National Pharmaceutical University
Department of Microbiology, Virology and Immunology

Lecture on Microbiology with immunology fundamentals specialty 226 Pharmacy

# HEPATITIS

Lecturer: associate professor Department microbiology virology and immunology Ph D. Dotsenko Roman Valeryevich

# LECTURE PLAN

1. The causative agent of viral hepatitis A, B.
2. Taxonomy. Morphology.
3. Epidemiology. Infection source and transmission mechanism.
4. Risk groups.
5. Pathogenesis.
6. Clinic. Methods of laboratory diagnostics of viral hepatitis B.
7. Treatment and prophylaxis of viral hepatitis B.

Questions for self-examination:

1.Pathogens herpes

# Recommended literature

General microbiology: synopsis of lectures to laboratory classes /N. I Filimonova, M.M. Velika, N. Yu. Shevelyova. – Kharkiv : NUPh : Golden Pages, 2011. – 128 p.

Special microbiology in tables / N. I Filimonova, A. Bocharov. – Kharkiv : NUPh : Golden Pages, 2012. – 28 p.

Microbiology: Sub. for stud/ I. L. Dyky, I. Yu.Holupyak, N.Yu. Shevelev, and others. 2nd form. - X .: Professional, 2006. - 433 pp.

Microbiology: A Guide to Laboratory Lessons. Study a manual for students of higher educational institutions / IL Wild, I.I. Sidorchuk, I.Yu. Kholupiak, N.E. Shevelev, MM Great, N.A. Volkova, L.F. Silayeva, O.P. Strilec, O.G. Heyderich, V.E. Litarov - Kh.: Publishing house of NfaU; Golden Pages, 2002. 444 p.

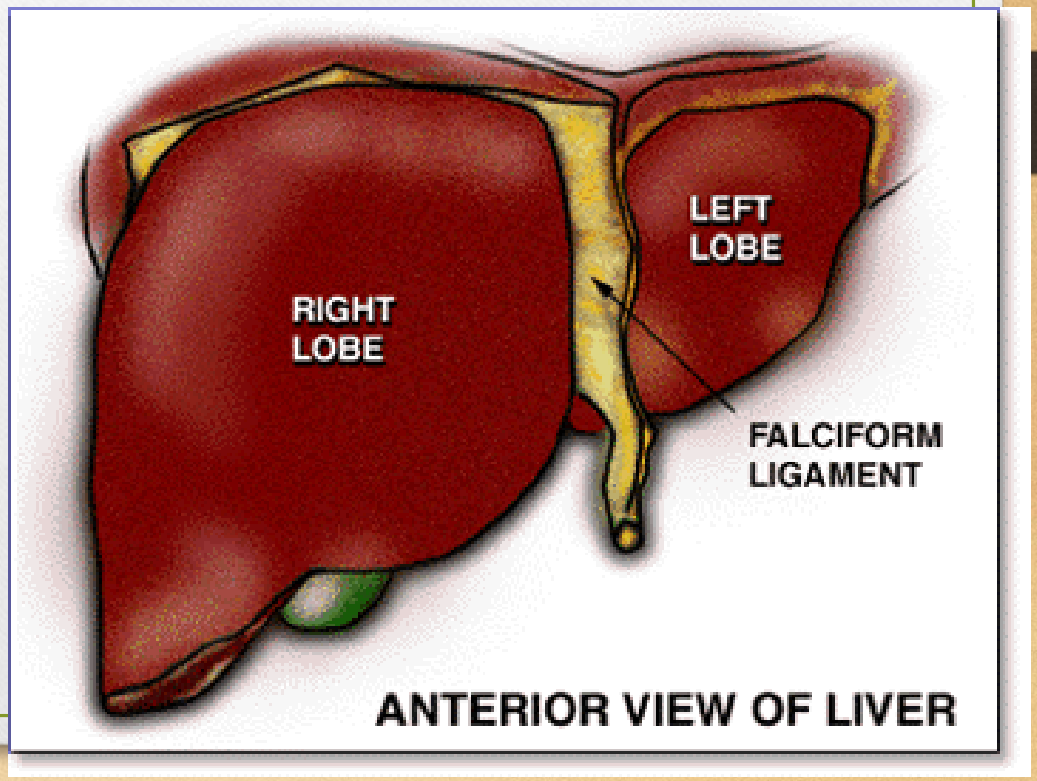
Microbiology Methodical recommendations for students of pharmaceutical higher educational institutions / IL Wild, I.Yu. Kholupiak, MM Great, NE Shevelev and others - X., 2004. - 144 p.

# Hepatitis Viruses

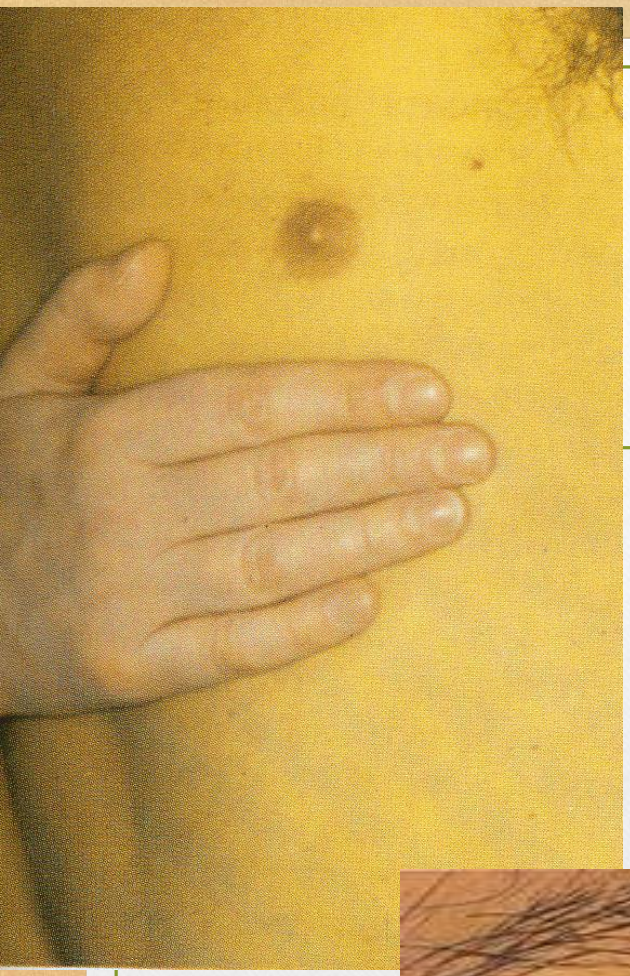
| Virus Family | Hepatitis A Picornavirus | Hepatitis E Calicivirus | Hepatitis B Hepadnavirus | Hepatitis C Flavivirus | Delta virus Satellite virus (only in combination with HBV) |
|---|---|---|---|---|---|
| Commonality | All generate conditions of illness in the liver | | | | |
| Symptoms (acute) | All the same – malaise, dark urine, anorexia, nausea, vomiting, jaundice | | | | |
| Transmission | Enteric (food and water) | | Sex, blood and close contact | | |
| Chronic condition | No | No | Yes | Yes | Yes |
| Virus genome | +ss RNA | +ss RNA | DNA with reverse transcriptase activity | +ss RNA | -ss RNA |
| Virus antigens | HA Ag | HEV ORF2 proteins | HBsAg<br>HBcAg<br>HBeAg | Many – core E1 E2 NS3 | Delta antigen |
| Incubation | 1 month (15 – 50 d) | | 4 months (45 – 160 d) | 2 months (15 – 150 d) | 1 – 2 months |
| Current therapeutics | No specific treatment | No specific treatment | Interferon alpha,<br>Lamivudine, Adefovir, Etecavir | Interferon alpha + ribavirin, Pegylated Interferon | Follow HBV therapy |
| Vaccines available? | Yes<br>Havrix (GSK)<br>Vacta (Merck) | No | Yes<br>Engerix-B (rHBsAg) GSK<br>Recombivax B (Merck) | No | Can be prevented by vaccination against HBV |

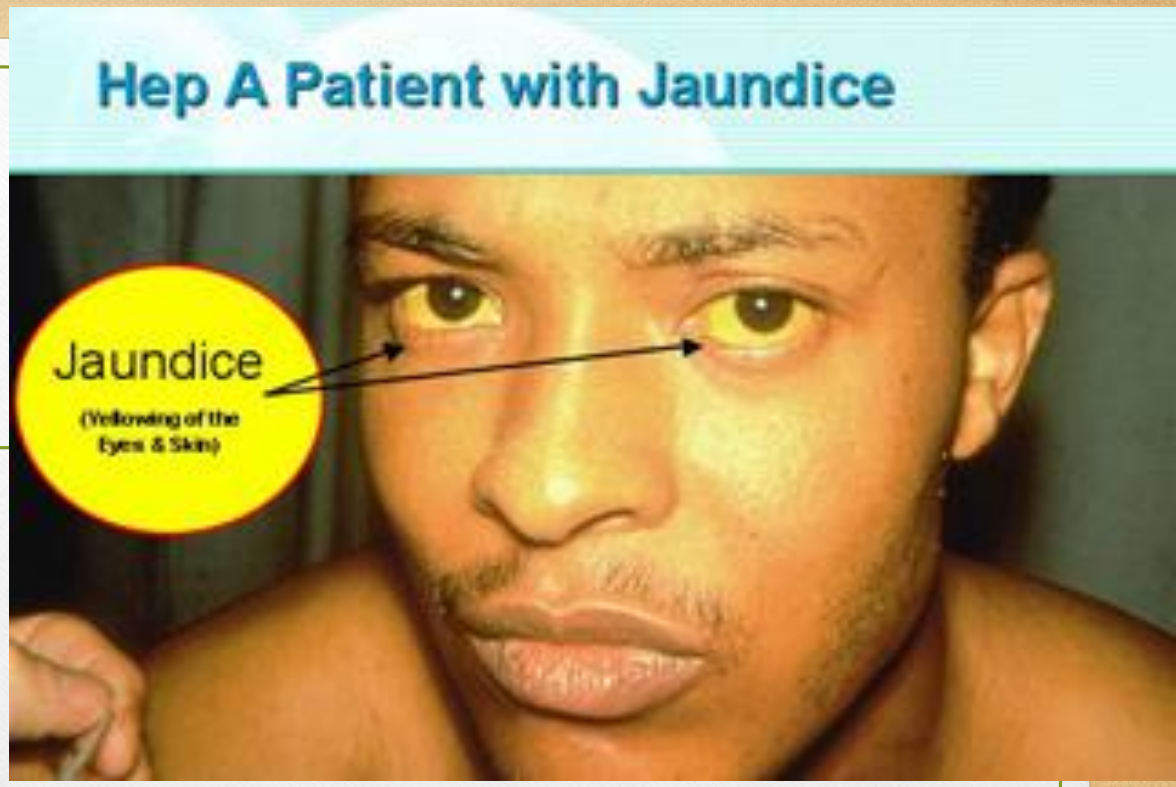
# *Common characteristics of hepatitis*

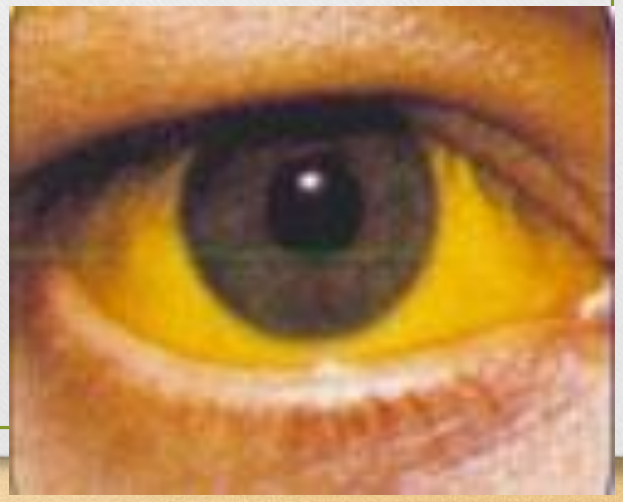
Viral hepatitis are caused by a heterogeneous group of viruses with a tropism for the liver.



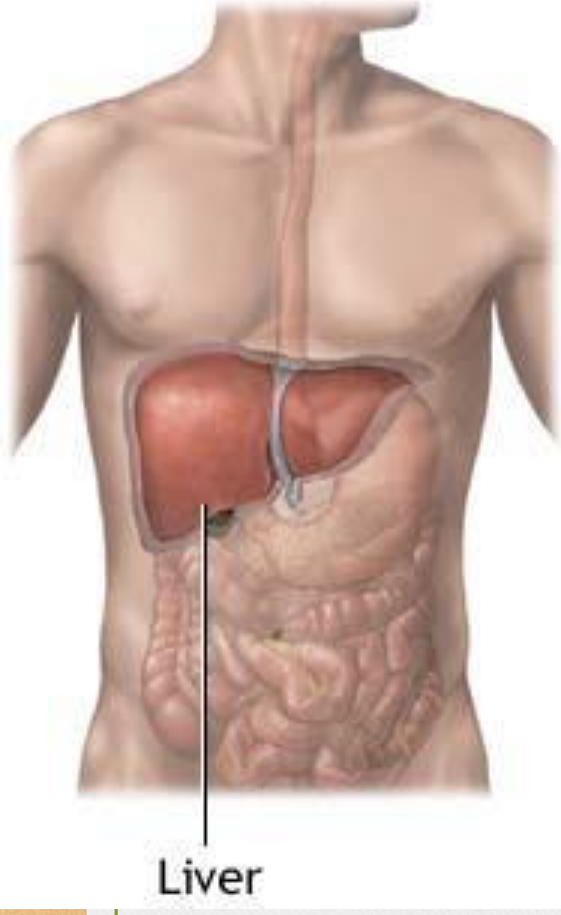
The clinical features of viral hepatitis are almost similar. The viruses cause acute inflammation of the liver, that is characterized by nonspecific symptoms of fever, anorexia, malaise, nausea, vomiting in pre-icteric stage. The pre-icteric stage lasts for a few days, sometimes it lasts longer (3 weeks or more). Symptoms tend to subside with appearance of right upper quadrant tenderness, jaundice with dark urine and pale stool. The icteric stage is characterized by raised serum levels of liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Many cases of viral hepatitis are anicteric and undiagnosed, especially in children. In these cases frank jaundice is lacking due to insufficient liver damage but liver function tests show abnormal results.



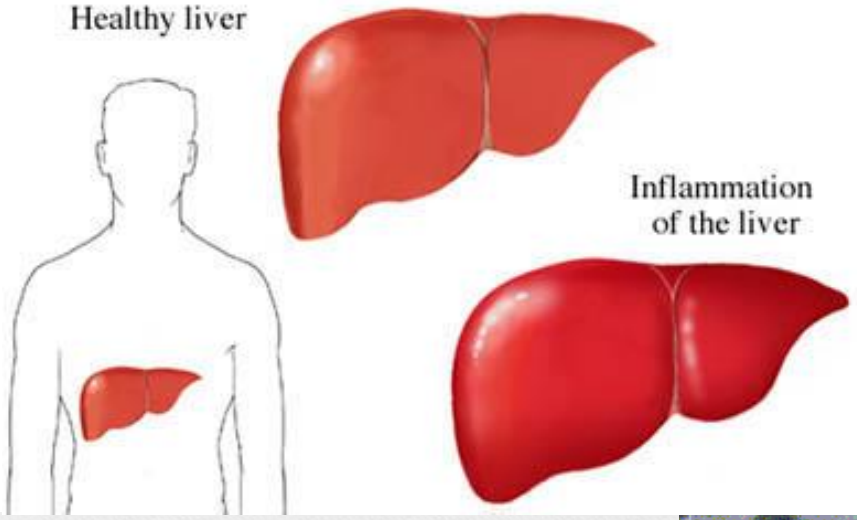

Hep A Patient with Jaundice
Jaundice
(Yellowing of the Eyes & Skin)

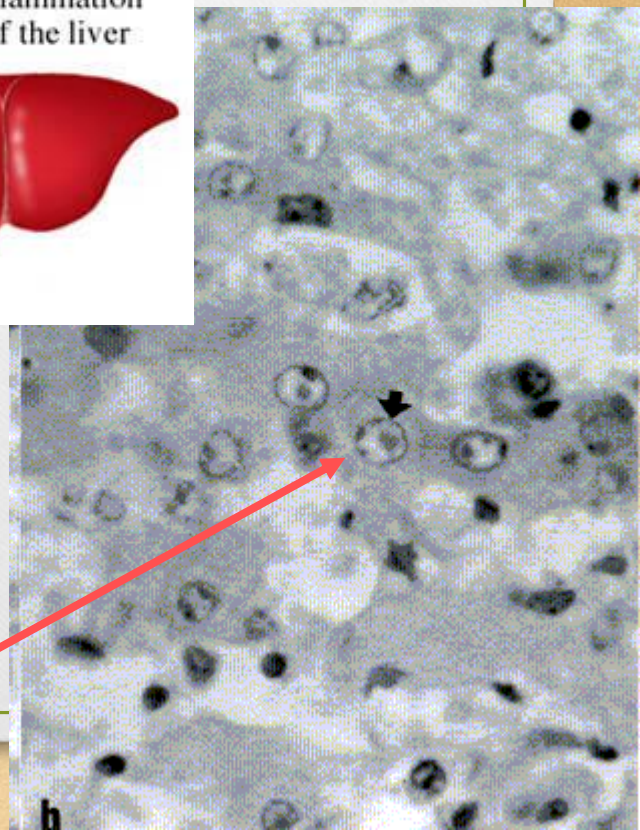


The morphological lesions in liver consist of panlobular infiltration with lymphocytes, hepatic cell necrosis, hyperplasia of Kupffer cells and variable degree of cholesteasis. Parenchymal cell damage consist of hepatic cell degeneration and necrosis, ballooning of single cells and appearance of acidophilic inclusions in hepatocytes. In healthy carrier and in chronic hepatitis due to HBV, large hepatocytes with a ground glass appearance of the cytoplasm may be observed. In chronic hepatitis, there is piecemeal necrosis at first and later on fibrosis occurs that leads to cirrhosis.

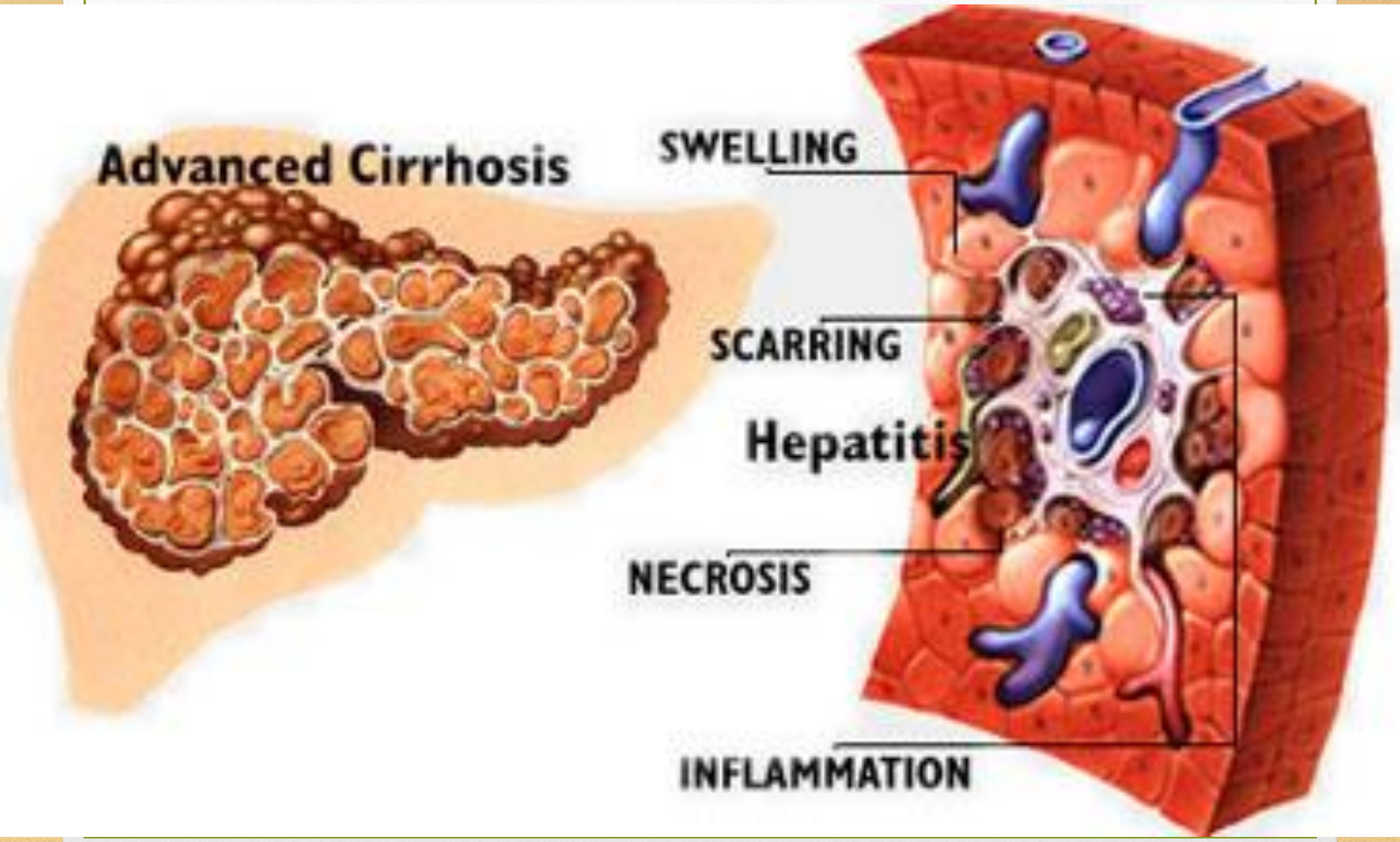



In aggressive hepatitis, the liver becomes chronically inflamed and fibrotic, shrinking slightly

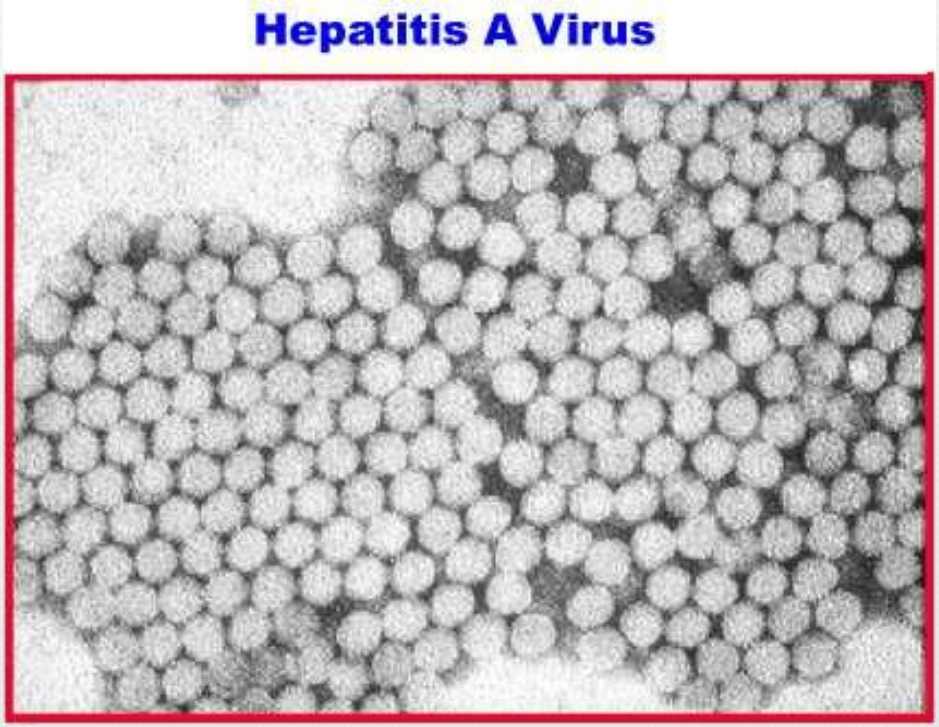


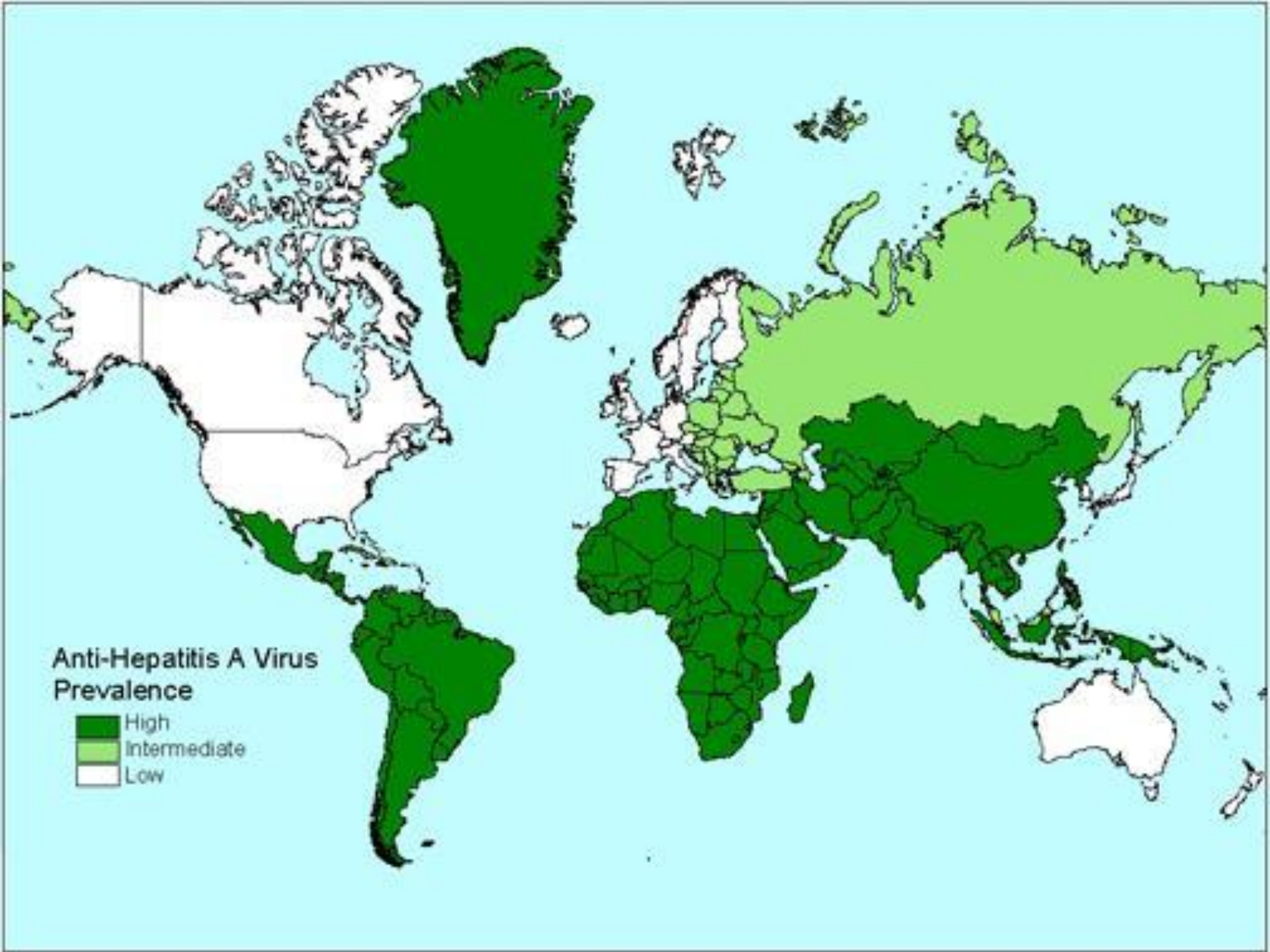



*Acidophilic inclusions in hepatocytes*


Advanced Cirrhosis
SWELLING
SCARRING
Hepatitis
NECROSIS
INFLAMMATION

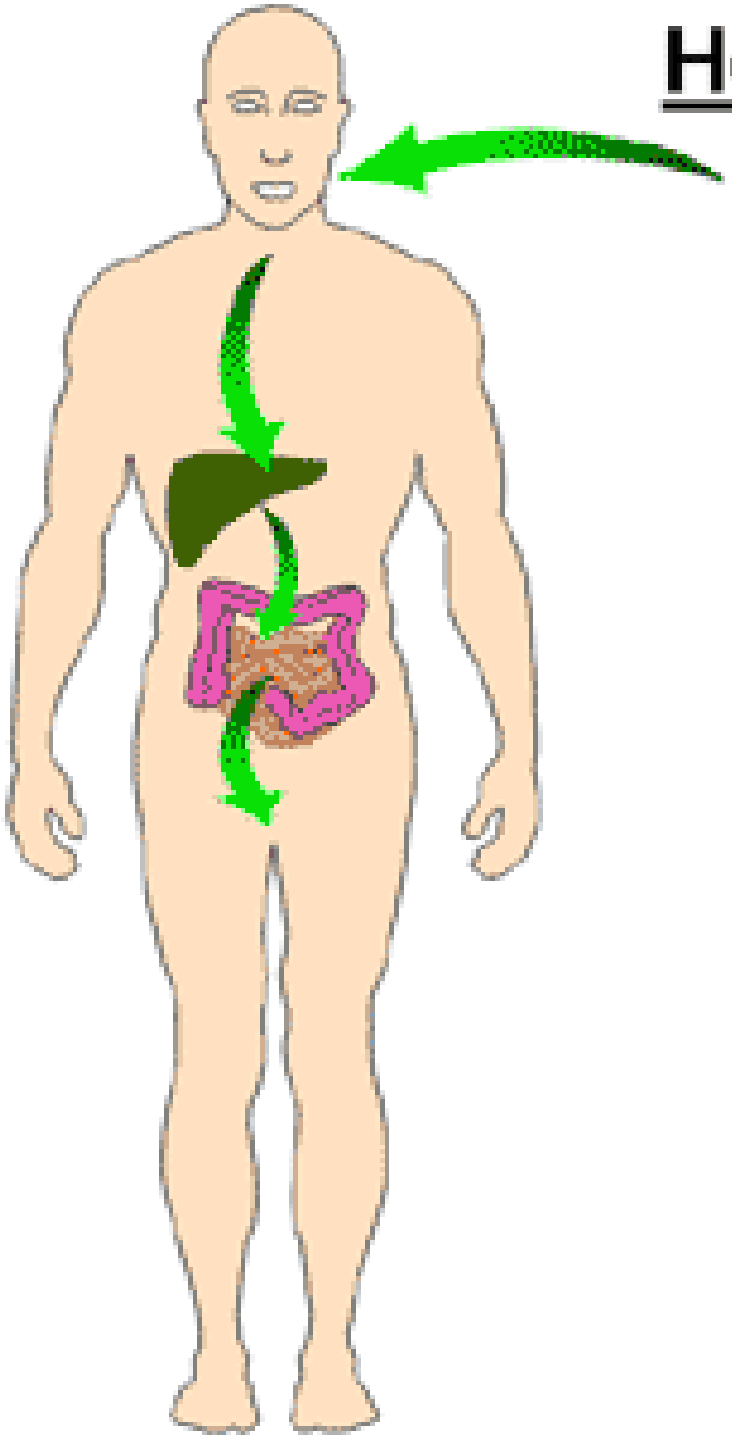
# Hepatitis A (Infectious hepatitis, Botkin`s disease)




Anti-Hepatitis A Virus
Prevalence
High
Intermediate
Low

The hepatitis A virus after entering the body by oral route through food and water, multiples in the intestinal epithelium and reaches the liver by viraemia. HAV is excreted in the stool of patients 2-3 weeks before and 8-10 days after the onset of jaundice. Infection by HAV is common on a global scale, especially in areas with poor sanitation. The mortality rate is less than 0,1% and is usually associated with fulminant HAV infection (hepatic necrosis leading to a loss of hepatic function).

# Hepatitis A Pathogenesis



- Ingestion
- Replication in oropharynx/GI tract
- Transported to liver - major site of replication
- Shed in bile, transported to intestines
- Shed in feces
- Brief viremia
- Cellular immune response: clinical disease and control

Incubation Period (15-50 days)

# Transmission

Flies may carry diseases such as hepatitis A, typhoid, amebic dysentery and polio by contaminating food or water

# ***SCHEME OF LABORATORY DIAGNOSIS OF HEPATITIS A***

- ***Detection of virus***
- ***Material:*** stools
- Viral particles is determined by IEM; viral antigen by EIA and RIA

- ***Detection of antibodies.***
- ***Material:blood*** Examination paired acute and convalescent sera to demonstrate increase of antibody titre. The finding of IgM anti-HAV antibodies indicates current or recent infection, while the finding of IgG anti-HAV antibodies (without IgM antibodies) indicates past exposure to the virus.

# Treatment

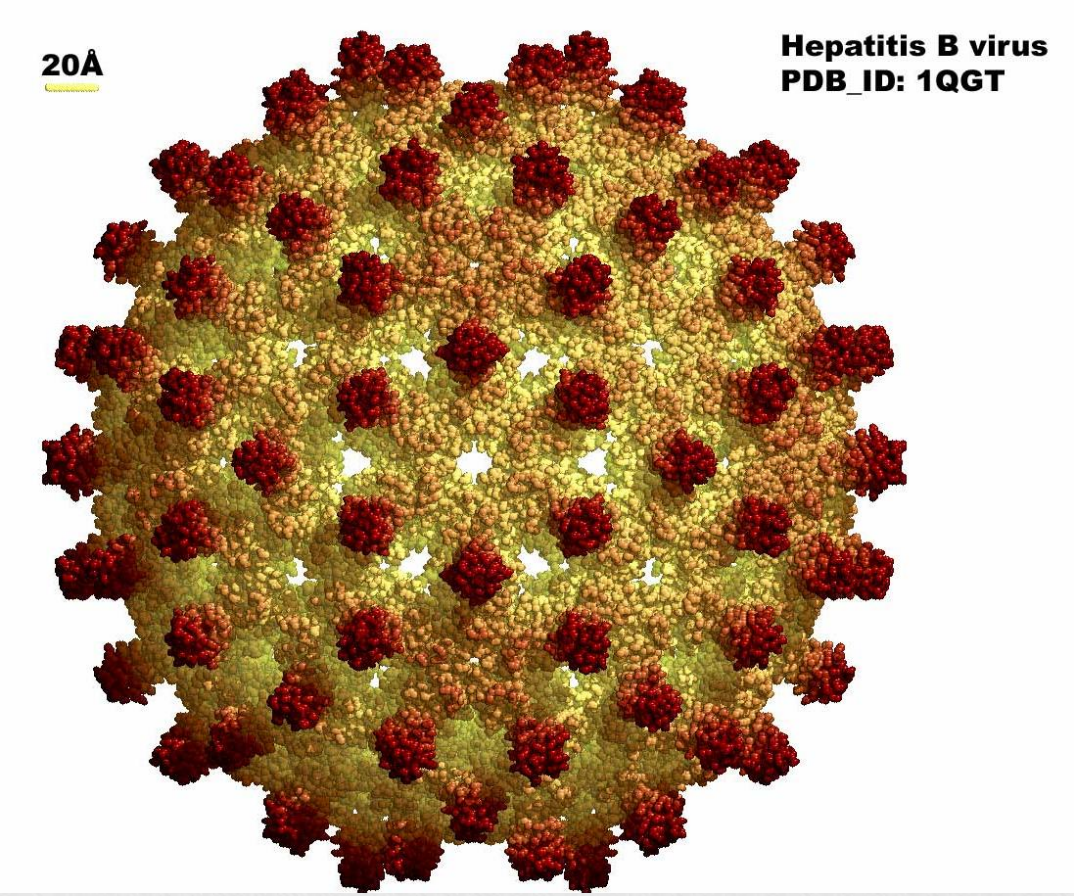
| Acute Hepatitis | Chronic Hepatitis |
| --- | --- |
| Insulation by 3 weeks after the start | Symptomatic therapy |
| Relaxation | diet |
| diet | relaxation |
| hepatoprotectors | hepatoprotectors |
| | immunomodulators |

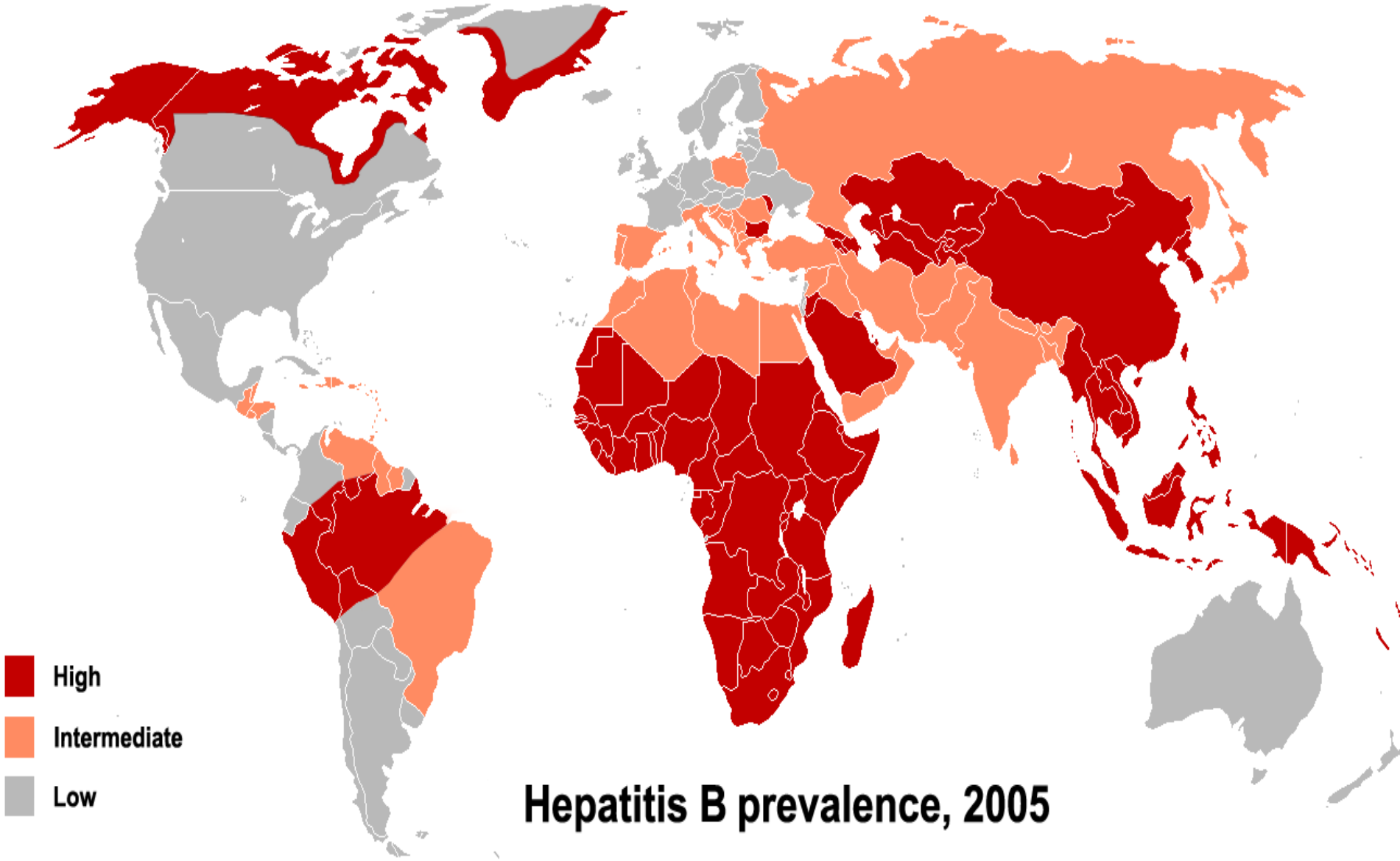
# ***Prophylaxis***

- *Active immunization*. Hepatitis A vaccine is now available for those at special risk, e.g. travelers and staff and patients of institutions for the mentally handicapped.
- Vaccine contains inactivated virus. One dose gives immunity for 1 year. Two doses give 10 years' protection.

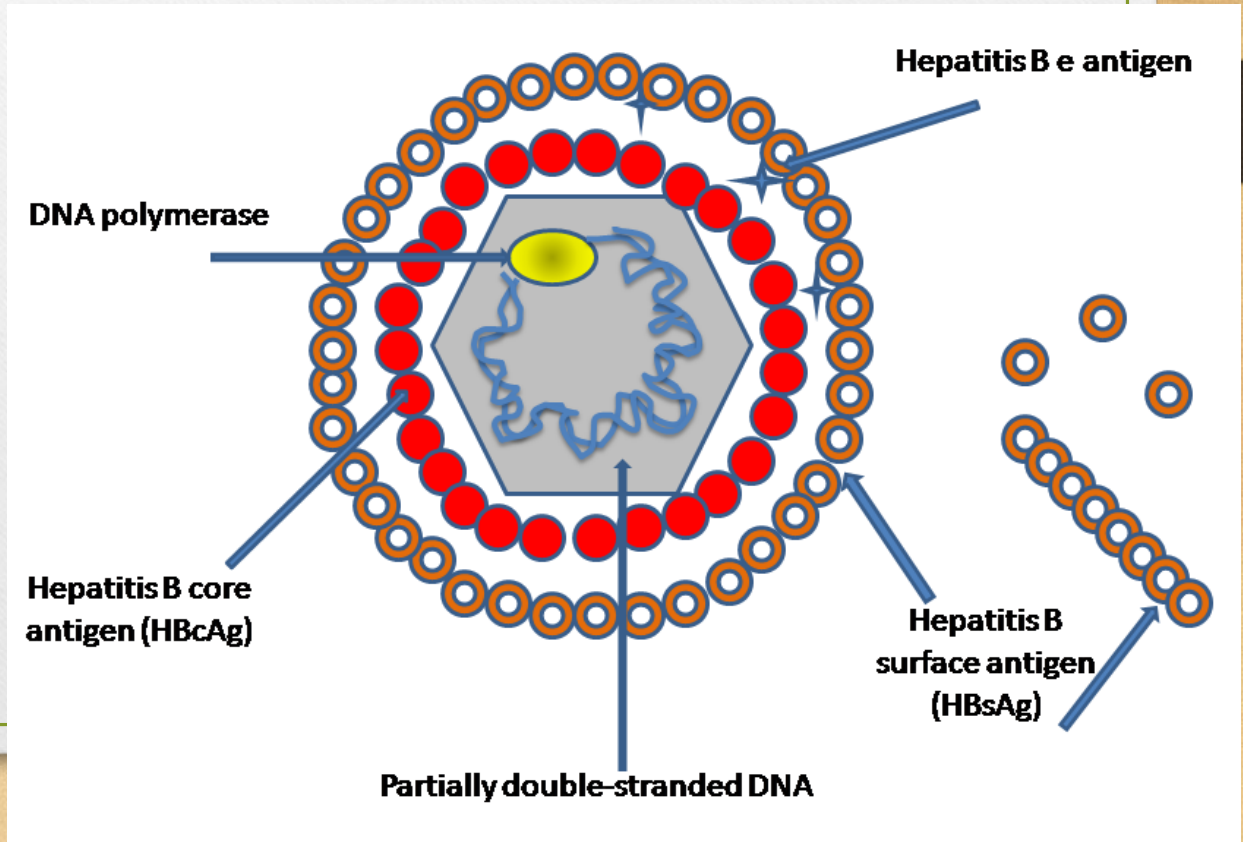
# Hepatitis B (Serum hepatitis)

HBV was discodered by electron microscopic examination of infected hepatic tissue.



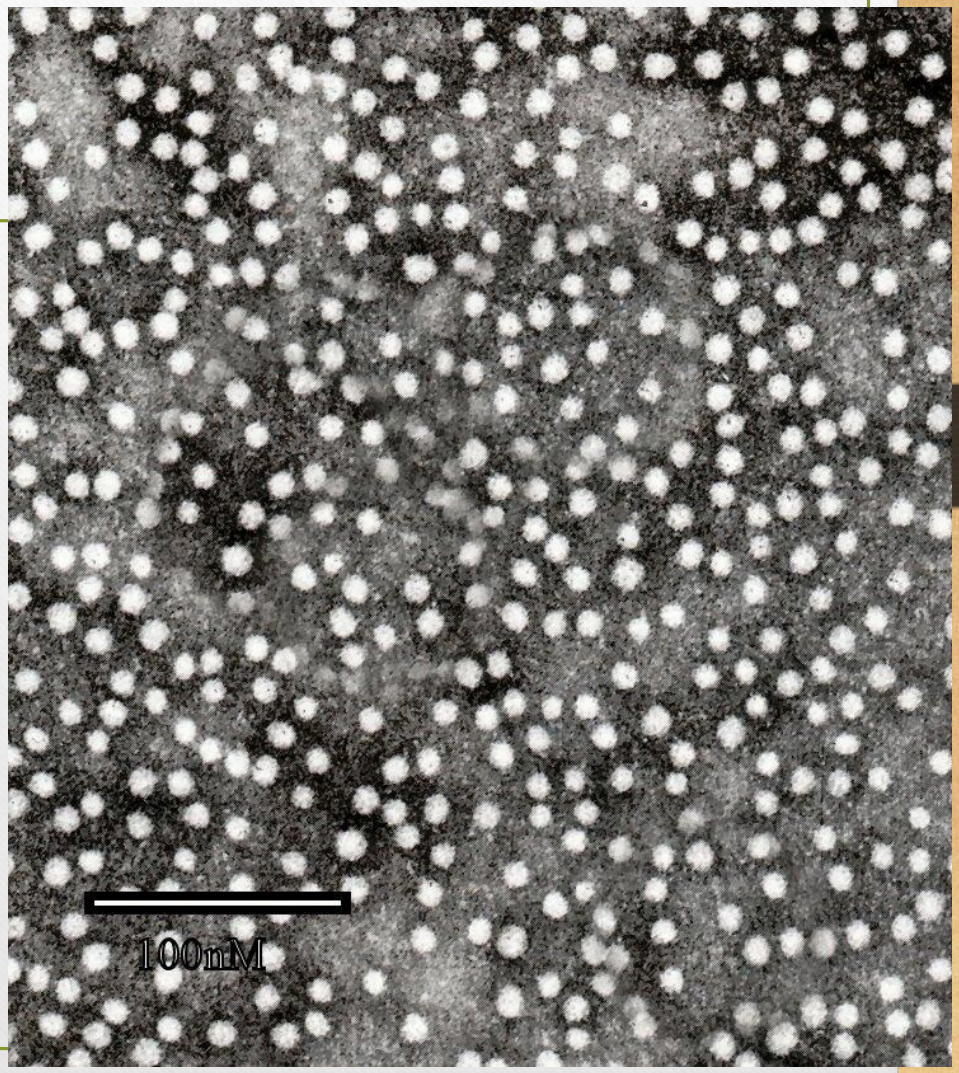

High
Intermediate
Low
Hepatitis B prevalence, 2005

HBV has: a lipid-containing outer envelope, which contains hepatitis B surface antigen (HBsAg); an inner protein core, made up of hepatitis B core antigen (HBcAg), that surrounds the viral nucleic acid; a genome of circular double-stranded DNA with an incomplete positive strand; a DNA polymerase, which also functions as a reverse transcriptase.



# HBsAg

The envelope of HBV is unique because it is 70% protein (HBsAg), which is strongly immunogenic. HBsAg tends to associate with itself to form noninfectious circular or filamentous aggregates 22 nm in diameter. They are released into the circulation as a replication by-product. The original HBV vaccine was made by purifying these aggregates.



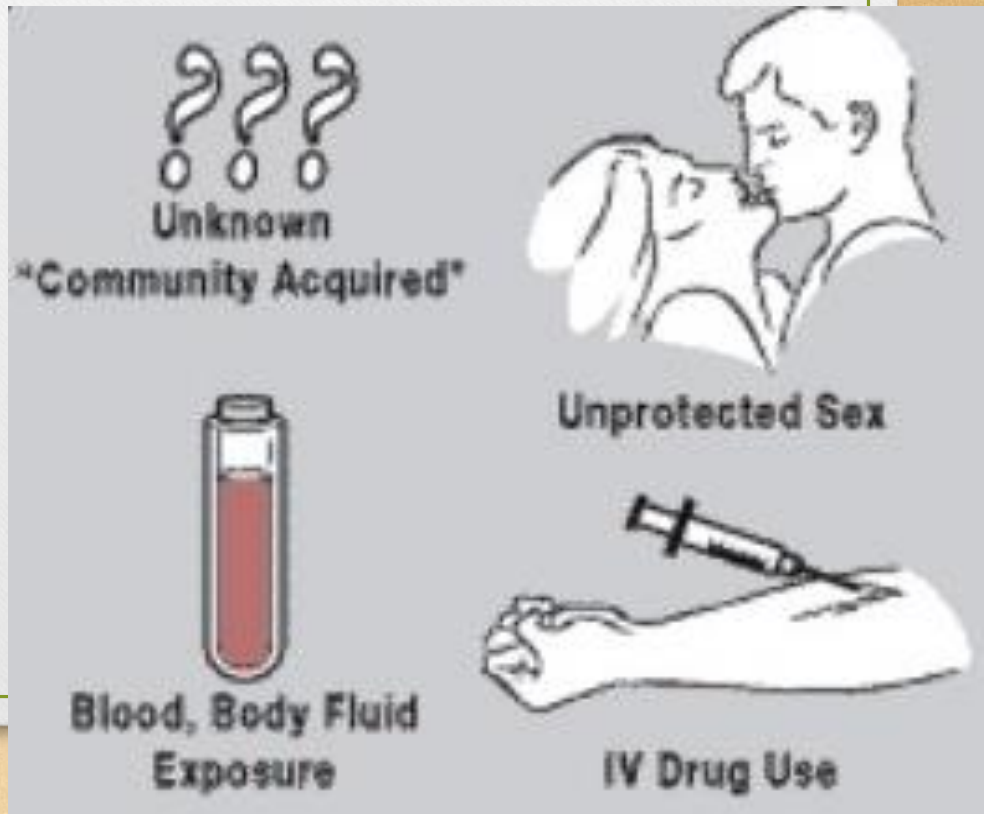
The core (nucleocapsid) of 27 nm diameter has an icosahedral symmetry and contains group specific protein (HBcAg) not detectable in patient blood.

Hepatitis Be antigen (HBeAg) is not part of the virus particle. This antigenic component of core appears to be a conversion product of HBcAg. HBeAg is translated from RNA that contains the pre-core and core (HBcAg) regions. After translation, the protein is truccated at the carboxy terminus and then released from the infected cell. HbeAg modulates the host immune response to HBV and is an important indicator of transmissibility.

Four antigenic strains of HBV (ayw, adw, ayr, adr) have been identified. The significance of serologic typing of HBV is both epidemiologic (e.g. to trace the source of a particular outbreak) and medical-legal (to help prove or dismiss allegations against a suspected carrier).

# Transmission

- HBV is found in blood and blood-products, tears, saliva, sen urine, feces, breast milk, synovial fluid and CSF in acutely affected patients as well as in carrier.
- Blood and blood by-products are the most important vehicles of parenteral transmission.
- Saliva and semen are involved in venereal transmission.
- Transplacental transmission.
- HBV can penetrate into organism through iris of the eyes and mucous membrane of the oral cavity in direct contact with blood or discharges of infected man.



- The incidence peaks in the 15-to19-year-old age group. Population at risk for HBV infection include: healthcare workers, intravenous drug users, hemophiliacs, renal dialysis patients, infants born to HBsAg-positive mothers, sexual partners of HBV carriers, individuals with multiple sexual partners (homosexual or heterosexual).
- Seven to ten percent of patients infected with HBV become chronic carriers. There are two types of hepatitis B carriers based on serological markers.
- Super carriers are called persons with HBeAg in blood. They are highly infectious since only 0,00004 ml of blood can transmit the disease.
- Simple carriers are called persons who

do not have HBeAg but low titre of HBsAg in blood. They are the most common type of carriers in whom HBV and DNA polymerase are absent. They contain anti-HBc in blood and the infection is transmitted only with large volume of blood.

- Subclinical infections are more common than clinical infections. Clinical infections vary in severity. The severity of the disease is related to the viral dose.
- Of the infected individuals who become chronic carriers, the majority (approximately 7% of HBV-infected individuals or 75% of carriers) develops chronic, persistent hepatitis B, while the remaining 3% of infected individuals develop chronic active hepatitis. Patients with persistent hepatitis remain clinically well but are potentially infectious. Persistent hepatitis B can lead to terminal liver failure.
- Chronic hepatocellular inflammation and necrosis from chronic HBV infection is associated with cirrhosis and hepatocellular carcinoma.

# ***SCHEME OF LABORATORY DIAGNOSIS OF HEPATITIS B***

- Electron Microscopy
- ***Material: blood*** Viral particles is determined by IEM
  - ***Serological***
  - ELISA assay
  - the detection of the hepatitis B surface antigen HBsAg - A positive test for the HBsAg indicates that the person has an active infection (either acute or chronic)
  - Testing for antibodies to the hepatitis B surface antigen – a positive test indicates that the person has either recovered from acute infection or has received a hepatitis B vaccine
  - Testing for antibodies to the hepatitis B core antigen – a positive test indicates that the person has had a resent infection or an infection in the past.
  - Direct fluorescent antibody testing

# *Treatment.*

Acute hepatitis B have not specific drugs

Chronic hepatitis B: interferon alfa
Lamivudine

Ribavirin

Tenofovir Entecavir

# ***Prophylaxis***

- *Active immunization*. Hepatitis B Vaccine

(recombinant genetically engineered vaccine containing HBsAg.)

# Conclusions:

- The incubation period of Hepatitis - several weeks - 10 and> years (on average 3 - 5 g.) Prevention of sexual transmission:
- • Sexual culture • Safe sex - Condom use.

Prevention of blood-borne infections:

• use of single-use medical equipment only, • use of personal hygiene devices only, • donor blood testing, transplantation organs

Prevention of infection with Hepatitis-infected mum's child: • watching for the expectant mother, • taking antiviral drugs during pregnancy, childbirth, • abandoning breastfeeding.

# Thank you for attention