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Supportive module 2: Basics of diagnosis, treatment
and prevention of major gastroenterological diseases

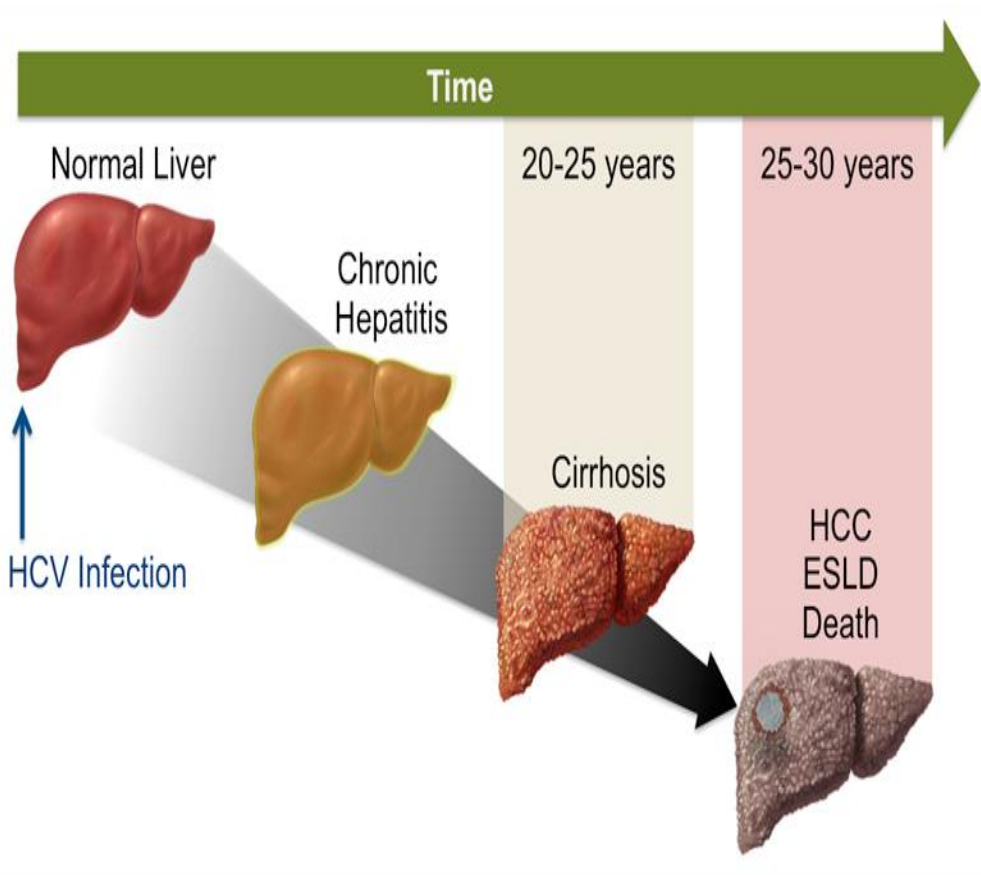
Chronic Hepatitis

LECTURE IN INTERNAL MEDICINE FOR IV COURSE STUDENTS

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Plan of the Lecture

Chronic Hepatitis



- Definition
- Epidemiology
- Mechanisms
- Classification
- Clinical presentation
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines

Definition

Chronic Hepatitis

Chronic hepatitis (CH) is defined as inflammatory disease of the liver lasting for more than six months with common causes include hepatitis B and C viruses, autoimmune liver disease (autoimmune hepatitis), steatohepatitis (nonalcoholic steatohepatitis or alcoholic hepatitis), and some drugs, characterized by liver enzymes elevation, the presence of autoantibodies, elevated gamma globulin and other proteins levels, interface hepatitis on histology, and may occur with limited or no symptoms, but often leads to yellow discoloration of the skin, mucus membranes, and conjunctivae, poor appetite and malaise, with progress to fibrosis (scarring) and cirrhosis.

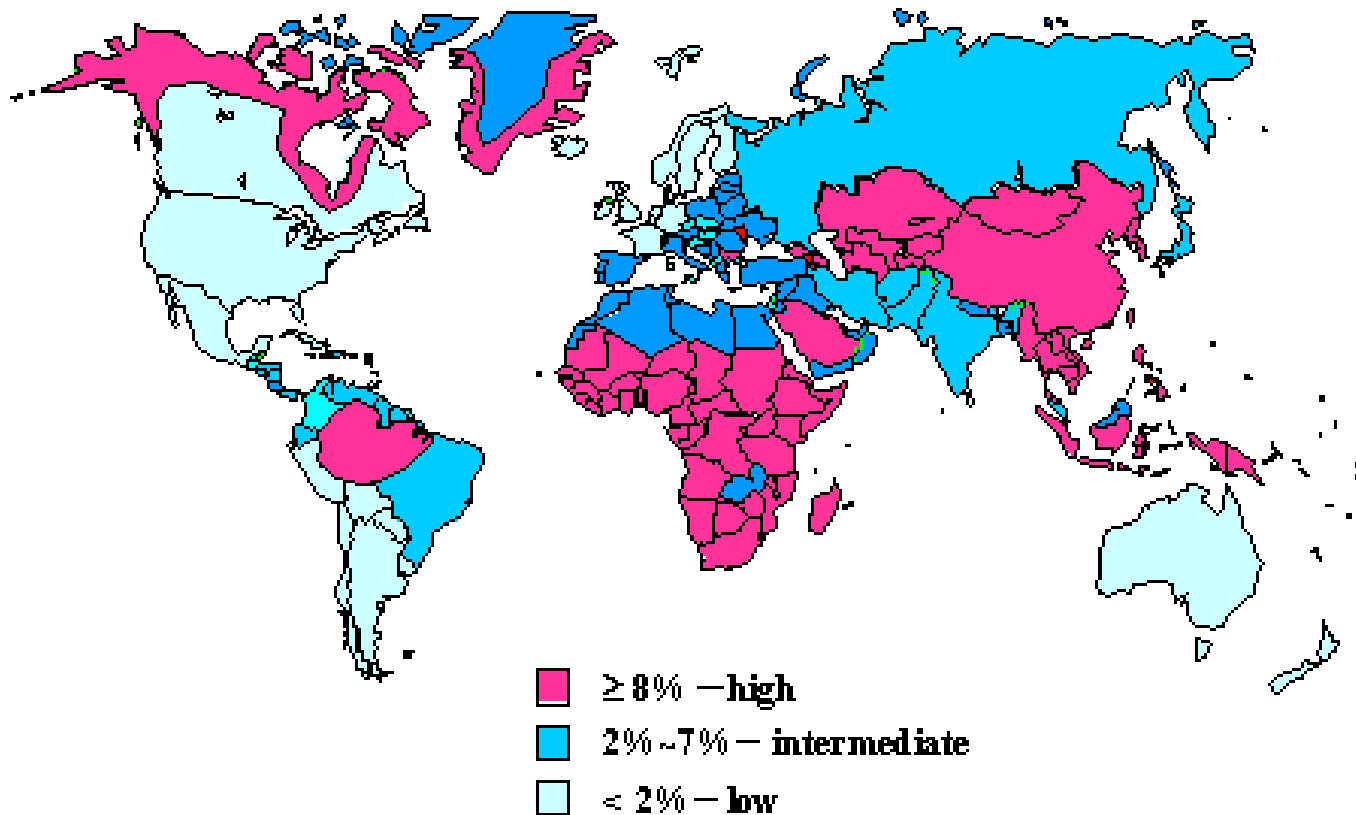
Epidemiology

Chronic Hepatitis

- Worldwide, viral hepatitis is the most common cause, followed closely by alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD)
- Chronic hepatitis B is estimated up to 240 million people in the world
- Chronic hepatitis C is estimated up to 180 million people in the world
- Other less common causes of hepatitis include autoimmune diseases, poisoning especially through toxication, certain medications (such as paracetamol), some industrial organic solvents, and plants.

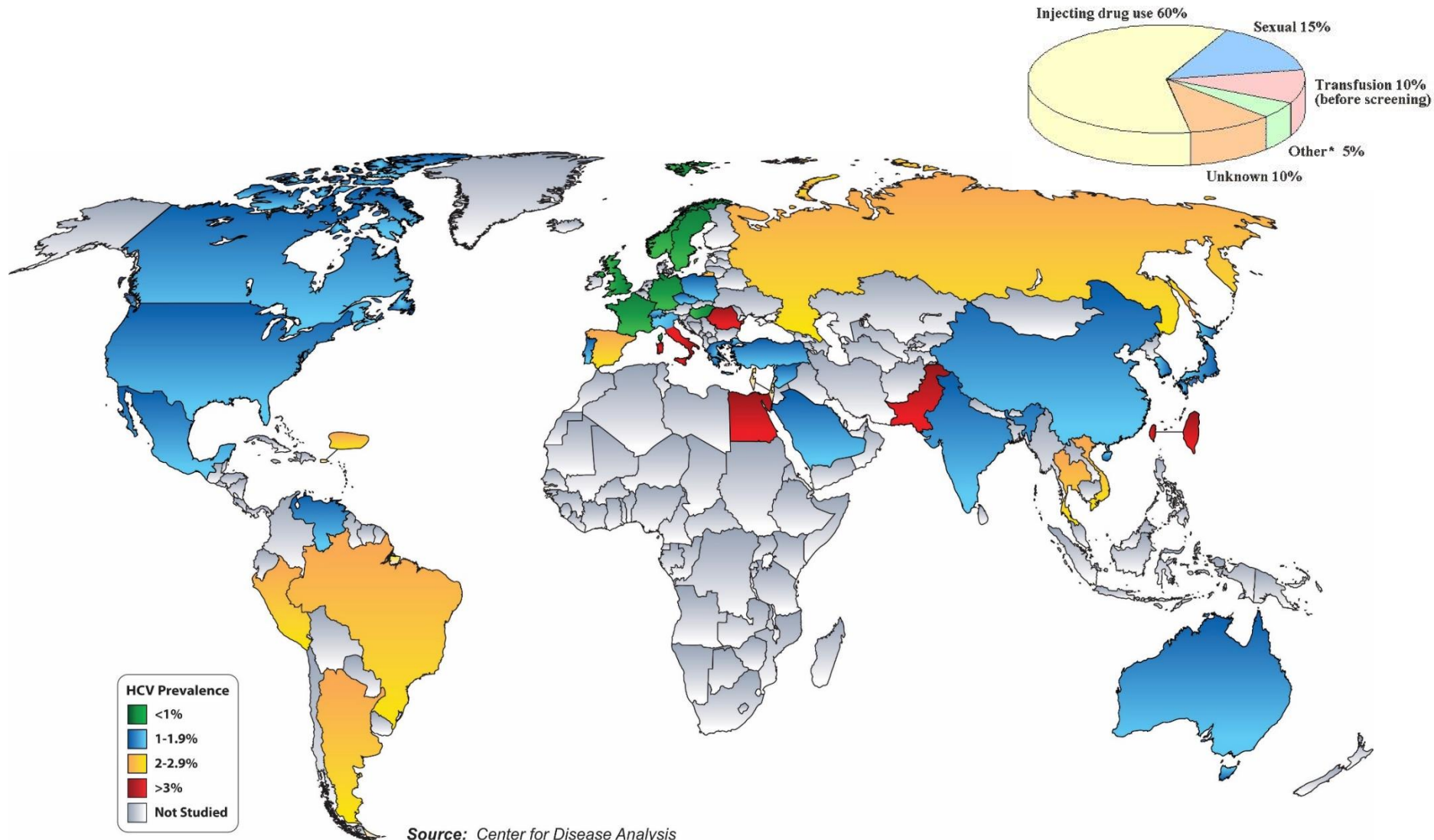
Epidemiology

Chronic Hepatitis: Hepatitis B Virus Infection



Epidemiology

Chronic Hepatitis: Hepatitis C Virus Infection



Risk Factors

Chronic Hepatitis

- Infectious agents
- Sex female
- Tattooing history
- Endoscopy, major surgery
- Phlebotomy, intravenous Drug Use
- High risk job included nurse and barber
- Dentist visit
- Obesity
- Dyslipidemia
- Glucose intolerance
- Excessive alcohol consumption
- More than 900 drugs, toxins, and herbs

Etiology

Chronic Hepatitis

- Infectious ((hepatitis B, C, D; parasitic hepatitis; bacterial hepatitis)
- Metabolic (alcoholic hepatitis, toxic and drug-induced hepatitis, non-alcoholic fatty liver disease)
- Ischemic (due to insufficient blood or oxygen)
- Autoimmune (an abnormal immune response against liver cells, often with other autoimmune diseases)
- Genetic (alpha-1-antitrypsin deficiency, hemochromatosis, Wilson disease (autosomal recessive inherited disorder of copper metabolism))
- Other

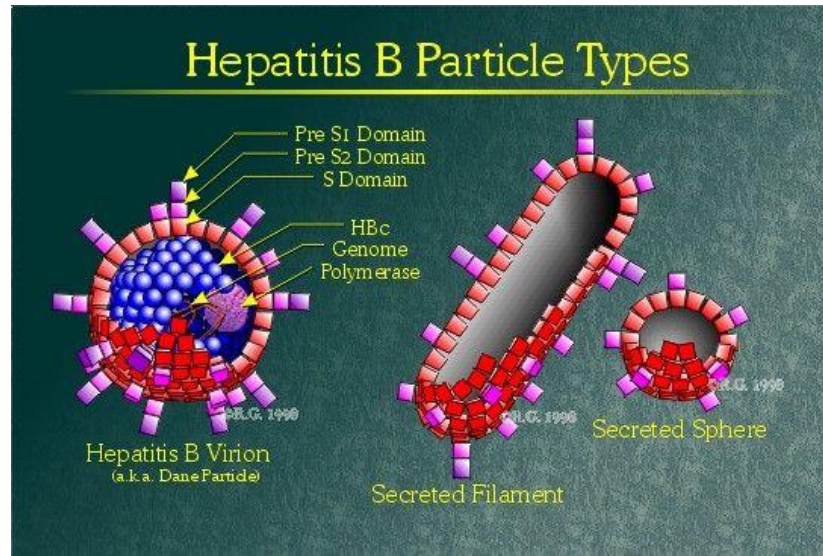
Etiology

Chronic Hepatitis: Viruses

	HBV	HCV	HDV
Transmission	Parenteral	Parenteral	Parenteral
Classification	Orthohepadnavirus	Hepacivirus	Deltavirus
Genome	dsDNA-RT	+ssRNA	–ssRNA
Antigens	HBsAg, HBeAg	Core antigen	Delta antigen
Incubation period	45–160 days	15–150 days	30–60 days
Severity/Chronicity[4]	occasionally severe; 5–10% chronic	subclinical; 70% chronic	exacerbates symptoms of HBV; chronic w/ HBV
Vaccine	3 injections, lifetime protection	None available	None available

Etiology

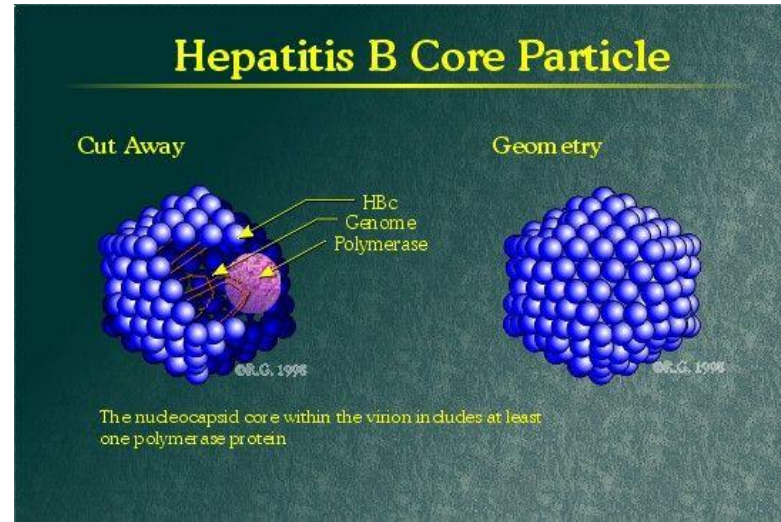
Chronic Hepatitis: Hepatitis B Particle Types



- The hepatitis B virion (HBV, the Dane particle) has a diameter around 42nm
- The outer envelope contains high amounts of hepatitis B surface proteins
- The envelope surrounds the inner nucleocapsid which is comprised of 180 hepatitis B core proteins arranged in an icosahedral arrangement with T=3 and T=4 symmetry
- The nucleocapsid also contains at least one hepatitis B polymerase protein as well as the HBV genome
- Two other subviral particles can be found in an infected individual's serum, namely the hepatitis B filament and hepatitis B sphere (a diameter of 22nm) that are composed solely of hepatitis B surface proteins without infectious nature.

Etiology

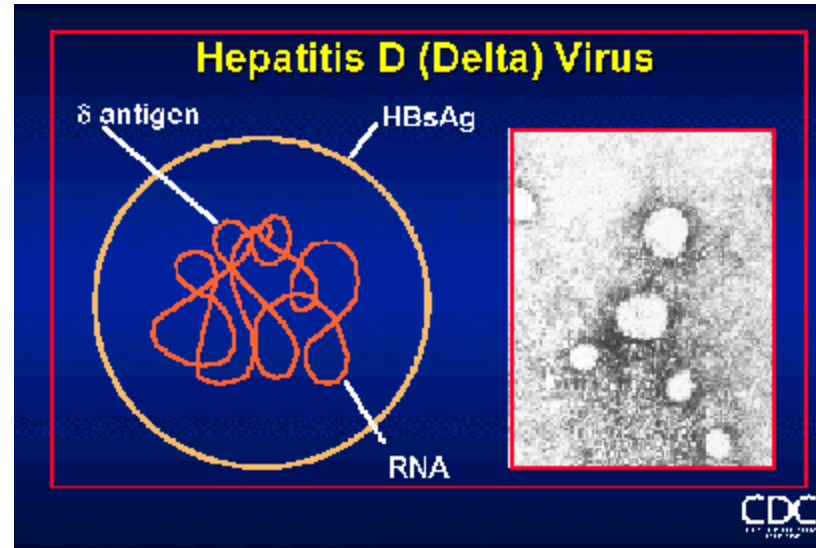
Chronic Hepatitis: Hepatitis C Particle Types



- The hepatitis C virus (HCV) particle consists of a core of genetic material (RNA), surrounded by an icosahedral protective shell of protein, and further encased in a lipid (fatty) envelope of cellular origin
- Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope
- The virus replicates mainly in the hepatocytes of the liver, where it is estimated that daily each infected cell produces approximately fifty virions with a calculated total of one trillion virions generated
- The virus may also replicate in peripheral blood mononuclear cells, potentially accounting for the high levels of immunological disorders found in chronically infected HCV patients.

Etiology

Chronic Hepatitis: Hepatitis D Particle Types



- In 1977, an Italian doctor named Mario Rizzetto discovered a new nuclear antigen in the liver cells of patients infected with Hepatitis B Virus (HBV)
- The antigen was thought to be a new protein encoded by HBV, and it was labeled as the delta antigen
- Subsequent research on chimpanzees, however, indicated that this antigen was derived from a new virus, named the Hepatitis Delta Virus (HDV)
- HDV is not classified into a viral family because it is a unique virus dependent on HBV.

Etiology

Chronic Hepatitis

Hepatitis B transmitted vertically in areas of high incidence (perinatally) from mother to baby during birth) or horizontally by being exposed to infected blood or blood products or less common through exposure to mucous membranes

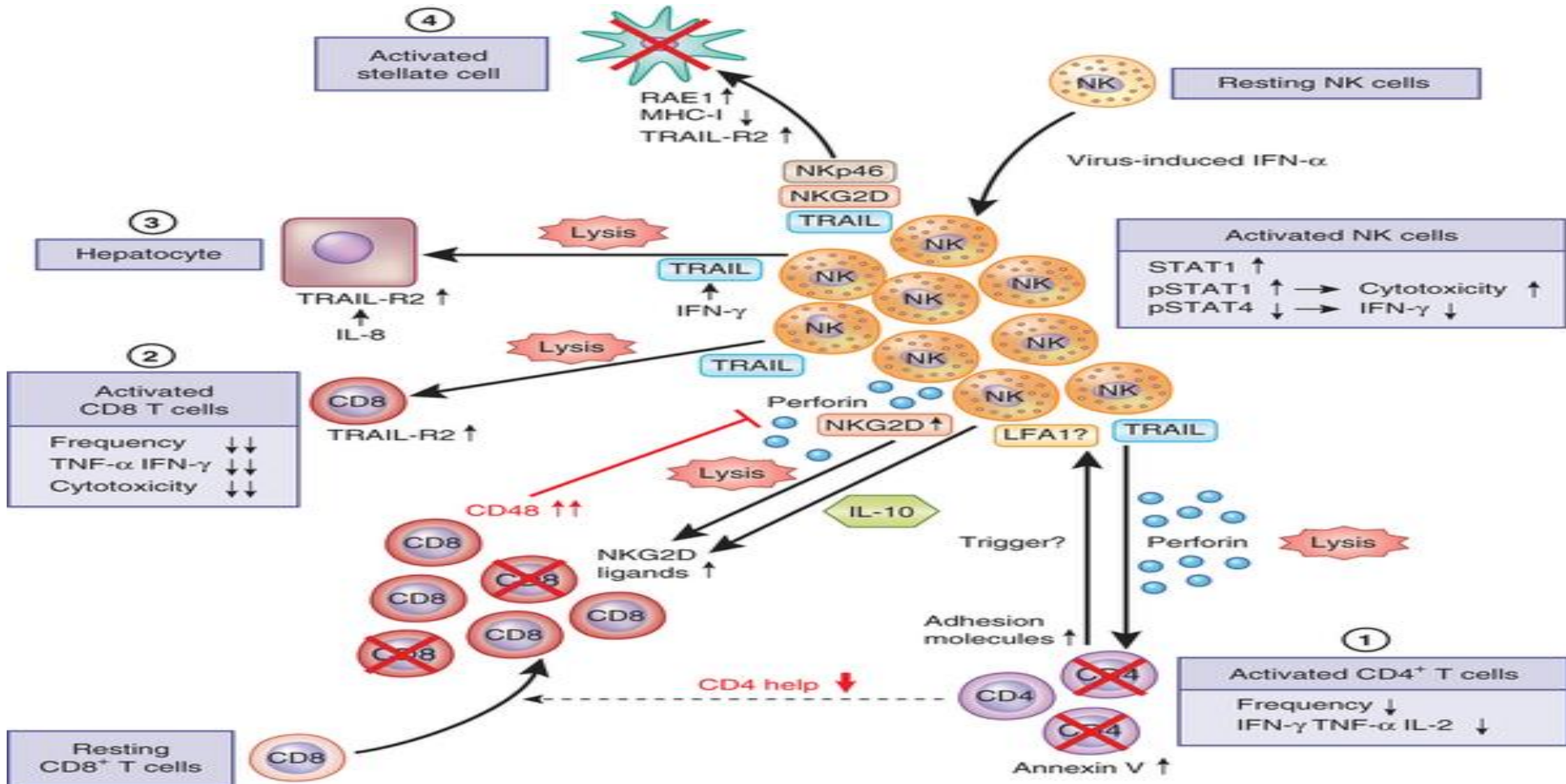
Hepatitis C transmitted in same ways and has become the most common viral hepatitis since widespread vaccination for Hepatitis B in the mid1980s.

Mechanism

Chronic Hepatitis

- The specific mechanism varies and depends on the underlying cause
- In viral hepatitis, the presence of the virus causes the immune system to attack the liver, resulting in inflammation and impaired function
- In autoimmune hepatitis, the immune system attacks the liver due to the autoimmune disease
- In some hepatitis, often including hepatitis caused by alcoholism, fat deposits accumulate in the liver, resulting in fatty liver disease (steatohepatitis)
- Chronic hepatitis in severe cases is occurring with portal based inflammation, fibrosis, disruption of the terminal plate, and piecemeal necrosis
- Chronic hepatitis without piecemeal necrosis (formerly called chronic persistent hepatitis) has no significant periportal necrosis or regeneration with a fairly dense mononuclear portal infiltrate.

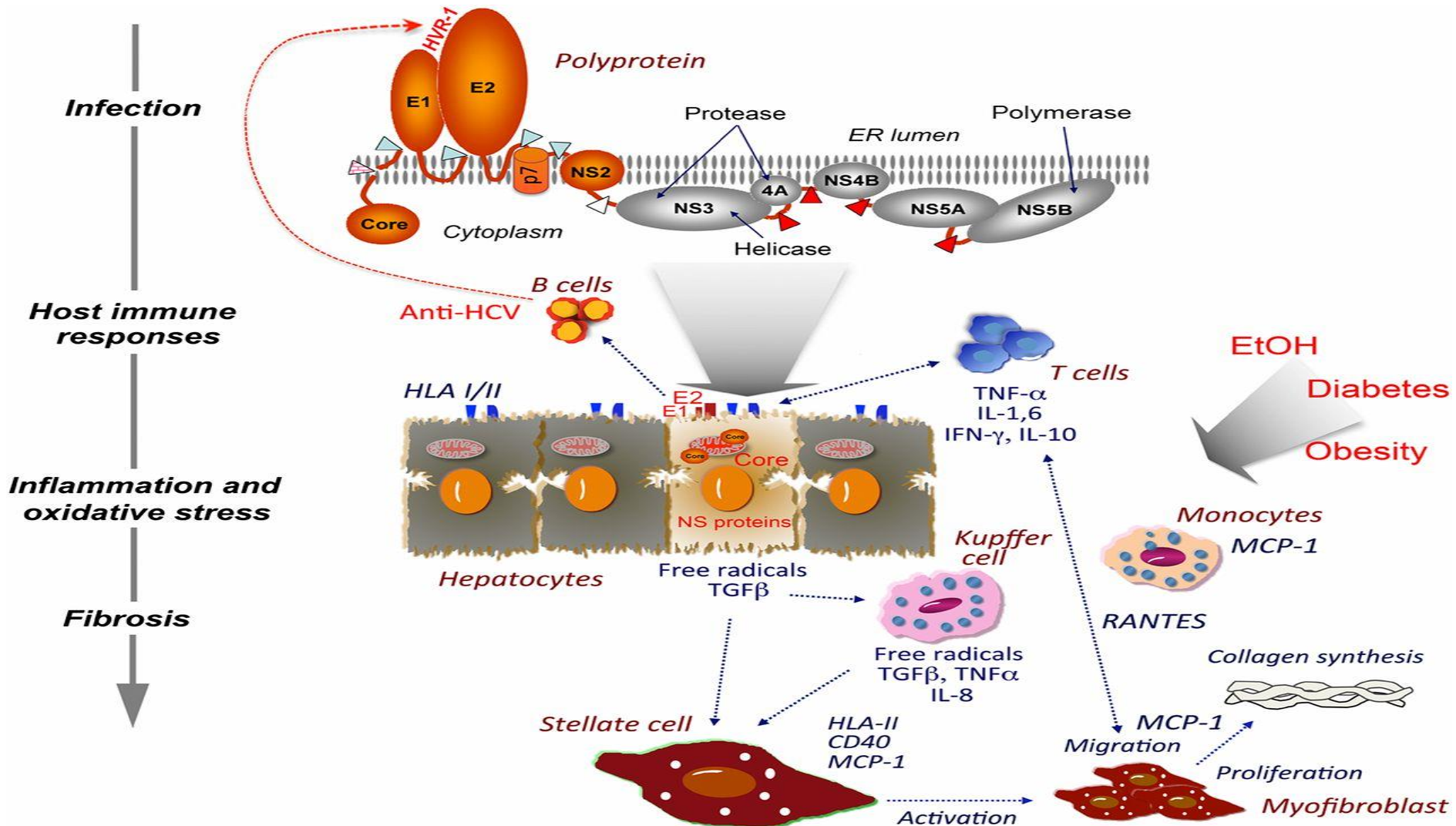
Chronic Hepatitis: NK Cell-mediated Lysis



NK cell-mediated lysis of intrahepatic cells involved in the pathogenesis of viral hepatitis.

Mechanism

Chronic Hepatitis: Fueling Fibrosis



Classification

International Classification of Diseases

XI Diseases of the digestive

B18 Chronic viral hepatitis

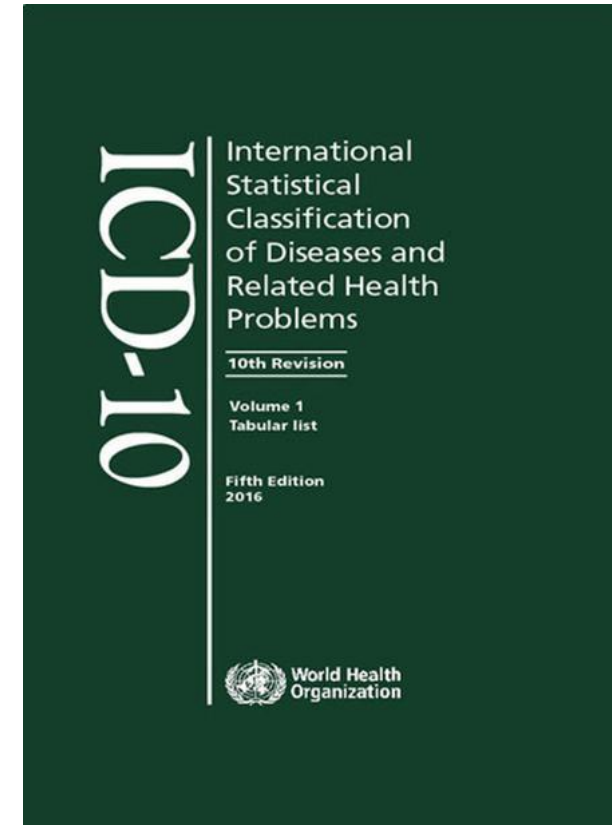
K70 Alcoholic liver disease

K71 Toxic liver disease

K73 Chronic hepatitis, not elsewhere
classified

K74 Fibrosis and cirrhosis of liver

K75 Other inflammatory liver diseases



Classification

Chronic Hepatitis

Cases of CH were once classified histologically as chronic persistent, chronic lobular, or chronic active hepatitis

A more useful recent classification system 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.

Signs and Symptoms

Chronic Hepatitis 1

- About 1/3 of cases develop after acute hepatitis, but most develop insidiously de novo
- Many patients are asymptomatic, especially in chronic HCV infection
- Malaise, anorexia, and fatigue are common, sometimes with low-grade fever and nonspecific upper abdominal discomfort
- Often, particularly with HCV, the first findings are signs of chronic liver disease and cirrhosis (e.g., splenomegaly, spider nevi, palmar erythema, portal hypertension, ascites, encephalopathy)
- A few patients develop manifestations of cholestasis (e.g., jaundice, pruritus, pale stools, steatorrhea)

Signs and Symptoms

Chronic Hepatitis 2

- 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 HCV is occasionally associated with lichen planus, mucocutaneous vasculitis, glomerulonephritis, porphyria cutanea tarda, and, perhaps, non-Hodgkin B-cell lymphoma
- About 1% of patients develop symptomatic cryoglobulinemia with fatigue, myalgias, arthralgias, neuropathy, glomerulonephritis, and rashes (urticaria, purpura, leukocytoclastic vasculitis); asymptomatic cryoglobulinemia is more common.

Clinical Investigation

Chronic Hepatitis

- CH is commonly identified on blood tests performed either for screening or to evaluate nonspecific symptoms
- The presence of jaundice indicates advanced liver damage
- On physical examination there may be enlargement of the liver
- Extensive damage leads to weight loss, easy bruising and bleeding, peripheral edema (swelling of the legs), and accumulation of ascites
- Acne, abnormal menstruation, lung scarring, and inflammation of the thyroid gland and kidneys may be present in women with autoimmune hepatitis
- CH associated aplastic anemia may occur 2–3 months after an acute attack
- Superinfection and coinfection with HDV results in more severe complications compared to infection with HBV alone.

Clinical Investigation

Chronic Hepatitis: Alcoholic

- Alcoholic CH characterized by a myriad of symptoms (feeling unwell, enlargement of the liver, ascites, and modest elevation of liver enzyme levels)
- Alcoholic CH can vary from mild with only liver enzyme elevation to severe liver inflammation with development of jaundice, prolonged prothrombin time, and even liver failure
- Severe cases are characterized by either dulled consciousness or the combination of elevated bilirubin levels and prolonged prothrombin time; the mortality rate in both severe categories is 50%
- Alcoholic CH is distinct from cirrhosis caused by long-term alcohol consumption.
- Neuropsychiatric features: asymmetric tremor, personality changes, dystonia, spasticity, rigidity, emotional lability, impulsiveness, etc.

Clinical Investigation

Chronic Hepatitis: Autoimmune

- Individuals with autoimmune CH often have no initial symptoms and the disease is detected by abnormal liver function tests
- Common initial symptoms include fatigue or muscle aches or signs of acute liver inflammation including fever, jaundice, and right upper quadrant abdominal pain, and occasionally systemic symptoms such as arthralgias, myalgias, polyserositis and thrombocytopenia
- Patients usually present with evidence of moderate to severe hepatitis with elevated serum ALT and AST activities in the setting of normal to marginally elevated alkaline phosphatase and gammaglutamyltranspeptidase activities
- The disease may occur in any ethnic group and at any age, but is most often diagnosed in patients between age 40 and 50
- There is a strong female predominance.

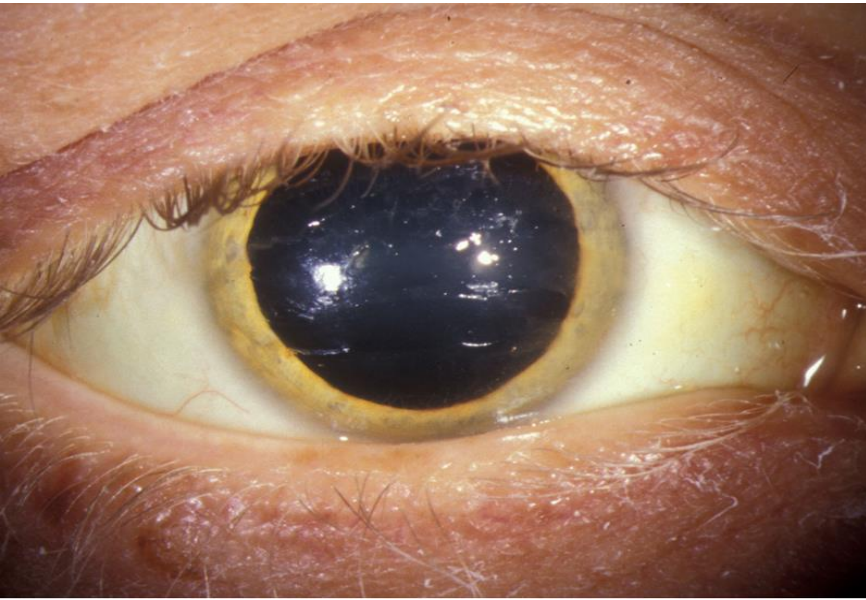
Clinical Investigation

Chronic Hepatitis: Wilson Disease

- The major patterns of hepatic involvement: active CH, cirrhosis and fulminant hepatic failure
- Neuropsychiatric features: asymmetric tremor, excessive salivation, ataxia, masklike facies, clumsiness with the hands, personality changes, dystonia, seizures, rigidity, emotional lability, etc.
- Musculoskeletal manifestations: osteoarthritis, osteoporosis, osteomalacia, rickets, spontaneous fractures
- Hematologic and renal manifestations: intravascular hemolysis, urolithiasis, hematuria
- Kayser-Fleischer rings: the deposition of copper in the Descemet membrane in the limbus of the cornea
- Skin pigmentation and a bluish discoloration at the base of the fingernails (azure lunulae).

Clinical Investigation

Chronic Hepatitis: Wilson Disease



Kayser-Fleischer rings.



Skin pigmentation and a bluish discoloration at the base of the fingernails (azure lunulae).

Clinical Investigation

The natural history of chronic hepatitis B

Stage 1: high viral loads and immune tolerance; in acute infection, this corresponds to the incubation period, but with neonatal chronic infection, this period often lasts for decades

Stage 2: an immunologic response develops leading to hepatocyte necrosis; may persist for 10-20 years and lead to cirrhosis

Stage 3: the immune response decreases the number of infected cells; HBeAg is no longer detectable, a marked decrease in HBV viral load is observed, and aminotransferase levels become normal; some patients continue to have high levels of serum HBV DNA and amino-transferases (referred to as HBeAg-negative chronic hepatitis)

Stage 4: patients become negative for HBeAg and positive for anti-HBs, and HBV DNA is usually no longer detectable in serum; patients with active HBV replication are at increased risk for cirrhosis, hepatic decompensation and hepatocellular carcinoma.

Clinical Investigation

Chronic Hepatitis: Activity

Grade 0: no significant inflammation or necrosis

Grade 1 (minimal activity): portal inflammation with predominantly mononuclear cells almost entirely confined to the portal areas, no interface hepatitis or lobular inflammatory foci

Grade 2 (mild activity): mild portal inflammation, interface hepatitis, and scant lobular spotty necrosis

Grade 3 (moderate activity): moderate portal inflammation, interface hepatitis, and lobular spotty necrosis

Grade 4 (severe activity): marked portal inflammation, interface hepatitis, and lobular necrosis, including bridging necrosis.

Clinical Investigation

Chronic Hepatitis: Fibrosis

Stage 0: no fibrosis

Stage 1: fibrous portal expansion

Stage 2: periportal fibrous extension

Stage 3: fibrous septa formation, including portal-to-central bridging fibrosis

Stage 4: cirrhosis.

Complications

Chronic Hepatitis

- 1 Fibrosis
- 2 Cirrhosis of the Liver
- 3 Cancer of the Liver
- 4 Liver Failure
- 5 5 Glomerulonephritis
- 6 6 Cryoglobulinemia
- 7 7 Hepatic Encephalopathy
- 8 8 Portal Hypertension
- 9 9 Porphyria
- 10 10 Viral Co-Infection

Diagnosis

Chronic Hepatitis

- Diagnosis is made by assessing an individual's symptoms, physical exam, and medical history, in conjunction with blood tests, liver biopsy, and imaging
- Blood testing includes blood chemistry, liver enzymes, serology and nucleic acid testing
- Abnormalities in blood chemistry and enzyme results may be indicative of certain causes or stages of hepatitis
- Imaging can identify steatosis of the liver but liver biopsy is required to demonstrate fibrosis and cirrhosis
- A biopsy is unnecessary if the clinical, laboratory, and radiologic data suggests hepatitis.

Diagnosis

Chronic Hepatitis: Special Blood Testing 1

- Hepatitis B: surface antigen (HBsAg), hepatitis B core antigen (HBcAg), IgM antibodies specific to the hepatitis B core antigen (anti-HBc IgM), hepatitis B e (a viral protein that is secreted by hepatitis B infected cells) antigen (HBeAg); the presence of HBeAg in a host's serum is associated with much higher rates of viral replication and enhanced infectivity; however, variants of the hepatitis B virus do not produce the 'e' antigen, so this rule does not always hold true
- Hepatitis C: HCV antibody enzyme immunoassay or ELISA, recombinant immunoblot assay, and quantitative HCV RNA polymerase chain reaction (PCR); HCV RNA can be detected by PCR typically one to two weeks after infection, while antibodies can take substantially longer to form and thus be detected

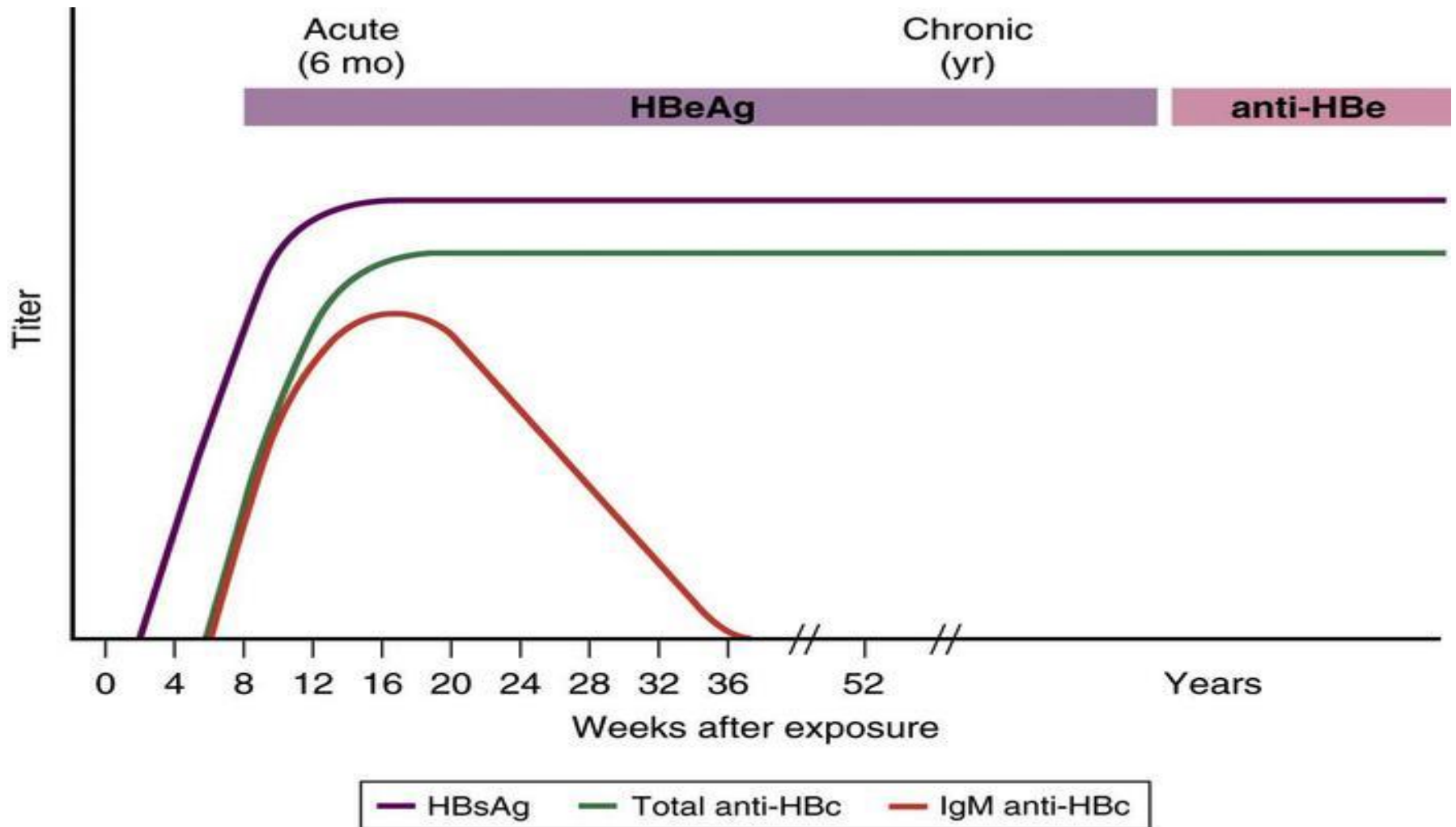
Diagnosis

Chronic Hepatitis: Special Blood Testing 2

- Hepatitis D: HDAg in two forms; a large (L)-HDAg, and a small (S)-HDAg of 24kDa. HDAg-S is produced in the early stages of an infection and enters the nucleus and supports viral replication. HDAg-L, in contrast, is produced during the later stages of an infection, acts as an inhibitor of viral replication, and is required for assembly of viral particles.
- Autoimmune hepatitis: antinuclear antibody (ANA), anti-smooth muscle antibody (SMA), liver/kidney microsomal antibody (LKM-1, LKM-2, LKM-3), anti soluble liver antigen and liver–pancreas antigen (SLA/LP) and anti-mitochondrial antibody (AMA)), increased Immunoglobulin G level. The diagnosis always requires a liver biopsy

Diagnosis

Chronic Hepatitis B: Typical Serological Course



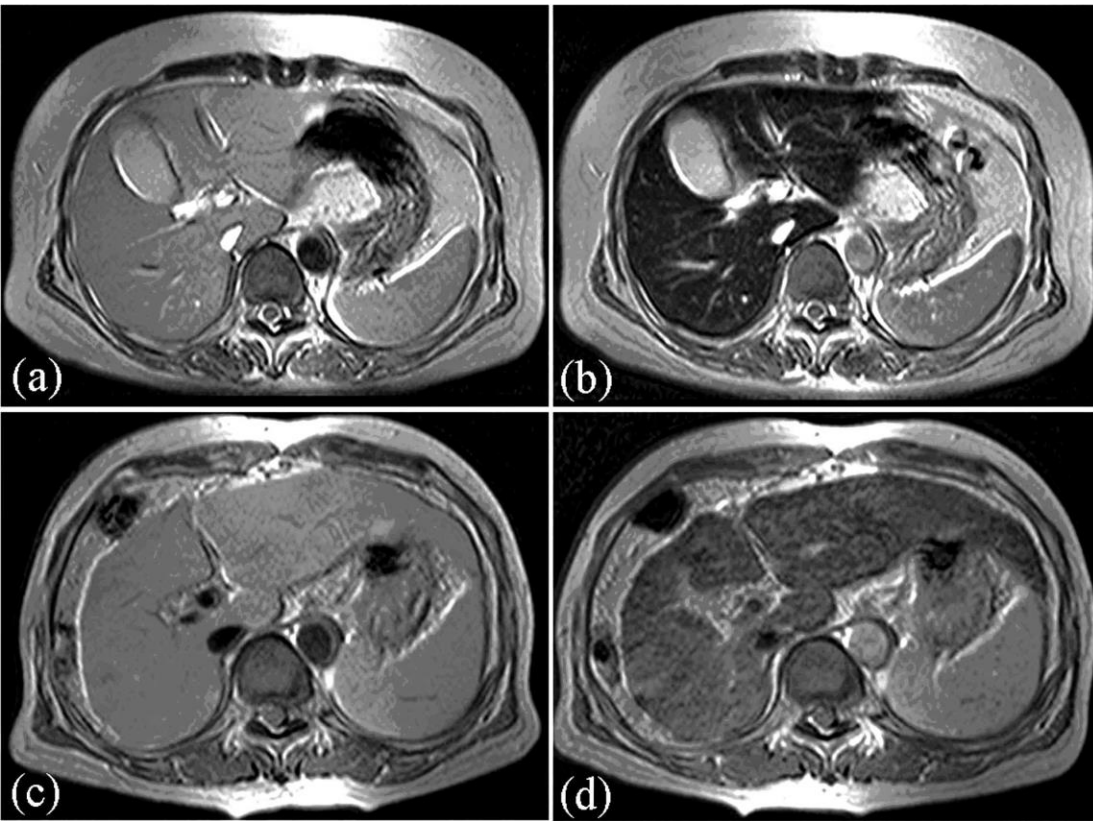
Diagnosis

Chronic Hepatitis B: Liver Chemistry Test

Liver chemistry test	Clinical implication of abnormality
Alanine transaminase Aspartate transaminase	Hepatocellular damage
Lactate dehydrogenase Bilirubin Alkaline phosphatase Gamma-glutamyl transpeptidase Bile acids	Cholestasis
Prothrombin time Albumin	Impaired synthetic function

Diagnosis

Chronic Hepatitis: Imaging Studies



Magnetic resonance images in a 51-year-old woman with chronic hepatitis (A and B) and a 65-year-old woman with liver cirrhosis (C and D).

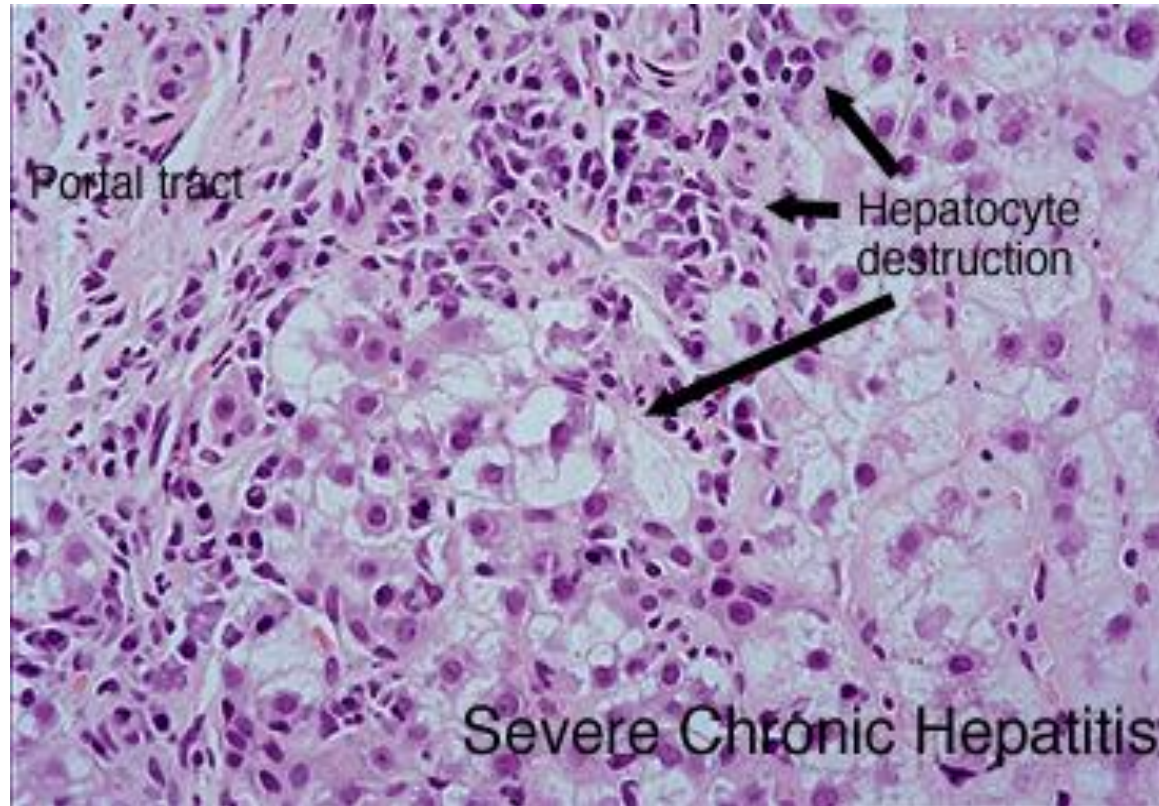
Diagnosis

Chronic Hepatitis: Biopsy

- Unlike in acute hepatitis, biopsy is necessary
- Mild cases may have only minor hepatocellular necrosis and inflammatory cell infiltration, usually in portal regions
- In more severe cases, biopsy shows periportal necrosis with mononuclear cell infiltrates accompanied by variable periportal fibrosis and bile duct proliferation
- In most cases, the specific cause of chronic hepatitis cannot be discerned via biopsy alone, although cases caused by HBV can be distinguished by the presence of ground-glass hepatocytes and special stains for HBV components
- Autoimmune cases have a more pronounced infiltration by lymphocytes and plasma cells.

Diagnosis

Chronic Hepatitis: Histopathologic Features



Severe Chronic Viral Hepatitis.

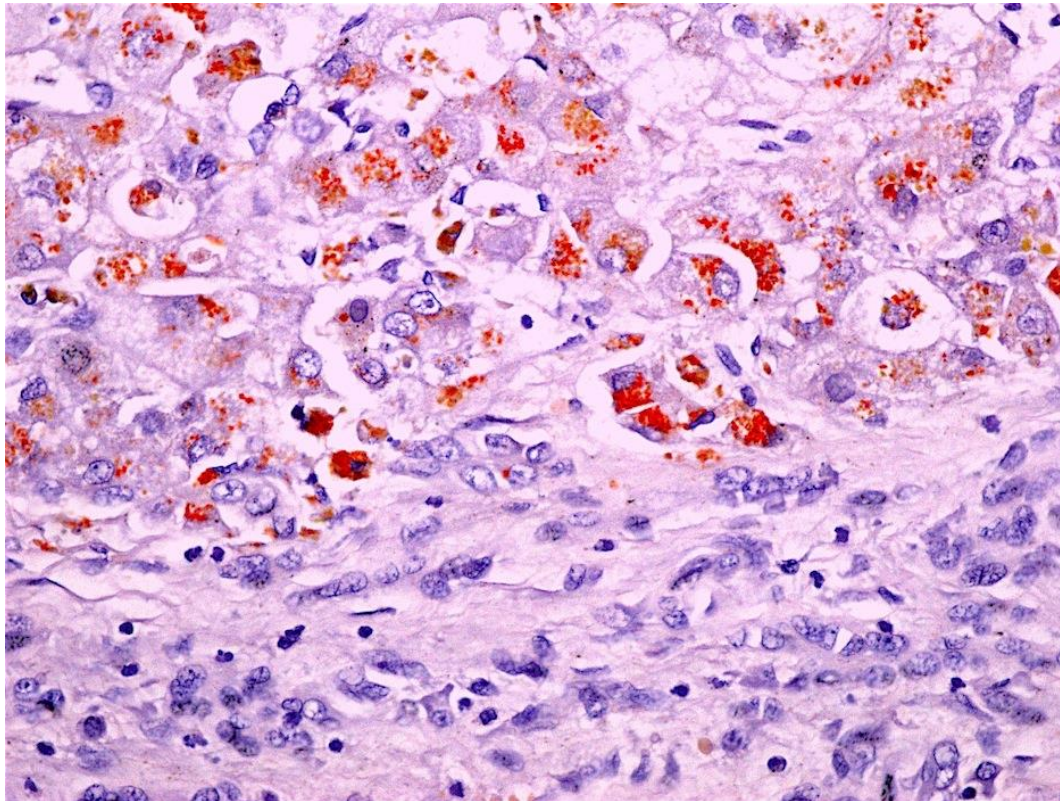
Diagnosis

Chronic Hepatitis: Wilson Disease

- Serum ceruloplasmin levels are less than 20 mg/dL (reference range, 20-40 mg/dL) in approximately 90% of all patients
- The urinary copper excretion rate is greater than 100 mcg/day (reference range, < 40 mcg/day) in most patients
- In a patient with Kayser-Fleischer rings, a serum ceruloplasmin level < 0 mg/dL and 24-hour urine copper excretion >40 mcg/day establish the diagnosis
- Hepatic copper concentration (criterion standard) on a liver biopsy specimen is >250 mcg/g of dry weight even in asymptomatic patients
- Radiolabeled copper testing directly assays hepatic copper metabolism
- Genetic testing is limited to screening of family members for an identified mutation detected in the index patient
- Brain imaging shows characteristic findings; MRI appears to be more sensitive than CT in detecting early lesions
- Resting ECG abnormalities include left ventricular or biventricular hypertrophy, early repolarization, ST segment depression, T-wave inversion, and various arrhythmias.

Diagnosis

Chronic Hepatitis: Wilson Disease' Histopathologic Features



Rhodamine stain for copper.

Management

Chronic Hepatitis: Lifestyle Modifications

- Lifestyle modifications are strongly recommended for patients with chronic hepatitis
- Even when efficacious pharmacologic interventions are identified, lifestyle changes will likely represent an adjuvant treatment because new drugs are inevitably expensive and may have unanticipated adverse effects after prolonged use
- Lifestyle modifications typically encompass both dietary intervention and physical activity goals.

Management

Chronic Hepatitis: Hepatitis B, D

- Patients with persistently elevated serum alanine aminotransferase, and HBV DNA levels are candidates for therapy
- Treatment lasts from six months to a year, depending on medication and genotype
- Although none of the available drugs can clear the infection, they can stop the virus from replicating, thus minimizing liver damage
- There are seven medications licensed for treatment of hepatitis (lamivudine, adefovir, tenofovir, telbivudine, entecavir, interferon alpha2a and PEGylated interferon alpha-2a)
- Interferon treatment may produce an e antigen seroconversion rate of 37% in genotype A but only a 6% seroconversion in type D
- The drug myrcludex B, which inhibits virus entry into hepatocytes, is in clinical trials as of October 2015.

Management

Chronic Hepatitis: Hepatitis C

- HCV induces chronic infection in 50–80% of infected persons
- Approximately 40–80% of these clear with treatment
- In rare cases, infection can clear without treatment
- Those with chronic hepatitis C are advised to avoid alcohol and medications toxic to the liver, and to be vaccinated for hepatitis A and hepatitis B
- Ultrasound surveillance for hepatocellular carcinoma is recommended in those with accompanying cirrhosis.

Management

Chronic Hepatitis: Alcoholic Hepatitis

- Clinical practice guidelines by the American College of Gastroenterology have recommended corticosteroid treatment with prednisolone 40 mg daily for four weeks followed by a taper. Prednisolone gave a small reduction in mortality at 28 days but this did not reach significance, and there were no improvements in outcomes at 90 days or 1 year
- Pentoxifylline (a xanthine derivative) is used to improve blood flow for 4 weeks to prevent one patient from dying. Pentoxifylline did not improve survival alone or in combination.

Management

Chronic Hepatitis: Autoimmune Hepatitis

- Treatment may involve the prescription of immunosuppressive glucocorticoids, with or without azathioprine, and remission can be achieved in up to 60–80% of cases, although many will eventually experience a relapse
- Budesonide has been shown to be more effective in inducing remission than prednisone, and result in fewer adverse effects
- Patients who do not respond to glucocorticoids and azathioprine may be given other immunosuppressives like mycophenolate, cyclosporin, tacrolimus, methotrexate, etc.
- Liver transplantation may be required if patients do not respond to drug therapy or when patients present with fulminant liver failure.

Management

Chronic Hepatitis: Wilson Disease

- The mainstay of therapy is lifelong use of chelating agents (e.g., penicillamine, trientine)
- Symptoms, particularly neurologic ones, may worsen with initiation of chelation
- Surgical decompression or transjugular intrahepatic shunting (TIPS) is reserved for recurrent or uncontrolled variceal bleeding unresponsive to standard conservative measures
- Orthotopic liver transplantation is curative
- Other treatments (anticholinergics, baclofen, GABA antagonists, levodopa, antiepileptics, neuroleptics)
- Protein restriction, lactulose, or both to treat hepatic.

Prognosis

Chronic Hepatitis

- Prognosis depends heavily on the disease or condition that is causing the symptoms
- Chronic damage to the liver can result in the formation of scar tissue (fibrosis) and can result in nodules that block the liver from functioning properly (cirrhosis)
- Another complication of chronic hepatitis is liver cancer, specifically hepatocellular carcinoma
- Some cases can require a liver transplant.

Prophylaxis

Chronic Hepatitis 1

- Vaccines are available to prevent hepatitis B
- Vaccines to prevent hepatitis B have been available since 1986 and have been incorporated into at least 177 national immunization programs for children
- Immunity is achieved in greater than 95% of children and young adults receiving the three-dose recombinant virus vaccine
- Vaccination within 24 hours of birth can prevent transmission from an infected mother
- Adults over 40 years of age have decreased immune response to the vaccine
- The vaccine for hepatitis B protects against hepatitis D virus because of the latter's dependence on the presence of hepatitis B virus for it to replicate.

Abbreviations

CH - Chronic hepatitis

NAFLD - non-alcoholic fatty liver disease

Diagnostic and treatment guidelines

Chronic Hepatitis

Overview of Chronic Hepatitis

[AASLD Guidelines for Treatment of Chronic Hepatitis B](#)

[Hepatitis B Treatment & Management](#)

[Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update](#)

[Management of Chronic Hepatitis B: An Overview of Practice Guidelines for Primary Care Providers](#)

Hepatitis