Liver
• **Function:**

1-**Metabolic**: Glucose
2-**Synthetic**: Albumin, clotting factors .....
3-**Detoxification**: Drugs, hormones, NH3
4-**Storage**: Glycogen, TG, Fe, Cu, vit
5-**Excretory**: Bile
- Net wt. 1400 – 1600gm (2.5% of body wt)
- Blood supply:
  Portal v : 60 – 70%
  Hepatic a : 30 0 40%

- Microstructure
- Hexagonal lobules →6 acini
- Acinus is divided into 3 zones:
  1-Zone 1
  Periportal areas – closet to the vascular supply
  2-Zone 3
  Pericentral area
  3-Zone 2
  Intermediate bet. Zone 1&2
Normal Liver
The parenchyma is organized into plates of hepatocytes.

Hepatocytes are radially oriented around terminal hepatic vein (central v.).

- Hepatocytes show only minimal variation in the overall size but nuclei may vary in size, number & ploidy esp. with advancing age.

- Vascular sinusoids present bet. cords of hepatocytes.
Hepatic injury

1- Inflammation (Hepatitis)

2- Ballooning degeneration:
   - irregularly clumped cytoplasm showing large, clear spaces.
   - Substances may accumulate in viable hepatocytes, including fat, iron, copper, and retained biliary material
3-Steatosis (fatty change)

microvesicular: ALD, Reye syndrome, acute fatty change of pregnancy

macrovesicular: DM, obese
fatty change
4-Necrosis

- Depending on the type:
  Coagulative necrosis: around central v.
  Councilman bodies
  Lytic necrosis

Depending on the cause
Ischemic
Toxic
-depending on location
Centrilobular necrosis:
Mid zonal:
Periportal: interface hepatitis
Focal:
  Piece meal necrosis
  bridging necrosis
Diffuse:
  massive & submassive necrosis
5-Regeneration
-evidenced by increased mitosis or cell cycle markers.
-the cells of the canal of Hering are the progenitor for hepatocytes & bile duct cells (oval cells ).
6-Fibrosis
- *portal or periportal fibrosis*
- pericentral- around the central vein.
- *pericellular fibrosis* or fibrous tissue may be deposited directly within the sinusoids around single or multiple hepatocytes
- *bridging fibrosis*
  bridging fibrosis
7-Cirrhosis
  micronodular
  Macronodular
8-Ductular proliferation
Hepatic Failure

- It results when the hepatic functional capacity is almost totally lost (80 – 90%)

-Causes
1. Massive hepatic necrosis
   - Fulminant viral hepatitis
   - Drugs & chemicals
     acetaminophen
     halothane
     anti TB drugs
     CCL4 poisoning
     Mushroom poisoning

2. Chronic liver disease
3-Hepatic dysfunction without overt cirrhosis
- Reye’s syndrome
- Tetracycline toxicity
- Acute fatty liver of pregnancy
Clinical features
1- Jaundice
2- Hypoalbuminemia → edema
3- Hyperammonemonia
4- Fetor hepaticus (musty or sweet & sour)
5- Palmar erythema
   hyperestrogenemia
6- Spider angiomas
7- Hypogonadism & gynecomastia
Consequences:
1- Multiple organ failure kidneys & lung
2- Coagulopathy → bleeding
def. factors II, VII, IX, X
3- Hepatic encephalopathy
↓level of consciousness
Rigidity
Hyperreflexia
EEG changes
Seizures
Asterixis
4-Hepatorenal syndrome

Renal failure in patients with severe liver disease with no morphologic or functional causes for renal failure
Massive hepatic necrosis

-Fulminant hepatic failure from the onset of symptoms to hepatic encephalopathy (within 2-3 wks).

Subfulminant (within 3 months).

**Causes:**
1- Viral hepatitis 50 – 65% (B, B-D, A,C hepatitis)
2- Drugs & chemicals 20 – 30%
3- Heat stroke
4- Hepatic vein obstruction
5- Wilson disease
6- Acute fatty liver of pregnancy
7- Massive malignant infiltration
8- Reactivation of chronic HBV hepatitis on HDV superimposed infection
9- Autoimmune hepatitis
Alcoholic liver disease

-Alcohol is most widely abused agent
-It is the 5\textsuperscript{th} leading cause of death in USA due to :
  1. accidents
  2. Cirrhosis
-80–100 mg/dl is the legal definition for driving under the influence of alcohol
-44 ml of ethanol is required to produce this level in 70kg person
-Short term ingestion of 80 gms/d of ethanol is associated with fatty change in liver
- In occasional drinkers, bl. Level of 200 mg/dl produces coma & death & resp. failure at 300-400 mg/dl

-Habitual drinkers can tolerate levels up to 700 mg/dl without clinical effect due to metabolic tolerance explained by 5-10X induction of cytochrome P-450 system that includes enzyme CYP2E1 which increases the metabolism of ethanol as well as other drugs as cocaine & acetaminophen
• **Forms of alcoholic liver disease**

1- Hepatic steatosis (90-100% of drinkers)

2- Alcoholic hepatitis (1- 35% of drinkers)

3- Cirrhosis (14% of drinkers)

- Steatosis & hepatitis may develop independently
Hepatic steatosis

- Can occur following even moderate intake of alcohol in form of microvesicular steatosis
- Chronic intake → diffuse steatosis
- Liver is large (4 – 6 kg) soft yellow & greasy
- Continued intake → fibrosis
- Fatty change is reversible with complete absetion from further intake of alcohol
Alcoholic hepatitis

Characteristic findings:
1- Hepatocyte swelling & necrosis
   - Accumulation of fat & water & proteins
   - Cholestasis
   - Hemosidrein deposition in hepatocytes & Kupffer cells

2- Mallory-hayline bodies
   - Easinophilic cytoplasmic inclusions in degenerating hepatocytes formed of cytokeratin intermediate filaments & other proteins
Mallory-hayline bodies
- Mallory-hayline inclusions are characteristic but not pathognomonic of alcoholic liver disease.
- they are also seen in:
  1. Primary biliary cirrhosis
  2. Wilson disease
  3. Chronic cholestatic syndromes
  4. Hepatocellular carcinoma
3-Neutrophilic reaction
4-Fibrosis
   - Sinusoidal & perivenular fibrosis
   - Periportal fibrosis
5-Cholestasis
6-Mild deposition of hemosiderin in hepatocytes & kupffer cells
Alcoholic cirrhosis
- Usually it develops slowly
- It can develop rapidly in the presence of alcoholic hepatitis (within 1-2 yrs).
Ethanol metabolism

Ethanol $\rightarrow$ acetaldehyde

- Alcohol dehydrogenase (stomach + liver)
- Cytochrome P-450
- Catalase (liver)
Acetaldehyde $\rightarrow$ Acetic acid

↑

Aldehyde dehydrogenase
- After absorption ethanol is distributed as Acetic acid in all tissues & fluid in direct proportion to blood level

- Women have lower levels of gastric alcohol dehydrogenase activity than men & they may develop higher blood Levels than men after drinking the same quantity of ethanol.
- less than 10% of absorbed ethanol is excreted unchanged in urine, sweat, and breathe.
- There is genetic polymorphism in aldehyde dehydrogenase that affect ethanol metabolism. 
  e.g., 50% of Chinese, Vietnamese, and Japanese have lowered enzyme activity due to point mutation of the enzyme. → accumulation of acetaldehyde → facial flushing, tachycardia, and hyperventilation.
Clinical features

- **Hepatic steatosis (reversible)**
  - ↑ liver
  - ↑ liver enz.
  - Severe hepatic dysfunction is unusual

- **Alcoholic hepatitis**
  1. 15-20 yr. of excessive drinking
  2. Non-specific symptoms, malaise, anorexia, wt. loss
  - ↑ liver & spleen
  - ↑ LFT
  - Each bout of hepatitis → 10-20% risk of death
    → cirrhosis in 1/3 in few yrs.

- **Cirrhosis**
  - Portal hypertension
• Causes of death in alcoholic liver disease

1- hepatic failure
2- Massive GI bleeding
3- Infections
4- Hepatorenal syndrome
5- HCC in 3-6% of cases
Cirrhosis

- It is a diffuse process characterized by fibrosis & the conversion of liver parenchyma into nodules.
• **Main characteristics**
  1. Bridging fibrous septae
  2. Parenchymal nodules encircled by fibrotic bands
  3. Diffuse architecture disruption
• **Types:**
Micronodules < 3mm in diameter
Macronodules > 3 mm in diameter
Micronodular cirrhosis
Macronodular cirrhosis
Cirrhosis
Causes of cirrhosis

1. Chronic alcoholism
2. Chronic viral infection HBV & HCV
3. Biliary disease
4. Hemochromatosis
5. Autoimmune hepatitis
6. Wilson disease
7. α-1- antitrypsin deficiency
8. Rare causes
Galactosemia
Tyrosinosis
Glycogen storage disease III & IV
Lipid storage disease
Hereditary fructose intolerance
Drug induced e.g. methyldopa

9. Cryptogenic cirrhosis 10%
Pathogenesis of cirrhosis

-The mechanism of cirrhosis involves:
1- Hepatocellular death
2- Regeneration
3- Progressive fibrosis
4- Vascular changes
Cell death should occur over a long period of time & accompanied by fibrosis.

- In normal liver the ECM collagen (types I, III, V & XI) is present only in:
  - Liver capsule
  - Portal tracts
  - Around central vein
-delicate framework of type IV collagen & other proteins lies in space of Disse
-In cirrhosis types I & III collagen & others are deposited in the space of Disse
The major source of collagen in cirrhosis is the perisinusoidal stellate cells (Ito cells) which lie in space of Disse.

Perisinusoidal stellate cells act normally as storage cells for vit A & fat upon stimulation myofibroblast-like cells

\[ \downarrow \]

transforming growth factor $\beta$ (TGF-$\beta$)
The stimuli for the activation of stellate cells & production of collagen are:

1- Reactive oxygen species
2- Growth factors
3- Cytokines  TNF, IL-1, lymphotoxins
-The vascular changes include:
1-Loss of sinusoidal endothelial cell fenestration
2-development of vascular shunts as Portal v - hepatic v
   Hepatic a – portal v
→ defect in liver function
-Loss of microvilli from hepatocytes → ↓ transport capacity of the cells
-Clinical features of cirrhosis:
  - Silent
  - Anorexia, wt loss, weakness

-Complications:
  1. Progressive hepatic failure
  2. Portal hypertension
  3. Hepatocellular carcinoma
Portal hypertension

- ↑ resistance to portal blood flow at the level of sinusoids & compression of central veins by perivenular fibrosis & parenchymal nodules
- Arterial – portal anastomosis develops in the fibrous bands → increase in the blood pressure in portal venous system
Causes of portal hypertension

I. Prehepatic
1. Portal vein thrombosis
2. Massive splenomegaly

II. Post hepatic
1. Severe Rt.-sided heart failure
2. Constrictive pericarditis
3. Hepatic vein outflow obstruction

III. Hepatic
1. Cirrhosis
2. Schistosomiasis
3. Massive fatty change
4. Diffuse granulomatosis as sarcoidosis, TB
5. Disease of portal microcirculation as nodular regenerative hyperplasia
Clinical consequence of portal hypertension

1-Ascitis
2-Portosystemic shunts
3-Hepatic encephalopathy
4-Splenomegaly
Ascitis

- Collection of excess fluid in peritoneal cavity
- It becomes clinically detectable when at least 500 ml have accumulated

**Features**

1. Serous fluid
2. Contains as much as 3g/ml of protein (albumin)
3. It has the same concentration as blood of glucose, Na\(^+\), & K\(^+\)
4. Mesothelial cells & lymphocytes
5. Neutrophils = infection
6. RBCs = DISSEMINATED CANCR
Pathogenesis

1- Sinusoidal ↑ Bp
2- Hypoalbuminemia
3- Leakage of hepatic lymph into the peritoneal cavity
   Normal thoracic duct lymph flow is 800-1000 ml/d
   in cirrhosis is 20L /d
4- Renal retention of Na⁺ & water due to 2ry hyperaldosteronism
Portosystemic shunt

-Because of ↑portal venous pressure bypasses develop wherever the systemic & portal circulation share capillary beds

-Sites:
1-Around & within the rectum (Hemorrhoids)
2-Gastroesophageal junction (varicies )
3-Retroperitoneum
4-Falciform ligament of the liver (periumbilical & abdominal wall collaterals ) → caput medusae

- Gastroesophageal varicies appear in 65% of pts. with advanced cirrhosis & cause death in 50% of then due to UG1 bleeding
caput medusae
Esophageal varicities
Splenomegaly

-Usu. 500-1000 gms (N <300gms)
-Not necessarily correlated with other features of portal ↑Bp
-May result in hypersplenism
splenomegaly
Hepatic encephalopathy

- It is a complication of acute & chronic hepatic failure
- Disturbance in brain function ranging from behavioural changes to marked confusion & stupor to deep coma & death
- The changes may progress over hrs. or days
Neurological signs:

Rigidity
Hyper-reflexia
Non-specific EEG
Seizures
Asterixis (non-rhythmic rapid extension flexision movements of head & extremities).
-Brain shows edema & astrocytic reaction
Pathogenesis

- Physiologic factors important in development of hepatic encephalopathy:
  1. Severe loss of hepatocellular function
  2. Shunting of blood around damaged liver
     ↘
     Exposure of Brain to toxic metabolic products

↑ NH3 level in blood → generalized brain edema impaired neuronal function
alteration in central nervous system AA metabolism
Drug – Induced liver disease

- Drug reactions:
  1. Predictable (intrinsic)
  2. Unpredictable (idiosyncratic)
- Predictable drug reactions depend on the dose (dose-dependent)

- Unpredictable drug reactions depend on:
  a. The immune response of the host to the antigenic stimulus
  b. The rate at which the host metabolizes the agent

- The injury m.b immediate or takes weeks to months

- Drug-induced chronic hepatitis is clinically & histologically indistinguishable from chronic viral or autoimmune hepatitis
Predictable drugs:
Acetaminophen
Tetracycline
Antineoplastic agents
CCL4
Alcohol

Unpredictable drugs
Chlorpromazine
Halothane
Sulfonamides
Methyldopa
Allopurinol
-Mechanism of drug injury:

1-Direct toxic damage
   e.g. acetaminophen
   CCl4
   mushroom toxins

2-Immune-mediated damage
Patterns of injury

1-Hepatocellular necrosis
2-Cholestasis
3-Steatosis
4-Steatohepatitis
5-Fibrosis
6-Vascular lesions
7-Granuloma
8-Neoplasms benign & malignant
Drugs that may cause acute liver failure

1- acetaminophen  most common
2- Halothane
3- antituberculosis drugs (rifampin, isoniazid)
4- antidepressant monoamine oxidase inhibitors
5- toxins as CCL4 & mushroom poisoning
Morphology:
Massive necrosis $\rightarrow$ 500 – 700 gm liver
Submassive necrosis
Patchy necrosis
Infections of Liver

1- Viral infections
   a- I.M   EBV
   b- CMV
   c- Yellow fever
   d- Rubella, herpesvirus
   e- Adenoviruses, enterovirus
   f- Hepatitis viruses  A  B  C  D  E  G

2- Miliary tuberculosis
3- Malaria
4- Staphylococcal bacteremia
5- Salmonelloses
6- Candida
7- Amebiasis
Hepatitis A virus

- Infectious hepatitis
- Benign & self limited
- 25% of clinically evident acute hepatitis
- I.P 15 to 50 days (average 28 days)
- HAV does not cause chronic hepatitis, carrier state & only rarely cause fulminant hepatitis
- Fatality rate is 0.1%
- Superimposed HAV infection on chronic hepatitis due to HBV, HCV or alcohol is more severe
- Transmission: Feco-oral rout
- Endemic in developing countries with low hygiene & sanitation → anti-HAV Abs by the age of 10yrs. → 50% by the age of 50yrs.
- Clinically the disease is mild to asymptomatic affecting children of school age & rare thereafter
- The virus is shed in bile & feces
- The virus is shed is the stool 2-3 wks before & 1wk after the onset of jaundice
- HAV is not shed in saliva, urine, or semen
- HAV viremia is transient & bl. Donors are not screened for the virus
Serologic dx
Anti HAV IgM: at the onset of symptoms → ↓ in few months
Anti HAV IgG: appears later & persists for life
-HAV vaccine is effective
• Detection of anti-HAV IgM antibody is the best diagnostic marker for the disease;
• IgG antibody persists beyond convalescence and is the primary defense against reinfection.
• there are no routinely available tests for IgG anti-HAV, and therefore the presence of this type of antibody is inferred from the difference between total and IgM anti-HAV.
In the United States, the prevalence of seropositivity increases gradually with age, reaching 50% by age 50 years.

Prevention and management of hepatitis A include

1. hygienic measures focused on the disposal of human wastes and personal hygiene
2. passive immunization with immune serum globulin for individuals exposed to the virus or those traveling to high-exposure areas.
3. pre-exposure prophylaxis using a virus-inactivated vaccine.
Hepatitis B Virus

- HBV is a hardy virus can withstand extremes of temperature & humidity
- Prolonged IP 4-26 wks
- Prolonged viremia
- Present in all body fluids as tears, saliva, sweat, breast milk, vaginal sec. semen & pathological body fluids except stool
Routes of transmission

Parenteral  bl. & bl. products
dialysis
needle – stick accidents
IV drug abuse

Homosexual activity

Vertical transmission (20-60% of births to infected mothers)

Unknown source in 1/3 of cases
Contact with body secretions
Epidemiology

Carrier rate: 350 million – 400 million
75% in Asia & Western Pacific

Chronic hepatitis B
> 8% in Asia, Western Pacific
2-7% in Southern & Eastern Europe
< 2% in Western Europe, North America & Australia

-HBV vaccine is effective
Phases of infection:
1. Proliferative phase
2. Integrative phase
HBV antigens:
1. HBc Ag - hepatocytes
2. HBe Ag - blood
3. HBs Ag - blood, hepatocytes
4. DNA polymerase (HBV-DNA) (reverse transcriptase activity)
5. HBx protein (transcriptional transactivator)
Serologic diagnosis

Acute phase lasts from wks-months

HBsAg: appears before the onset of symptoms, peaks during overt disease dissappears in 3 – 6 months

HBeAg:

HBV-DNA, DNA polymerase: appears in serum soon after HBsAg signifies active viral replication & persistent infection
Anti – HBc IgM: appears in serum shortly before the onset of symptoms & replaced by IgG after a month

Anti – HBe Abs: shortly after the disappearance of HBeAg indicating the end of the infection

Anti – HBs IgG: rise after the acute phase is over & remains detectable after wks or months after disappearance of HBsAg
Clinical syndromes associated with HBV infection

1- Acute hepatitis with recovery
2- Nonprogressive chronic hepatitis
3- Progressive chronic hepatitis ending in cirrhosis
4- Fulminant hepatitis with massive liver necrosis
5- Asymptomatic carrier state
Hepatitis C Virus

- The most common chronic blood-born infection & accounts for almost 50% of all patients in USA with chronic liver disease
- Asymptomatic acute hepatitis C occurs in 75% of cases
- l.p 2 – 26 wks
- Carrier rate 0.1 – 12%
Routes of transmission:

Parenteral

- bl. Transfusion 4%
- Inoculation < 5% of cases
- IV drug use 40% of cases
- Sexual transmission low

Perinatal transmission 6% of birth to infected mother

Unknown source 40%
epidemiology

- 40,000 new cases/yr in USA
- 1.8% of the population (4 millions) are seropositive 70% of which have chronic liver disease
- Anti HCV IgG occurring after active infection do not confer effective immunity due to genomic instability of the virus & antigenic variability
- Anti HCV vaccine is not effective
- Repeatd bouts of HCV infection are common causing hepatic damage is characteristic due to reactivation of a pre existing infection or emergence of newly mutated strains
Clinical syndromes associated with HCV:

1. Persistent infection with subclinical or asymptomatic acute infection
2. Chronic hepatitis
3. Fulminant hepatitis
4. Cirrhosis 20%
5. Hepatocellular carcinoma
Serological diagnosis

- I.P 2 – 26 wks (mean 6 – 12 wks)
  HCV RNA is detectable in bl. For 1 – 3 wks
  peak coincides with ↑ in serum transaminases
- Anti HCV Abs detected in 50 – 70% of patients during symptomatic acute infection
  In 30 – 50% of patients the anti HCV Abs emerge after
  3 – 6 wks
- In chronic HCV infection circulating HCV-RNA persists despite the presence of Abs in many patients (> 90%)
  Episodic elevations in serum aminotransferases with intervening normal or near-normal periods is quite
Hepatitis D Virus

- Hepatitis delta virus
- Replication defective virus
- Causes infection only when it is encapsulated by HBsAg
- Routes of transmission:
  Parenteral (close personal contact)
  I.P 4 – 7 wks in superinfection
Epidemiology

Prevalence rate: 20 – 40% in Africa, Middle east & Southern Italy (carriers of HBsAg)

1-10% in USA commonly in drug addicts & hemophils

Low risk in homosexuals & health care workers, HBsAg carriers in south east Asia & China
**SeroLogic diagnosis**

- HDV-RNA is detectable in blood & liver just prior to & in early days of acute symptomatic disease.
- Anti HDV IgM = recent HDV infection.
- Anti HDV IgM appears late & freq. short-lived.
- **Coinfection**: IgM against HDV Ag & HBV Ag.
- **Superimposed infection**: anti HDV IgM & HBsAg.
Hepatitis E virus

- Water-borne infection
- Young – middle – aged adults
- Rare in children
- Endemic infection in India, Africa, Mexico……
- Sporadic infection is uncommon & occurs mainly in travelers
- Self-limiting mild disease except in pregnant women with high mortality rate (20%)
- I.P: 6 wks (range 2-8wks)
- No chronic liver disease or carrier state
Serology

- HEV-RNA can be detected in stool & liver before the onset of clinical symptoms

- Anti HEV-IgM appears during acute illness & replaced by IgG when symptoms resolve (ie in 2 – 4 wks)
Clinicopathologic Syndromes

1- Acute asymptomatic with recovery: serologic evidence only A B C D E

2- Acute symptomatic hepatitis with recovery anicteric or icteric A B C D E

3- Chronic hepatitis with or without progression to cirrhosis B & C

4- Fulminant hepatitis with massive or submassive hepatic necrosis B, D very rare, A & C

5- Chronic carrier state
Acute asymptomatic infection with recovery

- Minimally ↑ serum transaminases
- HAV & HBV infections are freq. subclinical in childhood period
- HCV infection is subclinical in 75% of the cases
Acute symptomatic infection with recovery

- Can be caused by any hepatotropic viruses although it is uncommon in HCV infection

**Phases:**

1. Incubation period
2. Symptomatic preicteric phase
   . Malaise
   . General fatigability
   . Nausea
   . Loss of appetite
   . Fever, headaches, muscle pain, diarrhea
   . 10% of pts. Develop serum sickness-like synd. esp. with HBV infection (fever, rash, arthralgia) due to circulating immune complexes
3-Symptomatic icteric phase

. Usual in adults but not children with HAV

. Absent in 50% of cases of HBV & the majority of HCV

. Conj. hyperbilirubinemia, dark colored urine, pruritis

. Prolonged PT, hyperglobulinemia, ↑ serum alkaline phosphatase
Fulminant hepatitis

Hepatic in sufficiency that progresses from onset of symptoms to hepatic escephalopathy in 2-3 wks

Subfulminant (up to 3 mon)

Causes:
1- Viral hepatitis 50 – 65%
   HBV 2x > HCV
2- Drays & chemical 25-50%
   e.g. Isoniazid, halothane, methyldopa & acetaminophen
3- Obstruction of hepatic vein
4- Wilson’s disease
5- Acute fatty change of pregnancy.
6- Massive tumor infiltration
7- Reactivation of chronic hepatitis B
8- Acute immune hepatitis
• **Morphology**
  - ↓ liver size (500 – 700 gm)
  - Necrosis of hepatocytes
  - Collapsed reticulin tissue
  - Inflammatory infillrate
  - Regenerative activity of hepatocytes
  - Fibrosis
Chronic Hepatitis

-Symptomatic, biochemical or serologic evidence of continuing or relapsing hepatic disease for more than 6 months with histologically documented inflammation & necrosis

-Progressive or non progressive
-HBV , HCV, HBV-HDV
• **Morphology of chronic hepatitis**
  - Mild to severe
    1. Portal inflammation
    2. Lymphoid aggregate
    3. Necrosis of hepatocytes-councilman bodies
    4. Bile duct damage
    5. Steatosis
    6. Interface hepatitis
    7. Bridging necrosis & fibrosis
    8. Fibrosis
    9. Ground-glass appearance
    10. Sanded nuclei
    11. Lobular disarray
Carrier state

1. Serological evidence of viral infection but no clinical or histological effects
2. Serological evidence of viral infection, chronic liver disease but free of symptoms
3. Clinically symptomatic chronic disease

- Vertical transmission → 90 – 95% carrier state
- Immune deficiency ↑ the risk of development of carrier state
- HBV, HCV, ?HDV