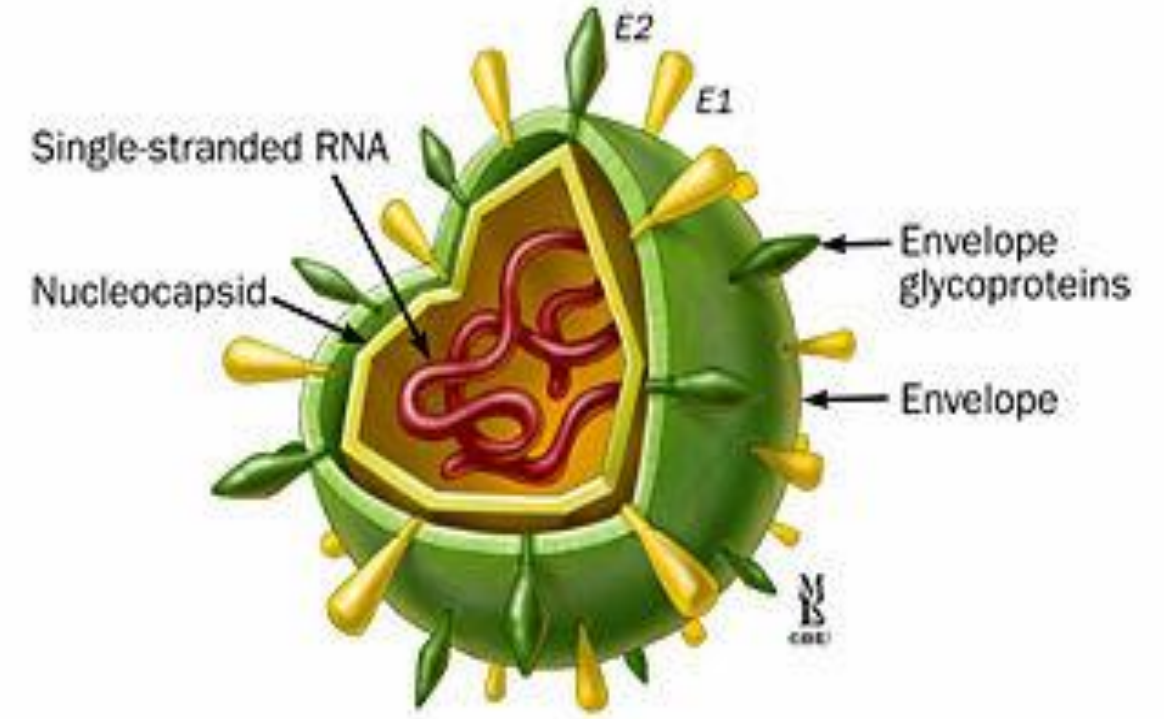
Hepatitis C

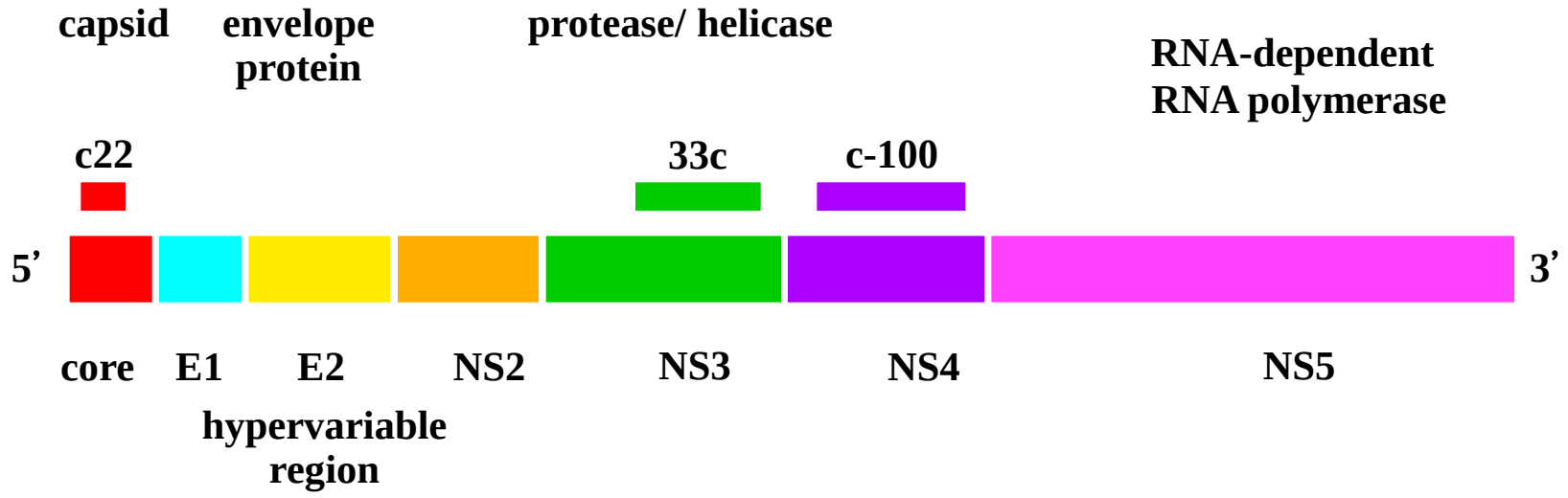
HEPATITIS C VIRION

- spherical, icosahedral, nucleic acid: ss (+) RNA
- Flaviviridae family, *Hepacivirus* genus
- Enveloped virus, virion thought to 30-60nm in diameter
- Morphological structure remains unknown
- HCV has been classified into a total of 11 genotypes on the basis of phylogenetic analysis
- Genotype 1 and 4 has a poorer prognosis and response to interferon therapy

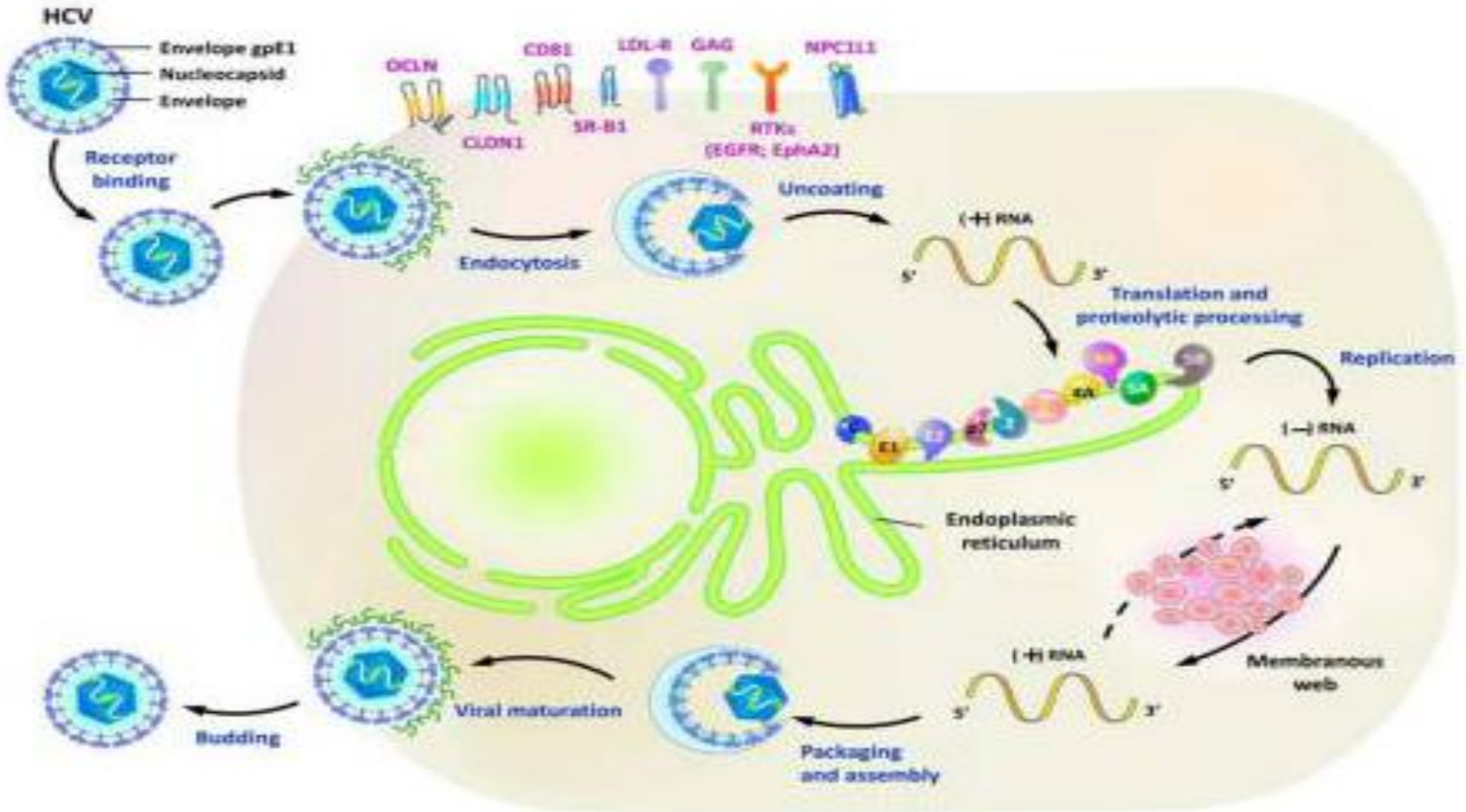


Hepatitis C Virus

- 1 single reading frame, structural genes at the 5' end, the non-structural genes at the 3' end
- Three structural proteins (C, core; E1(gp31) and E2 (gp70), envelope glycoproteins) and 5 nonstructural proteins
- The genome is encoded into a polyprotein, which is processed into individual proteins by proteases.
- HCV is highly mutable, RNA-dependent RNA polymerase lacks proof reading
- Mutations give rise to quasispecies and antigenic variation specially in E2 HVR1 and 2.
- E2 HVRs contain an epitope for neutralization
- Mutations: Allow the virus to escape the immune response; cause chronic or persistent infection in host



HCV replicates exclusively in the cytoplasm via an RNA intermediate



Lack tissue culture system

Risk Factors Associated with Transmission of HCV

- Transfusion or transplant from infected donor
- Injecting drug use
- Hemodialysis (yrs on treatment)
- Accidental injuries with needles/sharps
- Sexual/household exposure to anti-HCV-positive contact
- Multiple sex partners
- Birth to HCV-infected mother (during delivery)

HCV pathogenesis

- HCV infects B and T lymphocytes and monocytes and move to main site of infection the liver
- Very high replication rate in hepatocytes ($1x10^{12}$ a day)
- Liver damage in HCV infection occur as a result of:
  1. Activation of cytokines and INF (protective initially); evasion; liver damage
  2. NK release perforins; fragment nuclei of infected cells and induce apoptosis
  3. E1/E2 envelope glycoprotein expression; mutation; evasion of humoral immunity; persistent infection
  4. Ag-Ab complex formation; deposit in liver. Extrahepatic: vasculitis, arthritis and glomerulonephritis.
  5. CD4 T cells secret proinflammatory cytokines; hepatocyte death
  6. CD8 T cells eliminate HCV by apoptosis of infected hepatocytes
- Alcohol, cigarettes smoking and co-infections with HIV, HBV and HAV are associated with progression of hepatitis C.
- Pts may develop cirrhosis of liver with increased risk of HCC
- Infection, necrosis, regeneration cycle associated with HCC
- HCV core protein and NS5A proteins are implicated in oncogenesis

Hepatitis C - Clinical Features

Incubation period:	Average 6-7 wks Range 2-26 wks
Clinical illness (jaundice):	30-40% (20-30%)
Chronic hepatitis:	70% (10-18 yrs)
Persistent infection:	85-100%
Immunity:	No protective antibody response identified

Chronic Hepatitis C Infection

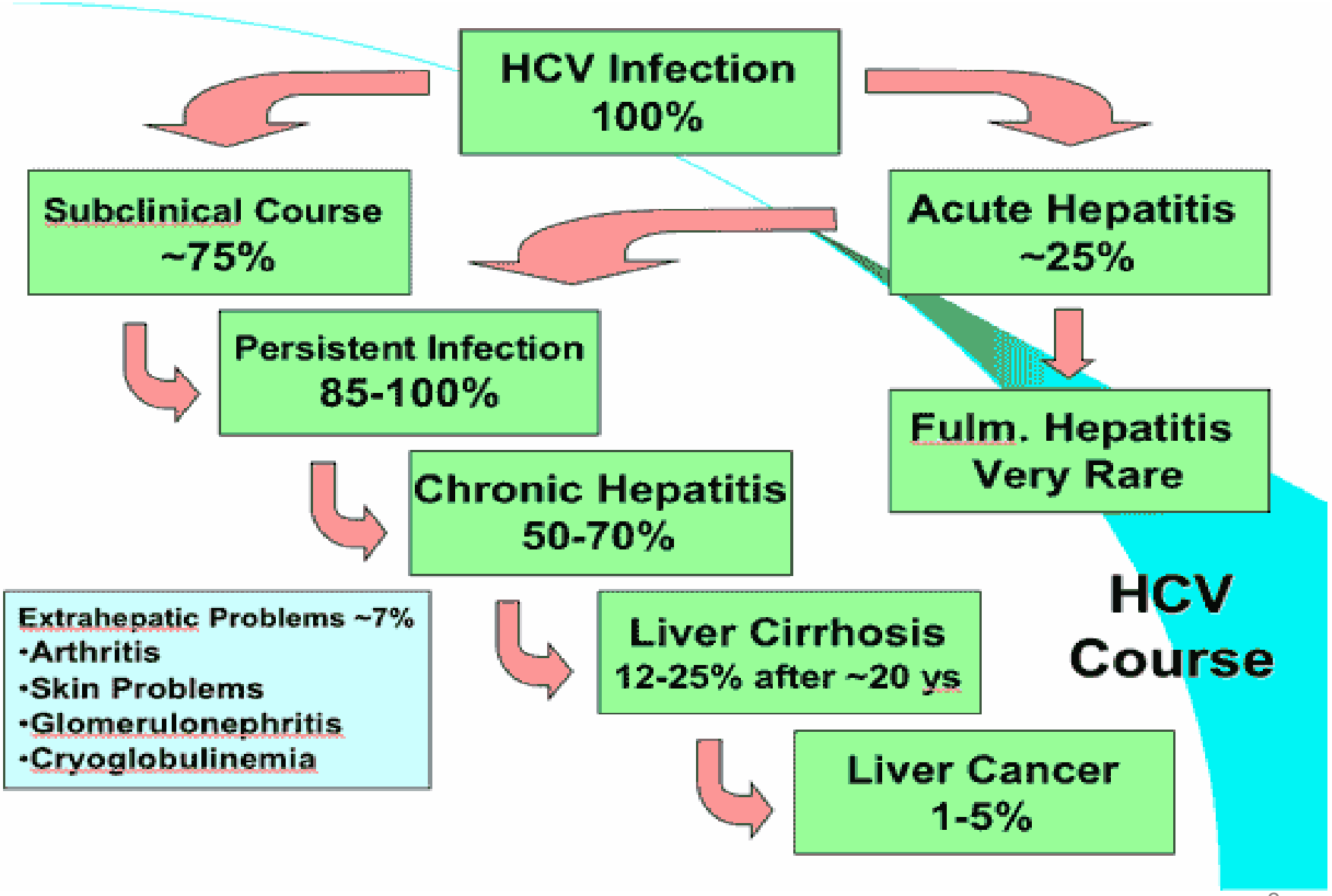
Acute infection

- Hepatitis C infection causes acute symptoms in 15% of cases.
- Symptoms are generally mild and vague, including a decreased appetite, fatigue, nausea, muscle or joint pains.
- Most cases of acute infection are not associated with jaundice.
- The infection resolves spontaneously in 10–50% of cases

Chronic infection

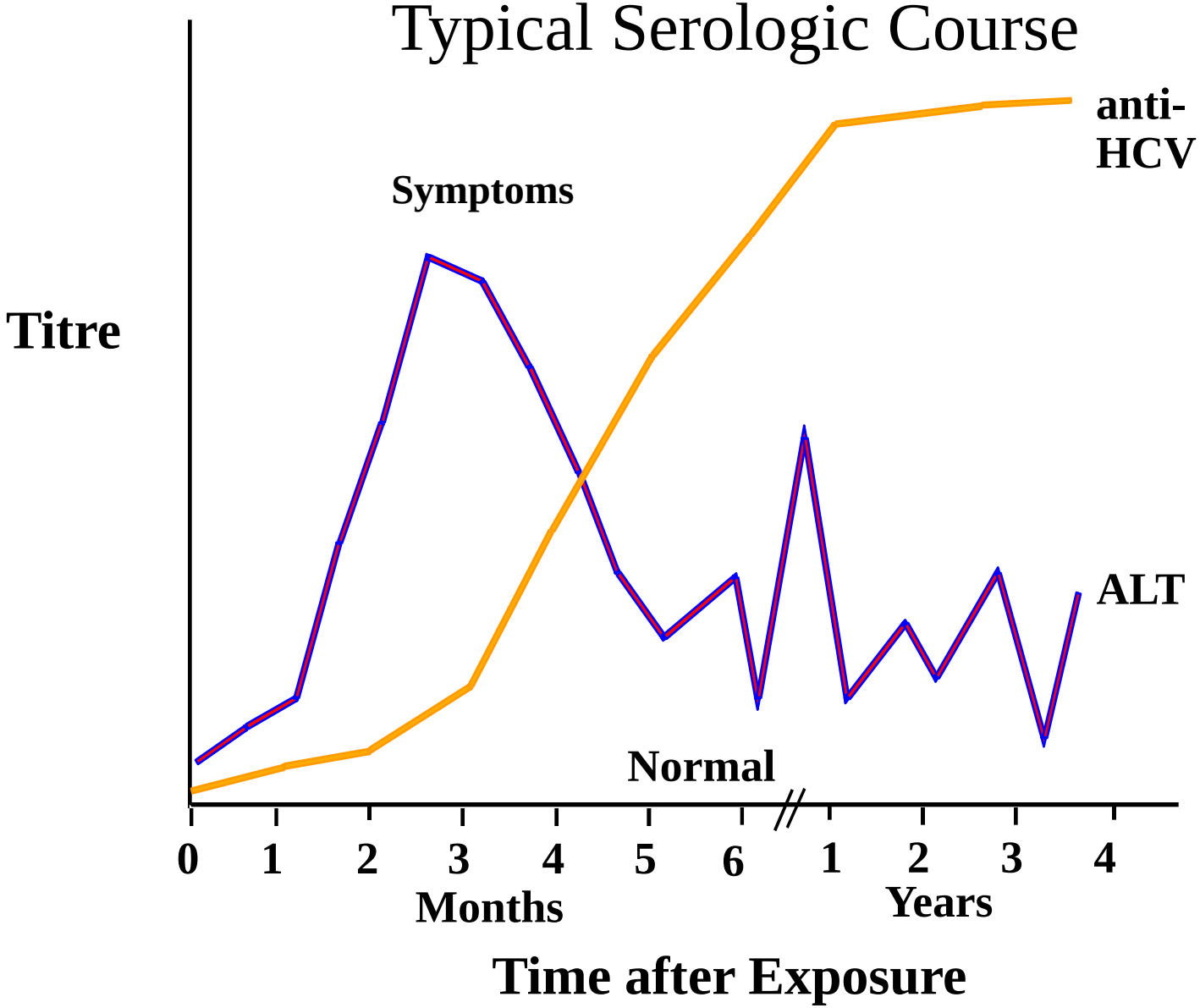
- About 85% of those exposed to the virus develop a chronic infection (detectable viral replication for at least six months).
- Most experience minimal or no symptoms during the initial few decades of the infection.
- Chronic infection after several years may cause cirrhosis or liver cancer

OUTCOMES of HCV hepatitis



Hepatitis C Virus Infection

Typical Serologic Course



Laboratory Diagnosis

- HCV antibody - generally used to diagnose hepatitis C infection. Not useful in the acute phase as it takes at least 4 weeks after infection before antibody appears.
- HCV-RNA - various techniques are available e.g. PCR. May be used to diagnose HCV infection in the acute phase. However, its main use is in monitoring the response to antiviral therapy.
- HCV-antigen - an EIA for HCV antigen is available. It is used in the same capacity as HCV-RNA tests but is much easier to carry out.
- HCV genotyping – type 1 require longest period of therapy, genotype 1 and 4 have a worse prognosis overall and respond poorly to interferon therapy
- Viral Load – patients with high viral load are thought to have a poorer prognosis. Viral load is also used for monitoring response to IFN therapy

Treatment

- HCV induces chronic infection in 50–80% of infected persons. Approximately 40–80% of these clear with treatment. In rare cases, infection can clear without treatment
- Treatment is recommended for those with proven HCV infection and signs of liver inflammation
- Interferon - may be considered for patients with chronic active hepatitis. The response rate is around 50% but 50% of responders will relapse upon withdrawal of treatment.
- Ribavirin - there is less experience with ribavirin than interferon. However, recent studies suggest that a combination of interferon and ribavirin is more effective than interferon alone.
- Sofosbuvir (Sovaldi): inhibits RNA polymerase; FDA approved sofosbuvir in combination with ribavirin (RBV) for oral dual therapy of HCV genotypes 2 and 3, and for triple therapy with injected pegylated interferon (pegIFN) and RBV for treatment-naive patients with HCV genotypes 1 and 4.

Prevention of Hepatitis C

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

GB virus C

FLAVIRUS: similar morphology and genome

- Investigation failed to identify any association between this virus and any clinical illness
- In risk groups: 10-20% infected HCV also infected with GB-virus C, 15-40 of HIV pts co-infected.

- Transmission: Parenteral, sexual and vertical transmission