

Infectious Diseases

Lesson 7

GASTROINTESTINAL AND HEPATOBIILIARY INFECTIONS

Part C – Viral Hepatitis

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Objectives and learning goal

Objectives

- To describe all clinically relevant information on viral hepatitis
- To know the main differential characteristics of the distinct hepatitis virus infections

Learning goal

To be able to recognize and properly manage a patient with acute viral hepatitis

Contents

- Clinical manifestations of acute hepatitis
- Hepatitis A
- Hepatitis E
- Hepatitis B
- Hepatitis D or delta
- Hepatitis C
- Key messages
- Further reading

Clinical manifestations of acute hepatitis

Introduction

- Acute viral hepatitis: **hepatitis A, B, C, D** (“delta agent”) and E viruses, similar clinical features
- Hepatitis in a context of multiple organ infection: **Epstein-Barr virus, cytomegalovirus**, herpes simplex viruses, varicella virus, coxsackievirus B, measles, rubella, and adenovirus
- Fulminant hepatitis, in 1% of icteric hepatitis, most commonly in hepatitis B or D, also in pregnant woman with hepatitis E

Confusing translations *

English	Español
Measles or rubeola	Sarampión
Rubella or German measles	Rubéola o rubeola

* Navarro FA. Glosario de dudas y dificultades inglés-español para pediatras (2.ª parte: J-Z). Rev Pediatr Aten Primaria 2008; 10:e1-e23
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Summary of the clinical characteristics of the various forms of viral hepatitis

Virus type	Incubation period	Epidemiology	Sequelae
Hepatitis A	4 weeks	Fecal-oral Foodborne Waterborne Sexually transmitted	Self-limiting disease; can relapse up to 6 months post- primary attack; fulminant hepatitis rare
Hepatitis B	12 weeks	Person to person Blood and blood products Other body fluids IV drug abuse Sexually transmitted	Chronic infection common (90% neonates, 20–50% children, 5–10% adults); hepatocellular carcinoma
Hepatitis C	6–10 weeks	Person to person Blood and blood products IV drug abuse Sexually transmitted (rare) Higher risk with HIV infection	Usually a chronic infection; cirrhosis in 25%; requires liver transplant; hepatocellular carcinoma
Hepatitis D + B	12 weeks	Person to person Blood and blood products Other body fluids IV drug abuse Sexually transmitted Household contacts	Same as hepatitis B; hepatic failure more common among IV drug abusers
Hepatitis E	4 weeks	Fecal-oral route Only in developing countries	Self-limiting disease; fulminant hepatitis in pregnancy

Clinical stages of acute viral hepatitis

- Incubation: from a few weeks to 6 months
- Preicteric stage: **malaise**, dull right upper quadrant pain, flu-like symptoms, serum-sickness syndrome: rash plus arthralgias, etc. due to virus plus antibody complex deposition; dramatically resolve with the onset of jaundice
- Icteric stage: begins 4-10 days after the onset of the preicteric stage; **jaundice, dark urine**, pale stools, itching, immune complex produced vasculitis (primarily hepatitis B), and glomerulonephritis (primarily hepatitis B or C)
- Convalescent stage: duration depends on severity of acute disease

Signs

- Icterus, in the sclera or under the tongue when bilirubin levels $> 2.5-3.0$ mg/dL
- Slight hepatic enlargement with mild-to-moderate tenderness
- Scratch marks as result of severe pruritus
- Fulminant hepatitis: encephalopathy, depression in mental status and asterixis (irregular flapping)

Laboratory tests

- Aspartate and alanine aminotransferases (AST y ALT) 1000 to 2000 IU, with ratio AST/ALT < 1
- Alkaline phosphatase and lactic dehydrogenase mildly elevated
- Direct and indirect bilirubin equally elevated; higher direct or conjugated: cholestasis, higher indirect or unconjugated: hemolysis
- Prothrombin time: significant elevation means bad prognosis, > 100 seconds indicates irreversible hepatic damage
- Fulminant hepatitis: disseminated intravascular coagulation with thrombocytopenia, etc.

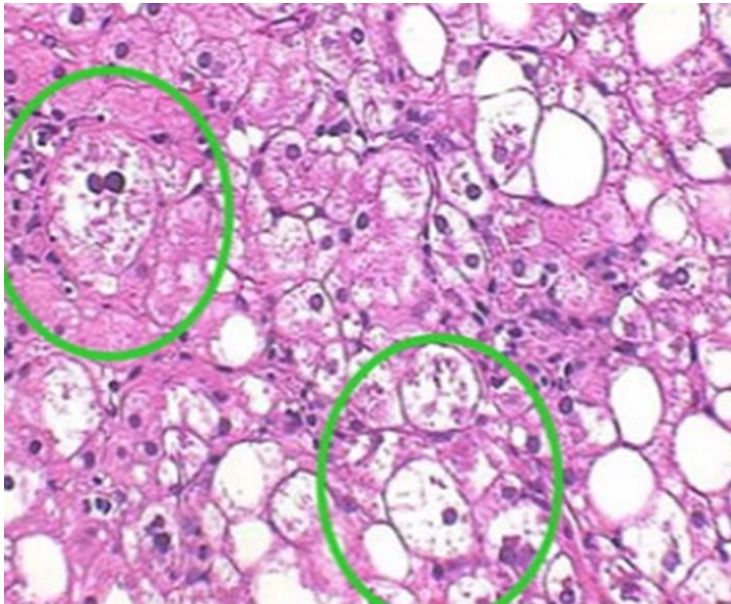


Jaundice



Biopsy

- Histopathologic exam: hepatocyte ballooning and necrosis, disarray of liver lobules, mononuclear cell infiltration, and cholestasis; but liver biopsy generally not required for diagnosis



Hepatocyte
ballooning

Chronic hepatitis

- Can follow acute hepatitis B and C, but acute hepatitis C is generally asymptomatic
- Most patients with chronic hepatitis experience no symptoms until they progress to liver failure, which happens:
 - > 20 years after hepatitis C infection
 - Several years after hepatitis B infection
- Elevations of aminotransferases up to 7-10 times normal values
- Mild fatigue may develop
- Membranous glomerulonephritis, vasculitis
- Polyarteritis nodosa after hepatitis B

Hepatitis A

Virology and pathogenesis

- A small, nonenveloped single-stranded RNA virus. A picornavirus
- Highly resistant to heating and drying, survives in protein solutions
- Enters the host via the gastrointestinal tract, traversing the intestine and infecting the hepatocyte cytoplasm
- Excreted into the bile, resulting in high levels of virus in the stool
- **Hepatocyte damage is caused by the host's cell-mediated immune response**

Epidemiology

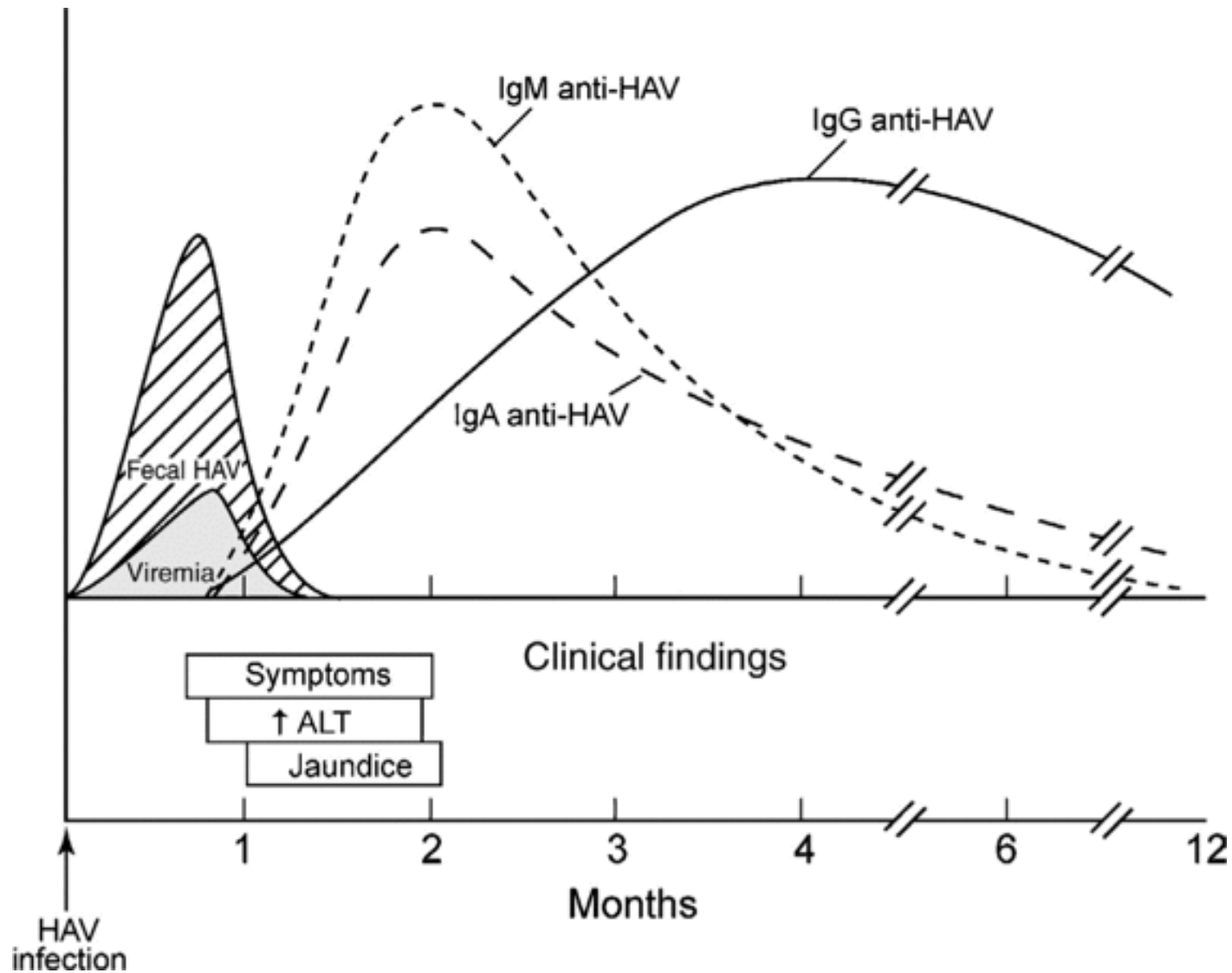
- Hepatitis A virus causes an estimated 1.4 million cases of acute hepatitis worldwide yearly
- Spread by fecal-oral route, for example in daycare centers
- Sexual transmission in male homosexuals, and parenteral transmission in drug abusers
- Common-source of outbreaks: water, milk, and food
- Inactivation of the virus can be accomplished with a 1:100 dilution of household bleach

Clinical course

- 4-week incubation
- Acute onset of a flu-like illness
- Usually self-limiting, resolving within 2-3 months, however a second episode of jaundice about 6-12 weeks later is possible
- Do not evolve into chronic hepatitis
- Young children have a less robust immune response to the virus and often have few symptoms and no jaundice
- Fulminant hepatitis rare, and occurs more frequently in patients coinfecting with hepatitis C or hepatitis B

Diagnosis

- Serum **antihepatitis A IgM antibody** titers; levels are detected at the time of symptomatic disease and usually persist for 6 months
- Anti-hepatitis A IgG antibodies progressively increase; low titers are observed during early symptomatic disease, but they continue to rise, peaking at about 4 months, and persist for decades



Clinical course of hepatitis A virus (HAV) infection. IgM, A, G = immunoglobulins M, A, G; ALT = alanine aminotransferase. Vertical axis = relative concentration.

Treatment and prevention

- Most people can be managed as outpatients
- No therapy is available to alter the course of infection
- Fulminant hepatitis, liver transplantation may be required
- Pooled human immunoglobulin **prevent** or **reduce symptoms**
- Prophylaxis, within 2 weeks of exposure, can be given as:
 - **Preexposure**, to travelers to areas outside the tourist routes
 - **Postexposure**, after recognition of the index case
- Vaccine, for patients with chronic liver disease and people at high risk of infection: homosexual men, intravenous drug abusers

Hepatitis E

Introduction

- Small, single-stranded RNA virus, genus hepevirus
- Pathogenesis, epidemiology, and clinical manifestations similar to those of hepatitis A
- Secreted in the stool and spread by the fecal-oral route
- Outbreaks associated with contaminated water in developing countries
- Self-limiting and does not result in chronic hepatitis
- **Fulminant hepatitis** in **pregnant women** in their third trimester, with mortality rates of 15-25%
- Diagnosis by **PCR of serum** and by a **rise in IgM antibody**
- Immunoglobulin is not protective, and no vaccine is available

Hepatitis B

Virology I

- Small, enveloped, spherical, partially double-stranded DNA virus, a **hepadnavirus**
- Unique tropism for hepatocytes
- Outer core: contains lipid and surface antigen (**HBsAg**); the host directs viral-neutralizing antibody (anti-HBV) against HBsAg
- Inner core:
 - Intracellular core antigen (**HBcAg**)
 - Secreted core antigen (**HBeAg**), formed by naked DNA strands and associated proteins
- Presence of **HBsAg** in blood indicates **infections** and **HBeAg** indicates **active viral replication**; HBcAg is not found in blood

Virology II

- Bloodstream contains:
 - Competent virus
 - Defective noninfectious viral particles, that form spheres and filaments, composed of HBsAg and host membrane lipid
- Hosts: humans and primates
- Survives in serum for months at 4 °C and for years frozen at -20 °C, but is killed within 2 minutes when heated to 98 °C and when treated with detergents
- Viral DNA can **integrate into host cell DNA**, which may alter the expression of critical regulatory genes and **upregulate** host **oncogenes**

Epidemiology

- Spread from person to person
- Sources of infections: **blood and blood products**, urine, bile, saliva, semen, breast milk, and vaginal secretions; it is not found in feces
- Can be spread to sexual partners, from mother to neonate at the time of delivery, etc.
- **Incidence has decreased** in developed countries, and it is estimated to have infected approximately 5% of the world's population

Clinical manifestations

- Clinical picture similar to that of hepatitis A, with two major differences:
 - Incubation period 12 weeks
 - Hepatitis B is not always self-limiting, the full virus may **remain in the liver** for a decade, and **elevation in transaminase** values may persist for more than **6 months**, which indicates progression to **chronic active hepatitis**
- The percentage that progresses to chronic disease is age dependent, being 90% in neonates, 20-50% in children 1-5 years of age, and < 5% in adults

Diagnosis: HBsAg

- Appearance in serum within 1-10 weeks after exposure
- Disappearance within 4-6 months indicates recovery
- Persistence beyond 6 months indicates chronic disease
- Disappearance of HBsAg may be **preceded** by the appearance of anti-HBs, and during this period, patients may develop a **serum-sickness-like illness**
- In most patients, anti-HBs do not rise to detectable levels for several weeks to months after the disappearance of HBsAg (**window period**); **IgM antibody directed against HBcAg allows diagnosis** then

Diagnosis: HBcAg

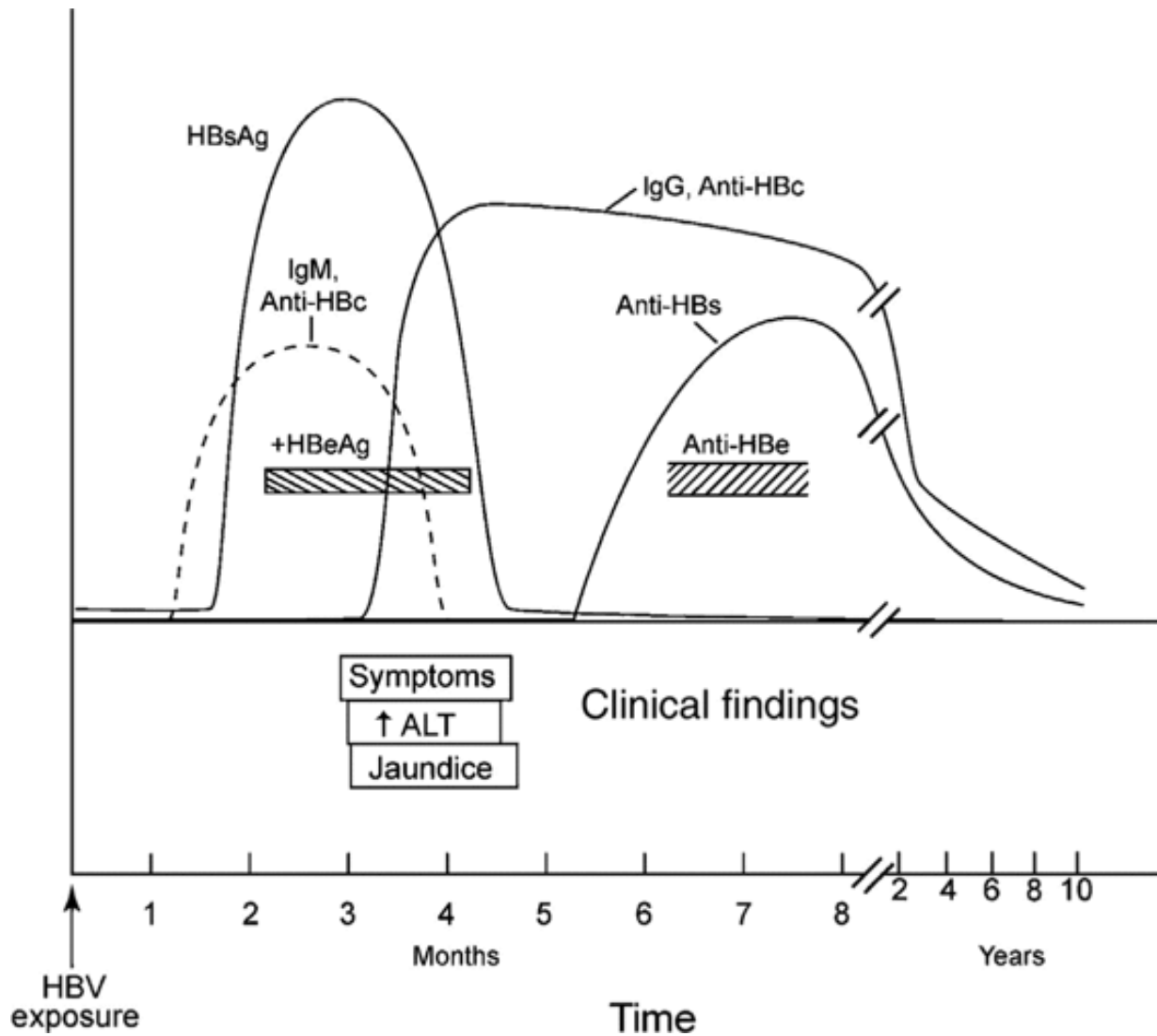
- HBcAg is detected in infected hepatocytes, but **not in serum**
- IgM anti-HBc is usually **the earliest anti-hepatitis B antibody** detected in the infected patient, and in some patients it can persist for up to 2 years, and in patients with chronic active hepatitis, it can rise during exacerbations
- IgG anti-HBc develop in the later phases of acute disease and usually persist for life

Diagnosis: HBeAg

- Presence of HBeAg in serum:
 - Indicates active viral replication
 - Persists in patients with chronic disease
 - Correlates with infectivity
- As acute hepatitis B recovers, HBeAg disappears, and **anti-HBe** appears
- Seroconversion from HBeAg to anti-HBe usually corresponds with the disappearance of hepatitis B virus DNA from the serum

Diagnosis: viral DNA

- Quantitation of viral DNA in serum is used in the assessment of patients with **chronic** active hepatitis
- In acute hepatitis provides no significant advantages over HBeAg
- Presence of both viral DNA and HBeAg indicate active viral replication
- In patients with **fulminant** hepatitis, hepatitis **B-DNA** may be **positive** in the absence of other markers for the infection



Clinical course of hepatitis B. HBsAg = hepatitis surface antigen; HBeAg = secreted core antigen; IgM = immunoglobulin M; ALT = alanine aminotransferase. Vertical axis = relative concentration

Treatment

- Acute hepatitis B: supportive care, lamivudine
- Prevention: education of those who engage in high-risk behaviors, screening of the blood supply, universal precautions by hospital personnel, etc.
- High-titer hepatitis B immunoglobulin reduces the incidence and severity of infection, if given within 7 days of exposure
- A highly effective recombinant vaccine is available

Chronic hepatitis B: concept

- Positive HBsAg for more than 20 weeks = chronic **carrier**
- Carrier state develops in 5 to 10 % of adults
- Course of chronic disease depends on the **balance** between viral replication and host's immune response

Chronic hepatitis B: stages

- Replicative with **immunotolerance**: active replication, hepatic inflammation minimal; can persist for 20-30 years, in neonates
- Replicative with **immunoreactivity**: active replication, hepatic inflammation ensues, symptoms of hepatitis may develop, although most patients remain asymptomatic, liver function tests become abnormal; the virus may clear or not
- **Nonreplicative** phase: HBeAg is negative, and anti-HBe appears

Chronic hepatitis B: complications and treatment

- Persistent HBsAg and hepatic inflammation →
 - Progression to **cirrhosis** and liver failure
 - Increased risk of **hepatocellular carcinoma** (1.6 % annual incidence in patients with cirrhosis)
- To prevent these complications, treatment is recommended in chronic carriers of hepatitis B virus, depending on HBeAg, viral DNA and transaminase level
- **Entecavir**, adefovir, tenofovir, lamivudine, emtricitabine, telbivudine, etc., generally for years
- Discontinuation has been associated with fulminant hepatitis

Hepatitis D or delta

Virology, pathogenesis, and clinical manifestations

- Small, single-stranded RNA virus that is surrounded by a single hepatitis D antigen and a lipoprotein envelope provided by hepatitis B
- When the D virus is present, hepatitis B replication is suppressed
- Replicates at very high rate in the nuclei of hepatocytes, cytotoxic effects
- Clinically, indistinguishable from hepatitis B; higher incidence of hepatic failure; similar progression to chronic active hepatitis

Epidemiology, diagnosis and treatment

- Endemic in the Mediterranean basin
- Person-to-person spread may be the result of mucosal contact or injection of blood or blood products
- Spread among household contacts is common
- Diagnosis is made by measuring **anti-hepatitis D** IgM and IgG serum titers
- No specific treatment is available for hepatitis D
- Measures to prevent hepatitis B also eliminate the risk of this virus

Hepatitis C

Virology

- Single-stranded RNA, probably enveloped
- Cannot be propagated by routine methods, explaining the great difficulty encountered in originally identifying it
- Ineffective proofreading on replication → **multiple mutations** (“quasispecies”) → evade host’s immune system → chronic disease
- Genotypes, at least 1 to 11, several subtypes, such as a, b, c, etc.
- Genotypes 1 the most prevalent

Pathogenesis

- Within the liver infects only hepatocytes
- Mechanism of hepatocyte damage probably:
 - Cytopathic
 - Immune-mediated
- Provokes:
 - Acute hepatitis
 - Chronic persistent hepatitis
 - Chronic active hepatitis: **periportal** infiltration with lymphocytes and piecemeal necrosis → fibrosis → cirrhosis

Epidemiology

- Infects only humans and chimpanzees
- Spreads primarily by **needle sharing** among intravenous drug abusers
- Worldwide distribution; incidence in developed countries is declining due to safer practices among intravenous drug abusers
- Most cases in individuals born between 1945 and 1965
- Sexual and perinatal transmission, much less frequent than in hepatitis B or HIV
- **Coinfection** with hepatitis C and HIV is very common

Clinical manifestations

- Incubation 6-10 weeks
- Acute symptomatic hepatitis in **only** $\frac{1}{4}$ of infected patients
- Does not cause fulminant hepatitis
- But **50-70 %** of infected patients progress to **chronic** hepatitis C
- Serum transaminase values fluctuate during chronic illness, from normal to up to 7-10 times normal values

Diagnostic testing recommended for anyone who...

- Was born between 1945 and 1965
- Ever **injected illegal drugs**
- Received clotting factors made before 1987, or received blood/organs before July 1992
- Was ever on chronic hemodialysis
- Has HIV infection
- Has unexplained elevation liver transaminase values

Diagnosis

- **ELISA** assay designed to measure **antibodies** directed against specific hepatitis C antigens
- Recent generation tests > 95 % sensitivity and a high positive predictive value
- In low-risk populations, the ELISA assay should be **confirmed** by recombinant **immunoblot** assay, that has a higher specificity
- **Serum viral RNA** by the **PCR** method allows for quantitation of the serum viral load, and some assays detect levels as low as 100 copies per milliliter

Prognosis

- Unlike hepatitis B, hepatitis C **seldom clears** spontaneously
- 20-25% progress to cirrhosis over 20-30 years
- Increased incidence of primary hepatocellular carcinoma
- One of the leading causes of hepatic failure requiring liver transplant

Treatment

- Pegylated interferon α -2a + ribavirin
- Pegylated interferon α -2a + ribavirin + (telaprevir or boceprevir)
- **Sofosbuvir** + (simeprevir, ledipasvir, etc.)
- Quantitative hepatitis C RNA test to check response
- Additional drugs, protease inhibitors and polymerase inhibitors, coming soon

Key messages

To remember...

- Acute viral hepatitis is a common disease worldwide. Three agents, hepatitis A, hepatitis B, and hepatitis C virus, are responsible of most cases of the disease
- Prognosis de acute viral hepatitis is generally good, but progression into chronic hepatitis and eventually into cirrhosis of the liver is common with hepatitis B and C

Further reading

Used references

- Southwick F. Infectious disease. A clinical short course. 3rd Edition. New York: McGraw-Hill, 2014. Chapter 8.
- Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill, 2012. Chapter 304.

Preparing the exam

- Southwick F. Infectious disease. A clinical short course. 3rd Edition. New York: McGraw-Hill, 2014. Chapter 8.
- These slides.