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**FACULTY OF MEDICINE**  
**DEPARTMENT OF INFECTIOUS DISEASES, EPIDEMIOLOGY,**  
**PARASITOLOGY AND TROPICAL MEDICINE**

**Lecture № 6**

**ACUTE VIRAL HEPATITIS**

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# Definition

- **Worldwide distributed polyetiological acute infectious diseases in that the major pathophysiological, pathomorphological and clinical characteristic is dystrophy and inflammatorial damage of the liver.**
- Hepatitis – inflammation of the liver.
- Hepatitis may be caused by:
  - alcohol,
  - drugs,
  - autoimmune diseases,
  - metabolic diseases,
  - and viruses.

# Etiology

- Viral hepatitis are though to be synonymous with diseases caused by the known *hepatotropic viruses* (*primary attack the liver*): A, B, C, D, and E.
- ❖ Viral hepatitis B and C are associated with a wide variety of extrahepatic manifestations.
- ❖ Uncommon cases of viral hepatitis include EBV, adenovirus, cytomegalovirus, rare HSV.
- ❖ Recently discovered TTV (candidate virus).

# Epidemiology

- VHA is the most common cause of acute viral hepatitis.
- VHC is the most common cause of chronic viral hepatitis.
- **Transmission:**
- Fecal-oral transmission
  - ❖ HAV
  - ❖ HEV
- Parenteral transmission
  - ❖ HBV
  - ❖ HCV
- Sexual transmission
  - ❖ HBV
- Perinatal transmission
  - ❖ HBV

# Natural history of acute viral hepatitis

- Subclinical disease – 30%
- Self-limited symptomatic disease – 70%
- Fulminant hepatic failure <1%
- Adults with hepatitis A and B are usually symptomatic.
- People with acute hepatitis C may be either symptomatic or asymptomatic (subclinical).
- Usual outcome of acute viral hepatitis is **recovery**.
- **Fulminant** hepatitis is **rare** and may occur in as many as 1% cases of acute hepatitis B (A)
- Rarely may evolve into **chronic** hepatitis (VHB!, VHC!!).
- Hepatitis A never progress to chronic.

# Clinical manifestations

- Clinical features of acute viral hepatitis are **almost identical** with several exceptions.
- Clinical course of acute viral hepatitis is separated in 4 clinical stages:
  - 1. Incubation period** – varies from a few weeks to 6 months, depending on particular virus.
- The patient is asymptomatic and feels well.

# Clinical manifestations

## 2. Preicteric phase – 3-10 (14) days

- Nonspecific initial symptoms are quite variable:
  - ❖ sudden onset (VHA), insidious (VHB);
  - ❖ malaise and weakness
  - ❖ anorexia, nausea, vomiting, lose of taste for tobacco.
  - ❖ flu-like symptoms: fever, chills (VHA,VHE)
  - ❖ fever subsides with jaundice
  - ❖ in 5-15% – serum-sickness-like syndrome: fever, rash, arthritis (more often VHB).
  - ❖ Symptoms resolve with the onset of jaundice.
  - ❖ In 20-50% have evident jaundice.
  - ❖ The reminder passed unnoticed without symptoms or unrecognized (“indigestion”, “flu”).

# Clinical manifestations

## 3. Icteric phase

- Prodromal symptoms usually diminished.
- Dark urine – the first specific sign that causes most patients to seek medical attention!!!
- Clay-colored stool – not universal.
- Jaundice – when total bilirubin level is  $>43\mu\text{mol/l}$  – easily seen on the sclera, under the tongue (not dark skin patient),
  - ❖ Most often – appearance of jaundice → improvement.
  - ❖ The degree of jaundice increases with age.
- Itching (possible) – due to deposition of bile acids in the skin.

# Clinical manifestations

- *Physical examination – few findings:*
- Enlarged tender liver with soft-elastic consistency.
- Enlarged spleen.
- Bradycardia due to prevalence of vagus.
- Hypotension.
- Fulminant hepatitis – flapping tremor is early sign of encephalopathy.

# *Laboratory findings*

- **Dramatic elevation of ASAT↑/ ALAT↑↑**
  - ❖ Precede the bilirubin rise (the rise begins during the preicteric phase, peak early in the icteric phase).
  - ❖ Quickly decreasing with recovery, remain slightly abnormal weeks after jaundice and symptoms have resolved.
- **Alkaline phosphatase (AF)** – ↑1-3x normal
- **Serum bilirubin** – elevated, both direct and indirect fractions, up to 500 μmol/L
- ❖ >3 months – cholestatic HAV

# *Laboratory findings*

- **Fibrinogen – normal or decreased** (**in severe case due to severe hepatic cytolysis!!!**)
- **Prothrombin index:**
  - ❖ usually normal
  - ❖ **when is decreased – more severe liver necrosis → fulminant hepatitis!!!**
- Other tests: rarely abnormal:
  - ❖ Total protein, albumin – normal or ↓
  - ❖ WBC – normal or slightly ↓;
  - ❖ ESR – normal or slightly ↑; **if is ↓ – B hepatitis!!!**
- **Anicteric hepatitis** – clinical features + ALAT/ASAT↑

# Clinical manifestations

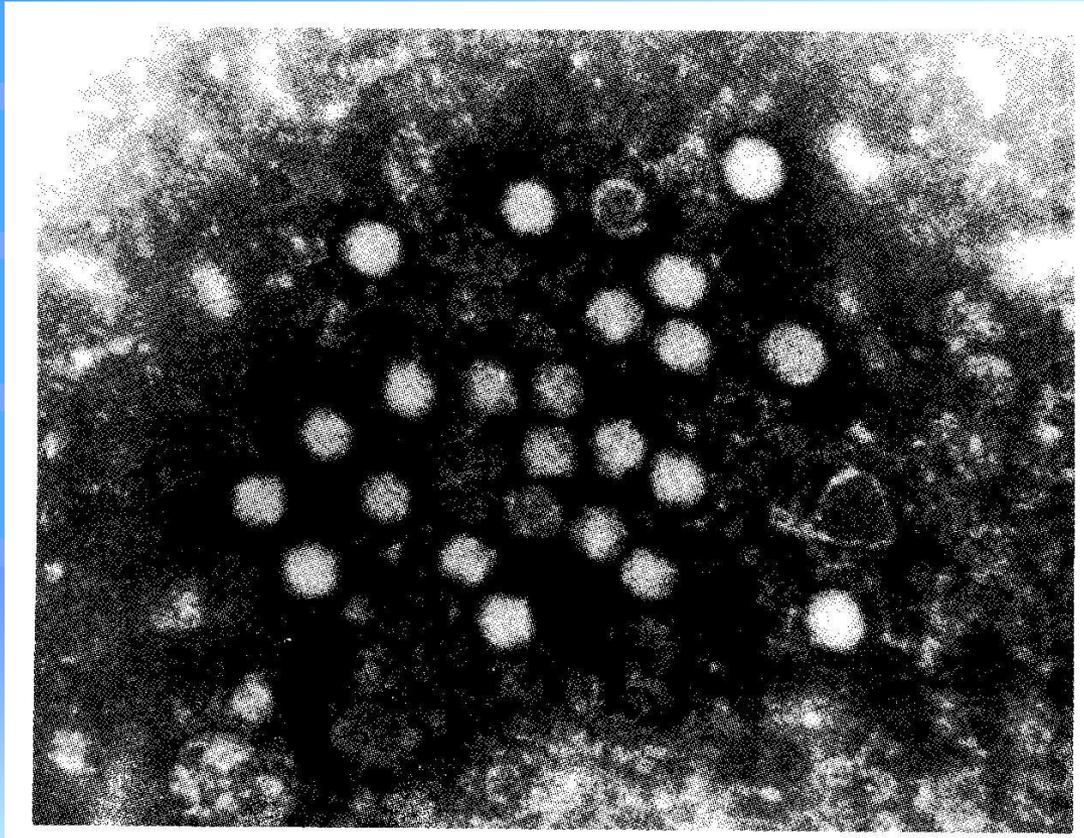
## 4. Convalescent (recovery) phase

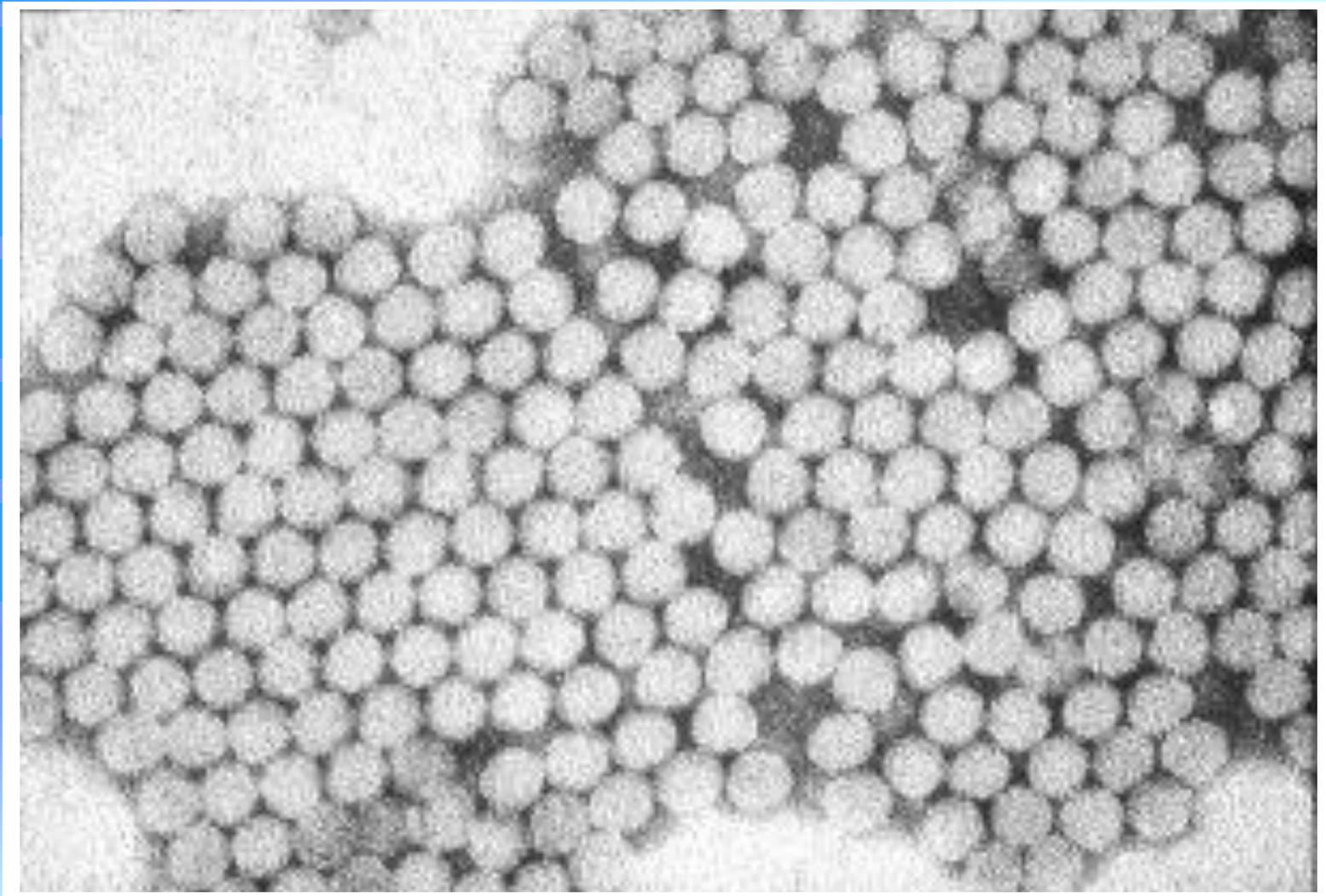
- ❖ Constitutional symptoms disappear.
- ❖ Still evident – some liver enlargement and liver biochemical tests' abnormalities.
- ❖ Complete recovery – VHA, VHE – 1-2 months.
  - $\frac{3}{4}$  VHB, VHC – 3-4 months.
  - The remainder – delayed.

# Acute viral hepatitis A – etiology

- Hepatitis A virus (HAV) is a picornavirus (member of Picornaviride family), RNA.
- High resistant – can survive months in the environment.
- Only one serotype is established with 7 serotypes (5 of them are human pathogens).
- Possesses only one antigen – HAV.

# *Hepatitis A virus*





# Acute viral hepatitis A – epidemiology

- **Transmission – by fecal-oral route** (close personal contact; contaminated food, water).
- **Highly contagious.**
- **Patient is *infectious* 2 weeks before and 1 week after the jaundice.**
- **Sporadic cases and epidemic outbreak.**
- **Globally distributed** – common infection in developing country in Africa, Asia, Central and South America. Nearly 70% of all cases of acute viral hepatitis are A type.
- **Source of infection – patient.** The major epidemiological significance – anicteric and subclinical forms.
- **High susceptibility – up to age 40 years more of population has specific immunity.**

# Acute viral hepatitis A – patophysiology

- Portal of entry – gastrointestinal tract.
- The virus reaches to the enterocytes → primary replication.
- By lymphogenic spread → regional lymph nodes – secondary replication → viraemia → lymph nodes, liver, spleen, bone marrow, and macrophages where in the onset pathological changes are absent – virus has not direct cytopathic effect!!!
- Damage of hepatocytes is secondary due to the host's immunologic response!!!
- Unlike HBV, HAV is not progressing to chronic infection and is not associated with hepatic cancer!!!

# Acute viral hepatitis A – clinical manifestations

- 1. Incubation period – most often 14-30 days** (minimal 7 days, maximal up to 50 days).
- 2. Preicteric phase – 1 to 7 days.**
  - Acute onset with:
    - ❖ adynamia, weakness, drowsiness, headache, dizziness, sweating;
    - ❖ loss of appetite, nausea and vomiting, heaviness in the abdomen after eating, feel of overeating, heaviness or dull pain in upper right abdominal quadrant or epigastria, belching, hyperacidity, lose of taste for tobacco.

# Acute viral hepatitis A – clinical manifestations

- Flu-like syndrome – in up to 60% of cases – fever, shivering, rarely runny nose, cough, sore throat.
- Rash – in up to 3% – maculo-papulous, urticarial or other rashes.
- Hepatomegaly – enlarged liver with soft-elastic consistence, rounded margin, smooth surface, tender or slightly painful.
- Splenomegaly – in to 60-70% of cases.
- Darkness of urine, clay-colored stool – appear 2-3 days before appearing of jaundice.

# Acute viral hepatitis A – clinical manifestations

## 3. Icteric phase – 1 to 4 weeks:

- Jaundice on the sclera, under the tongue, on the skin. Peak up to 3-5 days. Itching is possible.
- Signs and symptoms of preicteric phase persist.
- Bradycardia, hypotension.

## 4. Convalescent phase – 3 to 6 months.

# *Jaundice*



# Acute viral hepatitis A – laboratory findings

## 1. Blood cells:

- WBC – normal or leucopenia;
- lymphocytosis, monocytosis, neutropenia.
- Thrombocytes – normal or decreased.

## 2. ESR – normal or slightly elevated.

## 3. Urine – (+) bilirubin and increased urobilinogen.

## 4. Serum bilirubin – elevated, both direct and indirect fractions

## 5. Liver enzymes:

### ❖ dramatic elevation of ASAT↑/ ALAT↑↑

- ❖ In cholestasis – increased alkaline phosphatase (AP) and gamma glutamyltranspherase (GGT).

## 5. Hemostatic parameters – in severe course decreased fibrinogen and prolonged prothrombin time.

# Acute viral hepatitis A – clinical forms

## 1. According severity:

- mild,
- moderate,
- severe,
- fulminant – casuistic in acute viral hepatitis A.

## 2. According presence of jaundice:

- icteric,
- anicteric.

## 3. Uncommon:

- cholestatic,
- ascites.

# Acute viral hepatitis A – diagnosis

- **Clinically-epidemiological.**
- **Serological** – establishment of specific IgM antibodies (anti HAV IgM) by ELISA.

# Acute viral hepatitis A – management and treatment

- **Without etiologic treatment!!!**
- **Supportive:** infusions of glucose 5%, dextrose 5%; vitamins – B2, B6, C; blood products – plasma, Human albumin 5%; hepato-protective – Carsil, Legalone, Essentiale forte, l-ornitine (Hepa-merz), ademetionine (Transmethil).
- **Symptomatic** – antipiretics, spasmolytics.
- **Diet** – more carbohydrates and milk proteins, less animal fats.

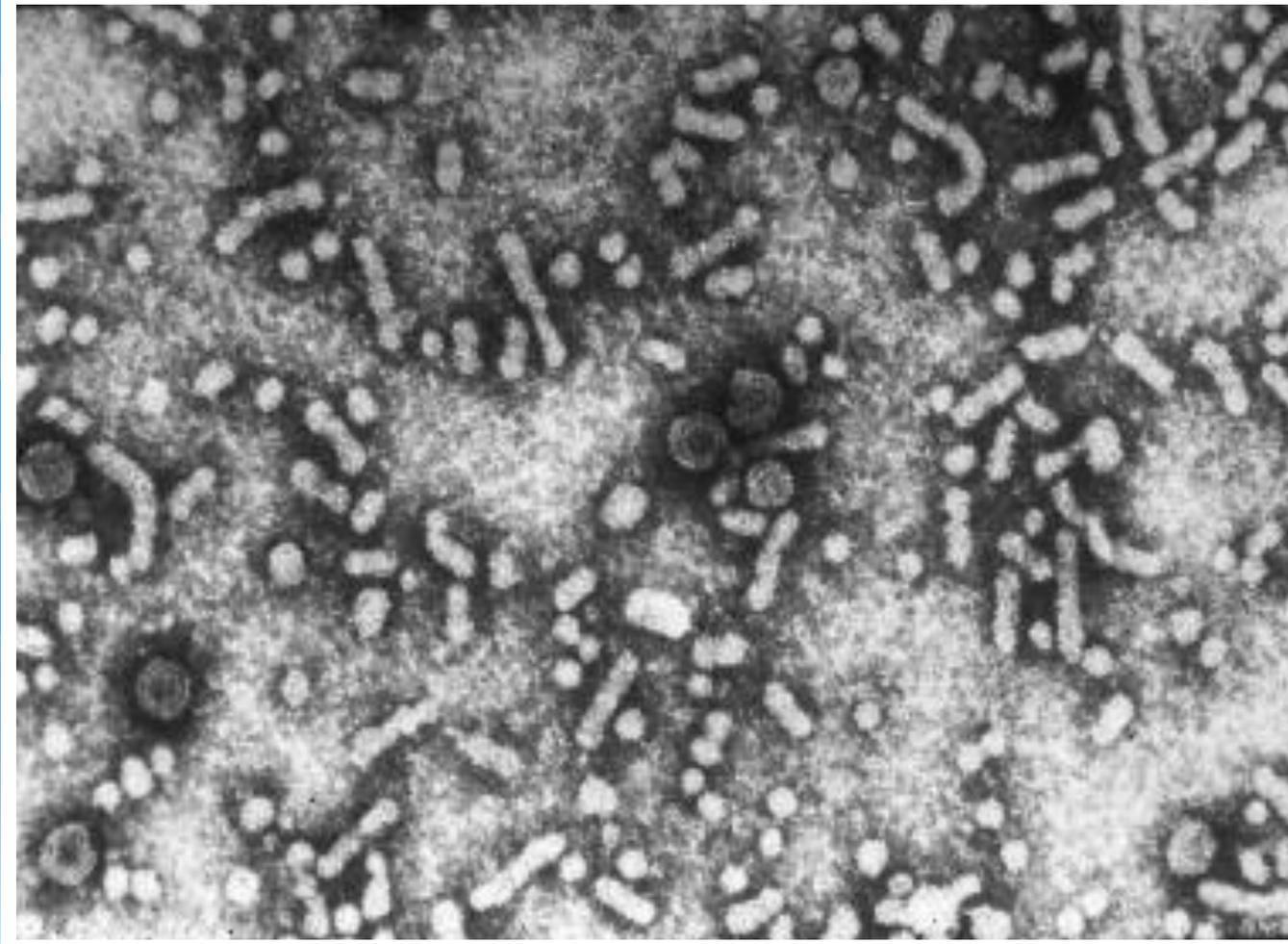
# Acute viral hepatitis A – prophylaxis

- **Specific** – vaccine.
- **Non specific** – gamma-globulin.
- Isolation of case – 7 days after appearing of jaundice.
- **Obligate hospital period – 5 days.**
- **Observation of contact people – 35 days.**

# Acute viral hepatitis B – etiology

- Causative agent – Human Hepadna virus – DNA virus (Hepadnaviridae family), low resistant in environment, sensitive to disinfectants. Without direct cytopathic effect. Posses >10 antigens. Significant for practice are 3:
  - ❖ HBsAg (surface, Australian)
  - ❖ HBeAg – marker for viral replication.
  - ❖ HBcAg – in the core of the virus, strong immunogenic. Each of these 3 antigens induces synthesis of specific antibodies – anti HBsAb, anti HBeAb, anti HBcAb – IgM (acute or recent infection) and IgG (past infection).

# *Hepatitis B virus*



# Acute viral hepatitis B – epidemiology

- One of most widespread infectious disease over the world. Annually 1 million to 2 million deaths.
- **Source of infection – acute and chronic cases and carriers.**
- **Routs of transmission – parenteral, sexual, vertical, direct contact with blood. It is not transmitted by respiratory, fecal-oral and transmissive mechanisms.**
- **Susceptibility – very high.**

# Acute viral hepatitis B – patophysiology

- Portal of entry – skin and mucosa.

Follow:

- Viremia → in hepatocytes, macrophages and mononuclears → viral epitopes and major complex of tissue compatibility both enter on the cells' surfaces and are found by receptors of cytolytic T lymphocytes (CD8).
- Activated T lymphocytes produce specific proteins (perforins), that perforate the cell wall and cause cytolysis (increased permeability of the cell membrane and leakage of cell contain into the blood) and necrosis. These processes appear and when NK cells (“natural killers”) activate. Cytokines also participate in this process.

# Acute viral hepatitis B – clinical manifestations

1. **Incubation period – 30-180 days** (rare more).
2. **Preicteric phase – to 6 days.**
  - Acute onset with:
    - ❖ adynamia, weakness, drowsiness, headache, dizziness, sweating;
    - ❖ loss of appetite, nausea and vomiting, heaviness in the abdomen after eating, feel of overeating, heaviness or dull pain in upper right abdominal quadrant or epigastria, belching, hyperacidity, lose of taste for tobacco.
  - **Arthralgia – suggestive for hepatitis B!!!**

# Acute viral hepatitis B – clinical manifestations

- Flu-like syndrome – fever, shivering, rarely runny nose, cough, sore throat.
- Rash – in up to 10% – maculo-papulous, urticarial or other.
- Hepatomegaly – enlarged liver with soft-elastic consistence, rounded margin, smooth surface, tender or slightly painful.
- Splenomegaly – in to 60-70% of cases.
- Darkness of urine, clay-colored stool – appear 2-3 days before appearing of jaundice.

# Acute viral hepatitis B – clinical manifestations

## 3. Icteric phase – 2 to $\geq 6$ weeks:

- Jaundice on the sclera, under the tongue, on the skin. Peak up to 3-5 days. Itching is possible.
- Signs and symptoms of preicteric phase persist.
- Bradycardia, hypotension.

## 4. Convalescent phase – to 12 months.

# **Acute viral hepatitis B – laboratory findings**

- **Same as in viral hepatitis A.**

# Acute viral hepatitis B – clinical forms

## 1. According manifestation:

- Unapparent – in 70% of cases,
- apparent.

## 2. According severity:

- mild,
- moderate,
- severe,
- fulminant – acute liver failure.

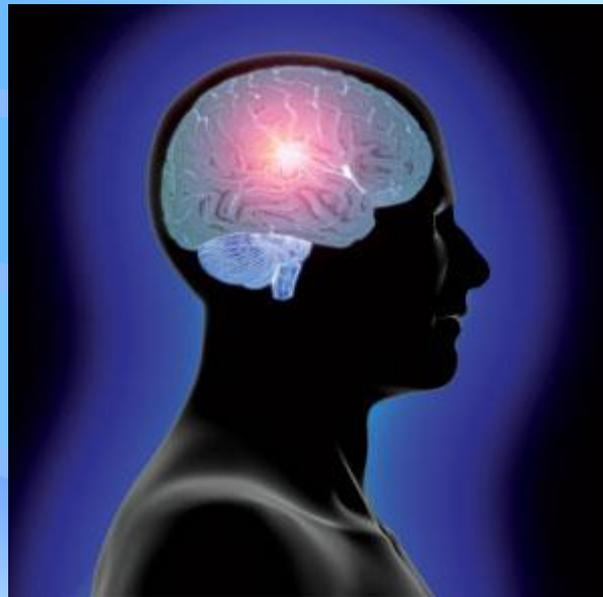
## 2. According presence of jaundice:

- icteric,
- anicteric.

## 3. Uncommon:

- cholestatic,
- Ascites,
- Syndrome of Gianotti-Crostti – often with papulous rash on the extremities (round the joints).

# *Acute liver failure – liver encephalopathy*



# Acute viral hepatitis B – diagnosis

- **Clinico-epidemiological.**
- **Serological** – establishment of HBsAg and specific IgM antibodies (anti HBc IgM) by ELISA.

# Acute viral hepatitis B – management and treatment

- **Etiologic treatment - Lamivudin!**
- **Supportive:** infusions of glucose 5%, dextrose 5%; vitamins – B2, B6, C; blood products – plasma, Human albumin 5%; hepato-protective – Carsil, Legalone, Essentiale forte, l-ornitine (Hepa-merz), ademetonine (Transmethil).  
**When danger of acute liver failure exists – methylprednisolone (3 mg/kg/24 h initial dose) with antibiotic protection!!!**
- **Symptomatic** – antipiretics, spasmolytic.
- **Diet** – more carbohydrates and milk proteins, less animal fats.

# Acute viral hepatitis B – prophylaxis

- **Specific – vaccine**, specific gamma globulin.
- **Non specific – isolation of the patient for 7 days.**
- Epidemic measures – investigation of blood products, unthreaded sex.

# Acute viral hepatitis C – etiology

- **Causative agent – Hepatitis C virus** – RNA, member of Flaviviridae family, highest resistance in environment; chlorine disinfectants kill it after 12-hours exposition.

# Acute viral hepatitis C – epidemiology

- **Source of infection – acute and chronic cases and carriers.**
- **Wide distribution.**
- **Anthroponosis.**
- **Routs of transmission – parenteral, sexual, vertical, direct contact with blood. It is not transmitted by respiratory, fecal-oral and transmissive mechanisms.**
- **Susceptibility – very high.**
- **Male : female – 2 : 1.**
- **15-16% of all acute viral hepatitis.**
- **70% of all chronic viral hepatitis.**
- **Major reason for liver transplantation.**
- **In 70-80% chronic evolution.**

# Acute viral hepatitis C – pathophysiology

- Portal of entry – skin and mucosa.

Follow:

- Viremia → in hepatocytes.
- The mechanisms for liver damage are not clear.

Hypothesis:

- ❖ Direct cytopathic effect of C virus
- ❖ Cell-mediated cyto-toxicity
- ❖ Activation of cytokines.

# Acute viral hepatitis C – clinical manifestations

1. **Incubation period – 35-90 days** (minimal 15, maximal 150 days).
2. **Preicteric phase.**
  - Insidious onset with:
    - ❖ adynamia, weakness, drowsiness, headache, dizziness, sweating;
    - ❖ Uncommon loss of appetite, nausea and vomiting, heaviness in the abdomen after eating, feel of overeating, heaviness or dull pain in upper right abdominal quadrant or epigastria, belching, hyperacidity, lose of taste for tobacco.
  - Flu-like syndrome – rare.
  - Hepato/splenomegaly.
  - Jaundice.

# Acute viral hepatitis C – clinical manifestations

3. **Icteric phase** – some days to 1 month, mean 8-11 days.
  - Jaundice – peak up to 3-5 days.
4. **Convalescent phase** – 3 to 6 months.

# Acute viral hepatitis C – laboratory findings

- WBC – normal or slightly ↓; lymphocytosis
- ESR – normal or slightly ↓;
- Urine – (+) bilirubin, ↑ urobilinogen
- Elevation of ASAT↑/ ALAT↑↑ – less than in A and B hepatitis!!!
- **Serum bilirubin** – elevated, both direct and indirect fractions
- Fibrinogen – normal or decreased **(in severe case due to severe hepatic cytolysis!!!)**
- Prothrombin time:
  - ❖ usually normal; in severe course prolonged.
- Other tests: total protein, albumin – normal or ↓

# Acute viral hepatitis C – clinical forms

## 1. According manifestation:

- Unapparent – in 70% of cases,
- apparent.

## 2. According severity:

- mild,
- moderate,
- severe,
- fulminant – <1%.

## 3. According presence of jaundice:

- icteric,
- anicteric.

# Acute viral hepatitis C – diagnosis

- **Clinico-epidemiological.**
- **Serological** – establishment of specific IgM antibodies (anti HCV).

# Acute viral hepatitis C – management and treatment

- **Supportive:** interferon – in each case of acute viral hepatitis C after investigation of viral RNA by PCR and their persistence; infusions of glucose 5%, dextrose 5%; vitamins – B2, B6, C; blood products – plasma, Human albumin 5%; hepato-protective – Carsil, Legalone, Essentiale forte, l-ornitine (Hepa-merz), ademetonine (Transmethil).
- **Symptomatic** – antipiretics, spasmolytic.
- **Diet** – more carbohydrates and milk proteins, less animal fats.

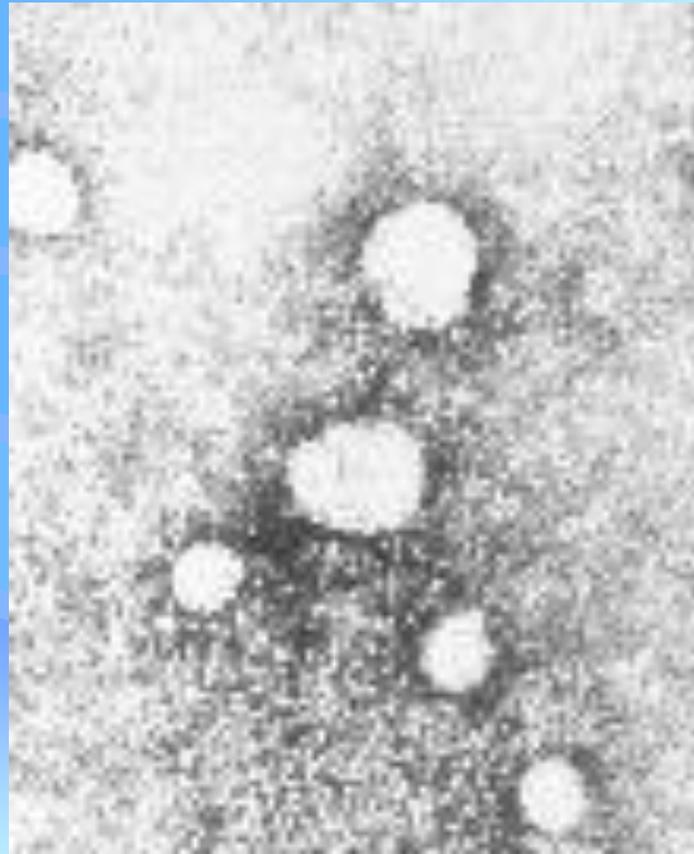
# Acute viral hepatitis C – prophylaxis

- **Without specific prophylaxis.**
- **Non specific – isolation of the patient for 7 days.**

# Viral hepatitis D – etiology

- Causative agent – hepatitis D virus (HDV)  
– defective virus, requires presence of HBsAg for replication!!!
- 3 genotypes.
- Resistant in environment but unstable to high temperature and disinfectants.

# *Hepatitis D virus*



# Viral hepatitis D – epidemiology

- **Same as in viral hepatitis B.**
- 9% of population and 72% of carriers of HBsAg are carriers of HDV.

# **Viral hepatitis D – pathophysiology**

- **Same as in viral hepatitis B.**

# Viral hepatitis D – clinical manifestations

- 2 clinical forms:
- Co-infection – clinical manifestations and laboratory findings are same as in viral hepatitis B. Severe and fulminant forms are more common than in viral hepatitis B, convalescent phase is prolonged.
- Super-infection – in every relapse of acute viral hepatitis B or exacerbation of chronic viral hepatitis B searching for hepatitis D virus!!!

# Viral hepatitis D – diagnosis

- **Clinico-epidemiological.**
- **Serological** – establishment of specific IgM antibodies (anti HDV IgM) and presence of HBsAg – by ELISA.

# **Viral hepatitis D – management and treatment**

- **Same as in viral hepatitis B.**

# Acute viral hepatitis E – etiology

- Causative agent – Hepatitis E virus –  
small RNA virus.

# *Hepatitis E virus*



# **Acute viral hepatitis E – epidemiology**

- **Same as in viral hepatitis A.**
- **Fecal-oral route of transmission.**
- **Severe course during pregnancy.**

# **Acute viral hepatitis E – clinical manifestations**

- **Same as in viral hepatitis A.**

# **Acute viral hepatitis E – management and treatment**

- **Same as in viral hepatitis A.**

# **Acute viral hepatitis E – prophylaxis**

- **Same as in viral hepatitis A.**

**THANK YOU  
FOR YOUR ATTENTION !**