International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 31, Issue 5, May 2025 ijppr.humanjournals.com ISSN: 2349-7203

The Liver Under Siege: A Comprehensive Review of Metabolic, Viral, Toxic and Structural Hepatic Disorders

S.Ruppana[1]*, Sabbathyan Balla[2], P. Amudha[3]

[1]Department of Pharmacology, C.L Baid Metha college of Pharmacy, Rajiv Gandhi Salai,Old Mahabalipuram Road, Jyothi Nagar,Thoraipakkam Chennai-600097, Tamil Nadu, India.
[2]Professor, Department of Pharmacology, C.L Baid Metha college of Pharmacy, Rajiv Gandhi Salai,Old Mahabalipuram Road, Jyothi Nagar,Thoraipakkam Chennai-600097, Tamil Nadu, India.
[3]Professor, Department of Pharmacology, C.L Baid Metha college of Pharmacy, Rajiv Gandhi Salai,Old Mahabalipuram Road, Jyothi Nagar, Thoraipakkam Chennai-600097, Tamil Nadu, India.

Received: 2025-04-20 Revised: 2025-05-02 Accepted: 2025-05-07

ABSTRACT

Liver diseases comprise a broad spectrum of conditions ranging from non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) to various forms of viral hepatitis (A, B, C, D, E), drug-induced liver injury (DILI), cirrhosis, jaundice, and complications like ascites. These disorders collectively represent a significant global burden, contributing to considerable morbidity and mortality. NAFLD, often linked to metabolic syndrome, obesity, and diabetes, is a silent yet progressive disease that can advance to cirrhosis and hepatocellular carcinoma. ALD, on the other hand, results from chronic excessive alcohol consumption and shares overlapping pathophysiological pathways with NAFLD. Viral hepatitis, especially types B and C, continues to be prevalent in both developed and developing nations, with chronic forms leading to liver failure and cancer. DILI remains a diagnostic and therapeutic challenge due to its unpredictable nature, often mimicking other liver diseases. Liver cirrhosis and fibrosis result from chronic hepatic inflammation and are now understood as potentially reversible with early intervention. This review explores the pathogenesis, diagnosis, and management strategies for major liver diseases, emphasizing the need for early detection, lifestyle modification, pharmacological interventions, and public health measures such as vaccination and safe healthcare practices.

Keywords: Liver disease, NAFLD, alcoholic liver disease, hepatitis, drug-induced liver injury, cirrhosis, jaundice, ascites, pathogenesis, treatment

INTRODUCTION

Liver is largest organ, making up between 2% and 3% of the average body weight, is the liver. The liver's exterior is smooth and its natural hue is brown. In an adult, the liver makes up around 2% of body weight, or roughly 1400 g for females and 1800 g for males[1].

Liver's two lobes are commonly defined using both morphologic and functional anatomy. One protected by the rib cage and held in place by peritoneal reflections known as ligamentous attachments, it is situated underneath the right hemidiaphragm in the right upper quadrant of the abdominal cavity. These attachments, which are avascular and continuous with the Glisson capsule or the liver's visceral peritoneum, are not actually ligaments[2].

The liver carries out the body's regular metabolic equilibrium in addition to biotransforming, detoxifying, and excreting a variety of endogenous and foreign substances including environmental and medicinal compounds. The liver performs over 5,000 vital biological functions, including aiding in blood clotting, detoxifying the blood, converting food into essential nutrients, regulating hormone levels, preventing infections and diseases, promoting healing from injuries, and metabolizing cholesterol, glucose, and iron[3].

Hepatitis, liver cirrhosis, hemochromatosis, benign tumors, liver cancer, Wilson disease, primary sclerosing cholangitis, primary biliary cirrhosis, Budd-Chiari syndrome, and Gilbert's syndrome are among the liver illnesses that frequently cause jaundice. The breakdown of hemoglobin from dead red blood cells, which are normally eliminated by the liver and expelled as bile, produces

bilirubin. Viruses, toxins, autoimmune illnesses, and hereditary disorders can all contribute to liver inflammation. Viral hepatitis, alcohol poisoning, and other toxic chemicals can also result in liver cell death. Specialized clinical investigations can verify proper liver function[4] We will see liver disease in detail in this review article.

Non-Alcoholic Fatty Liver

Patients who deny alcohol consumption may develop non-alcoholic fatty liver disease (NAFLD), a liver disorder that resembles alcohol-induced liver destruction and can progress to end-stage liver disease. From basic steatosis to severe fibrosis and cirrhosis, it encompasses a variety of liver disease. Because of secondary reasons such as medications, hepatotoxins, gastrointestinal surgery, and metabolic/genetic disorders, NAFLD needs to be distinguished from steatosis with or without hepatitis. Alcohol misuse and other liver illnesses with steatosis must be ruled out in order to make the diagnosis. Because NAFLD is so common and can lead to cirrhosis and liver failure, it has significant clinical significant implications[5].

Epidemiologic Features

The comorbid diseases of obesity, type 2 diabetes mellitus, and hyperlipidemia are frequently linked to non-alcoholic fatty liver disease (NAFLD). NAFLD is 4.6 times more common and severe in obese people. Even in healthy people, truncal obesity is a substantial risk factor for NASH. NAFLD is common in numerous racial groups and can impact people of any age. The majority of NAFLD patients are middle-aged women, although the prevalence is higher in men. NASH is being detected in an increasing number of people who do not have these risk factors[5].

Pathogenesis

Importing fatty acids and producing lipids, the liver plays a critical role in lipid metabolism. The pathogenesis of NAFLD is not entirely understood, though. It is unclear what causes hepatocellular injury following triglyceride buildup. Hepatic triglyceride buildup is caused by insulin resistance, which modifies both systemic and local variales. The liver is susceptible to inflammation, fibrosis, and secondary insults as a result of this sensitivity. Adipose tissue hormones, oxidative stress, and gut-derived bacterial endotoxin are among the factors that have been implicated.

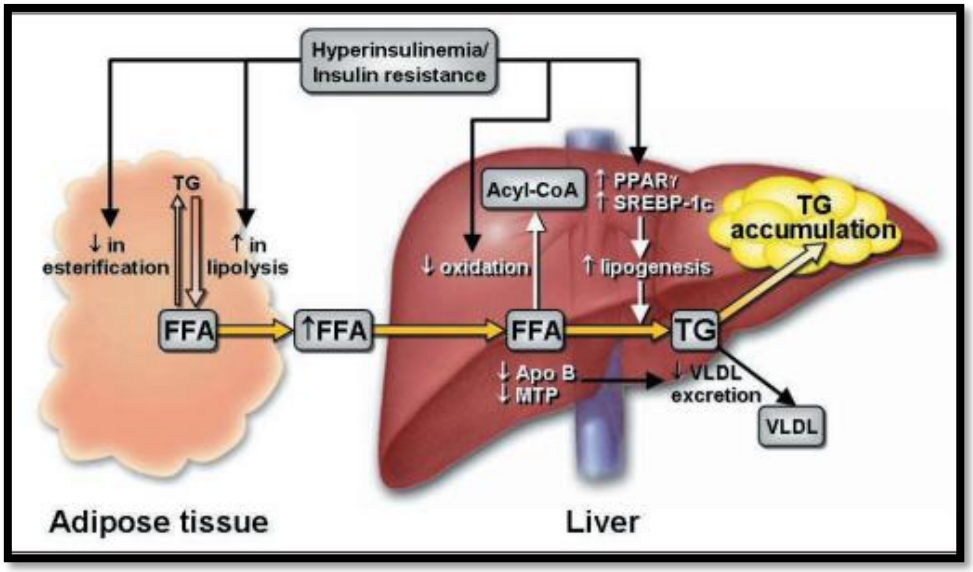


Fig 1: Development of nonalcoholic hepatic steatosis

Nonalcoholic hepatic steatosis development. Insulin resistance prevents free fatty acid (FFA) esterification in adipose tissue and increases triglyceride (TG) lipolysis. Serum FFA levels rise as a result, and the liver absorbs them. Increased FFA intake propels hepatic TG synthesis, which is further supported by insulin-upregulated lipogenic transcription factors like sterol regulatory element binding protein (SREBP)-1c and peroxisome proliferator-activated receptor gamma (PPARγ). Insulin inhibits the alternative oxidation-based metabolism of FFA. Reduced synthesis of apolipoprotein B (apo B) or decreased integration of TG with apo B by microsomal triglyceride transfer protein (MTP) may impede TG export via very-low-density lipoproteins (VLDL)[5,6].

Treatments for Nonalcoholic Fatty Liver Disease

For adults and children with non-alcoholic fatty liver disease (NASH), lifestyle changes like regular exercise, weight loss, and healthy diet are essential to treatment. As an alternative to a western diet, a Mediterranean diet is advised. Although bariatric surgery is only feasible for a small percentage of people, it can be helpful in some situations. Pharmacological treatment is required, and previous clinical studies indicate that vitamin E or pioglitazone may help non-diabetic NASH patients. When lipophilic substances are present, the nuclear receptors in the peroxisomal proliferator activated receptor (PPAR) family detect them and adjust gene expression accordingly. The GOLDEN study investigated the PPARα/δ ligand elafibranor, which seemed to resolve NASH in the segment with more severe disease at baseline. The FLINT trial assessed obeticholic acid, a ligand for the nuclear hormone receptor FXR produced from bile acids, at a dose of 10 mg per day, recently licensed for the treatment of primary biliary cholangitis. Although it has proven to be a useful adjunct in the treatment of type 2 diabetes, altering the glucagon-like-1 (GLP-1) incretin pathway is unlikely to be a significant part of monotherapy[7].

Drug induced liver damage

DILI is the term for liver damage brought on by prescription pharmaceuticals, over-the-counter medications, nutritional supplements, or herbs. Acute liver failure (ALF) and symptomatic increases in liver tests are two possible outcomes. Differentiating between intrinsic (predictable) and idiosyncratic (unpredictable) DILI is necessary for diagnosis. The most prevalent example of predicted DILI is acetaminophen, which has a short latency time and is dose-related. Idiosyncratic DILI is less frequent, has a longer delay, and is unpredictable. Based on liver biochemical markers, DILI can be classified as cholestatic, hepatitic, or mixed. The R ratio, which is the ratio of alanine aminotransferase (ALT) to alkaline phosphatase in relation to their respective upper limits of normal (ULN), is calculated using formulas established by the Food and Drug Administration (FDA) and the Council for International Organizations of Medical Sciences[8].

Drug-induced liver injury (DILI) is a complex condition involving various liver diseases, including hepatitis, cholestatic syndromes, and vascular lesions. The majority of cases involve idiosyncratic drug reactions. Newer agents like tyrosine kinase and tumor necrosis factor α inhibitors are associated with DILI, while telithromycin, troglitazone, and ximelagatran have been withdrawn due to hepatotoxicity. Drug- and host-related characteristics are associated with DILI, with pharmacogenetic factors becoming increasingly relevant. Interactions between drugs and other liver diseases are also better understood. Acetaminophen is the leading cause of acute liver failure in the US. Immediate cessation of the offending drug and supportive care are crucial for improving outcomes[9].

Mechanisms of Drug-induced Liver Injury

Direct medication toxicity or immune-mediated processes may cause DILI. Hepatocyte destruction brought on by direct drug toxicity may be exacerbated by ensuing inflammatory responses. DILI is more common with oral drugs that have a high liver metabolism. Most medications are liposoluble and undergo liver metabolism, where enzymes from the hepatic cytochrome p450 system mediate a phase I reaction as the initial step. Hepatocyte malfunction and cellular death may result from interactions between the intermediate bioactive molecules produced during this process and cellular organelles. In further phase II processes, these potentially hazardous intermediate compounds are rendered inactive by glucurono-, glutathione-, or sulfa-conjugation. Patients who abuse alcohol and consume acetaminophen may accumulate hazardous metabolites as a result of the chemicals that cause the phase II conjugation processes being depleted or lacking. The inhibition of the mitochondrial respiratory chain, which raises reactive oxygen species (ROS) and depletes adenosine triphosphate (ATP), is one of the first things that happens in DILI. Hepatocyte loss, increased hepatic inflammation, and intracellular damage are possible outcomes of this. Another significant mechanism of DILI is immune-mediated harm, which takes a long time to manifest liver toxicity after delivery[10].

Management of DILI

Correct diagnosis, offending agent identification, and withdrawal are all part of DILI management. When ALT > 8 x ULN, ALT > 5 x ULN for three weeks, ALT > 3 x ULN + bilirubin > 2 x ULN, or when liver injury symptoms are present, the drug is discontinued depending on liver enzyme levels. Complete remission or abrupt liver failure and death are possible outcomes. Except for acetaminophen overdose, n acetylcysteine is the only particular antidote now in use. A liver transplant may be necessary for acute liver failure, and the King's College Criteria can be used to predict transplantation and survival[10].

Alcoholic Liver Disease

Chronic alcohol usage is the cause of alcoholic liver disease (ALD), a common liver condition in both Europe and the US. The largest risk of ALD is associated with heavy alcohol use, over 40g daily. The risk of cirrhosis, a late stage of ALD, is increased by

even 12–24 grams of alcohol per day. The duration of alcohol consumption is correlated with the chance of developing cirrhosis. Starting with alcoholic fatty liver (AFL) and moving on to alcoholic steatohepatitis (ASH), ALD has a well-known development pattern. Hepatocellular carcinoma, cirrhosis, and progressive fibrosis can result from this progression. Prevention and treatment require a multidisciplinary strategy that includes surgical, pharmacological, and dietary measures[11].

Pathogenesis

Three processes are involved in the liver's metabolism of alcohol: mitochondrial catalase, cytochrome P-4502E1 (CYP2E1), and alcohol dehydrogenase (ADH). ADH is in charge of lowering alcohol consumption, whereas CYP2E1 is involved in excessive alcohol consumption. Alcoholic liver disease vulnerability may be increased by low stomach ADH activity. Alcohol is converted by both enzymes to acetaldehyde, which contributes to liver damage. Biochemical, genetic, cellular, immunological, and humoral abnormalities are all part of the complicated process of liver injury. Liver injury is caused by oxidative stress, a lack of antioxidants, and a change in the balance of cytokines like TNF-α. Obesity, metabolic syndrome, other liver problems, and individual vulnerability all raise the risk of alcoholism[11].

Liver Cirrhosis

Numerous processes can produce cirrhosis, a liver damage that results in fibrogenesis and necroinflammation. Histologically, it is typified by nodular regrowth encircled by thick fibrotic septa, which distorts the architecture of the hepatic arteries. Hepatic synthetic dysfunction, hypertension, and portal blood flow resistance are the outcomes of this distortion. Although cirrhosis was once thought to be an end-stage condition, new research indicates that it is a dynamic process with a changeable prognosis. The use of non-specific medicines for prevention and early intervention is a novel approach to controlling cirrhosis[12].

Pathophysiology

Hepatic stellate cell activation, inflammation, fibrogenesis, angiogenesis, and parenchymal extinction lesions are all factors in the progression of chronic liver disease to cirrhosis. Hepatic endothelial dysfunction, intrahepatic shunts, sinusoidal remodeling, and hepatic microvascular alterations result from this. The inadequate release of vasodilators, especially nitric oxide, is a hallmark of endothelial dysfunction. The main cause of elevated portal pressure in cirrhosis is increased hepatic resistance to portal blood flow. Portal pressure rises as a result of splanchnic vasodilation, an adaptive reaction to modifications in intrahepatic hemodynamics. Hepatopulmonary syndrome and arterial hypoxemia result from a pulmonary ventilation/perfusion mismatch brought on by systemic vasodilation. Portal hypertensive gastropathy is caused by dilatation of the stomach mucosal vessels. One of the main causes of hepatic encephalopathy, reduced medication first-pass efficacy, and impaired reticuloendothelial system function is the shunting of portal blood to the systemic circulation[12].

ROLE OF CYTOKINES IN LIVER FIBROSIS AND CIRRHOSIS

Strong HSC mitogen PDGF is overexpressed in fibrous tissues and rises in proportion to the severity of liver fibrosis. It causes transcription factors and signal molecules to become active, which in turn causes fibrogenesis and HSC activation. PDGF-D is essential for matrix remodeling because it activates HSCs and has mitogenic and fibrogenic effects. Hepatocytes, KCs, LSECs, and HSCs are the primary producers of TGF-β, a crucial inducer of fibrogenesis in hepatic fibrosis. It inhibits ECM degradation and promotes liver fibrosis by inducing matrix-producing genes and stimulating HSC activation. Monocytes, macrophages, HSCs, and KCs all produce TNF-α, which has cytotoxic and proinflammatory properties. It contributes to ECM formation and HSC activation, however its effects on fibrosis and HSCs are nuanced and contradictory. Blocking TGF-β1/Smad3 signaling has shown therapeutic value for liver fibrosis[13].

Diagnosis

Although cirrhosis requires a histology diagnosis, characteristics suggestive of the condition can now be more easily identified thanks to developments in imaging and laboratory procedures. Ultrasound is an inexpensive, non-invasive, and secure investigative technique, especially when combined with color Doppler imaging. In individuals with jaundice, computed tomography (CT) scanning can be utilized to rule out biliary obstruction as a complementary procedure to ultrasound imaging. Finding localized lesions such as nodular regeneration or hepatic metastases is much easier by magnetic resonance imaging (MRI). Ultrasound is still the first-line test, though. Percutaneous liver biopsy is still the mainstay of diagnosis, and in skilled hands, the risks are minimal. Alternative techniques that enable direct liver viewing and can be used on sedated patients with moderate coagulopathy include blocked liver biopsy, transjugular liver biopsy, and laparoscopic liver biopsy[14].

Management of Liver Cirrhosis (LC)

One of the main causes of Progressive Liver Failure (PEM) in LC patients is poor food intake; when progressive liver failure worsens, daily calorie intake decreases. According to the criteria set forth by the European Society for Clinical Nutrition and Metabolism (ESPEN), an individual should consume 35–40 kcal/kg of body weight and 1.2–1.5 g/kg of body weight daily for energy and protein, respectively. Energy metabolism can be affected by the timing of food consumption; to maintain good energy metabolism, a large number of little meals are suggested. BCAA supplementation may help LC patients recover from decreased protein metabolism and achieve better results since it promotes the skeletal muscles' production of albumin and protein[14].

Hepatitis A

The picornavirus, or enveloped RNA agent, that causes hepatitis A virus (HAV) can infect people with symptoms or without any symptoms. The virus is transmitted through fecal-oral contamination and food sources. Symptoms typically appear in young children, but can increase with age. Most patients recover within two months, but 10 to 15% may experience relapse within six months. Treatment typically involves supportive care, and routine vaccination is recommended for children 12 to 23 months old and certain vulnerable populations[15].

Signs and symptoms

After 28 days of incubation, the illness typically manifests abruptly. Symptoms include nausea, vomiting, diarrhea, fever, headache, weight loss, stomach pain, and a decreased desire to smoke or drink. The majority of children under six years old are asymptomatic and may be an infection source, and the incidence of symptoms increases with age. More than 70% of older children and adults infected with HAV have jaundice. Either two weeks prior to or one week following the onset of symptoms, peak infectivity may occur[16,17].

Immunization

Passive Immunization

Hepatitis A antibody is passively transferred by immunoglobulin. It can be used to prevent exposure before an event depending on the dosage, provides protection for varied lengths of time; nonetheless, the hepatitis A vaccine is typically advised. Immunoglobulin is most frequently used for preexposure prophylaxis for specific travelers or for postexposure prophylaxis under particular conditions. Depending on the dosage, it can provide 80–90% protection for up to five months[18,20].

Active Immunization

The CDC advised immunizing children between the ages of 12 and 23 months in 2006. Inactivated vaccinations are offered in the United States, including the combination vaccine Twinrix and the single-antigen vaccines Havrix and Vaqta. Twinrix is solely meant for active immunization and has a lower amount of HAV. One month after taking the recommended two doses, almost all immunocompetent patients have immunity, which is probably permanent. Adults may have adequate antibody levels for at least 25 years, while children may have them for at least 14 years[19,21].

Hepatitis -B

The double-stranded DNA virus that causes hepatitis B has a genomic size of roughly 3200 bps. Once within a hepatocyte, it transforms into covalently-closed-circular DNA (cccDNA), which is used as a template for viral RNA transcription. Reverse transcription of RNA intermediates to prime DNA synthesis and translation of hepatitis B proteins, such as hepatitis B surface antigen (HBsAg) and e antigen (HBeAg), are components of the virus replication cycle. At least eight primary genotypes of the virus exist, along with sub-genotypes that differ in sequence by at least 4%. Through percutaneous or permucosal exposure to contaminated blood or bodily fluids, it is parenterally spread. Sexual promiscuity, sharing syringes, tattooing, working in healthcare environments, receiving renal dialysis, transfusion of unscreened blood, and prolonged intimate non-sexual contact with an HBsAg-positive person are risk factors for infection. The majority of infections in high-prevalence areas happen during pregnancy or early childhood[22,23,25].

Pathophysiology

Innate and adaptive immune cells eliminate the hepatitis B virus, which appears 45–180 days after infection and is not cytopathogenic. Alongside clinical hepatitis and elevated blood alanine aminotransferase (ALT), there is a cytolytic immune

response that includes hepatocyte necrosis and apoptosis. The identification of infected hepatocytes by virus-specific CD8 cytotoxic T cells is the main mechanism for both virus control and liver injury. Cytotoxic T cells trigger immunological reactions that lead to necroinflammation. Immunoglobulins G and M, HBsAg and its antibody, and HBeAg and its antibody are important indicators for the diagnosis and detection of hepatitis B infection. Innate and adaptive immune cells eliminate the hepatitis B virus, which appears 45–180 days after infection and is not cytopathogenic[22,23,24,25].

Hepatitis-c

The hepatitis C virus (HCV), an RNA virus belonging to the Flaviviridae family, is the cause of the infectious illness hepatitis C. 50–80% of people acquire chronic hepatitis C, and it can cause acute hepatitis C. Liver fibrosis, cirrhosis, hepatocellular cancer, and mortality are the results of a chronic inflammatory disease process brought on by an HCV infection. Even in groups that are challenging to treat, most individuals with chronic HCV infection can be cured using regimens based on direct-acting antiviral agents (DAAs). Patients' quality of life improves throughout DAA medication, and a cure is defined as undetectable HCV RNA levels in the blood. This primer covers the most recent advancements and facets of the global fight against the hepatitis C pandemic in the age of extremely successful treatments in the absence of a preventative vaccine[26].

Pathophysiology

HCV has a diameter of 45–65 nm and is covered in a lipid bilayer. The non-icosahedral nucleocapsid, which houses the about 9.6 kb positive-strand RNA genome, is encased in the envelope. Both structural and non-structural proteins are present in the nucleocapsid. Lipoviroparticles are formed when HCV virions attach to host low-density lipoproteins (LDLs) and very-low-density lipoproteins (VLDLs). Apolipoprotein B (APOB) and other exchangeable apolipoproteins are also present in these lipoviroparticles. According to phylogenetic analysis, there are seven primary genotypes of HCV, making it a diverse virus. The course of the disease and the reaction to antiviral therapy are influenced by the genotype[27,29].

Signs and symptoms

Though a small percentage of people experience symptoms including jaundice, exhaustion, right upper abdomen discomfort, or arthralgia, acute hepatitis C (HCV) infections usually don't cause any symptoms or overt illness. The chronicity rate is lower when acute HCV infection is linked to acute hepatitis C symptoms. Patients may have symptoms including weariness, weight loss, joint and muscle soreness, or discomfort, pain, or itching in the right upper abdomen prior to developing decompensation symptoms.

Diagnostic and monitoring tools

A number of virological techniques, such as third-generation enzyme-linked immunosorbent tests for the detection of anti-HCV antibodies in blood or plasma, are used to diagnose and track HCV infection. These tests are automated, sensitive, specific, and reasonably priced. The serological window between infection and seroconversion, however, varies and might be anywhere from two to eight weeks. Anti-HCV antibodies can last for years or decades in patients who are recovering from a chronic infection. Increasingly, middle-to-low-risk populations are being screened for infections using rapid diagnostic tests. In order to diagnose active infection, select patients who require therapy, assess treatment response, and identify treatment resistance in patients taking DAAs, it is helpful to detect and quantify HCV RNA. HCV RNA is detected and quantified using transcription-mediated amplification techniques or real-time PCR. Determining the HCV genotype and subtype is necessary to provide treatment recommendations. An alternative to HCV RNA assays for infection diagnosis and antiviral therapy monitoring is the HCV core antigen, which is expressed on the HCV nucleocapsid protein[28,29].

Management

Antiviral treatment should only be administered to patients who have a confirmed HCV infection; there is no evidence that hepatitis C should be prevented. More frequently than not, a symptomatic HCV infection with elevated bilirubin and liver enzymes eliminates the virus on its own. IFN monotherapy has been used with greater than 90% success rates. After six weeks of sofosbuvir/ledipasvir treatment, 100% of patients with HCV genotype 1 infection were cured, marking the first success with DAT treatments. Research using the most recent therapy regimen, sofosbuvir/velpatasvir, is underway to determine the quickest course of action and to create a regimen among genotypes. Results are encouraging, at least for individuals with HCV mono infection, even if HCV DAA treatment is not yet approved for acute HCV infection. However, for the time being, participation in prospective clinical studies is preferred to verify efficacy[30].

Chronic hepatitis C

The way chronic Hepatitis C (HCV) infections are treated has changed dramatically with the advent of Drug-Assisted Antiviral Therapy (DAAs). DAAs target three proteins—NS5A protein, NS5B polymerase, and NS3/4A protease—that are essential to the HCV life cycle. Cure rates range from 90 to 100% when these DAAs are used with or without ribavirin. The EASL, AASLD, and IDSA are just a few of the national and international scientific bodies that update their HCV practice guidelines on a regular basis. HCV therapy still requires a customized strategy, with the ideal regimen based on cirrhosis, drug costs, prior treatment experience, virus genotype, and subtype. Elbasvir/grazoprevir in the US, Canada, and Europe, and sofosbuvir/velpatasvir in the US and Europe, are the most recent approved therapy regimens for HCV. Except for patients with pre-existing NS5A RASs and HCV genotype 1a or genotype 4, elbasvir/grazoprevir is administered for 12 weeks. The once-daily fixed-dose combination of sofosbuvir and velpatasvir has a >95% SVR at 12 weeks. With the exception of patients with HCV genotype 3 or Child-Pugh score B, it is administered for 12 weeks without ribavirin[30].

Hepatitis D

The faulty RNA virus that causes hepatitis D, the hepatitis D virus (HDV), needs the hepatitis B virus (HBV) to act as a helper in order to spread in vivo. Only when an HBV infection is present may HDV spread since it only replicates in the liver. The manner of HDV acquisition affects the clinical manifestation and prognosis of acute hepatitis D. In people who test positive for HBsAg, HDV is extremely harmful and can cause severe types of acute hepatitis as well as chronic liver disease. This study examines the clinical aspects of acute and chronic hepatitis D, the shifting epidemiology, and HDV's interactions with other viral diseases[31,32,33].

Acute Hepatitis D

After an incubation period of three to seven weeks, it starts with exhaustion, anorexia, lethargy, and nausea. A decrease in viral replication is followed with an increase in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity, which are biochemical indicators of hepatitis. When clinical symptoms go away, the convalescence phase starts. Because of the intricate interactions between HBV and HDV, the acute illness is typically more severe in the superinfection pattern. Acute liver failure (ALF), a rare consequence of acute viral hepatitis that is more common in HBsAg-positive individuals, can result from HDV superinfection. ALF may start with nausea and malaise, then progress to coagulopathy, hepatic encephalopathy, and jaundice. Because HDV replication is reduced, serum ALT and AST levels may be high or low at presentation. Within two to ten days, individuals might change from a healthy state to almost dying due to the clinical course's frequent rapidity[34,35].

Chronic hepatitis D

Symptoms and Course

Over 90% of instances of acute hepatitis D acquired through the superinfection pattern result in chronic hepatitis D. It is the rarest, most severe, and fastest-growing kind of chronic viral hepatitis at any age. Seventy percent of cases develop cirrhosis within five to ten years, and at a younger age. 15% of individuals develop cirrhosis within 1–2 years of the onset of acute hepatitis D. Although a significant percentage of patients eventually pass away from liver failure or hepatocellular carcinoma (HCC) unless they take OLT, HDV cirrhosis can be a stable condition for many years after it is established. The fast progression of HDV disease to end-stage liver disease and the faulty nature of HDV[36,37,38,39].

Hepatitis E

The hepatitis E virus (HEV), a tiny, nonenveloped virus with a single-stranded RNA genome, is the cause of hepatitis E, a liver illness. Four genotypes of the virus exist; genotypes 1 and 2 only infect humans, whereas genotypes 3 and 4 infect pigs and other mammals. HEV has a noncytopathic appearance, and the host immune response may be the cause of its liver damage. HEV infection is prevalent in unsanitary places and manifests as outbreaks and isolated cases of acute self-limited hepatitis. Those with underlying liver cirrhosis and pregnant women are especially affected. HEV is becoming more widely known in the developed world, where zoonotic transmission is linked to infrequent instances, usually in older males with comorbid conditions[40,41].

Diagnosis

Aspartate aminotransferases and ALT are two examples of serum aminotransferases that are sensitive markers of liver damage. Anti-HEV antibodies are the main basis for diagnosing hepatitis E; IgM indicates a present infection, whereas IgG indicates a previous exposure. High anti-HEV seroprevalence rates, however, indicate that this might not be the best course of action. The sensitivity

and specificity rates of current enzyme immunoassays are insufficient, and while HEV nucleic acid detection by amplification techniques can identify infection, its sensitivity may be compromised by transient viremia and viral shedding.[40,41]

Treatment

The majority of patients with acute or acute-on chronic liver failure don't need special care, but those who do might need liver transplantation, intensive care, and cerebral edema control. Prophylactic injections of uterine-muscle-constricting medications after birth can help reduce the risk of postpartum hemorrhage, which can be increased by pregnancy termination. Pegylated interferon alpha-2a/alpha-2b or ribavirin can be used to treat chronic HEV infection; however, lengthier follow-up studies are required. HEV viremia may go away if immunosuppressive medication dosages are stopped or decreased[42,43].

Ascites

The excess accumulation of intra-peritoneal fluid, referred to as ascites. Based on protein content, ascites is often divided into transudate and exudate. According to the protein composition, ascites is often classified as either transudate or exudate.

The usual cause of transudates (protein < 25 g/L) is increased leakage. Due to increased intravascular pressure, of fluid. This is typically brought on by an underlying systemic disease, including portal hypertension linked to liver cirrhosis or heart failure. Hypo-proteinemia, such as that caused by nephrotic syndrome or protein-losing enteropathy, causes a transudate and lowers oncotic pressure. On the other hand, an exudate is a fluid that is rich in protein (> 25 g/L) and is created as a result of bleeding, infection, inflammation, or neoplasia. In both emergency and outpatient settings, ultrasound (US) is a dependable and accurate diagnostic technique for abdominal indications and symptoms. Its capacity to assess solid intraabdominal organs, such as the liver, gallbladder, kidneys, and reproductive organs, is well known[44].

Technique

Physical examinations can identify ascites, although they are less common in obese persons. With careful technique, trans-abdominal ultrasonography (TAUS) can show fluid amounts. A standard sector transducer is used to routinely examine the viscera of the abdomen and pelvis in the US research. It is crucial to strike a balance between probe frequency and penetration depth. Reducing frequency can improve sight but decrease spatial resolution in people with high BMI. More information can be obtained through further evaluation using a linear high frequency probe[44].

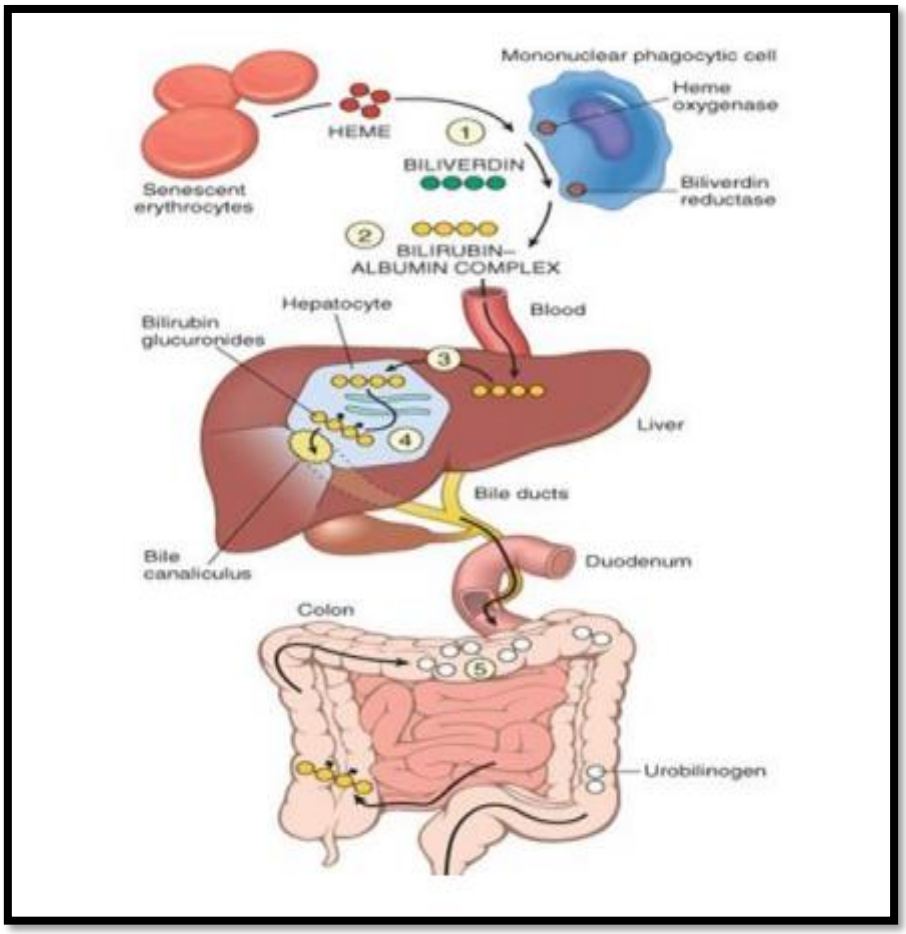
Jaundice

Actually, the name "jaundice" is derived from the French word "jaune," which means "yellow". One The condition known as jaundice is a sign of hyperbilirubinemia. Jaundice manifests clinically when the bilirubin level is higher than 34.2 µmol/L or 2 mg/dL.4.

Heme groups serve as the substrate for the synthesis of bilirubin. The term "jaundice" refers to the yellowing of the skin, mucous membranes, and sclera caused by the accumulation of bilirubin, a yellow-orange bile pigment.

The heme group is responsible for producing bilirubin, which is catabolized by an enzyme heme oxygenase, releasing iron, carbon monoxide, and biliverdin. The remaining 20% comes from sources like myoglobin and cytochromes. Normal adults produce around 250-300 mg of bilirubin daily, with neonates producing significantly more. The bilirubin is transported to the liver in bound form with plasma albumin, where it undergoes conjugation by UDP-glucronyltransferase. The conjugated bilirubin is then excreted into the bile, which is then passed to the duodenum via the biliary system. Some bilirubin is metabolized by intestinal flora into urinobilinogens, which are then removed by the kidney and excreted via the urinary system[45,46,47,48].

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 31, Issue 5, May 2025 ijppr.humanjournals.com ISSN: 2349-7203



Production and metabolism of bilirubin

Types[49,50]

On the basis of causes Jaundice can be classified into

Four types

- Pre-hepatic Jaundice
- Hepatic Jaundice
- Post hepatic Jaundice
- Pre-hepatic Jaundice

Diagnosis

Elevated levels of unconjugated bilirubin in the serum and conjugated bilirubin excreted in the urine are characteristics that differentiate pre-hepatic jaundice from hepatic and post-hepatic jaundice. Five times higher bilirubin levels distinguish hepatic jaundice from pre-hepatic jaundice, whereas diagnostic markers such as alpha-1 Antitrypsin, Ceruloplasmin, and Immunoglobulins can distinguish post-hepatic jaundice. One important diagnosis is post-hepatic jaundice, which is characterized by high conjugation and serum bilirubin levels. Serum bilirubin levels in pancreatic cancer might increase to 40 mg/dL. In malignant blockage, tumor markers such as CA-125, CA19-9, and CEA are typically high. Numerous imaging methods, such as computed tomography, endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, endoscopic ultrasound, magnetic

resonance cholangiopancreatography, cholescintigraphy, radionuclide scanning angiography, and staging laparoscopy, can be used to confirm the diagnosis of obstructive jaundice[51,52,53,54].

Management of Jaundice and its therapeutic approaches

Prehepatic jaundice

Immunoglobulin infusion serves as the main treatment for pre-hepatic jaundice. Phototherapy regarded as a successful treatment for pre-hepatic jaundice caused by elevated bilirubin levels. After phototherapy begins, bilirubin drops sharply after two hours.

However, the degree of hyperbilirubinemia determines the length of therapy and the intensity of light treatment. A potential therapy option for pre-hepatic jaundice is metaloporphyrins, which work by inhibiting the hemeoxygenase enzyme to reduce bilirubin generation[55,56,57].

Hepatic jaundice

Phototherapy is used to treat jaundice in newborns. Although phenobarbital can be used to cure physiological jaundice in newborns, its usage is not common because of certain side effects, including as somnolence and febrile convulsions.

Hepatitis A supportive therapy, which includes rest, fluids, and pain management. Refusing to drink alcohol and stopping drugs that cause liver problems. For autoimmune hepatitis, steroids are used. For autoimmune hepatitis, an immunosuppressive medication is used. For chronic hepatitis B and C, interferon is used. Liver transplantation for end-stage liver failure and fulminant hepatitis[58].

Post hepatic jaundice

Drugs such as dexchlorophenramine, hydroxyzine, cholestyramine, ursodeoxycholic acid, and naltrexone are used to treat and control post-hepatic jaundice[59].

Conclusion:

Liver diseases encompass a wide array of conditions with varied causes, including metabolic dysfunction, alcohol use, viral infections, and drug toxicity. Despite their differences, many of these conditions share overlapping mechanisms such as inflammation, fibrosis, and hepatocyte injury. Non-alcoholic and alcoholic liver diseases, as well as viral hepatitis and drug-induced liver injury, are among the most prevalent and clinically significant forms. Early diagnosis and intervention are key to preventing progression to cirrhosis, liver failure, or cancer.

Advancements in pharmacological treatments, antiviral therapies, imaging, and public health strategies such as vaccination have improved patient outcomes significantly. However, the global burden remains high, particularly in regions with limited healthcare access. A multidisciplinary, prevention-focused approach is essential to reduce liver disease-related morbidity and mortality. With ongoing research and greater awareness, there is strong potential to better manage and eventually reduce the impact of liver diseases worldwide.

Acknowledgement:

Our sincere thanks to Department of Pharmacology, Principle and Management of C.L .Baid Metha College of Pharmacy.

REFERENCES:

1. Abdel-Misih SR, Bloomston M. Liver anatomy. Surgical Clinics. 2010 Aug 1;90(4):643- 53.
2. Sibulesky L. Normal liver anatomy. Clinical liver disease. 2013 Mar 1;2:S1-3. 3. Kalra A, Yetiskul E, Wehrle CJ, Tuma F.
3. Sivakrishnan S, Pharm M. Liver disease overview. World Journal of Pharmacy and Pharmaceutical Sciences. 2019 Jan;8(1):1385-95.
4. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. Journal of hepatology. 2013 Mar 1;58(3):593-608.
5. Angulo P. Nonalcoholic fatty liver disease. New England Journal of Medicine. 2002 Apr 18;346(16):1221-31.
6. Adams LA, Angulo P, Lindor KD. Nonalcoholic fatty liver disease. Cmaj. 2005 Mar 29;172(7):899-905.
7. Neuschwander-Tetri BA. Non-alcoholic fatty liver disease. BMC medicine. 2017 Dec;15:1-6
8. Chitturi S, Farrell GC. Drug-induced liver disease. Schiff's diseases of the liver. 2011 Dec 9:703-83.

9. Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. InMayo clinic proceedings 2014 Jan 1 (Vol. 89, No. 1, pp. 95-106).
10. David S, Hamilton JP. Drug-induced liver injury. US gastroenterology & hepatology review. 2010 Jan 1;6:73.
11. Seitz HK, Bataller R, Cortez-Pinto H, Gao B, Gual A, Lackner C, Mathurin P, Mueller S, Szabo G, Tsukamoto H. Alcoholic liver disease. Nature reviews Disease primers. 2018 Aug 16;4(1):16.
12. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. The Lancet. 2014 May 17;383(9930):1749-61.
13. Zhou WC, Zhang QB, Qiao L. Pathogenesis of liver cirrhosis. World journal of gastroenterology: WJG. 2014 Jun 21;20(23):7312.
14. Williams EJ, Iredale JP. Liver cirrhosis. Postgraduate medical journal. 1998 Apr;74(870):193-202.
15. Centers for Disease Control and Prevention. Hepatitis A FAQs for health professionals. http://www.cdc.gov/hepatitis/HAV/HAVfaq.htm. Accessed June 1, 2012.
16. Gluud LL, Gluud C. Meta-analyses on viral hepatitis. Infect Dis Clin North Am. 2009;23(2):315-330.
17. Hadler SC, Webster HM, Erben JJ, Swanson JE, Maynard JE. Hepatitis A in day-care centers. A community-wide assessment. N Engl J Med. 1980; 302(22):1222-1227.
18. Winokur PL, Stapleton JT. Immunoglobulin prophylaxis for hepatitis A. Clin Infect Dis. 1992:14(2):580-586.
19. Günther M, Stark K, Neuhaus R, Reinke P, Schröder K, Bienzle U. Rapid decline of antibodies after hepatitis A immunization in liver and renal transplant recipients. Transplantation. 2001;71(3):477-479.
20. Tong MJ, Co RL, Bellak C. Hepatitis A vaccination. West J Med. 1993; 158(6):602-605.
21. Quaglio G, Pajusco B, Civitelli P, et al. Immunogenicity, reactogenicity and adherence with hepatitis A vaccination among drug users. Drug Alcohol Depend. 2004;74(1):85-88.
22. Murray JM, Wieland SF, Purcell RH, Chisari FV. Dynamics of hepatitis B virus clearance in chimpanzees. Proceedings of the National Academy of Sciences. 2005 Dec 6;102(49):17780-5.
23. Maini MK, Boni C, Lee CK, Larrubia JR, Reignat S, Ogg GS, King AS, Herberg J, Gilson RAlisa A, Williams R. The role of virus-specific CD8+ cells in liver damage and viral control during persistent hepatitis B virus infection. The Journal of experimental medicine. 2000 Apr 17;191(8):1269-80.
24. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology. 2007 Feb;45(2):507-39.
25. Liaw YF, Chu CM. Hepatitis B virus infection. The lancet. 2009 Feb 14;373(9663):582-92.
26. Burbelo PD, Dubovi EJ, Simmonds P, Medina JL, Henriquez JA, Mishra N, Wagner J, Tokarz R, Cullen JM, Iadarola MJ, Rice CM. Serology-enabled discovery of genetically diverse hepaciviruses in a new host. Journal of virology. 2012 Jun 1;86(11):6171-8.
27. Kapoor A, Simmonds P, Gerold G, Qaisar N, Jain K, Henriquez JA, Firth C, Hirschberg DL, Rice CM, Shields S, Lipkin WI. Characterization of a canine homolog of hepatitis C virus. Proceedings of the National Academy of Sciences. 2011 Jul 12;108(28):11608-13.
28. Lyons S, Kapoor A, Sharp C, Schneider BS, Wolfe ND, Culshaw G, Corcoran B, McGorum BC, Simmonds P. Nonprimate hepaciviruses in domestic horses, United Kingdom. Emerging infectious diseases. 2012 Dec;18(12):1976.
29. Simmonds P. The origin of hepatitis C virus. Hepatitis C virus: from molecular virology to antiviral therapy. 2013:1-5.
30. Manns MP, Buti M, Gane ED, Pawlotsky JM, Razavi H, Terrault N, Younossi Z. Hepatitis C virus infection. Nature reviews Disease primers. 2017 Mar 2;3(1):1-9.
31. Rizzetto M, Canese MG, Arico S, Crivelli O, Trepo C, Bonino F, Verme G. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. Gut. 1977 Dec 1;18(12):997-1003.
32. Rizzetto M, Canese MG, Gerin JL, London WT, Sly DL, Purcell RH. Transmission of the hepatitis B virus-associated delta antigen to chimpanzees. J Infect Dis 1980;141(5):590–602
33. Rizzetto M, Smedile A. Hepatitis D. In: Schiff ER, Sorrell M, Maddrey W, eds. Diseases of the Liver. Philadelphia, PA: Lippincott, Williams and Wilkins; 2002:863–875
34. Taylor J, Farci P, Purcell RH. Hepatitis D (Delta) virus. In: Knipe DM, Howley PM, eds. Field's Virology. 5th ed. Philadelphia, PA: Lippincott, Williams and Wilkins; 2006:3031–3046
35. Lee WM. Acute liver failure. N Engl J Med 1993;329(25): 1862–1872
36. Rizzetto M, Verme G, Recchia S, et al. Chronic hepatitis in carriers of hepatitis B surface antigen, with intrahepatic expression of the delta antigen. An active and progressive disease unresponsive to immunosuppressive treatment. Ann Intern Med 1983;98(4): 437–441
37. Saracco G, Rosina F, Brunetto MR, et al. Rapidly progressive HBsAgpositive hepatitis in Italy. The role of hepatitis delta virus infection. J Hepatol 1987;5(3):274–281
38. Fattovich G, Giustina G, Christensen E, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. The European Concerted Action on Viral Hepatitis (Eurohep). Gut 2000;46(3):420–426.
39. Farci P, Niro GA. Clinical features of hepatitis D. InSeminars in liver disease 2012 Aug (Vol. 32, No. 03, pp. 228-236). Thieme Medical Publishers.

40. King AM, Adams MJ, Carstens EB, Lefkowitz EJ. Virus taxonomy. Ninth report of the International Committee on Taxonomy of Viruses. 2012;9.
41. Okamoto H. Genetic variability and evolution of hepatitis E virus. Virus research. 2007 Aug 1;127(2):216-28.
42. Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. The Lancet. 2010 Jul 17;376(9736):190-201.
43. Kamar N, Rostaing L, Abravanel F, Garrousta C, Esposito L, CardeauDesangles I, et al. Pegylated interferon-alpha for treating chronic hepatitis E virus infection after liver transplantation. Clin Infect Dis 2010; 50:e30-e33
44. Rudralingam V, Footitt C, Layton B. Ascites matters. Ultrasound. 2017 May;25(2):69-79.
45. Abbas MW, Shamshad T, Ashraf MA, Javaid R. Jaundice: a basic review. Int J Res Med Sci. 2016 May;4(5):1313-9.
46. Roche SP, Kobos R. Jaundice in the adult patient. Am Fam Physician. 2004;69(2):299-304.
47. Tiribelli C, Ostrow JD. The molecular basis of bilirubin encephalopathy and toxicity: report of an EASL single topic conference. J Hepatol. 2005;43:156-6.
48. Blanckaert N, Heirwegh KP, Compernolle F. Synthesis andseparation by thin-layer chromatography of bilirubin-IX isomers. Their identification as tetrapyrroles and dipyrrolic ethyl anthranilate azo derivatives. Biochem J. 1976;155(2):405-17.
49. Briggs CD, M Peterson. Investigation and management of obstructive jaundice. Surgery. 2007;25(2):74-80.
50. Roche SP, Kobos R. Jaundice in the adult patient. Am Fam Physician. 2004;69(2):299-304.
51. Lidofsky SD, Kobos R. Jaundice. In: Sleisenger and Fordtrant's Gastrointestinal and Liver Disease. 8ed. Philadelphia, Saunders Elsevier; 2006:301-16.
52. Beckingham IJ, Ryder SD. ABC of diseases of the liver, pancreas and biliary system: investigation of liver and biliary disease. BMJ. 2001;322:33-6.
53. Ryder SD, Beckingham IJ. ABC of diseases of the liver, pancreas and biliary system: other causes of parenchymal liver disease. BMJ. 2001;322:290-2.
54. Kamisako T, Kobayashi Y, Takeuchi K, Ishihara T, Higuchi K, Tanaka Y. Recent advances in bilirubin metabolism research: the molecular mechanism of hepatocyte bilirubin transport and its clinical relevance. J Gastroenterol. 2000;35(9):659-64
55. Schwartz HP, Haberman BE, Ruddy RM. Hyperbilirubinemia: current guidelines and emerging therapies. Pediatric emergency care. 2011 Sep 1;27(9):884-9.-prehepatic
56. Watson R. Hyper bilirubinemia. Crit Care Nurs Clin North Am. 2011;21:97
57. Stevenson D, Wong R. Metalloporphyrins in the management neonatal hyperbilirubinemia. Seminars in Fetal & Neonatal Medicine. 2010;15(3):164-8.
58. Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures - effects on intelligence and on seizure recurrence. N Engl J Med. 1990;322:364-9.
59. Bergasa NV. Medical palliation of the jaundiced patient with pruritus. Gastroenterol Clin N Am. 2006;35:113-23

How to cite this article:
S.Ruppana et al. Ijppr.Human, 2025; Vol. 31 (5): 31-42.
Conflict of Interest Statement: All authors have nothing else to disclose.