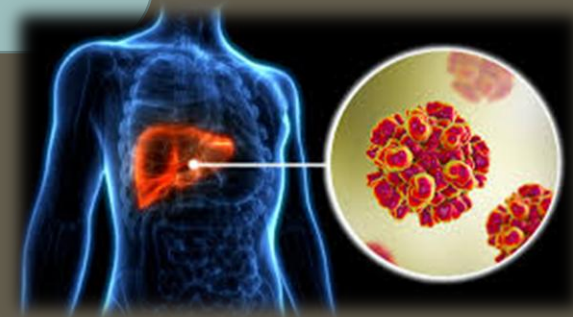


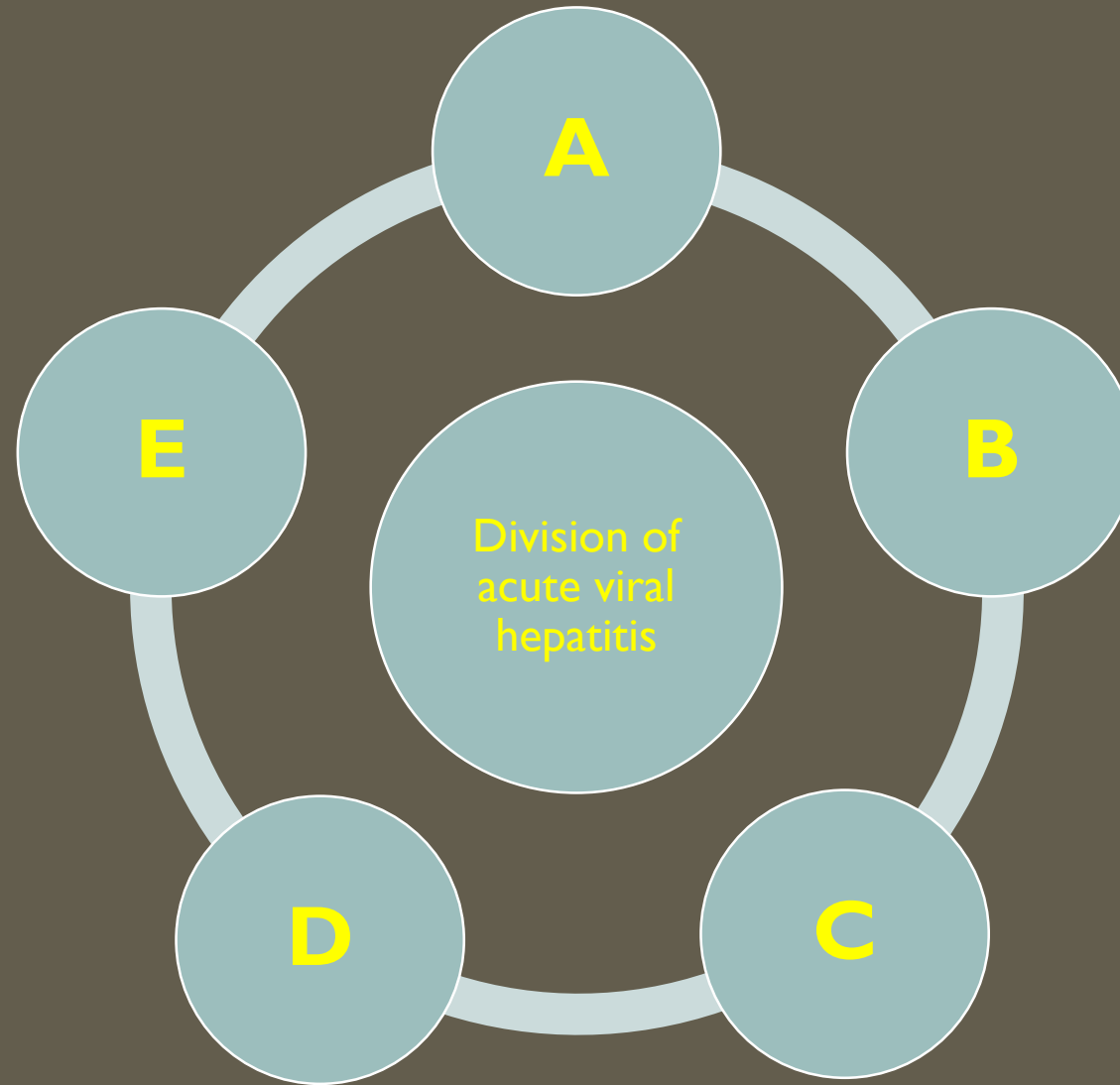
# ACUTE VIRAL HEPATITIS

## DEFINITION

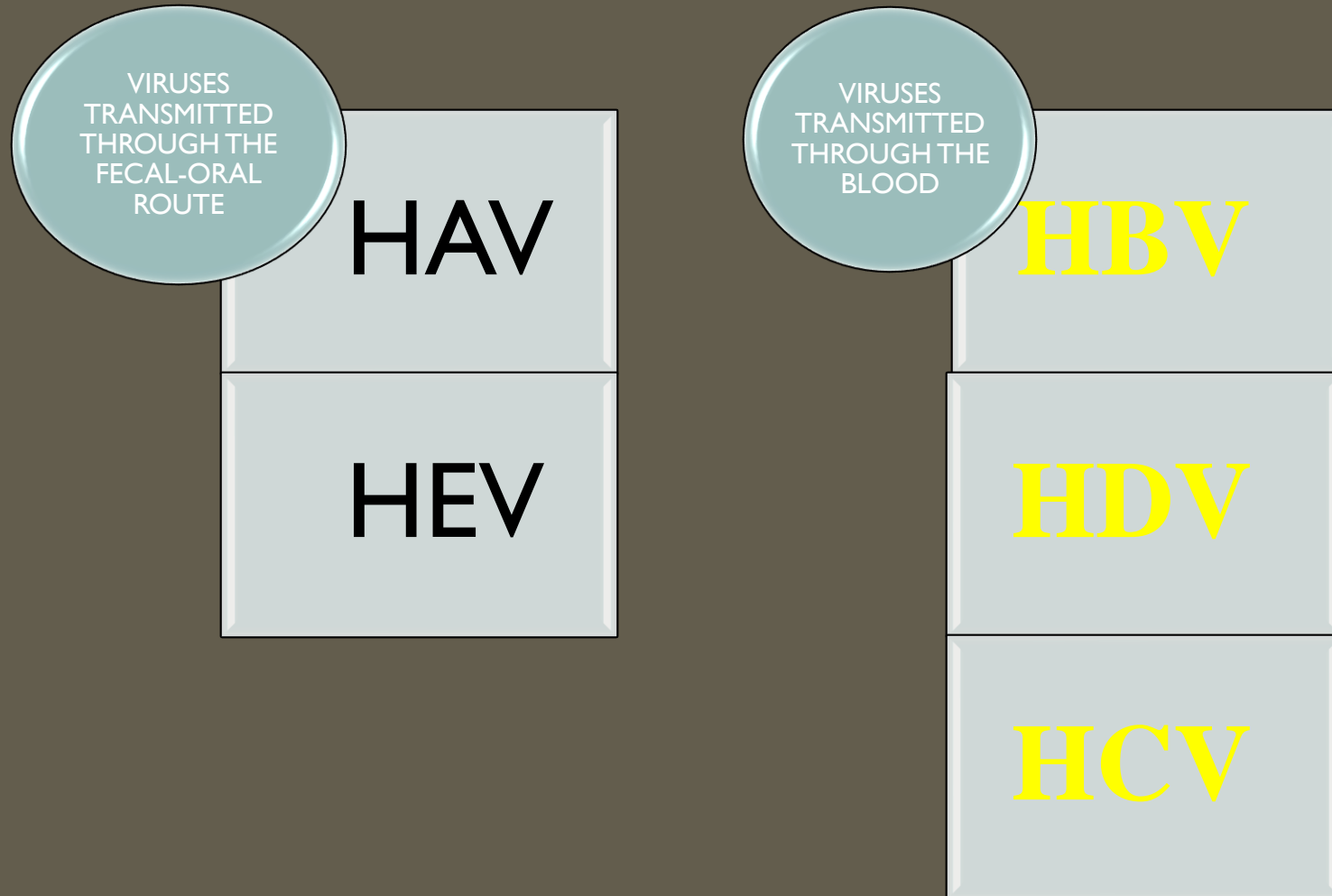
- Acute inflammation and necrosis of the liver parenchyma caused primarily by hepatotropic viruses



# DIVISION OF ACUTE VIRAL HEPATITIS



# PATHWAYS OF SPREAD OF VIRAL HEPATITIS



# ACUTE VIRAL HEPATITIS A

## GEOGRAPHIC DISTRIBUTION



Prevalence of antibody to hepatitis A virus, 2006. (From the Centers for Disease Control and Prevention (CDC): CDC Health information for international travel 2010, Atlanta, 2009, U.S. Department of Health and Human Services, Public Health Service.)

# VIRAL HEPATITIS A- ETIOLOGY

- RNA virus
- Family: Picornaviridae
- Spherical particle, linear single-stranded genome (RNA)
- Resistant to ether, acid and temperatures up to 60°C
- Relative resistance to disinfection methods→caution
- Sensitive to formalin, chlorine and UV radiation

HAV grows slowly in cell culture, does not produce a cytopathogenic effect, and is released from the infected cell without any visible lesion

# VIRAL HEPATITIS A- EPIDEMIOLOGY

- Hepatitis A Incubation: 15-50 days (30)
- Source of infection→sick person
- The virus is excreted in the stool in the second half of the incubation period and the first two weeks of the disease
- In more severe forms of hepatitis A→more massive and prolonged excretion (although it has also been proven in subclinical forms of the disease)
- The source of infection can also be monkeys (chimpanzees, marmosets, African green monkeys) as well as some shellfish (oysters)

# VIRAL HEPATITIS A- EPIDEMIOLOGY

- Transmission routes
  - Fecal-oral route (the only route of infection spread)
  - Direct contact -Disease of “dirty hands”
  - Transmission is easier and more frequent in children, mentally retarded people and people with undeveloped hygiene habits -Poverty, poor sanitary and hygienic housing conditions, wars and natural disasters facilitate the spread of HAV infection
- The highest concentration of virus in the stool, and thus the period of greatest infectivity, occurs during the 2 weeks before onset of symptoms



# VIRAL HEPATITIS A- EPIDEMIOLOGY

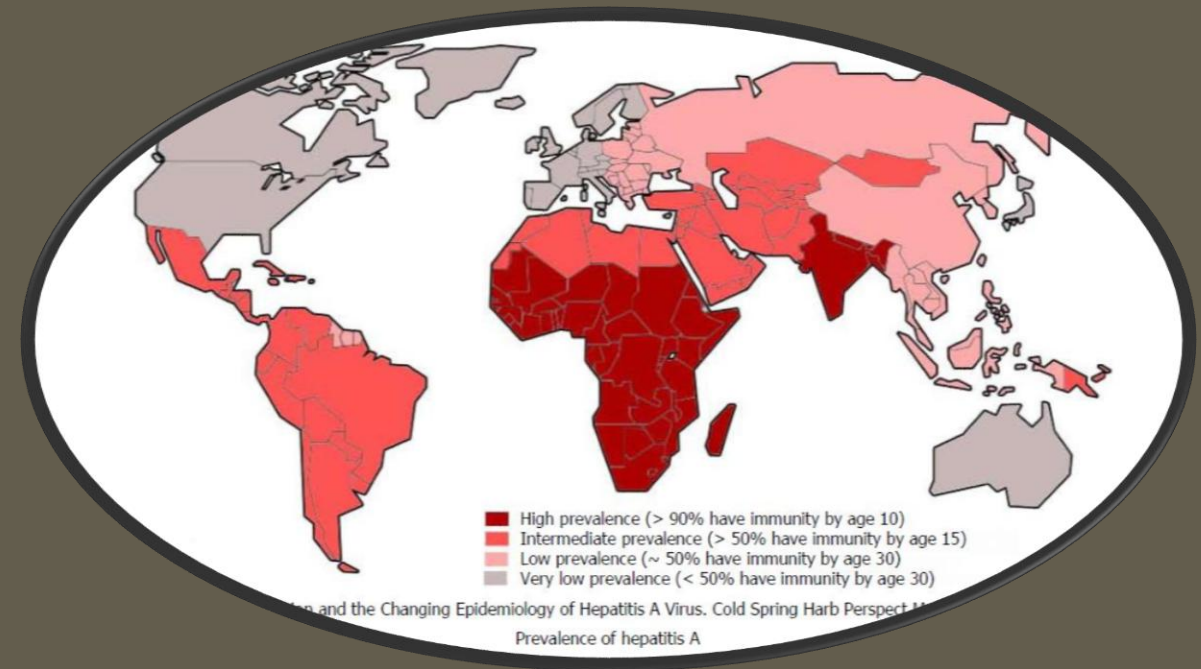
- **Contaminated water**

Mixing drinking water with feces hydric epidemics (explosive nature)

- **Contaminated food**

Food epidemics (student canteens, school and military kitchens)

Food that is not thermally processed or is prepared after thermal processing (salads, sandwiches, fruit, creams)



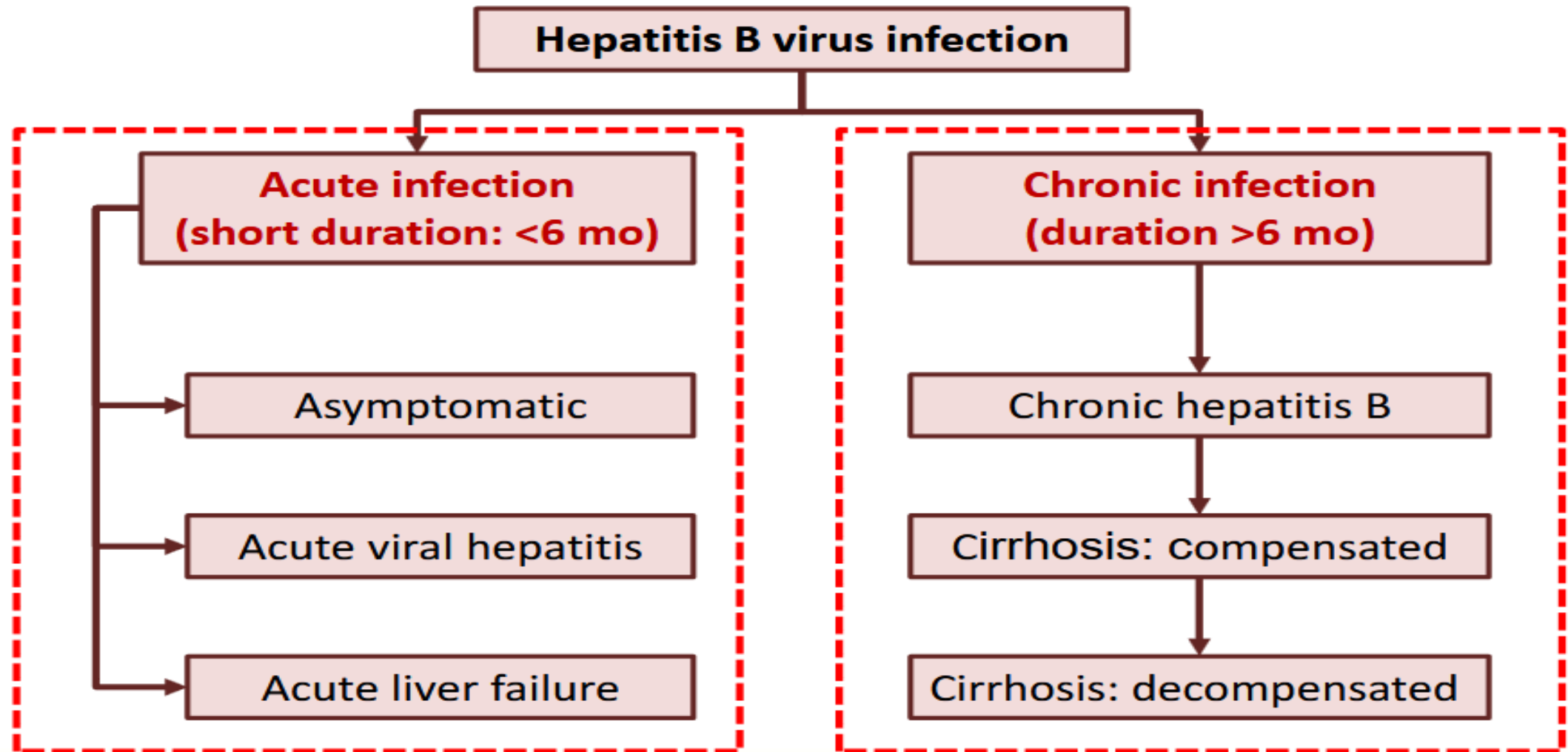
## VIRAL HEPATITIS A-PREVENTION

- Hepatitis A vaccine provides the best protection against hepatitis A infection, but other important preventative measures include improved sanitation and meticulous personal hygiene practices, such as good hand washing and proper food-handling techniques
- The hepatitis A vaccines currently available are prepared from purified, cell culture–grown HAV that is formalin-inactivated and are licensed for intramuscular use in persons 1 year of age and older
- HAV vaccines are highly immunogenic, resulting in excellent efficacy ( $\geq 94\%$  efficacy starting 2 weeks after one dose and  $>99\%$  1 month after the second dose)

## VIRAL HEPATITIS B-DEFINITION

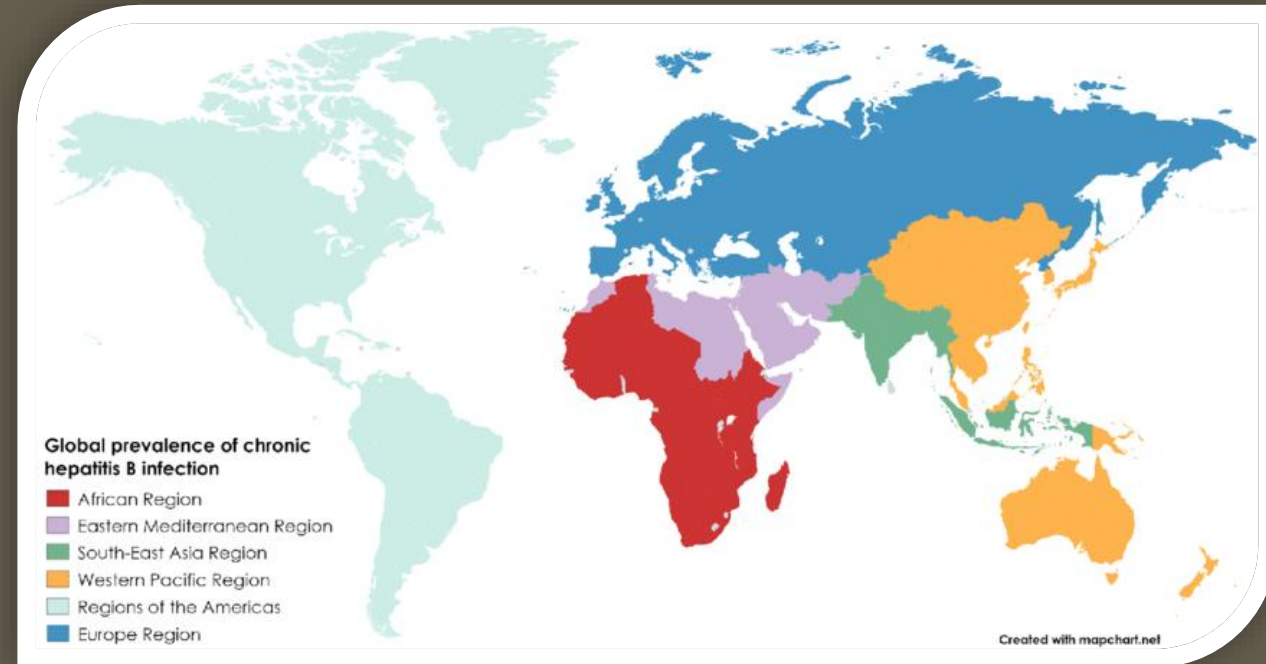
- **Acute hepatitis B** may be asymptomatic or cause clinical illness similar to infections caused by other hepatotropic viruses (hepatitis A to E)
- Most acute infections resolve without sequelae; however, progression to **chronic infection** may occur
- The main morbidity and mortality from hepatitis B occur secondary to chronic hepatitis B infection, which may result in cirrhosis or hepatocellular carcinoma

# Consequences of hepatitis B virus infection



# VIRAL HEPATITIS B - GEOGRAPHIC DISTRIBUTION

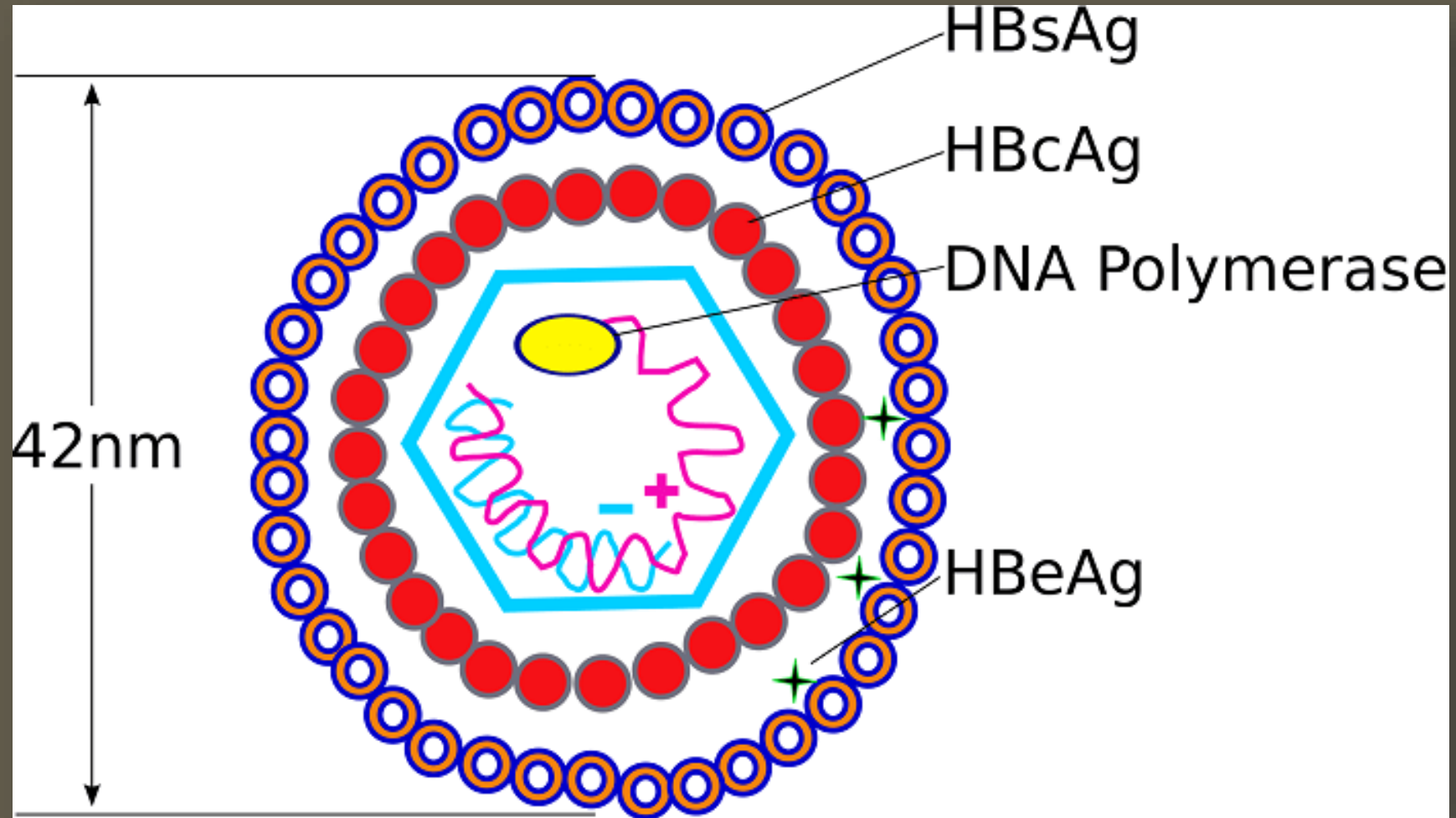
- Worldwide, more than 350 million individuals are infected with hepatitis B virus, and 5% of the world's population has chronic hepatitis B infection
- The highest prevalence of hepatitis B occurs in Asia (particularly in China and Taiwan), Africa, the Amazon basin, Greenland, and North America among Native North Americans in Canada and Alaska
- Since 1990 the incidence of hepatitis B infection has declined in all age groups in the United States, with the largest decline (approximately 98%) occurring in children younger than 15 years of age, largely attributable to use of hepatitis B vaccination



## VIRAL HEPATITIS B -ETIOLOGY

- Small DNA virus
- Very resistant in the external environment
- Family: Hepadnaviridae
- 6 genotypes, 9 subtypes
- Outer lipoprotein envelope (main part is HBsAg)
- Nucleocapsid contains:
  - HBcAg and HBeAg
- Viral genome (HBV DNA) - two enzymes (DNA polymerase and protein kinase) are covalently bound to it
- Free tubular or spherical forms (HBsAg in excess)

# HEPATITIS B VIRUS STRUCTURE



# VIRAL HEPATITIS B-EPIDEMIOLOGY

- Incubation: 30-160 days (60-90)
- Source of infection
- A person with acute or chronic hepatitis B
- Most contagious:
- When there are markers of viral replication in serum (HBV DNA, HBV DNA polymerase, HBeAg, anti-HBcIgM, pre-S1 antigen) and liver (HBcAg, HBV DNA) ↓ incubation, prodromal period, onset of icteric period, replicative phase of chronic hepatitis
- Hepatitis B occurs sporadically, endemically and in the form of small epidemics



# VIRAL HEPATITIS B-TRANSMISSION ROUTES

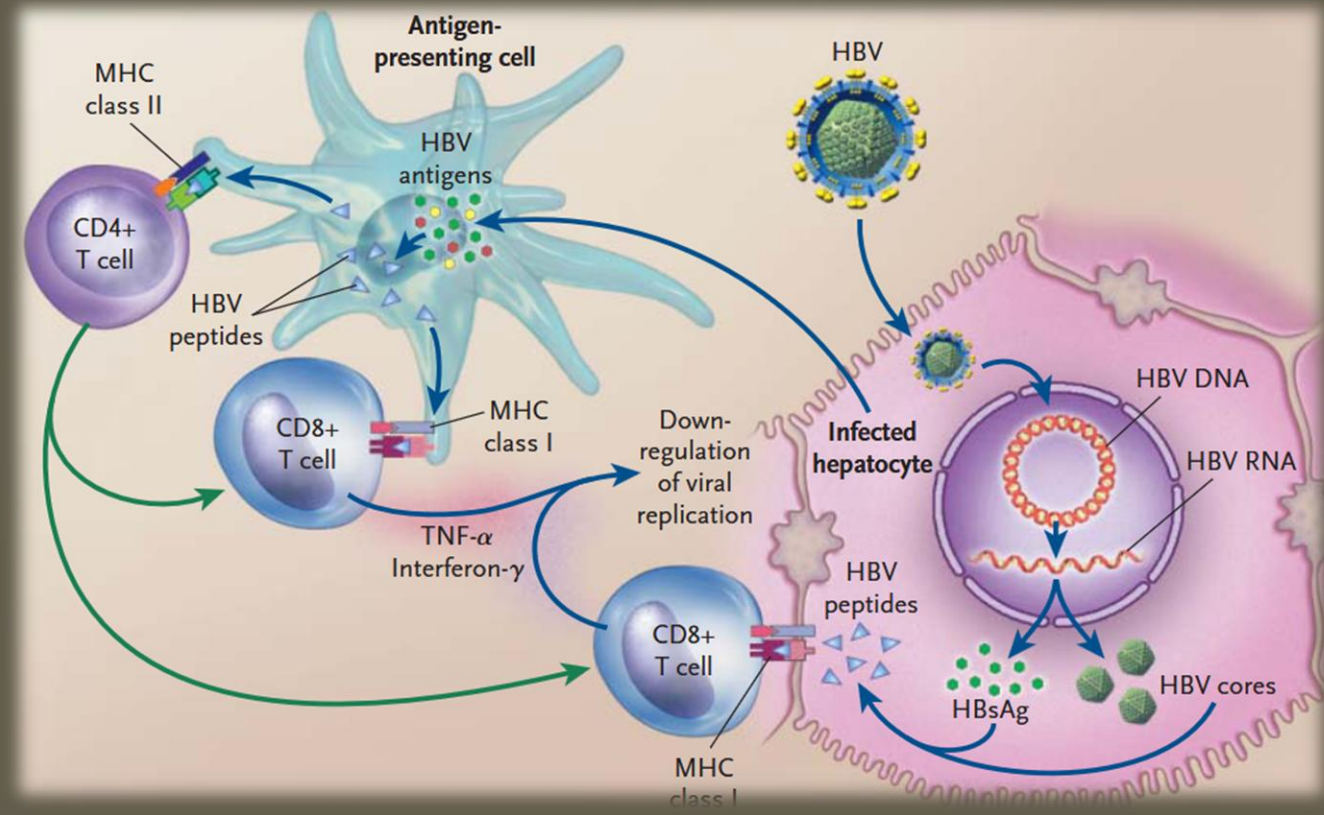
- Transmission through **exposure to blood** or other infected fluids:
  - ✓ Intravenous drug use
  - ✓ Hemodialysis
  - ✓ Blood transfusions
  - ✓ Tissue and organ transplantation
  - ✓ Tattooing
  - ✓ Acupuncture
  - ✓ Surgical, dental, endoscopic interventions

## VIRAL HEPATITIS B-TRANSMISSION ROUTES

- Transmission by contact with an infected person (horizontal transmission) - highly endemic areas: kissing sharing dental instruments, haircuts, shaving
- Transmission by sexual contact
- Transmission from mother to child at birth (perinatal-vertical transmission) - highly endemic areas:
  - during childbirth (most common)
  - early postnatal period (close contact)
  - intrauterine (via umbilical vein) - rare

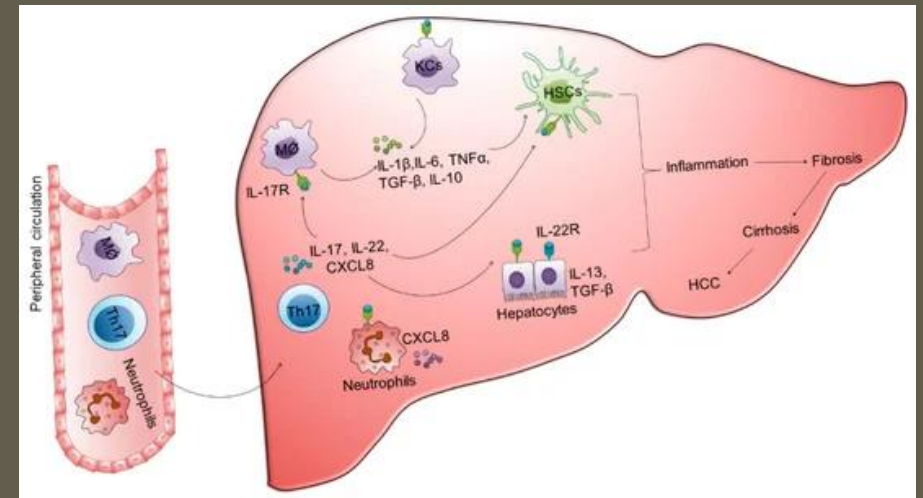
# VIRAL HEPATITIS B-PATHOGENESIS

- Cellular immune response plays a key role in the pathogenesis of hepatitis B
- Cellular immune response
- Cytotoxic T lymphocytes → major role in the eradication of HBV infection ↓ recognize viral peptides (HBeAg, HBcAg)
- Patients with self-limiting acute hepatitis B
- a) strong CTL response to a variety of envelope, nucleocapsid and polymerase epitopes
- b) strong polyclonal CD4+, T helper cell response to nucleocapsid epitopes (HBcAg, HBeAg)



# VIRAL HEPATITIS B-PATHOGENESIS

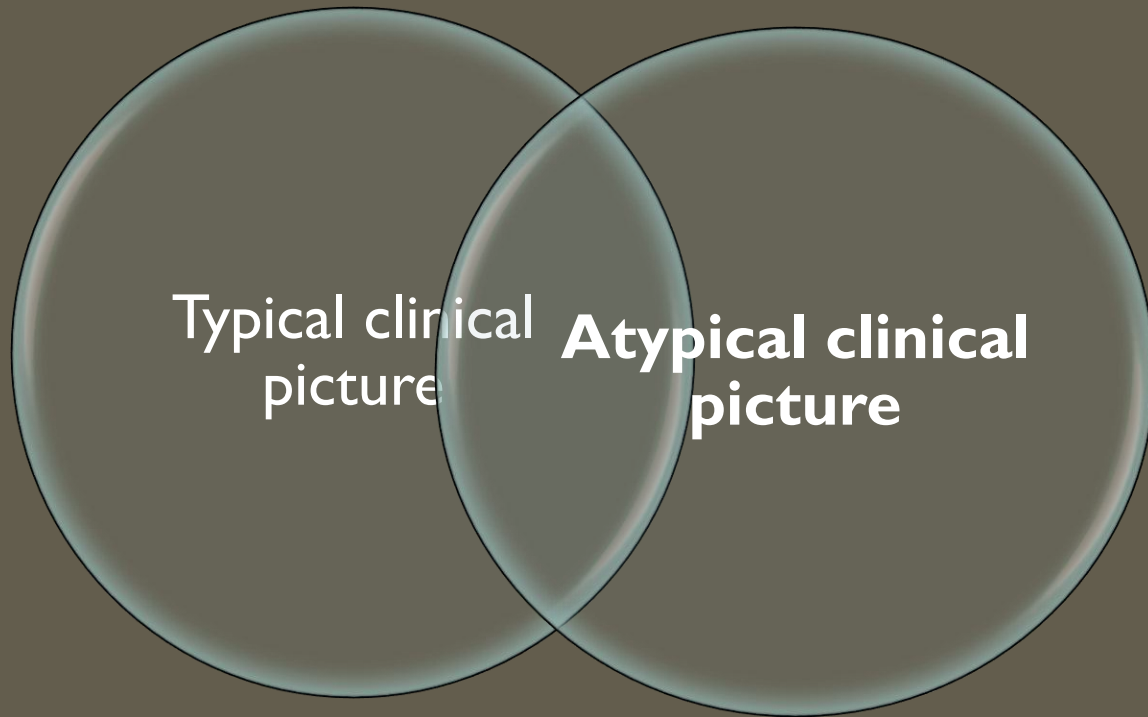
- **Humoral immune response**
- Neutralizing antibodies (anti-HBs) directed at viral envelope epitopes (HBsAg)
- Also responsible for the development of extrahepatic manifestations
- Chronic HBV infection→weak, suboptimal response of CTL and T helper lymphocytes to target antigens presented by class I and II molecules HLA



## CLINICAL PICTURE OF ACUTE VIRAL HEPATITIS (A AND B..OTHERS)

- All acute viral hepatitises may have a similar clinical picture of the disease

# CLINICAL PICTURE OF ACUTE VIRAL HEPATITIS



- Typical clinical picture includes:
  - ✓ Prodromal (preicteric) stage
  - ✓ Icteric stage
  - ✓ Convalescence stage

## TYPICAL ICTERIC FORM OF ACUTE VIRAL HEPATITIS

- PRODROMAL (PREICTERIC) STAGE (The preicteric stage lasts 3-10 days, up to 3 weeks at most)
- Onset is generally insidious with nonspecific signs and symptoms
  - ✓ Nausea
  - ✓ Vomiting
  - ✓ Abdominal pain
  - ✓ Fever
  - ✓ Malaise
  - ✓ Headache
  - ✓ Decreased appetite

Dark urine appears before the onset of jaundice

## Icteric stage

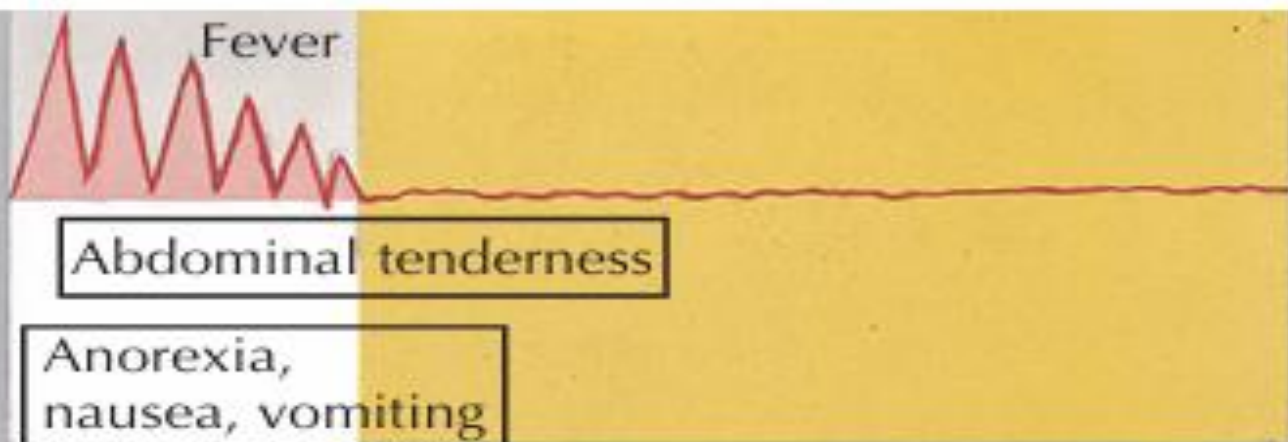
- Starts with icterus (jaundice): first on the whites of the eyes and hard palate
- The patient subjectively feels better, the symptoms from the preicteric phase decrease and disappear
- Slight pain in the liver area, as well as itching of the skin, may occur
- Hepatomegaly in 80% of patients
- Splenomegaly in 20% of patients
- At the beginning of the icteric stage (7-10 days), the jaundice progresses and the patients feel well (“more yellow than sick”)
- This stage lasts 1-4 weeks from the onset of jaundice



## Convalescence stage

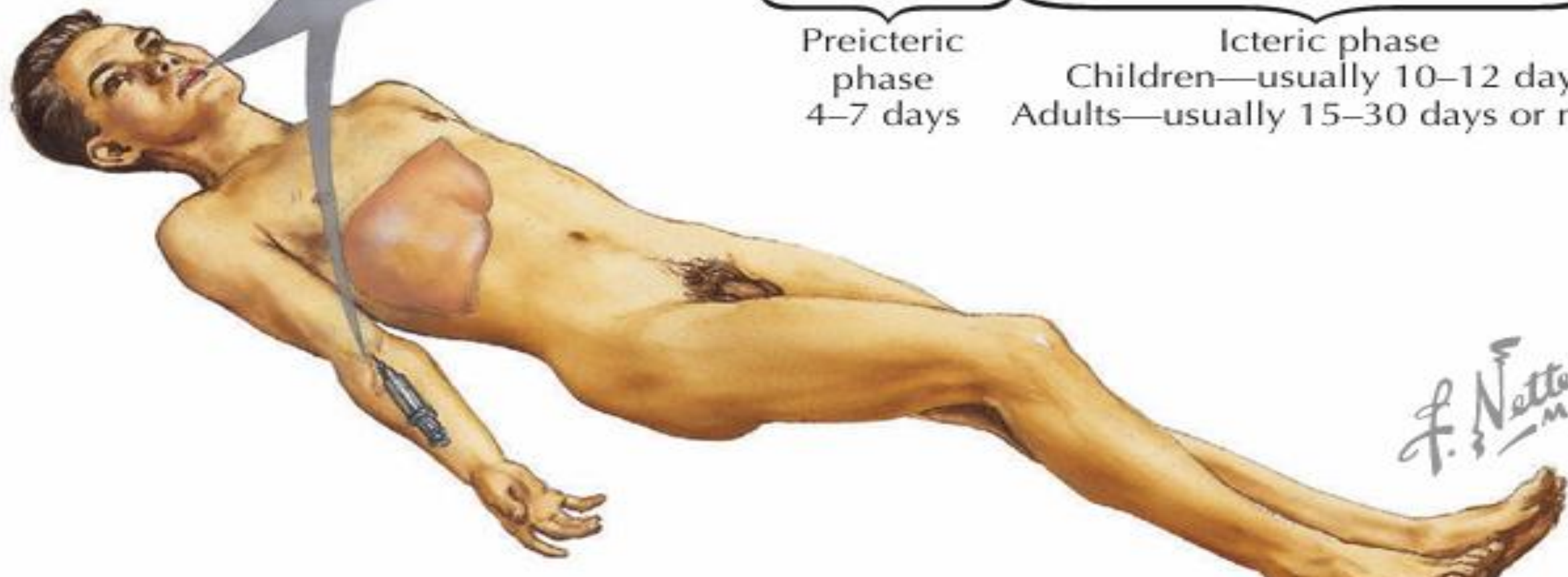
- All symptoms disappear, except fatigue (may last for weeks)
- Only pathological biochemical tests persist
- This phase is shorter in hepatitis A than in hepatitis B and C
- Complete clinical and biochemical recovery occurs in 1-2 months in hepatitis A and E, and 2-3 months (rarely up to 6 months) in hepatitis B

Infectious  
hepatitis (A)  
incubation period  
15–50 days  
Portal of entry  
mainly oral but  
also parenteral

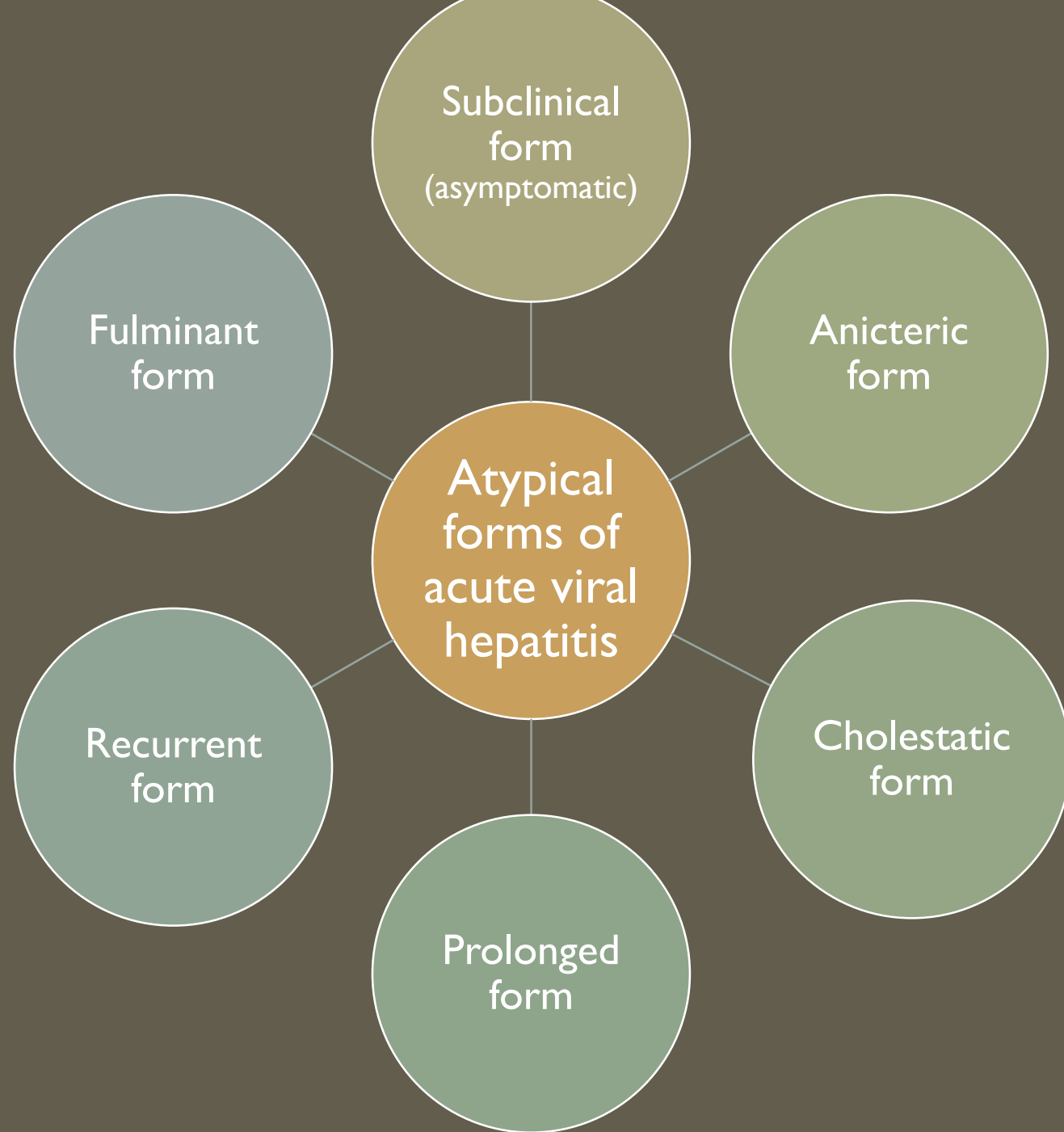


Preicteric  
phase  
4–7 days

Icteric phase  
Children—usually 10–12 days  
Adults—usually 15–30 days or more



*F. Netter  
M.D.*

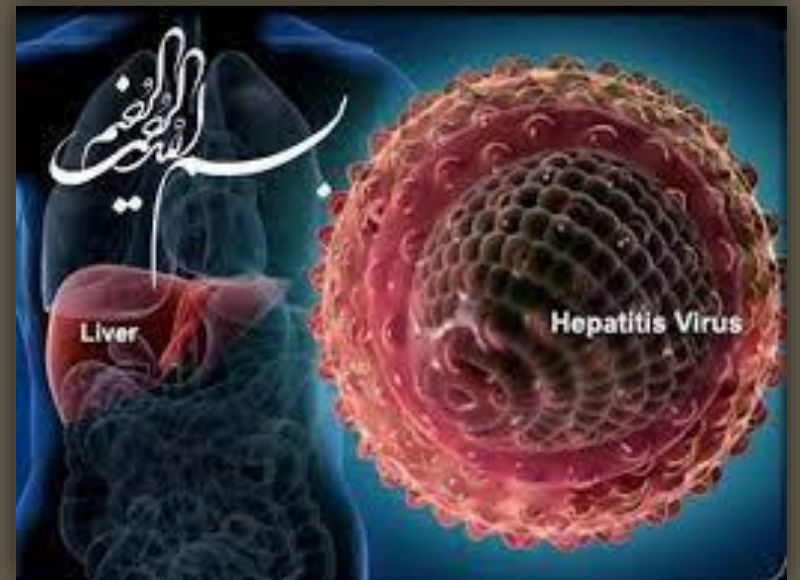


ATYPICAL FORMS OF ACUTE VIRAL HEPATITIS	
SUBCLINICAL FORM (ASYMPTOMATIC)	<ul style="list-style-type: none"> <li>No symptoms of the disease with normal physical findings</li> <li>Diagnosis→elevated transaminases and presence of hepatitis virus markers in serum</li> <li>This clinical form is more common in children (hepatitis A and E)</li> </ul>
ANICTERIC FORM	<ul style="list-style-type: none"> <li>Symptoms of the preicteric stage are less intense and last shorter</li> <li>No jaundice</li> <li>Common in hepatitis C (75-90%) and in children with hepatitis</li> </ul>
CHOLESTATIC FORM	<ul style="list-style-type: none"> <li>Most common in hepatitis A in adults</li> <li>Icterus increases, accompanied by itching of the skin</li> <li>The patient feels well all the time</li> <li>The course of the disease is prolonged (3-8 months)</li> <li>There is a decrease in transaminases with persistence of hyperbilirubinemia</li> <li>Prognosis good, complete recovery</li> </ul>
PROLONGED FORM	<ul style="list-style-type: none"> <li>Lasts longer than 3 months (increased transaminase activity up to 3 times above normal values)</li> <li>Patients are anicteric</li> <li>Symptoms of the initial phase (especially fatigue) persist</li> </ul>

Atypical forms of Acute Viral Hepatitis	
Recurrent form	<ul style="list-style-type: none"> <li>• Most common in hepatitis A</li> <li>• Relapse clinically and biochemically resembles the acute phase of the disease and hepatitis A virus is again excreted in the stool</li> <li>• The interval between the two phases of the disease is 30-90 days</li> <li>• The prognosis is good, recovery is complete</li> </ul>
Fulminant form	<ul style="list-style-type: none"> <li>• The most severe clinical form of acute viral hepatitis A syndrome of rapid and severe liver function impairment in previously healthy individuals, accompanied by encephalopathy, coagulopathy and other metabolic disorders, with possible deterioration of respiratory, cardiac and renal function</li> <li>• Fulminant hepatitis→a consequence of massive liver necrosis</li> <li>• Frequency→acute hepatitis B (1%), coinfection D (2-5%), hepatitis A (0.1%), hepatitis E in pregnant women in the third trimester of pregnancy in endemic areas (20%)</li> </ul>

## FULMINANT FORM ACUTE VIRAL HEPATITIS

- According to the time elapsed from the onset of jaundice to the onset of encephalopathy:
- Hyperacute (less than 7 days)
- Acute (8-28 days)
- Subacute (29 days to 12 weeks)



# HEPATIC ENCEPHALOPATHY

- ✓ Stage I: euphoria or depression, mild confusion, dysarthria, sleep inversion, flapping tremor +/-
- ✓ Stage II: more pronounced drowsiness, lethargy, rude behavior, flapping tremor + Stage III: confusion, incoherent speech, psychomotor restlessness, drowsy but wakes up, follows simple commands, flapping tremor +
- ✓ Stage IV: coma, flapping tremor – Hepatic stench (smell of rotten leaves or fresh liver)
- ✓ Hypotension, cardiac arrhythmias, central respiratory failure, ARDS, hypoxia, hypoglycemia, acid-base and electrolyte disturbances, ascites, gastrointestinal bleeding, hepatorenal syndrome, sepsis (bacterial and fungal infection)

## DIAGNOSIS

- Based on history, epidemiological survey, physical examination and laboratory findings
- Laboratory diagnosis of acute hepatitis A.
- Hematological analyses Normal or reduced number of leukocytes with predominance of lymphocytes in the leukocyte formula Fulminant hepatitis→leukocytosis with polynucleosis
- B. Biochemical analyses Serum glutamatoxal transaminase (SGOT,AST)↑ Serum glutamatopyruvic transaminase (SGPT,ALT)↑ ↓ 10 times or more SGPT>SGOT



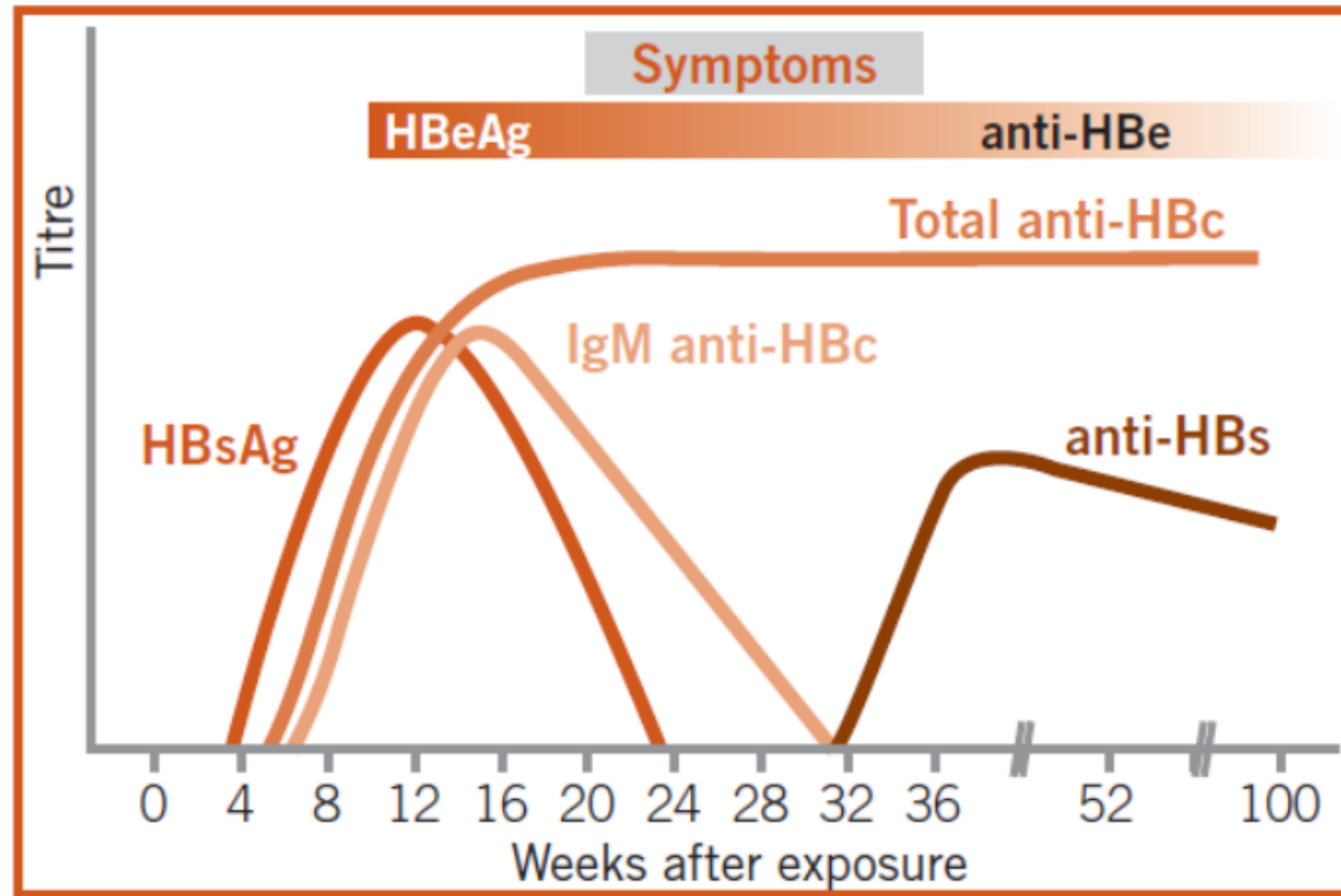
## DIAGNOSIS

- Hyperbilirubinemia (total and conjugated) → icteric forms of the disease Anicteric forms → normal values of total bilirubin (possible increase of only conjugated)
- Icterus → total bilirubin over 30  $\mu\text{mol/l}$  The level of bilirubinemia correlates with the severity of the disease → except in cholestatic forms Serum bile acids  $\uparrow$  (at the beginning of the disease)
- Hypoalbuminemia → severe and long-term forms of acute viral hepatitis
- Prolonged prothrombin time Beta- and gamma-globulins  $\uparrow$  (infection and RES reaction)

# SEROLOGICAL DIAGNOSIS OF ACUTE HEPATITIS

- Hepatitis A
  - Anti-HAV IgM↑, Anti-HAV IgG↓-acute phase Anti-HAV IgM↓, Anti-HAV IgG↑-convalescence
- Hepatitis B
  - HBsAg+, anti-HBc IgM+
  - Early seroconversion:
    - HBeAg-/anti-HBe+ ↓
  - Good prognostic sign
  - HBsAg > 6 months HBeAg > 10 weeks chronicity HBV DNA > 8 weeks

# Serological pattern of acute HBV infection



## Summary: Serological markers of HBV infection

- HBsAg positivity indicates current HBV infection
- If HBsAg remains positive for >6 months: chronic infection
- Presence of IgM anti-HBc implies recent (acute) infection
- Presence of anti-HBc (total) indicates
  - If HBsAg-negative: Prior exposure to HBV with clearance
  - If HBsAg-positive: Current HBV infection
- Anti-HBs indicates immunity against HBV infection, either because of prior cleared infection (anti-HBc +) or immunization (anti-HBc –)
- HBeAg, anti-HBe and HBV DNA helps in identifying the various phases in a patients with chronic HBV
- For HBV screening, 1-assay or 2-assay approach may be used, depending on disease prevalence

# TREATMENT OF ACUTE VIRAL HEPATITIS

- A. Hygiene and dietary regimen
  - Food adapted to the patient's appetite
  - Avoid fatty foods in severely jaundiced patients
  - Avoid preservatives, additives and alcohol
  - Bed rest at the beginning of the disease (malaise)
- B. Symptomatic therapy
  - Intravenous glucose administration (5%, 10%) - anorexia, vomiting
  - Multivitamin therapy
  - H antagonists

# TREATMENT OF ACUTE VIRAL HEPATITIS

- Corticosteroids are not used in the treatment of any form of acute viral hepatitis
- Vitamin K→cholestatic hepatitis and hepatitis with prolonged prothrombin time
- Cholestyramine→cholestatic forms of acute hepatitis
- Sofosbuvir/Velpatasvir (Epclusa®), Glecaprevir/Pibrentasvir (Maviret®)-8 weeks-acute viral hepatitis C
- Tenofovir, entecavir, lamivudine →fulminant hepatitis B

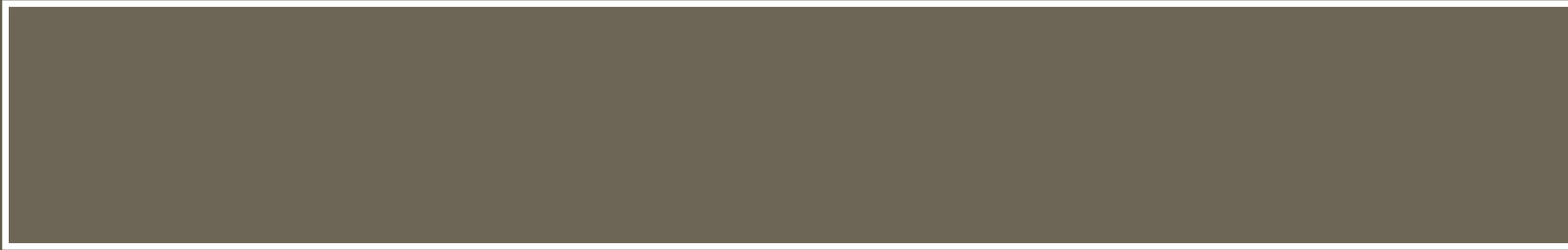
# FULMINANT HEPATITIS TREATMENT

- Intensive care unit
- Hepatic encephalopathy therapy
- Protein restriction (20g daily)
- Lactulose (10-30ml 3 times daily)
- Deep lactulose enemas
- Intestinal sterilization (Neomycin)
- Brain edema therapy Mannitol 20% 1g/kg Furosemide
- Hypoglycemia therapy
- Continuous infusion of 10% glucose up to 3l/24h

# FULMINANT HEPATITIS TREATMENT

- Infection prevention
- Prophylactic use of antibiotics (3rd generation cephalosporins) and antifungals
- Frequent urine, blood and sputum cultures
- Prevention and treatment of bleeding
- Hydrogen pump inhibitors, i.v. Vitamin K
- Fresh frozen plasma
- Treatment of hepatorenal syndrome
- Hemodialysis
- Continuous arteriovenous hemofiltration
- Treatment of respiratory failure
- Treatment of hypotension





- Specific prophylaxis
- Active Hepatitis B vaccine (recombinant) 3 doses of 20 $\mu$ g (adults), 10 $\mu$ g (children) are given→0,1,6m Protection→96% of vaccinated, lasts 10 years or more
- Active+passive (vaccine+hepatitis B immune globulin) newborns of HBsAg+ mothers needlestick contaminated with HBsAg+ blood unprotected sexual contact with HBsAg+ person

# CHRONIC VIRAL HEPATITIS

# CHRONIC VIRAL HEPATITIS

- Definition
- Inflammation and necrosis of the liver parenchyma, lasting longer than 6 months and caused primarily by hepatotropic viruses
- Etiology
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Hepatitis D (delta) virus (HDV)
  - Hepatitis G virus (HGV)

## COURSE OF INFECTION AND CLINICAL PICTURE

- Exacerbation and remission phases of the disease
- **Acute hepatitis B** → in 5-10% of cases it becomes chronic
- ↓
- 15-30% liver cirrhosis
- **Acute hepatitis C** → in 80-90% of cases it becomes chronic
- 10-20% liver cirrhosis 1-7% hepatocellular carcinoma

- **Exacerbation phase**→clinical picture as in the acute phase of the disease
- **Remission phase**→no subjective disorders, normal objective findings
- In 75-90% of cases, the disease is asymptomatic and is discovered by chance
- Most common symptoms: malaise, feeling of pressure or dull pain under the DRL
- Physical findings→poor: anicteric (except in rare exacerbations), hepatomegaly, rarely splenomegaly
- In 10-25% of patients→the disease has a more progressive course (a year after infection): liver cirrhosis is histologically verified (still scanty symptomatology)

- After several years→pronounced clinical signs of compensated liver cirrhosis: hepatosplenomegaly, palmar erythema, spider nevi, parotid swelling
- First decompensation (ascites, peritibial edema, encephalopathy)  
↓
- functional liver reserves exhausted  
↓
- disease enters terminal phase
- Decompensation, encephalopathy, bleeding, bacterial infections→threaten the patient's life

- Chronic HBV/HDV infection
- Chronic delta hepatitis → more serious in course and outcome than other chronic viral hepatitis
- Chronic delta hepatitis → 70-80% of patients develop liver cirrhosis
  - ↓
  - 15% of these patients have a progressive course of the disease
    - ↓
    - develop liver cirrhosis within two years
    - Clinically indistinguishable from other viral hepatitis

# EXTRAHEPATIC MANIFESTATIONS

- Membranoproliferative glomerulonephritis
- Essential mixed cryoglobulinemia
- Porphyria cutanea tarda
- Sicca syndrome
- Muren corneal ulcer
- Autoimmune thyroiditis
- Polyarteritis nodosa
- Aplastic anemia
- Myocarditis
- Polyradiculoneuritis
- Pancreatitis



# COMPLICATIONS

- Liver cirrhosis
- End-stage liver failure (encephalopathy, coagulopathy, infections, etc.)
- Hepatocellular carcinoma
- Diagnosis
- Socio-epidemiological survey (risk factors)
- Physical examination
- Laboratory diagnostics
- Chemical picture and sedimentation rate (without significant changes)
- Elevated serum transaminase activity (AST,ALT) → usually 2-5 times above normal values (except in phases of severe exacerbation)

# LABORATORY ANALYSES

- Lower albumin values, elevated globulin values → more severe impairment of liver synthetic function (terminal disease)
- Prolonged prothrombin time (decreased coagulation factors: II, V, VII)
- Serological diagnostics
- Chronic hepatitis B
- HBsAg+
- Anti-HBcIgG+, IgMØ (in the replication phase it can be+)
- HBeAg+, antiHBe Ø (mutant forms lose HBeAg)
- Chronic hepatitis C
- Anti-HCV total+
- Chronic hepatitis D
- HBsAg+, anti-HBcIgM Ø, anti-HDV total +

- Virological diagnostics
- Polymerization chain reaction (PCR)
- Qualitative PCR→determination of the presence of the virus
- Quantitative PCR→determination of the number of copies of viral NK in 1 ml of serum
- HCV genotyping-determination of the genotype of the virus
- Determination of DNA polymerase activity
- Liver biopsy and pathohistological verification of the disease
- Necroinflammatory activity
- Stage of the disease

# THERAPY CHRONIC HEPATITIS B

- Pegylated interferon  $\alpha$ -2a
- Nucleoside/nucleotide analogues
- Vaccine therapy
- Cytokine therapy
- SVR-stable virological response
- Immunomodulatory action
- Th/Ts  $\uparrow$
- Increases expression of MHC class I molecules
- Increases NK cell activity,
- Stimulates maturation of cytotoxic T lymphocytes (via T cell receptor rearrangement)

- Antiproliferative action
- Reduces the level of procollagen III peptide (a marker of liver fibrosis)
- Reduces the elevated level of TGF beta (transforming growth factor beta) - enhances collagen synthesis
- Antiviral action
- Activation of 2,5-oligoadenylate synthetase



activation of oligonucleotide



activation of cellular ribonuclease



destruction of viral mRNA

## PEGYLATED INTERFERON A-2A → 180 MG/WEEK/12 MONTHS

- **Goal of therapy**
- **Biochemical:** normalization of ALT
- **Virological:** undetectable HBVDNK or drop below 2000 IU/ml serum;  
disappearance of HBsAg from serum with or without seroconversion to anti-HBs;  
in HBeAg+ (disappearance of HBeAg, with formation of anti-HBe)
- Reduction of necroinflammatory index by 2 or more, without worsening fibrosis

- Nucleoside analogues
- Tenofovir, entecavir, (lamivudine)
- Suppresses HBV replication but cannot eradicate infection
- Duration of therapy (????)
- HBeAg+ → 6-12 months (up to 2 years ???) after HBeAg/antiHBe seroconversion or HBeAg negativity without anti-HBe formation
- HBeAgØ → HBsAg loss
- Tenofovir, entecavir (recommendation)!!!

- HBeAg (+) : after achieving seroconversion in anti HBeAt and undetectable HBV DNA (6-12 months)
- HBeAg (-) : if they achieve loss of HBsAg!!!
- This is a rare event - the therapy is long-term, probably lifelong



## CHRONIC HEPATITIS C A WORLD REALITY (EASL, 2020)

- Therapeutic options:
- Sofosbuvir (400mg)/Velpatasvir (100mg) 1x1-Epclusa®
- Grazoprevir (100mg)/Elbasvir (50mg) 1x1-Zepatier®
- Glecaprevir (100mg)/Pibrentasvir (40mg) 1x3 (with food)-Maviret®
- Sofosbuvir (400mg)/Velpatasvir (100mg)/voxilaprevir (100mg) 1x1 (with food)-Vosevi®

SVR: 95-100%  
Minimalno neželjenih događaja

# PATHOANATOMICAL CHARACTERISTICS

- Stage determination
- No fibrosis-stage 0
- Mild fibrosis-stage 1
- Moderate fibrosis-stage 2
- Severe fibrosis-stage 3
- Cirrhosis-stage 4

Recommendations for genotype/subtype-based treatment of hcv-monoinfected or HCV-HIV coinfectd adult (>18 years) and adolescent (12-17 years) patients with chronic hepatitis C without cirrhosis or with compensated (child-pugh A) cirrhosis, including treatment-naïve patients (defined as patients who have never been treated for their HCV infection) and treatment-experienced patients

Type of treatment	Genotype	Cirrhosis status	Prior treatment experience	Sofosbuvir/ velpatasvir	Glecaprevir/ pibrentasvir	Sofosbuvir/ velpatasvir/ voxilaprevir	Grazoprevir/ elbasvir
Genotype/subtype determination-based treatment	Genotype 1a, 1b, 2, 4, 5 and 6	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	12 weeks (genotype 1b only)
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve		12 weeks		
			Treatment-experienced				
	Genotype 3	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	No
			Treatment-experienced				12 weeks
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve	12 weeks with weight- based ribavirin <sup>a</sup>	8-12 weeks <sup>b</sup>	12 weeks <sup>a</sup>	No
			Treatment-experienced		16 weeks		No
	Subtype 1l, 4r, 3b, 3g, 6u, 6v or any other subtype naturally harbouring one or several NS5A RASs <sup>c</sup>	No cirrhosis	Treatment-naïve	Unknown	Unknown	12 weeks	No
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve				
			Treatment-experienced				

Recommendations for simplified, genotyping/subtyping-free treatment of hcv-monoinfected or HCV-HIV coinfectd adult (>=18 years) and adolescent (12–17 years) patients with chronic hepatitis C without cirrhosis or with compensated (child-pugh A) cirrhosis, including treatment-naïve patients (defined as patients who have never been treated for their HCV infection) and treatment-experienced patients (defined as patients who were previously treated with pegylated ifn-a and ribavirin; pegylated ifn-a, ribavirin and sofosbuvir; or sofosbuvir and ribavirin)

Type of treatment	Genotype	Cirrhosis status	Prior treatment experience	Sofosbuvir/ velpatasvir	Glecaprevir/ pibrentasvir	Sofosbuvir/ velpatasvir/ voxilaprevir	Grazoprevir/ elbasvir
Simplified treatment, no genotype/subtype determination <sup>a</sup>	All genotypes	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	No
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve		12 weeks		
			Treatment-experienced				

