Viral hepatitis

Hepatitis, a general term referring to inflammation of the liver, may result from various causes, both infectious (ie, viral, bacterial, fungal, and parasitic organisms) and noninfectious (eg, alcohol, drugs, autoimmune diseases, and metabolic diseases)

The term viral hepatitis can describe either a clinical illness or the histologic findings associated with the disease. Acute infection with a hepatitis virus may result in conditions ranging from subclinical disease to self-limited symptomatic disease to fulminant hepatic failure. Adults with acute hepatitis A or B are usually symptomatic. Persons with acute hepatitis C may be either symptomatic or asymptomatic (subclinical).

Hepatitele virale – grup de maladii acute și cronice, provocate de variate virusuri, pentru care ficatul este ţinta principală a proceselor patologice.

- Hepatitele virale A,B,C,D,E.
- Alfabetul HV.
- Cedează ca răspîndire doar IRVA.
- Alte virusuri hepatotrope

Hepatitele virale. Răspândire – Incidență – Morbiditate

HVB – 2 mlrd infectați (1⁄3)
350 mln → 290 mln- infecție cronică
RM – 4-6 % (8-20%)

HVC – 71 mln bolnavi
RM – 4-5%

HVD – 15 mln bolnavi
25% - din cei cu HVB în R.Moldova

HVA- RM
a.2002 – 8754
a.2011 – 4
a.2013 – 96

HVE – 11% anticorpi în România

Importanța HV

- Hepatite fulminante – letalitate 70 – 100%
- Potențial de cronicizare

HVC - 70 – 80%

HVB – 5 – 10%

HVD supr. – 100%

- Potențial oncogen

Hepatite virale – istoric

Antichitate – Avicena

Botkin S.P

1960…

Hepatita infecţioasă

Hepatita serică

1963 VHB – B. Blumberg

1973 VHA – Feinstone

1977 VHD – M. Rizetto

1980…

Hepatita A, B, non-A, non-B (fecalo-oral, posttransfuzional)

1983 – VHE – Mihail Balayan

1989 – VHC – “Chiron”

1995 … F, G, H , TTV, sen

Hepatitele virale A,B,C,D,E

Se deosebesc după:

- Apartenența taxonomică a virusurilor;
- Mecanismul de infectare;
- Căile de transmitere;
- Patogenie;
- Imunogeneză;
- Manifestări clinice;
- Gravitatea maladiei;
- Sechele;
- Posibilități ce cronizare;
- Posibilități de malignizare;
- Criterii de diagnostic specific;
- Program de tratament;
- Profilaxie.

Trăsături comune:

- Tabloul clinic;
- Diagnostic primar nespecific;
- Criterii de clasificare clinică;
- Programul tratamentului nespecific patogenetic;
- Regimul igieno- dietetic;
- Sistemul de dispensarizare a convalescenților.

Particularity of acute viral hepatitis evolution depending on etiological agent

	VHA	VHB	VHD coinfection	VHD superinfection	VHC	VHE
Nucleic acid	RNA Piconarvirus	DNA Hepadnaviridae	RNA Deltavirus HDAg are encapsidated by HBsAg		RNA Flaviviridae	RNA
Major transmission	Fecal–oral: -person-person -contaminated food/water	Parenteral Sexual	Parenteral Sexual		Parenteral Sexual-rare Perinatal 5%	-G/type 1,2: fecal - water -G/type 3,4: swine
Epidemics	Yes	Sporadic	Sporadic		Sporadic	Yes
Most common	Young children in endemic area	All	All		All	Symptomatic in 15-40 years
Maximum infectivity	1/2 incub.→ few days onset	Latter half of incubation period → all the period of viremia				Same as in VHA
Incubation	7-50 days	45-180	as in VHB	1-2mo	20-120	14-50 days
Cause of liver injury	direct cytopathic effects of viral proteins	immune mediated	VHB - immune mediated VHD - direct cytopathic effects of viral proteins		combination of direct cytopathic and immune mediated	direct cytopathic effects of viral proteins
Integration into host DNA	No	episomal-free integrated	VHD - No		No	No

Prejaundice period						
Length	0-2 weeks	0 -6 weeks	0-10 days	0-10 days	0-2 weeks	0-2 weeks
Dyspeptic syndrome	+	+	++	++	+/-	+
Arthralgic syndrome	-	+	+	-	-	-
Intoxication syndrome	+	+	++	++	+/-	+
Fever	+	-	+/-	+/-	-	+
Hepatomegalia	+	+	+	++	+	+
Splenomegalia	-	-	-	+	-	-

Jaundice period						
State after jaundice	better	same or worse	worse	worse	same	same
Hepatomegalia	+	+	++, soft	+++, firm	+	+
Splenomegalia	-	+	+	++	+	-
Length of jaundice period	1-2 weeks	2-4 weeks	2-6 weeks	2-8 weeks	2-4 weeks	1-2 weeks
Extrahepatic manifestations	-	+	+ because of HBV		+	-
Fulminant	<0,5%	1%	2-20%		<0,1%	20%pregnant: -liver failure -haemorrhage -Hb-uria, acute renal failure
Chronicity	No	5-7% in adults; 90% at birth	coinf. 5-7%, super. 100%		50-70%	No
Cause of chronicity					highly variable nucleotide sequence	
Liver cancer	No	Yes	Yes		Yes	No

Hepatitis A is an inflammatory liver disease caused by infection with the hepatitis A virus (HAV). HAV is a single-stranded 27 nm non-enveloped, icosahedral RNA virus, which was first identified by immune electron microscopy in 1973 . The virus belongs to the hepadnavirus genus of the *Picornaviridae.* Recent structure-based phylogenetic analysis placed HAV between typical picornavirus and insect picorna-like viruses. Recent work suggests a rodent origin of HAV based on a large screening for hepatoviruses in more than 200 small mammal species .

HAV uses host cell exosome membranes as an envelope which leads to protection from antibody mediated neutralisation but also facilitates detection of HAV by plasmacytoid dendritic cells which are main sources for type I interferon during infection . Of note, only blood but not bile HAV shows host-derived membranes. Seven different HAV genotypes have been described, of which four are able to infect humans

Acute hepatitis A is associated with a limited type I interferon response, which may be explained by cleavage of essential adaptor proteins by an HAV protease-polymerase precursor. Recently HAV has been shown to interact with the mitochondrial antiviral signaling (MAVS) protein resulting in interferon-independent intrinsic hepatocellular apoptosis and hepatic inflammation.

A dominant role of CD4+ T cells to terminate HAV infection has been established in HAV infected chimpanzees. However, in humans strong HAV-specific CD8 T cells have also been described, potentially contributing to resolution of infection. A failure to maintain these HAV-specific T cell responses could increase the risk for relapsing HAV.

Risk groups for acquiring an HAV infection in high-income countries are health care providers, military personnel, psychiatric patients and men who have sex with men. Parenteral transmission by blood transfusion has been described but is a rare event. Mother-to-fetus transmission has not been reported. Distinct genetic polymorphisms including variants in ABCB1, TGFB1, XRCC1 may be associated with a susceptibility to HAV.

Recently it was shown that the number of reported HAV infections in the USA decreased from 6 cases/ 100000 in 1999 to 0.4 cases/ 100000 in 2011, while the percentage of hospitalisations due to HAV increased from 7.3% to 24.5% indicating that HAV is becoming a rare condition but can still cause serious morbidity, especially in elderly and patients with underlying liver disorders (Ly 2015). In line with this report the overall immunity to HAV is declining in United States suggesting that vaccination coverage needs to be improved.

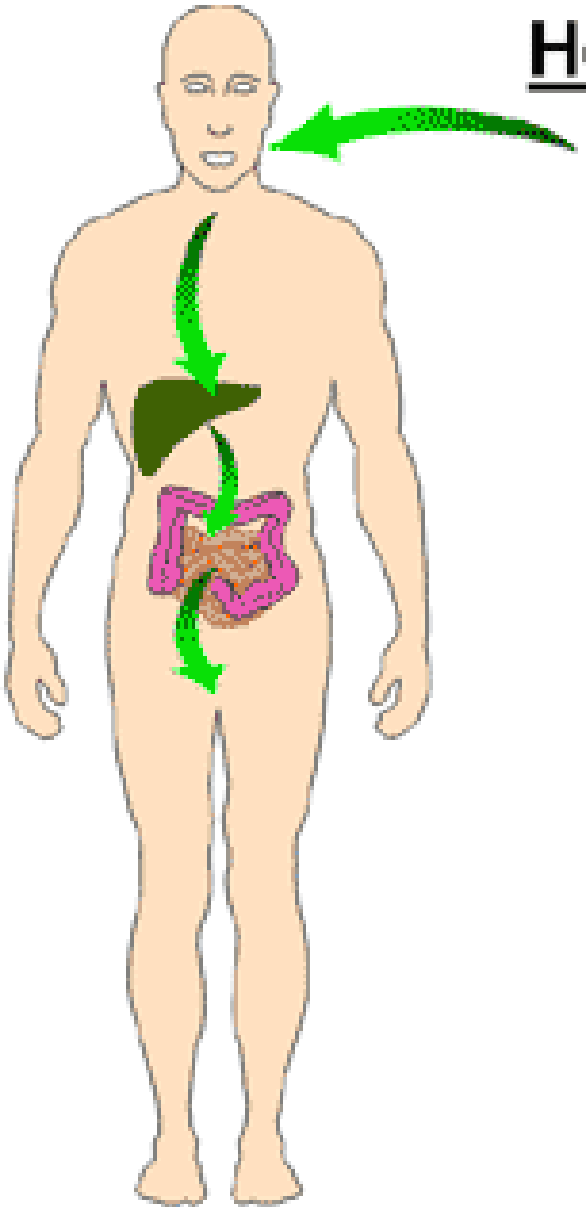
The hepatitis A virus was identified in 1973 (Feinstone 1973). It is a 27 nm, positive-
stranded RNA, non-enveloped, icosahedral virus of the heparnavirus genus of the Picornaviridiae. Its viral genome contains 7474 nucleotides that are grouped into three regions: a 5’ and a 3’ non-coding region and a 6681 nucleotide open reading frame. The polypeptide encoded by the open reading frame is processed by a viral protease, resulting in eleven proteins of which four are structural and seven are non-structural. Four distinct HAV genotypes in humans have been identified, although significant biological differences have not been found

Hepatitis A infection occurs worldwide sporadically or in epidemic outbreaks. There is an estimated caseload of 1.4 million cases per year . As it is transmitted and spread via the faecal-oral route, it shows higher prevalence in areas with low socio-economic
status where adequate sanitation or adequate hygienic practices are lacking. The incidence of 1.5 per 100,000 in industrialised countries, e.g., the United States or Germany , is low compared to developing countries (parts
of Africa, Asia, Central and South America) where it may reach up to 150 per 100,000 per year (WHO).

HAV is generally acquired via the faecal-oral route either by person-to-person contact or ingestion of contaminated food or water, as well as other types of sex like analingus. Hepatitis A is an enteric infection spread by contaminated excreta. High concentrations of virus are shed in the stools of patients 3 to 10 days prior to the onset of illness and until one to two weeks after the onset of jaundice.

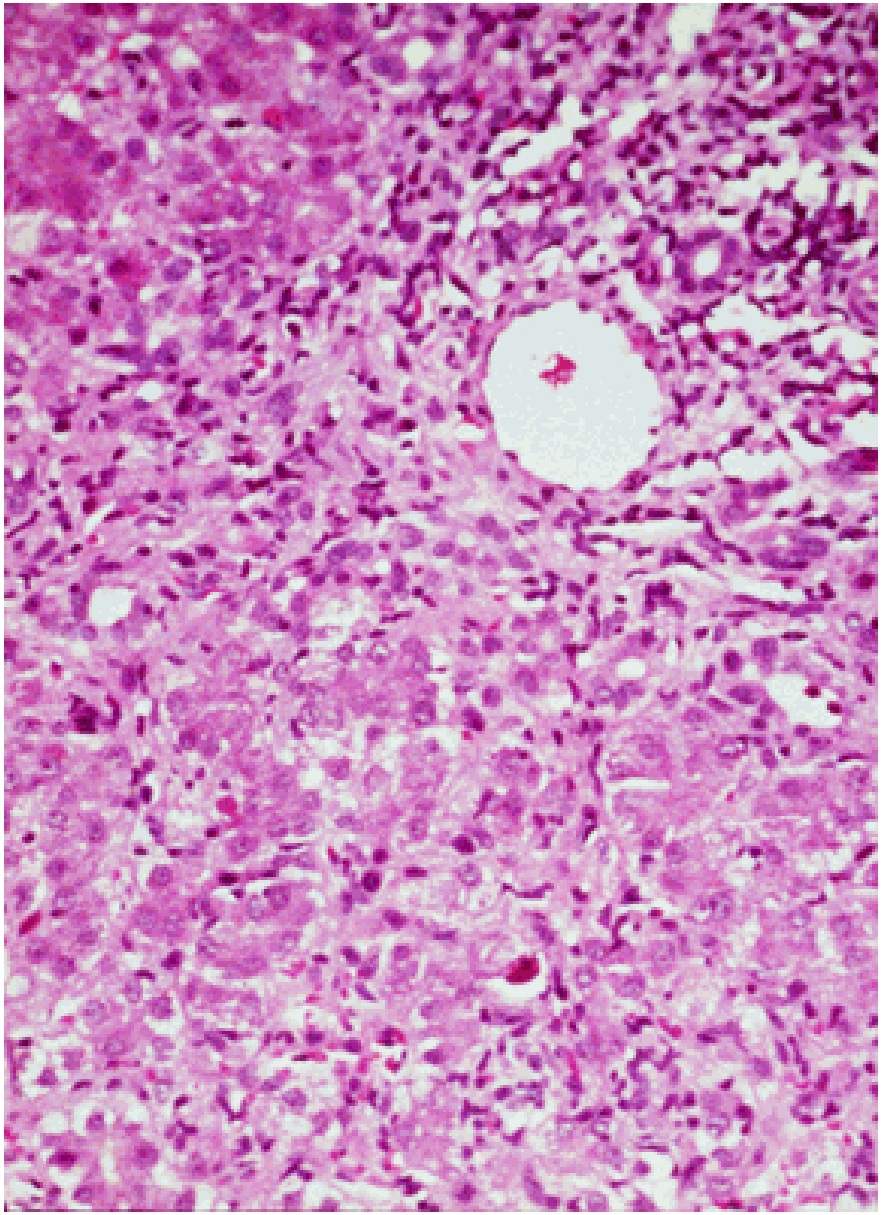
Faecal excretion of HAV persists longer in children and in immunocompromised persons (up to
4 to 5 months after infection) than in otherwise healthy adults (Hollinger 1996). Persons in psychiatric institutions, day-care centres, health care providers, military personnel, and men who have sex with men (especially when practicing anal intercourse) are at higher risk of infection. Parenteral transmission via IV drug use or transfusion of blood products is rare because of the short viraemia of HAV during acute infection. Mother-to-foetus transmission has not been reported.

Hepatitis A Pathogenesis



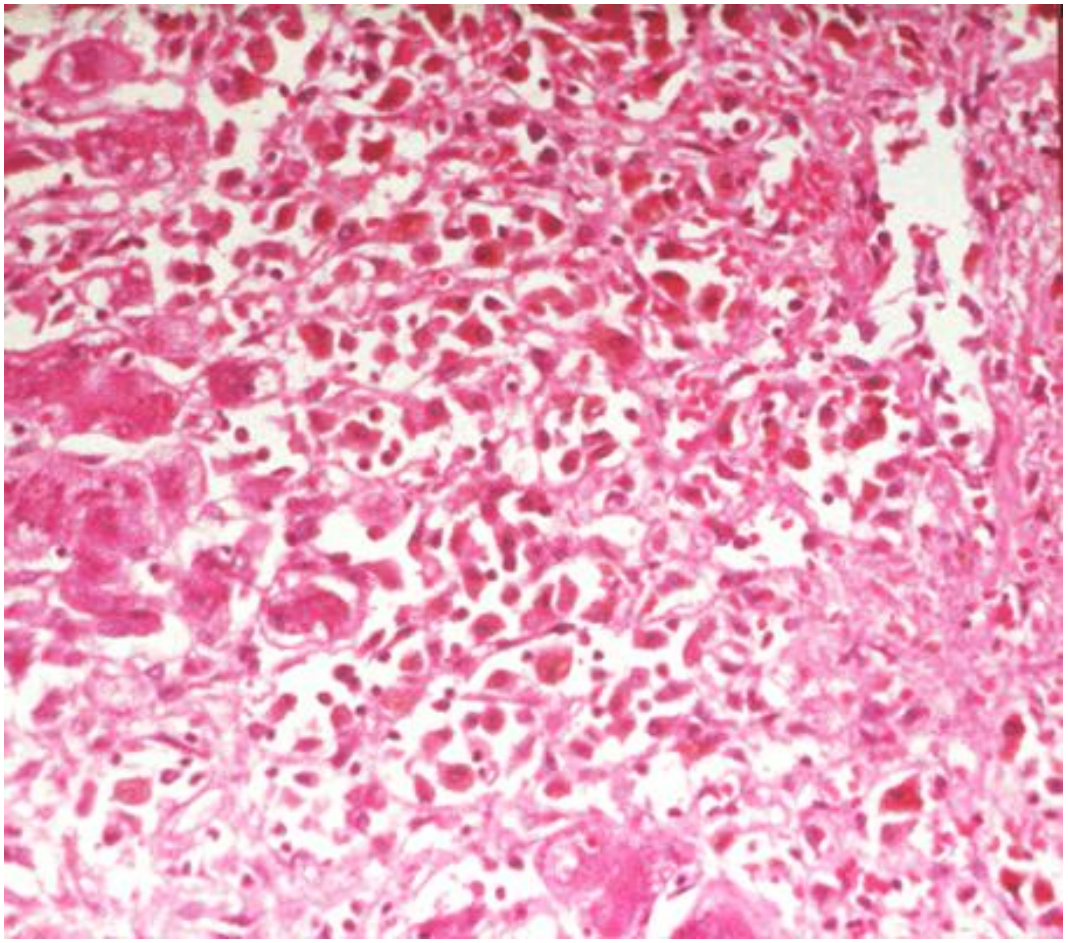
- Ingestion
- Replication in oropharynx/GI tract
- Transported to liver - major site of replication
- Shed in bile, transported to intestines
- Shed in feces
- Brief viremia
- Cellular immune response: clinical disease and control

Incubation Period (15-50 days)



Acute viral hepatitis: hystological section of liver showing hepatocytes in degeneration, necrosis and regeneration.

Hystological section of liver showing massive hepatic necrosis due to hepatitis A virus infection. There is a paucity of hepatocytes and large numbers of pigment-laden macrophges.



Clinical course

Hepatitis A infection can take a wide spectrum of clinical courses ranging from asymptomatic or subclinical infection to cholestatic presentation or even to fulmi nant liver failure. In children most infections are asymptomatic, while in adults 70% show clinical illness. Anicteric symptomatic HAV is more frequent than icteric disease, as only 30% of patients develop jaundice.

The incubation time averages 30 days (15 to 49 days). The illness begins with the abrupt onset of unspecific prodromal symptoms including fatigue, malaise, nausea, vomiting, anorexia, fever, abdominal discomfort, and right upper quadrant pain . Within one week, patients with an icteric course note darkened urine, light-coloured acholic stool, jaundice, and often pruritus. The prodromal symptoms usually diminish when jaundice appears. The jaundice is typically most intense within the first two weeks. Decrease and subsequent normalisation of serum aminotransferases occurs rapidly and before a decrease or normalisation of serum bilirubin.

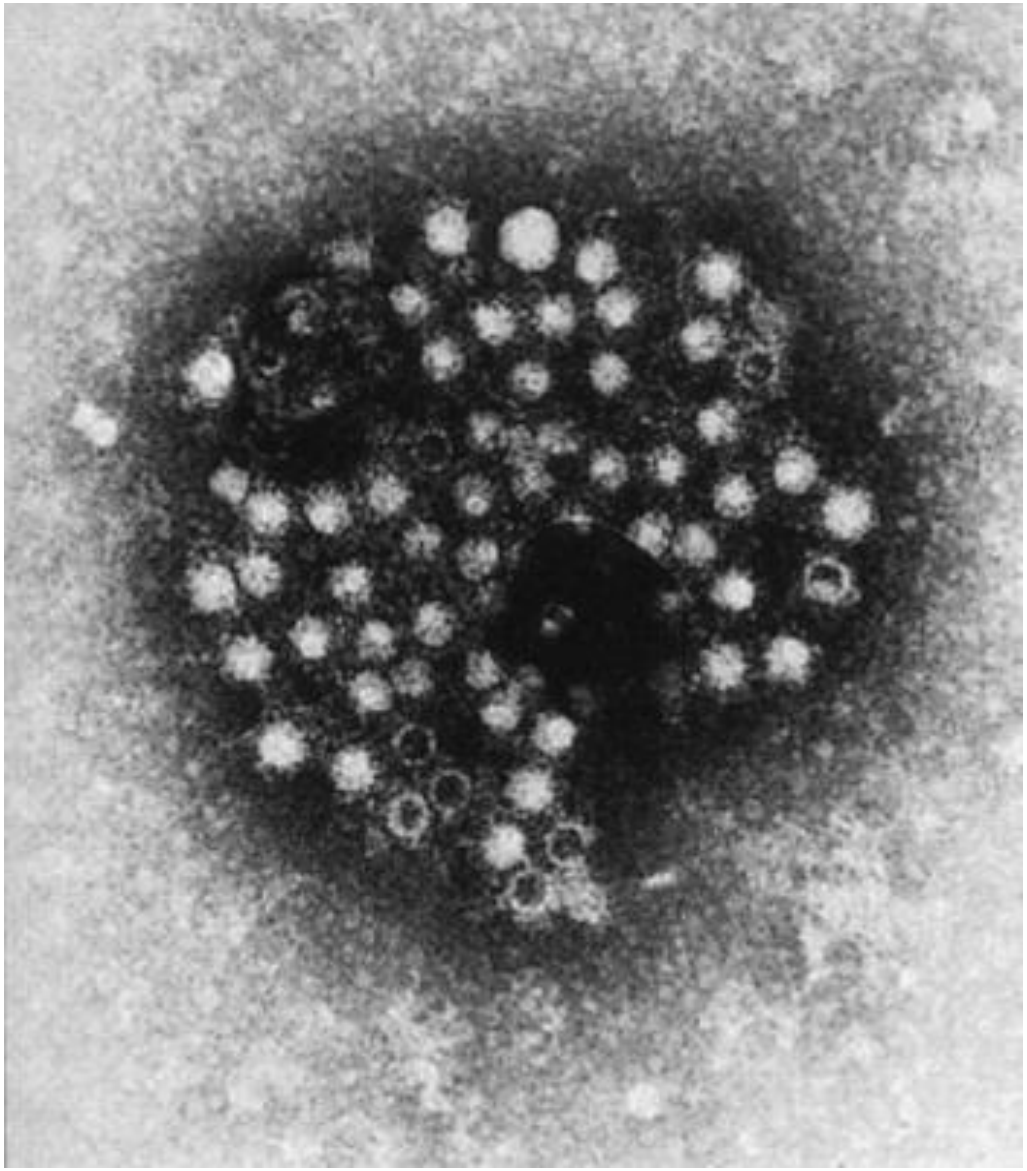
A biphasic or relapsing form of viral hepatitis A occurs in 6–10% of cases. The initial episode lasts 3-5 weeks and is followed by a period of remission characterised by normal liver chemistries lasting 4-5 weeks. Relapse may mimic the initial episode of the acute hepatitis. The full duration of the illness ranges from 16-40 weeks from the onset, and HAV-IgM antibodies persist throughout the clinical course (Schiff 1992).

Severe fulminant courses of HAV with hepatic failure are found more often in patients with underlying liver disease. Patients with chronic Hepatitis C have a greatly increased risk of hepatic failure, while HBV coinfection is less perilous (Vento 1989). Other risk factors are old age, malnutrition and immunosuppression.

The available data on HAV in pregnant women is not conclusive. Some data show a risk of gestational complications and premature birth (Elinav 2006; Zhang 1990) while others have not observed such complications (Tong 1981).

Hepatitis A infection has been reported as a trigger for autoimmune chronic active hepatitis (CAH) in genetically susceptible individuals (Vento 1991). In 58 monitored relatives of patients with CAH, three cases of subclinical HAV occurred. Two of these developed CAH within 5 months of HAV infection. Both showed a defective T-cell control of immune responses to the asialoglycoprotein receptor with ongoing T helper cell activation after the clearance of HAV.

Overall, a lethal course of HAV occurs in 0.1% of children, in 0.4% of persons aged 15-39 years, and in 1.1% in persons older than 40 years (Lemon 1985). Although a relapsing form of HAV (see above) is known, the infection does not progress to a chronic state.



Electron micrograph of the hepatitis A virus.

The micrograph discloses virus particles, 27 to 28 nm in diameter, aggregated by antibody.

Virusul hepatitic B

- Virionul de HBV conţine atât DNA cât şi RNA
- Mai mult decât atât, anumite regiuni ale genomului compactat pot fi mono, dublu sau chiar triplu - catenare.
- În genom se descriu patru unităţi ORF (open reading frames) suprapuse a căror rezultat constă în transcripţia şi expresia a şapte proteine diferite la nivelul HBV via codoni de star diferiţi din interiorul reţelei (in-frame start codons):
  - ORF P ocupă majoritatea genomului şi condifică pentru HBV polimerază.
  - ORF S codifică cele trei proteine de suprafaţă[4]
  - ORF C codifică atât pentru proteina e cât şi pentru proteinele de miez[5]
  - ORF X codifică pentru proteina BX a HBV[6,7]
- Transcripţia celor patru ORFs este controlată de patru elemente promotoare (preS1, preS2, miez şi X), şi de două elemente de mărire Enh I and Enh II (enhancer elements).

4. Heermann K.H. et al. 1984. Large surface proteins of hepatitis B virus containng the pre-S sequence. J. Virol; 52: 396-402. 5. Ou, J.H. et al. 1986. Hepatitis B virus gene function: the precore region targets the core antigen to cellular membrances and causes the secretion of the e antigen. Proc. Natl. Acad. Sci USA; 83: 1578-1582. 6. Kwee, L. et al. 1992. Alternate translation initiation on hepatitis B virus X mRNA produced multiple polypeptides that differentially transactive class II and III promoters. J. Virol.; 66: 4382-4389. 7. Tiollais, P. et al. 1985. Nature; 317: 489-

The human hepatitis B virus (HBV) is a small-enveloped DNA virus causing acute and chronic hepatitis. Despite the availability of a safe and effective vaccine, HBV infection still represents a major global health burden, with about 240 million people chronically infected worldwide . Many epidemiological and molecular studies have shown that chronic HBV infection represents the main risk factor for hepatocellular carcinoma development.

The rate for chronicity is approximately 5% in adult infections, but it reaches 90% in neonatal infections. HBV transmission occurs vertically and horizontally via exchange of body fluids. In serum, up to 1012 HBV genome equivalents per mL serum can be found. Although HBV does not induce direct cytopathic effects under normal infection conditions, liver damage (fibrosis, cirrhosis, and eventually hepatocellular carcinoma) is believed to be induced by the ongoing immune reaction and a consistent inflammation of the liver.

HBV is the prototype member of the *Hepadnaviridae* family, which are the smallest known DNA-containing, enveloped animal viruses. Characteristic of HBV is its high tissue- and species-specificity, as well as a unique genomic organisation with asymmetric mechanism of replication. Since all hepadnaviruses use a reverse transcriptase to replicate their genome, they are considered distantly related to retroviruses.

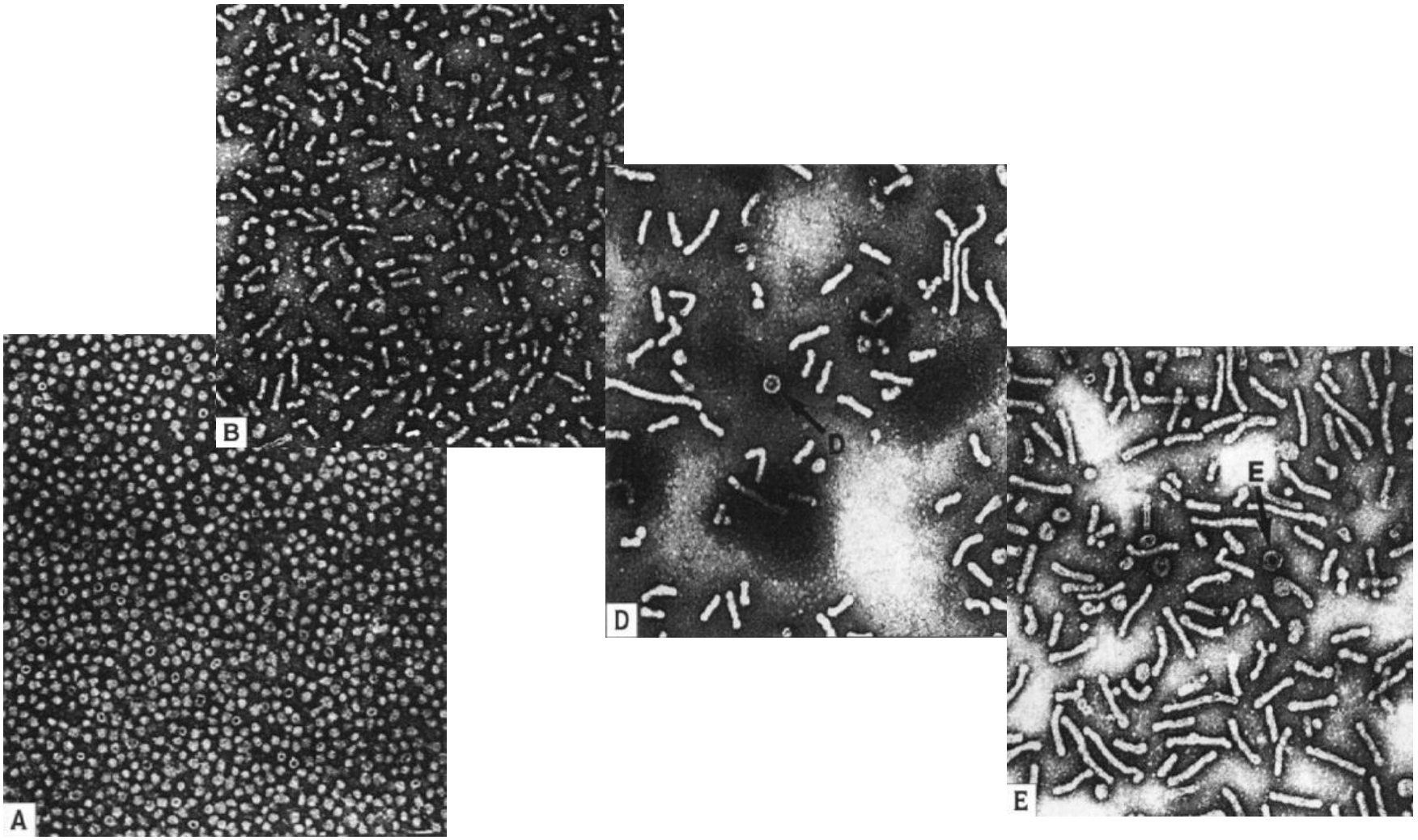
Despite decades of research and significant progress in understanding the molecular virology of HBV, important steps of the infection have not yet been clarified. Nevertheless, the discovery of the cellular receptor and the establishment of innovative infection models and molecular techniques have opened up new possibilities to investigate specific steps of the lifecycle as well as the organisation and activity of the covalently closed circular DNA (cccDNA), the viral minichromosome that serves as the template of HBV transcription in the nucleus of the infected hepatocytes, enabling maintenance of chronic HBV infection.

Taxonomic classification and genotypes

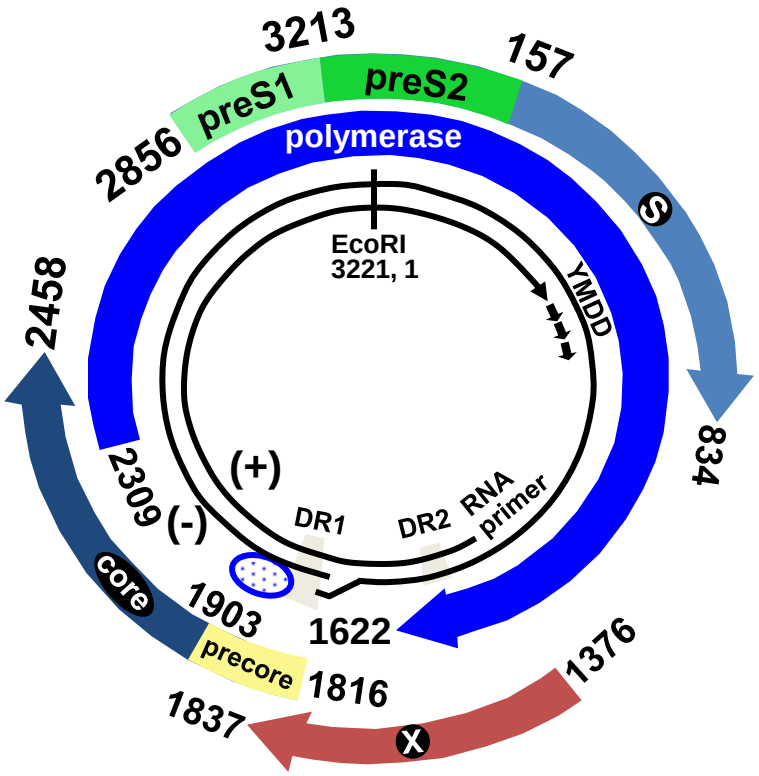
The *Hepadnaviridae* form their own taxonomic group as their biological characteristics are not observed in any other viral family. Based on host and phylogenetic differences, the family of *Hepadnaviridae* contains two genera: the *orthohepadnaviruses* infecting mammals, and the *avihepadnaviruses* that infect birds. To date, *orthohepadnaviruses* have been found in human (HBV), woodchuck (WHV) (Korba 1989), ground squirrel (GSHV), arctic squirrel (ASHV) and woolly monkey (WMHBV) (Lanford 1998). *Avihepadnaviruses* include duck HBV (DHBV) (Mason 1980), heron HBV (HHBV) (Sprengel 1988), Ross's goose HBV, snow goose HBV (SGHBV), stork HBV (STHBV) (Pult 2001) and crane HBV (CHBV) (Roggendorf 2007, Funk 2007, Dandri 2005b, Schaefer 2007). Moreover, three unique hepadnavirus species antigenically related to human HBV and capable of infecting human hepatocytes were also identified in bats (Drexel 2013). The relatedness of these viruses to HBV suggests that bats might constitute ancestral sources of primate hepadnaviruses.

VIRIONUL COMPLET

Electron micrograph of hepatitis B viral forms in blood of an infected patient showing sucrose density gradient fractions after rate-zonal sedimentation of particles.



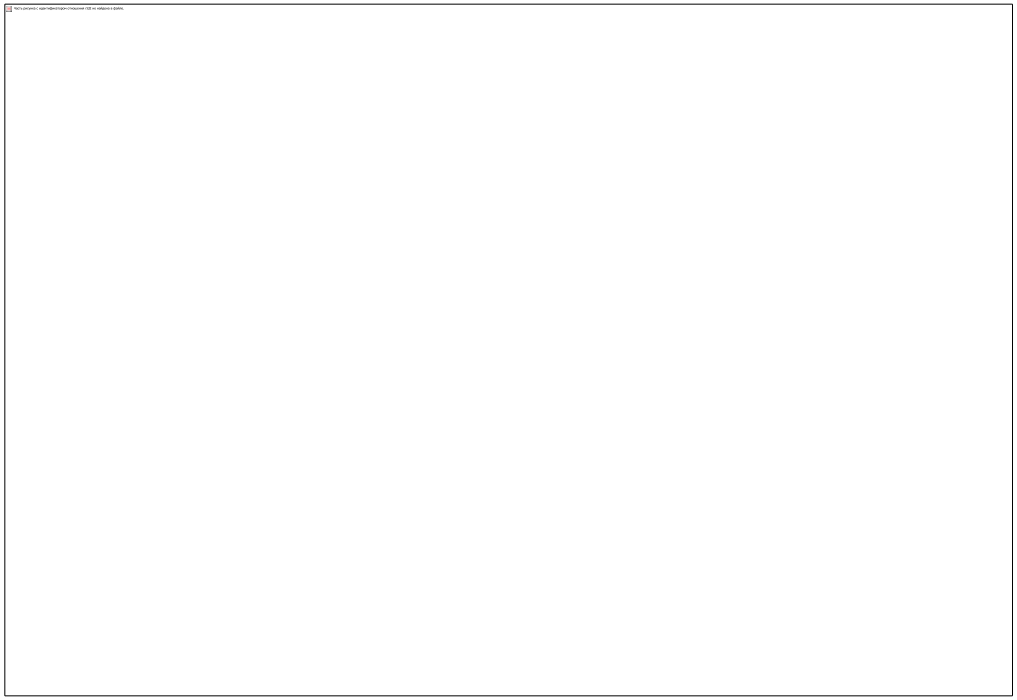
Hepatitis B Virus (HBV)



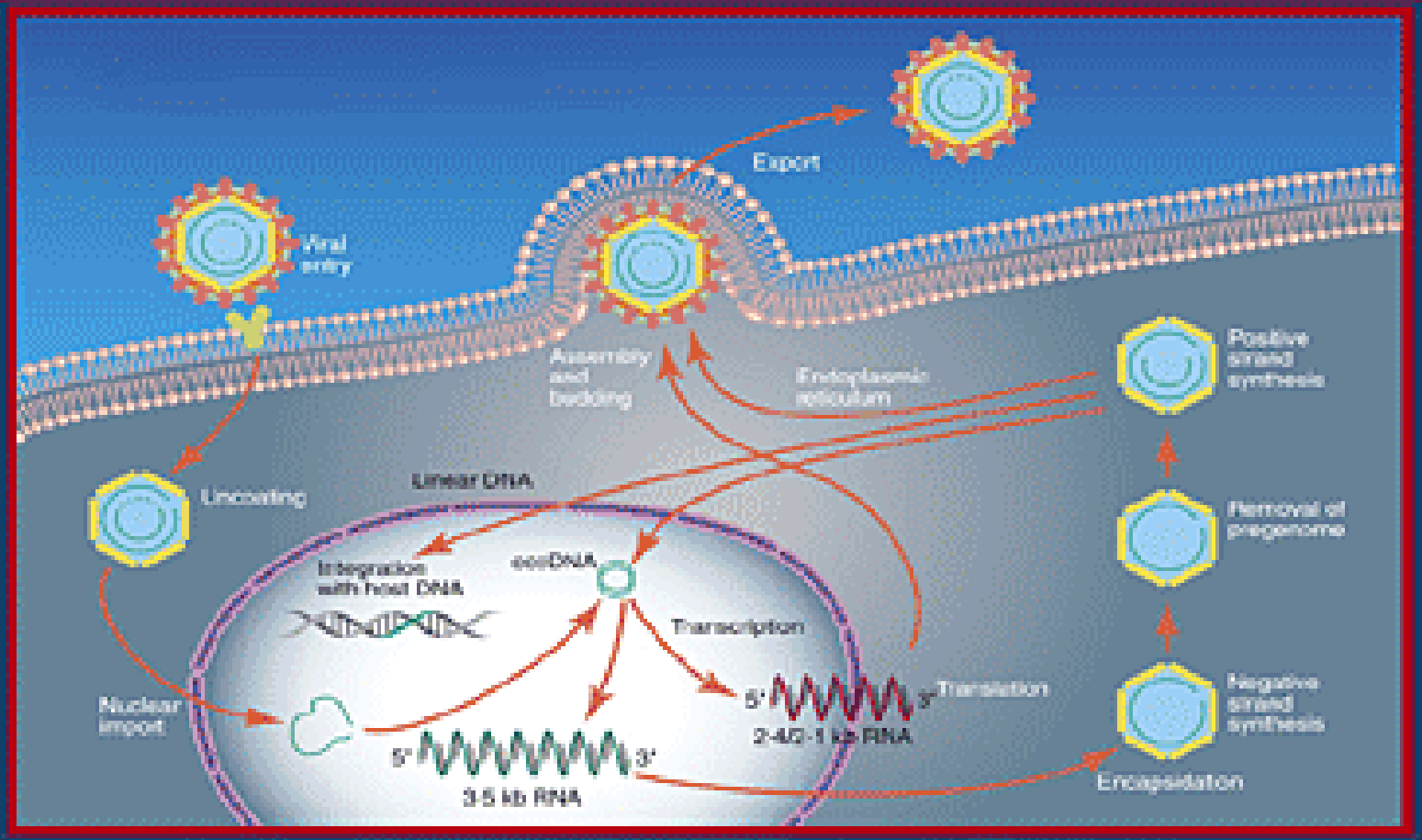
- 4 ORF - suprapuse
- Revers transcriptaza/ DNA polimeraza suprapusă cu genele de suprafață
- De 100 ori mai infectant ca HIV-ul
- Găsit în sânge și fluidele organismului

MMWR. 2003;52:1-33. Ott MJ and Aruda M. J Pediatr Health Care. 1999;13:211-216. Ribeiro RM, et al. Microbes and Infection. 2002;4:829-835.

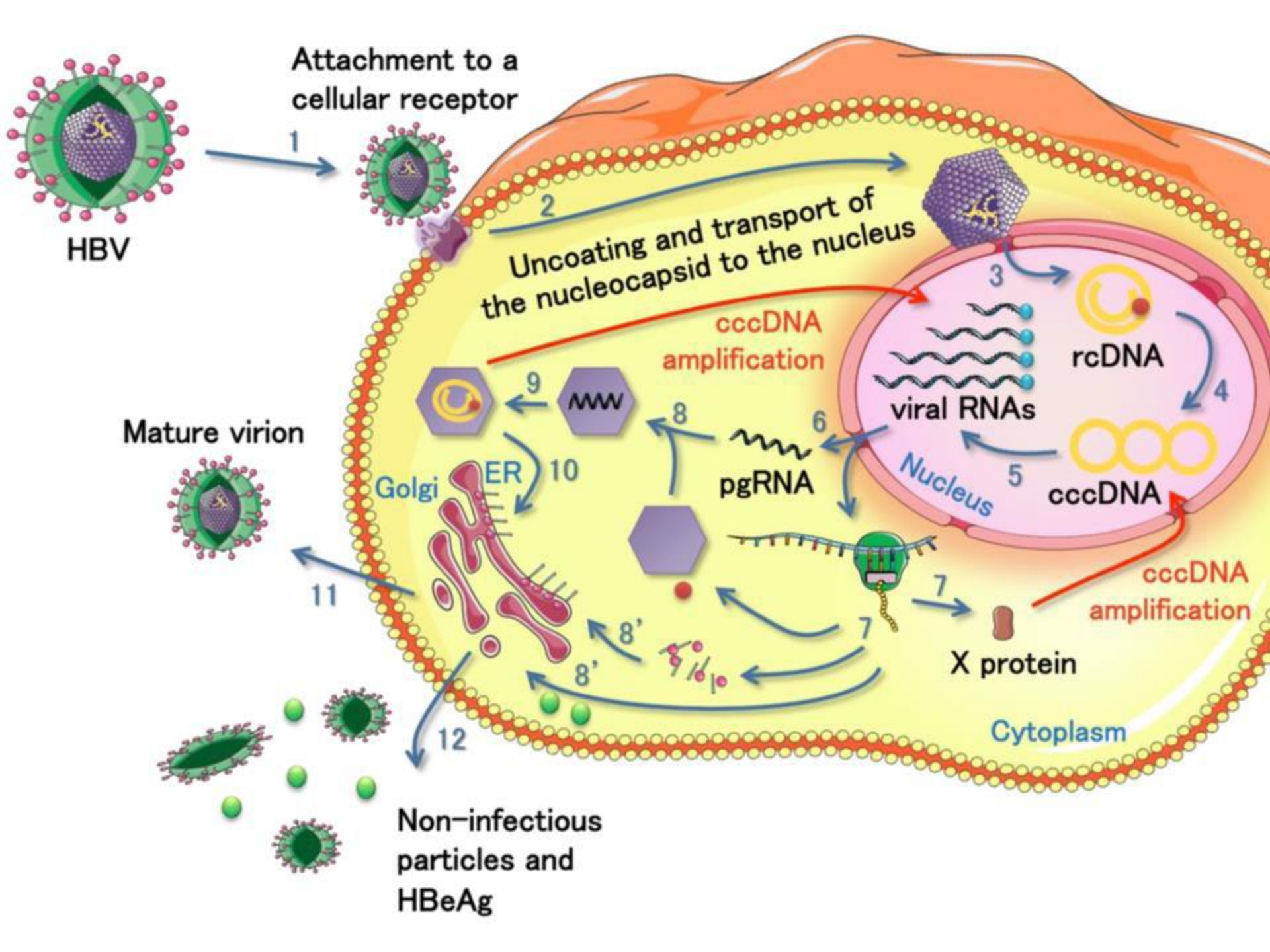
Часть документа с идентификатором отсутствует. Будет не найдено в файле.

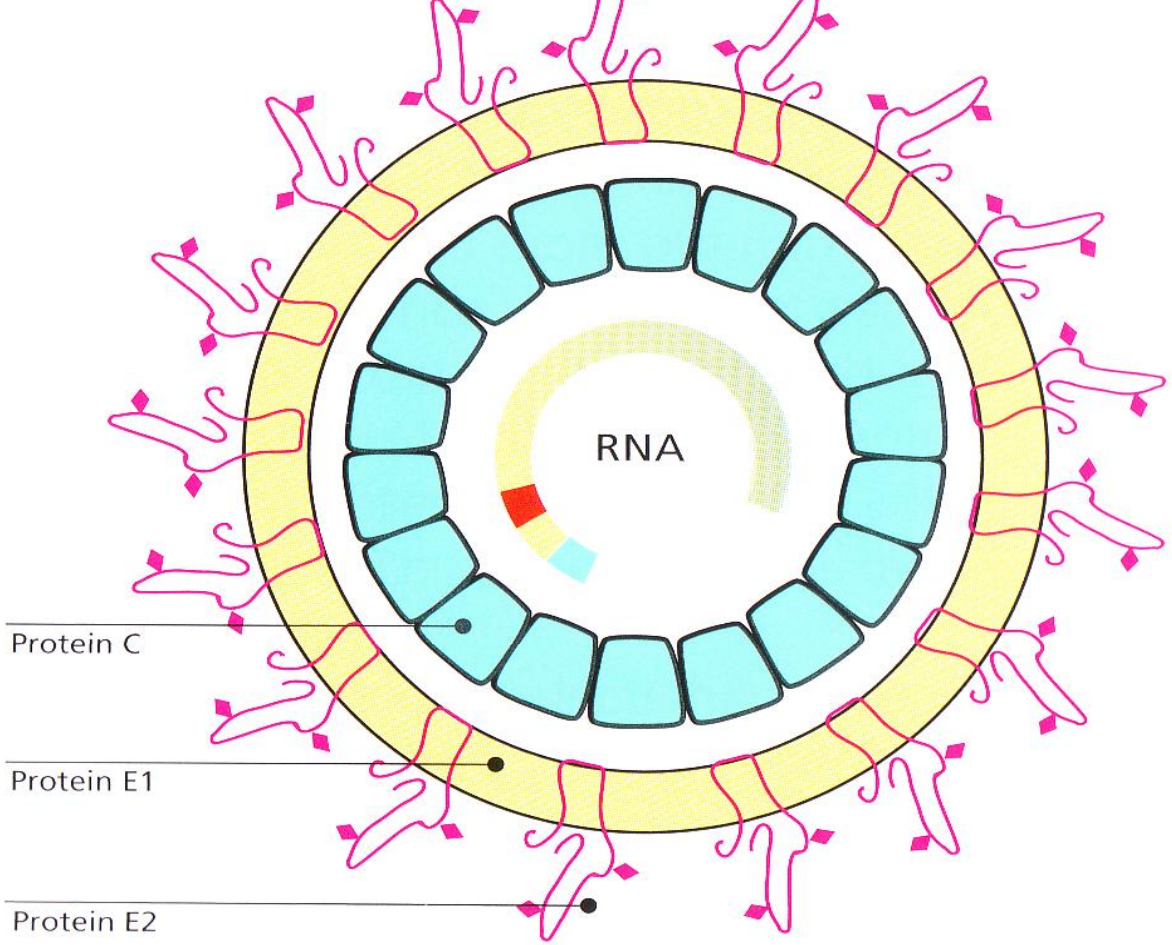

Часть рисунка с идентификатором отношения r100 не найдена в файле.

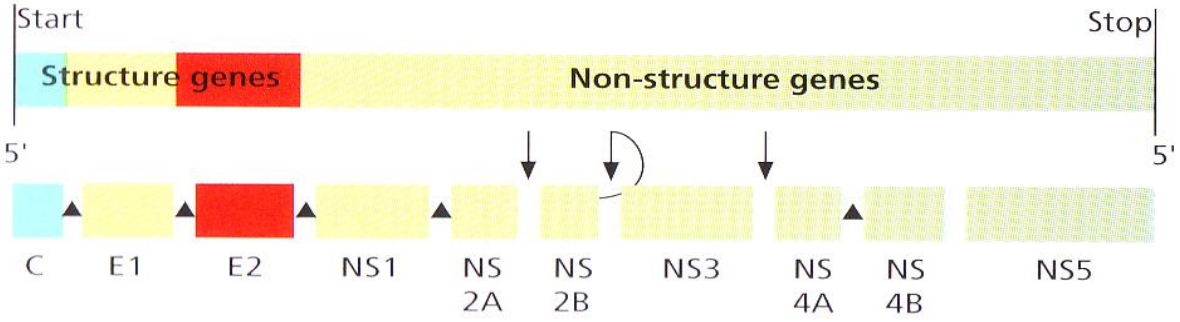
Replication of the hepatitis B virus



- cccDNA is the template for viral replication; persists long term
- cccDNA explains inactive carriership and capacity to reactivate
- Not directly targeted by antiviral therapy


HBV
Attachment to a cellular receptor
1
2
Uncoating and transport of the nucleocapsid to the nucleus
3
rcDNA
4
viral RNAs
5
cccDNA
Nucleus
cccDNA amplification
6
pgRNA
8
9
10
Golgi
ER
Mature virion
11
7
X protein
cccDNA amplification
8'
8'
7
12
Cytoplasm
Non-infectious particles and HBeAg


RNA
Protein C
Protein E1
Protein E2


Start
Stop
Structure genes
Non-structure genes
5'
5'
C
E1
E2
NS1
NS 2A
NS 2B
NS3
NS 4A
NS 4B
NS5

Transmission

The routes of HBV transmission:

- Sexual
- Percutaneous (Intravenous Drug Use)
- Perinatal
- Horizontal
- Transfusion
- Nosocomial infection (including needle-stick injury)
- Organ transplantation

There is considerable variation in the predominance of transmission modes in different geographic areas. For example, in low prevalence areas such as Western Europe, the routes are mainly unprotected sexual intercourse and intravenous drug use. In high prevalence areas like Sub-Saharan Africa perinatal infection is the predominant mode of transmission. Horizontal transmission, particularly in early childhood, is regarded as the major route of transmission in intermediate prevalence areas.

Perinatal Transmission

Transmission from an HBeAg-positive mother to her infant may occur in utero, at the time of birth, or after birth. The rate of infection can be as high as 90%. HowTransmission 27

ever, neonatal vaccination is highly efficacious (95%). Its efficacy indicates that most infections occur at or shortly before birth. On the other hand, caesarean section seems not be protective as it is in other vertically transmitted diseases like HIV.

The risk of transmission from mother to infant is related to the HBV replicative rate in the mother. There seems to be a direct correlation between maternal HBV DNA levels and the likelihood of transmission. In mothers with highly replicative HBV the risk of transmission may be up to 85 to 90%, and it continusously lowers with lower HBV DNA levels . In some studies there has been almost no perinatal transmission if the mother has no significant replication (<105 log copies/ml).

Nosocomial transmission. Needle-stick risk

VHB- 15-20%, 0,00001 ml

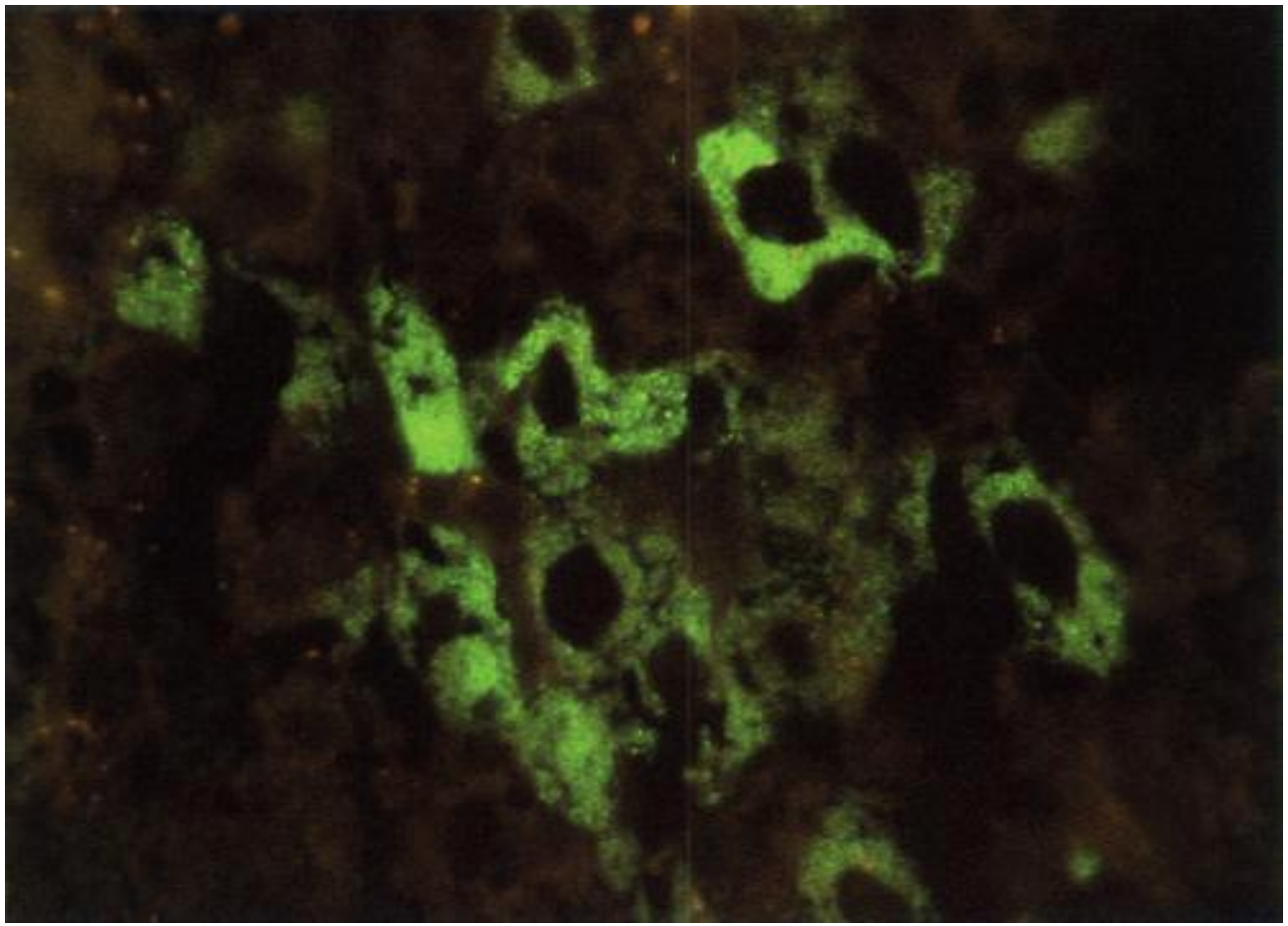
VHC – 5-7%

HIV- 0,5%

It is possible to reduce the risk of perinatal transmission in several ways. The first step is identification of persons at risk. Testing for HBsAg should be performed in all women at the first prenatal visit and repeated later in pregnancy if appropriate. Newborns born to HBV-positive mothers can be effectively protected by passiveactive immunization (>90% protection rate) (del.

Hepatitis B immunoglobulin for passive immunization should be given as early as possible (within 12 hours), but can be given up to seven days after birth, if seropositivity of the mother is detected later. Active immunization follows standard schemes and is given at three time points (10 µg at day 0, month 1, and month 6). Anti-HBV treatment of the mother with nucleoside analogues may be discussed especially in mothers with high HBV DNA levels, although it is not known whether antiviral treatment has a protective effect in addition to immunization. At the moment there are no substantiated guidelines. If appropriate, lamivudine seems to be the treatment of choice. Telbivudine may be an alternative, whereas adefovir, entecavir and tenofovir are not recommended in pregnancy, unless clearly indicated .

As mentioned earlier, caesarean section should not be performed routinely, whereas it is recommended in the setting of other infectious diseases like HIV (according to the viral replication rate). If vaccination was performed in the child, the child may be breastfed.



Hepatitis C virus antigen (HCVAg) in cytoplasm of hepatocytes, identified by fluorescein isothiocyanate–labeled polyclonal IgG anti-HCVAg. Liver biopsy specimen from a hepatitis C virus–infected patient shows very prominent deposits of HCVAg, with a distinct granular pattern in the hepatocyte located in the center of the field.

Prezentare generală: principalele trăsături distinctive virale ale HIV, VHB și VHC

Virus	HIV	VHB	VHC
Producția zilnică de virioni pe zi	10^{10}	10^{12}–10^{13}	10^{12}
Timp de înjumătățire al virionilor liberi (ore)	1	3–24	2–3
Timp de înjumătățire al virionilor intracelulari	Zile (în funcție de $t_{1/2}$ al celulelor infectate)	Luni (în funcție de $t_{1/2}$ al celulelor infectate)	Ore (independent de $t_{1/2}$ al celulelor infectate)
Rata mutațiilor	Foarte înaltă	Înaltă	Foarte înaltă
Constrângeri din cauza cadrelor de citire deschisă ale enzimelor virale țintă	Moderate	Mari	Deloc
Mutații ”de scăpare” mediate imun	Frecvente	Infrecvente	Frecvente
Principalele celule țintă	Celulele T $CD4^+$	Hepatocite	Hepatocite
Timp de înjumătățire al celulelor infectate	Zile	Luni	Săptămâni
Rezervor viral intracelular	Da (ADNc integrat)	Da (ADN ccc)	Nu

HIV: virusul imunodeficienței umane
VHB: virusul hepatitei B
ADNc: ADN complementar
ADNccc: ADN circular covalent închis

Virusurile hepatitice implicate în etiologia hepatitelor acute/cronice

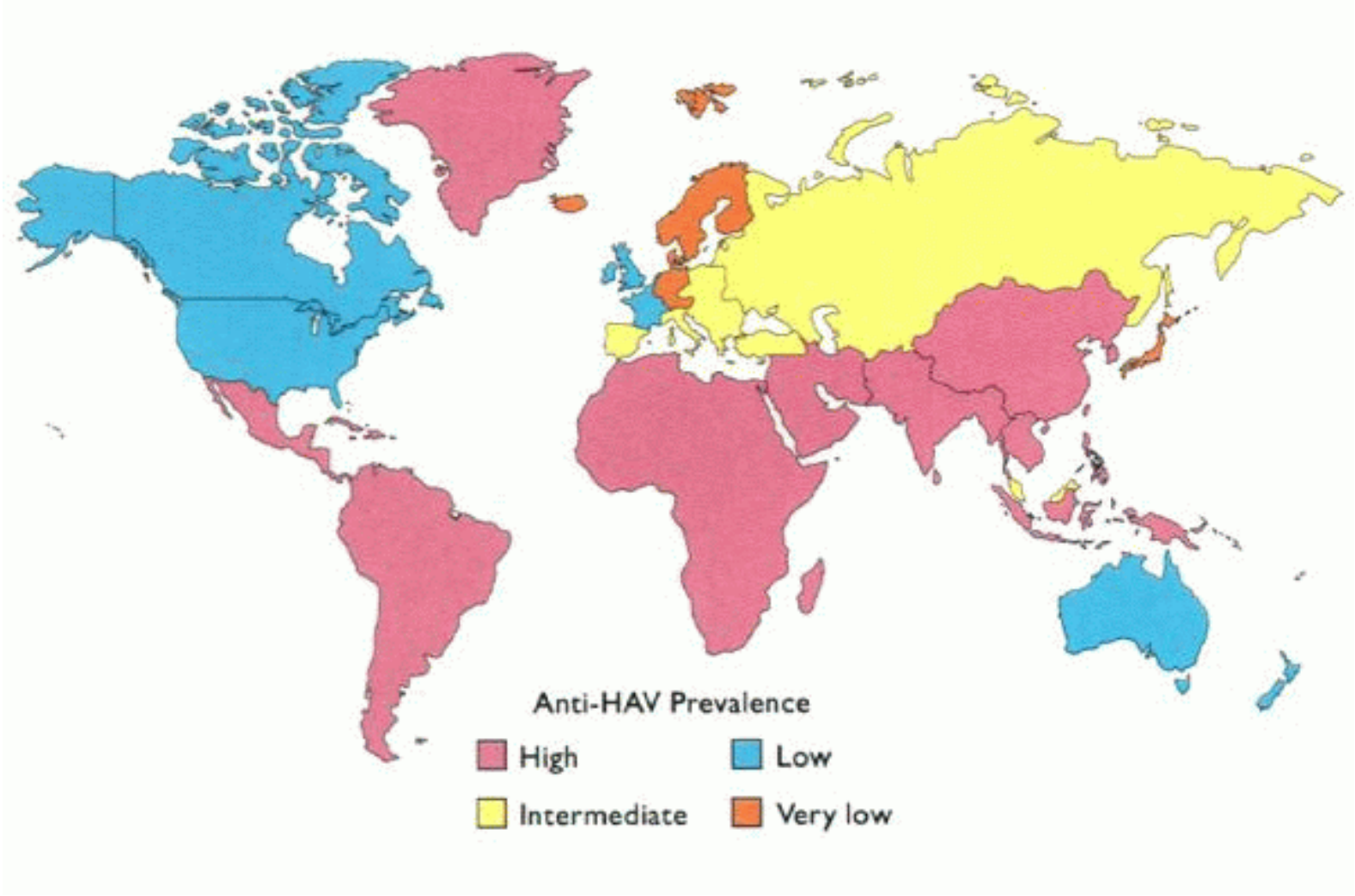
Nosocomial transmission. Needle-stick risk

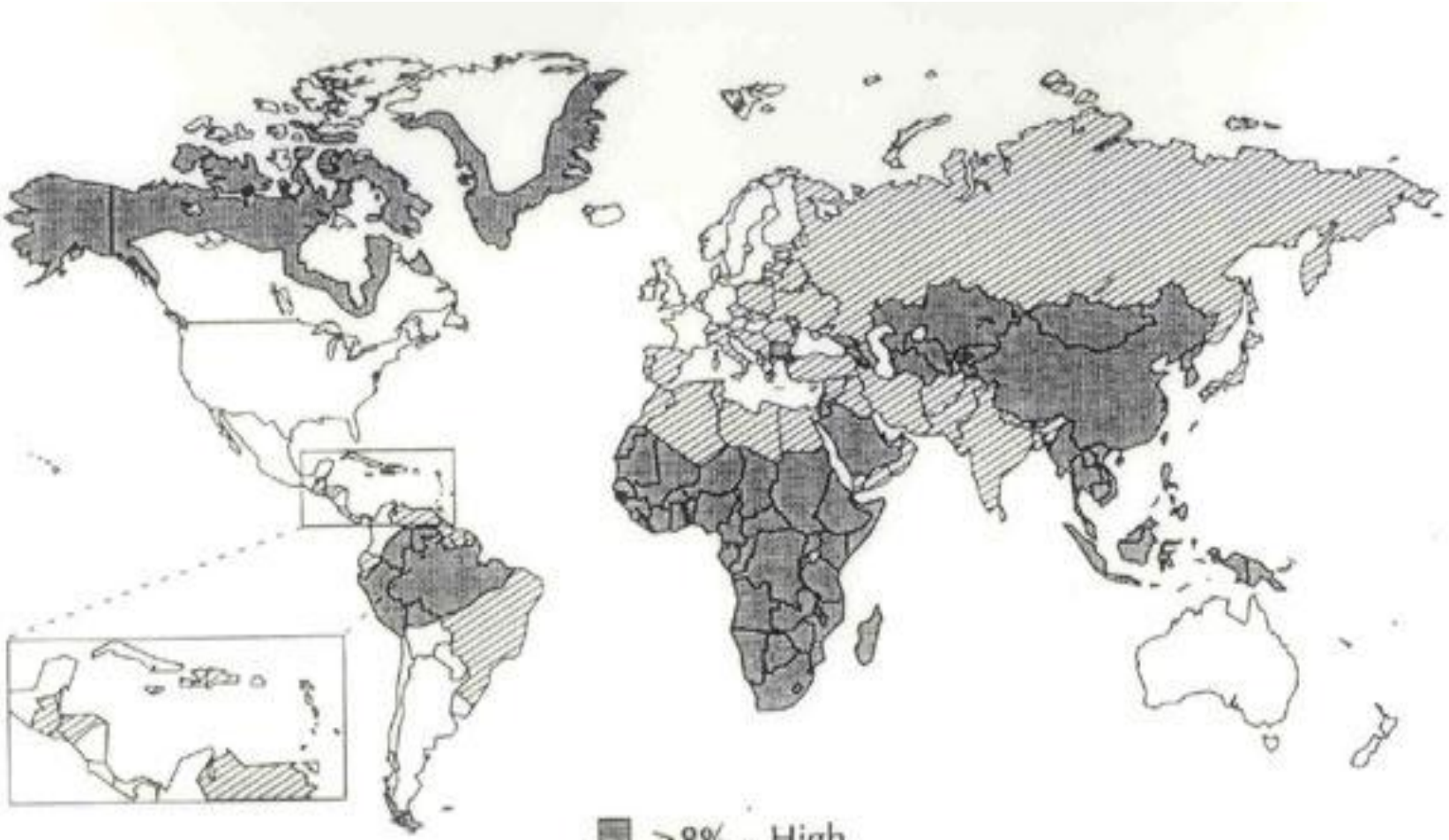
VHB- 15-20%, 0,00001 ml

VHC – 5-7%

HIV- 0,5%

Worldwide prevalence of hepatitis A virus (HAV)

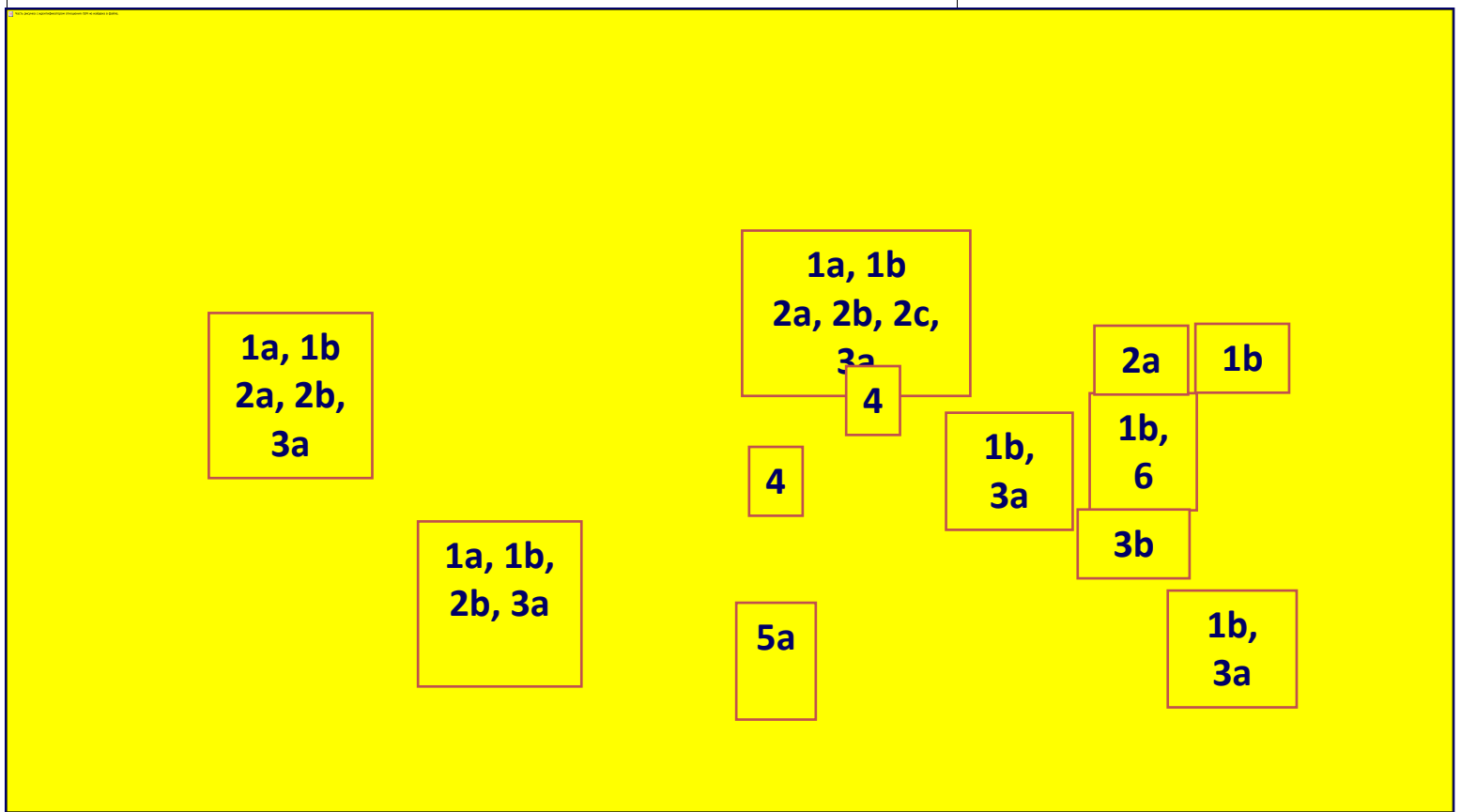


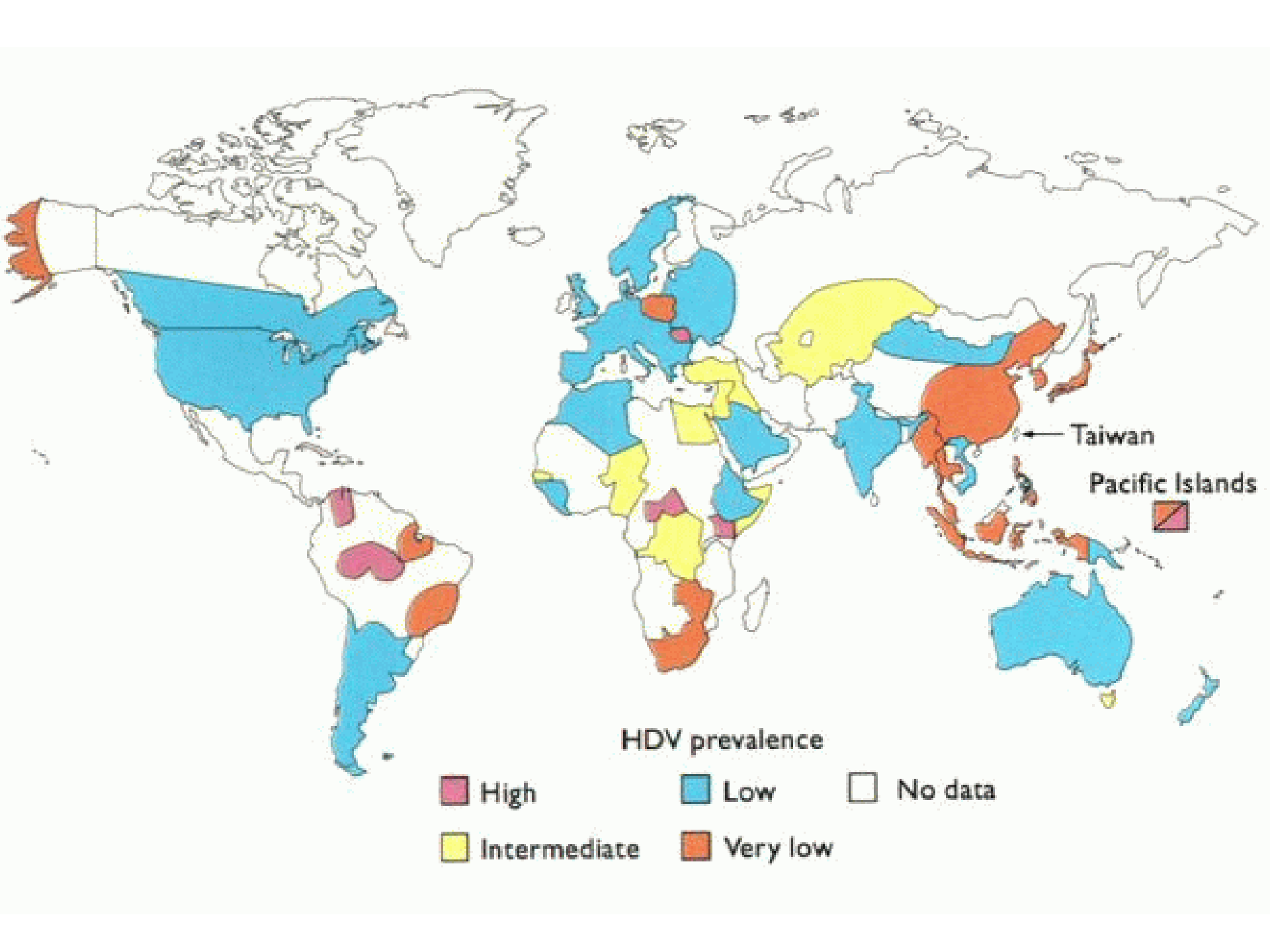


hepatitis B

Часть рисунка с идентификатором отношения rId3 не найдена в файле.

HCV Infection: Worldwide Prevalence




Taiwan
Pacific Islands
HDV prevalence
High
Low
No data
Intermediate
Very low

Gheographic distribution of HVE

Patogenie

Modelul general, cu unele particularităţi în funcţie de etiologie

După pătrunderea în organism are loc multiplicarea:
VHA şi VHE– în orofaringe, glandele salivare şi epiteliul intestinului
VHC – în mononuclearele circulante
VHB, VHD se presupune că primar se multiplică intrahepatic
Din aceste focare pătrunde în sânge şi se dezvoltă viremia
Diseminarea hepatică şi multiplicarea virusului în hepatocite
Activarea reacţiilor de apărare contra infecţiei a sistemului imun celular (macrofage, limfocite T şi B) cu eliberarea de citokine (IL, interferoni şi al.) şi (formarea de anticorpi specifici contra antigenelor virale circulante şi intracelulare).
În HVA, C, D, E multiplicarea virusului în hepatocite duce la distrugerea lor.

În HVB şi C pe membrana hepatocitelor are loc expresia antigenelor virale, alături de propriile antigene de histocompatibilitate HLA de tipul I. aceste celule devin ţinta reacţiilor de apărare celulară şi umorală, suferind o agresiune indirectă, secundară din partea acestora (citotoxică prin limfocite NK,T-citotoxice mediate prin complexe imune, CD8 – supresoare) şi inflamatorie la care participă macrofagele şi celulele limfoplasmocitare ce infiltrează spaţiile periportale şi perilobulare în cazurile de infecţie persistentă cronică.

Clinical course

Hepatitis A infection can take a wide spectrum of clinical courses ranging from asymptomatic or subclinical infection to cholestatic presentation or even to fulmi nant liver failure. In children most infections are asymptomatic, while in adults 70% show clinical illness. Anicteric symptomatic HAV is more frequent than icteric disease, as only 30% of patients develop jaundice.

The incubation time averages 30 days (15 to 49 days). The illness begins with the abrupt onset of unspecific prodromal symptoms including fatigue, malaise, nausea, vomiting, anorexia, fever, abdominal discomfort, and right upper quadrant pain. Within one week, patients with an icteric course note darkened
urine, light-coloured acholic stool, jaundice, and often pruritus. The prodromal symptoms usually diminish when jaundice appears. The jaundice is typically most intense within the first two weeks. Decrease and subsequent normalisation of serum aminotransferases occurs rapidly and before a decrease or normalisation of serum bilirubin.

A biphasic or relapsing form of viral hepatitis A occurs in 6–10% of cases. The initial episode lasts 3-5 weeks and is followed by a period of remission characterised by normal liver chemistries lasting 4-5 weeks. Relapse may mimic the initial episode of the acute hepatitis. The full duration of the illness ranges from 16-40 weeks from the onset, and HAV-IgM antibodies persist throughout the clinical course (Schiff 1992).

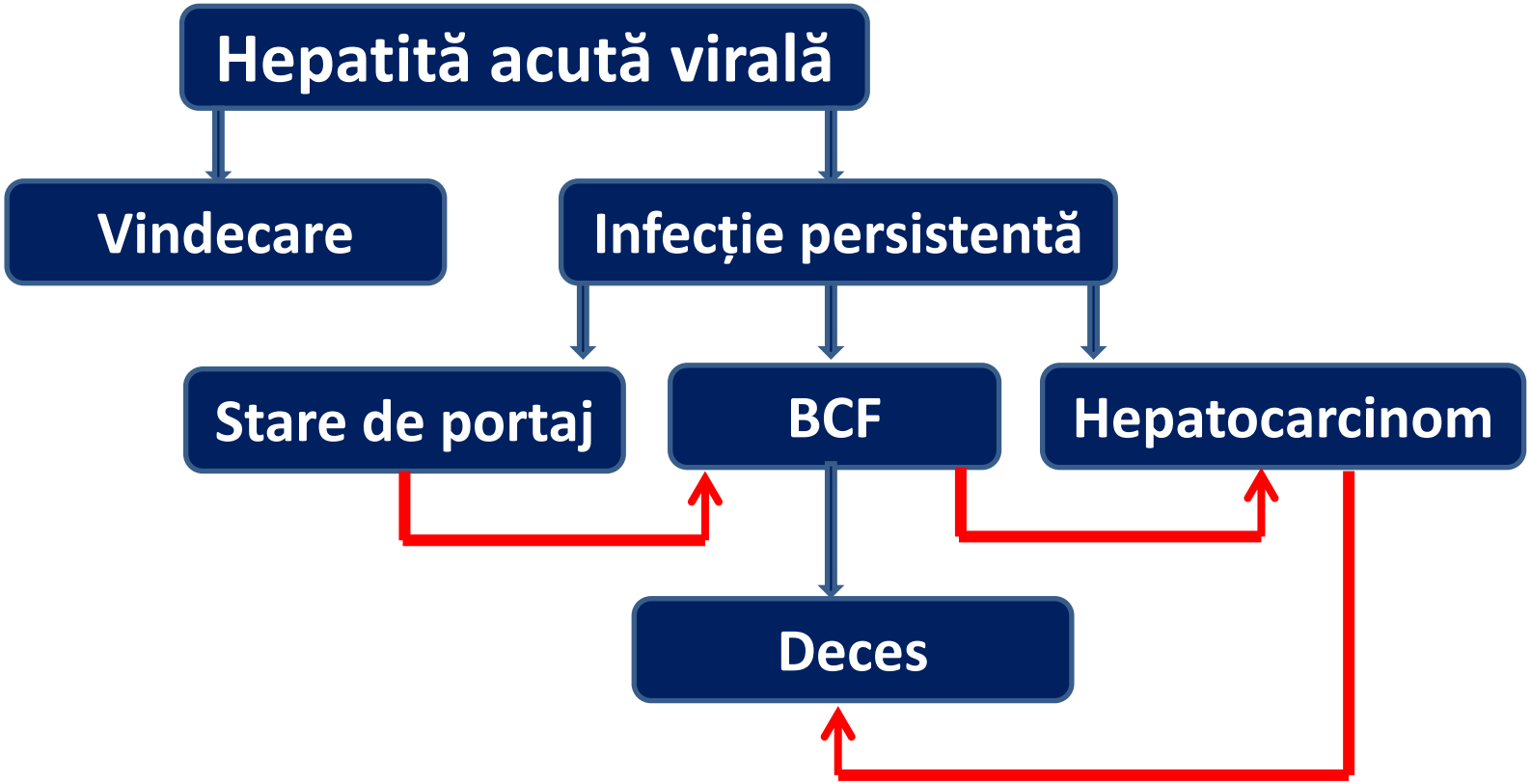
Severe fulminant courses of HAV with hepatic failure are found more often in patients with underlying liver disease. Patients with chronic Hepatitis C have a greatly increased risk of hepatic failure, while HBV coinfection is less perilous. Other risk factors are old age, malnutrition and immunosuppression.

The available data on HAV in pregnant women is not conclusive. Some data show a risk of gestational complications and premature birth
while others have not observed such complications.

Hepatitis A infection has been reported as a trigger for autoimmune chronic active hepatitis (CAH) in genetically susceptible individuals. In 58 monitored relatives of patients with CAH, three cases of subclinical HAV occurred. Two of these developed CAH within 5 months of HAV infection. Both showed a defective T-cell control of immune responses to the asialoglycoprotein receptor with ongoing T helper cell activation after the clearance of HAV.

Overall, a lethal course of HAV occurs in 0.1% of children, in 0.4% of persons aged 15-39 years, and in 1.1% in persons older than 40 years . Although a relapsing form of HAV (see above) is known, the infection does not progress to a chronic state.

Dinamica infecţiei cu virusuri hepatitice



Clasificarea hepatitelor virale

I După etiologie:
HVA; 2) HVB; 3) HVC; 4) HVD; 5) HVE şi alte provocate de VHG, TTV, sen-virus etc.

II După formele clinice:
Tipice;
Atipice;
- subclinice;
- anicterice;
- fruste;
- inaparente;
- portaj

III După gravitate:
- uşoare
- medii
- severe
- fulminante

IV După evoluţia clinică:
- acute (până 3 luni);
- trenante (3-6 luni);
- cronice (peste 6 luni)

V Hepatitele virale cronice B, C, D:
- faza replicativă (prezenţa ADN sau ARN viral);
- faza integrativă (lipsa ADN sau ARN viral)