VIRAL HEPATITIS

REFERENCES: HARRISONS INFECTIOUS DISEASE 2ND ED., OXFORD HANDBOOK OF MICROBIOLOGY AND ID

ACUTE HEPATITIS

- An acute inflammation of the liver characterized by hepatocyte damage and elevations in serum AST and ALT.
- May be caused by a variety of infectious and non-infectious agents.

CAUSES

- Viral hepatitis

Hepatitis viruses (HAV,HBC,HCV, HDV, HEV)

Other viruses (EBV, CMV, HSV.,VZV, Measles, Rubella, Adenovirus, Coxsackie, yellow fever)

Non viral infectious diseases

-Leptospirosis, Q fever (*Coxiella burnetti*), sepsis, legionella, TB, Brucellosis, plague (*Yersinia pestis*)

-Drug induced, toxins, alcohol, ischemia, autoimmune, HELLP (hemolysis, elevated liver, low platelet syndrome)

VIRUS	HAV	HBV	HCV	HDV	HEV
FAMILY	PICORNA	HEPADNA	FLAVIVIRUS	DELTAVIRUS	HEPVIRUS
GENOME	RNA	DNA	RNA	RNA	RNA
TRANSMISSION	FECO-ORAL	BLOOD, SEX	MAINLY BLOOD	BLOOD, SEX	FECO-ORAL
PROGNOSIS	GOOD	MOSTLY GOOD (NOT FOR NEONATES)	MAY PROGRESS TO HCC, CIRRHOSIS		MOSTLY GOOD (NOT FOR PREGNANTS)
HCC RISK	NO	YES	YES	YES	NO
CARRIER STATE	NO	YES	YES	*YES	NO

HEPATITIS A VIRUS

- Hepatitis A virus (HAV) is an enterically transmitted picornavirus.
- Outbreaks of infectious hepatitis have been recognized for centuries, but it was first demonstrated in the stool of infected volunteers in 1973.
- HAV is a 27–28nm spherical, non-enveloped virus, upon purification three distinct types are demonstrated:
- Mature virions, Empty capsids or partial genome particles less stable particles with a more open structure.
- The HAV genome is a ssRNA of 7474 nucleotides.
- As with other picornaviruses, the coding region is divided into three parts: P1 (encoding the four capsid proteins VP1–4), P2, and P3 (encoding seven non-structural proteins).
- Four genotypes have been identified; all belong to the same serotype.
- Viral infection of hepatocytes is not cytopathic, but the cytotoxic T-cell response results in cell death.

EPIDEMIOLOGY

- HAV has a worldwide distribution and is associated with overcrowding and poor sanitation, and is endemic in the developing world where it is an infection of childhood.
- Improved hygiene caused reduction in the incidence in children but causes greater susceptibility in adults.
- Main risk groups: occur among homosexuals, IV abusers, and homeless people.
- Other risk groups : children and staff in childcare facilities, patients and staff in mental health institutions, and travelers to endemic areas (Indian subcontinent, Far East, Eastern Europe)
- Transmission is faeco–oral, →community outbreaks have occurred as a result of water or food contamination.

CLINICAL FEATURES

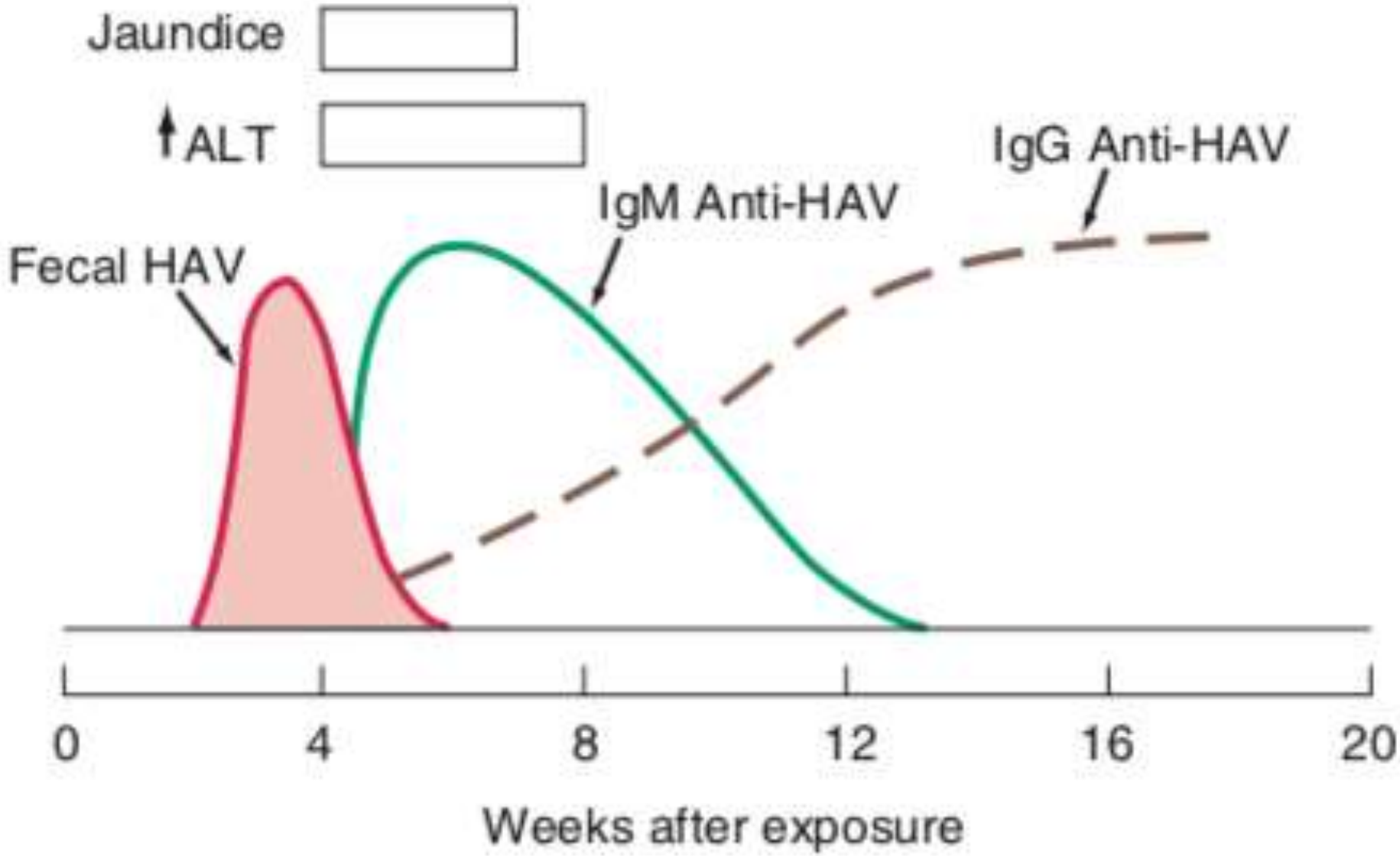
- Incubation period of 4 weeks
  - *Subclinical infection*—common in children (>90% if <5 years of age).
- *Acute hepatitis*—this occurs more frequently with increasing age.
- An abrupt prodrome of fever, headache, malaise, anorexia, vomiting, and right upper quadrant pain is followed <7 days after by dark urine, pruritus, and pale stools. Occasionally, diarrhoea, cough, coryzal symptoms, or arthralgia may occur (commoner in children).
- Physical findings: jaundice, hepatomegaly, splenomegaly (5–15%). People feel better once jaundice appears, which peaks within 14 days.
- *Complications*—include prolonged cholestasis, relapsing disease, fulminant hepatitis (rare, commoner in older patients), extrahepatic disease, and triggering of autoimmune chronic active hepatitis.

Diagnosis

- One serotype (for diagnostic purposes)
- Replication limited to liver, but its present in liver, bile, STOOL, BLOOD during preicteric phase and incubation period
- Once jaundice is apparent infectivity in stool and blood is diminished
- Anti HAV (IgM) antibodies can be detected during acute illness while stool shedding is still present and ALT is high
- These ABs can persist for several months, after convalescence IgG becomes predominant (thus diagnosis is during acute illness)
- IgG Abs provide lifelong immunity

DIAGNOSIS

- LFTs are elevated, with very high aspartate transaminase (AST) and ALT levels.
- Bilirubin and ALP are usually only mildly elevated.
- Serology—detection of anti-HAV IgM confirms the diagnosis and remains positive for 3–6 months.
- It is present at the onset of symptoms.
- Anti-HAV IgG becomes positive at 2–3 months and persists for life.


Jaundice
ALT
IgG Anti-HAV
IgM Anti-HAV
Fecal HAV
0
4
8
12
16
20
Weeks after exposure

TREATMENT

- Acute hepatitis—symptomatic (avoid paracetamol and alcohol); 85% have full clinical/biochemical recovery by 3 months, and nearly all by 6 months.

- Fulminant hepatitis—patients should be treated with supportive therapy and referred for consideration of liver transplantation.
- Fatalities are commoner with advancing age and in those with hepatitis C co-infection.

PREVENTION

- Can be inactivated by boiling for 1 minute, UV light, chlorine, formaldehyde
- Pre-exposure prophylaxis → vaccination (Several inactivated HAV vaccines exist) and these have largely superseded the use of immunoglobulin.
- Two doses of HAV vaccine are given, at 0 and 6–12 months, and provide protection for at least 10 years.
- Indications for immunization include: people at risk; travelers to endemic areas, homosexuals, IV drug users, chronic liver disease, regular recipients of blood products, people that work in high risk institutions (childcare, mental health and military personnel).

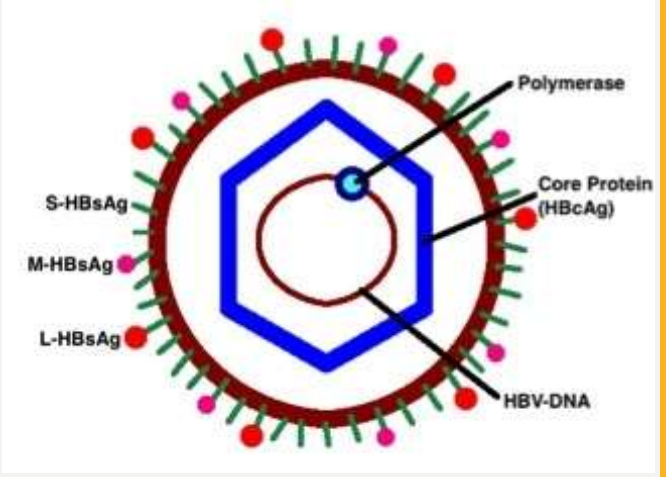
HH

- HEPATITIS B VIRUS

HBV

- HBV; a DNA virus causes acute and chronic viral hepatitis in humans.
- It has a diameter of 42nm, the outer envelope that contains HBsAg proteins, glycoproteins, and cellular lipid.
- Three morphologic forms, nuclear and capsid antigens form antibodies
- Replicate in liver but exists extrahepatically
- Have dsDNA and partial ssDNA

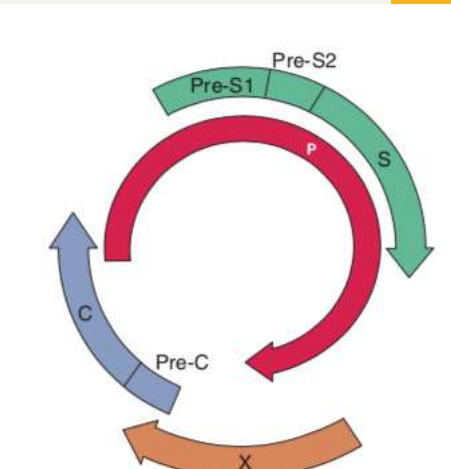
HEPATITIS B VIRUS



- HBsAg proteins may be released from infected cells as small spherical or filamentous particles.
- Beneath the envelope is the internal core or nucleocapsid, which contains hepatitis B core antigen (HBcAg).

  The third antigen HBeAg is a truncated form of the major core polypeptide. It is released from infected liver cells in which HBV is replicating.
- HBV has small compact circular DNA genome with eight genotypes (A–H) and four long (ORFs):
- • C (core/nucleocapsid) gene, encodes HBcAg and HBeAg. Mutations in the pre-core region result in HBV mutants that lack HBeAg;
- S (surface/envelope) gene, which includes the pre-S1, pre-S2, and s regions; encodes HBsAg;
- P (polymerase) gene, encompasses 3/4 of the viral genome, encodes a polypeptide (DNA polymerase with ribonuclease H activity)

  X gene, encodes a polypeptide, with several functions.



EPIDEMIOLOGY

- HBV is a global public health problem ~400 million chronically infected and ~1 million deaths per year.
- Prevalence ranges from 0.1–2% in low-prevalence countries (USA, West EU), 10–20% in parts of China and sub-Saharan Africa.
- Variation reflects differences of age which infection occurs (risk of chronicity is greatest in the very young) (90% for perinatal infections), compared to adults (5% become chronic).
- HBV may be transmitted vertically/perinatally (^ high-prevalence areas), sexually, blood, by IV drug use, by needlestick injury, and horizontally (especially between children in intermediate-prevalence areas).
- Perinatal transmission rates reach 90% in HBeAg-positive mothers the majority occur at or after birth (neonatal vaccination is 95% protective).

CLINICAL FEATURES

- Acute hepatitis—incubation 1–4 months.
- 70% asymptomatic; 30% develop acute hepatitis.

Symptoms include malaise, nausea, abdominal pain, and jaundice.

- Symptoms subside over 1–3 months, but fatigue may persist.
- Fulminant hepatic failure occurs in 0.1–0.5% of acute infections and is thought to be immunologically mediated, rather than directly due to the virus.
- Severe cases of acute disease should be considered for antiviral therapy.

- Chronic hepatitis
- 5–10% of adult acute infections.
- May be asymptomatic for many years.
- Exacerbations of infection may occur, mimicking acute hepatitis or presenting as liver failure.
- Extrahepatic manifestations (immune complex-mediated?) → serum sickness, polyarteritis nodosa, and membranous glomerulonephritis, with most cases seen in children (presents as nephrotic syndrome).

CHRONIC FEATURES,THREE PHASES:

- **Replicative immune-tolerant phase** (perinatal infections only)—high levels of virus (HBeAg-positive) but no hepatitis, normal ALT, and a largely normal liver;
- **Replicative immune clearance**—HBeAg seroconversion may occur, often associated with biochemical exacerbations (due to an increase in immune lysis of infected hepatocytes) which may be misinterpreted as acute hepatitis B.
- **Inactive carrier state (most)** in which liver disease is in remission and patients are HBeAg-negative, anti-HBe-positive, ALT usually normal, although some cases may still have histologically active liver disease.

Several normal ALTs and HBV viral loads over 12 months are required to confirm someone is inactive due to the fluctuating nature of disease.

Some patients have moderate HBV replication and active liver disease but remain HBeAg-negative, some variants cannot produce HBeAg due to pre-core or core promoter mutations. Such patients tend to be older with more advanced liver disease and fluctuations in HBV DNA and ALT.

- A few patients with chronic HBV infection may show delayed clearance of HBsAg (around 0.5–2% patients per year). Some remain HBV DNA-positive.
- Complications of chronic HBV:

End-stage liver disease (15-40 % of cases), hepatocellular carcinoma (HCC).

Disease progression
is associated with HBeAg positivity, high DNA levels, those with prolonged replicative phase, alcohol, and co-infection with HCV or hepatitis D virus (HDV).

DIAGNOSIS = SEROLOGY

- **HBsAg**

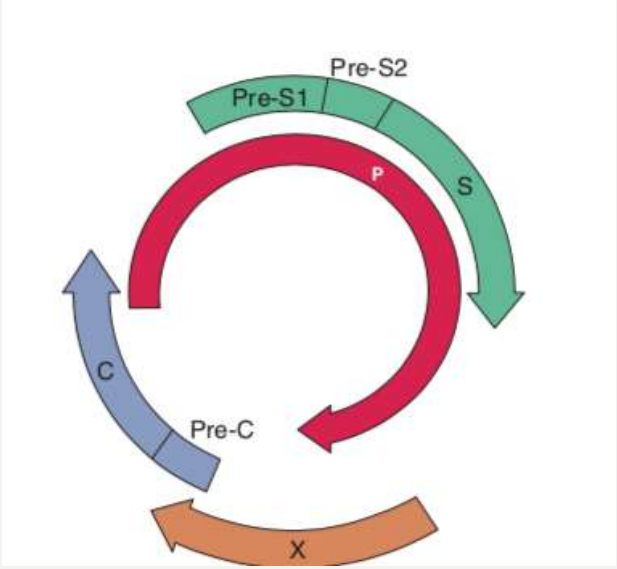
appears 1–10 weeks after acute infection, prior to symptoms.

- Those who clear infection become negative after 4–6 months.
- Positivity beyond this time indicates chronic HBV.
- Its disappearance is followed by the development of anti-HBs antibody.
- A few patients may be positive for HBsAg and anti-HBs, suggesting that the antibody cannot neutralize the virus and patients are therefore carriers.

HBCAG

- an intracellular antigen and not detectable in serum.
- Anti-HBc is predominantly IgM in early infection and may be the only indicator of infection in the window between HBsAg loss and anti-HBs production.
- It may remain for a couple of years, and titers can rise during flares, which may lead to the mistaken diagnosis of acute infection.
- Isolated anti-HBc may be seen in two other situations: many years after recovery from acute HBV (anti-HBs fallen to undetectable levels), many years after chronic HBV (HBsAg fallen to undetectable levels).
- HBV DNA may be detected in the liver of these patients.

HBEAG

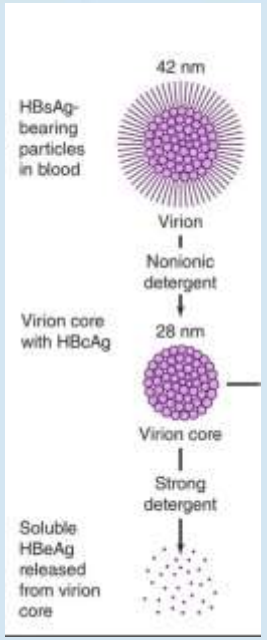


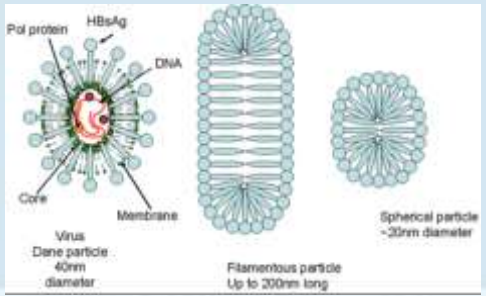
- A secretory protein and marker of HBV replication and infectivity.
- Associated with high levels of HBV DNA.
- HBeAg seroconversion to anti-HBe may be delayed for years in patients with chronic HBV.
- When it occurs, it is usually associated with a decrease in DNA and reduction in liver inflammation.
- Pre-core mutants however, may have active liver disease in the absence of HBeAg.

TABLE 95-1

NOMENCLATURE AND FEATURES OF HEPATITIS VIRUSES

HEPATITIS TYPE	VIRUS PARTICLE, nm	MORPHOLOGY	GENOME[a]	CLASSIFICATION	ANTIGEN(S)	ANTIBODIES	REMARKS
HAV	27	Icosahedral nonenvel-oped	7.5-kb RNA, linear, ss, +	Hepatovirus	HAV	Anti-HAV	Early fecal shedding Diagnosis: IgM anti-HAV Previous infection: IgG anti-HAV
HBV	42	Double-shelled virion (surface and core), spherical	3.2-kb DNA, circular, ss/ds	Hepadnavirus	HBsAg HBcAg HBeAg	Anti-HBs Anti-HBc Anti-HBe	Bloodborne virus; carrier state Acute diagnosis: HBsAg, IgM anti-HBc Chronic diagnosis: IgG anti-HBc, HBsAg Markers of replication: HBeAg, HBV DNA Liver, lymphocytes, other organs
	27	Nucleocapsid core			HBcAg HBeAg	Anti-HBc Anti-HBe	Nucleocapsid contains DNA and DNA polymerase; present in hepatocyte nucleus; HBcAg does not circulate; HBeAg (soluble, nonparticulate) and HBV DNA circulate—correlate with infectivity and complete virions
	22	Spherical and filamentous; represents excess virus coat material			HBsAg	Anti-HBs	HBsAg detectable in >95% of patients with acute hepatitis B; found in serum, body fluids, hepatocyte cytoplasm; anti-HBs appears following infection—protective antibody





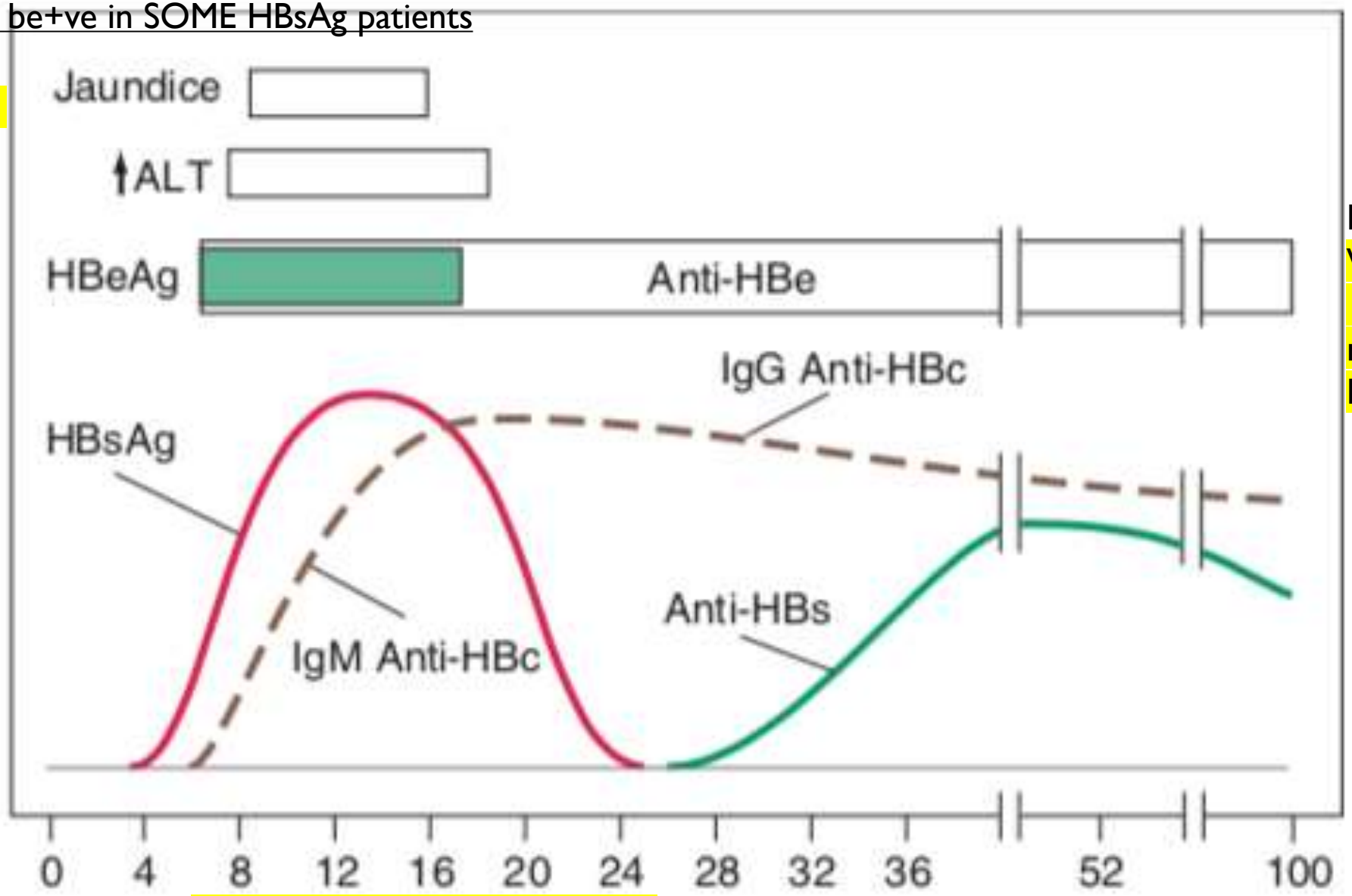
- The outer surface HBsAg , is the envelope protein on of the virion, eight genotypes are identified according to this antigen (genotypes B and C are dominant in Asia, A and D in the US)
- Subtype does not correlate to clinical picture, however genotype B is associated with less rapid progressive liver disease and lower chance or HCC than genotype C
- Genotype A in patients is likely to be cleared (viremia) and patients achieve HBsAg seroconversion (with or without therapy)

- Nucleocapsid core genes forms HBcAg (no signal added, not secreted) or HBeAg (with a signal protein added, secreted) this there are no naked core particles in serum HBcAg (only inside hepatocytes), however the secreted part HBeAg gives a good prediction on replication activity.

- In serum → HBsAg +ve, and HBeAg +ve is highly infectious, thus detectable DNA is expected in this form rather than HBeAg –ve or with HBeABs
- So a mother with HBsAg +ve and HBeAg +ve will >90% transmit HBV to child, HBeAg-ve mothers have 10-15% chance only
- Resolution of HBeAg predict resolution of disease, having it +ve for more than 3 months → chronic state
- Anti-HBs are deemed the protective antibody, as it seems to protect from reinfection, thus susceptiple people are given Anti-HBs for protection

HBcAg is intracellular, thus not found in serum. AntiHBc within 1-2 weeks after HBsAg, and B4 Anti HBs. THUS window c
No HBsAg and AB, we can only detect Anti HBc (this gap can be weeks, errors of blood transfusion).
AntiHBc might be+ve in SOME HBsAg patients

ALT ^ following HBsAG



HBeAg appear
With HBsAg,
refers to high
replication and
DNA.

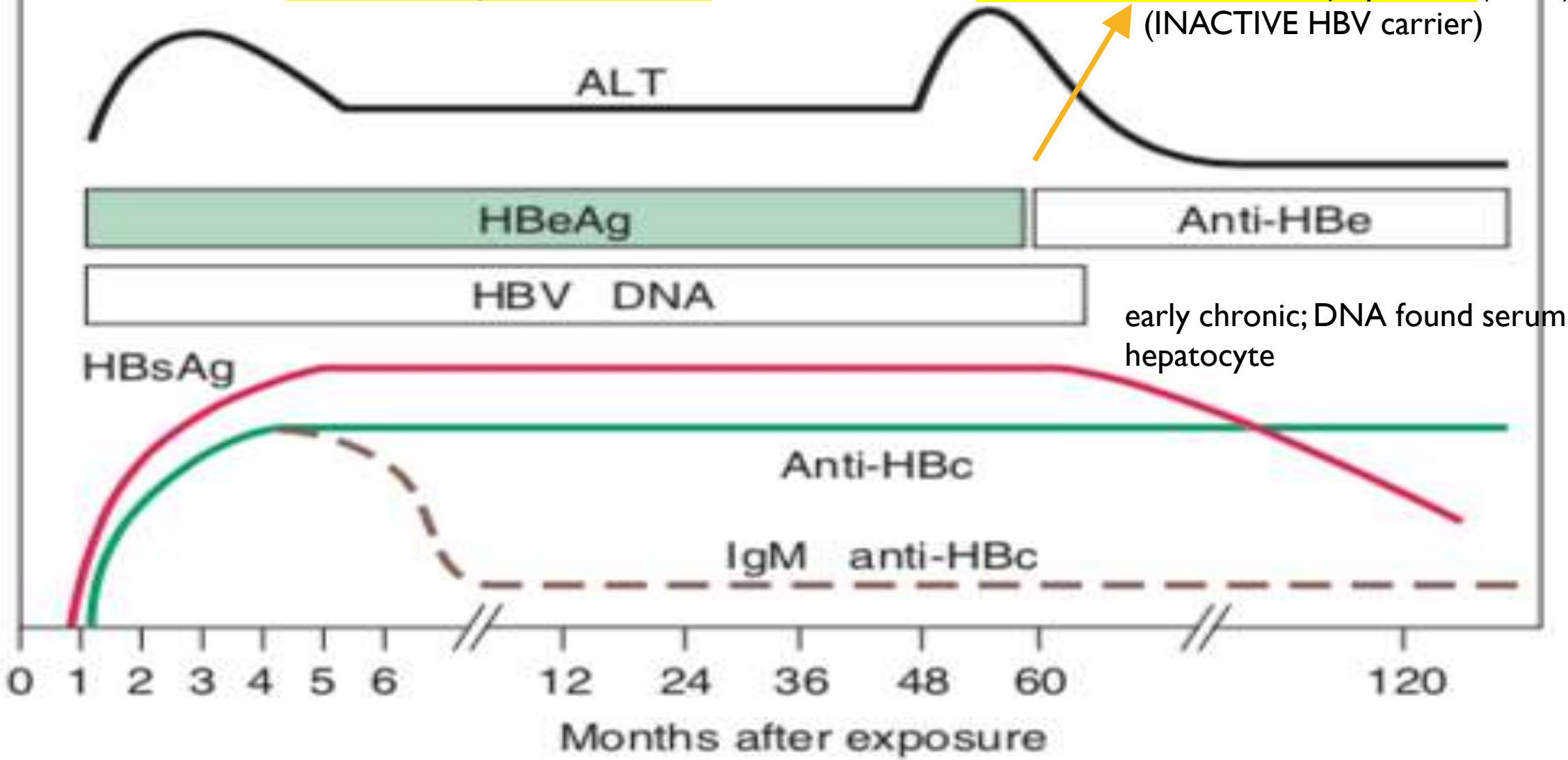
HBsAg as early as 1-2 weeks, detected b4 ALT and symptoms by as much as 2-6 weeks, undetectable after 1-2 mths,
rare after 6, after HBsAg disappears → antiHBs are seen, remain forever

Table 8.3 Diagnosis of hepatitis B virus

	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc IgM	Anti-HBc IgG	HBV DNA
Acute infection	✓		✓				+++
Window					✓		+
Prior infection		✓				✓	
Vaccinated		✓					
Chronic (high infectivity)	✓		✓			✓	+++
Chronic (low infectivity)	✓			✓		✓	±
Pre-core mutant	✓			✓		✓	++

- Chronic HBV → HBsAg remains detectable after 6 months
- → Anti HBc is primarily IgG
- → no or very low Anti HBs

Non (low) replicative phase, 10% per year, coincides With another peak in ALT, unlike replicative phase only spherical and tubular forms, NO intact virions, liver injury is less (v low) (INACTIVE HBV carrier)



early chronic; DNA found serum & hepatocyte

HBV DNA ASSAYS

- Real-time PCR techniques allow quantification of HBV DNA.
- This is useful in determining whether a patient will benefit from therapy, as high levels are associated with cirrhosis and its complications.
- DNA may remain detectable in the serum after recovery from acute infection, suggesting 'clearance' is more about 'control' by the immune system.
- This contrasts with patients who become HBeAg negative during nucleoside/nucleotide therapy who generally have undetectable DNA by PCR.
- Rare cases of occult HBV (detectable DNA, but negative HBsAg, and even absent anti-HBc) have been described—this may be due to mutations leading to altered expression or structure of HBsAg.

OTHER INVESTIGATIONS:

- LFTs, gamma-glutamyl transferase (GGT), clotting, screening for other blood-borne viruses and haemochromatosis, liver biopsy (disease severity).
- Liver biopsy is especially important in those who do not meet treatment criteria but have high HBV DNA, as they may benefit from treatment if the disease is histologically active.
- A normal ALT does not predict mild findings in someone with active viral replication.

TREATMENT

- General:
- avoid alcohol, practice safe sex, hepatitis A vaccination (low-prevalence areas), avoid occupations with high risk of transmission such as surgery, dentistry; HBV immunization of household members, monitor for HCC and varices.
- Treatment
- **Treatment to prevent hepatitis B infection after exposure**
- Exposure with no previous vaccination history → immunoglobulin (AntiHBs) within 12 hours + vaccine
- **Treatment for acute hepatitis B infection**
- Supportive care unless severe cases or patients with underlying illness → antiviral drugs or a hospital stay is needed to prevent complications.
- **Treatment for chronic hepatitis B infection**
- Chronic HBV may require lifelong treatment to reduce risk of complications (HCC, liver failure) also reduce risk of transmission

- **Antiviral medications.** Several antivirals: including entecavir (Baraclude), tenofovir (Viread), lamivudine (Epivir), adefovir (Hepsera) and telbivudine (Tyzeka), all help reduce amount of virus and thus reduce liver damage.
- **Interferon injections.** Interferon alfa-2b (Intron A) mainly used for younger patients hepatitis B who wish to avoid long-term treatment or women who might want to get pregnant (cant be used in pregnancy) within a few years, usually given after a course of antiviral therapy.
- **Liver transplant.** In the event of severe liver damage

PREVENTION

- Education
- Screening of blood products
- Immunization (e.g. HCWs, MSM, close family contacts of an infected individual, those regularly receiving blood products, haemodialysis recipients)
- Post- exposure vaccination (sexual contacts, needlestick recipients, neonates born to infected mothers).
- Hepatitis B immunoglobulin should be given to neonates born to HBsAg-positive mothers (unless anti-HBe positive) and unvaccinated needlestick recipients from HBsAg-positive dono

HEP C VIRUS

- HCV is a spherical, enveloped RNA flavivirus.
- Its genome is a positive ssRNA moleculeCodes for a single gene of large polyprotein (3k aa), cleaved to yield 10 proteins.
- 4 structural proteins, a nucleocapsid protein (C), two envelope glycoproteins (E1, E2), membrane protein (P7).
- Envelope proteins are coded in hypervariable regions, core is conserved.
- At least seven major genotypes (genotypes 1–7) exist, and these may be further grouped into subtypes (e.g. 1a, 1b, 1c).
- Different subtypes predominate in different geographical locations.
- The high replication rate and absence of proofreading by NS5b polymerase result in the rapid accumulation of mutations (multiple quasi-species exist at any one time).

EPIDEMIOLOGY

- HCV infects an estimated 170 million people worldwide.
- In developed countries, HCV prevalence is low (0.5–2%), injecting drug users.
- HCV is commoner in certain areas (Egypt, Japan, Italy) and may be related to reuse of needles for injection, acupuncture, or folk remedies.
- Transmission routes: **transfusion**, **injecting drug use**, nosocomial (needle- sticks, dialysis, inadequate sterilization of colonoscopes).
- Vertical or sexual transmission is rare

PATHOGENESIS

- 15% of people with acute infection clear the virus in 3–24 months
- 85% develop chronic infection.
- HCV-specific cytotoxic T- lymphocyte (cellular) responses play an important role in suppressing HCV RNA levels.
- There is a broad humoral response to HCV epitopes, but these are not sufficient to clear the virus.
- Infection results in hepatic inflammation, steatosis and hepatic fibrosis and HCC (estimated risk 5–25% after 10–20 years).
- Factors associated with cirrhosis include alcohol, HBV or HIV co-infection, HLA B54, HCV genotype 1b, and high levels of HCV viraemia. (Quasi species –high variance in subtypes within same host)

CLINICAL FEATURES

- ***Acute hepatitis C*** → 75% of infections are anicteric (non jaundice)
- Symptomatic infection is similar to acute HAV and HBV, but with lower transaminases. Presents 7–8 weeks (range 2–26) after exposure. If diagnosed early, treatment is appropriate.
- ***Fulminant hepatitis C*** → unusual in the Western countries. Commoner in HBV co-infection. And in 40–60% of cases in Japan.
- ***Chronic hepatitis C*** → 85% of patients, associated with fatigue, malaise, and reduced quality of life indices. ALT levels fluctuate independently of symptoms, whereas HCV RNA levels remain fairly constant. Eventually progresses to cirrhosis, decompensated liver disease, and HCC.
- ***Extrahepatic manifestations*** → essential mixed cryoglobulinaemia, membranoproliferative glomerulonephritis, sporadic porphyria cutaneatarda, Mooren's corneal ulcers, Sjögren's syndrome, lichen planus, pulmonary fibrosis, thyroid hormone abnormalities. (hallmark: autoimmune syndromes)

DIAGNOSIS

Serology

Detection of antibody to recombinant HCV peptides.

Third- generation enzyme linked assays have a sensitivity of ~97% and can detect HCV antibody within 6–8 weeks. The positive predictive value is ~95%, but much lower in low-prevalence populations such as blood donors; thus, confirmatory testing by HCV RNA detection is essential. Immunocompromised patients (including HIV) may have false-negative serology.

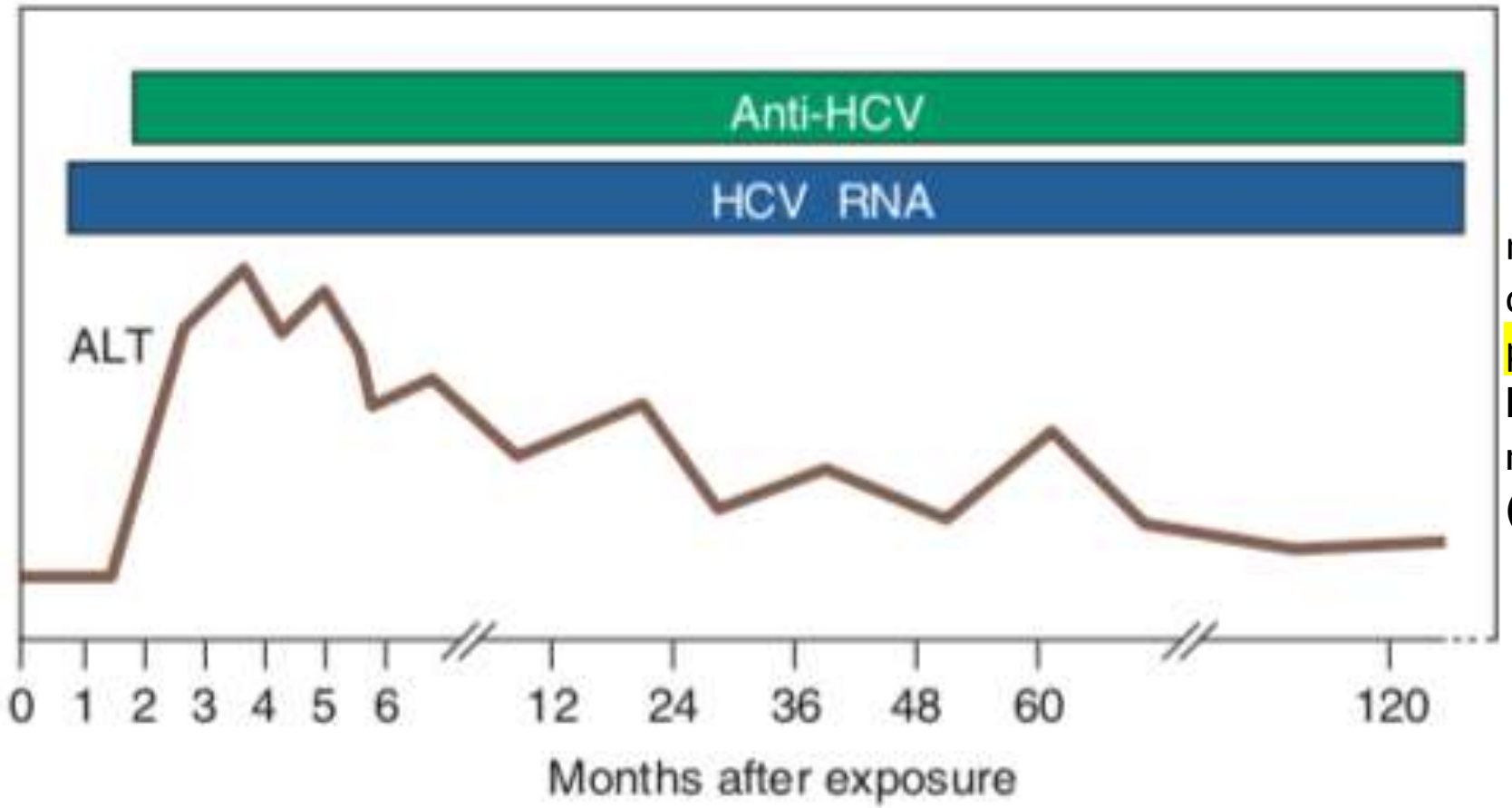
HCV RNA

Detectable within days to 2 months after exposure (varies with inoculum size). Qualitative tests can detect <50 IU/mL HCV RNA and are used to confirm diagnosis and achievement of a sustained virological response (SVR). Quantitative tests report a viral titre and are used to assess response to treatment. New real-time PCR assays detect <10–15 IU/mL and may be sensitive enough for both purposes.

- **Genotype testing**—essential before treatment. The line probe assay reports the genotype and subtype. Currently only the genotype is used in planning therapy.
- **Liver disease severity**—assessed prior to therapy. Important to identify cirrhosis, as prognosis and treatment selection are altered. Fibrosis can be assessed non-invasively (elastography), with liver biopsy reserved for those cases in which there is uncertainty or
- **Acute hepatitis C**—diagnosis is confirmed by newly positive HCV RNA PCR and conversion to HCV antibody-positive within 12 weeks.

In the absence of a documented initial negative test, distinguishing acute from chronic is problematic. Circumstantial evidence, clinical features, timing of aminotransferase changes, and presence of liver fibrosis may help.

- **Chronic hepatitis C**—positive ELISAs should be confirmed with a HCV RNA test. High-risk patients with negative PCRs should be retested a few months later, in case of false-negative results.



most sensitive indicator of HCV infection is the presence of **HCV RNA, by** PCR or transcription-mediated ampli- fication (TMA)

FIGURE 95-7

Scheme of typical laboratory features during acute hepatitis C progressing to chronicity. HCV RNA is the first detectable event, preceding alanine aminotransferase (ALT) elevation and the appearance of anti-HCV.

HCV	Approx. 40–60	Enveloped	9.4-kb RNA, linear, ss, +	Hepacivirus	HCV C100-3 C33c C22-3 NS5	Anti-HCV	Bloodborne agent, formerly labeled non-A, non-B hepatitis Acute diagnosis: anti-HCV (C33c, C22-3, NS5), HCV RNA Chronic diagnosis: anti-HCV (C100-3, C33c, C22-3, NS5) and HCV RNA; cytoplasmic location in hepatocytes
HDV	35–37	Enveloped hybrid particle with HBsAg coat and HDV core	1.7-kb RNA, circular, ss, –	Resembles viroids and plant satellite viruses	HBsAg HDV antigen	Anti-HBs Anti-HDV	Defective RNA virus, requires helper function of HBV (hepadnaviruses); HDV antigen present in hepatocyte nucleus Diagnosis: anti-HDV, HDV RNA; HBV/HDV co-infection—IgM anti-HBc and anti-HDV; HDV superinfection—IgG anti-HBc and anti-HDV
HEV	32–34	Nonenveloped icosahedral	7.6-kb RNA, linear, ss, +	Hepevirus	HEV antigen	Anti-HEV	Agent of enterically transmitted hepatitis; rare in USA; occurs in Asia, Mediterranean countries, Central America Diagnosis: IgM/IgG anti-HEV (assays not routinely available); virus in stool, bile, hepatocyte cytoplasm

[a] *Abbreviations:* ss, single-strand; ss/ds, partially single-strand, partially double-strand; –, minus-strand; +, plus-strand.

TREATMENT

- The aim is to achieve a 'sustained virological response' (SVR, the absence of HCV RNA by PCR at 6 months after finishing treatment). An SVR is associated with 98–100% chance of being RNA-negative in the longer term and reduces all-cause mortality.
- Treatment has been revolutionized by direct-acting antivirals such as sofosbuvir.
- Response is affected by the genotype, race, baseline viral load, and certain host genetics

Cirrhotic patients achieving an SVR should continue to be monitored, as they remain at risk of HCC.

TABLE 95-2

CLINICAL AND EPIDEMIOLOGIC FEATURES OF VIRAL HEPATITIS

FEATURE	HAV	HBV	HCV	HDV	HEV
Incubation (days)	15–45, mean 30	30–180, mean 60–90	15–160, mean 50	30–180, mean 60–90	14–60, mean 40
Onset	Acute	Insidious or acute	Insidious	Insidious or acute	Acute
Age preference	Children, young adults	Young adults (sexual and percutaneous), babies, toddlers	Any age, but more common in adults	Any age (similar to HBV)	Young adults (20–40 years)
Transmission					
Fecal-oral	+++	–	–	–	+++
Percutaneous	Unusual	+++	+++	+++	–
Perinatal	–	+++	±[a]	+	–
Sexual	±	++	±[a]	++	–
Clinical					
Severity	Mild	Occasionally severe	Moderate	Occasionally severe	Mild
Fulminant	0.1%	0.1–1%	0.1%	5–20%[b]	1–2%[e]
Progression to chronicity	None	Occasional (1–10%) (90% of neonates)	Common (85%)	Common[d]	None
Carrier	None	0.1–30%[c]	1.5–3.2%	Variable[f]	None
Cancer	None	+(Neonatal infection)	+	±	None
Prognosis	Excellent	Worse with age, debility	Moderate	Acute, good Chronic, poor	Good
Prophylaxis	IG, inactivated vaccine	HBIG, recombinant vaccine	None	HBV vaccine (none for HBV carriers)	Vaccine
Therapy	None	Interferon Lamivudine Adefovir Pegylated interferon Entecavir Telbivudine Tenofovir	Pegylated interferon plus ribavirin, telaprevir, boceprevir	Interferon or pegylated interferon (efficacy moderate)	None

HDV

- Hepatitis delta virus (HDV) is a defective virus whose replication requires HBV.
- Hence those with HDV are always co-infected with HBV.
- Virions of HDV consist of a core of delta antigen and single-stranded circular RNA enclosed in an envelope **provided by HBV** (with HBsAg).
- 8 genotypes.
- Most patients with delta antigen in the liver have anti-delta antibodies in their serum.
- HDV superinfection usually results in the suppression of HBV replication by mechanisms as yet unknown (HBsAg and HBV DNA levels drop).

EPIDEMIOLOGY

- It is thought that 5% of chronic HBV carriers worldwide may be infected with HDV.
- However, the prevalence of HDV in HBV carriers varies around the world—it is endemic in Mediterranean countries (around 10% in Italy) and the Far East (90% in the Pacific islands, 5% in Japan), but largely confined to at-risk groups in other Western countries.
- There is a higher incidence of HDV infection in HBsAg-positive patients with acute and chronic hepatitis, compared with asymptomatic

CLINICAL FEATURES

- • Symptoms range from asymptomatic to fulminant liver failure (rare, but still ten times commoner than in other viral hepatitis).
- Clinical features seem to cluster in geographical areas that may relate to the prevailing genotype in that area, Western countries see higher rates of fulminant disease that may relate to genotype I (which is dominat in these areas)
- Simultaneous co-infection with HBV/HDV—causes acute hepatitis indistinguishable from classical acute hepatitis B (maybe with higher rates of liver failure, esp in IV drug abusers).
- 5% of people develop chronic HDV.
- HDV superinfection of a carrier of HBV—may cause liver flare (may present as severe acute hepatitis if HBV is undiagnosed). up to 80% of people become chronically infected.
- In the longer term, HDV seems to exacerbate the pre-existing liver disease due to HBV, with potentially rapid progression of cirrhosis (within 2 years).

HEV

- Hepatitis E virus (HEV) is transmitted feco oral route
- A member of the family *Hepeviridae*.
- It is the commonest cause of acute hepatitis in certain parts of Asia (prevention for travelers).
- Infection with hepatitis E may be asymptomatic or range in severity from mild to fulminant hepatitis
- Fulminant disease is more common in pregnant women and elder men.

THE VIRUS

- An icosahedral, non-enveloped ssRNA virus (30–32nm in diameter).
- The genome is 7.2kb in length, encoding three ORFs—ORF1 encodes
- non-structural proteins; ORF2 encodes the capsid; ORF3 encodes an
- immunogenic protein of unknown function.
- There are four genotypes—1 and 2 appear to be confined to humans;
- 3 and 4 infect humans and animals (pigs in the case of 3).
- Genotype 3 may cause milder disease.

EPIDEMIOLOGY

- Epidemiology similar to HAV
- Highest incidence is in Africa, Asia, Central America, and the Middle East, and rising in the west.
- HEV has a wide host range and has been shown experimentally to infect New and Old World monkeys, swine, rodents, and sheep
- Transmission: Many epidemics of HEV have been waterborne(contaminated water), some food-borne (maybe undercooked meats), and infection may follow blood transfusion in endemic areas.
- Transmission from animal (esp. swine) may occur (high seroprevalence amongst those with occupational exposure to animals). Person-to-person transmission (e.g. within a household) seems to be uncommon.
- Perinatal transmission has been reported, and severe neonatal disease can occur.
- Seroprevalence—the presence of anti-HEV antibodies is 15–60% in endemic countries, and higher than expected in non-endemic regions (overall uS rate reported at 21%, higher in those consuming organ meat).
- In the US,UK most cases are due to genotype 3 (may not have clinical manifestations).
- Peak incidence in 15–35 year olds (males>females) low in infants and children.

CLINICAL FEATURES

- Maybe asymptomatic or range in severity from mild to fulminant hepatitis.
- Acute cases of HEV are clinically indistinguishable from other viral hepatitis (more severe than HAV)
- Symptoms: fever, nausea, vomiting, jaundice, and abdominal tenderness. Cholestasis may be prolonged; arthralgia and urticarial rash may occur.
- Fulminant hepatitis is commoner in the third trimester of pregnancy and older men, and carries a high mortality (up to 20%) this accounts for the overall fatality rate of 0.5–3%
- Outcome can be poor in those with chronic liver disease.
- Chronic HEV infection occurs amongst organ transplant recipients

DIAGNOSIS

- **Serology**
- Anti-HEV IgM can be detected in up to 90% of cases 1–4 weeks after acute infection, usually within the same period as symptoms occur.
- By 3 months, anti-HEV IgM is only detectable in 50% of patients.
- Anti-HEV IgG is detectable 2–4 weeks after onset of symptoms (one high titer or rising current titer suggest infection).
- **PCR**
- HEV is detectable by RT-PCR in blood and stool (viremia is short but may last upt o 4 months in some patients)
- In stool, it appears around 1 week before illness onset, remaining until 2 weeks after.

TREATMENT

- Supportive.
- Transplant for liver failure
- Reductions in immunosuppressive therapy can help chronically infected patients.

DIAGNOSIS OF VIRAL HEPATITIS

- First, diagnose HBV—HDV cannot exist without it. Consider HDV in those with acute HBV if they have HDV risk factors or experience particularly severe hepatitis, and in those with established HBV with severe liver flare.
- HDV antibodies—appear late (4 weeks) and may vanish after resolution of acute infection.
- Present in high titers in chronic infection.
- HDV RNA—can be detected in serum by hybridization or RT-PCR assays.
- Differentiating between HBV/HDV co-infection and HDV superinfection relies on the detection of high levels of IgM anti-HBc (in those co-infected).

CLINICAL FEATURES

- There are no clinical features that distinguish the various causes.
- Acute viral hepatitis can be divided into four clinical stages:

incubation period, pre-icteric phase, icteric phase, and convalescence.

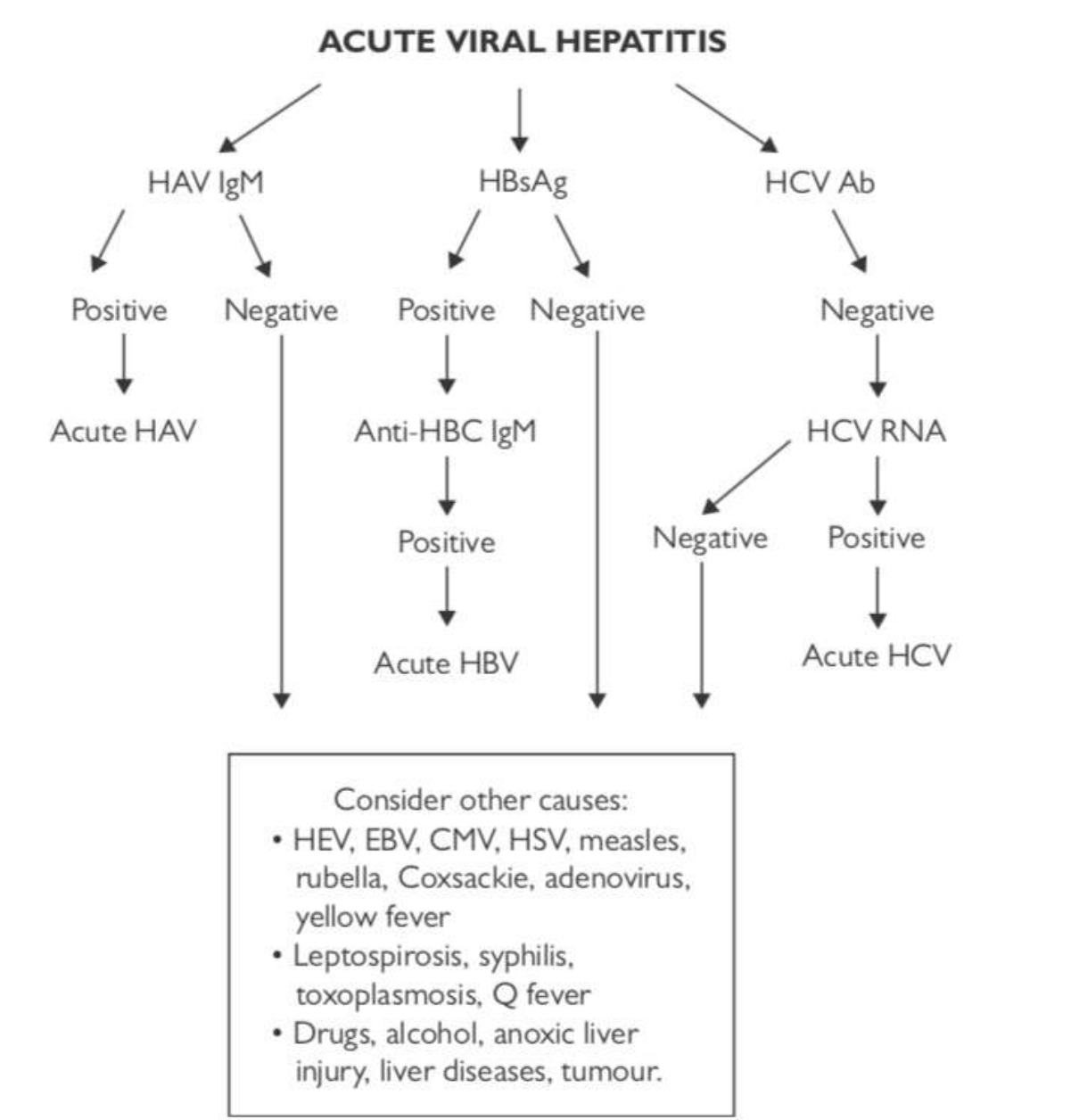
- Clinical features may range from

asymptomatic disease to anorexia, malaise, abdominal pain, and jaundice to fulminant hepatic failure.

- hepatitis B and C may cause immune complex-mediated diseases, e.g. serum sickness, polyarteritis nodosa (hBV), glomerulonephritis, mixed cryoglobulinaemia.
- Fulminant viral hepatitis, characterized by liver failure and hepatic encephalopathy, occurs within 8 weeks after onset of symptoms.

DIAGNOSIS

- routine blood tests—AST and ALT are usually very high, with bilirubin levels variably increased.
- A prolonged PT is rare and suggests severe hepatic necrosis.
- Serology—anti-hAV IgM, hBsAg and anti-hBc IgM, and anti-hCV should be performed initially (see next slide).
- If these are negative, other diagnoses should be considered.
- Liver ultrasound is usually normal in acute viral hepatitis.
- Other abnormalities such as hepatic lesions, cirrhosis, portal hypertension, or ascites suggest alternative diagnoses.
- Liver biopsy may be performed to establish the diagnosis in acute hepatitis with negative serology.



g. 8.1 Investigation of acute hepatitis.

CHRONIC HEPATITIS

CLINICAL FEATURES

- There are no specific clinical features, and many patients remain asymptomatic, until they develop end-stage liver disease.
- Non-specific features (e.g. fatigue and right upper quadrant discomfort) are common.
- Symptoms, such as jaundice, weight loss, abdominal distension, or confusion, suggest decompensation.
- Examination may show signs of chronic liver disease (e.g. palmar erythema, Dupuytren's contractures, jaundice, spider naevi, hepatosplenomegaly, caput medusae, ascites).
- Clinical features of hepatic encephalopathy include confusion, drowsiness, asterixis, ophthalmoplegia, and ataxia.