Chronic Hepatitis

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Plan of lecture

- **Chronic Hepatitis**: etiology and pathogenesis;
- **Chronic Hepatitis**: diagnosis;
- **Chronic Hepatitis**: treatment.

Chronic Hepatitis

- Chronic hepatitis is hepatitis that lasts > 6 months. Common causes include hepatitis B and C viruses, nonalcoholic steatohepatitis (NASH), alcohol-related liver disease, and autoimmune liver disease (autoimmune hepatitis). Many patients have no history of acute hepatitis, and the first indication is discovery of asymptomatic aminotransferase elevations. Some patients present with cirrhosis or its complications (eg, portal hypertension). Biopsy is sometimes necessary to confirm the diagnosis and to grade and stage the disease. Treatment is directed toward complications and the underlying condition (eg, corticosteroids for autoimmune hepatitis, antiviral therapy for viral hepatitis). Liver transplantation is often indicated for decompensated cirrhosis (By Sonal Kumar, MD, MPH, Weill Cornell Medical College, New York Presbyterian Hospital, Last full review/revision Dec 2020| Content last modified Dec 2020
- MSD publication [1]: https://www.msdmanuals.com/professional/hepatic-and-biliary-disorders/hepatitis/overview-of-chronic-hepatitis?query=chronic%20hepatitis

Chronic Hepatitis etiology and pathogenesis[1]

Common causes

The most common causes of chronic hepatitis are:

- Hepatitis B virus
- Hepatitis C virus
- Nonalcoholic steatohepatitis (NASH)
- Alcohol-related liver disease
- Hepatitis B virus (HBV) and hepatitis C virus (HCV) are frequent causes of chronic hepatitis; 5 to 10% of cases of HBV infection, with or without hepatitis D virus (HDV) coinfection, and about 75% of cases of HCV infection become chronic. Rates are higher for developing chronic HBV infection in children (eg, up to 90% of infected neonates and 25 to 50% of young children). Although the mechanism of chronicity is uncertain, liver injury is mostly determined by the patient's immune reaction to the infection.
- Rarely, hepatitis E virus genotype 3 has been implicated in chronic hepatitis.

Hepatitis A virus does not cause chronic hepatitis.

Chronic Hepatitisetiology and pathogenesis **[1]**

NAFLD develops most often in patients with at least one of the following risk factors:

- Obesity
- Dyslipidemia
- Insulin resistance
- NASH is the progressive form of NAFLD that causes chronic hepatitis.
- Alcohol-related liver disease (a combination of fatty liver, diffuse liver inflammation, and liver necrosis) results from excess alcohol consumption.

Chronic Hepatitis etiology and pathogenesis [1]

Less common causes:

- Autoimmune hepatitis (immune-mediated hepatocellular injury) accounts for a high proportion of hepatitis not caused by viruses or steatohepatitis; features of autoimmune hepatitis include the following:
- The presence of serologic immune markers (eg, antinuclear antibodies, anti–smooth muscle antibodies, liver-kidney microsomal antibodies)
- An association with histocompatibility haplotypes common in autoimmune disorders (eg, HLA-B1, HLA-B8, HLA-DR3, HLA-DR4)
- A predominance of T cells and plasma cells in histologic liver lesions
- Complex in vitro defects in cellular immunity and immunoregulatory functions
- An association with other autoimmune disorders (eg, rheumatoid arthritis, autoimmune hemolytic anemia, proliferative glomerulonephritis)
- A response to therapy with corticosteroids or immunosuppressants

Chronic Hepatitis etiology and pathogenesis **[1]**

- Primary biliary cholangitis (formerly, primary biliary cirrhosis) is an immune-mediated process resulting in bile duct injury. Patients usually present with a positive antimitochondrial antibody (AMA) test and elevated alkaline phosphatase. Most patients with primary biliary cholangitis are women. Symptoms include fatigue, joint pain, and pruritus.
- Sometimes chronic hepatitis has features of both autoimmune hepatitis and another immune-mediated chronic liver disorder (eg, primary biliary cholangitis, primary sclerosing cholangitis). These conditions are called overlap syndromes.

Chronic Hepatitis etiology and pathogenesis**[1]**

Many drugs, including isoniazid, methotrexate, methyldopa, nitrofurantoin, tamoxifen, amiodarone, and rarely acetaminophen, can cause chronic hepatitis. The mechanism varies with the drug and may involve altered immune responses, development of steatohepatitis, cytotoxic intermediate metabolites, or genetically determined metabolic defects.

Less often, chronic hepatitis results from alpha-1 antitrypsin deficiency, celiac disease, a thyroid disorder, hereditary hemochromatosis, or Wilson disease.

Chronic Hepatitis, Classification [1]

Cases of chronic hepatitis were once classified histologically as chronic persistent, chronic lobular, or chronic active hepatitis. Current classification specifies the following:

- Etiology
- Intensity of histologic inflammation and necrosis (grade)
- Degree of histologic fibrosis (stage)
- Inflammation and necrosis are potentially reversible; fibrosis usually is not.

Chronic Hepatitis: Symptoms and Signs [1]

Clinical features of chronic hepatitis vary widely. About one third of cases develop after acute hepatitis, but most develop insidiously de novo.

Many patients are asymptomatic, regardless of the etiology. However, malaise, anorexia, and fatigue are common, sometimes with low-grade fever and nonspecific upper abdominal discomfort. Jaundice is usually absent.

Often, the first findings are:

- • Signs of cirrhosis (eg, splenomegaly, spider nevi, palmar erythema)
- • Complications of cirrhosis (eg, portal hypertension, ascites, encephalopathy)

A few patients with chronic hepatitis develop manifestations of cholestasis (eg, jaundice, pruritus, pale stools, steatorrhea).

Chronic Hepatitis: Symptoms and Signs [1]

In autoimmune hepatitis, especially in young women, manifestations may involve virtually any body system and can include acne, amenorrhea, arthralgia, ulcerative colitis, pulmonary fibrosis, thyroiditis, nephritis, and hemolytic anemia.

Chronic hepatitis C is occasionally associated with lichen planus, mucocutaneous vasculitis, glomerulonephritis, porphyria cutanea tarda, mixed cryoglobulinemia, and, perhaps, non-Hodgkin B-cell lymphoma. Symptoms of cryoglobulinemia include fatigue, myalgias, arthralgias, neuropathy, glomerulonephritis, and rashes (urticaria, purpura, leukocytoclastic vasculitis); asymptomatic cryoglobulinemia is more common.

Chronic Hepatitis: Diagnosis [1]

Diagnosis:

- Liver test results compatible with hepatitis
- Viral serologic tests
- Possibly autoantibodies, immunoglobulins, alpha-1 antitrypsin level, and other tests
- Occasionally biopsy
- Serum albumin, platelet count, and prothrombin time/international normalized ratio (PT/INR)

Chronic Hepatitis: Diagnosis [1]

Chronic hepatitis is suspected in patients with any of the following:

- Suggestive symptoms and signs
- Incidentally noted elevations in aminotransferase levels
- Previously diagnosed acute hepatitis
- In addition, to identify asymptomatic patients, the CDC recommends testing of all adults ≥ 18 years at least once.

Diagnosis by additional data [1] :

Liver tests are needed if not previously done and include serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and bilirubin.

Aminotransferase elevations are the most characteristic laboratory abnormalities (ALT normal values: 29 to 33 IU/L [0.48 to 55 microkat/L] for males and 19 to 25 IU/L [0.32 to 0.42 microkat/L] for females [1]). ALT is usually higher than AST. Aminotransferase levels can be normal during chronic hepatitis if the disease is quiescent, particularly with HCV infection and nonalcoholic fatty liver disease (NAFLD).

Alkaline phosphatase is usually normal or only slightly elevated but is occasionally markedly high, particularly in primary biliary cholangitis.

Bilirubin is usually normal unless the disease is severe or advanced.

Diagnosis by additional data [1] *:*

Other laboratory tests

If laboratory results are compatible with hepatitis, viral serologic tests are done to exclude HBV and HCV (see tables Hepatitis B Serology and Hepatitis C Serology). Unless these tests indicate viral etiology, further testing is required.

The next tests done include:

- Autoantibodies (antinuclear antibody, anti–smooth muscle antibody, antimitochondrial antibody, liver-kidney microsomal antibody)
- Immunoglobulins
- Serum transferrin saturation and ferritin
- Thyroid tests (thyroid-stimulating hormone)
- Tests for celiac disease (tissue transglutaminase antibody)
- Alpha-1 antitrypsin level
- Ceruloplasmin

Diagnosis by additional data [1] *:*

Autoimmune hepatitis is normally diagnosed based on the presence of antinuclear (ANA), anti–smooth muscle (ASMA), or anti-liver/kidney microsomal type 1 (anti-LKM1) antibodies at titers of 1:80 (in adults) or 1:20 (in children) and usually elevations in serum immunoglobulins. Antimitochondrial antibodies most often present in primary biliary cholangitis. (See also the American Association for the Study of Liver Disease's practice guideline Diagnosis and management of autoimmune hepatitis in adults and children.)

Serum transferrin saturation > 45% and elevated ferritin suggests hereditary hemochromatosis and should be followed by genetic testing for the hemochromatosis gene (HFE).

Serum albumin, platelet count, and PT should be measured to assess liver function and disease severity; low serum albumin, a low platelet count, or prolonged PT may suggest cirrhosis and even portal hypertension.

If the cause of hepatitis is identified, noninvasive tests (eg, ultrasound elastography, serum markers) can be done to assess the degree of liver fibrosis.

Diagnosis by additional data [1] *:*

Biopsy:

Unlike in acute hepatitis, biopsy may be necessary to confirm the diagnosis or etiology of chronic hepatitis.

Mild cases may have only minor hepatocellular necrosis and inflammatory cell infiltration, usually in portal regions, with normal acinar architecture and little or no fibrosis. Such cases rarely develop into clinically important liver disease or cirrhosis.

In more severe cases, biopsy typically shows periportal necrosis with mononuclear cell infiltrates (piecemeal necrosis) accompanied by variable periportal fibrosis and bile duct proliferation. The acinar architecture may be distorted by zones of collapse and fibrosis, and frank cirrhosis sometimes coexists with signs of ongoing hepatitis.

Biopsy is also used to grade and stage the disease.

Diagnosis by additional data [1] *:*

Screening for complications:

- If symptoms or signs of cryoglobulinemia develop during chronic hepatitis, particularly with HCV, cryoglobulin levels and rheumatoid factor should be measured; high levels of rheumatoid factor and low levels of complement suggest cryoglobulinemia.
- Patients with chronic HBV infection or cirrhosis due to any underlying liver disorder should be screened every 6 months for hepatocellular carcinoma with ultrasonography and sometimes serum alpha-fetoprotein measurement, although the cost-effectiveness of this practice, particularly alpha-fetoprotein measurement, is debated. (See also the Cochrane review abstract on Alpha-foetoprotein and/or liver ultrasonography for liver cancer screening in patients with chronic hepatitis B.)

Diagnosis reference: 1. Kwo PY, Cohen SM, Lim JK: ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. Am J Gastroenterol 112 (1):18–35, 2017. doi: 10.1038/ajg.2016.517 Epub 2016 Dec 20.

Chronic Hepatitis: treatment **[1]**

Treatment :

- Supportive care
- Treatment of cause (eg, corticosteroids for autoimmune hepatitis, antivirals for HBV and HCV infection)

General treatment

Treatment goals for chronic hepatitis include treating the cause and, if cirrhosis and portal hypertension have developed, managing complications (eg, ascites, encephalopathy).

Drugs that cause hepatitis should be stopped. Acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease. NSAIDs should also be avoided in patients with severe hepatic impairment.

Underlying disorders should be treated. Lifestyle changes should be recommended for patients with NAFLD or alcohol-related liver disease.

Liver transplantation may be required for decompensated cirrhosis.

Chronic Hepatitis: treatment **[1]**

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- Liver transplantation may be required for decompensated cirrhosis.

Chronic Hepatitis: treatment **[1]**

Chronic hepatitis B and C:

There are specific antiviral treatments for chronic hepatitis B (eg, entecavir and tenofovir as first-line therapies) and antiviral treatments for chronic hepatitis C (eg, interferon-free regimens of direct-acting antivirals).

In chronic hepatitis due to HBV, prophylaxis (including immunoprophylaxis) for contacts of patients may be helpful. No vaccination is available for contacts of patients with HCV infection.

Corticosteroids and immunosuppressants should be avoided in chronic hepatitis B and C because these drugs enhance viral replication. If patients with chronic hepatitis B have other disorders that require treatment with corticosteroids, immunosuppressive therapies, or cytotoxic chemotherapy, they should be treated with antiviral drugs at the same time to prevent a flare or reactivation of hepatitis B or acute liver failure due to hepatitis B. A similar situation with hepatitis C being activated or causing acute liver failure has not been described.

Chronic Hepatitis: treatment **[1]**

- Nonalcoholic steatohepatitis (NASH)

Treatment of NASH aims to

- Reduce weight
- Control risk factors and comorbidities

It may involve

- Recommending weight loss of 7 to 10% of body weight via dietary changes and exercise
- Treating concomitant metabolic risk factors such as hyperlipidemias and insulin resistance
- Stopping drugs associated with NASH (eg, amiodarone, tamoxifen, methotrexate, corticosteroids such as prednisone or hydrocortisone, synthetic estrogens)
- Avoiding exposure to toxins (eg, pesticides)

Chronic Hepatitis: treatment **[1]**

Autoimmune hepatitis:

Corticosteroids, with or without azathioprine, prolong survival.

Prednisone is usually started at 30 to 60 mg orally once a day, then tapered to the lowest dose that maintains aminotransferases at normal or near-normal levels. To prevent long-term need for corticosteroid treatment, clinicians can transition to azathioprine 1 to 1.5 mg/kg orally once a day or mycophenolate mofetil 1000 mg twice a day after corticosteroid induction is complete and then gradually taper the corticosteroid. Most patients require long-term, low-dose, corticosteroid-free maintenance treatment.

Hereditary hemochromatosis:

Hereditary hemochromatosis is treated with phlebotomy.

Key Points of Chronic Hepatitis [1] :

Key Points: Chronic hepatitis is usually not preceded by acute hepatitis and is often asymptomatic.

- If liver test results (eg, unexplained elevations in aminotransferase levels) are compatible with chronic hepatitis, do serologic tests for hepatitis B and C.
- If serologic results are negative, do tests (eg, autoantibodies, immunoglobulins, alpha-1 antitrypsin level) for other forms of hepatitis.
- Consider a liver biopsy to confirm the diagnosis and assess the severity of chronic hepatitis if noninvasive testing is nondiagnostic.
- Noninvasive tests (eg, elastography, serum markers) can be used to assess the degree of liver fibrosis.
- Consider entecavir or tenofovir as first-line therapies for chronic hepatitis B.
- Treat chronic hepatitis C of all genotypes with interferon-free regimens of direct-acting antivirals.
- Treat autoimmune hepatitis with corticosteroids and transition to maintenance treatment with azathioprine or mycophenolate mofetil.
- Encourage diet and exercise for weight loss in patients with nonalcoholic fatty liver disease.
- Treat hereditary hemochromatosis with phlebotomy.

More Information about Chronic Hepatitis [1]:

More Information:

- American Association for the Study of Liver Disease (AASLD) Practice Guidelines: A multidisciplinary panel of experts developed guidelines for diagnosing and managing various hepatic disorders using clinically relevant questions, which are answered by systematic reviews of the literature and followed by data-supported recommendations. The panel rated the quality (level) of the evidence and strength of each recommendation.
- U.S. Preventive Services Task Force's Hepatitis C Virus Infection in Adolescents and Adults: Screening: This web site summarizes the recommendations for hepatitis C screening and provides links to the full recommendations. It discusses assessment of risk and use of screening tests, including screening intervals.

More Information about Chronic Hepatitis [1] :

More Information:

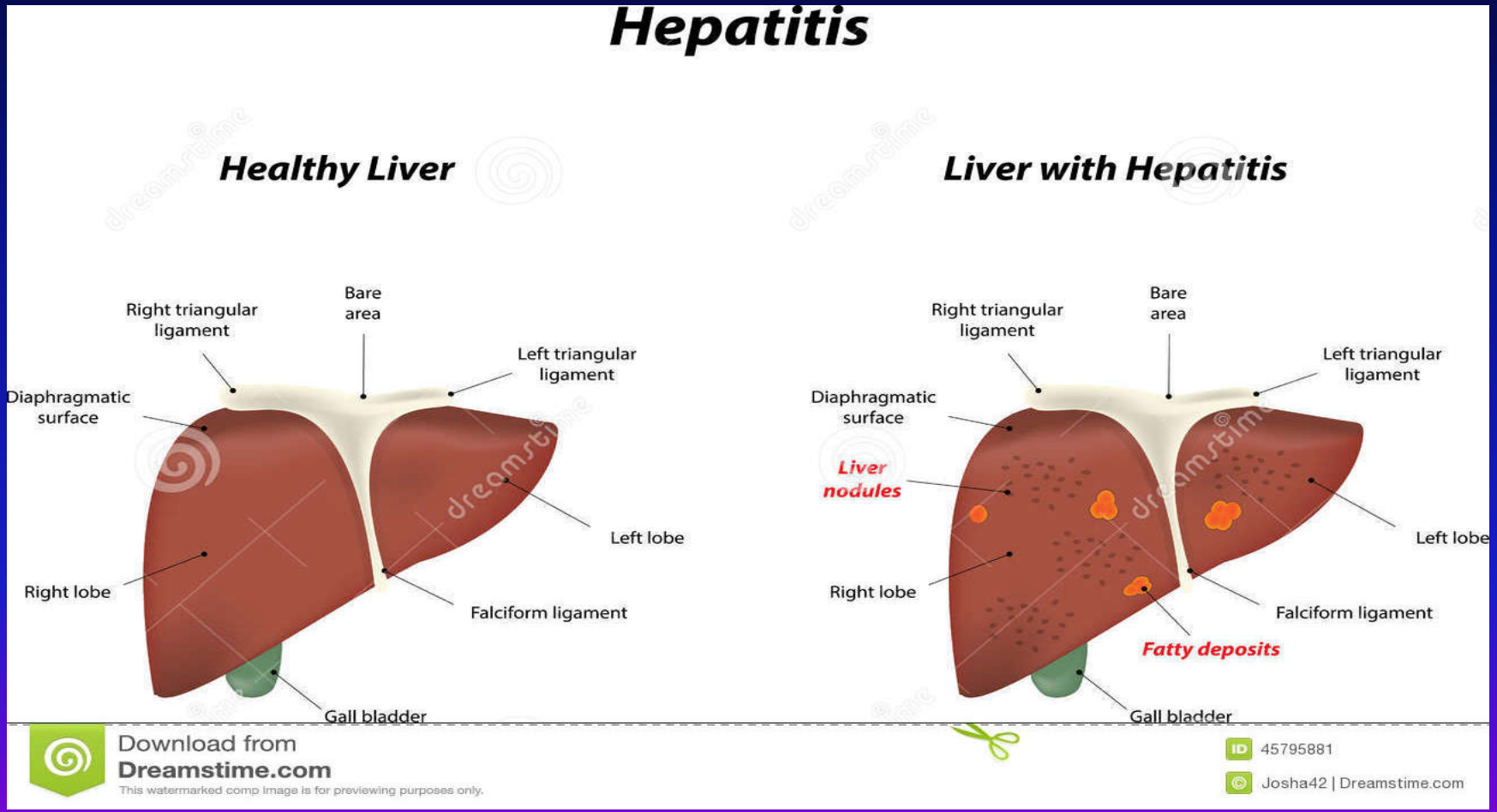
- AASLD Practice Guidelines: Diagnosis and management of autoimmune hepatitis in adults and children: This 2019 guideline addresses clinically relevant questions, using current evidence, expert opinion, systematic reviews of the literature, and the quality of evidence. This guideline updates the epidemiology, diagnosis, management, and outcomes of autoimmune hepatitis in adults and children from the 2010 guidelines.
- Alpha-foetoprotein and/or liver ultrasonography for liver cancer screening in patients with chronic hepatitis B: This study evaluates the beneficial and harmful effects of using alpha-fetoprotein, ultrasonography, or both to screen for hepatocellular carcinoma in patients with chronic hepatitis B.

More Information about Chronic Hepatitis [1]:

More Information:

- AASLD Practice Guidelines: The diagnosis and management of nonalcoholic fatty liver disease: This article provides guidance for diagnosing and managing nonalcoholic fatty liver disease, rather than guidelines. Guidance, developed by a panel of experts, is intended to help clinicians understand and implement the most recent evidence. It includes guidance for screening, initial evaluation, evaluation for fibrosis, use of biopsy, and specific treatment.

Hepatitis


Hepatitis
Healthy Liver
Right triangular ligament
Bare area
Left triangular ligament
Diaphragmatic surface
Left lobe
Right lobe
Falciform ligament
Gall bladder
Liver with Hepatitis
Right triangular ligament
Bare area
Left triangular ligament
Diaphragmatic surface
Liver nodules
Left lobe
Right lobe
Falciform ligament
Fatty deposits
Gall bladder
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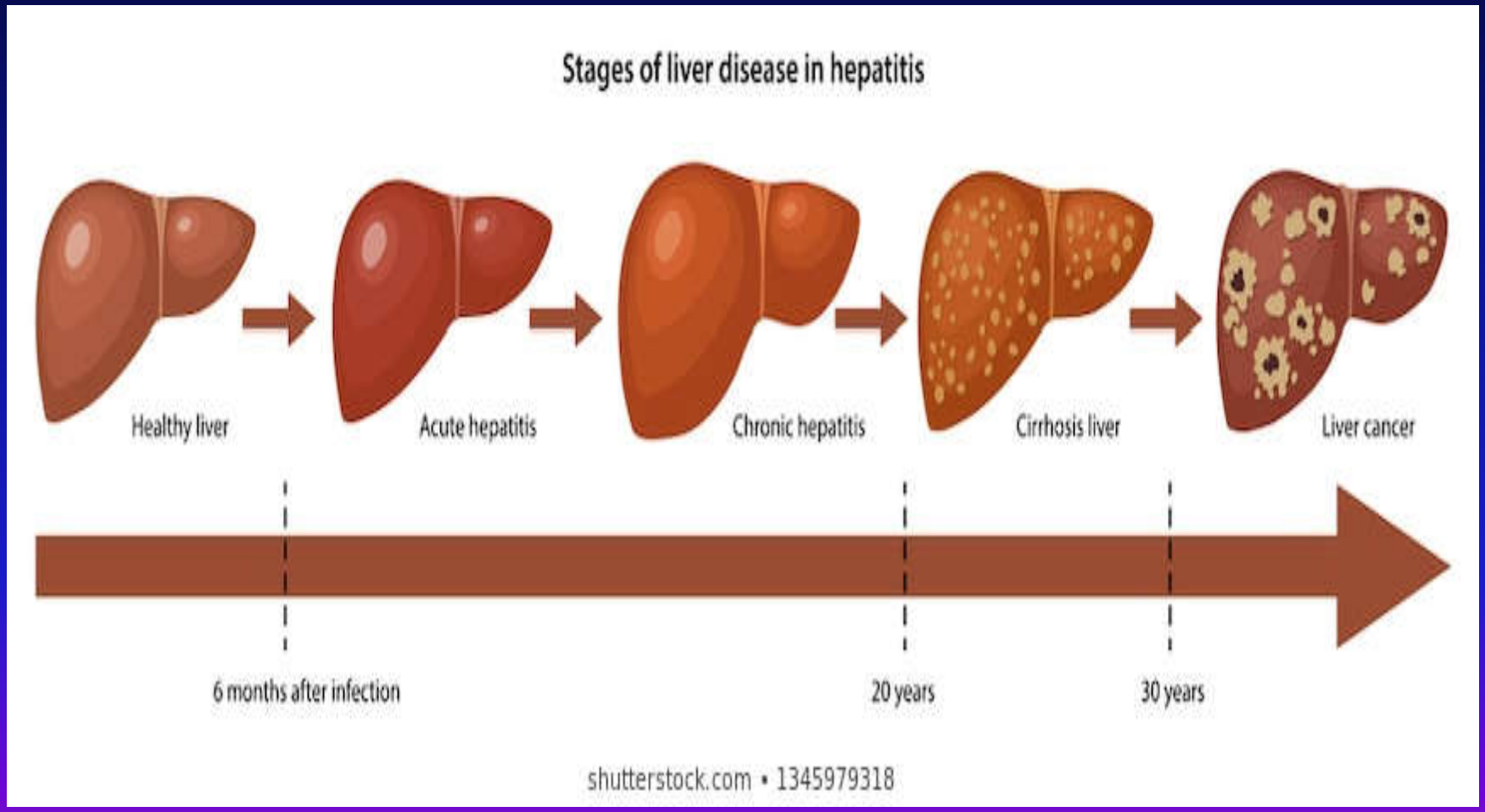
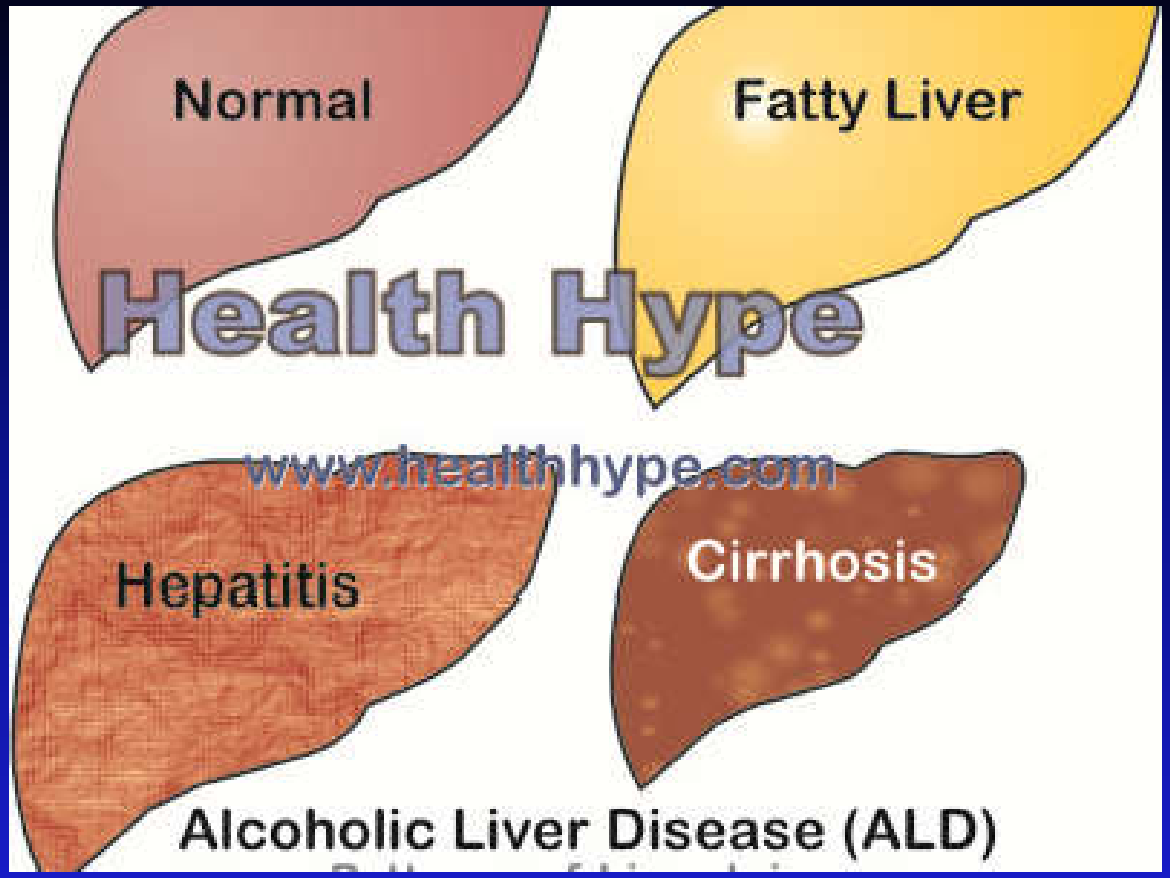
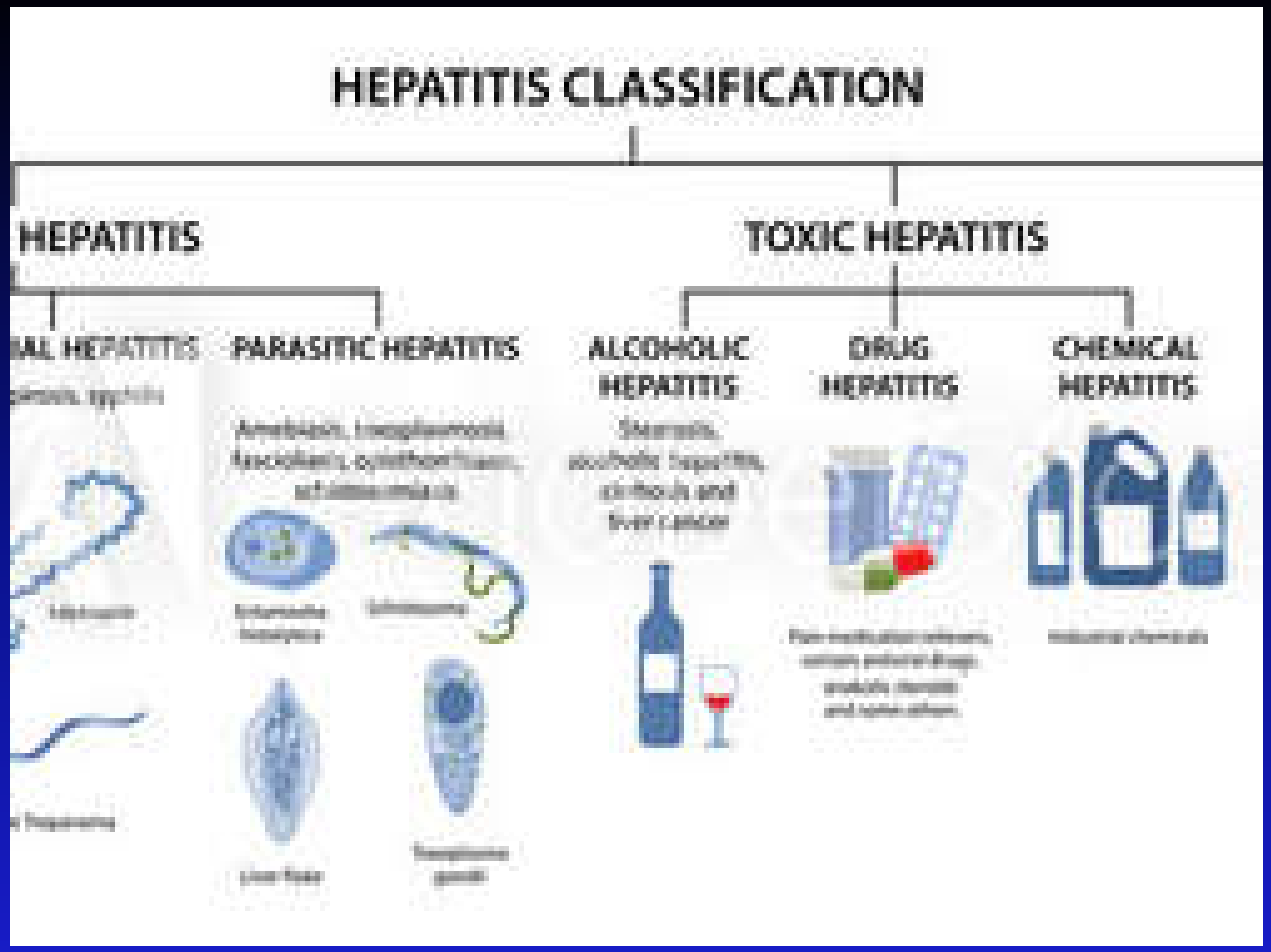
Stages of liver disease in hepatitis



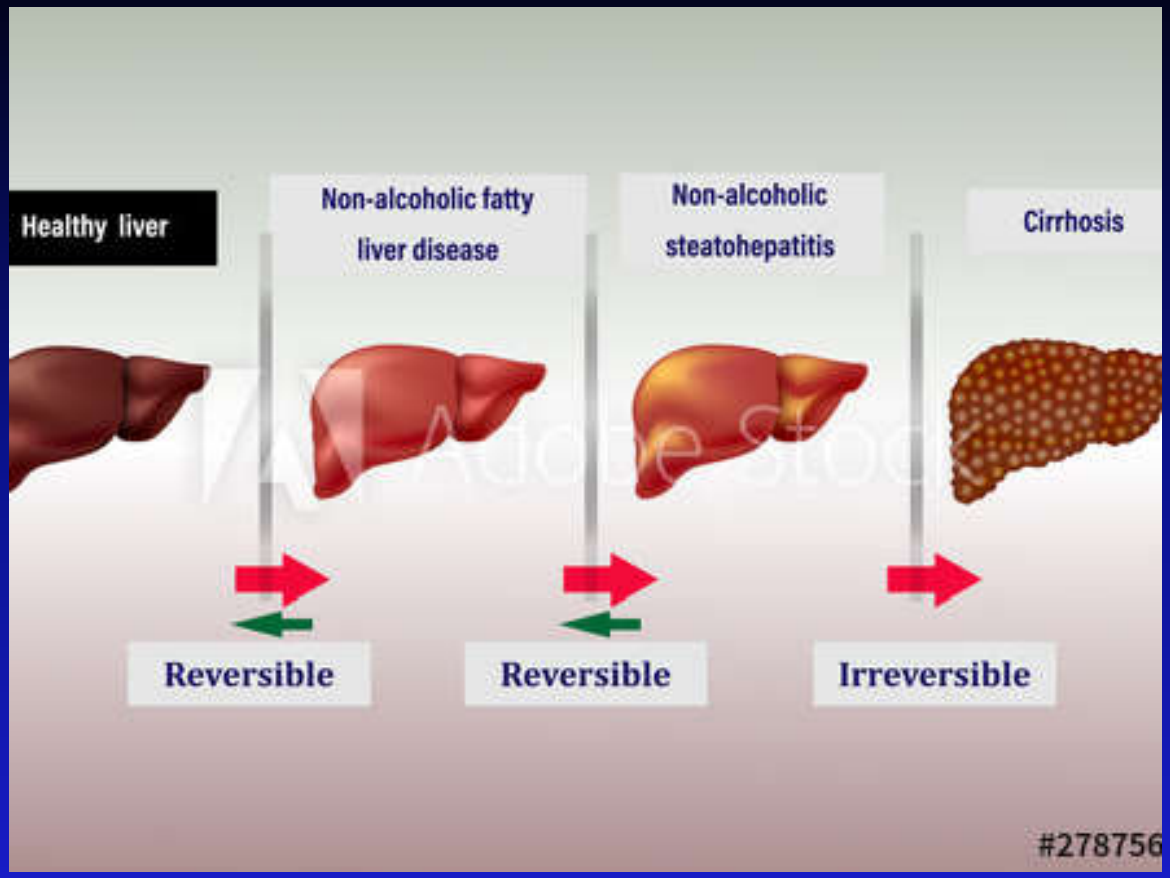


Alcoholic Liver Disease



Hepatitis Classification

Hand Yellowish as a symbol of the disease



stage disease of the liver , arrows indicate reversible and irreversible stages