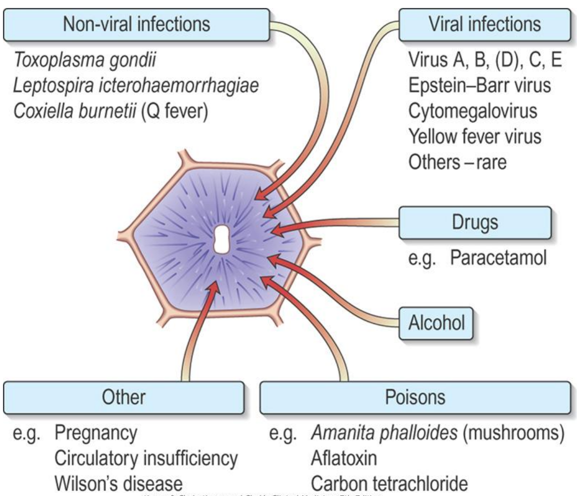
"Acute Viral Hepatitis"

- **Hepatitis :** inflammation of the liver
  - **Infectious types**
    - HAV , HBV , HCV, HDV , HEV
    - EBV , CMV , HSV(not common in immubocompetent patients .)
  - **Non-infectious types**
    - Drug-induced hepatitis
    - Autoimmune &hereditary hepatitis
    - Alcoholic hepatitis

Viral Hepatitis - Overview

Type of Hepatitis

	A	B	C	D	E
Source of virus	feces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	no
Prevention	pre/post-exposure immunization	pre/post-exposure immunization	blood donor screening; risk behavior modification	pre/post-exposure immunization; risk behavior modification	ensure safe drinking water



Diagnosis of hepatitis :

- Patient history
- Physical examination
- Liver function tests
- Serologic test

Symptoms and Signs

Pre-icteric phase (before appearance of Jaundice)	Icteric phase (jaundice appeared)	Post-icteric phase
Anorexia & fatigue	Enlarged Liver,	
Nausea & vomiting	Splenomegaly.	
Arthralgia & myalgia	Discomfort .	
Headache & Photophobia	General adenopathy	
Pharangitis	Tender upper Quadrant. (usually RUQ)	

Lab findings :

1. LFT increase >5-10 times of normal
2. Markers of hepatitis B or C or A might be positive (markers are the most important findings)

Pathological findings

1. Panlobular infiltration with mononuclear cells
2. Hepatic cell necrosis
3. Reticulum framework are intact

Differential Diagnosis :

1. Infectious Mononucleosis (caused by Epstein Bar Virus “EBV” , ruled out by mononucleosis lab tests)
2. Drug Induced Hepatitis (ruled out by exclusion)
3. Chronic Hepatitis.
4. Alcohol Hepatitis
5. Cholecystitis, Cholelithiasis (; gall stone , ruled out by Ultra Sound)

Complications

1. Chronic hepatitis (HBV & HCV) → cirrhosis- HCC " hepatocellular carcinoma"
2. Fulminant hepatitis .

FULMINANT HEPATITIS

- **Definition:** Hepatic Failure Within 8 Weeks Of Onset Of Illness.
- **Manifestation:** Encephalopathy , ascites , decreased albumin and Prolonged PT (Prothrombin time (**PT**) is a blood test that measures the time it takes for the liquid portion (plasma) of your blood to clot.)
- **Histopathology:** Massive Hepatic Necrosis.
- **Rare :** less than 1% of acute hepatitis progress to Fulminant hepatitis .
- **Treatment :** usually needs liver transplantation , if left untreated death rate 50% .

HAV INFECTION

Epidemiology :

- Hepatitis A is the most common type of viral hepatitis occurring world-wide, often in epidemics.
- The disease is commonly seen in the autumn and affects children and young adults
- There is no carrier state.

Pathology :

- It replicates in the liver, is secreted in bile and is then excreted in the faeces of infected persons for about 2 weeks before the onset of clinical illness and for up to 7 days after.
- The disease is maximally infectious just before the onset of jaundice.
- HAV particles can be demonstrated in the feces by electron microscopy.

Hepatitis A Virus Transmission :

- Close personal contact (e.g. household contact , sex contact , child day care centers)
- Contaminated food , water (e.g. infected food handlers)
- Blood exposure (RARE) (e.g. IV drug abusers, rarely by transfusion)

Modes of transmission :

- **Feco-oral rote (95%) :**
  - Person to person contact .
  - Contaminated food or water.
  - Salads and fruits washed in contaminated water.
  - Contaminated shellfish .
- **Infected plasma (<5%)**
- **Sexual rote (<5%)**

Hepatitis A ; Clinical features :

- **Pre-icteric (Viraemia) :**
  - The patient feels unwell with non-specific symptoms (nausea, anorexia and a distaste for cigarettes)
  - Many recover at this stage and remain anicteric.
- **Icteric (jaundice) :**
  - Appears after 1 – 2 weeks .
  - Symptoms often improve
  - Urine becomes dark with pale stools (intrahepatic cholestasis)
  - The liver is moderately enlarged and the spleen is palpable in about 10% of patients
  - Tender lymphadenopathy is seen, with a transient rash in some cases.
- **Post-icteric :**
  - The majority of cases the illness is over within 3-6 weeks

Occurrence of Jaundice by age group :	<6 yrs <10% 6-14 yrs 40-50% >14 yrs 70-80%
Rare complications : Extra-hepatic complications (Rare) :	Fulminant hepatitis Cholestatic hepatitis Relapsing hepatitis Renal Failure Vasculitis Arthritis Myocarditis
Incubation period :	Average 30 days Range 15-50 days

Investigations :

- **Liver biochemistry :**
  - Pre-icteric phase :
    - ✓ Raised serum AST & ALT .
    - ✓ Normal bilirubin .
  - Icteric phase :
    - ✓ Raised serum AST . (reachs the maximum after 2 days from jaundice appearance)
    - ✓ Raised bilirubin.
  - Post-icteric phase :
    - ✓ After the jaundice has subsided, the aminotransferases may remain elevated for some weeks and occasionally for up to 6 months.

- **Haematological tests :**
  - Leucopenia
  - Lymphocytosis
  - Raised ESR (erythrocyte sedimentation time)
  - High PT in severe cases
- **Viral markers ; antibodies to HAV :**
  - Acute HAV infection :
    - ✓ Presence of IgM anti HAV in the serum .
  - Past HAV infection :
    - ✓ Presence of IgG anti HAV in the serum .

Treatment : no specific treatment , usually supportive **.**

Preventing hepatitis A :

- Hygiene (e.g. hand washing)
- Sanitation (e.g. clean water sources)
- Hepatitis A vaccine (pre-exposure)
- Immune globulin (pre- and post- exposure) .

Means to control hepatitis A :

- Provision clear water .
- Proper disposal of feces .
- **Active immunization .**
  - ✓ Inactivated strain of the virus .
  - ✓ Given to : travelers to high prevalence areas , chronic liver disease patients , hemophilia patients , homosexuals and occupational risk .
- **Passive immunization .**
  - ✓ Immunoglobulins.
  - ✓ Given to : close contacts of confirmed cases of HAV to prevent the infection .

HBV infection

Epidemiology :

- HBV is present worldwide .

Modes of Transmission

- Sexual
- Parenteral
- Prenatal

Possible transmission route of HBV in KSA

1- Horisontal transmission (person to person) is the main transmission route
2- Perintal transmission (positive HB_sAG mothers) especially if they are HB_eAG positive (but not by breast feeding) .
3- Heterosexual transmission
4- IV drug abusers.
5- Contaminated equipment used for therapeutic injections and other health care related procedures.
6- Folk medicine practice.
7- Blood and blood products transfusion without prior screening .

Concentration of Hepatitis B Virus in Various Body Fluids

High	Moderate	Low/Not Detectable
blood	semen	urine
serum	vaginal fluid	feces
wound exudates	saliva	sweat
		tears
		breastmilk

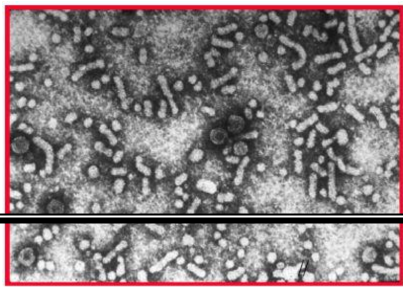
HBV structure :

- Double stranded DNA virus .
- Consist of :

- **Outer surface coat:**

✓ Hepatitis B surface Antigen (HB_SAg)

- circulates in blood as 22-nm spherical and tubular particles
- is the primary component of hepatitis B vaccine; this antigen induces a protective, neutralizing antibody that provides long-term protection against HBV infection.



- **Inner core :**
  - ✓ Double stranded DNA .
  - ✓ DNA polymerase transcriptase .
  - ✓ Hepatitis B core Antigen (HB_CAg).
  - ✓ Hepatitis B e Antigen (HB_eAg)

HBV proteins

HBV protein	Significance
Core	Protein of core particle; kinase activity (role in replication?)
Pre-core (HBeAg)	Pre-core/core cleaves to HBeAg; good marker of active replication and role in inducing immunotolerance
Surface (HBsAg)	Envelope protein of HBV; basis of current vaccine
Pre-S_2 , Pre-S_1	HBV binding and entry into hepatocytes
Polymerase	Viral replication
X protein	Transcriptional and transactivator activity

HBV infection

Factors affecting transmission ability (very important)

1.Replicative status(high viral load)

- HBeAg
- high HBV-DNA

2.Route of infection :

- percutanouse
- Transmucosal

3. Exposure frequency : Single vs. Multiple

4. Inoculums size : transfusion vs. needle stick

Pathogenesis :

1- Attachment: Pre-S_1 and pre-S_2 regions are involved in attachment to an unknown receptor on the hepatocyte.

2- Penetration into the cell,

3- Transportation to the nucleus : the virus loses its coat and the virus core is transported to the nucleus.

4- Transcription of HBV into mRNA :

it takes place by the HBV DNA being converted into a closed circular form (Yc DNA), which acts as a template for RNA transcription.

5- Translation and replication of the genome : takes place in the endoplasmic reticulum
6- Exportation out of the cell to circulation .
- There is an excess production of non-infective HbsAg particles which are extruded into the circulation.

HBV and immunity :

✓ The HBV is **not directly cytopathic** and the liver damage produced is by the cellular immune response of the host.
✓ Viral persistence in patients with a very poor cell-mediated response leads to a **healthy inactive chronic HBV infective state.**
✓ A better response, however, results in continuing hepatocellular damage with the development of chronic hepatitis.

Chronic HBV infection:

- goes through a **replicative** and an **integrated** phase.
- ***replicative phase* :**
- there is active viral replication with hepatic **inflammation**
- the patient is highly infectious with **HBeAg** and **HBV DNA** positivity.
- ***integrated phase :***
- the viral genome becomes *integrated* into the host **DNA** and the viral genes are then transcribed along with those of the host
- . At this stage, the level of **HBV DNA** in the serum is low and the patient is **HBeAg** negative and HBe antibody positive.
- The aminotransferases are now normal or only slightly elevated and liver histology shows little **inflammation**, often with **cirrhosis**.
- **Hepatocellular carcinoma (HCC)** develops in patients with this late-stage disease, but the mechanism is still unclear.

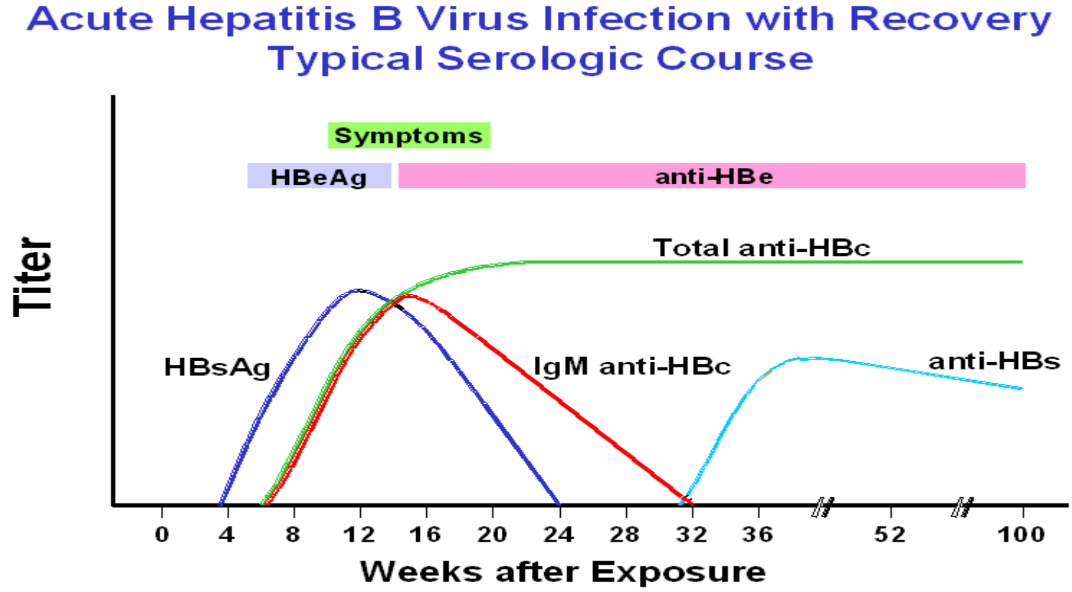
Clinical Features

- The infection is subclinical.
- If there is an acute clinical episode the virus is cleared in approximately 99% of patients 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.

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

Hepatitis B serology

- HBV-DNA→ viral replication.
- Anti-HBc→ exposure (IgM = acute)
- HBsAg → infection (carrier)
- Anti-HBs → immunity
- HBeAg → viral replication
- Anti-HBe → seroconversion
  - ✓ Seroconversion is the development of detectable specific antibodies to microorganisms in the blood serum as a result of infection or immunization
  - ✓ Prior to seroconversion the blood test is *seronegative* for the antibody; after seroconversion, the blood test is *seropositive* for the antibody



Serologic markers of HBV infection vary depending on whether the infection is acute or chronic.

"Very Important "

1- **HBsAg**
- The first serologic marker to appear following acute infection .
- Can be detected as early as 1 or 2 weeks and as late as 11 or 12 weeks (mode, 30-60 days) after exposure to HBV.
- In persons who recover, **HBsAg is no longer detectable in serum** after an average period of about 3 months.

2- **HBeAg :**
- Detectable in patients with **acute** infection
- The presence of HBeAg in serum correlates with higher titters of HBV and greater infectivity.

3- **(IgM anti-HBc)**
- A diagnosis of acute HBV infection can be made on the basis of the detection of IgM class antibody to hepatitis B core antigen in serum
- Detectable at the time of clinical onset and declines to sub-detectable levels within 6 months.

4- **IgG anti-HBc**
- Marker of past infection.

5- **Anti-HBs**
- Detectable during convalescence after the disappearance of HBsAg in patients who do not progress to chronic infection.
- The presence of **anti-HBs** following acute infection generally indicates recovery and

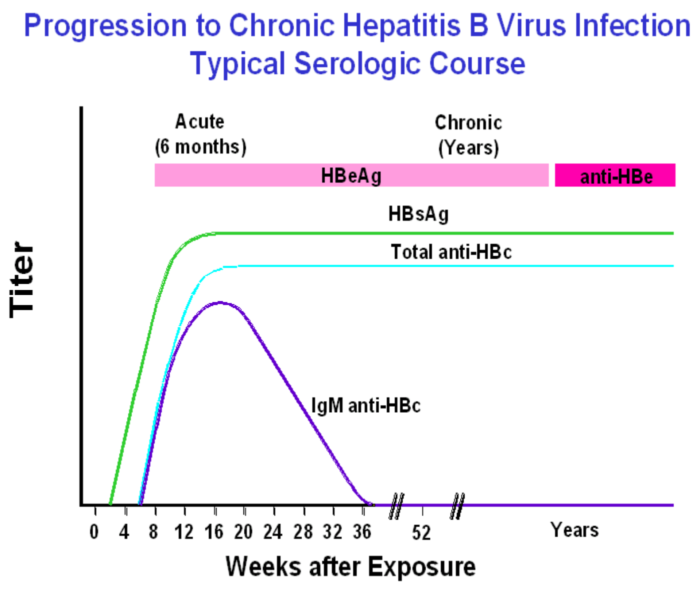
In chronic HBV infection:

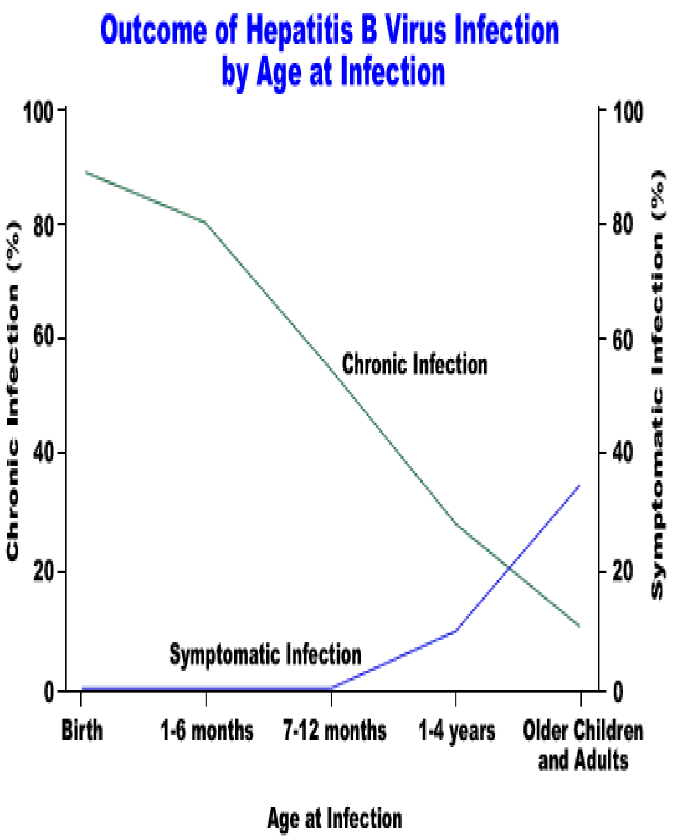
1- **HBsAg** and **IgG anti-HBc** :
- remain persistently detectable, for life.

2- **HBeAg :**
- variably present in chronic HBV infection.

3- **HBsAg** :
- The presence of HB_S Ag for 6 months or more is generally indicative of chronic infection.

4- Negative test for **IgM anti-HBc** together with a positive test for **HBsAg** in a single serum specimen :
- indicates that an individual has chronic HBV infection.





The outcome of acute HBV infection:

It varies substantially depending on the age at which infection occurs.

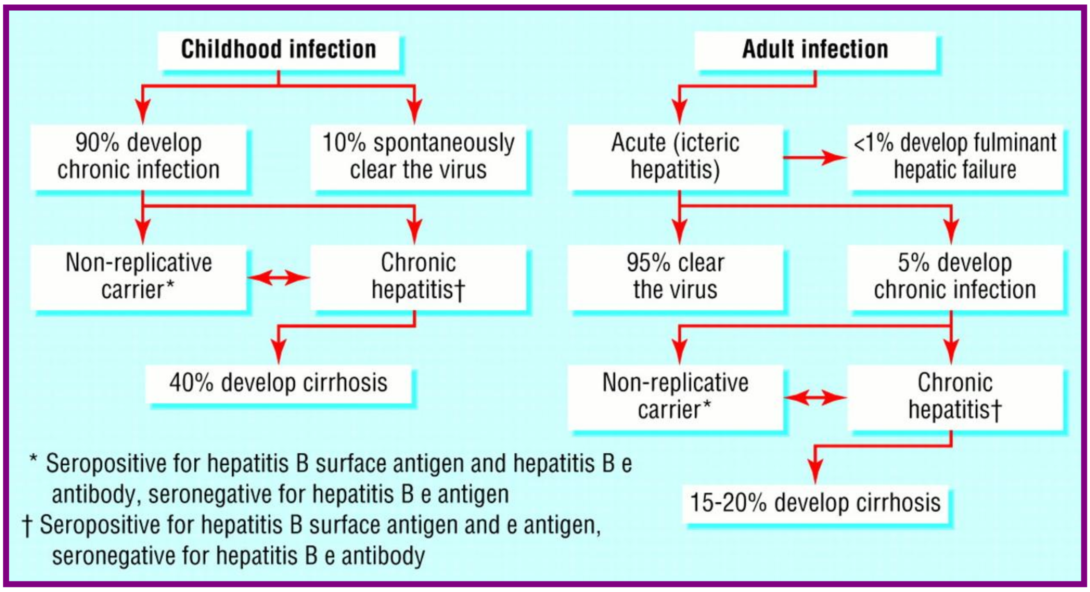
- In **children** less than 5 years of age, <5% of acute HBV infections are symptomatic.
- 30%-50% of **adults** with acute HBV infection are symptomatic, but

- **Who develop chronic infection?**

Children :
- 80%-90% of infants infected during the first year of life
- 30%-50% of children infected between 1-4 years of age.

Adults :
- only 2%-10% develop chronic infection.

Natural History



PREVENTION STRATEGIES OF MINISTRY OF HEALTH IN KSA

- Introducing HBV vaccine in EPI program; and
- Mandatory screening of blood donors and expatriates.
- Vaccination of risk groups.
- Health education especially among medical personnel.

THE CURRENT EPI IN THE KINGDOM OF SAUDI ARABIA

1. **At birth** **BCG +HB1**
2. **At 6 weeks** **DPT1 + OPV1** **Hb2**
3. At 3 months DPT2 + OPV2
4. At 5 months DPT3 + OPV3
5. **At 5months** **Measles** **HB3**
6. At 12 months MMR
7. At 18 months (DPT + OPV) Booster 1
8. At 4-6 years (DPT + OPV) Booster 2

Global Patterns of Chronic HBV Infection

Pattern	lifetime risk of infection	Age group
High (≥8%): 45% of global population	>60%	early childhood infections common
Intermediate (2%-7%): 43% of global population	20%-60%	infections occur in all age groups
Low (<2%): 12% of global population	<20%	most infections occur in adult risk groups

Investigations

- These are generally the same as for hepatitis A.

Course

- The majority of patients recover completely,
- Fulminant hepatitis occurring in up to 1%.
- Some patients go on to develop chronic hepatitis, cirrhosis and hepatocellular carcinoma or have inactive chronic HBV infection .
- The outcome depends upon several factors, including the virulence of the virus and the immunocompetence and age of the patient.

HCV INFECTION

Epidemiology :

- rates as high as 19% in Egypt owing to parenteral antimony treatment for schistosomiasis ,
- EGYPT, mass campaigns of parenteral antischistosomal therapy(discontinued only in the 1980) may represent the WORLD, largest iatrogenic transmission of BLOOD BORNN PATHOGENS **(imp)**
- in blood donors , less than 1% is positive .

Hepatitis C virus (HCV)

- HCV is a single-stranded RNA virus of the Flaviviridae family.
- There is a rapid change in envelope proteins, making it difficult to develop a vaccine

transmission of HCV :

- **Percutaneous**
  - IV drug abusers.
  - Clotting factors before viral inactivation
  - Transfusion, transplant from infected donor
  - Therapeutic (contaminated equipment, unsafe injection practices)
  - Occupational (needle stick)
- **Permucosal**
  - Prenatal
  - Sexual (rare)

Household Transmission of HCV

- Rare but not absent
- Could occur through percutaneous/mucosal exposures to blood
  - Theoretically through sharing of contaminated personal articles (razors, toothbrushes)
  - Contaminated equipment used for home therapies
- ✓ Injections
- ✓ Folk remedies

Sexual Transmission of HCV

- **Occurs, but efficiency is low**
  - Rare between long-term steady partners
  - Factors that facilitate transmission between partners unknown (e.g., viral titer)
- **Accounts for 15-20% of acute and chronic infections in the United States**
  - Sex is a common behavior
  - Large chronic reservoir provides multiple opportunities for exposure to potentially infectious partners
  -

Nosocomial Transmission of HCV

- **Recognized primarily in context of outbreaks**
- **Contaminated equipment**
  - hemodialysis
  - endoscopy
- **Unsafe injection practices**
  - plasmapheresis, phlebotomy
  - multiple dose medication vials
  - therapeutic injections

Prenatal Transmission of HCV

- **Transmission only from women HCV-RNA positive at delivery**
  - Average rate of infection 6%
  - Higher (17%) if woman co-infected with HIV
  - Role of viral titer unclear
- **No association with**
  - Delivery method
  - Breastfeeding
- **Infected infants do well**
  - Severe hepatitis is rare

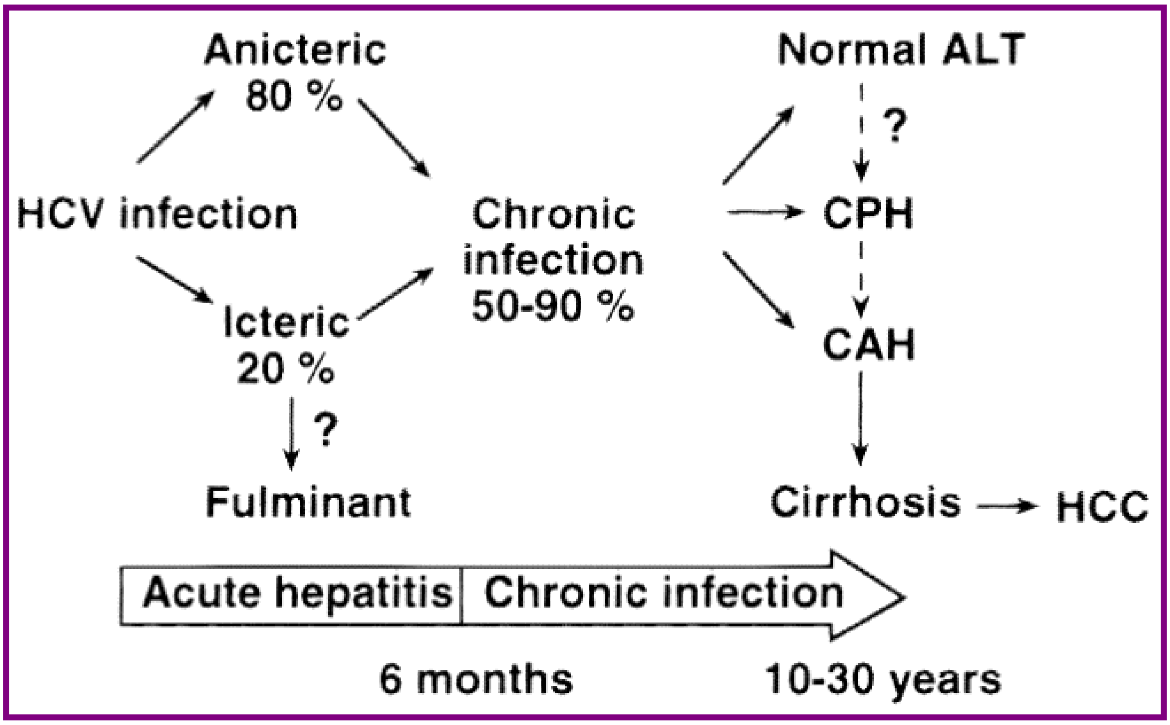
Occupational Transmission of HCV

- **Inefficiently transmitted by occupational exposures**
- **Average incidence 1.8% following needle stick from HCV-positive source**
  - Associated with hollow-bore needles
- **Case reports of transmission from blood splash to eye**
  - No reports of transmission from skin exposures to blood
- **Prevalence 1-2% among health care workers**
  - Lower than adults in the general population
  - 10 times lower than for HBV infection
- **Presence of recognized risk factor does not necessarily equate with "increased risk"**

Prevention Of HCV Transmission

- Avoiding shared use of Razors or brushes and any item that pierces the skin.
- Strict adherence of the universal precautions in health facilities.
- Educating and training of HCW's to the proper use of standard precautions
- Folk medicine

Natural history



Features of Hepatitis C Virus Infection

- Incubation period Average 6-7 weeks

  Range 2-26 weeks

- Acute illness (jaundice) Mild (≤20%)
- Case fatality rate Low
- Chronic infection 75%-85%
- Chronic hepatitis 70% (most asx)
- Cirrhosis 10%-20%
- Mortality from CLD 1%-5%
- Most acute infections are asymptomatic, with about 10% of patients having a mild flu-like illness with jaundice and a rise in serum aminotransferases.
- Most patients will not be diagnosed until they present, years later, with evidence of abnormal transferase values at health checks or with chronic liver disease.
- Extrahepatic manifestations are seen, including arthritis, glomerulonephritis associated with cryoglobulinaemia, and porphyria cutanea tarda.
- There is a higher incidence of diabetes, and associations with lichen planus, sicca syndrome and non-Hodgkin's lymphoma.

Diagnosis

- by exclusion in a high-risk individual with negative markers for HAV, HBV and other viruses.
- A drug cause for hepatitis should be excluded if possible.
- HCV RNA can be detected from 1 to 8 weeks after infection. Anti-HCV tests are usually positive 8 weeks from infection.

Treatment

- **Interferon** has been used in acute cases to prevent chronic disease **(imp)**
- **Note : HAV , HBV are self limiting viruses that do not need treatment , but HCV needs interferon for 3-6 months .**

Course

- 85% to 90% of **asymptomatic** patients develop chronic liver disease.
- A higher percentage of **symptomatic** patients 'clear' the virus with only 48-75% going on to chronic liver disease
- Cirrhosis develops in about 20-30% within 10-30 years and of these patients between 7% and 15% will develop hepatocellular carcinoma.
- The course is adversely affected by co-infection with HBV and/or HIV, and by alcohol consumption, which should be discouraged

☒ Chronic Hepatitis C

Clinical features

- Patients with chronic hepatitis C infection are usually asymptomatic,
- the disease being discovered only following a routine biochemical test when mild elevations in the aminotransferases

Factors Promoting Progression or Severity

- Increased alcohol intake
- Age > 40 years at time of infection
- HIV co-infection
- Other
  - ✓ Male gender
  - ✓ Other co-infections (e.g., HBV)

Summary :

Table 7-5. Some features of viral hepatitis

	A	B	D	C	E
Virus	RNA	DNA	RNA	RNA	RNA
	27 nm	42 nm	36 nm (with HBsAg coat)	approx. 50 nm	27 nm
	Picorna	Hepadna	Deltaviridae	Flavi	Hepevirus
Spread					
Faeco-oral	Yes	No	No	No	Yes
Blood/blood products	Rare	Yes	Yes	Yes	No
Vertical	No	Yes	Rare	Occasional	No
Saliva	Yes	Yes	Yes	? No	?
Sexual	Rare	Yes	Yes (rare)	Uncommon	No
Incubation	Short (2-3 weeks)	Long (1-5 months)	Long	Intermediate	Short
Age	Young	Any	Any	Any	Any
Carrier state	No	Yes	Yes	?	No
Chronic liver disease	No	Yes	Yes	Yes	No
Liver cancer	No	Yes	Rare	Yes	No
Mortality (acute)	< 0.5%	< 1%		< 1%	1-2% (pregnant women10-20%)
Immunization					
Passive	Normal immunoglobulin serum i.m. (0.04-0.06 mL/kg)	Hepatitis B immunoglobulin (HBIg)	No	No	No
Active	Vaccine	Vaccine	HBV vaccine	No	No

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