NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS
MEDICAL SCHOOL

Acute and Chronic Hepatitis

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A 35-year-old patient is admitted to the emergency department with nausea, fever, fatigue, and a change in the color of urine

- He had been taking Amoxicillin/Clavulanic acid for an upper respiratory infection for the last 6 days.
- He did not have a fever for all these days, but started feeling fatigued over the last two days.
- He noticed a change in the color of his urine (it became darker).
- On the day of admission, he had a fever and a yellow skin discoloration.
- During the clinical examination, jaundice was observed, and a rash was noted.
- The blood tests indicated SGPT 530 U/L, SGOT 420 U/L, total bilirubin 3.2 mg/dL, ALP 124 U/L, γ-GT 89 U/L, WBC: 12,000, PLTs: 153,000, Ht: 41%.
- He used to eat raw meat very frequently.

What is the possible diagnosis?

- Acute hepatitis B
- Acute hepatitis A
- Acute hepatitis E
- Alcoholic hepatitis
- Drug-Induced hepatitis
- Autoimmune hepatitis
- None of the above

Are the patient’s findings compatible with an acute or a chronic disease?

Is this a hepatocellular-derived disease or a cholestatic liver disease?

Hepatocellular Disease-Hepatitis

- It is defined as inflammation and necrosis in the hepatocellular parenchyma.
- It is characterized by SGOT and SGPT elevation in serum.

Cholestatic Liver Disease

- It is defined as intrahepatic or extrahepatic bile duct dysfunction
- Cholestasis refers to the difficulty in bile secretion and/or circulation.
- It is characterized by increased ALP and/or γgt.

Chronic diseases are those that last for longer than 6 months.

Causes of acute hepatitis

Acute viral hepatitis (A, B, C, E).

Other viruses, such as EBV, CMV, and HSV, may affect the liver.

Acute drug-induced liver disease.

Autoimmune hepatitis.

Ischemic hepatitis.

Alcoholic hepatitis.

Acute Wilson disease.

An Acute Hepatitis may be:

Mild, asymptomatic: Where an elevation of SGOT and SGPT is usually found in a random blood test.

Symptomatic: Accompanied by symptoms such as fatigue, nausea, and fever.

Icteric: Where jaundice is present (increased bilirubin levels (More severe form).

Severe icteric: It is a rare condition that may result in acute liver failure.

An Acute Viral Hepatitis has 3 phases

- **The pre-icteric phase:**

It lasts for 3-4 days up to 1-2 weeks.

Symptoms: Fatigue, malaise, nausea, fever, upper right quadrant tenderness or pain.

- **The Icteric phase:**

It lasts between 1 and 4 weeks

Symptoms: Dark urine, stool discoloration (becoming more white or yellow), icterus (yellow discoloration of the skin and sclera of the eyes), and pruritus.

- **The phase of recovery:**

It lasts up to 6 months (no longer!)

Symptoms: Gradual improvement in blood tests and a decline in symptoms.

Acute Viral Hepatitis

- **Blood tests:**

An SGOT, SGPT elevation up **to 5-10 times the UNL** is found.

Increased total bilirubin is present.

There may be mild elevation of ALP and/or γgt

How do we assess the severity of acute hepatitis and the risk of acute liver failure?

- By estimating the SGOT/SGPT levels (i.e., a patient with SGPT of 10,000 U/L is at a higher risk than one with SGPT of 5,000 U/L)?
- By estimating the bilirubin levels?
- By estimating albumin levels, which decline as liver function deteriorates, representing the liver's reduced ability to produce the appropriate amounts of proteins?
- By estimating the INR (which indicates the reduced liver's ability to produce clotting factors)?

Viral Hepatitis

Route of transmission:

HAV: It is transmitted via the fecal-oral route

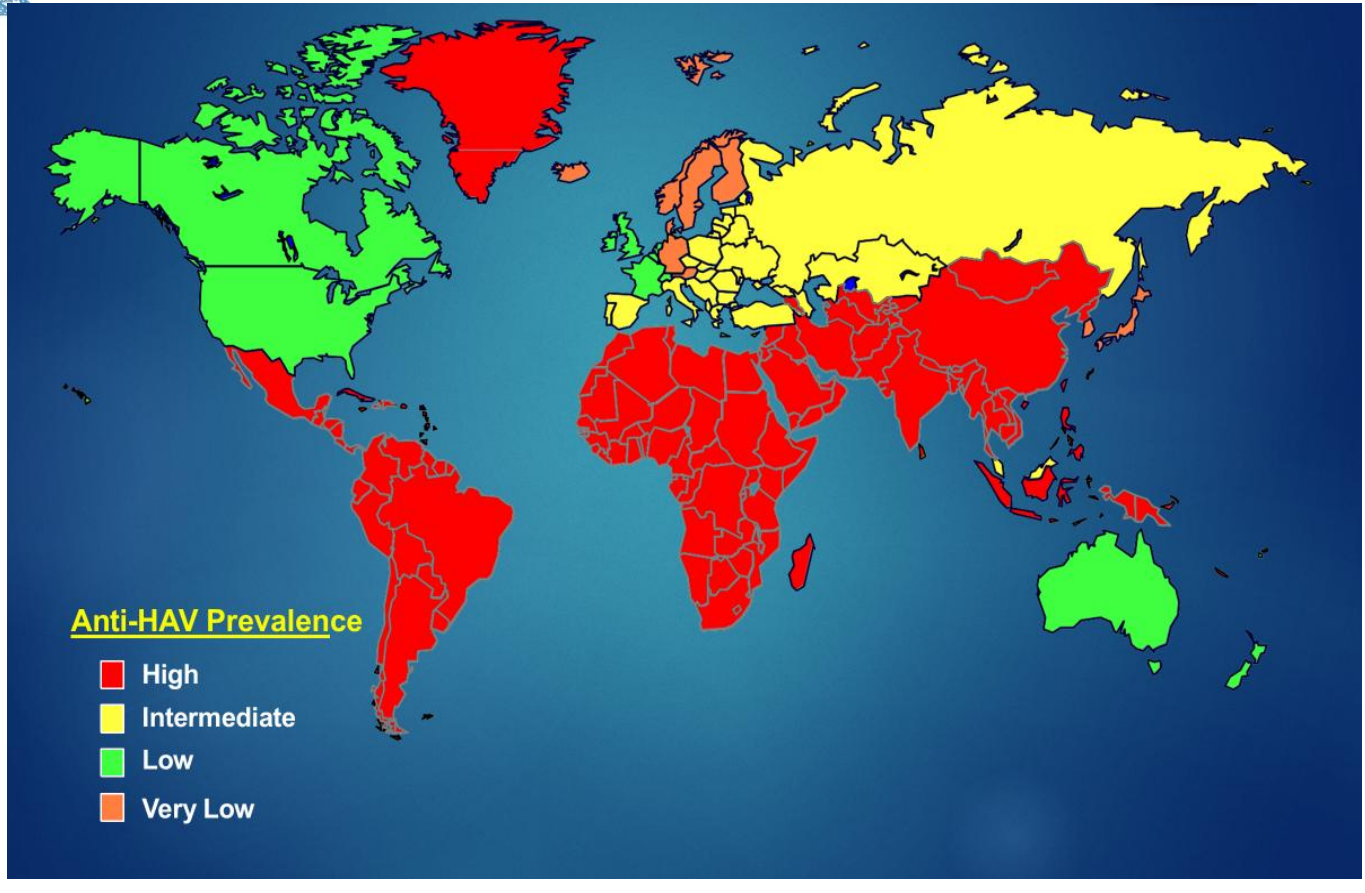
HBV: It is transmitted sexually and hematogenously

HCV: It is transmitted hematogenously

HDV: It needs the presence of HBV

HEV: It is transmitted via the fecal-oral route or hematogenously

HAV



HAV

- **There is an incubation period:** it lasts 30 days (from 15 to 50 days)
- **Route of transmission:** Fecal-oral (Contaminated water or food)
- **There is a period of high transmissibility:** 2 weeks before the clinical event
- Not transmitted by kissing, sneezing, saliva
- **Does not progress to chronicity!!**
- **Very rarely may lead to acute liver failure**
- **Very low mortality**

HAV

- **Diagnosis and treatment**:

- Serological tests: The diagnosis is made by finding IgM anti-HAV positive, 1st week to 3-6 months.

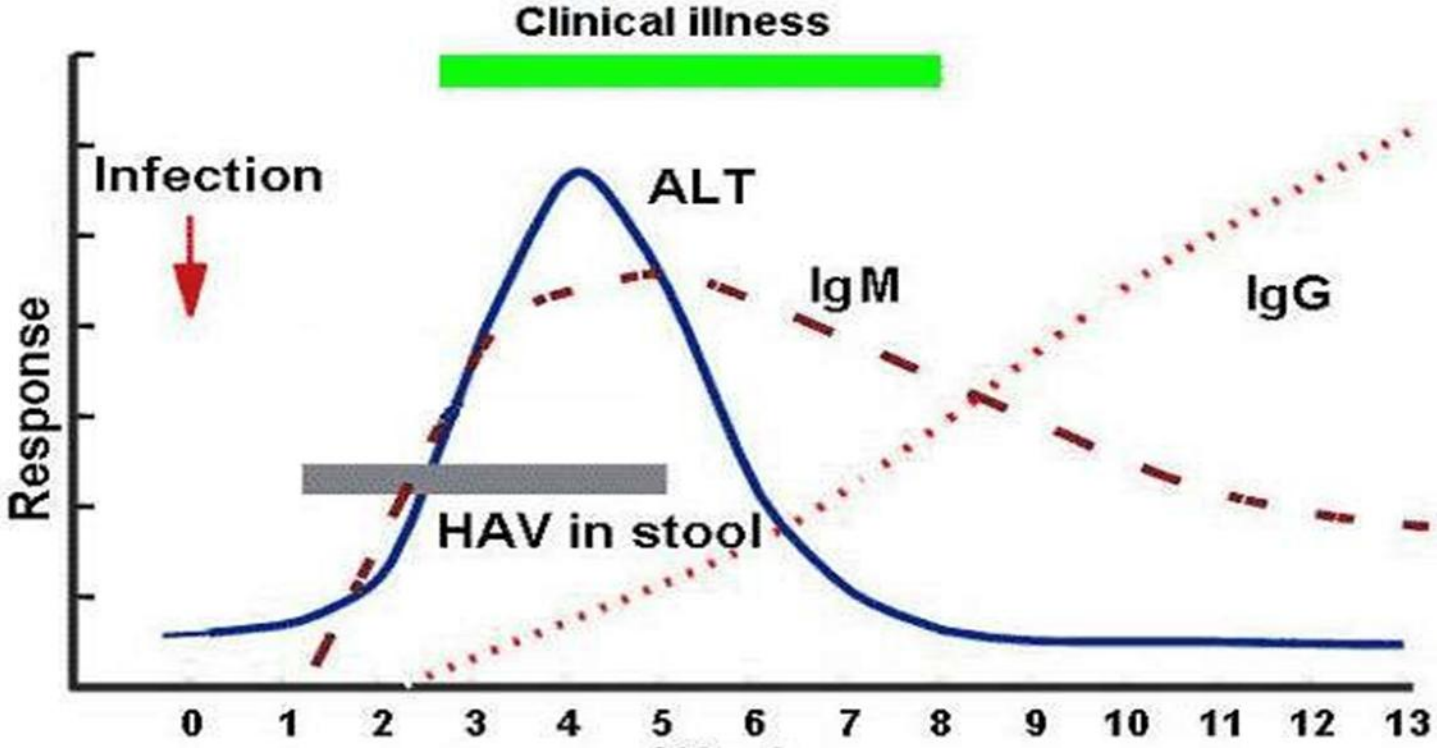
IgG anti-HAV positive are not diagnostic as they are also positive in cases where a patient has been vaccinated against HAV.

There is no need for a specific treatment.

Rest, hydration, and symptomatic treatment (i.e, paracetamol administration in case of fever).

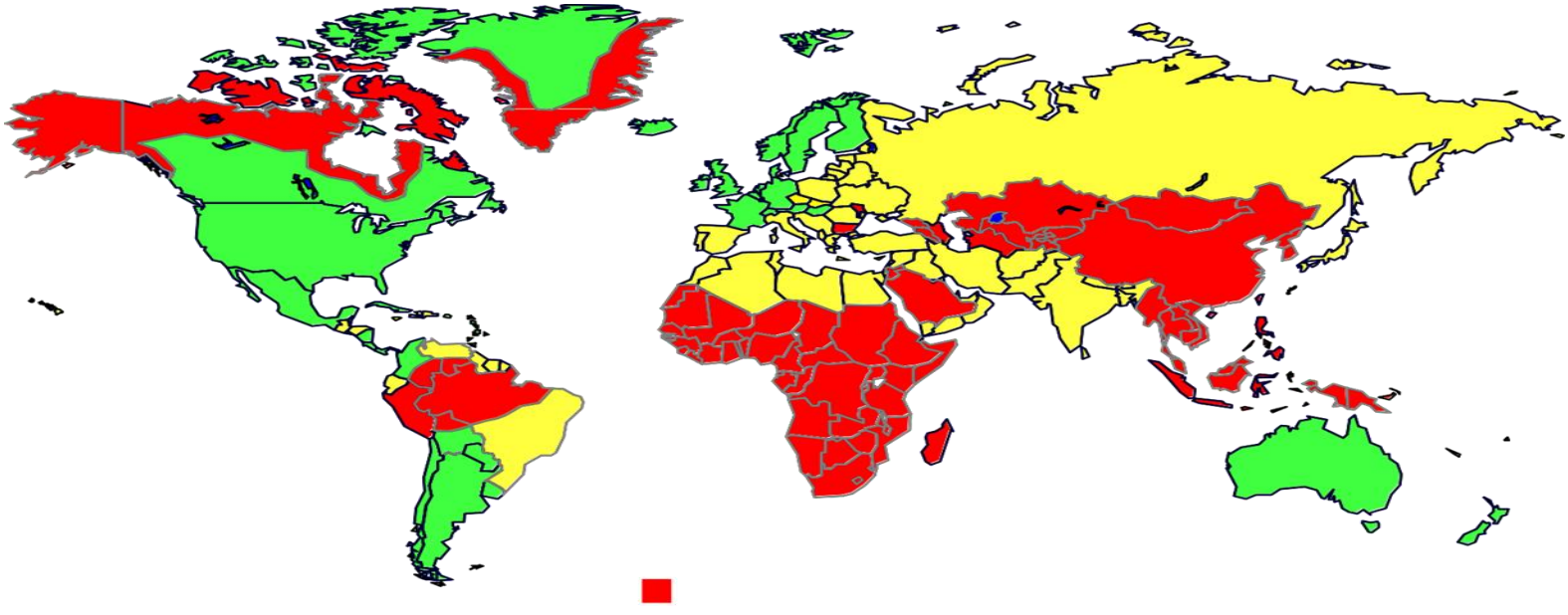
Most patients make a full recovery and become immune sufficient.

In the first weeks of the infection, the patients remain asymptomatic but may transmit the virus, as HAV is found in stool. IgM HAV is increased after the 1st week and gradually declines after the first 2 months. IgG HAV remains positive for life.



- **Prevention:** There is a vaccine (2 doses; day 0 and 6 months later)

HBV



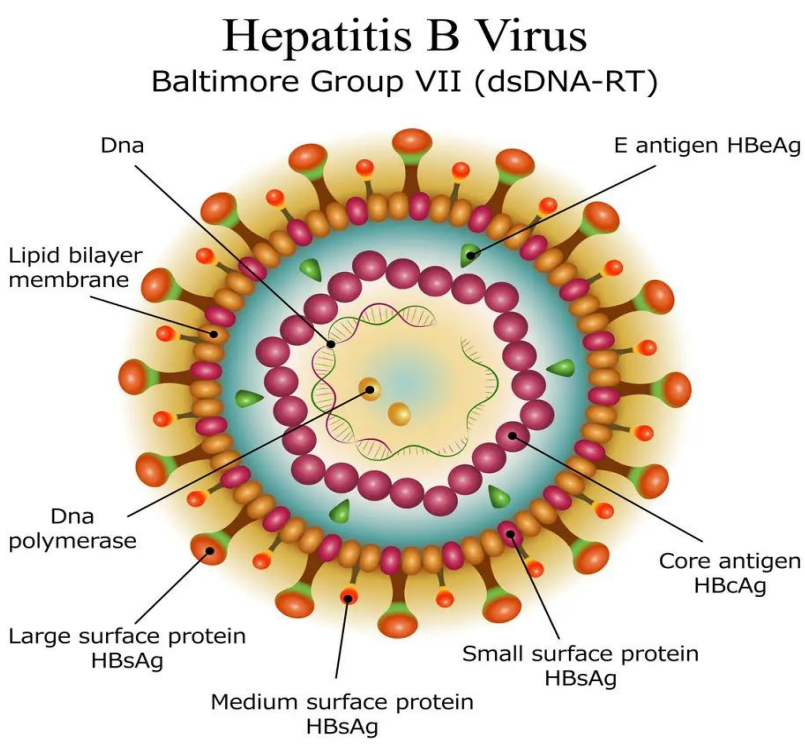
HBsAg Prevalence
8% - High
2-7% - Intermediate
<2% - Low

HBV

Envelope
HBsAg

Nucleocapsid
HBcAg, HBeAg

HBVDNA
DNA polymerase



The viral structure consists of the envelope, built by the HBsAg, and the core (nucleus), which is built by the HBcAg and the HBeAg and contains the HBVDNA and the DNA polymerase.

HBV

- **Surface antigen s (HBsAg):** Certifies the presence of infection, acute or chronic

✓ Earliest indicator of acute infection

✓ In chronic infection, it is consistently detected

✓ Its disappearance indicates clearance.

- **Antigen e (HBeAg):** Index of active proliferation

✓ Detected in serum almost simultaneously with HBsAg and disappears shortly before HBsAg

✓ In chronic infection, it may remain positive for many decades

✓ Seroconversion of HBeAg to anti-HBe indicates regression of the infection and long-term viral suppression

HBV

- **Incubation period:** 60-90 days (45-180)

- **Ways of transmission:** Direct contact with blood or body fluids of an infected person.

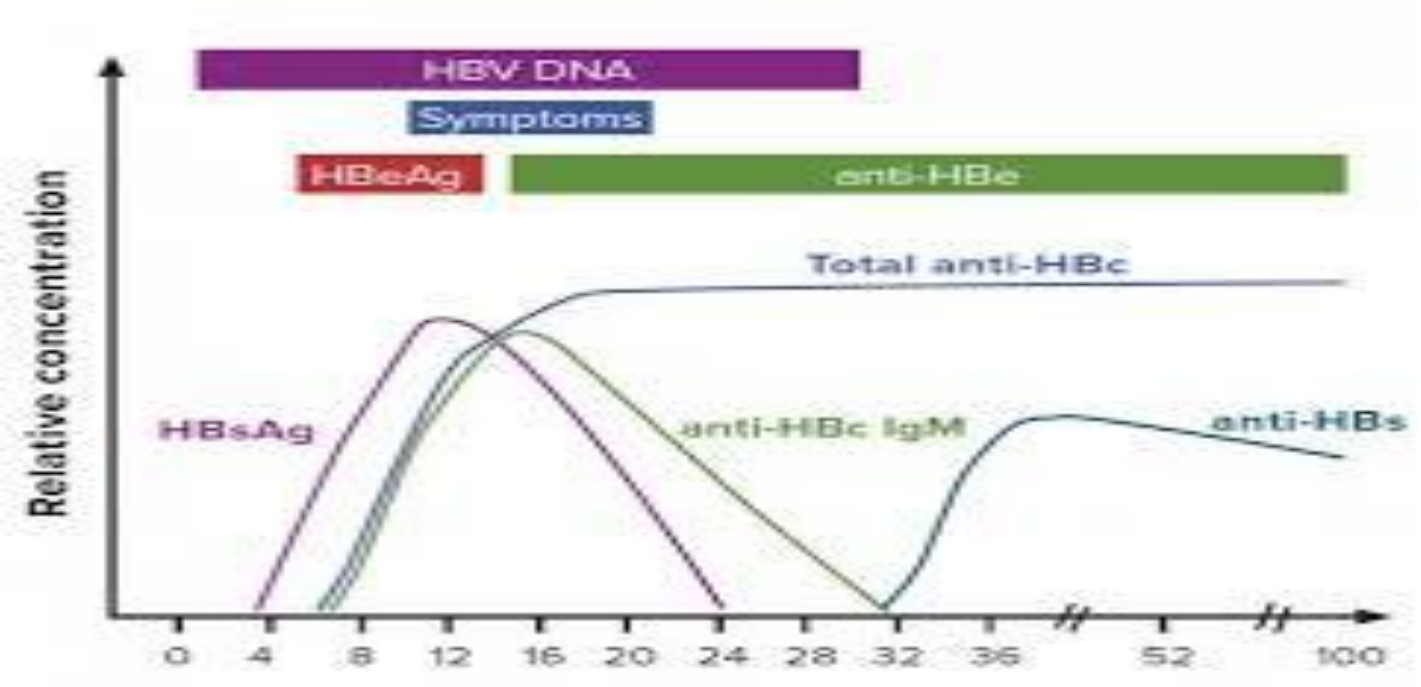
  "Sharing of needles"

  “Sexual intercourse"

  “Vertical transmission during childbirth”

Not transmitted through food, water, or normal daily contact

No symptoms are present during the incubation period of HBV infection, but HBV DNA can be detected, and both HBsAg and HBeAg levels begin to rise. After 2 to 3 weeks, HBsAg levels start to decline, and anti-HBs levels have not yet increased. At this stage, known as the "window period," a diagnosis of HBV infection can be confirmed by positive anti-HBc IgM. While total anti-HBc will also be positive, it cannot differentiate between a current infection and a past one.



HBV may cause an acute or a chronic infection

- **ACUTE HEPATITIS:** May rarely lead to acute liver failure (1%)
- **CHRONIC HEPATITIS:** Persistence of HBsAg >6 months

✓ The younger the age at which the infection is acquired, the higher the rate of progression to chronicity. Young patients' immune systems are immature.

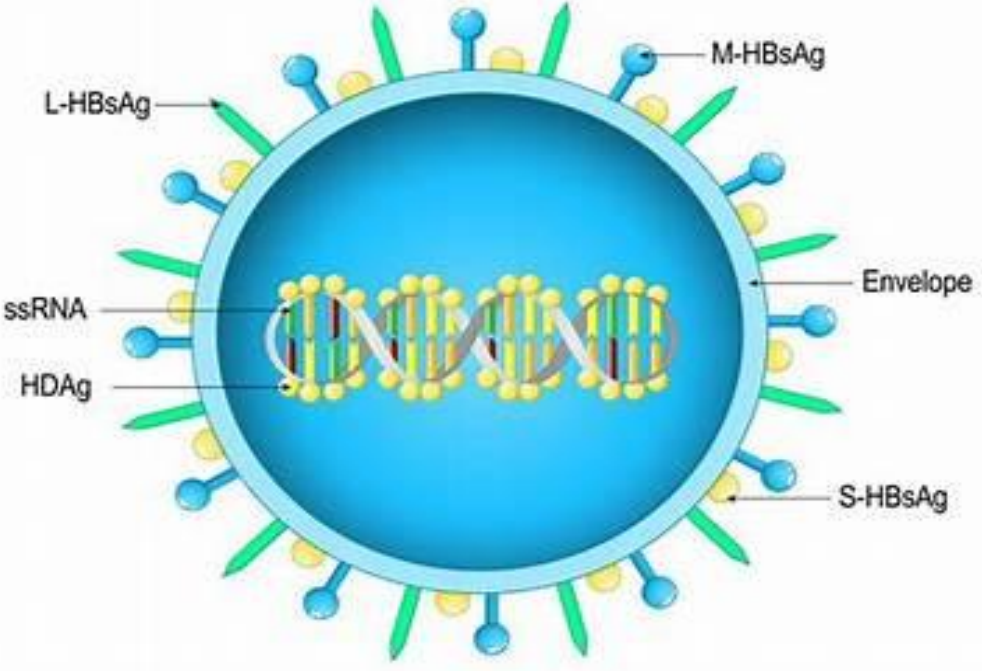
✓ Therefore, an HBV infection **during adulthood** has a higher possibility of presenting as an acute infection (90-95%) rather than leading to a chronic disease (5-10%).

✓ On the other hand, infected neonates have a higher possibility (90-95%) of not eliminating the virus, resulting in a chronic disease.

HDV

- It is a defective RNA virus that requires the presence of HBV to replicate. It uses the HBsAg to create an envelope for the delta viral particle.
- It is transmitted in similar ways to HBV
- Super-infection in patients who are already HBV carriers
- Co-infection in patients who are simultaneously infected with both viruses

Hepatitis D virus

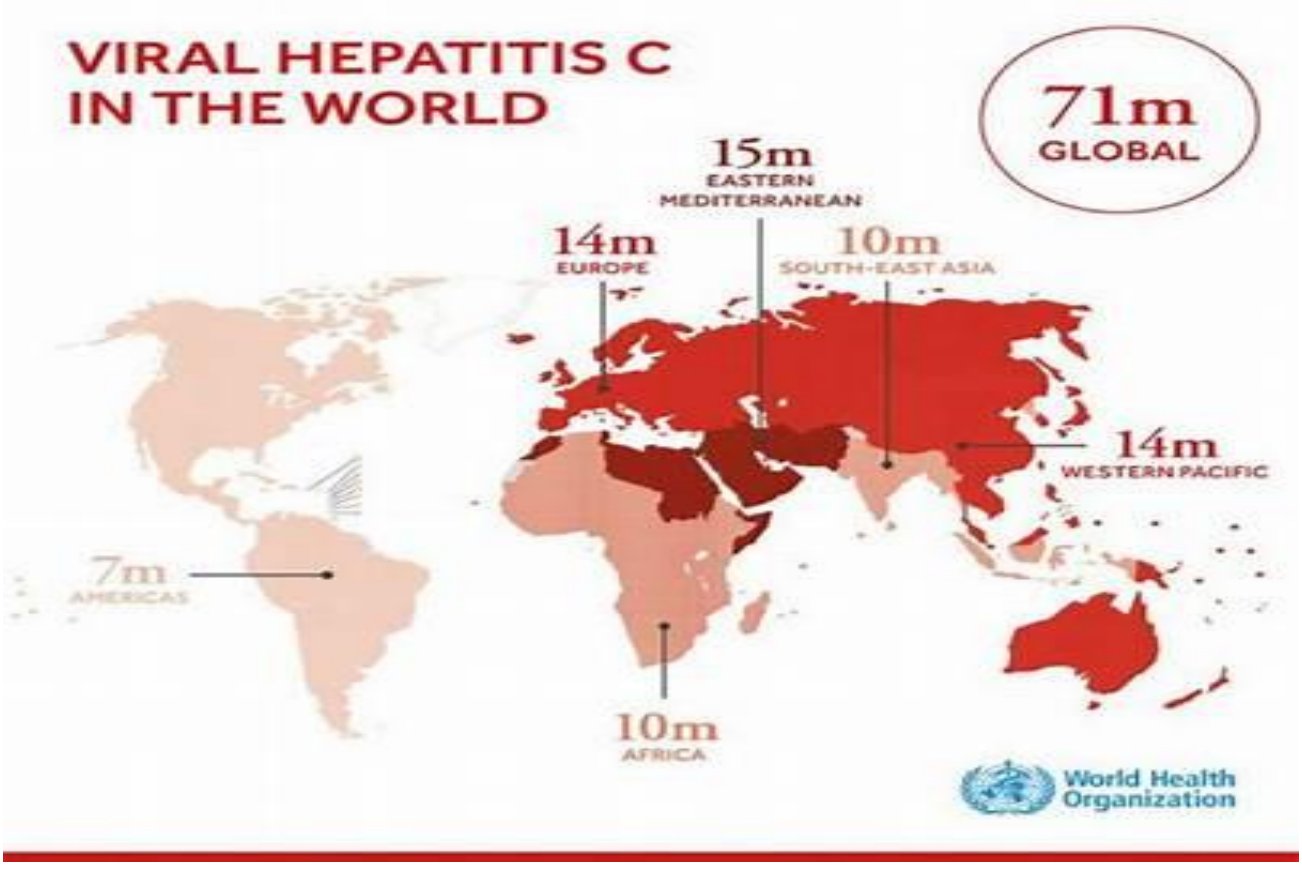


HDV

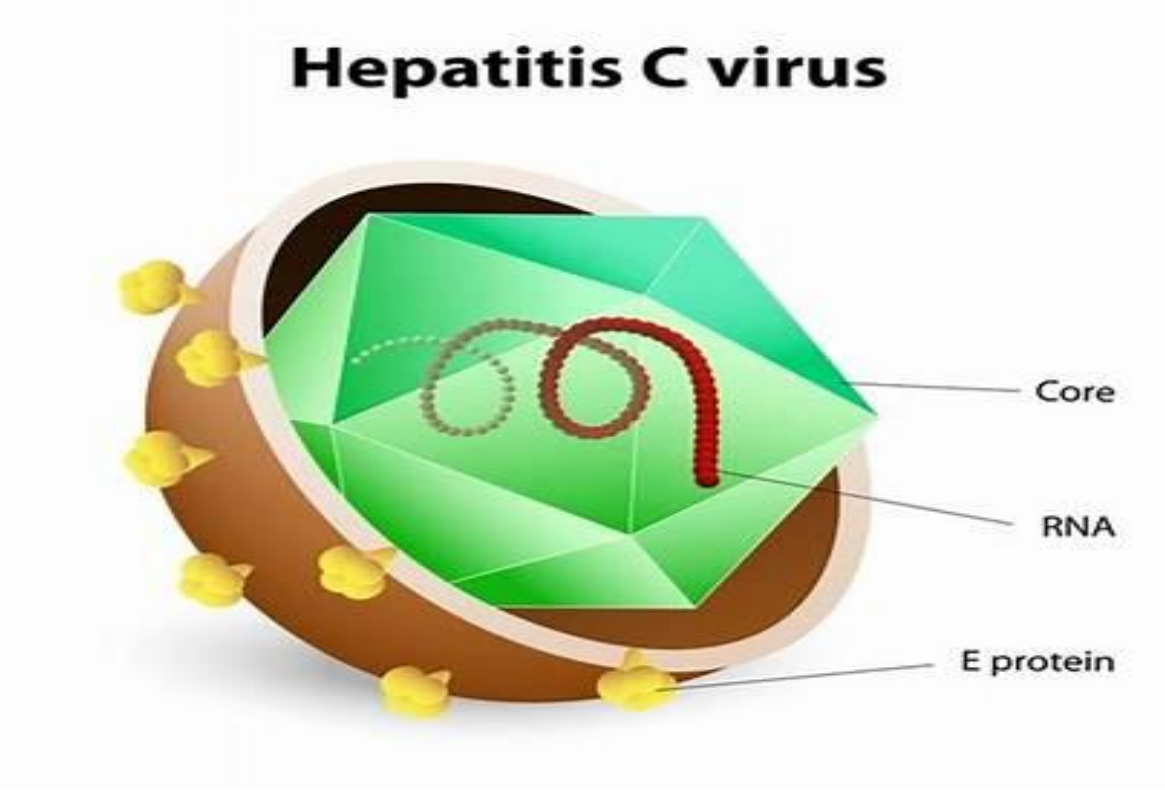
- HBV and HDV co-infection is a rare case.
- HDV super-infection is the most common case. It leads to chronic infection in more than 80% of HBV patients and modifies the natural progression of chronic HBV infection towards rapidly progressive chronic hepatitis and liver cirrhosis.
- In most patients (70%) with chronic HDV, cirrhosis develops much more rapidly than in HBV mono-infection.
- **The diagnosis is made by finding positive anti-HDV and/or positive HDV RNA**

HCV

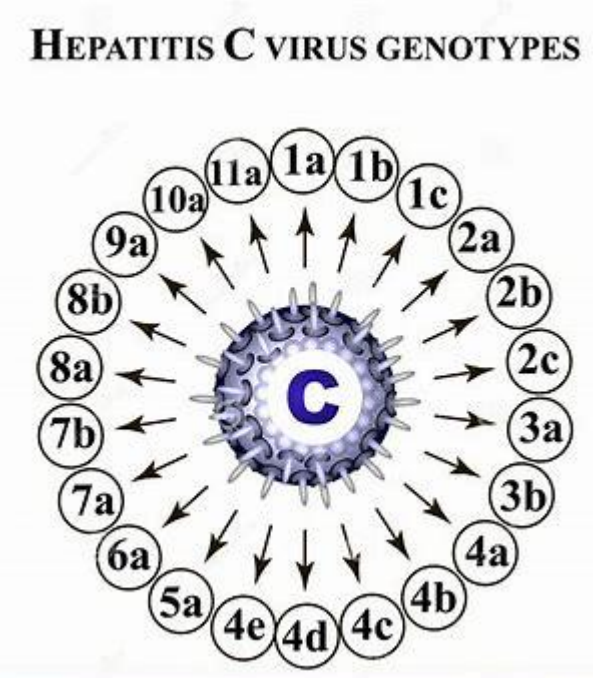
- It has a global distribution.
- Acute HCV is rare, representing only 15% of cases.
- A chronic course of the disease is more common (85%).

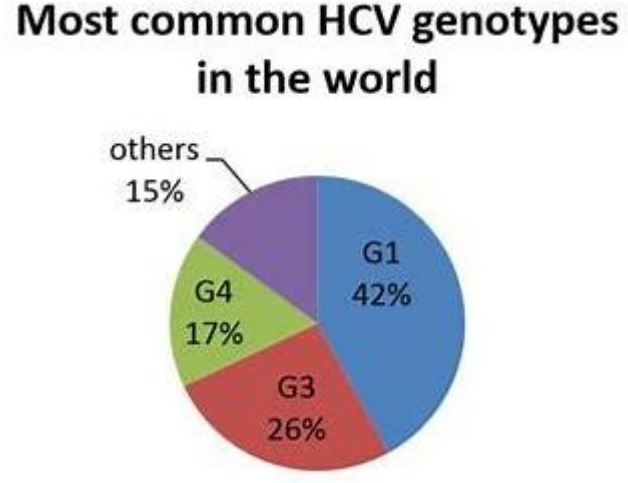

VIRAL HEPATITIS C
IN THE WORLD
71m
GLOBAL
15m
EASTERN
MEDITERRANEAN
14m
EUROPE
10m
SOUTH-EAST ASIA
14m
WESTERN PACIFIC
7m
AMERICAS
10m
AFRICA
World Health
Organization

It is an RNA virus, characterized by an envelope consisting of proteins E1 and E2, and a core (nucleus) composed of the capsid protein C and containing a single viral RNA.

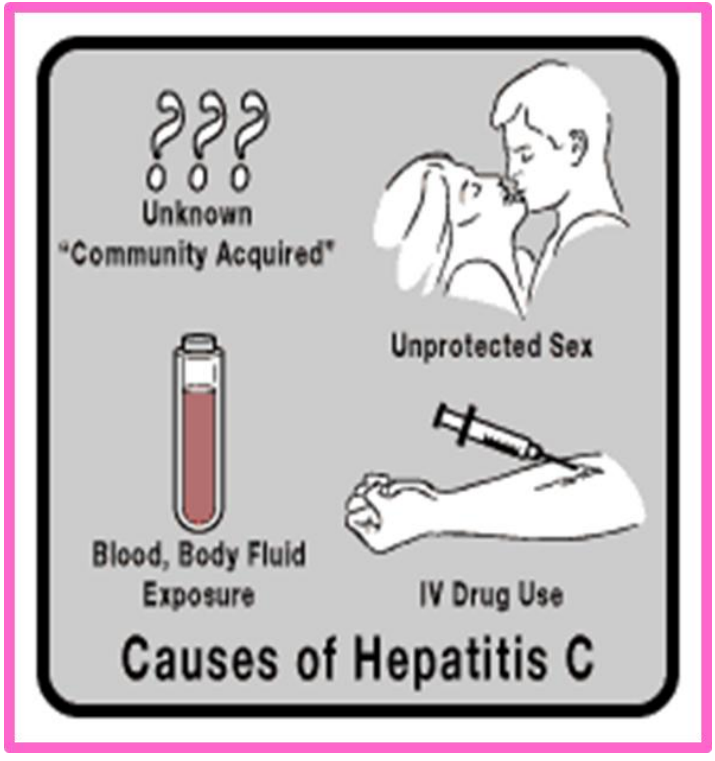


There have been found 11 different HCV genotypes



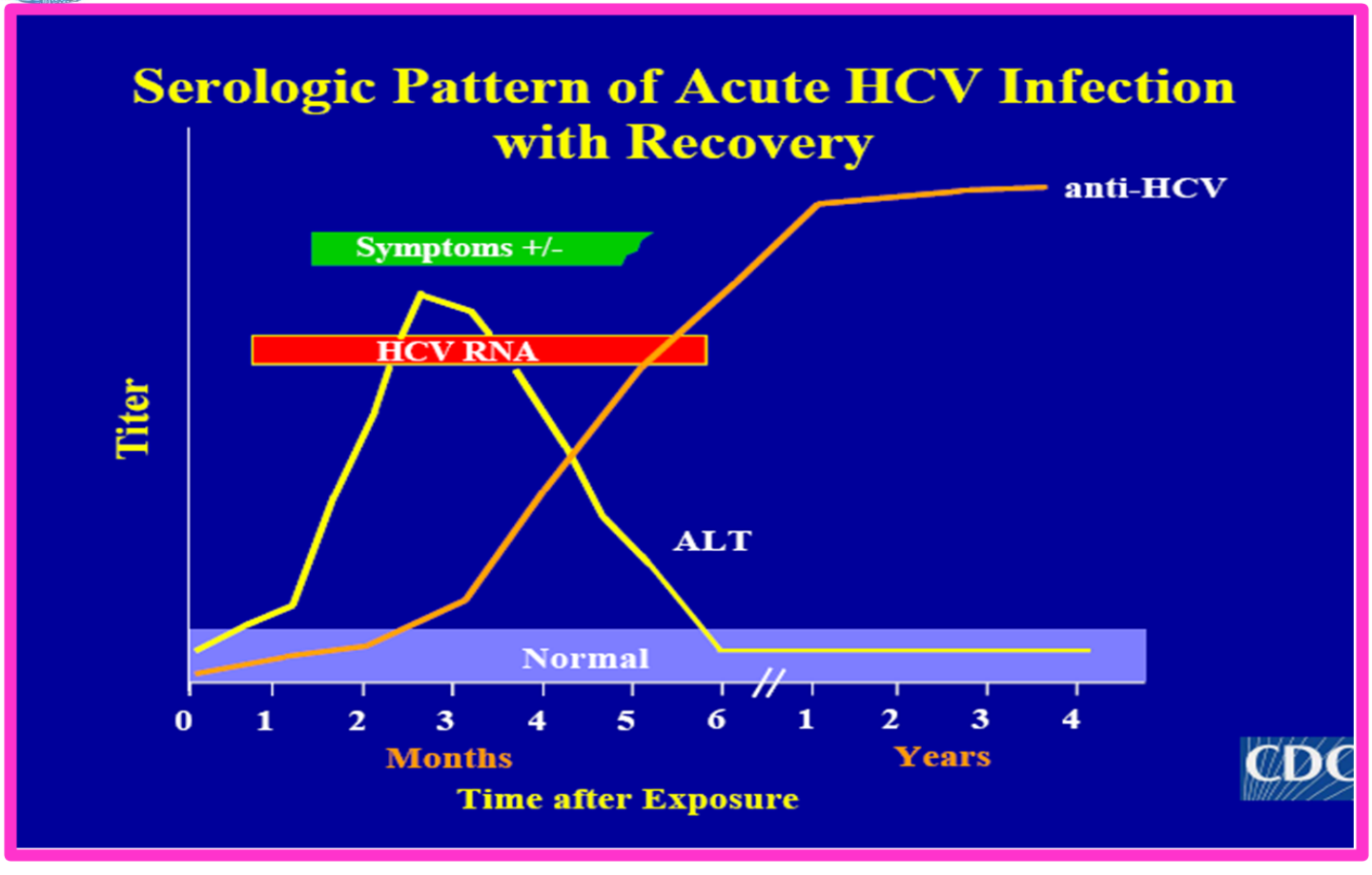


- It is transmitted by using shared needles in intravenous drug users.
- By sexual intercourse (rare)
- By transfusing contaminated blood and blood products
- Tattoos (in cases of use of non-sterilized needles, which is not common anymore)
- Other routes (iatrogenic, perinatal transmission?-very rare)



Acute HCV

- It is a rare condition.
- Jaundice occurs in 10-20% of cases. Most acute HCV infections are asymptomatic, making them difficult to diagnose.
- HCV RNA typically becomes positive 1 to 2 weeks after infection.
- Levels of SGPT and SGOT are mildly elevated and remain elevated for 2 to 8 weeks.
- Anti-HCV antibodies become positive later in the course of the disease.
- Anti-HCV may be negative in immunocompromised patients.


Serologic Pattern of Acute HCV Infection with Recovery
anti-HCV
Symptoms +/-
HCV RNA
Titer
ALT
Normal
0 1 2 3 4 5 6 1 2 3 4
Months
Years
Time after Exposure
CDC

Anti-HCV+ remain for life but are not protective against a new HCV infection.

Anti-HCV+ cannot differentiate between a new infection and a past infection.

Every time we suspect an HCV infection, we check the anti-HCV, and if this is positive, we confirm the results by doing an HCVRNA.

HEV

- **Route of transmission**: It is transmitted via the fecal-oral route (Contaminated water or food.
- It's common in areas with poor sanitation.
- Ingesting contaminated water or undercooked meat (especially pork) can spread the virus.
- It may be transmitted by transfusing contaminated blood or blood products.
- It causes an acute infection.
- It may progress to chronicity in immunodeficient patients
- Low mortality rates
- BUT: increased mortality rates have been found in acute HEV infection during the 3rd trimester of a pregnancy.
- The diagnosis is made by finding positive anti-HEV and HEV RNA.

Regarding our patient
Which tests would you evaluate to diagnose a possible acute HBV infection?

- HBsAg
- Anti-HBc
- HBeAg
- Anti-HBc IgM
- Anti-HBe
- Anti-HBs

Regarding our patient
Which tests would you evaluate to diagnose a possible acute HBV infection?

- **HBsAg**
- Anti-HBc
- HBeAg
- **Anti-HBc IgM**
- Anti-HBe
- Anti-HBs

Do not forget the "window" where a patient still has symptoms, while the HBsAg has started to decline and the anti-HBs has not increased yet. At this point, only the anti-HBc IgM remains positive.

Which other tests are you going to check to exclude other causes of viral hepatitis?

- Anti-HAV
- Anti-HEV
- Anti-HAV IgM
- Anti-HCV
- HCV-RNA

Which other tests are you going to check to exclude other causes of viral hepatitis?

- Anti-HAV
- **Anti-HEV**
- **Anti-HAV IgM**
- Anti-HCV
- **HCV-RNA**

Positive anti-HAV is not indicative of an acute HAV infection.

The patient may have been vaccinated against HAV (resulting in an anti-HAV antibody response).

The diagnosis of acute HAV infection is made by finding anti-HAV IgM+.

In rare cases of acute HCV infection, the anti-HCV test is initially negative and becomes positive later. Thus, only a positive HCV RNA confirms the diagnosis.

Other causes of acute hepatitis

Drug-induced hepatitis

Intrinsic hepatotoxicity:

- ✓ Characteristically in high doses of acetaminophen.
- ✓ Hepatotoxicity may result from metabolite-mediated hepatocellular necrosis or interference with specific hepatocellular metabolic pathways, leading to structural injury.
- ✓ In some cases, there may be a disruption of hepatic excretory pathways resulting in cholestasis
- ✓ This form of injury is always dose-dependent and reproducible in laboratory models
- ✓ It may happen to everybody taking high doses of the suspected drug without exception

Drug-induced hepatitis

Idiosyncratic hepatotoxicity

- ✓ May occur unpredictably in a small number of recipients of medication as an expression of some unidentified reaction
- ✓ There is no dose dependency, and toxicity is not reliably reproduced in laboratory animals
- ✓ It usually develops after a sensitization period of several days
- ✓ However, if the patient had already been exposed to this drug in the past, then a new exposure may rapidly lead to liver injury in a very short period, even after taking a minimum dose of the medicine.
- ✓ The pathogenetic mechanism resembles that of an allergic reaction

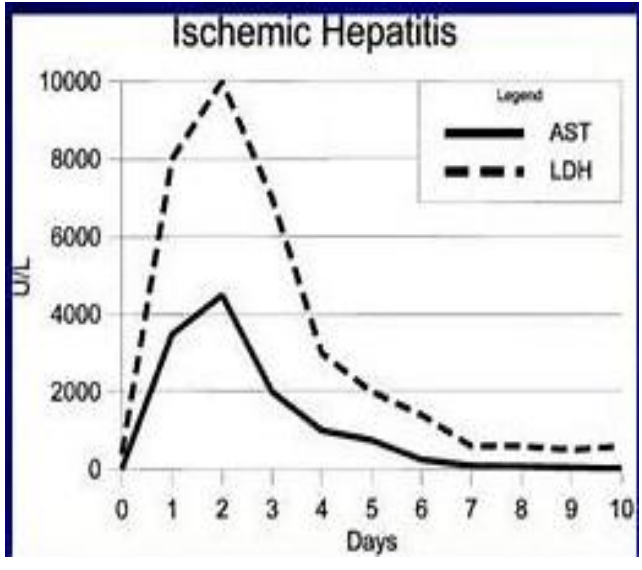
Table 1. Drug-Induced Liver Injury According to Type.*

Variable	Direct Hepatotoxicity	Idiosyncratic Hepatotoxicity	Indirect Hepatotoxicity
Frequency	Common	Rare	Intermediate
Dose-related	Yes	No	No
Predictable	Yes	No	Partially
Reproducible in animal models	Yes	No	Not usually
Latency (time to onset)	Typically rapid (days)	Variable (days to years)	Delayed (months)
Phenotypes	Acute hepatic necrosis, serum enzyme elevations, sinusoidal obstruction, acute fatty liver, nodular regeneration	Acute hepatocellular hepatitis, mixed or cholestatic hepatitis, bland cholestasis, chronic hepatitis	Acute hepatitis, immune-mediated hepatitis, fatty liver, chronic hepatitis
Most commonly implicated agents	High doses of acetaminophen, niacin, aspirin, cocaine, IV amiodarone, IV methotrexate, cancer chemotherapy	Amoxicillin–clavulanate, cephalosporins, isoniazid, nitrofurantoin, minocycline, fluoroquinolones, macrolide antibiotics	Antineoplastic agents, glucocorticoids, monoclonal antibodies (against tumor necrosis factor, CD20, checkpoint proteins), protein kinase inhibitors
Cause	Intrinsic hepatotoxicity when agent given in high doses	Idiosyncratic metabolic or immunologic reaction	Indirect action of agent on liver or immune system

* IV denotes intravenous.

Ischemic hepatitis

- **In cases of severe liver hypoperfusion**



✓Hypovolemic shock

✓Prolonged severe arrhythmia

✓Elevation of LDH and SGOT>SGPT

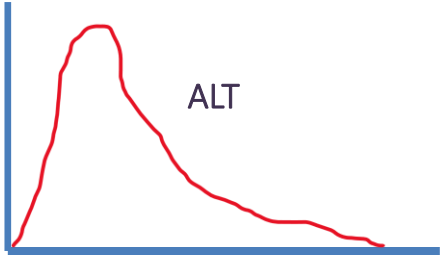
✓Rapid elevation of liver enzymes with a rapid decline

Acute autoimmune hepatitis

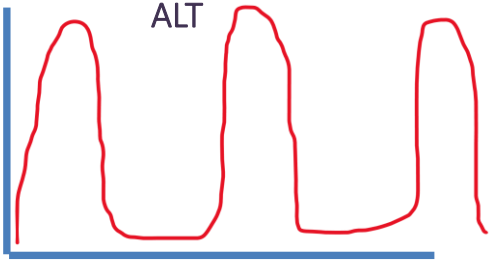
- Immune-derived liver injury
- Lymphocytes and plasma cells participate in the pathogenesis
- ANA (antinuclear antibodies)
- ASMA (smooth muscle antibodies)
- Anti-LKM1 (liver/kidney microsome 1) (more frequently in young patients)
- ← Increased γ-globulin levels
- ✓ IgG elevation

Different autoimmune hepatitis patterns

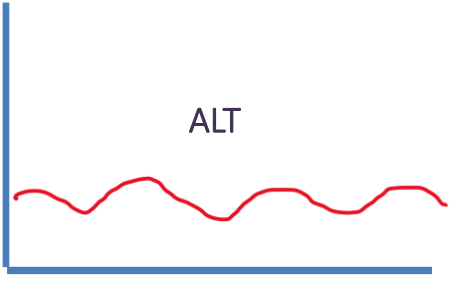
In acute episodes of autoimmune hepatitis, the IgG levels may be normal



One acute episode



Multiple acute episodes with normal liver function tests in between



Chronic asymptomatic disease
(it is the most common pattern)

Simplified criteria for the diagnosis of autoimmune hepatitis

Variable	Cut-off	Points
ANA or SMA	≥1:40	1
ANA or SMA	≥1:80	2[a]
or anti-LKM-1	≥1:40	
or SLA	Positive	
IgG	> upper limite of normal	1
	>1.10 times upper limit of normal	2
Liver histology	Compatible with AIH	1
	Typical of AIH	2
Absence of viral hepatitis	Yes	2

Score ≥6: probable AIH; ≥7: definite AIH.

ANA, anti-nuclear antibody; *SMA*, anti-smooth muscle antibody; *anti-LKM-1*, anti-liver kidney microsomal antibody type 1; *SLA*, soluble liver antigen; *IgG*, immunoglobulin G; *AIH*, autoimmune hepatitis.

[a] Addition of points achieved for all autoantibodies cannot exceed a maximum of 2 points.

Adapted from Hennes EM, Zeniya M et al. Hepatology 2008; 48: 169-176.

Alcoholic hepatitis

Fever

Leukocytosis

Anorexia

Icterus

Painful hepatomegaly

Persistent diarrhea

Manifestations of portal hypertension (Ascites, variceal bleeding, hepatic encephalopathy)

- Fever
- Leukocytosis
- Anorexia
- Icterus
- Painful hepatomegaly
- Persistent diarrhea
- Manifestations of portal hypertension (Ascites, variceal bleeding, hepatic encephalopathy)

Diagnostic criteria

Jaundice onset within previous 8 weeks

Long-term consumption of alcohol: > 40 g (roughly 3 standard drinks) daily for women or > 60 g (roughly 4 standard drinks) daily for men for ≥ 6 months, with < 60 days of abstinence before onset of jaundice

AST > 50 U per L (0.83 μkat per L), AST/ALT ratio > 1.5, and both AST and ALT < 400 U per L (6.68 μkat per L)

Total bilirubin > 3 mg per dL (51.31 μmol per L)

Absence of confounding factors

MOST OF THE TIME, A PROLONGED PERIOD OF HEAVY ALCOHOL CONSUMPTION PRECEEDS

It is a severe disease that increases patient's mortality

It is associated with an increased probability of severe infections.

Chronic hepatitis

- **Hepatocellular disease characterized by inflammation and necrosis in the hepatocellular parenchyma lasting for > 6 months**

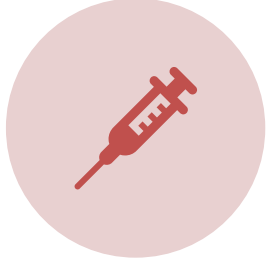
- **Common causes**

✓Chronic HBV
✓Chronic HBV/HDV
✓Chronic HCV
✓Chronic HEV (only in immunodeficient patients)
✓ Metabolic-associated steatotic liver disease (MASLD)
✓Alcoholic liver disease (ALD)
✓Chronic autoimmune hepatitis
✓Other metabolic liver diseases (Wilson disease, Hemochromatosis)

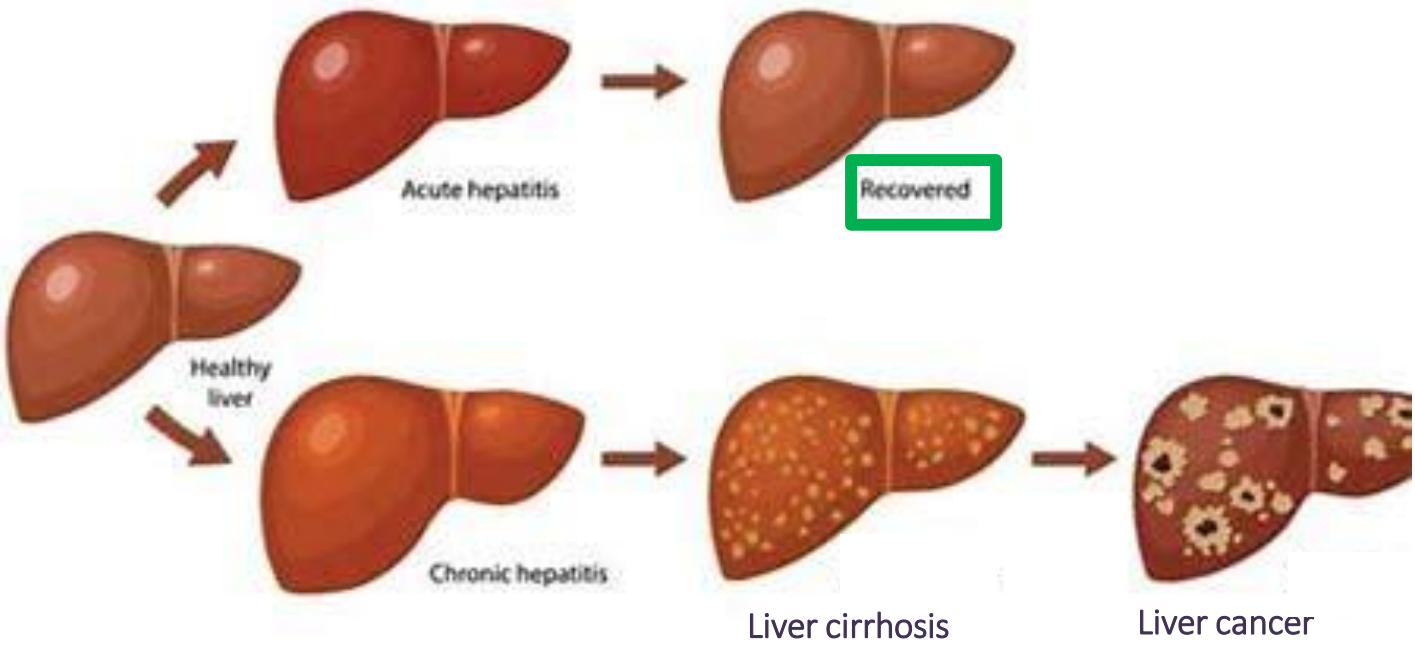
Chronic hepatitis

CHRONIC HEPATITIS IS USUALLY ASYMPTOMATIC (REGARDLESS OF THE ETIOLOGY)

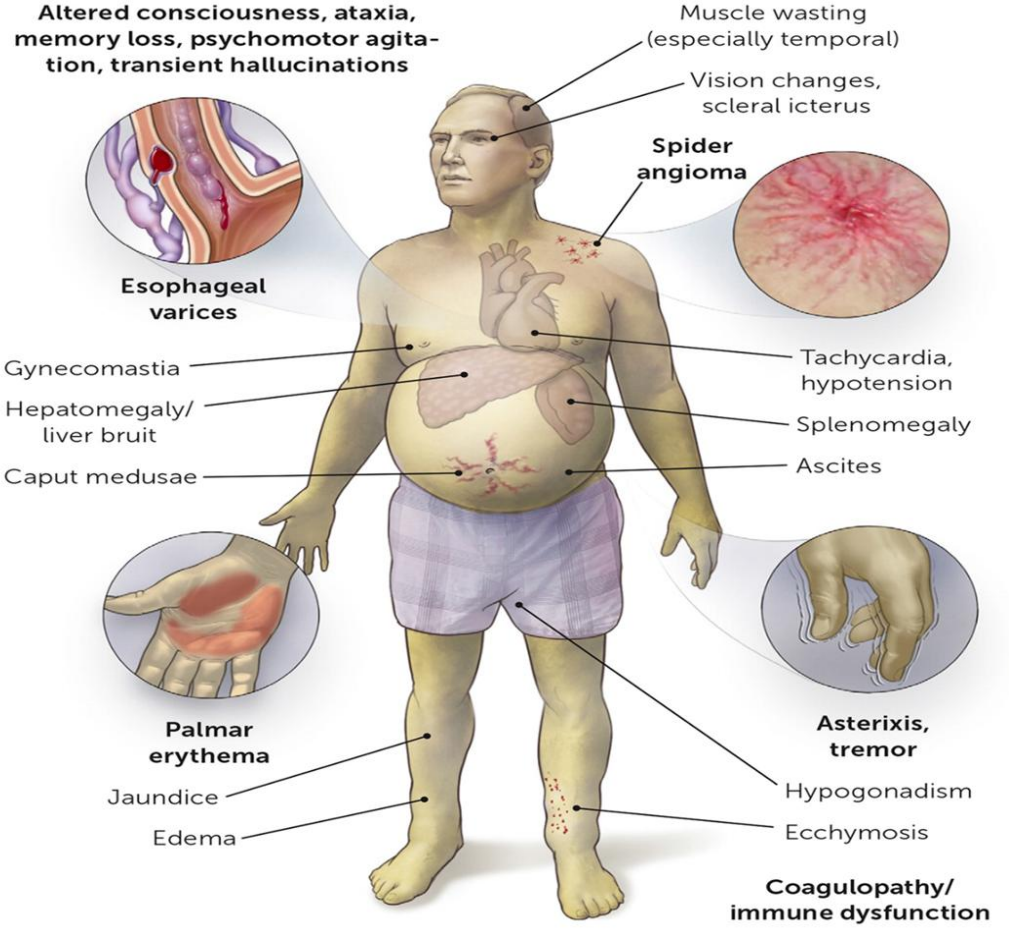
MODERATE INCREASE IN ALT LEVELS IN A RANDOM BLOOD TEST



MAY SILENTLY LEAD TO LIVER CIRRHOSIS


Acute hepatitis
Recovered
Healthy liver
Chronic hepatitis
Liver cirrhosis
Liver cancer

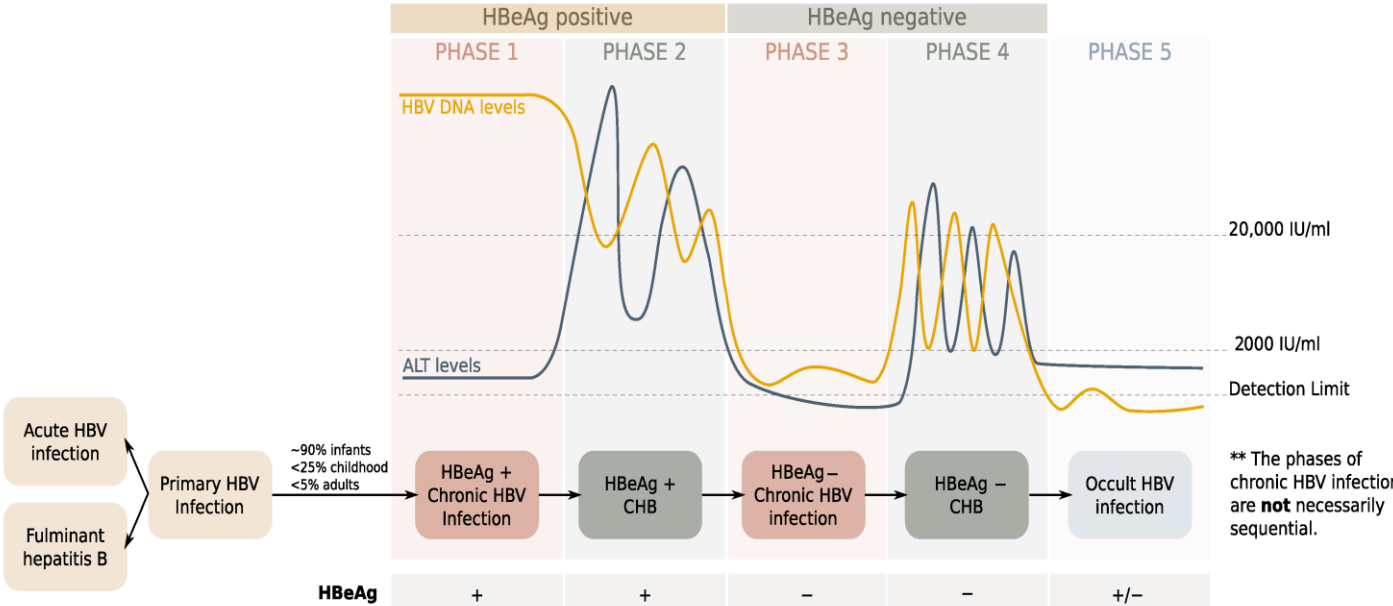
Liver Cirrhosis



Chronic HBV

- It is crucial to understand that liver damage in chronic HBV mainly occurs due to the immune cells' attack against the infected liver cells, rather than from a direct negative effect of HBV on the liver cells' function and life.

Chronic HBV



HBeAg	+	+	–	–	+/–
HBsAg	High	High/Intermediate	Low	Intermediate	–
Anti-HBe	–	–	+	+	–/+
Anti-HBs	–	–	–	–	+
Anti-HBc	+	+	+	+	+
ALT levels	Normal	Elevated	Normal	Elevated	Normal
HBV DNA levels (IU/ml)	$>10^7$	$10^4 – 10^7$	< 2000	> 2000	Undetectable
Liver Fibrosis	Minimal	Progressing	Progressing	Moderate/Severe	Variable (result of previous phases)

Chronic HBV/HDV coinfection

- **HBsAg+**
- **HDV-RNA+**
- HBV-DNA + (Most of the time, HBV-DNA is detected at very low levels or even undetectable. As an RNA virus, HDV replicates more rapidly than HBV, leaving little room for HBV replication.)
- Usually, the HBV/HDV coinfection leads to liver cirrhosis more rapidly than the HBV mono-infection.

Chronic HCV

- anti-HCV+
- HCV RNA +
- Mild ALT elevation (sometimes ALT is normal)
- Absence of symptoms

Other causes of chronic hepatitis

Alcohol Associated Liver Disease (ALD): Chronic liver damage related to prolonged *excessive* alcohol consumption (> 60 gr of alcohol per day in men and > 50 gr in women)

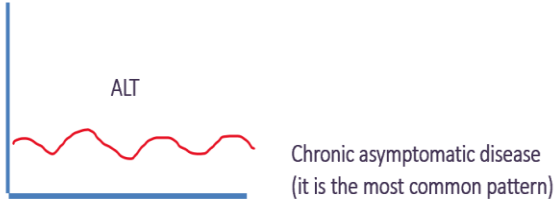
SGPT ↑ and/or γgt ↑, MCV ↑	Neurological, cardiac, and musculoskeletal diseases may coexist	Liver ultrasound will reveal liver fat deposition

Metabolic Associated Steatotic Liver Disease (MASLD): Liver fat deposition related to metabolic diseases such as Diabetes Mellitus type II, Obesity, and Hyperlipidemia (High LDL levels, Low HDL levels, High Triglyceride levels)

Alcohol consumption < 30 gr per day in men and < 20 gr in women	SGPT ↑ and/or γgt ↑	Liver ultrasound will reveal liver fat deposition

Metabolic Associated Alcoholic Liver Disease (MetALD): Combination of metabolic disease plus *moderate* alcohol consumption (> 30 but < 60 gr per day in men and >20 but <50 gr in women)

- **Chronic autoimmune hepatitis**



- **Wilson disease**

✓ It is an inherited disease characterized by excessive accumulation of copper in the body, primarily in the liver and brain.

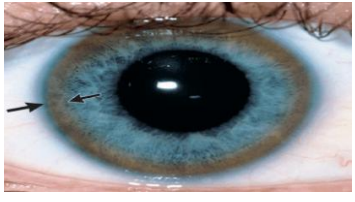
✓Brain-related symptoms include tremors, muscle stiffness, trouble speaking, personality changes, anxiety, and psychosis.

✓ Wilson's disease is caused by a mutation in the ATP7B gene, which encodes the ATP7B protein, also known as the Wilson disease protein. This protein transports excess copper into bile, which is excreted in waste products.

✓It is an autosomal recessive disease


Kayser-
Fleischer ring
Cardiac
Renal tubular
dysfunction
Arthritis
CNS disorders
Behavioral changes
Dystonia
Dysarthria
Excessive salivation
Dysphagia
Mask-like facies
Hepatomegaly
Jaundice
Acute hepatitis
Fulminant hepatic failure
Cirrhosis
Wilson's Disease

- **Diagnosis: decreased ceruloplasmin levels, increased urinary copper excretion, typically exceeding 40 μg/24 hours and often exceeding** 100 μg/24 hours. Kayser-Fleischer rings, resulting from copper deposition in the eyes.



- Sometimes, a liver biopsy is necessary

- Genetic testing may be used to screen family members of individuals affected.

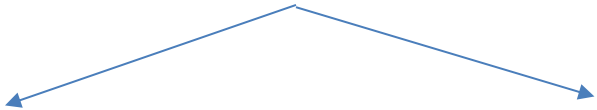
Hemochromatosis

Hemochromatosis is a condition that causes the body to absorb excessive amounts of iron from food. Excess iron is stored in the liver, heart, and pancreas. Too much iron can lead to liver cirrhosis, heart failure, and diabetes.

- Joint pain.
- Belly pain.
- Fatigue.
- Weakness.
- Diabetes.
- Loss of sex drive.
- Impotence.
- Heart failure.
- Liver failure.
- Bronze or gray skin color.
- Memory fog.

There 5 subtypes of hereditary hemochromatosis due to different mutated genes.
They have different prognoses.
Liver biopsy is often necessary for the diagnosis

- Evaluation of liver fibrosis is necessary for all patients with chronic hepatitis
- Liver biopsy represents the gold standard method to evaluate liver fibrosis
- Nowadays, non-invasive tests, serological or imaging, tend to substitute liver biopsy for the evaluation of liver fibrosis



FIB-4 Liver Elastography

- All patients with cirrhosis should be screened every 6 months using an ultrasound for the early detection of hepatocellular carcinoma.

Fibrosis-4 (FIB-4) Index for Liver Fibrosis

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy.

When to Use | Pearls/Pitfalls | Why Use

Age
Use with caution in patients <35 or >65 years old, as the score has been shown to be less reliable in these patients

years

AST
Aspartate aminotransferase

Norm: 15 - 41 U/L

ALT
Alanine aminotransferase

Norm: 1 - 35 U/L

Platelet count

Norm: 150 - 350 $\times 10^3/\mu L$

Result:

Please fill out required fields.

Fibroscan


E
XL
Valid measures 10
Invalid measures 1
Comments
E (kPa)
VELITIAN
IQR
6.3
0.1
IQR/med.
2 %
Probe advice

Regarding our patient, he had:

- Anti-HAV +
- HBsAg-
- Anti-HBc+
- Anti-HBs +
- Anti-HCV-
- Anti HDV –
- Anti HEV -

What else are you going to check?

The HBV DNA

What is the final diagnosis?

DRUG-INDUCED LIVER DISEASE