

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Viral Hepatitis

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The term viral hepatitis refers to liver inflammation that occurs because of a viral infection. There are 5 **hepatotropic** viruses (hepatitis A, B, C, D, and E) that selectively infect the liver. Acute hepatitis caused by these viruses may resolve without intervention or may develop into chronic infection in some instances.

Nonhepatotropic viruses target different organs in the body but are also known to cause hepatitis, although these infections are typically mild in immunocompetent hosts. The significance of nonhepatotropic viruses is most notable in immunocompromised hosts, particularly in transplant recipients.

Viral hepatitis

Type	Classification	Nucleic acid	Transmission
A	Enterovirus	RNA	<u>Enteral</u>
B	Hepadnavirus	<u>DNA</u>	Parenteral
C	Flavivirus like	RNA	Parenteral
D	Viroid-related	RNA	Parenteral
E	Calicivirus	RNA	<u>Enteral</u>
G	Flavivirus	RNA	Parenteral

Hepatitis Viruses

- **Hepatitis – inflammation of the liver**
- **Several families**
 - Hepatitis B *Hepadnaviridae*
 - Hepatitis A *Picornaviridae*
 - Hepatitis C, D, E, G (different families)
- **All tropic for liver**
- **Mode of spread differs**
 - **Enterically transmitted (A, E)**
 - **Parenterally transmitted (B,C,D)**

Acute infection may lead to chronic diseases (B,C,D)

Clinical Stages

- *Incubation period*
- *Prodromal (preicteric) phase*
- *Icteric phase*
- *convalescence*

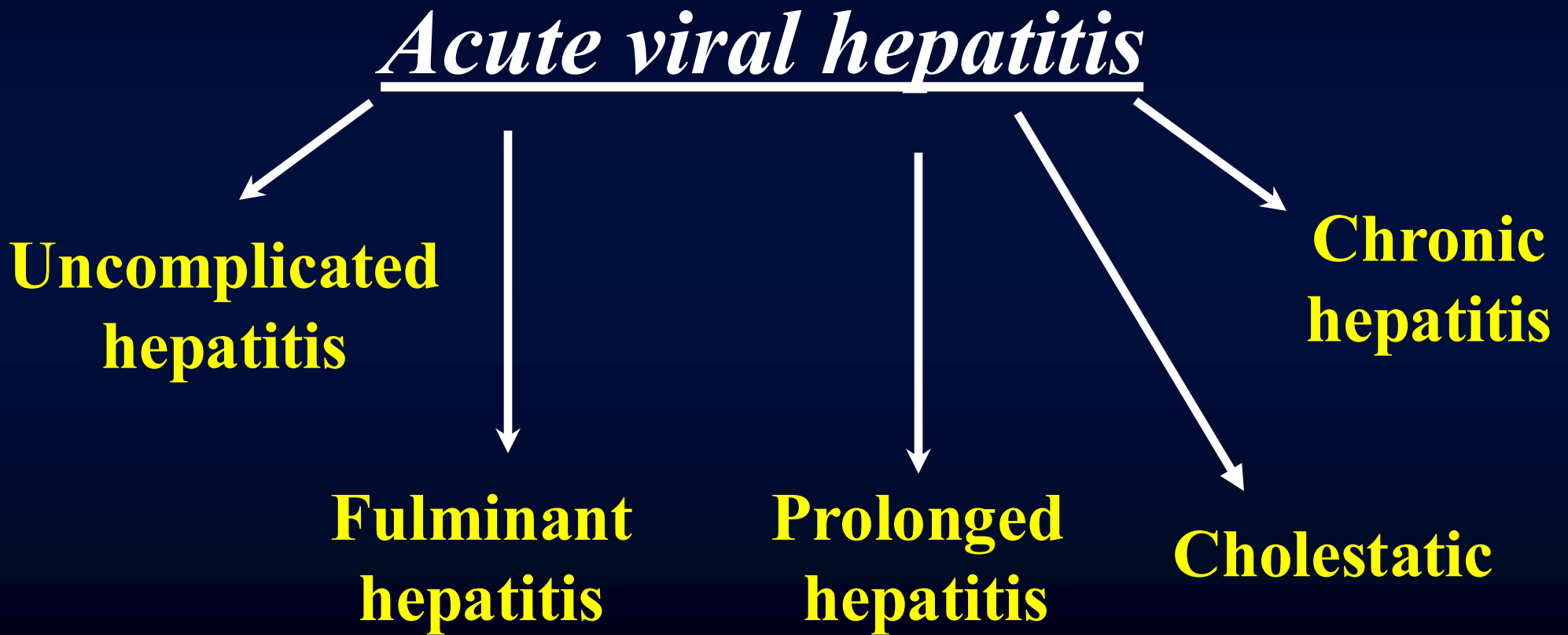
Jaundice



Jaundice



Sequelae of acute viral hepatitis



Hepatitis A (HAV)

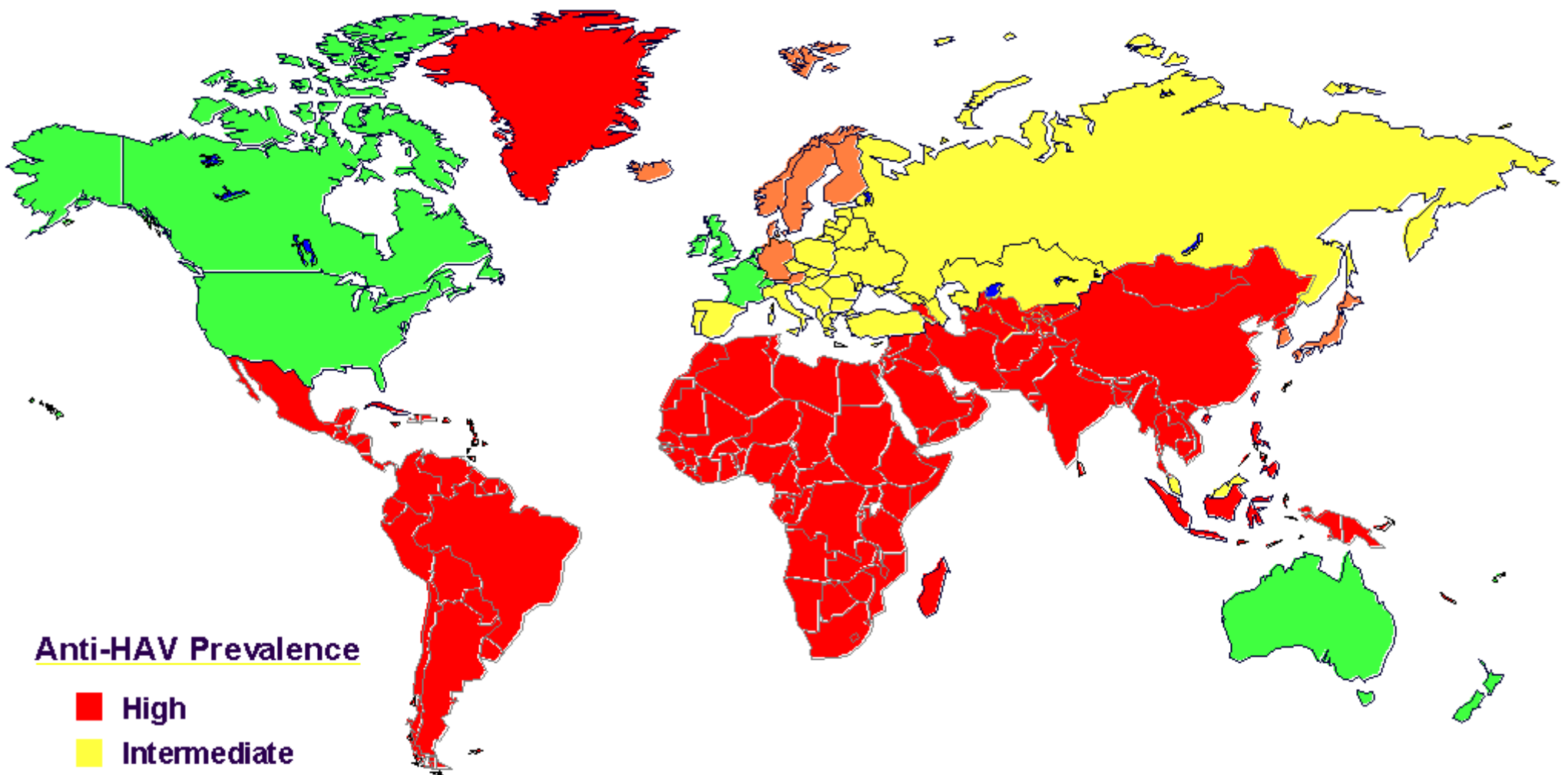
Acute “infectious” hepatitis- picornavirus

- not blood-borne
- occurs in epidemics
- no animal reservoir
- effective vaccine since 1995

Hepatitis A virus (HAV) is a picornavirus .It has a single Serotype

It replicates in the liver, is excreted in bile, and then excreted in the faeces for about 2 weeks before the onset of clinical illness and for up to 7 days

Geographic Distribution of HAV Infection



Anti-HAV Prevalence

- High
- Intermediate
- Low
- Very Low

Modes of HAV transmission

- Faeco-oral route (95%)
 - ==> person-to-person contact
 - ==> contaminated food or water
 - ==> salads and fruits washed in contaminated water
 - ==> contaminated shellfish
- Infected plasma (<5%)
- Sexual route (<5%)

Clinical features

The viraemia causes the patient to feel unwell, with non-specific stage and remain anicteric . An anicteric infection is common in children and confers lifetime immunity

In the developing world, improvements in hygiene have reduced early infection and, paradoxically, lead to an increase in symptomatic infection in exposed adults. After 1 or 2 weeks, some patients become jaundiced and symptoms often improve.

Persistence of nausea, vomiting or any mental confusion warrants assessment in hospital. As the jaundice deepens, the urine becomes dark and the stools are pale.

The liver is moderately enlarged and the spleen may be palpable. Occasionally, tender lymphadenopathy

Hepatitis A - Clinical Features

- Incubation period: Average 30 days
Range 15-50 days
- Jaundice by age group:
 - <6 yrs, <10%
 - 6-14 yrs, 40%-50%
 - >14 yrs, 70%-80%
- Complications: Fulminant hepatitis
Cholestatic hepatitis
Relapsing hepatitis
- Chronic sequelae: None

Hepatitis A

Atypical Features

- **Death is uncommon**
 - Overall mortality rate is 0.14%
 - If age > 40, mortality rate is 1.1%
- **Prolonged cholestasis >3 months**
 - Severe pruritis, fatigue, weight loss, diarrhea
 - May improve with steroids
- **Relapsing hepatitis**
 - Occurs in 6-12% of cases, 4-15 weeks after recovery
- **Extrahepatic manifestations**
 - Rash (14%), arthralgias (11%),
 - Immune complex diseases: leukocytoclastic vasculitis, glomerulonephritis, arthritis, cryoglobulinemia
 - Extremely rare: myocarditis, transverse myelitis, optic neuritis, polyneuritis, aplastic anemia

Investigations

- *Prodromal stage:*

The serum bilirubin is usually normal. A raised serum AST or ALT, which can sometimes be over many thousands, precedes the jaundice.

- *Icteric stage:*

The serum bilirubin reflects the level of jaundice. Serum AST reaches a maximum 1–2 days after the appearance of jaundice, and may rise above 500 IU/L. Serum ALP is usually less than 300 IU/L.

After the jaundice has subsided, the amino transferases may remain elevated for some weeks and occasionally for up to 6 months.

Haematological tests

There is leucopenia with a relative lymphocytosis. Very rarely, there is a Coombs'-positive haemolytic anaemia or an associated aplastic anaemia. The PT is prolonged in severe cases.

Viral markers

- Acute infection is diagnosed by the detection of HAV-IgM in serum by EIA.
- Past Infection i.e. immunity is determined by the detection of HAV-IgG by EIA.

Management

Supportive care in the outpatient setting is usually sufficient, unless persistent vomiting or severe anorexia leads to dehydration and the need for inpatient admission

Hepatitis A Prevention

- **General prevention**
 - Water chlorination
 - Boil water 20 minutes
 - Wash hands
 - Avoid contaminated food
- **HAV Immunoglobulin**
 - Can prevent 85-95% infections if given within two weeks of exposure
 - Household and sexual contacts
 - Day care contacts
 - Common source outbreaks
- **HAV Vaccine**
 - 90-98% successful with one injection, 100% with two injections
 - Protection begins after 1-2 weeks, may last 20 years
 - Give to all of the above
 - Travelers to endemic areas
 - Homosexuals, IV drug abusers
 - Persons with HCV and HBV
 - Military

Prognosis

The prognosis is excellent, with most patients making a complete recovery. The mortality in young adults is 0.1% but increases with age. Death is due to acute hepatic necrosis.

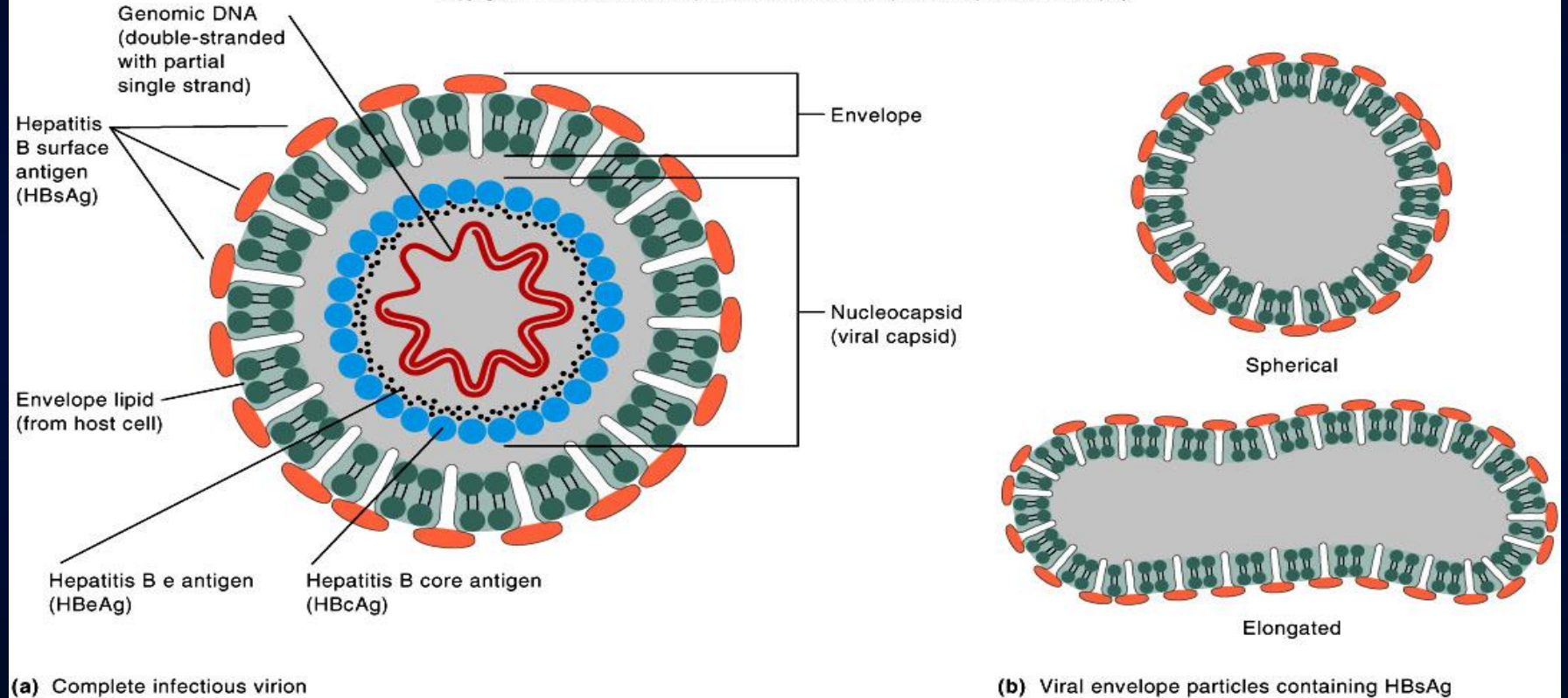
Hepatitis B Virus (HBV)

Hepadnaviridae

- originally called "serum hepatitis"
- epidemiology – major worldwide prevalence and impact
- blood borne transmission
- unique virion structure and biology
 - enveloped particle
 - lipid + HBsAg, nucleocapsid protein, HBcAg
 - circulating HBsAg "Australian antigen" (22nm)
 - incomplete ds DNA genome in particle
 - unique polymerases include a reverse transcriptase

Hepatitis B virus structure

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Hepatitis B Virus

Modes of Transmission

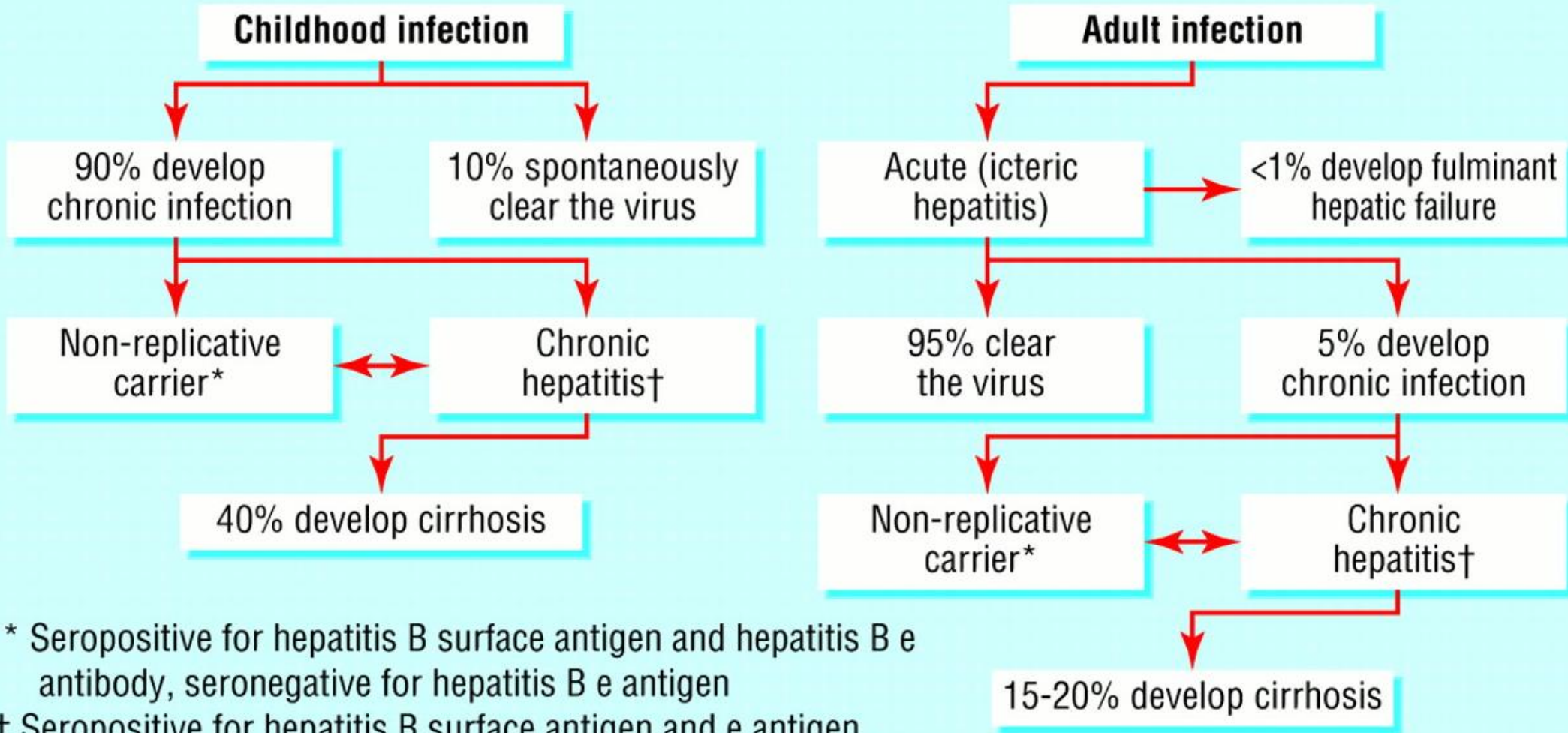
- Sexual - sex workers and homosexuals are particular at risk.
- Parenteral - IVDA, Health Workers are at increased risk.
- Perinatal - Mothers who are HBeAg positive are much more likely to transmit to their offspring than those who are not. Perinatal transmission is the main means of transmission in high prevalence populations.

HBV:

Clinical Features Are Age-Dependent

Incubation period	Average: 60-90 days Range: 45-180 days
Clinical illness (jaundice)	<5 years: <10% >5 years: 30%-50%
Acute case-fatality rate	0.5%-1%
Chronic infection	<5 years: 30%-90% >5 years: 2%-10%
Premature mortality from chronic liver disease	15%-25%

Natural History



* Seropositive for hepatitis B surface antigen and hepatitis B e antibody, seronegative for hepatitis B e antigen

† Seropositive for hepatitis B surface antigen and e antigen, seronegative for hepatitis B e antibody

Clinical Features

- In many cases the infection is subclinical
- When HBV infection is acquired perinatally, an acute hepatitis usually does not occur as there is a high level of immunological tolerance and the virus persists in over 90%
- If there is an acute clinical episode the virus is usually cleared as there is a good immune reaction
- The clinical picture is the same as that found in HAV infection, although the illness may be more severe
- A serum sickness-like immunological syndrome may be seen, this consists of rashes (e.g. urticaria or a maculopapular rash) and polyarthritits affecting small joints occurring in up to 25% of cases in the prodromal period
- Fever is usual
- Extrahepatic immune complex-mediated conditions such as an arteritis or glomerulonephritis are occasionally seen

Diagnosis

- A battery of serological tests are used for the diagnosis of acute and chronic hepatitis B infection.
- **HBsAg** - used as a general marker of infection.
- **HBsAb** - used to document recovery and/or immunity to HBV infection.
- **anti-HBc IgM** - marker of acute infection.
- **anti-HBcIgG** - past or chronic infection.
- **HBeAg** - indicates active replication of virus and therefore infectiveness.
- **Anti-Hbe** - virus no longer replicating. However, the patient can still be positive for HBsAg which is made by integrated HBV.
- **HBV-DNA** - indicates active replication of virus, more accurate than HBeAg especially in cases of escape mutants. Used mainly for monitoring response to therapy.

Stages of Chronic HBV

- HBeAG +VE chronic infection(immune tolerant= high PCR , normal enzymes).
- HBeAG +VE chronic hepatitis(immune active= positive PCR , high enzymes).
- HBeAG -VE chronic infection(inactive carrier=-ve PCR,normal enzymes,+ve HBsAG)
- HBeAG -VE chronic hepatitis(= positive PCR , high enzymes)

When to treat chronic HBV?

- HBV DNA by PCR > 2000 iu/ml and /or,
- ALT and AST >1.5 ULN(19 in females and 30 in males) and / or,
- Liver fibrosis $> F1$.
- Compensated and decompensated cirrhosis.
- >30 years old HBeAg +ve with normal ALT, high DNA(immune tolerant) .
- HBeAg +ve or-ve with family history of HCC or cirrhosis or with extrahepatic manifestations

Treatment of chronic HBV

- Pegylated interferon weekly for one year or
- First line antivirals: Daily tablet of Entecavir(0.5,1 mg) or Tenofovir(300mg) or Tenofovir alafenamide (For renal and bone diseases,25 mg) or
- Second lines antivirals: Daily tablet of Lamivudine(100mg) or adefovir(10 mg).

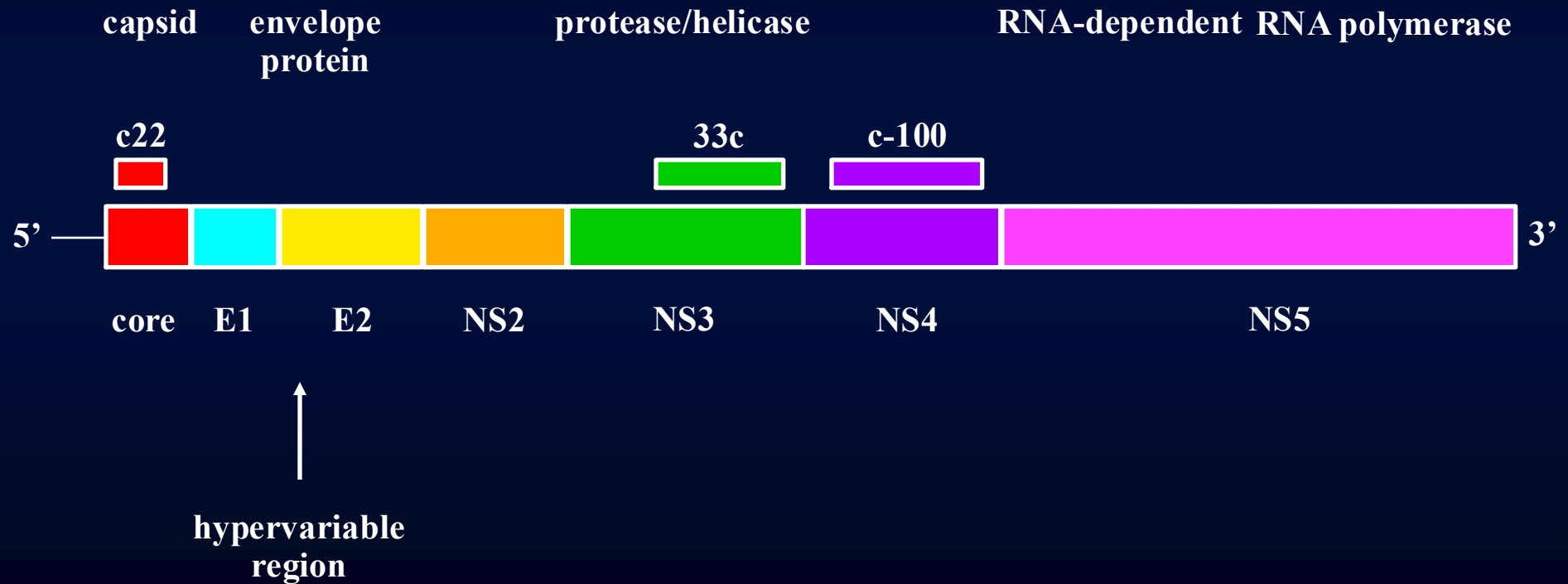
HBV prevention and control

- **highly protective vaccines**
 - HBsAg from serum of carriers (1980's)
 - yeast recombinant HBsAg since 1986
 - recommended for all, especially healthcare and high risk
 - approved combination vaccine for HAV and HBV
- **treatment and control**
 - HBIG hepatitis B immune globulin is protective
 - education of vaccine and avoiding contact with transmitting agents

Hepatitis C Virus (HCV)

- **major cause of “nonA, nonB hepatitis”**
 - genome cloned from transfusion-associated hepatitis patients in 1989
 - most common chronic blood borne infection in USA
 - current a diagnostic test for HCV
- **Flavivirus family**
 - ss (-) RNA genome
 - envelope with glycoproteins
 - core protein
 - several nonstructural proteins
 - family of closely related viruses, 6 genotypes, >90 subtypes
 - HCV is not easy to grow in tissue culture

Hepatitis C Virus



Hepatitis C - Clinical Features

Incubation period:	Average 6-7 wks Range 2-26 wks
Clinical illness (jaundice):	30-40% (20-30%)
Chronic hepatitis:	70%
Persistent infection:	85-100%
Immunity:	No protective antibody response identified

Hepatitis C virus
Acute infection

15%

85%

Recovery and
clearance

Persistent infection

Chronic hepatitis

6%

20%

4%

Liver failure

Cirrhosis

Hepatocellular
carcinoma

Extrahepatic Manifestations

Hematologic

cryoglobulinemia
B-cell lymphoma
Plasmacytoma
MALT lymphoma

Autoimmune

Autoantibodies
Thyroiditis
Sjogren's syndrome
ITP

Renal

GN
Membranous GN

Dermatologic

Leukocytoclastic vasculitis
Lichen planus
Porphyria cutanea tarda

Rheumatologic

Inflammatory arthritis

Laboratory Diagnosis

- **HCV antibody** - generally used to diagnose hepatitis C infection. Not useful in the acute phase as it takes at least 4 weeks after infection before antibody appears.
- **HCV-RNA** - various techniques are available e.g. PCR and branched DNA. May be used to diagnose HCV infection in the acute phase. However, its main use is in monitoring the response to antiviral therapy.

Direct Acting Antiviral treatment of chronic HCV

- Protease inhibitors:
Simeprevir(Olyseo), Paritaprevir(Qurevo, Viekera pak), grazoprevir(Zepatier), Glecaprevir(Mavyret), voxilaprevir(Vosevi).
- NS5B Polymerase inhibitors:
Sofosbuvir(Sovaldi, Harvoni, Epclusa, Vosevi), Dasabuvir(Viekera pak).
- NS5A inhibitors:
Ledipasvir(Harvoni), Daclatasvir(Daklinza), Ombitasvir(Qurevo, Viekera pak), elbasivir(Zepatier), velpatasvir(Epclusa, Vosevi), Pibrentasvir(Mavyret).

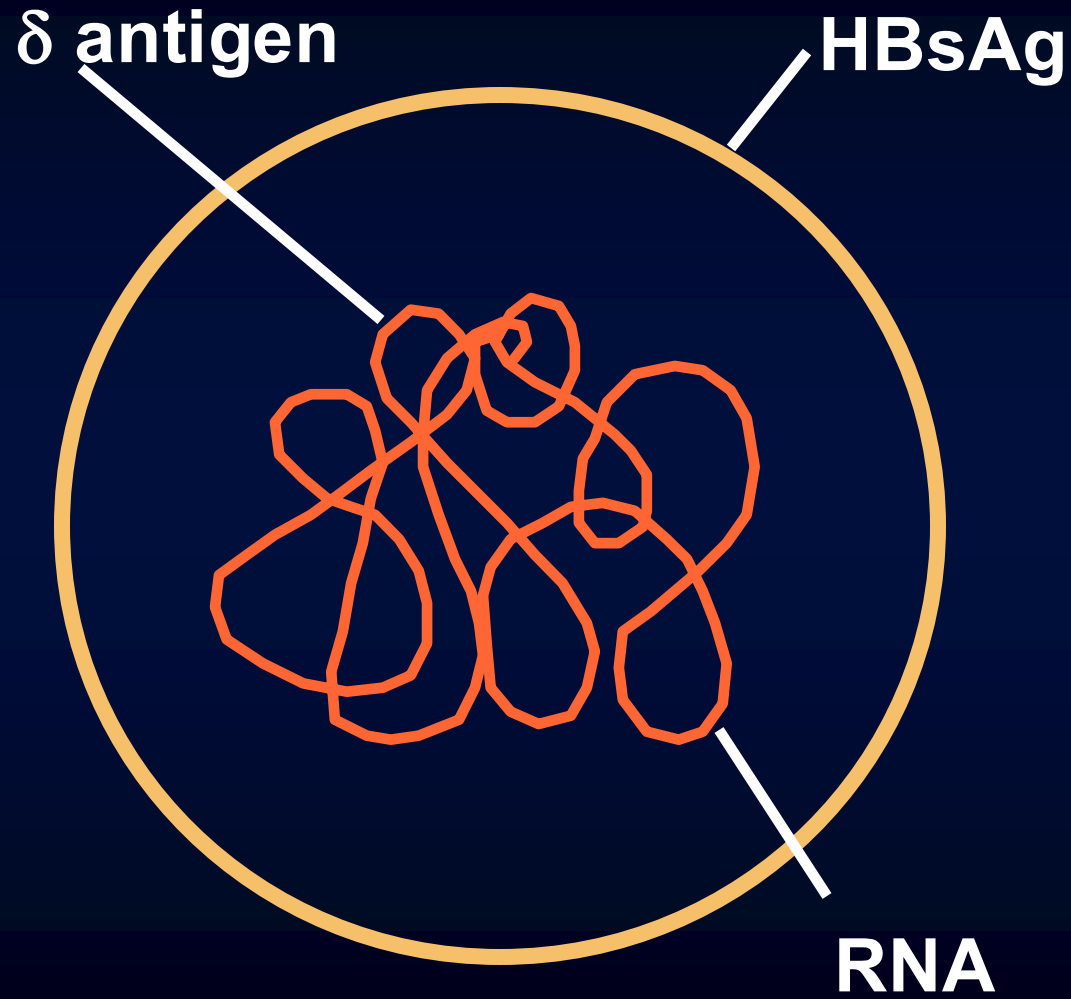
Prevention of Hepatitis C

- Screening of blood, organ, tissue donors
- High-risk behavior modification
- Blood and body fluid precautions

HCV prevention and control

- no vaccine
- diagnosis is important
- transmission means is not always obvious
- milder clinical symptoms than HBV
- major area of study is biology of virus

Hepatitis D (Delta) Virus



Hepatitis D - Clinical Features

- **Coinfection**
 - severe acute disease
 - low risk of chronic infection
- **Superinfection**
 - usually develop chronic HDV infection
 - high risk of severe chronic liver disease

Hepatitis D Virus

Modes of Transmission

- Percutaneous exposures
 - injecting drug use
- Per mucosal exposures
 - sex contact

Treatment of chronic Hepatitis D

- Pegylated interferon alpha

Hepatitis E Virus



-HEV is one of the hepeviruses , spherical non-enveloped ,
positive sense , single stranded RNA

- There are 4 types :

HEV 1 and 2 : restricted to humans and transmitted by
contaminated water. HEV 1 is prevalent in Asia while
HEV 2 is prevalent in Africa and Mexico

HEV 3 and 4 : present in humans and pigs mainly and
transmitted by consumption of raw or undercooked pork

HEV 3 can cause chronic infection i.e >6 months in
immunocompromised patients

Hepatitis E - Clinical Features

- Incubation period: Average 40 days
Range 15-60 days
- Case-fatality rate: Overall, 1%-3%
Pregnant women, 15%-25%
- Illness severity: Increased with age
- Chronic sequelae: None identified

Hepatitis E - Epidemiologic Features

- Most outbreaks associated with fecally contaminated drinking water
- Minimal person-to-person transmission
- U.S. cases usually have history of travel to HEV-endemic areas

HEV can cause extrahepatic manifestations in about 50% of cases especially HEV1 and 3 :

- GBS
- Bells palsy
- Acute transverse myelitis
- Acute meningoencephalitis
- Membrano-proliferative glomerulonephritis
- Acute pancreatitis
- Thrombocytopenia

Complications of HEV

- Fulminant hepatitis in 1-2%
- Mortality rates of 20-25% in pregnancy
- Fetal outcomes : preterm delivery , abortion , stillbirth , intrauterine fetal and neonatal death

TABLE 62-1. Comparative Features of Hepatitis Viruses

Feature	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Common name	"Infectious"	"Serum"	"Non-A, non-B-post-transfusion"	"Delta agent"	"Enteric non-A, non-B"
Virus structure	Picornavirus; capsid, RNA	Hepadnavirus; envelope, DNA	Flavivirus; envelope, RNA	Viroid-like; envelope, circular RNA	<i>Calicivirus</i> -like; capsid, RNA
Transmission	Fecal-oral	Parenteral, sexual	Parenteral, sexual	Parenteral, sexual	Fecal-oral
Onset	Abrupt	Insidious	Insidious	Abrupt	Abrupt
Incubation period (days)	15-50	45-160	14-180	15-64	15-50
Severity	Mild	Occasionally severe	Usually subclinical; 80% chronicity	<i>Co-infection</i> with HBV occasionally severe; <i>superinfection</i> with HBV often severe	Normal patients, mild; pregnant women, severe
Mortality	<0.5%	1%-2%	~4%	High to very high	Normal patients, 1%-2%; pregnant women, 20%
Chronicity/carrier state	No	Yes	Yes	Yes	No
Other disease associations	None	Primary hepatocellular carcinoma, cirrhosis	Primary hepatocellular carcinoma, cirrhosis	Cirrhosis, fulminant hepatitis	None
Laboratory diagnosis	Symptoms and anti-HAV IgM	Symptoms and serum levels of HBsAg, HBeAg, and anti-HBc IgM	Symptoms and anti-HCV ELISA	Anti-HDV ELISA	—

THANK YOU

