

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

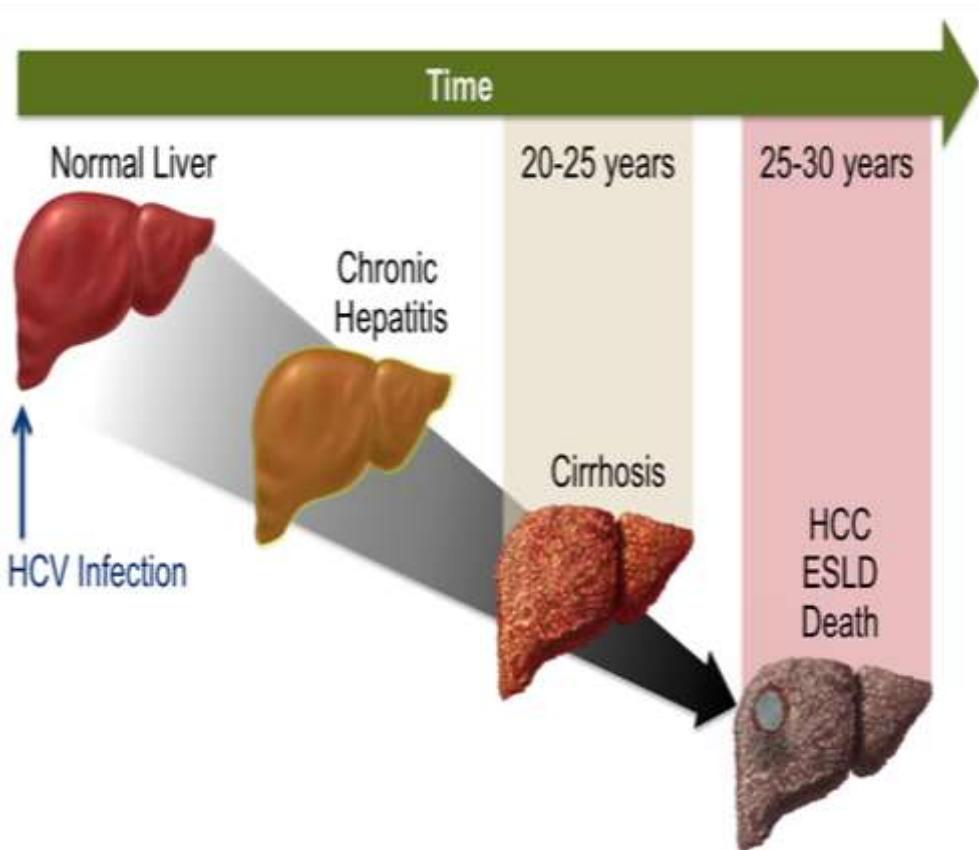
# Chronic Hepatitis

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.

# USMLE TEST

A 56-year-old former intravenous drug user presents for his routine appointment at the infectious disease clinic. He was diagnosed 5 years ago with hepatitis C and is followed closely. He has had multiple liver biopsies that have yet to show cirrhotic changes. His current liver function tests (LFTs) are: AST: 25 IU/L and ALT: 40 IU/L. What is the most appropriate next step in the management of this patient?

1. No treatment indicated,
2. Treatment with ribavarin,
3. Treatment with interferon,
4. Liver transplantation,
5. Treatment with sofosbuvir

# USMLE TEST

The correct answer is 5

This patient has chronic hepatitis C with normal liver enzymes and stable findings on biopsy. Previously, no treatment would have been indicated due to extensive side effects; however, the development of new antiviral drugs such as sofosbuvir have shown great efficacy in clearing the virus with minimal side effects.

Incorrect answers:

Whereas old treatments may have been withheld due to their side effects, this is no longer the standard of care, 2 and 3: Ribavirin and interferon are both treatments that were previously used and are no longer the mainstay of treatment. They are important to know because they may still be on the boards, 4: With normal LFTs it is unlikely that this patient has developed liver cirrhosis; therefore, he is not a candidate for transplantation.

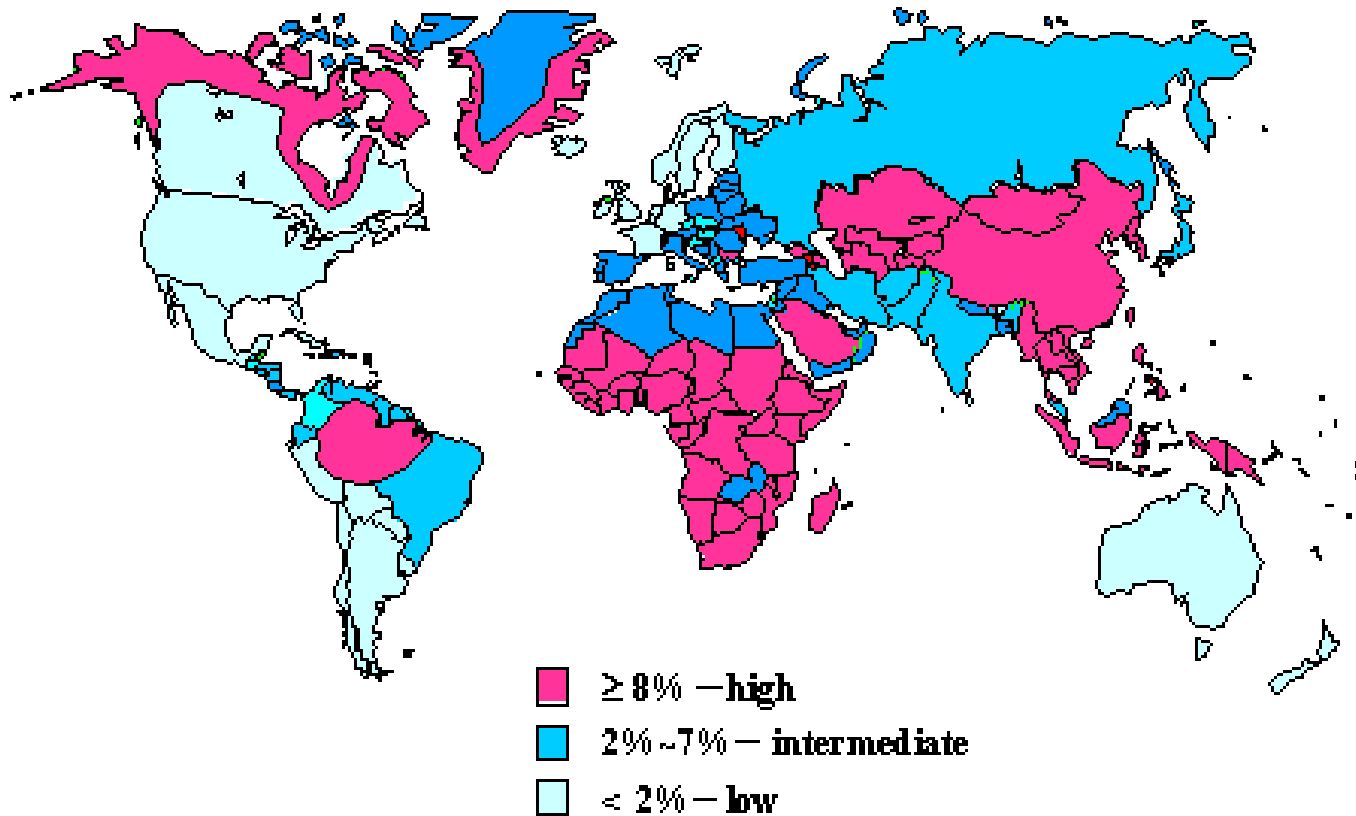
# Epidemiology

## 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.

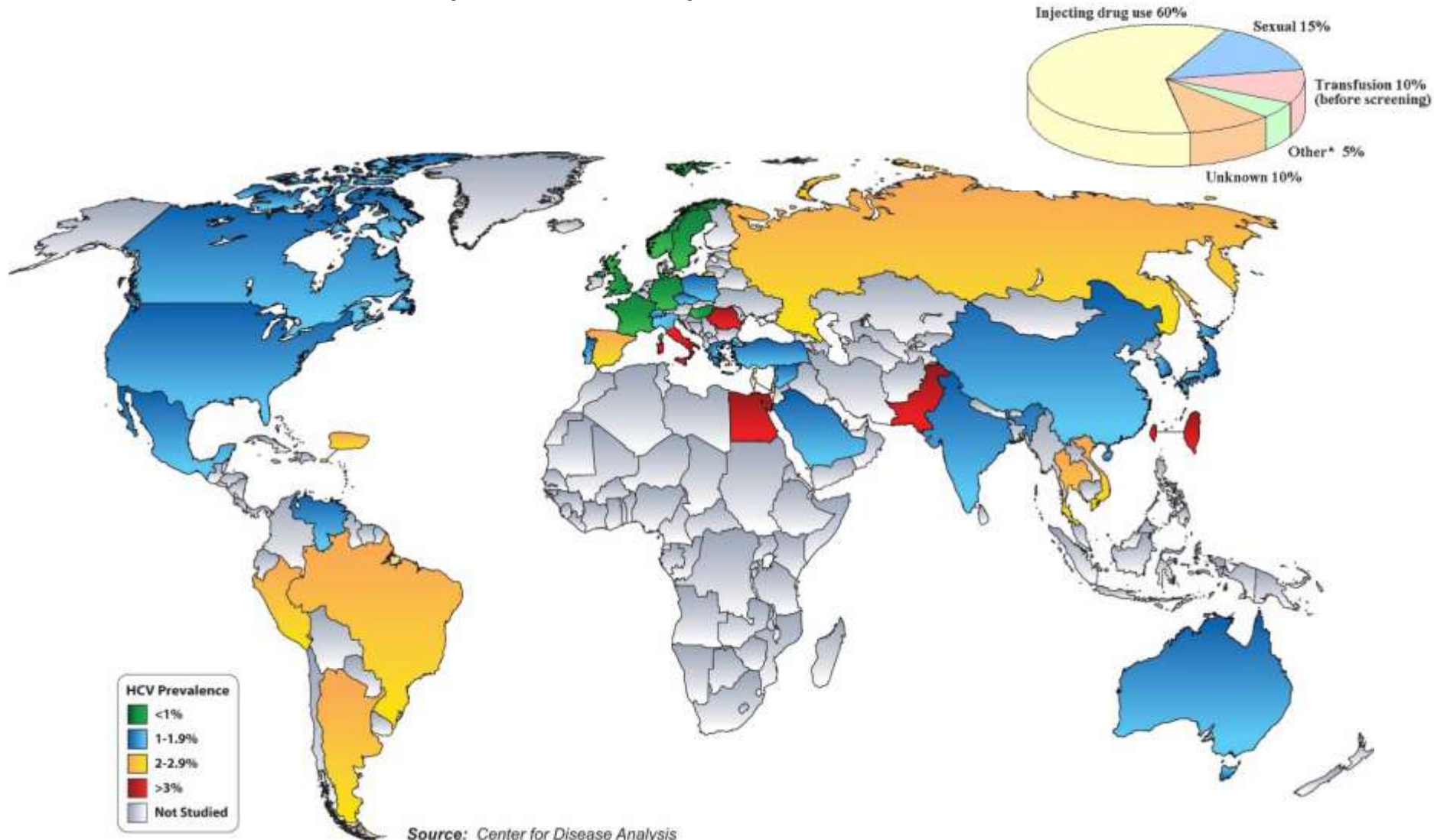
# Epidemiology

## Chronic Hepatitis: Hepatitis B Virus Infection



# Epidemiology

## Chronic Hepatitis: Hepatitis C Virus Infection





# Risk Factors

## Chronic Hepatitis 1

- Infectious agents
- Sex female
- Tattooing history
- Endoscopy, major surgery
- Phlebotomy, intravenous Drug Use
- High risk job included nurse and barber
- Dentist visit
- Obesity

# Risk Factors

## Chronic Hepatitis 2

- 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

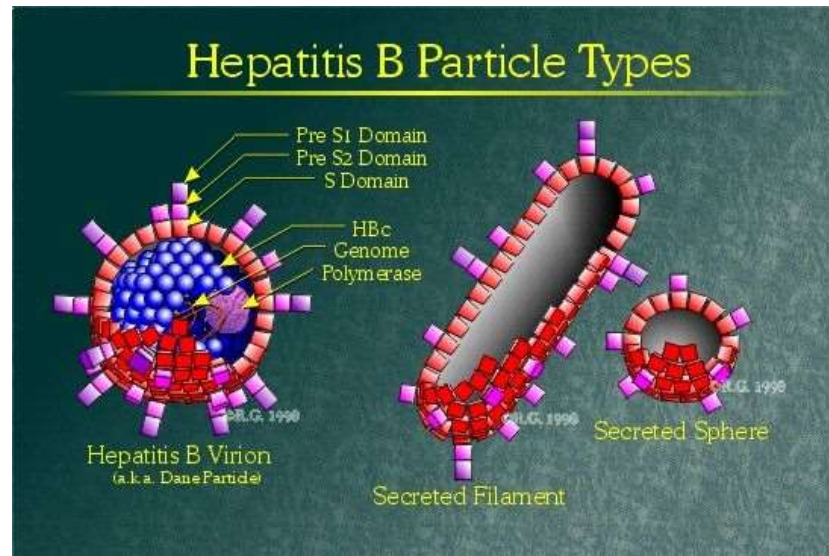
# Etiology

## 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

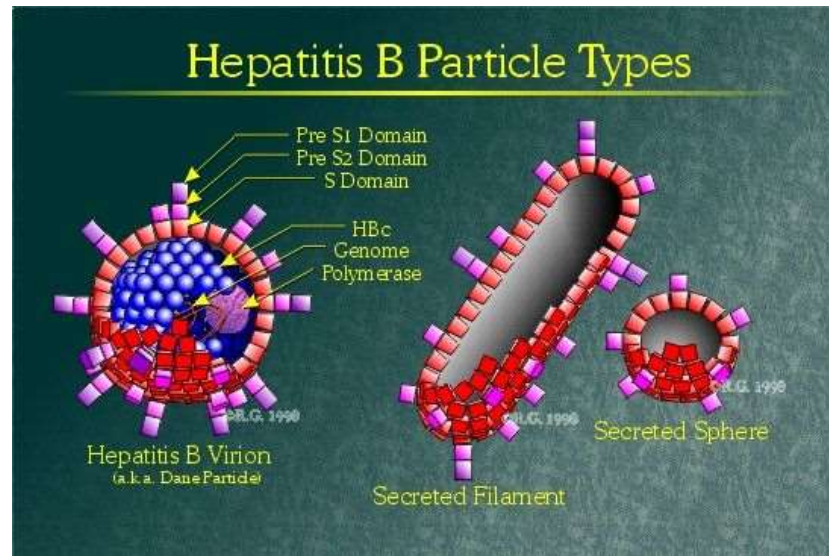
## Chronic Hepatitis: Hepatitis B Particle Types 1



- The hepatitis B virion (HBV, the Dane particle) has a diameter around 42nm
- The outer envelope contains high amounts of hepatitis B surface proteins .

# Etiology

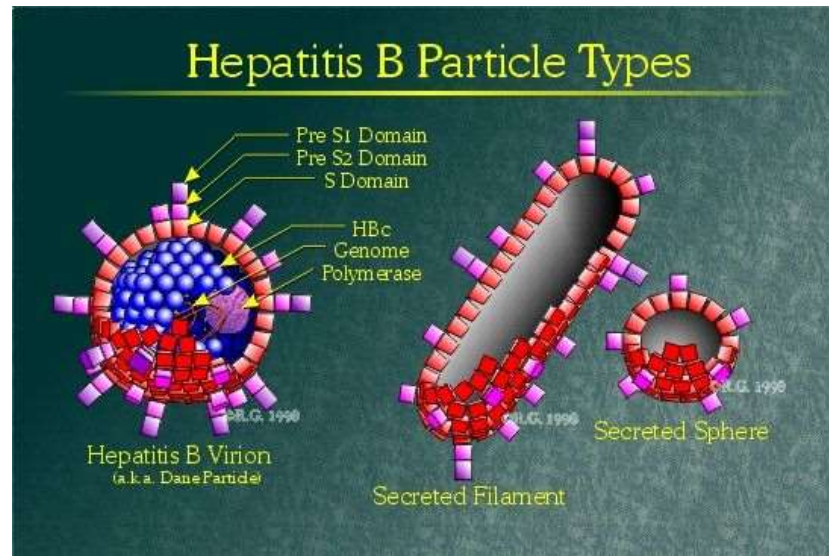
## Chronic Hepatitis: Hepatitis B Particle Types 2



- 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

# Etiology

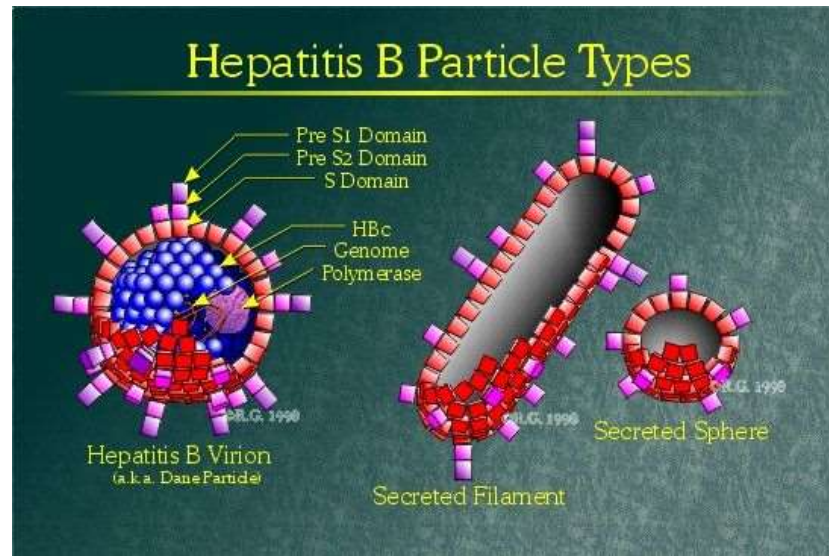
## Chronic Hepatitis: Hepatitis B Particle Types 3



- The nucleocapsid also contains at least one hepatitis B polymerase protein as well as the HBV genome

# Etiology

## Chronic Hepatitis: Hepatitis B Particle Types 4

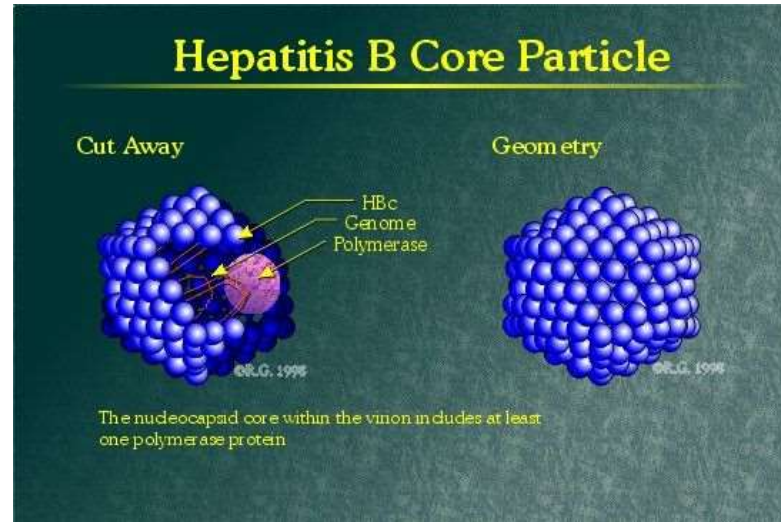


- Two other subviral particles can be found in an infected individual's serum, namely the hepatitis B filament and hepatitis B sphere (a diameter of 22nm) that are composed solely of hepatitis B surface proteins without infectious nature.



# Etiology

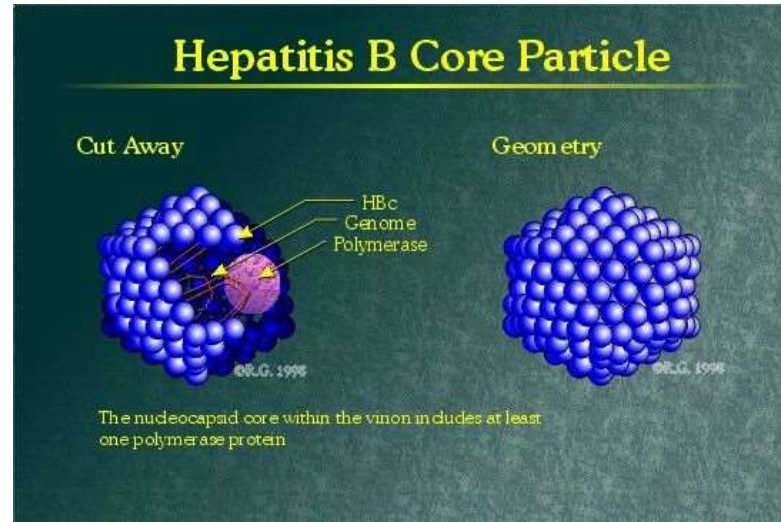
## Chronic Hepatitis: Hepatitis C Particle Types 1



- 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

# Etiology

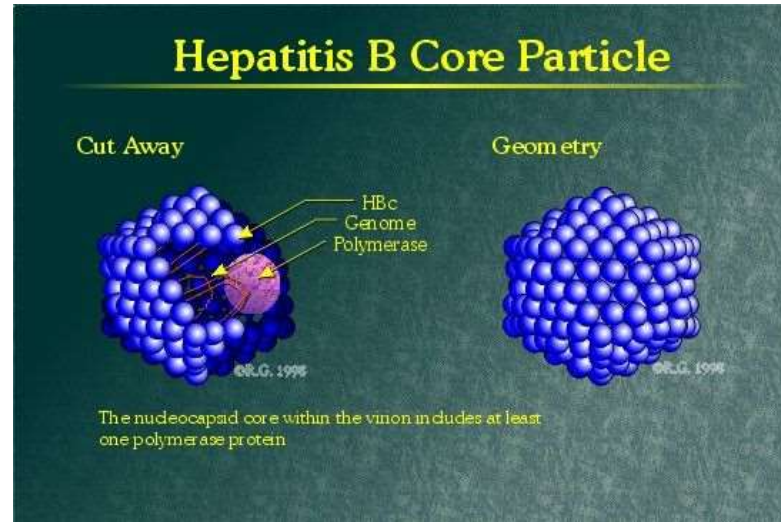
## Chronic Hepatitis: Hepatitis C Particle Types 2



- Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope

# Etiology

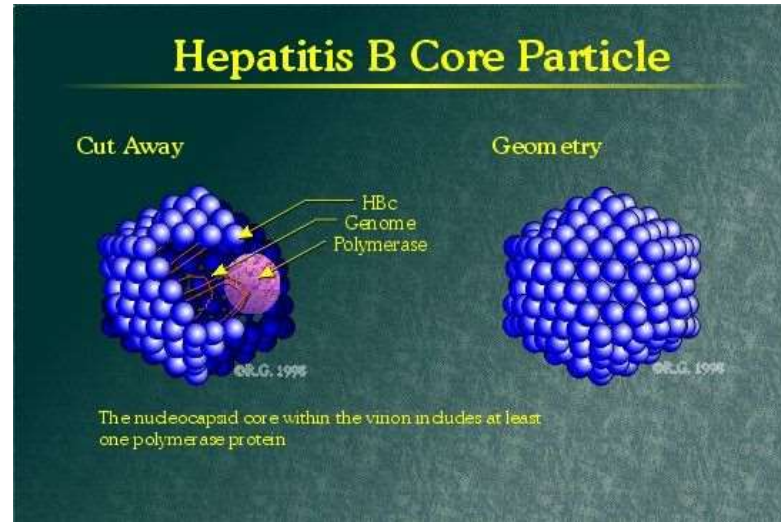
## Chronic Hepatitis: Hepatitis C Particle Types 3



- 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

# Etiology

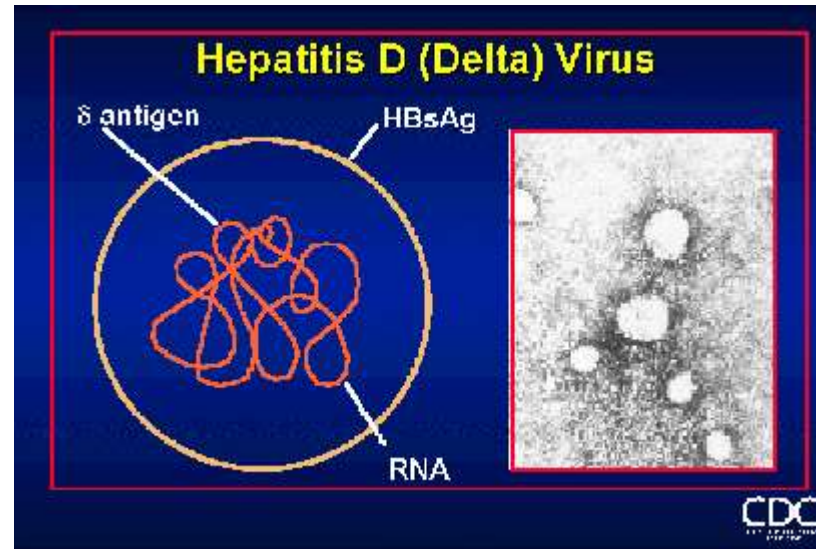
## Chronic Hepatitis: Hepatitis C Particle Types 4



- 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

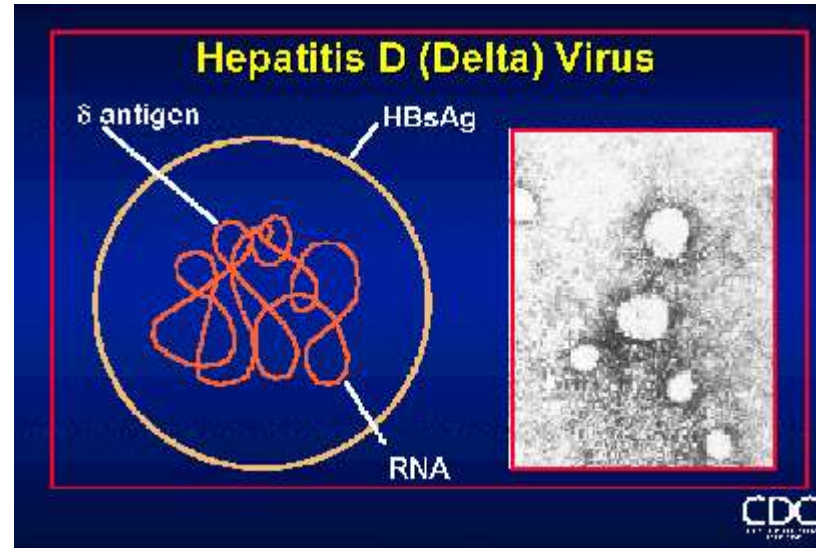
## Chronic Hepatitis: Hepatitis D Particle Types 1



- 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)

# Etiology

## Chronic Hepatitis: Hepatitis D Particle Types 2

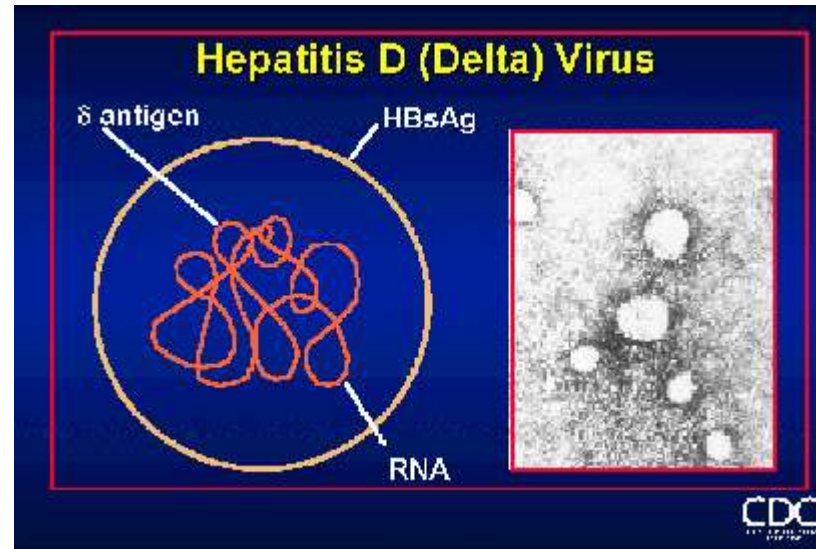


- The antigen was thought to be a new protein encoded by HBV, and it was labeled as the delta antigen



# Etiology

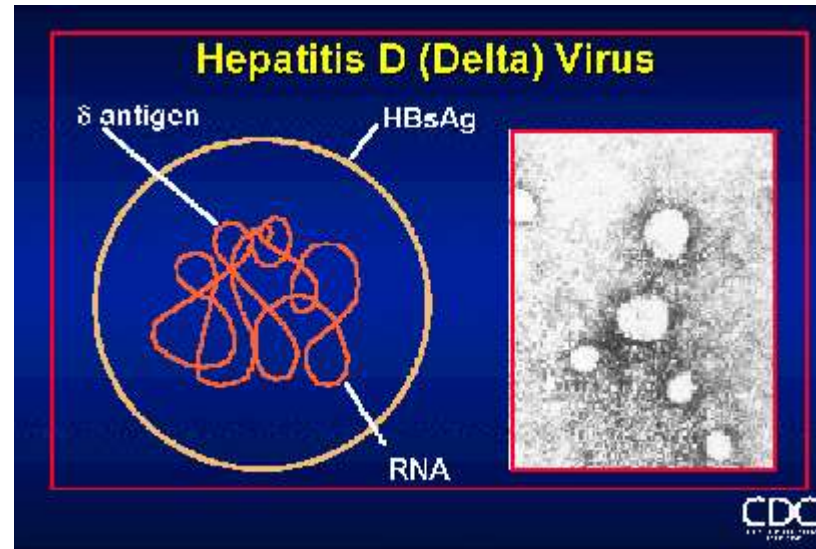
## Chronic Hepatitis: Hepatitis D Particle Types 3



- Subsequent research on chimpanzees, however, indicated that this antigen was derived from a new virus, named the Hepatitis Delta Virus (HDV)

# Etiology

## Chronic Hepatitis: Hepatitis D Particle Types 4



- 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.

# USMLE TEST

A 64-year-old Vietnam veteran who has just moved to the area from another state presents to a primary care physician to establish care. The patient reports that his only medical issue is hypertension for which he takes hydrochlorothiazide. He recalls only one prior hospitalization (he jokes that it was on his 20th birthday in 1971) for gallbladder surgery and received a blood transfusion. Because of his transfusion history, for which of the following should this patient be screened?

1. Hepatitis B,
2. Hepatitis C,
3. Hepatitis B & C,
4. Post-transfusion purpura,
5. HIV infection

# USMLE TEST

The correct answer is 3

This patient should be screened for hepatitis B and hepatitis C. Individuals who received a blood transfusion before 1992 should be screened for hepatitis C and individuals who received transfusions before 1986 should be screened for hepatitis B.

Incorrect answers:

1 & 2: This individual received a blood transfusion in the late 1960s, necessitating that he be screened for both hepatitis B and C, 4: Post-transfusion purpura is a non-infectious complication of blood transfusions resulting in sudden severe thrombocytopenia developing about 9 days following transfusion. This is not relevant to this patient, 5: The first reported cases of transfusion-related HIV were not noted until the 1980s. This patient's blood transfusion took place far before that time.

# Mechanism

## Chronic Hepatitis 1

- 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)

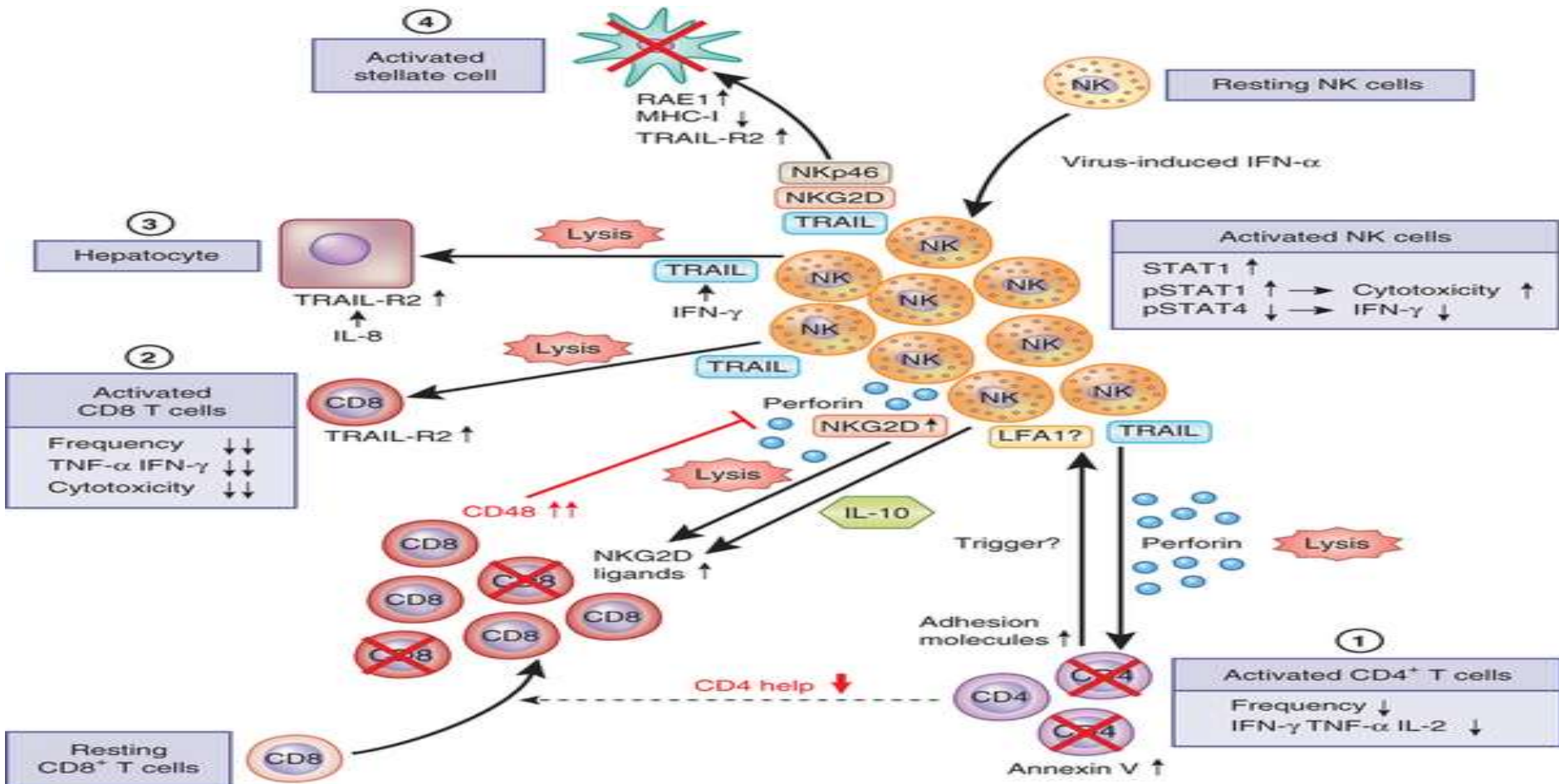
# Mechanism

## Chronic Hepatitis 2

- 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.

# Mechanism

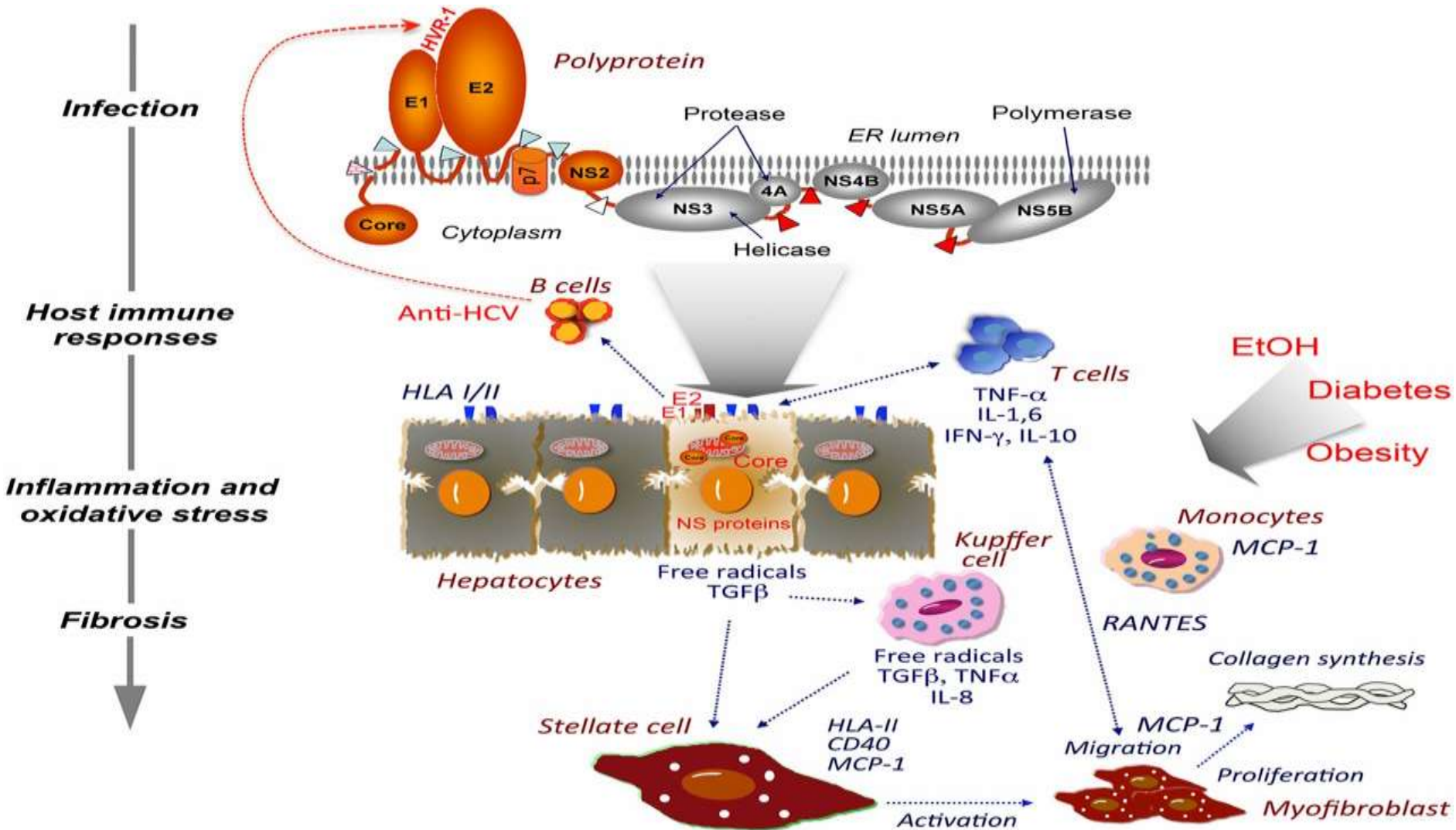
## Chronic Hepatitis: NK Cell-mediated Lysis



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

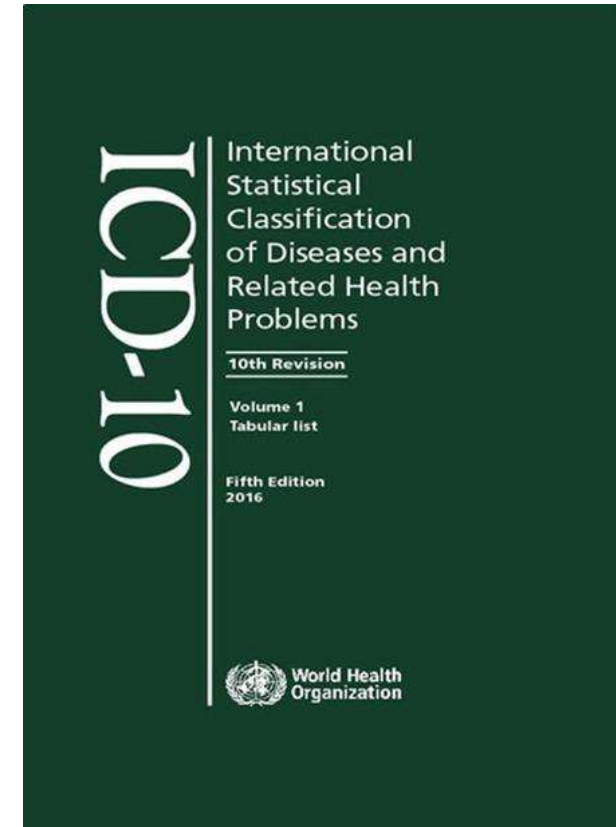
K70 Alcoholic liver disease

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.

# USMLE TEST

A 32-year-old male with a long history of injection drug use is seen in your clinic complaining of fatigue and loss of appetite. Physical exam is largely unremarkable. Tests reveal serum positive for anti-HCV antibodies and positive HCV RNA. Which of the following tests will give the best information regarding the patient's prognosis?

1. Liver ultrasound,
2. Liver biopsy,
3. Physical exam,
4. AST:ALT ratio,
5. AST only

# USMLE TEST

The correct answer is 2

This patient likely has chronic hepatitis C infection. Liver biopsy is the most appropriate test to determine the extent of fibrosis and liver damage in individuals with chronic hepatitis.

Incorrect answers:

1: Hepatic ultrasound can be negative in cases where biopsy shows disease histologically, therefore it is not a sensitive diagnostic test,

3: Alkaline phosphatase is an enzyme in cells that line the liver biliary ducts, and so is a marker of cholestatic disease or bile duct obstruction but not particularly appropriate for assessing fibrosis,

4-5: Levels of ALT and AST can vary widely and be normal or elevated in patients with chronic hepatitis, so they are not a good marker of progression of disease.

# 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

# Signs and Symptoms

## Chronic Hepatitis 2

- 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 3

- 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

# Signs and Symptoms

## Chronic Hepatitis 4

- 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 1

- 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



# Clinical Investigation

## Chronic Hepatitis 2

- 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 1

- 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

# Clinical Investigation

## Chronic Hepatitis: Alcoholic 2

- 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 1

- 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

# Clinical Investigation

## Chronic Hepatitis: Autoimmune 2

- 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 2

- 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

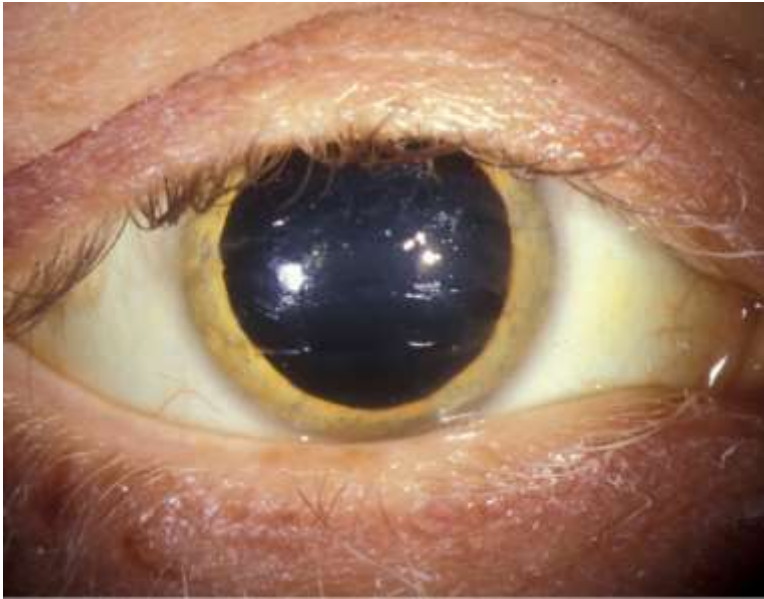
# Clinical Investigation

## Chronic Hepatitis: Wilson Disease 1

- 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 1

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

# Clinical Investigation

The natural history of chronic hepatitis B 2

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)

# Clinical Investigation

The natural history of chronic hepatitis B 3

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 1

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

# Clinical Investigation

## Chronic Hepatitis: Activity 2

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.

# USMLE TEST

A 31-year-old woman with well-controlled hypertension and history of compensated liver disease secondary to hepatitis C virus (HCV) has just learned she is 4 weeks pregnant. Her current medications include interferon, ribavirin, and hydrochlorothiazide. Two weeks ago, she was vaccinated for hepatitis A and hepatitis B. Assuming the patient's hepatic function is stable throughout her pregnancy, which of the following poses the greatest risk for the patients' future child?

1. Infection with HCV from vertical transmission,
2. Infection with HCV from breast feeding,
3. Adverse birth outcomes due to patient's medications,
4. Adverse birth outcomes due to patient's vaccination history,
5. Intrauterine growth restriction due to patient's hepatitis C status

# USMLE TEST

The correct answer is 3

The most concerning aspect of this patient's history is use of ribavirin. Ribavirin is highly teratogenic and contraindicated during pregnancy.

Incorrect answers:

1: Overall incidence of vertical transmission of HCV is approximately 2-5%.

2: HCV is not thought to be transmitted through breast feeding, although HCV RNA can be detected in colostrum.

4: All patients with chronic hepatitis C, regardless of pregnancy, should be vaccinated for Hepatitis A and B if not immune already.

5: Intrauterine growth restriction is not known to be related to maternal HCV infection.



# 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

# USMLE TEST

A 32-year-old female presents to the emergency room with jaundice and altered mental status. She is afebrile with all other vital signs normal. When she extends her wrists her hands tremor. Initial labs reveal markedly elevated transaminases and prolonged prothrombin time. Total bilirubin is 6mg/dL and serum creatinine is 3 mg/dL. The patient's husband reports that she pricked herself with a needle in a hospital where she was volunteering several weeks ago. She is admitted to the intensive care unit with institution of supportive cares, but her condition continues to deteriorate, with further elevation in her bilirubin and INR and worsening encephalopathy. What is the appropriate next step in management?

1. Administer N –acetylcysteine,
2. ERCP,
3. Evaluation for emergent liver transplantation,
4. Hepatic artery embolization,
5. Portohepatic shunt procedure

# USMLE TEST

The correct answer is 3

This patient has fulminant liver failure, likely from acute hepatitis B infection from dirty needle exposure. Emergent liver transplant may be required for fulminant liver failure that progresses despite supportive cares.

Incorrect answers:

1: N-Acetylcysteine may be administered in acetaminophen overdose and may improve transplant-free survival in other forms of acute liver failure with mild encephalopathy, but definitive therapy is liver transplantation, 2: ERCP would be helpful in an ascending cholangitis caused by an obstructive stone, but has no role for fulminant viral hepatitis, 4: Hepatic artery embolization may be used for some primary hepatic tumors and neuroendocrine tumors that metastasize to the liver, but would not be helpful in fulminant liver failure from viral hepatitis, 5: A portohepatic shunt may be used in cases of worsening portal hypertension but does not have a role in acute liver failure.

# Diagnosis

## Chronic Hepatitis 1

- 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

# Diagnosis

## Chronic Hepatitis 2

- 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

# Diagnosis

## Chronic Hepatitis: Special Blood Testing 2

- 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 3

- 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.



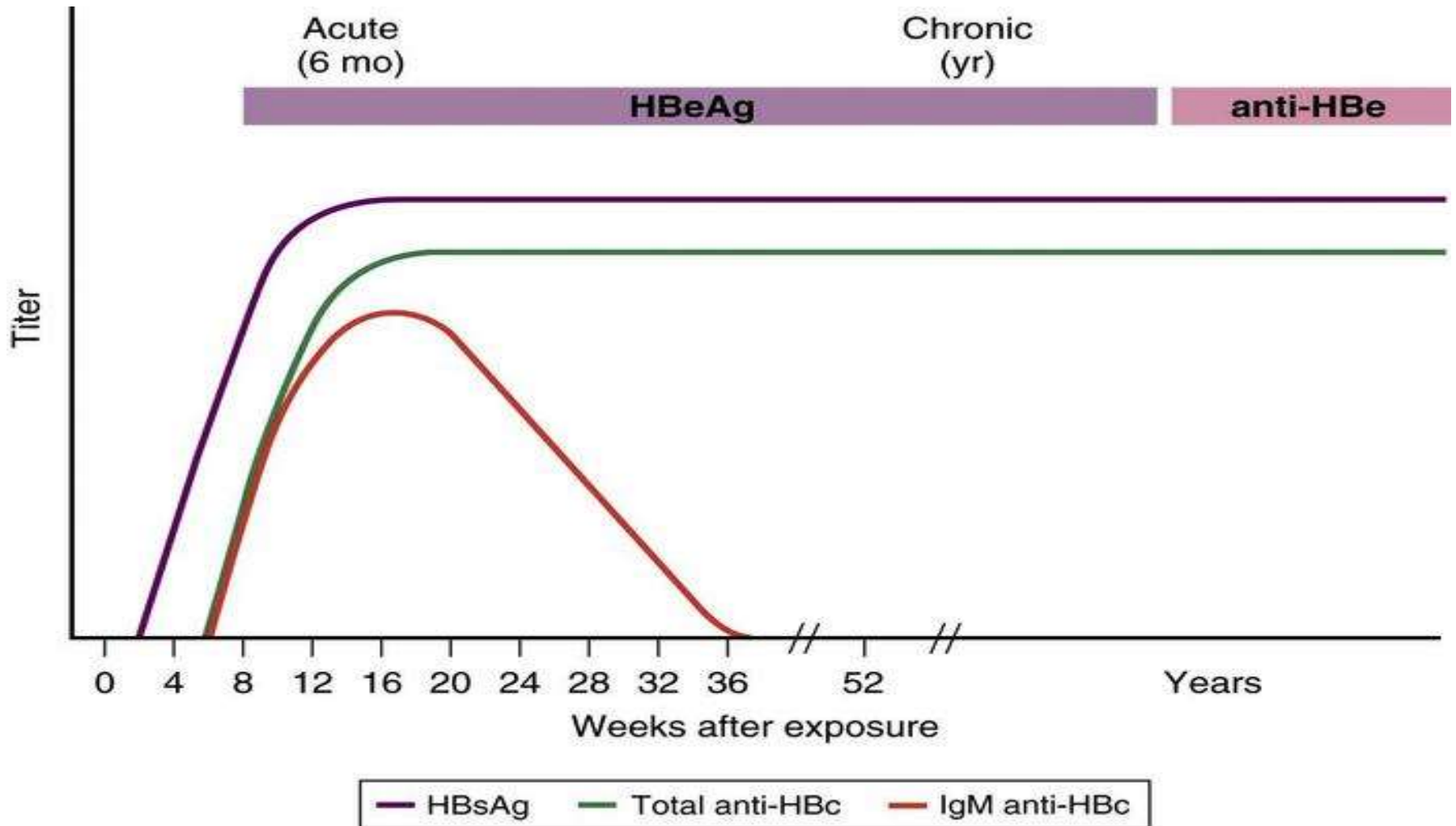
# Diagnosis

## Chronic Hepatitis: Special Blood Testing 4

- 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 abnormality

Alanine transaminase

Aspartate transaminase

Lactate dehydrogenase

Bilirubin

Alkaline phosphatase

Gamma-glutamyl transpeptidase

Bile acids

Prothrombin time  
function

Albumin

### Clinical implication of

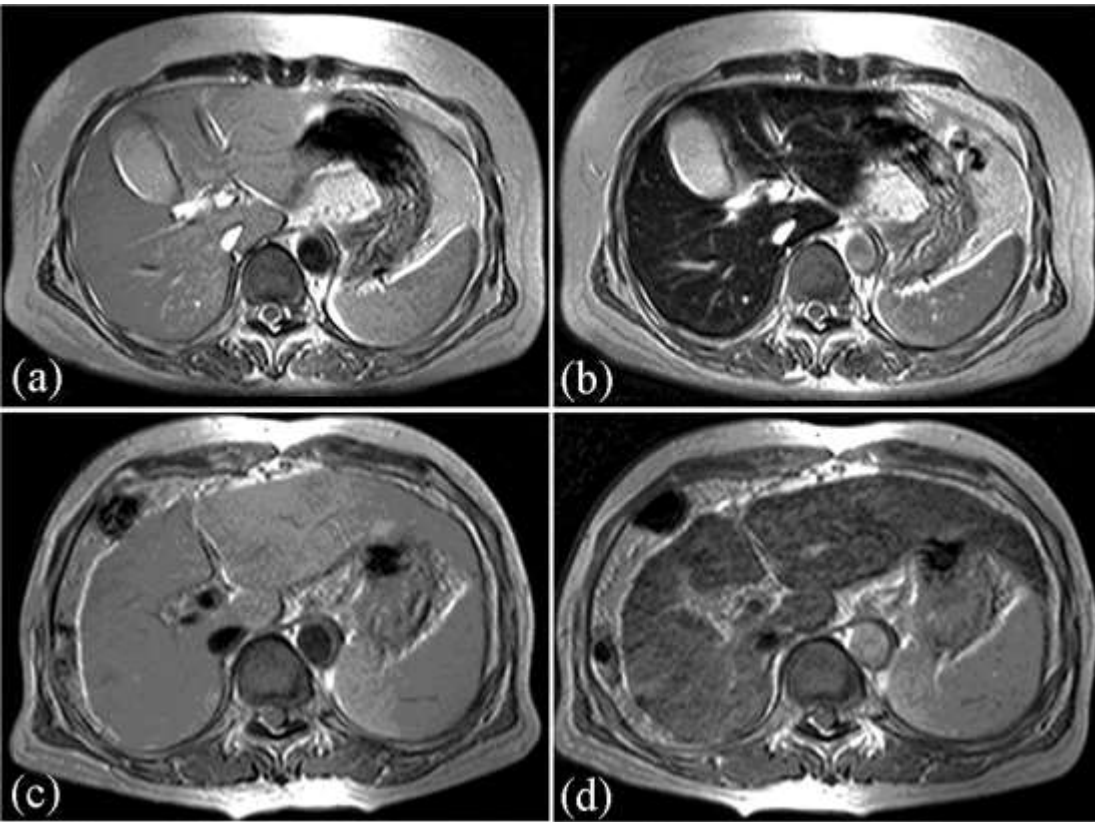
Hepatocellular damage

Cholestasis

Impaired synthetic

# 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 1

- 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

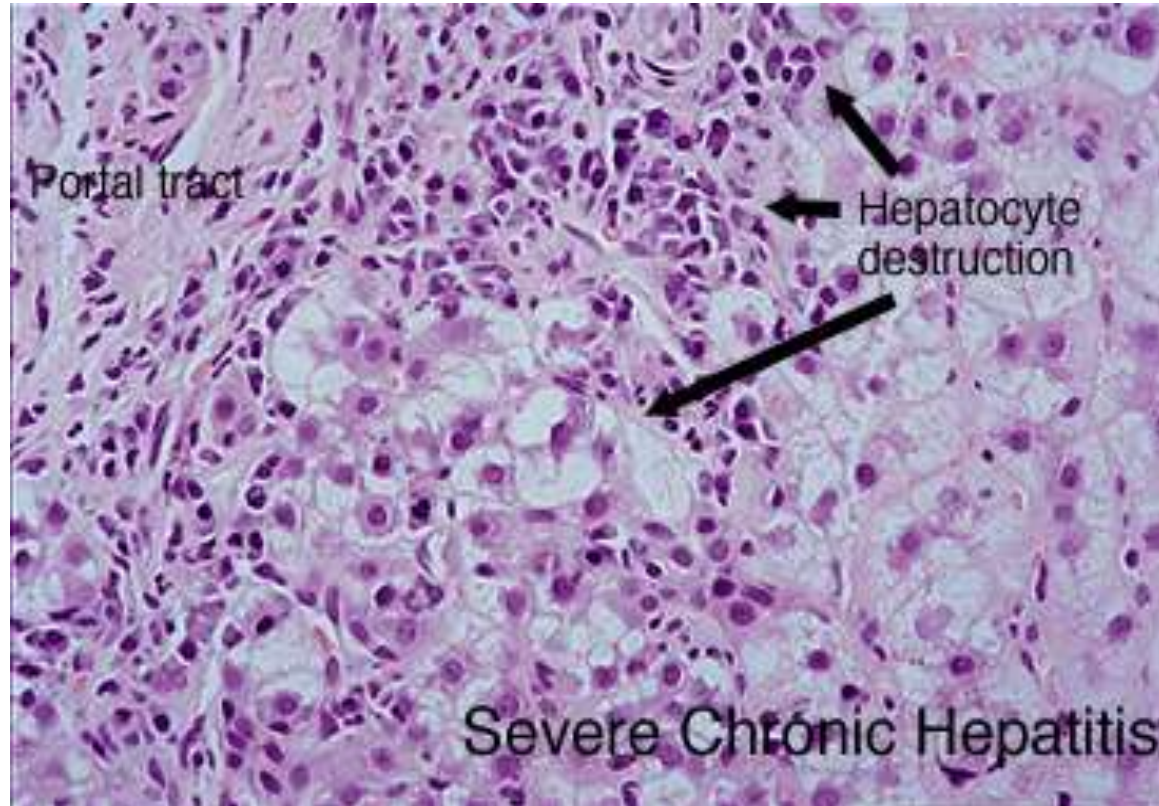
# Diagnosis

## Chronic Hepatitis: Biopsy 2

- 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 1

- 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-hoyr urine copper excretion >40 mcg/day establish the diagnosis



# Diagnosis

## Chronic Hepatitis: Wilson Disease 2

- 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

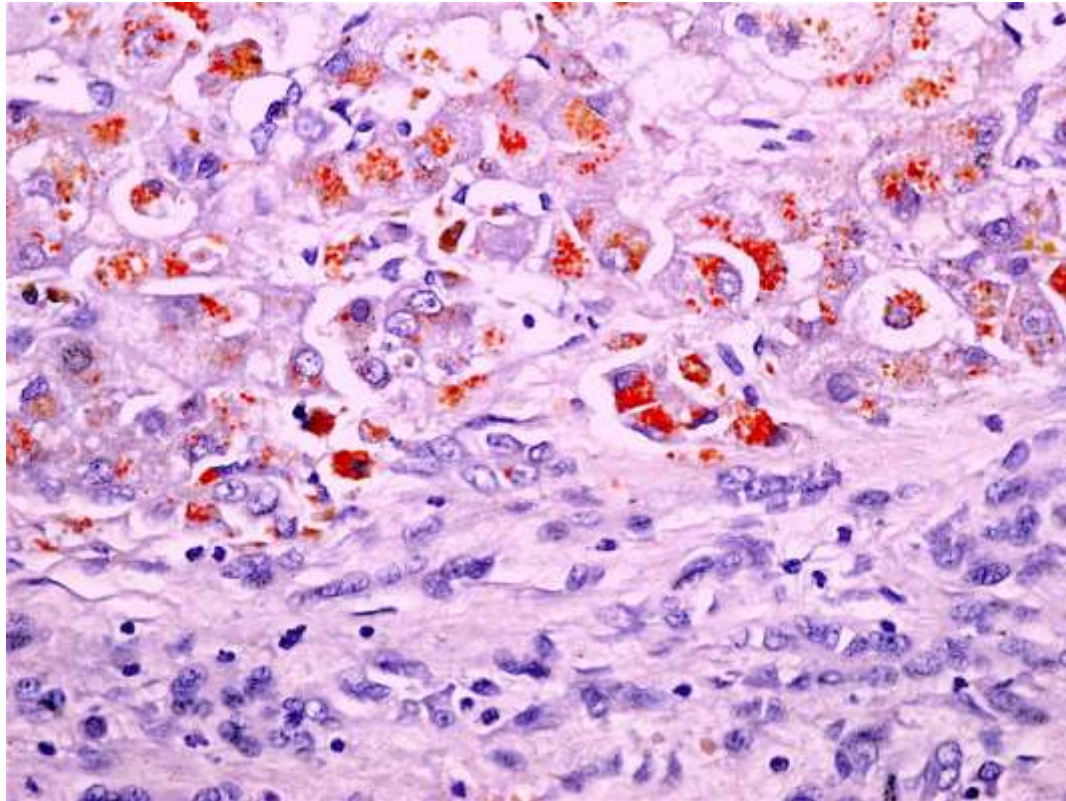
# Diagnosis

## Chronic Hepatitis: Wilson Disease 3

- 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.

# USMLE TEST

A 30-year-old G1P0 at 26 weeks presents to your office concerned about a recent news report relating to a pregnant woman with hepatitis. Per the patient, this woman contracted hepatitis in her third trimester and, within several weeks, died. Which viral hepatitis has the highest rate of progression to fulminant hepatitis in pregnant women?

1. Hepatitis A,
2. Hepatitis B,
3. Hepatitis C,
4. Hepatitis D,
5. Hepatitis E

# USMLE TEST

The correct answer is 5

In pregnant women, hepatitis E (HEV) has an unusually high rate of progression to fulminant hepatitis.

Incorrect answers:

1, 2, 3, 4: Pregnant women with HEV hepatitis appear to have worse obstetric and fetal outcomes compared to pregnant women with other viral hepatitis infections.

# 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 1

- 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

# Management

## Chronic Hepatitis: Hepatitis B, D 2

- 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
- 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 1

- 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

# Management

## Chronic Hepatitis: Autoimmune Hepatitis 2

- 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.

# USMLE TEST

A 42-year-old male commercial sex worker comes to the emergency department complaining of persistent fatigue and malaise for the past three weeks. On physical exam, you observe a lethargic male with icteric sclera and hepatomegaly. AST and ALT are elevated at 600 and 750, respectively. HBV surface antigen is positive. Albumin is 3.8 g/dL and PT is 12. A liver biopsy shows significant inflammation with bridging fibrosis. What is the most appropriate treatment at this time?

1. Zidovudine,
2. Ribavirin,
3. Maraviroc,
4. Combined lamivudine and interferon,
5. Combined interferon and ribavirin

# USMLE TEST

The correct answer is 4

Combined therapy of interferon and lamivudine is warranted in patients with hepatitis B (HBV) who show signs of active disease.

Incorrect answers:

1, 3: Zidovudine and Maraviroc are used in the treatment of HIV, 2, 5: Combined ribavirin and interferon is the treatment for HCV.

# Management

## Chronic Hepatitis: Wilson Disease 1

- 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

# Management

## Chronic Hepatitis: Wilson Disease 2

- 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

# Prophylaxis

## Chronic Hepatitis 2

- 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