JAUNDICE & CHOLESTASIS :

- Jaundice or icterus is yellow discoloration of skin & sclera.
- It occurs due to bilirubin overproduction, hepatitis or obstruction to bile flow, which leads to disturbed equilibrium between bilirubin production & clearance.
- It causes accumulation of bilirubin in tissue & interstitial fluids.
- It becomes visible when bilirubin level > 2 - 3 mg/ dl.

- Bilirubin is derived from ,
  (1) 85% from breakdown of R.B.C.
  (2) 15% from breakdown of nonHb heme protein in liver(e.g. cytochrome p-450)
  (3) Small fraction from lysis of immature R.B.C. in bonemarrow.

BILIRUBIN METABOLISM

- Bilirubin bound to albumin.
  Transported via blood to liver sinusoids.
  Transfer into hepatocytes.
  Intracellular binding to glucuronic acid by UGT
  (Uridine Glucuronyl Transferase)
- CONJUGATED BILIRUBIN (bilirubin glucuronides) :
  Enter bile flow – reaches intestine.
  Converted in stercobilinogen (fecal urobilinogen)
  excreted in stool.
  Small fraction is excreted in urine (urobilinogen).

UNCONJUGATED BILIRUBIN :

- Soluble in lipid.
- Insoluble in water at physiological pH.
- Tightly complexed to albumin.
- Cannot excreted in urine even blood level is high.
- Unbound unconjugated bilirubin may diffuse into tissues especially in brain, producing toxic injury.
- Affinity to brain causing KERNICTERUS in erythroblastosis fetalis.

CONJUGATED BILIRUBIN :

- Water soluble.
- Loosely bound to albumin.
- Non - toxic.
- Excreted in urine due to solubility in water.

CLASSIFICATION OF JAUNDICE :

(A) UNCONJUGATED HYPERBILIRUBINEMIA :

1. Excess production of bilirubin :

① hemolytic anemias

② resorption of blood from internal hemorrhage

(eg. alimentary tract bleeding, hematomas)

③ ineffective erythropoiesis

(eg. Pernicious anemia,thalassemia)

2. Reduced hepatic uptake :

① drug interference with membrane carrier systems

② some cases of Gilbert syndrome

3. Impaired bilirubin conjugation :

① physiological jaundice of the newborn

(↓ed UGT1A1 activity, ↓ed excretion)

② breast milk jaundice (β- glucuronidases in milk)

③ Gilbert syndrome

④ diffuse hepatocellular disease

(eg.viral or drug - induced hepatitis,cirrhosis)

(B) CONJUGATED HYPERBILIRUBINEMIA (Cholestasis):

Failure of bile to reach duodenum ---
Accumulation of bile in hepatocytes & bile canaliculi.

(a) Intrahepatic cholestasis :

Hereditary -

(1) Dubin Johnson
(2) Rotors syndrome.

Acquired -

(1) Viral hepatitis.
(2) Drugs eg. chlorpromazine.
(3) Alcoholic hepatitis.

(b) Extrahepatic cholestasis :

Mechanical obstruction.

(1) Gallstone

(2) Inflammatory stricture

(3) Ca. head of pancreas

(4) Extrahepatic biliary atresia

CHOLESTASIS PROGRESSES TO CIRROSIS.

Most frequent causes of jaundice

- VIRAL HEPATITIS.
- CIRRHOSIS.
- EXTRAHEPATIC BILIARY OBSTRUCTION.
- DRUG REACTION.

VIRAL HEPATITIS

- Primary hepatic infection caused by group of specifically hepatotropic viruses.
- Hepatitis A virus. (HAV)
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- Hepatitis D virus (HDV)
- Hepatitis E virus (HEV)
- Hepatitis G virus (HGV) Not considered pathogenic.

Viral Hepatitis Transmission

Transmission Route	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Food Borne	★	■	■	■	★
Fecal - Oral	★	■	■	■	★
Water Born	★	■	■	■	★
Raw Shelfish	★	■	■	■	●
Intra-Institutional	★	★	★	★	★
I.V. Drug Use	▲	★	★	★	■
Transfusion	▲	★	★	★	▲
Hemodialysis	■	★	★	★	■
Sexual	▲	★	▲	★	▲
Anal- Oral Contact	★	■	■	■	▲
Oral-Oral Contact	★	▲	■	■	●
Household	★	▲	▲	▲	★
Mother to New Born child	▲	★	▲	★	▲

★ Common ▲ Infrequent ■ Never ● Suspected

Hepatitis A Virus

- Produces only acute hepatitis.
- Rarely acute hepatic failure.
- Also called as infectious hepatitis.
- Incubation period – 2 to 6 weeks.
- Benign self- limited disease.
- Viremia transient so transfusion acquired hepatitis does not occur. Therefore donor's blood is not screened for it.
- Virus spread by feco-oral route.

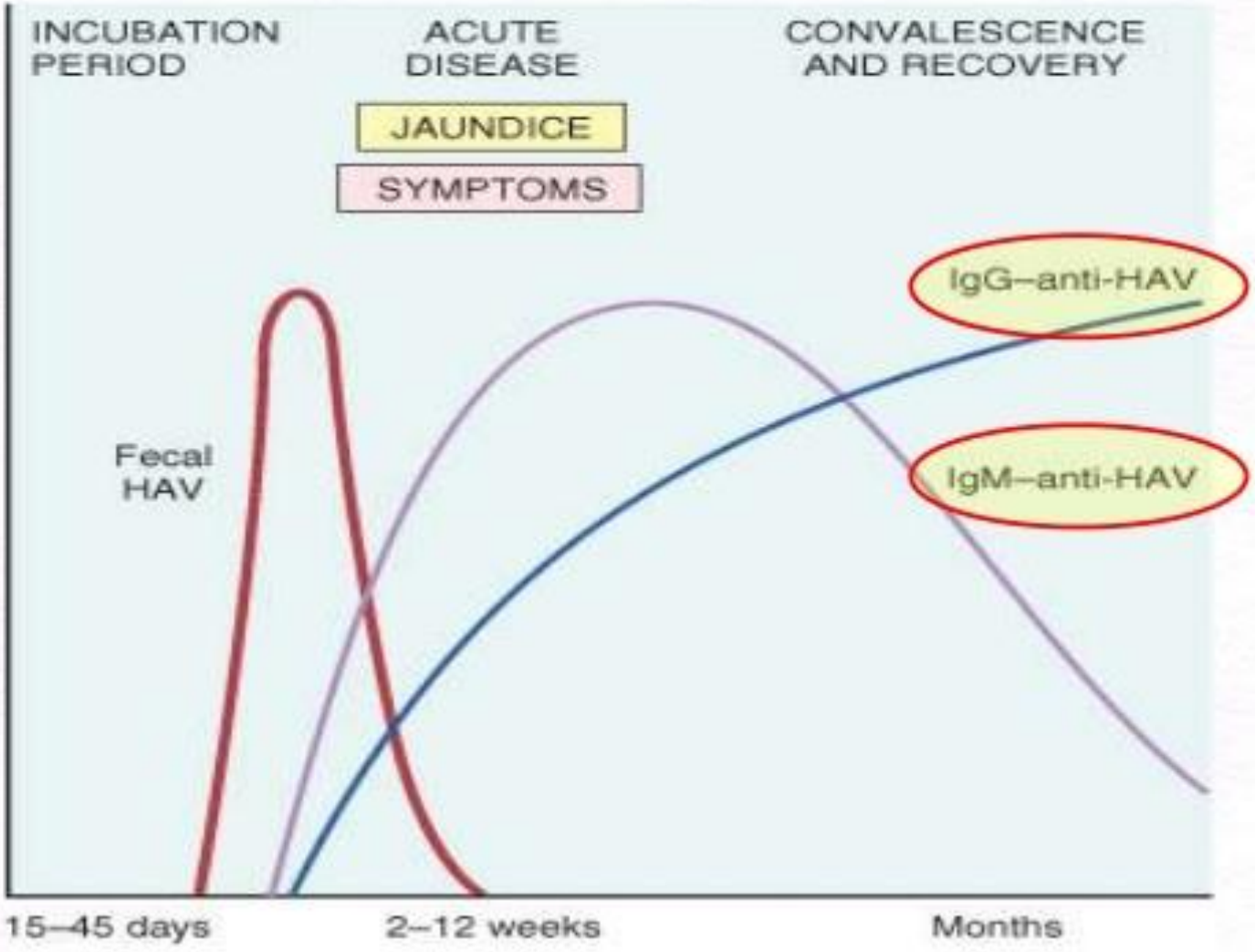
STRUCTURE OF HAV :

- Picorna virus.
- Small nonenveloped single stranded RNA virus.
- E/M : Roughly spherical particle.
- About 27 nm. in diameter.
- Having icosahedral symmetry.

PATHOGENESIS :

- Immunologic mechanism suspected.
- HAV evokes formation of antibodies initially IgM type followed by IgG type.
- IgG antibodies persist for several years confer long term immunity.
- Elevated IgG antibodies do not indicate acute infection only exposure to HAV.
- Diagnostic test of acute hepatitis is IgM Anti-HAV.

Viral Hepatitis A: Serology

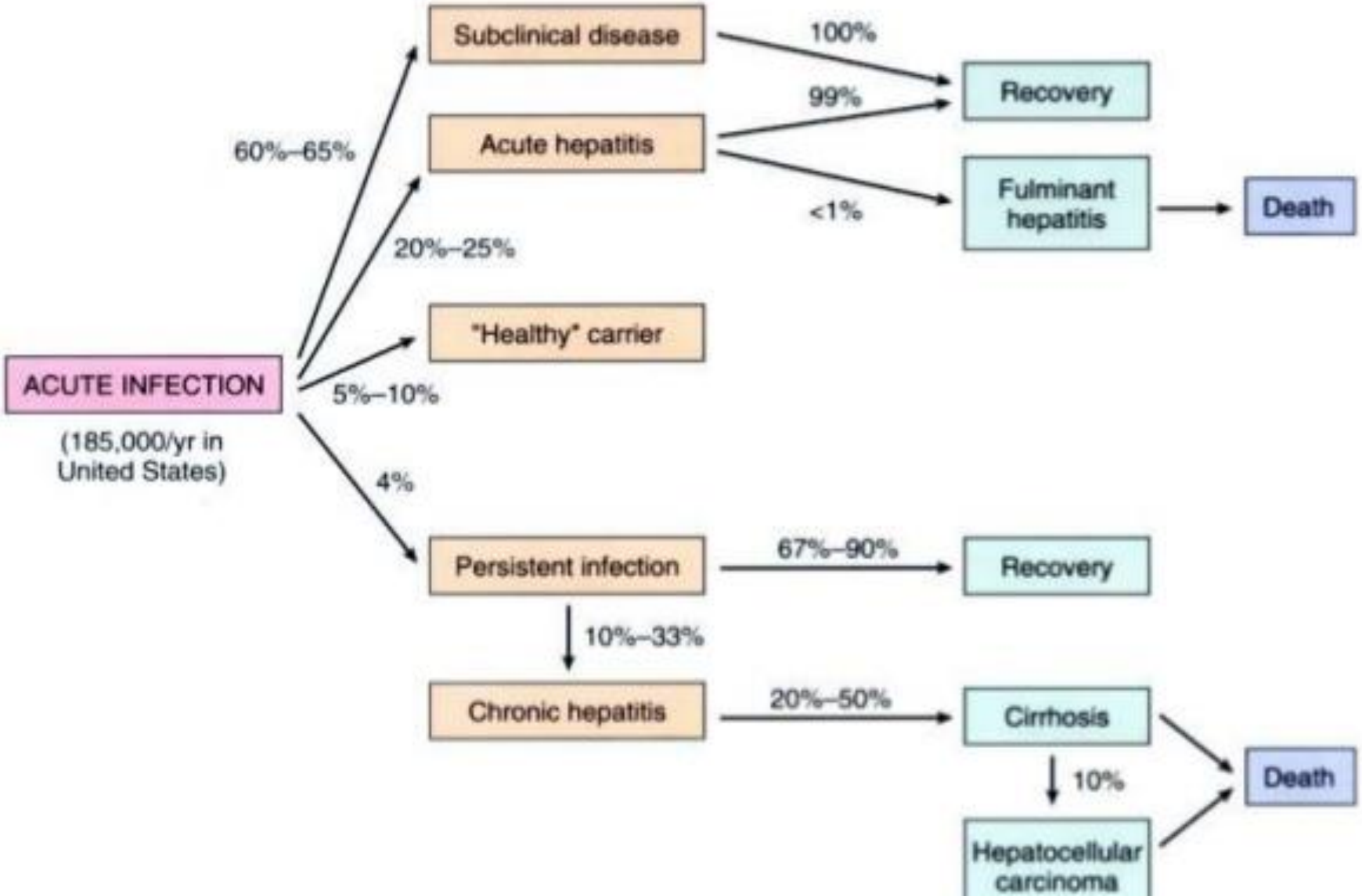


Hepatitis B virus (HBV)

- Asymptomatic , healthy carrier state.
- Acute hepatitis .
- Chronic hepatitis.
- Cirrhosis.
- Acute hepatic failure with massive hepatic necrosis.
- Hepatocellular carcinoma.

  (even in absence of cirrhosis)

Spectrum of disease



Spread of HBV

- Parenterally such as recipients of blood & blood products.
- Intravenous drug abuse.
- Mother to baby (vertical transmission).
- Unprotected sex.
- Patients treated by renal dialysis.
- Hospital workers exposed to blood.
- HBV can withstand extremes of temperature & humidity.

Hepatitis B Virus – Modes of Transmission

From mother to baby (perinatal transmission)

From child to child during play or from an adult to child by contact of body fluids; **(Most common cause in India)**

Unscreened blood transfusions and organ transplant

Through unsafe needles and injections

Through unprotected sexual contact

STRUCTURE OF HBV

- Also called as Dane particle.
- DNA virus Hepadnaviridae family.
- Genome is double stranded circular DNA.
- Virus is spherical-diameter of 42 nm.
- Viral coat made of protein, lipid, carbohydrate gives rise HBsAg (envelope).
- Envelope encloses 28 nm hexagonal core containing

  HBcAg & HBeAg

- HBs Ag 1st discovered by Blumberg in Australian aborigine, so known as Australia antigen.
- envelope glycoprotein (HBsAg) consists of 3 proteins large, middle & small.
- A polymerase (Pol) that exibits both, DNA polymerase & RNA transcriptase activity.
- HBx protein is necessary for viral replication & is responsible for hepatocellular carcinoma in HBV infection.
- HBsAg particle not infectious used to induce protective antibodies(vaccine).

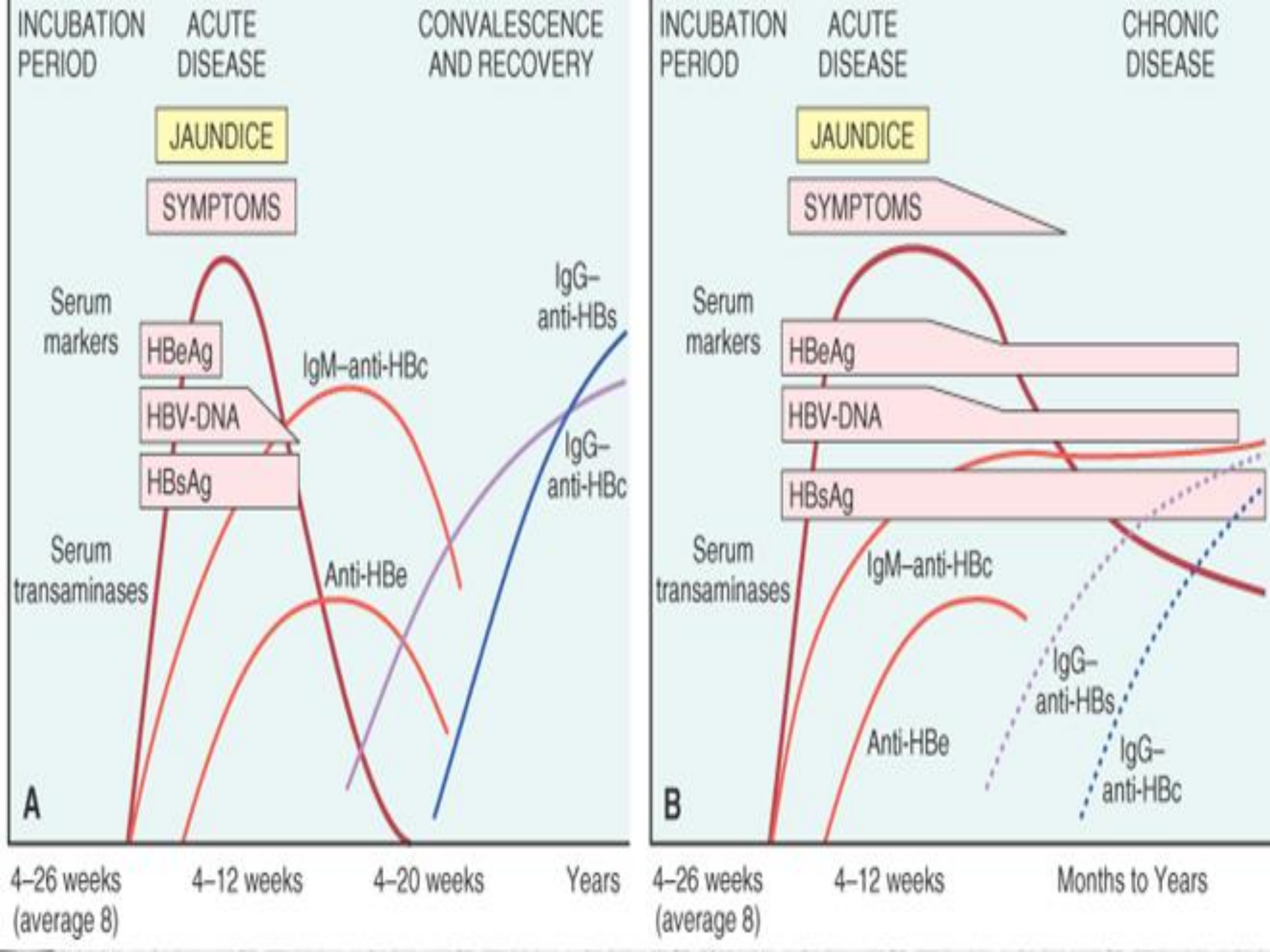
SEROLOGICAL MARKERS OF HBV

- HBsAg 1st appear in blood during incubation period, peaks during overt disease & decline to undetectable level in 12 weeks.
- HBcAg-core antigen never found in serum.

HBeAg, DNA- P, HBV-DNA appear following HBsAg signify active viral replication.

- persistence of HBeAg is an important indicator of continued viral replication, infectivity & progression to chronic hepatitis.

- Anti –HBc : 1st antibody appear at end of incubation period , persist during acute illness & several months to yrs. (valuable diagnostic marker).
- Anti-HBe : appear as HBeAg begins to disappear. It implies that acute infection has peaked & is on the wane.
- Anti-HBs : doesn't rise until acute disease is over concomitant with disappearance of HBsAg.
- In some cases anti-HBsAg is not detected for few weeks to several months after the disappearance of HBsAg.(window period).
- During this period, only IgM anti-HbC is detectable. It persist for life providing protection against reinfection with HBV.


INCUBATION PERIOD
ACUTE DISEASE
CONVALESCENCE AND RECOVERY
JAUNDICE
SYMPTOMS
Serum markers
HBeAg
HBV-DNA
HBsAg
IgM–anti-HBc
IgG–anti-HBs
IgG–anti-HBc
Serum transaminases
Anti-HBe
A
4–26 weeks (average 8)
4–12 weeks
4–20 weeks
Years
INCUBATION PERIOD
ACUTE DISEASE
CHRONIC DISEASE
JAUNDICE
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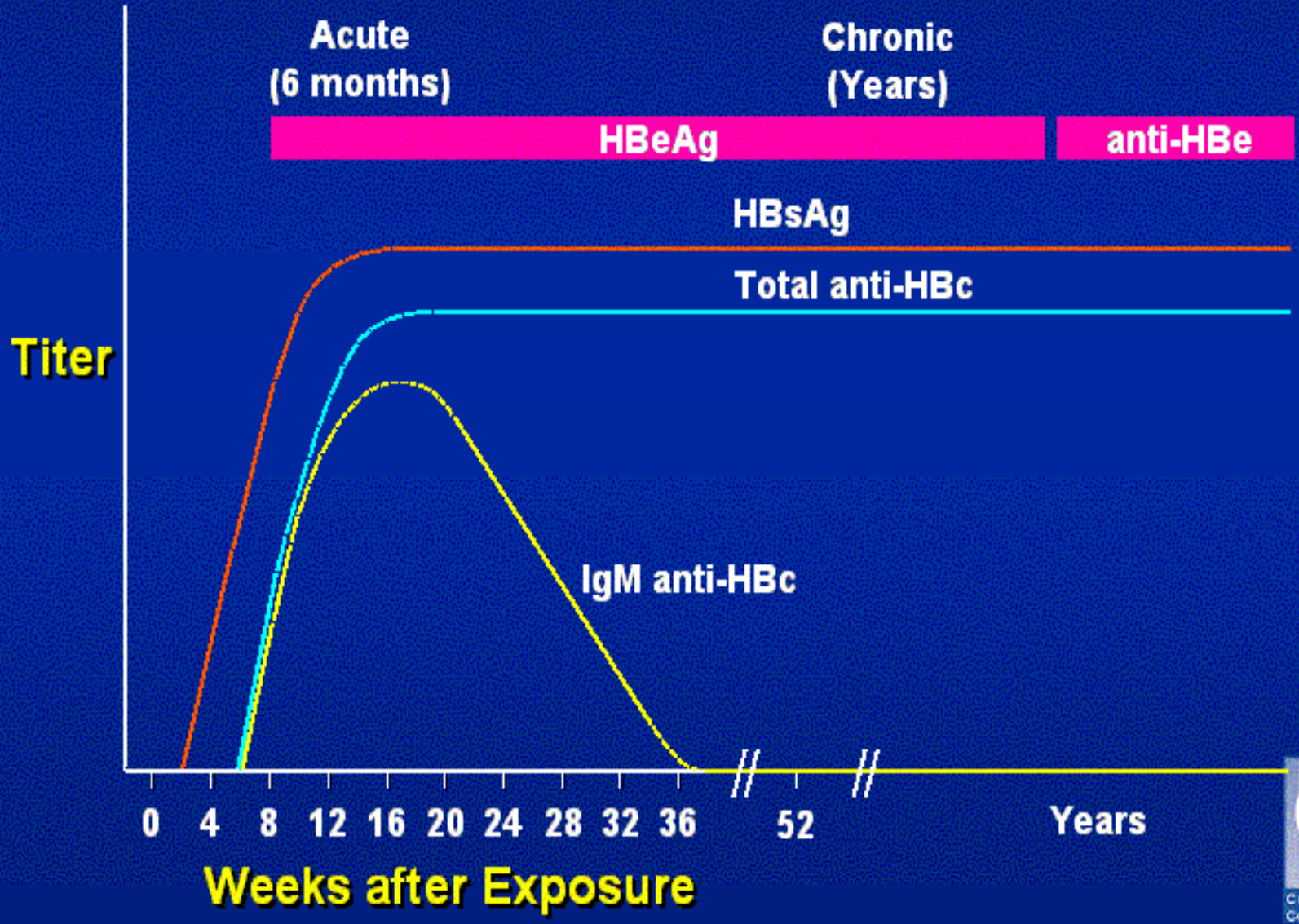
IgM–anti-HBc
IgG–anti-HBs
Anti-HBe
IgG–anti-HBc
B
4–26 weeks (average 8)
4–12 weeks
Months to Years

Progression to Chronic Hepatitis B Virus Infection

Typical Serologic Course



CDC
Centers for Disease Control and Prevention

Interpretation of serological tests in hepatitis B

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Diagnostic Interpretations of Hepatitis B markers

HBsAg	Non infectious component of viral coat	Indicator of disease. If > 6 months: chronic HBV
Anti-HBs	Antibody response to HBsAg	Indicates recovery and/or immunity
HBeAg	Antigen that correlates with replication and infectivity	High level of infectivity and replication
Anti-HBe	Antibody response to HBeAg	Decreasing level of replication Remission/resolution
Anti-HBc IgM	Non protective antibody to the HBcAg	Recent HBV infection
Anti-HBc IgG	As above	Acute or remote exposure to HBV
HBV DNA	Replictative genetic material of HBV; infectious agent	Viral replication and continues infection

PATHOGENESIS :

- Immunologic mechanism.
- Viruses – not directly cytotoxic.
- HBV infection pass thro' two phases.

(1) Proliferative phase :

Constitute viral replication.

Cytotoxic T cell found at the site of liver cell damage.

(2) Integrative phase :

Virions no longer produced.

Viral DNA incorporated in genome of host.

HEPATITIS DELTA VIRUS (HDV)

- HDV : very small defective RNA virus.
- HDAg(delta antigen) is the only protein produced by the virus.
- IgM anti-HDV is the reliable indicator of infection.
- Can replicate & cause infection when encapsidated by HBsAg.
- Delta hepatitis only occur when there is concomitant HBV infection.
- Hepatitis occurs in 2 settings.

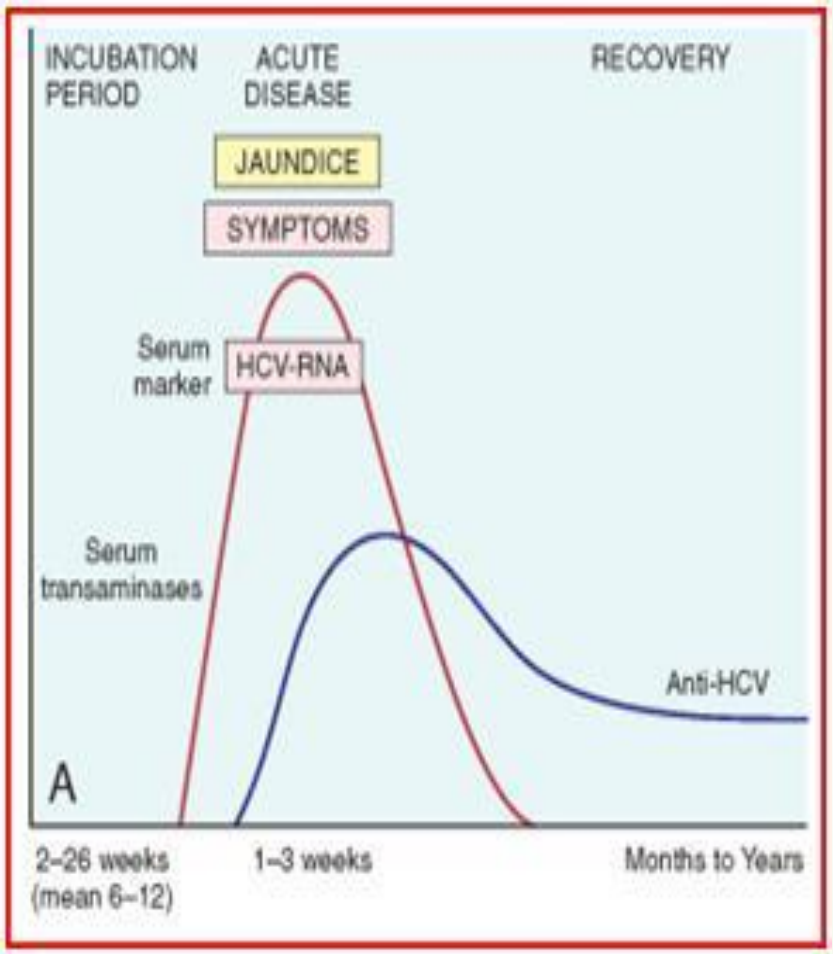
(1) Acute co infection: higher rate of acute hepatic failure in I.V.drug abuser. Both IgM HDV & IgM anti HBcAg are present.

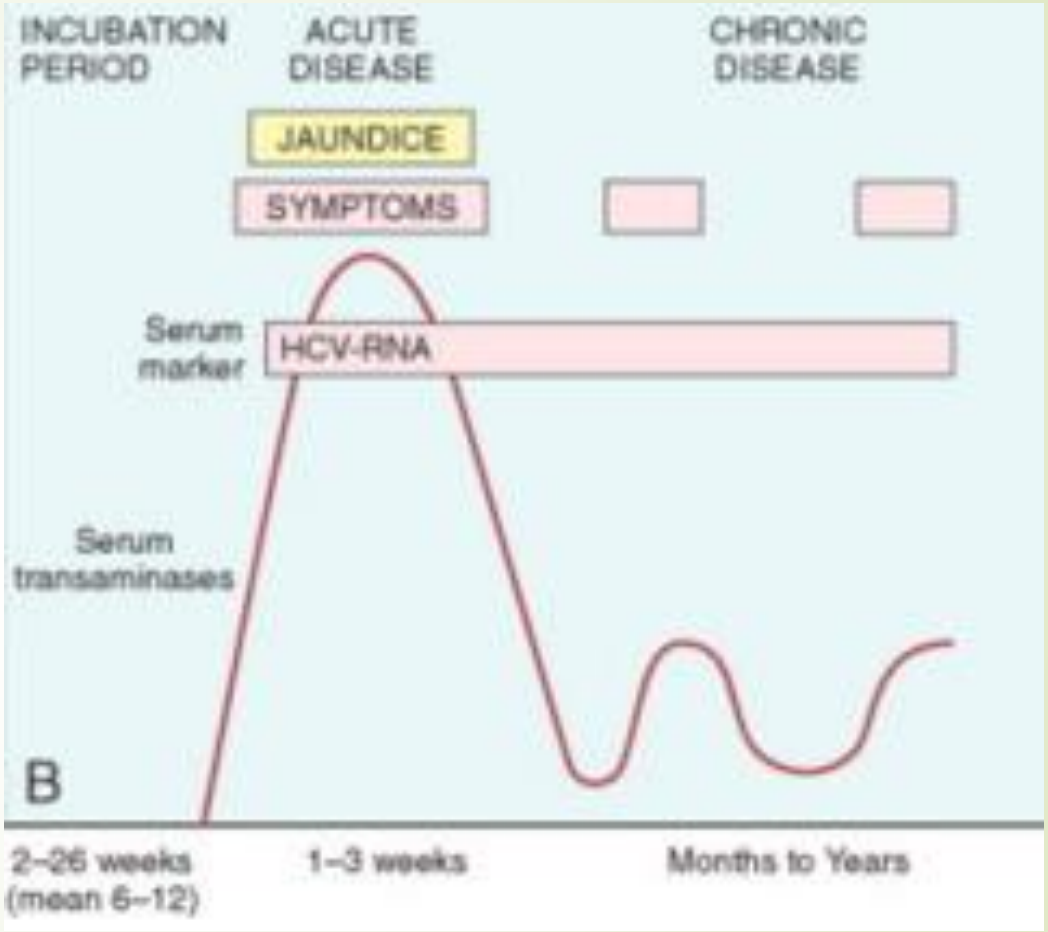
(2) Super infection : HDV infection in chronic carrier of HBV. Anti HDV & HBsAg are present.

HEPATITIS C VIRUS (HCV)

- Causes transfusion associated hepatitis.
- mother to child transmission(vertical transmission) less (6 %) as compare to HBV (20 %)
- High rate of progression to chronic disease or cirrhosis or carcinoma.
- Small enveloped single stranded RNA virus. Flaviviridae family.
- Virus is unstable giving rise to multiple types & subtypes.
- So difficult to develop vaccine.
- Elevated titre of antibody do not confer effective immunity.

- Risk factors for HCV infection are,
  - I.V.drug abuse.
  - multiple sex partners
  - surgery within last six months
  - needle stick injury
  - multiple contacts with HCV infected person
  - employment in medical & dental fields
  - unknown.
- Repeated bouts of hepatic damage due to reactivation of pre-existing infection or emergence of new mutant strain.
- Persistent infection & chronic hepatitis are the hallmarks of HCV infection.


INCUBATION PERIOD
ACUTE DISEASE
RECOVERY
JAUNDICE
SYMPTOMS
Serum marker
HCV-RNA
Serum transaminases
Anti-HCV
A
2–26 weeks (mean 6–12)
1–3 weeks
Months to Years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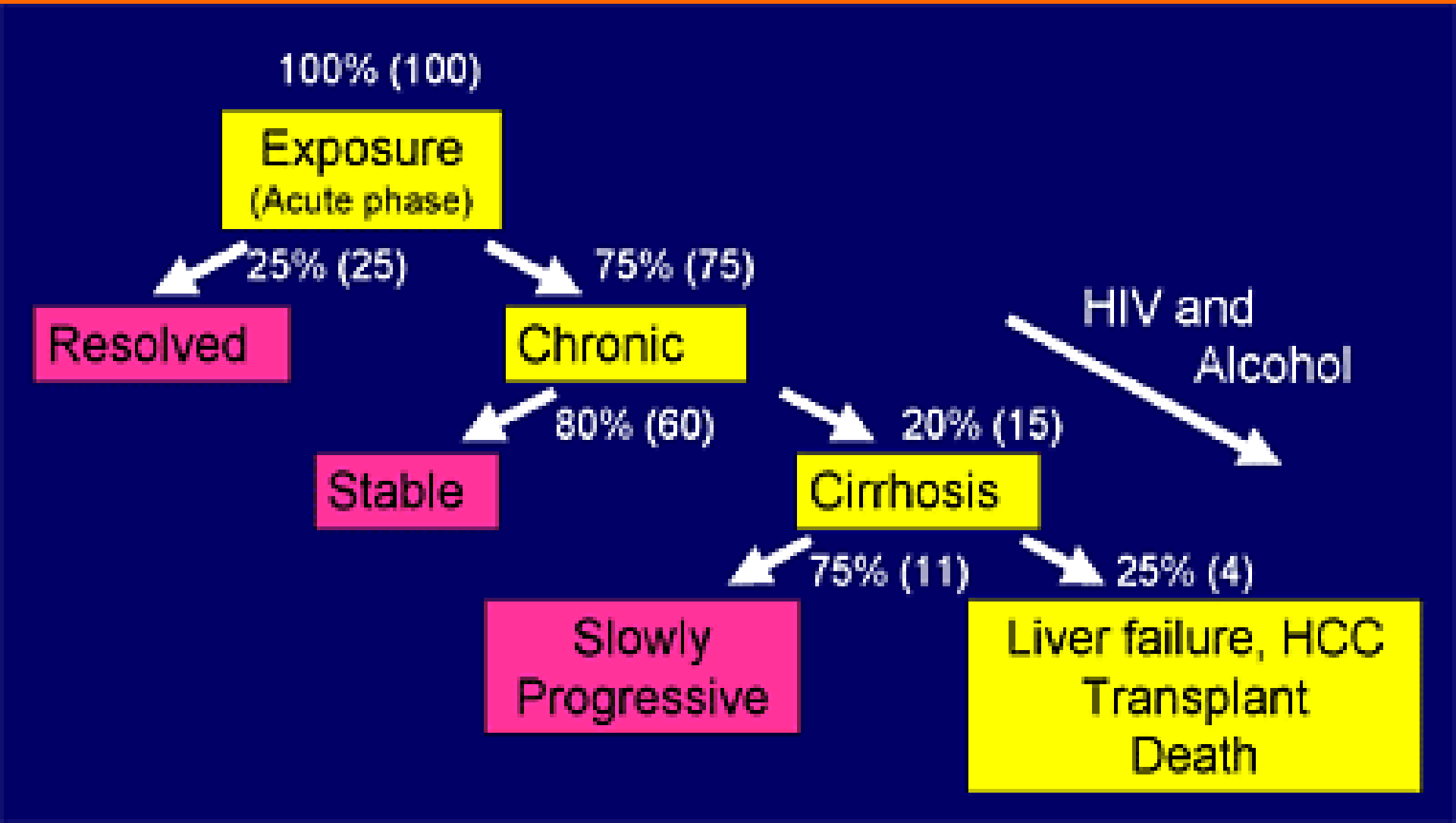
Outcome of Hepatitis C Virus

Medscape® www.medscape.com



HEPATITIS E VIRUS (HEV)

- Share many features of HAV.
- Infection occurs primarily in young to middle aged adults.
- HEV : Hepevirus genus.
- Non enveloped RNA virus.
- Transmission by feco-oral route.
- No risk of subsequent chronic liver disease.(except patient with AIDS or immunosuppressed patients.)
- Causes acute hepatitis.
- High mortality rate in pregnant women (20 %) due to development of fulminant hepatitis.

	Viral Hepatitis A	Viral Hepatitis B	Viral Hepatitis C	Viral Hepatitis D	Viral Hepatitis E
Agent	Hepatitis A virus (HAV); ssRNA	Hepatitis B virus (HBV); dsDNA	Hepatitis C virus (HCV); ssRNA	Hepatitis D virus (HDV); ssRNA	Hepatitis E virus (HEV); ssRNA
Route of Transmission	Fecal-oral	Parenteral, Vertical, Sexual.	Parenteral	Parenteral	Fecal-oral
Age affected	Children	Any age	Adults	Any age	Young adults
Carrier state	Nil	Common	Present	Nil (only with HBV)	Nil
Incubation period	10-50 days (avg. 25-30)	50-180 days (avg. 60-90)	40-120 days	2-12 weeks	2-9 weeks
Chronic infection	No	Yes	Yes	Yes	No
Specific Prophylaxis	Ig and Vaccine	Ig and Vaccine	Nil	HBV vaccine	Nil


Thanks
THANK YOU EVERYONE!