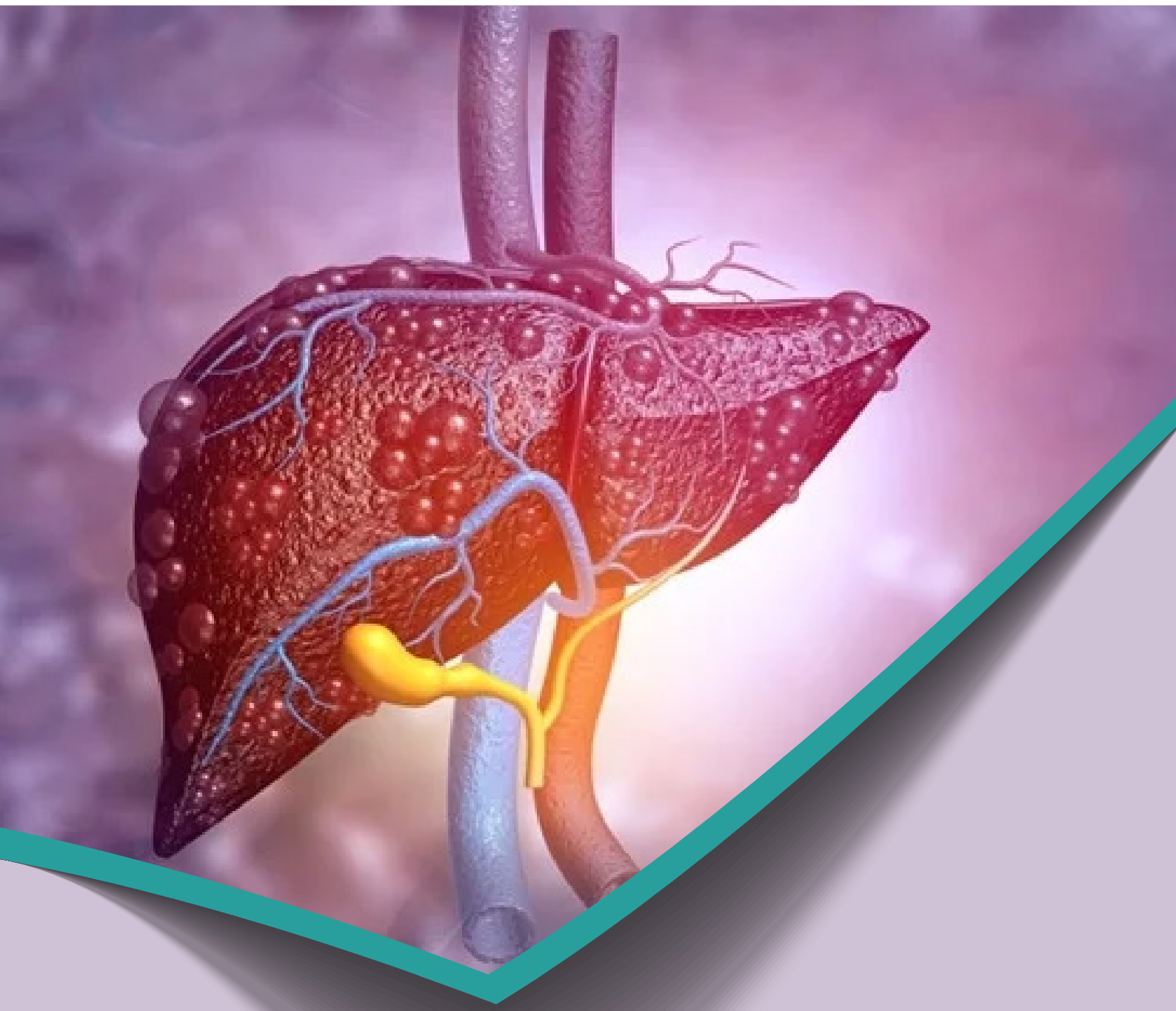

MODULE

Updates on Liver Disorders and Its Management

CONTENT

INTRODUCTION

Liver is the second largest organ in human body, more than 5,000 separate bodily functions including helping blood to clot, cleansing the blood of toxins to converting food into nutrients to control hormone levels, fighting infections and illness, regenerating back after injury and metabolizing cholesterol, glucose, iron and controlling their levels. Most people never give their liver a thought until something goes wrong, yet, liver diseases on rise, affecting one in ten. Liver diseases can be inherited or caused by a variety of factors that damage the liver. In fact, there are many types of liver diseases that can be caused by a virus, damage from drugs or chemicals, obesity, diabetes or an attack from own immune system, when the condition is left untreated, it can become life threatening and can permanently damage the liver or the bile duct. This damage leads to malignancy and cause liver cancer.

UPDATES ON LIVER DISEASES

Liver Diseases

Numerous liver diseases are accompanied by jaundice caused by augmented levels of bilirubin in the body. Bilirubin is the result of degradation of hemoglobin of dead red blood cells which are normally removed by the liver and excreted via bile. In hepatitis, inflammation of the liver, is caused by different viruses, but also some toxic substances, autoimmune diseases and inherited conditions; Liver cirrhosis is the formation of fibrous tissue in the liver to kill hepatocytes, respectively. Liver cell death can be caused by viral hepatitis, alcohol poisoning or other toxic substances; Hemochromatosis is an inherited disorder that causes iron accumulation in the body, leading to long-term liver damage; Benign tumors such as adenoma, "angioma" focal nodular hyperplasia. Liver cancer as the primary tumor or carcinoma cholangiocarcinoma or metastasis of cancer to other parts of the digestive system; Wilson disease is an inherited disorder that causes copper accumulation in the body; Primary sclerosing cholangitis, an inflammatory autoimmune disease carries bile; Primary biliary cirrhosis, autoimmune disease of minute rage ducts; Budd-Chiari syndrome or hepatic vein obstruction; Gilbert's syndrome, a genetic disorder of bilirubin metabolism. There are also many pediatric liver diseases. Proper liver function can be verified by a number of specialized clinical studies, which measure the presence or absence of typical enzymes, metabolites or substances associated with the regular activities.

Acute Liver Failure (Julie Polson et al., 2005)

Acute liver failure occurs when your liver rapidly loses its ability to function. More commonly, liver failure develops slowly over the course of years. But acute liver failure, develops in a matter of days. Acute liver failure can cause many complications, including excessive bleeding and increasing pressure in the brain. Another term for acute liver failure is fulminant hepatic failure. Acute liver failure is a medical emergency that requires hospitalization. Some causes of acute liver failure can be reversed with treatment. But in other situations, a liver transplant may be the only cure for acute liver failure.

Hepatitis (Dienstag JL, 2008)

Hepatitis is swelling and inflammation of the liver. The term is often used to refer to a viral infection of the liver. Hepatitis can be caused by immune cells in the body attacking the liver and causing autoimmune hepatitis, infections from viruses (such as Hepatitis A, B,C, D and E), bacteria or parasites, liver damage from alcohol, poisonous mushrooms or other poisons, medications such as an overdose of acetaminophen, which can be deadly, Liver disease can also be caused by inherited disorders such as cystic fibrosis or hemochromatosis, a condition that involves having too much iron in our body (the excess iron deposits in the liver). Other causes include Wilson's disease (excess copper deposits in the body).

The symptoms of hepatitis include: Abdominal pain or distention, breast development in males, dark urine, pale or clay colored stools, fatigue, usually low-grade fever, general itching, jaundice (yellowing of the skin and eyes), loss of appetite, nausea, vomiting and weight loss.

Hepatitis A

Hepatitis A is an inflammation (irritation and swelling) of the liver from the hepatitis A virus. The hepatitis A virus is found mostly in the stools and blood of an infected person about 15 - 45 days before symptoms occur and during the first week of illness. Symptoms will usually show up 2 - 6 weeks after being exposed to the hepatitis A virus. They are usually mild, but may last for up to several months, especially in adults. Dark urine, fatigue, itching, loss of appetite, low-grade fever, nausea, vomiting, anorexia, malaise(Koff RS,1998[6] & Elisabetta Franco, Cristina Meleleo et al, 2012[7]), pale or clay-colored stools and yellow skin.

Hepatitis B

Hepatitis B is an irritation and swelling (inflammation) of the liver due to infection with the hepatitis B virus (HBV). Hepatitis B spread by contact with the blood or body fluids (such as semen, vaginal fluids, and saliva) of a person who has the virus. Symptoms of hepatitis B may not appear for up to 6 months after the time of infection. Early symptoms include loss of appetite, fatigue, low fever, muscle and joint aches, nausea and vomiting, jaundice, dark urine right upper quadrant pain and hepatomegaly (Lee W, 1997[8]).

Hepatitis C

Hepatitis C is a viral disease that leads to swelling (inflammation) of the liver. Hepatitis C infection is caused by the hepatitis C virus (HCV). Hepatitis C spreads by contact with the blood of someone who has hepatitis C. The following symptoms may occur with hepatitis C infection like pain in the right upper abdomen, abdominal swelling due to fluid (ascites), clay-colored or pale stools, dark urine, fatigue, fever, itching, jaundice, loss of appetite, nausea and vomiting.

Delta Agent (Hepatitis D)

Delta agent is a type of virus called hepatitis D. It causes symptoms only in people who also have a hepatitis B infection. Hepatitis D virus (HDV) is found only in people who carry the hepatitis B virus. HDV may make a recent (acute) hepatitis B infection or an existing long-term (chronic) hepatitis B liver disease which is worse. It can even cause symptoms in people who carry hepatitis B virus but who never had symptoms. Risk factors include abusing intravenous (IV) or injection drugs, being infected while pregnant (the mother can pass the virus to the baby), carrying the hepatitis B virus, men having sexual intercourse with other men, receiving many blood transfusions. Symptoms may include abdominal pain, dark-colored urine, fatigue, jaundice, joint pain, loss of appetite, nausea and vomiting.

Hepatitis E

Hepatitis E is inflammation of the liver caused by infection with hepatitis E virus. It is one of five known human hepatitis viruses. A,B,C,D and E. Heapatitis E Virus is a positive –sense, single stranded non enveloped RNA icosahedral virus. HEV is predominantly transmitted by faecal contamination of drinking water as a result of poor sanitation.(WHO. Hep. E Fact Sheet. 2017[9] & Khuroo MS & Khuroo NS et al, 2016[10]) other routes of transmission include consumption of contaminated food, such as raw or undercooked meat (eg: pork and shellfish) derived from infected animals (Coloson P, Borentain P et al. 2010[11], Lewis Hc, Wichmann O et al, 2010[12], Li TC, Chijiwa K et al. 2005[13] & Berto A, Martelli F et al, 2012[14]). and through transfusion of infected blood products which is more common in highly endemic areas. (Khuro MS, Kamili S et al, 2004[15]). Symptoms may include jaundice, malaise, anorexia nausea, vomiting, abdominal pain, hepatomegaly, pruritis and arthralgia.

Alagille Syndrome (Kamath BM et al., 2007)

Alagille syndrome is sometimes an autosomal dominant disorder, meaning a person inherits it from one parent who has the disorder. In other cases, a gene mutation develops spontaneously, meaning neither parent carries a copy of the mutated gene. A child who has a parent with Alagille syndrome has a 50 percent chance of developing the disorder. Most people with Alagille syndrome have a mutation or defect, in the Jagged1 (JAG1) gene. Mutations in the NOTCH2 gene are seen in less than 1 percent of people with Alagille syndrome. Infants with Alagille syndrome may have symptoms of liver disease and poor bile drainage from the liver in the first few weeks. These symptoms can also occur in children and adults with Alagille syndrome.

Alcohol-Related Liver Disease (O'Shea RS et al., 2010 & Choi G et al., 2012)

Alcohol can damage or destroy liver cells. The liver breaks down alcohol so it can be removed from body. Liver can become injured or seriously damaged if drink more alcohol than it can process. There are three main types of alcohol-related liver disease: fatty liver disease, alcoholic hepatitis and alcoholic cirrhosis. Many heavy drinkers will progress from fatty liver disease to alcoholic hepatitis to alcoholic cirrhosis over time. However, some heavy drinkers may develop cirrhosis without having alcoholic hepatitis first. Others may have alcoholic hepatitis but never have symptoms.

Fatty Liver

Fatty liver disease is the build up of extra fat in liver cells. It is the earliest stage of alcohol-related liver disease. There are usually no symptoms. If symptoms do occur, they may include fatigue, weakness, and weight loss. Almost all heavy drinkers have fatty liver disease. However, if they stop drinking, fatty liver disease will usually go away.

Alcoholic Hepatitis

Alcoholic hepatitis causes the liver to swell and become damaged. Symptoms may include loss of appetite, nausea, vomiting, abdominal pain, fever and jaundice. Up to 35 percent of heavy drinkers develop alcoholic hepatitis. Alcoholic hepatitis can be mild or severe. If it is mild, liver damage may be reversed. If it is severe, it may occur suddenly and quickly lead to serious complications including liver failure and death.

Alcoholic Cirrhosis

Alcoholic cirrhosis is the scarring of the liver (hard scar tissue replaces soft healthy tissue). It is the most serious type of alcohol-related liver disease. Symptoms of cirrhosis are similar to those of alcoholic hepatitis. Between 10 to 20 percent of heavy drinkers affect by cirrhosis. The damage from cirrhosis cannot be reversed and can cause liver failure. Stoping alcohol consumption can help to prevent further damage.

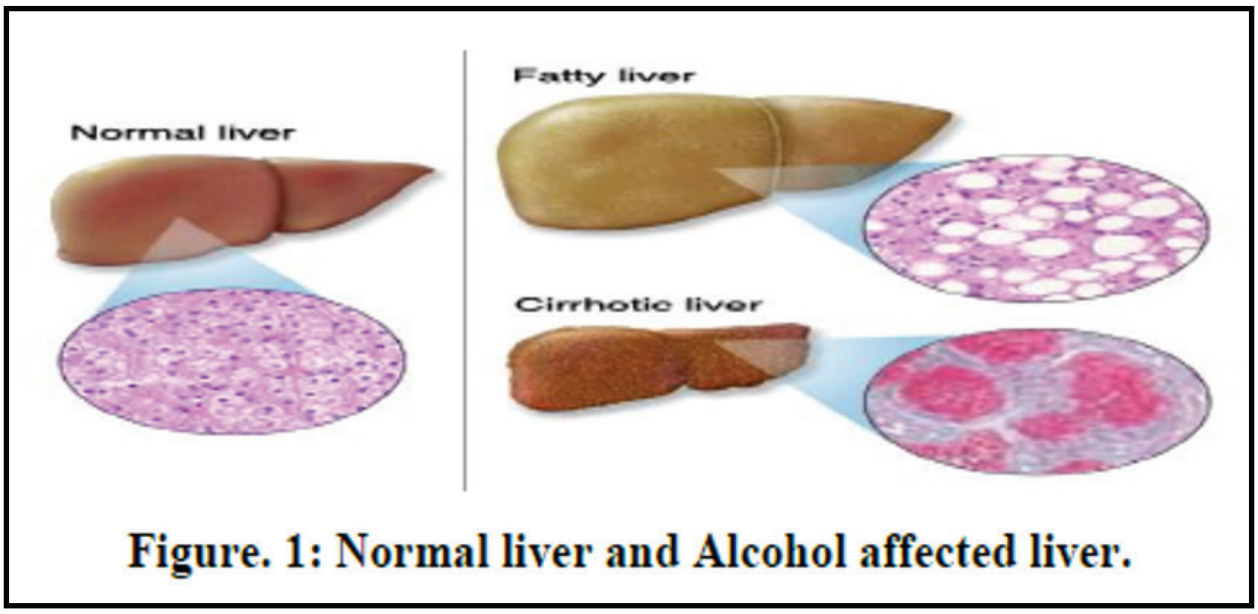

Figure. 1: Normal liver and Alcohol affected liver.

Enlarged Liver (Ferri FF, 2012 & Goldman L et al., 2012)

An enlarged liver is one that's bigger than normal. The liver is a large, football-shaped organ found in the upper right portion of abdomen. The medical term for enlarged liver is hepatomegaly (hep-uh-to-MEG-uh-le). Enlarged liver isn't a disease. It's a sign of an underlying problem, such as liver disease, congestive heart failure or cancer. Treatment for enlarged liver involves identifying and controlling the underlying cause of the condition. Many diseases and conditions can cause an enlarged liver, including: Liver diseases, Cirrhosis, Hepatitis caused by a virus (including hepatitis A, B and C) or caused by infectious mononucleosis, Non alcoholic fatty liver disease, Alcoholic fatty liver disease, amyloidosis (a disorder that causes abnormal protein to accumulate in liver), Wilson's disease (a disorder that causes copper to accumulate in liver), hemochromatosis (a disorder that causes iron to accumulate in liver), Gaucher's disease (a disorder that causes fatty substances to accumulate in liver), liver cysts (Fluid-filled pockets in the liver), Noncancerous liver tumors, including hemangioma and adenoma, Obstruction of the gallbladder or bile ducts and toxic hepatitis.

Alpha-1 Antitrypsin Deficiency (Czaja AJ, 1998)

Alpha-1 antitrypsin deficiency (Alpha-1) is a hereditary genetic disorder which may lead to the development of lung and/or liver disease. It is the most common genetic cause of liver disease in children. Adults can also be affected by Alpha-1 and may develop lung conditions such as emphysema as well as liver problems. Fortunately, many persons diagnosed with Alpha-1 never develop any of the associated diseases.

Budd-Chiari Syndrome (Eldon A. Shaffer, 2007)

Budd-Chiari syndrome is caused by blood clots that completely or partially block the large veins that carry blood from the liver (hepatic veins) into the inferior venacava. Usually, the cause is a disorder that makes blood more likely to clot, such as excess red cells (polycythemia), sickle cell disease, inflammatory bowel disease and connective tissue disorders.

Enlarged Liver (Ferri FF, 2012[19] & Goldman L *et al.*, 2012[20])

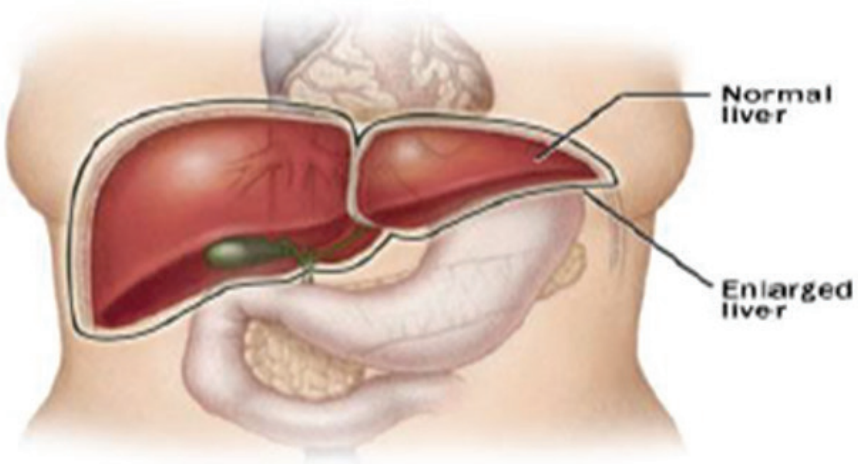

Figure. 2: Enlarged liver.

Gilbert's Syndrome (Claridge LC et al., 2011)

Gilbert's syndrome is a common, mild liver condition in which the liver doesn't properly process a substance called bilirubin. Bilirubin is produced by the breakdown of red blood cells. Gilbert's (zheel-BAYRZ) syndrome typically is harmless and doesn't require treatment. Gilbert's syndrome is caused by an inherited gene mutation. Person born with Gilbert's syndrome, may often goes undiscovered for many years. Gilbert's syndrome is often discovered by accident, such as a person have a blood test that shows elevated bilirubin levels. Gilbert's syndrome is also known as constitutional hepatic dysfunction and familiar non hemolytic jaundice.

Liver-Hemangioma (Assy N et al., 2009)

Liver hemangioma (he-man-jee-O-muh) is a noncancerous (benign) mass that occurs in the liver. Liver hemangioma is made up of a tangle of blood vessels. Most cases of liver hemangioma are discovered during a test or procedure for some other condition. Most people who have a liver hemangioma never experience signs and symptoms and don't need treatment. There's no evidence that an untreated liver hemangioma can lead to liver cancer. Nonalcoholic Steatohepatitis (American Liver Foundation, 2006[25]) Nonalcoholic steatohepatitis or NASH is a common, often "silent" liver disease. It resembles alcoholic liver disease, but occurs in people who drink little or no alcohol. The major feature of NASH is fat in the liver, along with inflammation and damage. Most people with NASH feel well and are not aware that they have a liver problem. Nevertheless, NASH can be severe and can lead to cirrhosis, in which the liver is permanently damaged and scarred and no longer able to work properly. Although having fat in the liver is not normal, by itself it probably causes little harm or permanent damage. If fat is suspected based on blood test results or scans of the liver, this problem is called nonalcoholic fatty liver disease (NAFLD). If liver biopsy is performed in this case reports will show that some people have NASH while others have simple fatty liver.

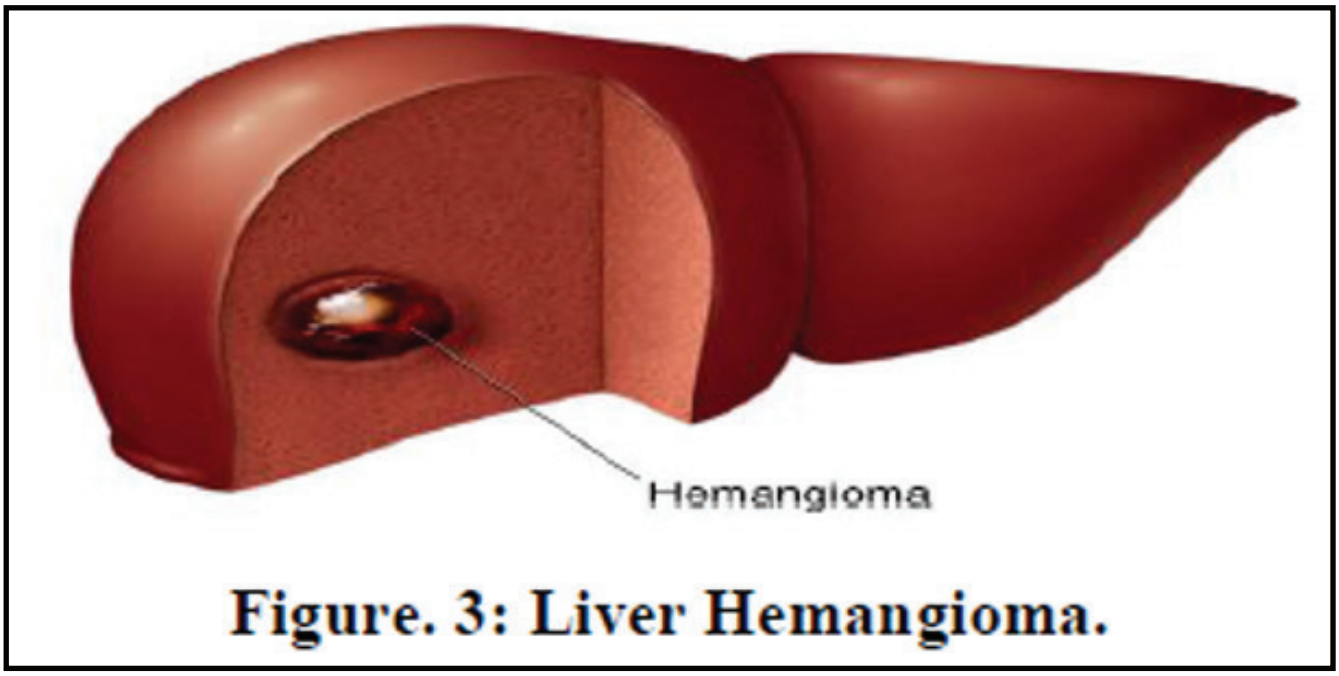

Figure. 3: Liver Hemangioma.

Portal Hypertension (Steven K. Herrine, 2012)

Portal hypertension is abnormally high blood pressure in the portal vein (the large vein that brings blood from the intestine to the liver) and its branches. Cirrhosis (scarring that distorts the structure of the liver and impairs its function) is the most common cause in Western countries. Portal hypertension can lead to a swollen abdomen, abdominal discomfort, confusion, and bleeding in the digestive tract.

Hepatic Encephalopathy: Hepatic encephalopathy (portosystemic encephalopathy, liver encephalopathy or hepatic coma) is deterioration of brain function that occurs because toxic substances normally removed by the liver build up in the blood and reach the brain. Hepatic encephalopathy may be triggered by bleeding in the digestive tract, an infection, failure to take drugs as prescribed, or another stress in people who have a long-standing (chronic) liver disorder. People become confused, disoriented, drowsy with changes in personality, behavior, and mood. Ascites: Ascites is the accumulation of protein-containing (ascitic) fluid within the abdomen. Many disorders can cause ascites, but cirrhosis is the most common. If large amount of fluid accumulates, the abdomen becomes very large, sometimes making people lose their appetite and feel short of breath and uncomfortable. Analysis of the fluid can help to determine the cause. Usually, a low-sodium diet and diuretics can help to eliminate excess fluid. The symptoms may include sudden weight gain, distended abdomen, abdominal pain, heart burn, nausea and vomiting.

Cholestasis: Cholestasis is reduction or stoppage of bile flow. Disorders of the liver, bile duct or pancreas can cause cholestasis. The symptoms of cholestatis is like skin and sclera of the eyes look yellow, itching of skin, dark coloured urine, light-coloured and foul smelling stool. With cholestasis, the flow of bile (the digestive fluid produced by the liver) is impaired at some point between the liver cells (which produce bile) and the duodenum (the first segment of the small intestine). When bile flow is stopped, the pigment bilirubin (a waste product formed when old or damaged red blood cells are broken down) escapes into the bloodstream and accumulates. Normally, bilirubin binds with bile in the liver, moves through the bile ducts into the digestive tract and it is eliminated from the body via stool.

Jaundice: In jaundice, the skin and sclera of the eyes look yellow. Jaundice occurs when there is too much bilirubin (a yellow pigment) in the blood (a condition called hyperbilirubinemia). Bilirubin is formed when hemoglobin (the part of red blood cells that carries oxygen) is broken down as part of the normal process of recycling old or damaged red blood cells. These symptoms may include nausea, vomiting, abdominal pain, and small spider like blood vessels that are visible in the skin (spider angiomas). Men may have enlarged breasts, shrunken testes, and pubic hair that grows as it does in women.

Primary Sclerosing Cholangitis (PSC): PSC is a disease that damages and blocks bile ducts inside and outside the liver. Bile is a liquid secreted by liver. Bile ducts are tubes that carry bile out of the liver to the gallbladder and small intestine. In the intestine, bile helps in break down of fat in food. In PSC, inflammation of the bile ducts leads to scar formation and narrowing of the ducts over time. As scarring increases, the ducts become blocked. As a result, bile builds up in the liver and damages liver cells. Eventually, scar tissue can spread throughout the liver, causing cirrhosis and liver failure.

Biliary Atresia (Hartley JL et al., 2009)

Biliary atresia is a life-threatening condition in infants in which the bile ducts inside or outside the liver do not have normal openings. The two types of biliary atresia are, fetal and perinatal. Fetal biliary atresia appears while the baby is in the womb. Perinatal biliary atresia is much more common and does not become evident until 2 to 4 weeks after birth. Some infants, particularly those with the fetal form, also have birth defects in the heart, spleen or intestines. Symptoms may include weight loss, irritability, jaundice, liver may become harden and distended abdomen, pale grey stools and dark urine.

TEST FOR LIVER DISEASES

A number of liver function test are available to test the proper function of the liver, (serum proteins, serum albumin, bilirubin (direct and indirect), ALT, AST, GGT, ALP, PT and PTT). Imaging tests such as transient elastography, ultrasound and magnetic resonance imaging can be used to examine the liver tissue and bile ducts. Liver biopsy can be performed to examine liver tissue to distinguish between various conditions; tests such as elastography may reduce the need for biopsy in some situations (Tapper EB, Lok AS, 2017.). Liver Biomarkers as well as the related in vitro diagnostic antibodies used for diagnosis being provided.

TREATMENT / MANAGEMENT

Treatment and Prophylaxis

The treatment goal is to stop the progression of the disease and complications and require a multidisciplinary approach. The principle of management is mainly underlying cause correction, Portal hypertension management, and specific treatments for individual disease. A brief outline regarding treatment for various CLD and related complications is given below.

General Management

Patients with chronic liver disease mostly present with one of the complications.

Esophageal varices - Varices related bleeding are one of the deadly complications, and the treatment includes aggressive fluid resuscitation, vasopressors (octreotide, terlipressin), and endoscopy. Endoscopic band ligation and injection sclerotherapy are the usual modalities to treat variceal bleed in an emergency. In some patients, early transjugular intrahepatic portosystemic shunt (TIPS) can increase the survival rate. Propranolol is used for primary and secondary prophylaxis for esophageal varices. Diuretics (furosemide, spironolactone) and sodium restriction are essential treatment options for ascites. For tense ascites, therapeutic paracentesis is done. Albumin infusion can also be considered. Initially, broad-spectrum antibiotics are the treatment of choice for SBP and then specific antibiotics after culture.

Hepatic encephalopathy - The basic principle of treatment is to address the precipitating factors. Patients with hepatic encephalopathy usually improve with precipitating cause correction along with rifaximin and lactulose.Lactulose acts by converting ammonia to ammonium ions and decreases its absorption from the gastrointestinal tract. Lactulose also relieves constipation through its osmotic effect, which further helps to ease the symptoms of hepatic encephalopathy. Rifaximin is used to decrease ammonia production by gut flora. Liver transplant is a curative treatment in patients with hepatorenal syndrome.

Hepatorenal syndrome - HRS based on severity divided into two categories. HRS 1 is more severe compared to HRS 2 (less severe). The primary goal is to correct underlying cause correction to reverse acute kidney injury. Treatment modalities depend on the severity and location of the patient. Treatment modalities include norepinephrine or terlipressin with albumin infusion or midodrine, octreotide with albumin infusion. TIPS procedure in some patients can help and liver transplantation the only definite treatment in the patient who fails to respond to all other treatments.

Hepatocellular carcinoma (HCC) - Treatment is based on the Barcelona clinic liver cancer staging system in the management of HCC:

- Initial stage (single HCC lesion): Resection and ablation.
- Intermediate stage: Transarterial chemoembolization and radio-embolization.
- Metastatic disease: Sorafenib

Specific Treatment

Viral Hepatitis

- Continuous viral suppression with nucleoside and nucleotide analogs
- Direct-acting antivirals achieving HCV eradication
- Interferon-alpha

Alcoholic liver disease: Alcohol abstinence

Non-alcoholic fatty liver disease: Treatment of metabolic syndrome components

Autoimmune hepatitis: Corticosteroids and other immunosuppressive drugs

Hereditary hemochromatosis: Phlebotomy, iron-chelators

Copper overload (Wilson disease): Copper chelators

Alpha-1-antitrypsin deficiency: Transplant

Drugs and toxins: Identify and stop the factor

Primary biliary cholangitis (PBC): Ursodeoxycholic acid (UDCA)

Primary sclerosing cholangitis: Transplant

Budd-Chiari syndrome: Anticoagulation, thrombolysis or angioplasty with or without stenting, TIPS, or liver transplant Liver diseases can be inherited or caused by a variety of factors that damage the liver (virus, drugs or chemicals, obesity, diabetes or an attack from own immune system), when the condition is left untreated, it can become life threatening and can permanently damage the liver or the bile duct. This damage can then become malignant. The liver disease prognosis depends on how quickly the condition was diagnosed and treated. In beginning stages, liver disease usually responds to treatment, but in advanced liver disease, the damage done by fibrosis, cirrhosis and liver failure cannot be reversed. This advanced stage leads to eventual death. While diagnosing liver disease, the condition causing the disease must be treated. If caught early, and are treated correctly, the damage to the liver may heal. In the middle stages of disease, treatment may work to help heal the damage, but as the disease progresses, treatments focus on managing the disease and prolonging the diagnosis.

MANAGEMENT OF CHRONIC LIVER DISEASES AND CIRRHOSIS

Management of chronic liver diseases and cirrhosis: current status and future directions

Despite the successful HBV vaccination plans in high endemic areas and effective anti-HBV and anti-HCV treatments, the age-standardized prevalence of CLD and cirrhosis caused by HBV and HCV kept rising at a rate of 9.0% and 10.2%, respectively, in the last decade (2007–2017). Moreover, the age-standardized prevalence of CLD and cirrhosis caused by NAFLD, leading cause of CLD and cirrhosis, increased by 23.5% within the same period.

Early diagnosis of CLD and cirrhosis is of great importance to start effective intervention and subsequently improve the prognosis. Both identification of etiology and assessment of disease severity are essential before making a treatment decision. To identify the etiology, screening tests for HBV markers, HCV markers, and metabolic panels are generally used. Collecting and analyzing information about alcohol intake and drug exposure is also necessary.

Chronic drug-induced liver injury (DILI) is an emerging field of study and more prevalent than previously thought. Antibiotics are the drugs most likely to cause chronic DILI. Detecting the levels of immunoglobulin G, immunoglobulin M, and autoantibodies are pivotal to diagnose autoimmune liver diseases. Markers related to Wilson disease, hemochromatosis, a1-antitrypsin deficiency, and other rare liver diseases need to be tested when the disease is indicated. Liver biopsy for histopathological examination is optional when the routine non-invasive tests fail to determine the etiology, but become inevitable in the diagnosis of some CLD, such as autoimmune hepatitis (AIH). Regular follow-up and assessment of the disease's severity are essential to initiate treatment in time, given that CLD and cirrhosis can be asymptomatic and neglected until the occurrence of decompensation, characterized by ascites, hepatic encephalopathy, variceal bleeding, or hepato-renal syndrome. Advanced fibrosis is usually "silent" but life-threatening. For example, advanced fibrosis in patients with NAFLD dramatically increases the risk of hepatocellular carcinoma (HCC) and other complications of cirrhosis. Early diagnosis and treatment of fibrosis is the key to improve the prognosis of CLD. Liver biopsy is currently the gold standard to diagnose liver fibrosis and cirrhosis. Referral for liver biopsy should be considered if a thorough serologic and radiographic evaluation fails to confirm a diagnosis of fibrosis or cirrhosis. Given patients' preference to avoid liver biopsy and the limitations of liver biopsy, including invasiveness, associated risk of complications, costliness, and occurrence of intra- and inter-observer variability, noninvasive alternatives of liver fibrosis and cirrhosis are in high demand. Transient elastography (TE), aspartate transaminase (AST) to platelet ratio index (APRI), and Fibrosis-4 (FIB-4) are commonly used to assess liver fibrosis in clinical practice at present.

To assess the severity of CLD and cirrhosis, a liver panel, a complete blood count (CBC) with platelets, and a prothrombin time/international normalized ratio (INR) test should be performed. Common tests in liver panels include the serum enzymes such as alanine transaminase (ALT), AST, alkaline phosphatase, and g-glutamyltrans-ferase; total serum bilirubin, direct serum bilirubin and indirect serum bilirubin; and serum albumin. Scoring systems involving multi-organ function such as Child- Turcotte-Pugh score and model for end-stage liver disease are used to predict the survival of cirrhosis patients. The Chinese group on the study of severe hepatitis B-acute-onchronic liver failure score (COSSH-ACLFs) is useful to predict the evaluate the severity and short-term prognosis of patients with HBV-related acute-on-chronic liver failure (ACLF). Imaging tests, including ultrasonography, computed tomography, and magnetic resonance imaging can suggest the presence of cirrhosis and provide information about complications, such as ascites, esophageal varices, and HCC.

In addition, assessment of extra-hepatic manifestations is substantially important in the management of some forms of CLD and cirrhosis, such as HCV infection. Hematologic diseases such as cryoglobulinemia and lymphoma, autoimmune disorders such as thyroiditis, renal disease, and dermatologic conditions such as lichen planus and porphyria cutanea tarda are quite uncommon in chronic HCV infection. Furthermore, evaluations of complications, including ascites, esophageal and gastric variceal bleeding, hepatic encephalopathy (HE), hepato-renal syndrome (HRS), hepatopulmonary syndrome (HPS) and others, are necessary for cirrhosis patients, which have been detailed in the guidelines. It is particularly important to monitor liver malignancies through the combination of serum markers, including alpha-fetoprotein (AFP) and protein induced by vitamin K absence-II (PIVKA-II), and imaging tests in the long-term management of CLD and cirrhosis.

With regard to the treatment of CLD and cirrhosis, comprehensive measures consisting of etiological treatment and complication management should be taken immediately. Anti-inflammatory and anti-fibrosis treatments should be started when indicated. Recommendations for the treatment of cirrhosis and its complications are detailed in the guidelines. In terms of etiological treatment, efficacy and effectiveness varies among CLDand cirrhosis caused by different etiologies. For the management of non-alcoholic steatohepatitis (NASH), which is the inflammatory subtype of NAFLD and is associated with disease progression, no disease-specific medication is approved so far. Hence, lifestyle modification is still the mainstay of treatment.

Weight loss through dietary changes, physical exercise, and bariatric surgery when indicated, is correlated with substantial improvement in histologic outcomes, including fibrosis. However, only a small portion of NASH patients can achieve and maintain the necessary degree of weight loss required for therapeutic effect, and half patients failed to achieve fibrosis regression through weigh loss. NASH specific medications are urgently needed since the prevalence of NASH keeps rising dramatically worldwide. The interim analysis of a multi-center, randomized, placebo controlled phase 3 trial showed that obeticholic acid, an agonist of farnesoid X receptor, improved fibrosis in patients with NASH. More emerging medications, such as C-C chemokine receptor types 2 and 5 inhibitor, peroxisome proliferator-activated receptor agonists, glucagon- like peptide-1 agonist, vitamin E, and some novel drugs are being studied and potentially provide new solutions.

The most gratifying progress in the area of hepatitis therapy in the last decade is the development of safe and highly effective direct-acting antivirals (DAAs). DAAs offer a sustained virologic response of greater than 95%, making chronic HCV infection curable in most patients. However, challenges remain, including high cost, limited availability, and drug-drug interactions (DDI) between DAAs and medicines used to treat comorbidities, such as human immunodeficiency virus (HIV) infection, coronary heart diseases, and hyperlipidemia. The potential risks posed by DDI should be considered when selecting DAAs regimens. On the contrary, to cure chronic HBV infection is extremely challenging. Less than 20% of patients with chronic hepatitis B (CHB) who receive currently approved anti-HBV regimens can achieve HBV surface antigen (HBsAg) loss, which is associated with functional remission and improved long-term outcome, and is considered to be a "functional cure" (also referred to as clinical or immunologic cure) for CHB. In addition, combination strategies are less cost-effective than first-line nucleos(t)ide analog monotherapy even though they might lead to higher HBsAg loss rate in some specific subgroup of CHB patients. Forty-nine percent of CHB patients failed to achieve fibrosis regression after a 5-year treatment with tenofovir disoproxil fumarate, one of the first-line anti- HBV agents. This failure suggests the necessity of longterm anti-HBV treatment and the urgent need of adding anti-fibrosis medication on the basis of antiviral therapy. Recently, 2 strategies, namely curing HBV infection without killing infected cells and inducing immune control to safely eliminate HBV-infected cells were proposed by the International Coalition to Eliminate HBV (ICE-HBV) to achieve the goal of HBV cure. Given the fact that persistence of viral covalently closed circular DNA (cccDNA) transcriptional template is a major barrier to curing HBV, cccDNA elimination will be the most direct and efficient strategy to cure chronic HBV infection. A better understanding of the HBV lifecycle, host immune response, and virus-immune interaction must be achieved to implement these strategies. Novel direct anti-HBV agents with superior efficacy and safety profile and immunotherapy are the predominant approaches to achieve HBV cure. On one hand, several direct anti- HBV agents that target directly the replication cycle of HBV presented promising efficacy and safety in phase 2 clinical trials. For example, nucleic acid polymers that inhibit assembly and secretion HBV subviral particles increased the rates of HBsAg loss and HBsAg seroconversion during therapy and functional cure after therapy.

On the other hand, better understanding of host immune response in HBV infection contribute to the development of immunotherapy of HBV. Host immune response plays an important role in HBV clearance and HBV infection control by modulating the innate and adaptive immune response. In terms of the innate immune response, pathogen recognition receptors, including Toll-like receptors, retinoic acid-inducible gene (RIG)-1-like receptors and nucleotide-binding oligomerization domain (NOD)- like receptors, natural killer cells, antigen presenting cells, Patient education is one of the critical factors that can play a pivotal role in the prevention of chronic liver disease. Most of the causative factors of chronic liver disease damage the liver over a long period; therefore, it is necessary to stop its progression to avoid cirrhosis and its complications. such as dendritic cells and Kupffer cells, are potential targets for HBV immunotherapy. In terms of the adaptive immune response, modulating of HBV-specific CD4+ and CD8+ T cell, regulatory T cell, HBV-specific B cell may contribute to HBV cure. However, none of the above agents has been investigated in phase 3 clinical trials.

For the treatment of chronic DILI, cessation of drugs is necessary and immunosuppressive therapy may be indicated if the injury does not resolve with drug cessation.

The mainstay of AIH treatment consists of predniso(lo)ne to induce remission, in combination with azathioprine, which is used to maintain it. Mycophenolate mofetil (MMF) is a standard second-line treatment for those with azathioprineintolerance. Ursodeoxycholic acid (UDCA) is the first line therapy for primary biliary cirrhosis (PBC). As a major consequence of the progression of CLD, portal hypertension (PHT) can lead to death or liver transplantation. In the past three decades, the prognosis of patients with PHT has improved dramatically due to the effective intervention of variceal bleeding, ascites, and other related complications. Currently, terlipressin, somatostatin, and octreotide are first-line drugs in the treatment of acute variceal bleeding in cirrhotic PHT. Administration of nonselective beta-blockers (such as carvedilol and propranolol) is the key to prevent secondary bleeding. The use of dedicated covered esophageal stents and balloon occluded retrograde trans-venous obliteration contribute to improved prognosis of PHT as well. More interestingly, along with a better understanding of pathophysiology in the progression of portal hypertension, some "new" medicines have been investigated in the management of CLD and cirrhosis. For example, accumulating evidence shows that statins have potential beneficial effects in the progression of CLD and cirrhosis, which have changed statins from previously thought risky drugs to kind of wonder drugs for patients with CLD and cirrhosis.

In summary, CLD and cirrhosis are substantial health burdens. Although HBV vaccination, screening of viral infection, anti-HBV and anti-HCV treatment have significantly reduced the burden in some areas, the prevalence of CLD and cirrhosis, especially those caused by NAFLD, keeps rising globally. In the evaluation of CLD and cirrhosis, noninvasive assessment of fibrosis and cirrhosis is greatly demanded. Concerning the treatment of CLD and cirrhosis, efficacy varies among CLD and cirrhosis caused by different etiologies. In the era of DAAs, chronic HCV infection becomes curable in most patients, but HBV cure and NASH management are still challenging. DAAs targeting the HBV life cycle and immunotherapy approaches are still on the way. Treatment of NASH has been a hotspot in the field of liver research for quite a few years, but few or none specific medicines have been approved. The development of novel medications to improve the prognosis of NASH is urgently required.

CONSULTATIONS

- Gastroenterology/hepatology consultation for patients with decompensated chronic liver disease
- Nephrology consultation in patients with hepatorenal syndrome
- Dietician consultation for advice on the diet
- Referral to a transplant center in patients needing a liver transplant

RECOMMENDATIONS FOR PREVENTIVE CARE IN CHRONIC LIVER DISEASE

- Avoid various types of alcohol (wine, liquor, mixed drinks, beer).
- Regular screening for hepatitis B and hepatitis C
- Vaccination against hepatitis A and B
- Avoid iron supplementation unless there is an iron deficiency.
- Avoid over-the-counter painkillers (aspirin, acetaminophen) and other hepatotoxic drugs.
- Maintain a good lipid profile to avoid metabolic syndrome and NAFLD.

PEARLS AND OTHER ISSUES

To prevent complications, patients with chronic liver disease will need surveillance. These patients should undergo routine monitoring of their CBC, CMP, and prothrombin time at least 3 to 4 times per year.

Routine diagnostic endoscopy should be performed for asymptomatic esophageal varices, and a follow-up endoscopy should be done in 2 years if varices are not present. Treatment with a nonselective beta-blocker to reduce heart rate by 25% in patients with esophageal varices, offers primary prophylaxis with variceal bleeding. Patients with large esophageal varices should have prophylactic endoscopic variceal banding to avoid the risk of rupture and bleeding.

The incidence of hepatocellular carcinoma has risen in the United States, and patients with cirrhosis should undergo surveillance with ultrasonography every six months. A 4-phase CT scan or an MRI scan should be done to rule out hepatocellular carcinoma in patients with a liver nodule on the ultrasound.

For the use or a Registered Medical Practitioner or a Hospital or a Laboratory only

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