contactInfected 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

VI. VIRAL HEPATITIS

According to WHO global hepatitis report 2017 stated that around 1.34 million peoples were lost their life caused by viral hepatitis in 2015 which is higher as compared to HIV. Majority of deaths were due to the chronic liver infection an estimation projected that 720,000 deaths caused by cirrhosis and 470,000 from hepatocellular carcinoma. World widely approximately 257 million people were suffering with chronic Hepatitis B infection and 71 million with Hepatitis C infection [8].

1. **Hepatitis A:** Hepatitis A virus (HAV) is the most 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. Most population of urban South America, Asia and Africa reported highest seropositivity (e.g. the highest rate of antibody to HAV) where nearly everyone has been infected in the past [9, 10].

   HAV is a Picornaviridae family single-stranded, positive-sense, linear RNA enterovirus. In humans, viral replication is dependent on hepatocyte uptake and synthesis, and viral assembly occurs only in liver cells of patients.The virus is mainly acquired by ingestion (fecal-oral transmission), although in rarely mother to child transmission might be occurred. The incubation period usually lasts 2-6 weeks, and the time to the onset of

symptoms may be related to the infective dose. Among low income countries the HAV infection occurs commonly in children mostly in 0 to 2 years age group.

In Western countries, infection is most common in people aged 5 17 years. The range of illness could be mild or subclinical however, severe disease, including acute hepatic failure, does occur at any age. Clinical manifestation of HAV infection includes several weeks of malaise, anorexia, nausea, vomiting, and elevated transaminases. The period of greatest shedding of HAV is during the icteric prodrome (14-21 d) of infection and corresponds to the time of transmission is the shown in figure 1.

The primary goal is to control the source of the disease by treating contacts. Immunization should be secondary aim to minimise the risk of outbreaks. Moreover, education and awareness like safe hygiene practice and food source are also play crucial role in control and prevention of infection[9,10].

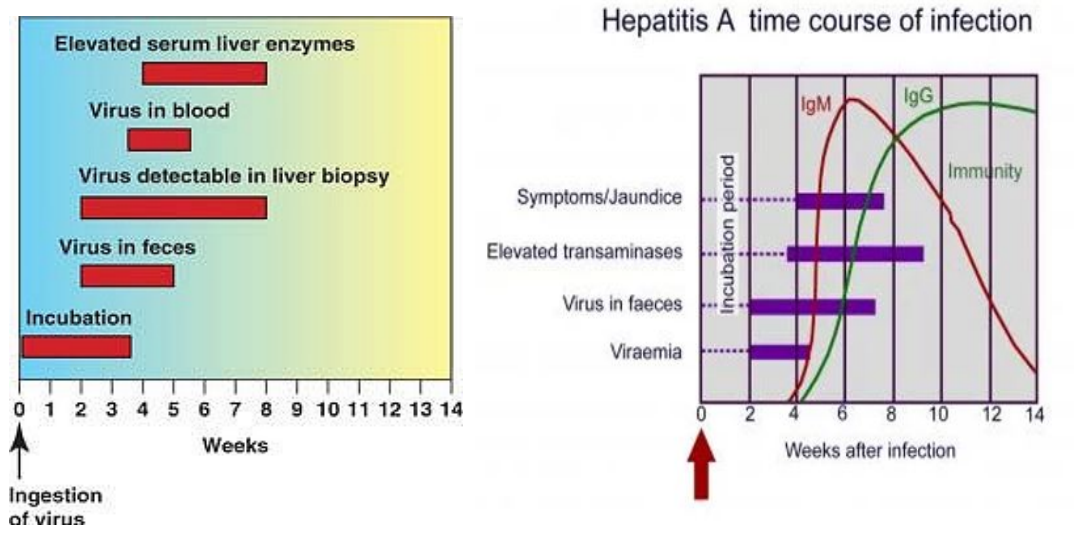

Figure 1: Time course of hepatitis A infection [9, 10]

2. **Hepatitis B:** HBV is the most common deadlyhepatotropic 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, In spite of this HBV infection has low incidence due to the widely distribution of HBV vaccine[8].

The mode of transmission of infection is mainly occur through the exposure of blood and other body fluid of infected person, unsafe sexual intercourse and perinatal transmission mostly seen 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, statistically approximately 65 % subclinical infection defined as the presence of one or more viral antibodies in the patient blood. Around 25 % remaining shows acute resolving infection and other remaining 10% patients develop chronic infection which means presence of virus and it s antigen in patient blood for more than six months[13].

Further research has shown that Various components of the immune system, including CD4+ and CD8+ T cells, natural killer cells, Fas, different interferons, and their receptors, all play a role in eliminating the virus. This indicates that there are multiple pathways that work together to suppress HBV replication in the liver[14,15].
The development of an effective adaptive immune response against viruses relies on CD4+ T cells and their activation early in the infection process. This is likely triggered by subviral antigens in the inoculum, rather than by the infectious virions themselves. If the early CD4+ T cell response is not triggered, as can happen in low-dose infections, the CD8+ T cell response becomes functionally impaired, leading to persistent infection. In chronic HBV infection, the immune response is inefficient, resulting in ongoing infection characterized by chronic liver damage, regeneration, inflammation, widespread DNA damage, and long-term disruption of cellular growth control genes. Collectively, these lead to fibrosis, cirrhosis and steatosis of the liver and hepatocellular carcinoma [13,14]. figure 1 [13].

- **Role of HBV proteins:** In the mechanism of pathogenesis, it is also possible that certain HBV proteinshepatitis B surface antigen (HBsAg) HBV precore protein (HBeAg)andHBV X proteinmay directly participate in chronic liver disease (CLD) development.

  Studies have shown that HBeAg can inhibit the immune response to HBcAg in adult Transgenic mice with T cell receptors. This suggests that HBeAg may prevent the elimination of infected cells by HBcAg-specific T cells, contributing to the persistence of the virus in chronically infected adults. This is supported by clinical observations that viral mutations that prevent the production of HBeAg are often associated with worsening liver disease and, in some cases, viral clearance in chronically infected patients. The hepatitis B surface antigen (HBsAg) may also prevent the elimination of infected cells by acting as a high-dose tolerogen, as high serum levels of HBsAg are often seen in chronically infected patients.

  In addition, the HBV X protein, which activates virus gene expression and replication, is often found in serum and liver replication complexes along with HBe and HBcAg. This suggests that HBx expression is associated with virus replication. There is evidence to suggest that persistent, high levels of HBV replication are correlated with the progression of chronic liver disease to hepatocellular carcinoma[13,14]. Fig. 2

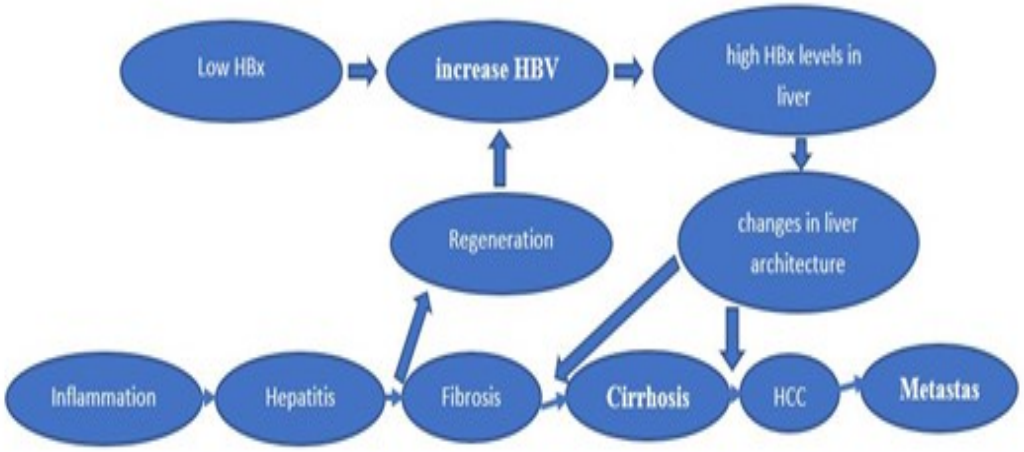

Figure 2: Pathogenesis of Hepatitis B infection in liver disease [53]

3. **Hepatitis C:**As per the WHO data, HCV found to be positiveamong the 1% of the world population in 2015. In comparison to HBV, althoughlower the positivity rate in theHCV infection but it is more unevenly distributed. Eastern Mediterranean Region (2.3%), followed by the European Region (1.5%) had the highest prevalence[8, 16].

HCV is a small, enveloped virus that belongs to the Flaviviridae family [8,17]. Its genetic structure is composed of a positive sense single-stranded RNA that has two terminal regions, 5'- and 3'untranslated regions. There is a single open reading frame which encodes the polyprotein with approx. 300 amino acids. N – terminal of polyprotein cleaves into 3 three structural protein, envelope (E1) 1 and envelope 2 (E2) and the nucleocapsid (core) are included in structural organization of HCV. The Carboxyterminus of polyprotein claves into 6 non-structural protein NS2 to NS4 (NS4A and NS4B) and NS6 are responsible for the life cycle of virus [18].

The liver serves as the primary site for HCV replication. When entering the host cell, HCV E2 and E1 proteins interact with CD81 receptors on the surface of hepatocytes and lymphocytes [19,20]. After the virus envelope binds with the host cell membrane, HCV enters the cell through endocytosis. Inside the cytoplasm, messenger RNA undergoes translation, leading to the processing of polyproteins. Subsequently, the HCV RNA replicates, and the new viral 'RNA's are packaged and transported to the host cell's surface to complete a new cycle [21]. The replication rate of HCV is considerably high, estimated at approximately 1 × 1012 virions per day. Additionally, its mutation rate, which is around 10-3 nucleotide substitutions per year, results in significant heterogeneity, giving rise to quasi-species [17]. Host adaptation to HCV quasispecies selection has led to the emergence of new virus genomics with distinct genotypes [22]. The diversity of HCV quasispecies has been associated with the progression of fibrosis in chronic hepatitis C [23]. To maintain a balance, the progeny of new virus is counteracted through the lysis of infected cell stimulate the tissue apoptosis peripheral blood degradation,as the virus's half-life in peripheral blood is approximately 2.7 hours [7]. Some previous researchsuggests that NS3 and NS5 proteins induce apoptosis in infected hepatocytes [24].

HCV displays a significant potency and persistent infection in most cases. This infection often develops into chronic hepatitis, liver steatosis, cirrhosis, and, ultimately, 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 antibodies shows a significant delay, with detection becoming apparent between 7 to 31 weeks after infection [26]. Exerting pressure on HCVleading to a high nucleotide variation and the emergence of mutations in the envelope proteins. Consequently, the virus selects genetic variationto evade recognition by the immune response [27]. The extensive diversity of HCV quasispecies enables the virus to escape the antibody response, and the impact of HCV neutralizing antibodies seems insufficient to infection control, resulting in its persistence. [28,29]. The immune response invaded by the persistence of HCV extensive replication and viremia resulting in chronic liver damage leading to cirrhosis, hepatic steatosis, and development of hepatocarcinoma. [30,31].

- **Cell Response to HCV:** Due to the observedlack of appropriateantibody response in cases of HCV infection, for viral clearance is thought to lie with cytotoxic T-lymphocytes (CTLs) or CD8+ T cells. These CD8+ T cells react to the continual high viral load that characterizes chronic HCV infection [30, 31]. In conjunction with CD8+ T cells, CD4+ T cells are also implicated in the viral-associated damage, marked by an increase in the expression of MHC class II molecules. there are some studies attributing the vigorous and persistent CD4+ T cell response to the elimination of HCV during the acute infection phase [30, 31]. Nevertheless, the diminishing reactivity of specific CD4+ T cells towards HCV has been linked to both viral persistence and the progression of liver injury. This decline in responsiveness is one of the contributing factors to the establishment of chronic infection [26,31,32,67,68].See fig. 2

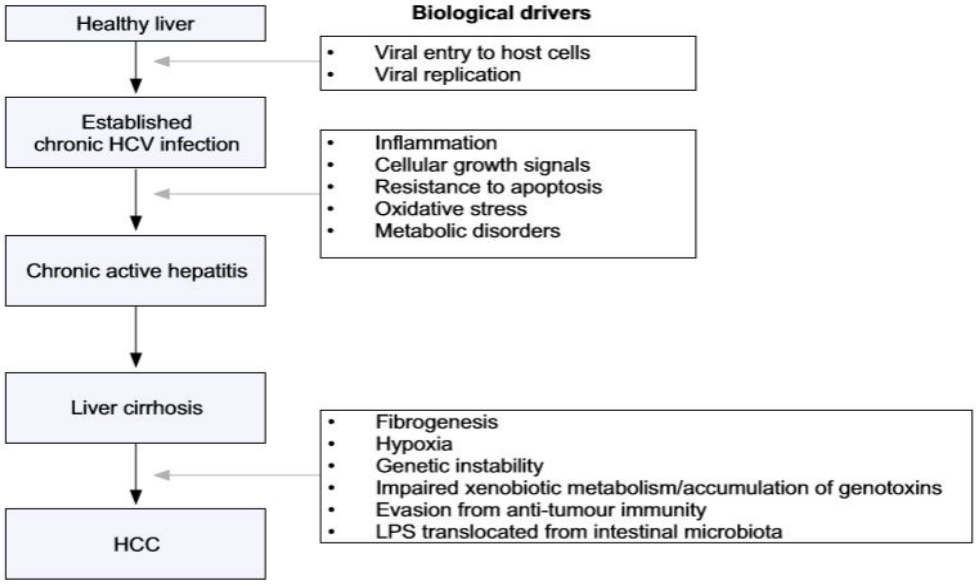

Figure3: Pathogenesis of Hepatitis C infection in liver disease[33]

4. **Hepatitis D:** Virus is also called HDV, stems from an incomplete virus denoted by the same acronym. Its primary mode of transmission is predominantly through the percutaneous route, typically via contact with contaminated blood. It's important to note that HDV exclusively targets individuals who are already afflicted with HBV infection. When an individual already infected with HBV contracts HDV (referred to as "superinfection"), the prognosis of the HBV infection is aggravated. Consequently, HDV plays a role as a contributing factor in the chronic liver disease development. Statistical projections by most experts indicate that approximately 5% of those affected by HBV also experience co-infection with HDV [34, 35]. It's worth highlighting that immunization against HBV also confers protection against HDV infection [8].

5. **Hepatitis E:** Hepatitis E virus (HEV) primarily triggers acute hepatitis. Its transmission occurs through the faecal-oral route, primarily stemming from water sources contaminated with the virus. Each year, approximately 20 million cases of HEV infections are estimated globally, resulting in around 3.3 million instances of symptomatic acute hepatitis E [36]. In 2015, the World Health Organization (WHO) approximated that hepatitis E was responsible for approximately 44,000 deaths, constituting about 3.3% of the total mortality attributed to viral hepatitis. Generally, hepatitis E is a self-limiting illness; however, a subset of patients might progress to acute liver failure. Notably, pregnant women experience a more severe outcome, with higher case fatality rates, contributing to significant maternal mortality. HEV infection has been reported across the world, but it is particularly prevalent in East and South Asia. Notably, a vaccine is also licensed in China and other countries also running trials [8,37].

The virus primarily transmits through the fecal-oral route, consuming contaminated food and/or water, or through direct person-to-person contact. The specific mode of transmission can vary based on the genotype of the virus. Infections can also arise from the consumption of inadequately cooked meat, particularly from animals such as deer or pigs, as well as through the consumption of contaminated shellfish. Pregnant women are

especially vulnerable to this virus. the disease typically resolves on its own within a span of two weeks and tends not to result in chronic infection. Furthermore, it's worth noting that the Hepatitis A virus (HAV) vaccine offers protection against HEV as well. [38,39].

6. **Human Immuno-Deficiency Virus (HIV):** In the year 2015, the count of individuals living with HIV totalled 36.7 million. Among these, an estimated 2.7 million were infected with chronic HBV infection, while 2.3 million had contracted HCV at some point. [8]. Throughout the course of HIV infection, the liver and biliary tracts are frequently affected. This can manifest in various ways, as a range of viral, bacterial, fungal, and opportunistic infections might involve the hepatobiliary system either as the primary site of infection or as a result of a disseminated process. It's important to highlight that co-infection with hepatitis B and C viruses is particularly prevalent, attributed to the shared modes of transmission of these viruses alongside HIV[40].

   In HIV infection, AIDS-related liver disease has also been defined as cholangiopathy and cholangitis. Direct involvement by HIV has also been postulated as a possible cause [41]. Patients with co infection of HIV and hepatitis should be diagnosed timely and treat effectively.[8].

7. **Epstein Barr Virus (EBV):** EBV, a member of the herpes virus group, exhibits a high seropositivity rate in the adult population. This virus typically induces an infectious mononucleosis syndrome, characterized by symptoms such as fever, sore throat, and lymphadenopathy. Adolescents and young adults with no prior exposure are the most susceptible to this syndrome. A few of cases (ranging from 2% to 15%) may experience gastrointestinal symptoms like nausea and abdominal pain, while only 5% might develop jaundice. Upon physical examination, up to 14% of patients exhibit hepatomegaly, and around half of them have splenomegaly [6, 42, 43].

   Severe, fulminant hepatitis stemming from EBV infection is extremely rare and typically presents in individuals with compromised immune systems. Despite the relatively low frequency of clinically observed liver-related symptoms and signs, the majority of patients with EBV-associated infectious mononucleosis exhibit abnormal liver function tests. Slight elevations in alkaline phosphatase (seen in 60% of patients) and bilirubin (observed in 45% of patients) are also noted. Cases of cholestasis are infrequent, occurring in less than 5% of instances [6, 42, 43, 44, 45].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:** Cytomegalovirus (CMV), belonging to the herpes virus family, exhibits high seroprevalence rates in adults, ranging from 60% to 100% [6]. CMV is also responsible for inducing an infectious mononucleosis syndrome accompanied by hepatitis. The mononucleosis syndrome caused by CMV in individuals with intact immune systems closely resembles the illness associated with EBV, although splenomegaly is less commonly observed. Elevated aminotransferase levels are frequently observed, with abnormal AST levels found in as much as 91% of immunocompetent patients; only 2.8% display a total bilirubin level exceeding 2.0 mg/dl [44]. Liver biopsies from immunocompetent patients typically show sinusoidal and portal lymphocytic

infiltration, as well as granulomas [6, 47]. Owl's eye nuclear inclusion bodies may also be detected in hepatocytes and bile duct epithelium [47, 48].

In the context of liver transplantation, the incidence of CMV hepatitis varies widely, ranging from 2% to 34% [6, 49]. Factors such as the immunosuppressive regimen, antiviral prophylaxis, and the serostatus of both the donor and recipient are likely contributors in incidence. of CMV [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].Involvement of the liver by HSV-1 and HSV-2 is a rare occurrence, and the majority of documented cases in medical literature have been associated with acute liver failure. As a result, the complete spectrum of liver involvement in cases of disseminated HSV infection remains poorly understood, with a leaning towards more severe instances of hepatitis. From an approximate total of 100 cases reported in the literature, fewer than 10 have been noted in individuals with intact immune systems. The risk factors for these cases have encompassed various degrees of compromised immunity, including neonates, undernourished children, pregnant women, and patients under immunosuppressive medications [51].

   Common clinical manifestations entail fever (82%), severe abdominal pain (33%), concurrent mucocutaneous lesions indicative of HSV infection (57%), and hepatomegaly (45%). Jaundice, on the other hand, has been less frequently observed. The presence of acute liver failure accompanied by fever, leukopenia, and thrombocytopenia in the absence of jaundice, even without evident mucocutaneous lesions suggestive of HSV, should raise suspicion for HSV hepatitis [6, 52].

10. **Yellow Fever**: Yellow fever is a viral hemorrhagic fever caused by the yellow fever virus, belongs to the Flavivirus genus. Unlike other viral hemorrhagic fevers, it has the unique ability to induce hepatitis and jaundice. The virus is primarily transmitted by Aedes mosquitoes in Africa and Haemagogus mosquitoes in South America.

    The range of clinical manifestations linked to yellow fever varies, ranging from asymptomatic infections (occurring in 5-50% of cases) to a multisystem hemorrhagic fever marked by fever. The incubation period lasts around 3-6 days post exposure to the virus [6].

    Histopathological examination of liver tissues in yellow fever typically reveals mid-zonal hepatocyte necrosis. This damage is often concentrated in the middle region of the liver lobule, while the central vein and portal tracts are generally spared. Infected hepatocytes often undergo apoptosis, characterized by the presence of Councilman bodies - eosinophilic condensed nuclear chromatin [53].Among individuals who develop jaundice as a symptom, mortality rates range from 20% to 50%, typically occurring 7-10 days after the onset of jaundice. The exact mechanism driving severe disease is not yet fully elucidated to prevent yellow fever virus infection, a 17D live-attenuated vaccine is available for the prophylaxis and control [6].

11. **Dengue Virus:** Dengue virus is a flavivirus spread by the mosquito, Aedesaegypti cause the febrile zoonotic illness commonly known as break bone fever disease, The disease's geographical distribution is closely linked to that of its vector, with a prevalence in tropical and subtropical regions of Africa, the Americas, Asia, and Australia.

The clinical presentation and severity of dengue fever are influenced by the patient's age. Classic dengue fever typically manifests with symptoms such as fever, intense muscle, and joint pain (myalgias and arthralgias), headache, retro-orbital pain (pain behind the eyes), gastrointestinal issues, and a rash. In certain cases, minor bleeding from mucous membranes, hemoptysis (coughing up blood), and gastrointestinal hemorrhages can occur. In contrast, there are more severe forms of the disease known as Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). These conditions are marked by increased permeability of blood vessels, leading to spontaneous bleeding and low blood pressure (hypotension) [6,54].

Elevated levels of serum amino transaminases are a common finding in dengue cases (60–80% of cases), often accompanied by symptoms resembling acute hepatitis, such as pain in the right upper quadrant of the abdomen, enlargement of the liver (hepatomegaly), and jaundice. While the presence of hepatic dysfunction generally doesn't necessarily indicate a worse prognosis, liver involvement has been reported to be more severe in cases of DHF and DSS. In rare casesfulminant hepatic failure can occur. Parvovirus B-19, Adenovirus and Coxsackie B virus may also cause a narrow spectrum of liver disease if they persist as primary infection.

VII. 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. There are various bacterial pathogens are responsible for liver infection varies according to the site of involvement. Bacterial associated Liver abscess is one of the common manifestations and enter the liver through the biliary tract,

portal vein and hepatic artery or by direct extension [55] See table-2 for bacterial aetiology of liver infection.

Bacteria	**Mode of Transmission**	**Liver Disease**	**Lab Diagnosis**	**Treatment**
Gram positive cocci (GPCs)	Feco-oral route, 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	May cause pyogenic liver abscesses, liver	Gram staining, culture,	4th generation cephalosporin, Carbapenems,

	Oropharyngeal contact Conjunctiva Abraded skin or Mucosa from any site and fomites	cirrhosis and Hepatomegaly in some condition	antibiotic sensitivity testing serology and detection of bacterial nucleic acid by PCR	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 depends upon the risk factors	Gram staining, culture, antibiotic sensitivity testing serology and detection of bacterial nucleic acid by PCR	Doxycycline, 3rd generation cephalosporin and carbapenem

Table 2: Bacterial aetiology of liver disease

1. **Enterobacteriaceae:** Infections caused by Escherichia coli, Klebsiellapneumoniae, and Proteus vulgaris that invade the biliary system leads to 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,Klebsiellapneumoniae, Proteus vulgaris[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 termed as spontaneous bacterial peritonitis (SBP) [58,60].

- **Pathogenesis of Microbial Translocation:** It has been seen that sometimes microbial translocation may occurs due to the gut bacterial infection or overgrowth 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] [fig 4].

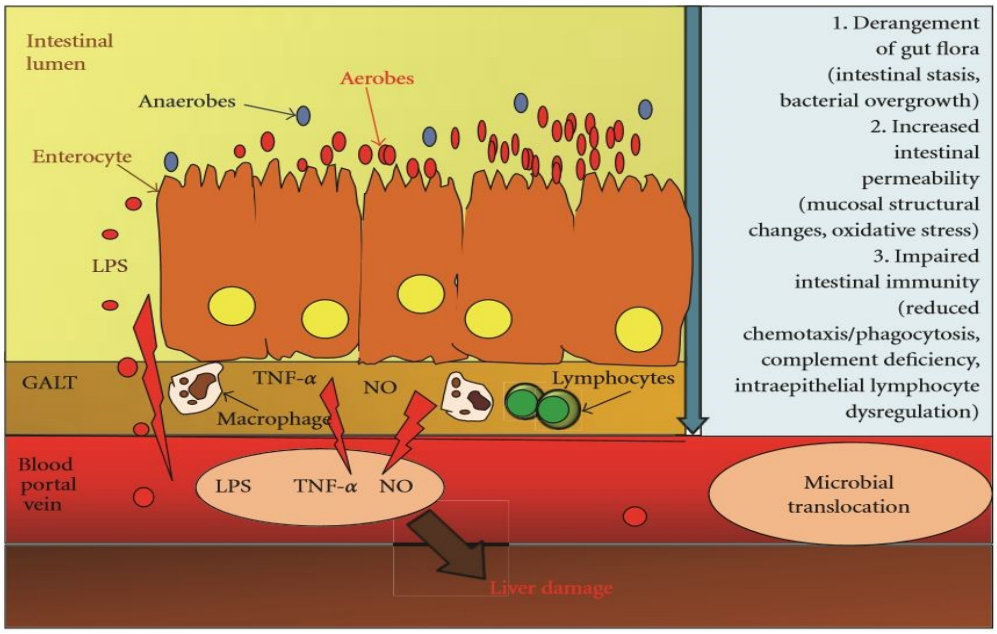

Figure 4: Microbial translocation in the mechanism of chronic liver diseases.; TNF-α; tumour necrosis factor, NO: nitric oxide, LPS: lipopolysaccharide; GALT: gut-associated lymphatic tissue [4].

2. **Salmonella Enterica Serotype Typhi:** It is the causative agent of enteric fevercommonaly known as typhoid fever that involves an immediate onset of fever and gastrointestinal discomfort. Other clinical signs of enteric 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].

3. **Helicobacter Pylori:** This infection refers to a range of human disorders, inclusive of 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].

4. **Brucella Species:** It causes zoonotic disease in human being called Brucellosis characterized as acute febrile illness caused by Brucella spp.There are four species of Brucella responsible for diseases in humans. Bacteria is small, intracellular Gram-negative coccobacilli. The most common agent responsible for human infections is B. melitensis. These infections are typically acquired through exposure to domestic animals.

   Hepatitis linked to Brucella infections is generally considered to be mild, and there are no documented cases of acute liver failure directly attributed to brucellosis. However, in its more severe manifestations, brucellosis can lead to the development of hepatic abscesses. This particular complication is historically associated with the strain B. suis[6].

   A hepatic brucelloma is an abscess that forms in the liver and is caused by the Brucellamelitensis bacterium. This condition is an infrequent complication of brucellosis and can give rise to a variety of clinical symptoms and manifestations [58].

5. **Mycobacterium tuberculosis:** Hepatic tuberculosis can manifest in a range of clinical forms, prompting scientifically categorize them as miliary, granulomatous, and localized forms. [62, 63]. The term "granulomatous disease" is used to describe instances of caseating granulomatous hepatitis accompanied by fever, which typically respond to empirical antitubercular therapy. Localized hepatic tuberculosis can occur with or without involvement of the biliary system. This form encompasses conditions like hepatic tuberculous abscesses and tuberculomas, but it's relatively rare, representing less than 1% of tuberculosis cases based on various case series [6, 64,65].

6. **Rickettsia:** Coxiella burnetii is an intracellular Gram-negativecoccobacillus. It was previously categorized as a member of the rickettsiae group. This microorganism is responsible for causing Q fever, a zoonotic disease worldwide. Several animals act as reservoirs for Q fever infection, with cattle, goats, and sheep being the primary sources of human infections. Acute Q fever can present in various ways, such as resembling a flu-like illness, causing hepatitis (inflammation of the liver), and leading to pneumonia. Q fever-induced hepatitis is commonly observed among younger patients and its prevalence can vary based on geographical regions; it seems to be more frequently reported in cases originating from southern Europe [6,63].

7. **Spirochaetes:** The Leptospira genus of spirochetes causes leptospirosis in humans. Spirochaetes are the most common source of zoonotic infections acquired through rodents or other infected animals in human beings. The liver may occur in the chronic stage of infection causing hepatomegaly and acute liver failure [6].Liver dysfunction associated with Treponema pallidum, the bacterium responsible for syphilis, is referred to as 'syphilitic hepatitis'. This condition is uncommon and primarily occurs in cases of congenital and tertiary syphilis. In congenital syphilis, which is present at birth due to transmission from an infected mother, and tertiary syphilis, which is the late stage of the disease, generalized pathological changes can affect multiple organs, including the liver.These stages can be effectively managed using antibiotics such as penicillin, doxycycline [58].

8. **Others Gram Negative Bacteria causing liver disease:**Pseudomonas aeruginosa, Yersinia species, species, Serratia speciesetc may cause liver abscess, liver abscess,

cirrhosis, and hepatomegaly. Secondary hepatitis is caused by risk factors such as illness severity, geographical dispersion, immunocompromised status, starvation, and so on[6,7].

9. **Gram Positive Bacteria causing liver disease:**Streptococcus species including pyogenes and pneumoniae, Staphylococcus aureus, Enterococcus species, Listeria monocytogenesalso 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 patients diagnosed with liver cirrhosis, there has been a notable rise in the occurrence of infections caused by Gram-positive bacteria, primarily Staphylococcus species. Alongside this increase, there is a concerning trend of escalating antibiotic resistance, encompassing pathogens such as methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE)[5].

VIII. PARASITES CAUSING LIVER DISEASE

Assessing parasitic infections necessitates a meticulous clinical assessment that encompasses an individual's travel history and potential sources of exposureto further work-up. Liver infection caused by parasites enumerate in table 3. The most common parasites are entamoebahistolytica, malaria and schistosomadistributed worldwide as given below in table 3.

1. **Entamoebahistolytica:** It is endemic small outbreaks seen globally, affecting approximately 10% of the world's population. Amoebic liver abscess stands out as the predominant extraintestinal complication of amebiasis, manifesting in around 8.5% of cases. Invasion of the liver occurs as colonic trophozoitesascend through the portal vein and infiltrate the parenchymal tissue [67, 68]. Individuals afflicted with amoebic abscess generally exhibit more acute symptoms compared to those with pyogenic abscesses, often experiencing elevated body temperature and abdominal discomfort. Treatment with amoebicidal agents is commonly effective, with catheter-based drainage of amoebic abscesses being an infrequent necessity[7, 67,69].

2. **Malaria Parasite (Plasmodium spp.):** Malaria is the result of infection by one of four distinct species of the protozoan parasite. There are four common species of Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale caused malaria diseases. According to the World Health Organization (WHO), the year 2006 witnessed an estimated 246 million instances of malaria, which contributed to nearly one million fatalities [70]. Transmission occurs through the bite of a mosquito from the anopheline genus that is infected with the parasite. Roughly 60 percent of patients diagnosed with either Plasmodium falciparum or Plasmodium vivax may exhibit hepatomegaly and/or splenomegaly. The prevalence of jaundice among malaria patients seen considerable variation, ranging from 2.58 to 5.3% for those afflicted with falciparum malaria. Nonetheless, during epidemics, jaundice reports have reached levels of 11 to 62% in affected individuals. The appropriate treatment for malaria hinges on the specific species responsible for the infection and the extent of resistance demonstrated by antimalarial drugs within the geographical area where the malaria is prevalent. Chloroquine is the drug of choice for the treatment of malaria [6, 70,71].

3. **Echinococcusgranulosus:** The causative agent of hydatid cyst disease is Echinococcus granulosus affect the liver.Infection start with the tapeworm Echinococcusgranulosus occurs when its eggs are ingested, often through consumption of contaminated food or via contact with infected dogs. Once ingested, the embryos from these eggs infiltrate the intestinal mucosal lining and then migrate to the liver through the portal venous system. Although the liver effectively filters out the majority of these embryos, any that manage to survive this process give rise to 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]. Schistosoma japonicum, S. haematobium, and S. mansoniare the three most significant species that infect humans [6]. Hepatic disease is commonly caused by S. mansoni, S. japonicum, or S. mekongi. The extent and seriousness of liver disease observed in schistosomiasis can differ based on the duration of infection and the organism's burden.In the early stages of the disease, the deposition of eggs in tributaries of the portal vein leads to an immune response characterized by the formation of granulomas, hepatomegaly (enlargement of the liver), and splenomegaly (enlargement of the spleen). This inflammatory hepatic form of schistosomiasis is typically seen in children.This condition is a result of chronic inflammation. Importantly, hepatic parenchymal perfusion, or blood flow within the liver tissue, generally remains intact in these cases. This means that hepatocyte (liver cell) dysfunction is not commonly observed, and the overall lobular architecture of the liver is preserved [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 lumbricoidescausebiliary hyperplasia, Babesia spp. Cause Kupffer cell hyperplasia or infection,Toxoplasma gondii cause hepatitis, hepatocyte necrosis**,** Trypanosomacruzican cause Kupffer cell infection, fatty degeneration and fibrosis, Visceral LeishmaniacauseKupffer cell infection, rare noncaseating granulomas, Cryptosporidium spp. cause Biliary strictures, cholangitis, Fasciolahepaticacausefibrosis and necrosis, cholangitis, biliary obstruction and biliary cirrhosis, Strongyloidesstercoralis can causePeriportal inflammation, granulomatous hepatitis and Toxocaraspp.causegranulomatous hepatitis.

Parasites	**Mode of Transmission**	**Liver disease**	**Lab diagnosis**	**Treatment**
Entamoebahistolytica	Consumption 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	Hepatomegaly and splenomegaly	Peripheral blood smear, Rapid Immunochrom	Antimalarial drug however chloroquine is the drug of

	anopheline mosquito		atographic test, ELISA,and PCR	choice
Echinococcusgranulosus	Consumption 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
Schistosomaspp.	Penetration of skin by larva present in contaminated water	Hepatic disease hepatome galy	Microscopy, Biopsy, ELISA	Praziquantel
Fasciola hepatica	By eating water plant	Liver cirrhosis and liver abscesses	Stool microscopy, ELISA Western blot technique, PCR, USG and CT scan	Triclabendazole and Praziquantel
Others	Ingestion of contaminated food and Transmitted through the bite of an infected vector and Penetration of skin	Fibrosis, Cirrhosis Granulo matous Hepatitis	Stool microscopy, ELISA Western blot technique, PCR, USG and CT scan	Albendazole,Pra ziquantel

Table 3: Parasitological aetiology of liver diseases

IX. 7 FUNGI CAUSING LIVER DISEASE

The cause of liver involvement is disseminated fungal infections occurs in individuals with hematologic malignancies or compromised immune systems. Occurrence of disseminated fungal infection to range from 20% to 40%. In some cases, these infections also affect the spleen and, on occasion, the kidneys. Among these cases, hepatic fungal micro-abscesses are predominantly observed in patients with leukemia patients commonly affected by Candida albicans and other species.

Other fungal-related conditions encompass Cryptococcus infection, histoplasmosis, and Mucor mycosis. There have been isolated instances of liver infections caused by Aspergillus species as well. [72].

X. SUMMARY

Hepatic illness is an important cause of morbidity and mortality globally. The increasing trends of microbial liver infection responsible for high morbidity and mortality Liver illnesses could be happened by a variety of causes, including mode of infection, co morbidity genetic predisposition, infections severity, 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 diagnosis and guided treatment decisions in terms of drug selection and timing.

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