ACUTE HCV

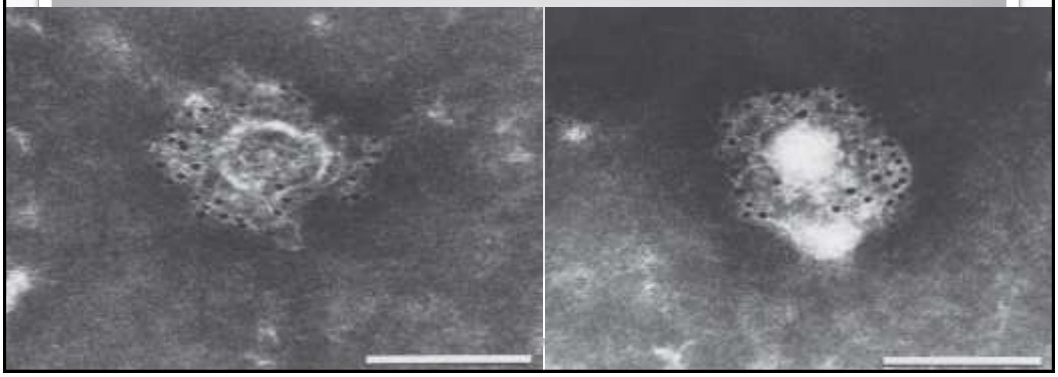
Dr. hadizadeh M.R.

Mashhad medical faculty

clinical infectious disease sp.

HEPATITIS C VIRUS

- HCV is a roughly spherical, enveloped, positive-strand RNA virus.
- Member of the family Flaviviridae



Epidemiology of HCV Global Hepatitis Report 2017

- More than 1 750 000 new infections in 2015 (defect in hemovigilance and harm reduction in PWID)
- 1 % of the population HCV-infected (71 millions)
- 2.3 millions HIV/HCV co-infected
- 720 000 deaths related to cirrhosis
- 470 000 deaths related to hepatocellular carcinoma
- 22 % increase since 2000

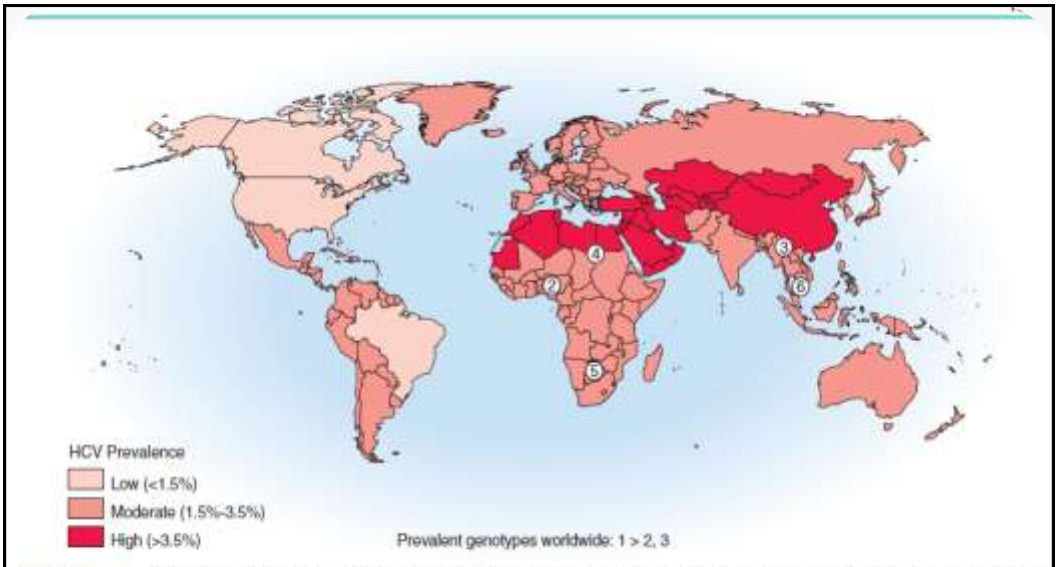


FIGURE 156-5 **World map indicating prevalence of hepatitis C virus (HCV) infection *(shading)* and subtypes *(numerals)*.** Genotypes 1, 2, and 3 are prevalent with variable dominance worldwide; genotypes particularly diverse (e.g., genotype 2 in central/west Africa) or associated with a geographic region (e.g., genotype 5 in South Africa) are indicated by *circled numbers*. *(Prevalence estimates are modified from the Global Burden of Diseases, Injuries, and Risk Factors 2010 study [Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013;57:1333-1342.])*

- Acute HCV infection may result from exposure to the virus through various routes.
- The highest risk is associated with repeated parenteral exposure from contaminated equipment in an injection drug use setting.
- Transmission rates among HIV-infected men who have unprotected sex with men are much higher, particularly among those who engage in high-risk sexual practices that increase trauma to the mucosal membranes and exposure to blood.

- Lower rates of HCV transmission occur from needle-stick injuries in which healthcare workers are exposed to the blood of an HCV-infected patient.
- Heterosexual exposure risk is very low.

List of Potential Hepatitis C Exposures

Potential Source of Exposure to Hepatitis C Virus
Recent injection drug use
Needle stick injury
Procedures involving potentially reused needles: tattooing, body-piercing, acupuncture
Exposure to re-used sharp objects or re-used vials of injectable materials
Nosocomial exposure to contaminated equipment, or potential direct exposure to blood
High risk sexual practices: fisting, bleeding during sex, use of sharp objects during sex
Sexual contact with a known HCV-infected partner
Sexual contact with known HIV positive partner
Sexual contact with known sexually transmitted infections in patient or their partner
Blood transfusion or unsafe therapeutic procedures during travel in a developing country

Clinical Manifestations

- The clinical manifestations of acute viral hepatitis are similar among the five hepatitis viruses, and no clinical features unequivocally distinguish one from the other, although certain epidemiologic patterns of transmission may suggest a particular virus.

- Although usually not associated with symptoms, acute HCV infection may cause malaise, nausea, and right upper quadrant pain, followed by dark urine and jaundice.

- HCV RNA can be detected in blood within days of exposure and is followed by elevations in serum levels of the liver-specific enzyme, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and in some cases bilirubin.

- Incubation (time to elevated ALT or symptoms), which ranged from 6 to 112 days (median, 46 days).
- Shorter incubation was associated with higher ALT, and jaundice was only detected in 21%.

- The frequency with which HCV causes fulminant hepatitis is controversial.
- HCV infection has been associated with 40% to 60% of fulminant non-A, non-B hepatitis in Japan, but it is an uncommon cause of fulminant liver disease in Western countries.
- This discordance might arise from variation in either host factors or viral strains, or both.

- There appears to be an increased likelihood of fulminant liver disease following acute HAV infection in persons with underlying chronic hepatitis C.
- Seventy-five percent or more of persons with acute hepatitis C infection develop persistent infection with long-term viremia.

- Individuals suspected of having acute HCV infection often do not have a discrete exposure or have no prior baseline testing, making a diagnosis of acute infection more difficult.

- Acute infection should be suspected if there is a new rise in the ALT level without an alternate cause .

No Discrete Exposure

- Acute infection should also be suspected when there are low (especially $<10^4$ IU/mL) or fluctuating (>1 $\log_{10}$ IU/mL) HCV RNA values, or spontaneous clearance.
- These patterns do not commonly occur outside of the first 6 months after HCV infection.
- A low signal-to-cutoff ratio of HCV antibody along with detectable HCV RNA might also be suggestive of the early weeks of acute primary infection, although this information may need to be specifically requested from the testing laboratory.

- NS5B sequence diversity assessed by deep sequencing can differentiate acute from chronic HCV infections and, with further validation, could become a powerful population-level surveillance tool for incidence estimation.

- Patients suspected of having acute HCV infection should also have a laboratory evaluation to exclude other or coexisting causes of acute hepatitis (eg, hepatitis A virus, hepatitis B virus, hepatitis delta virus if chronically infected with hepatitis B, and autoimmune hepatitis) .

- Patients should also have HIV testing.

Diagnosis of Acute HCV

- Diagnosis of acute HCV infection enables estimation of annual incidence rates and transmission patterns, thereby facilitating implementation and assessment of prevention programs.
- At the individual level, a diagnosis of acute infection expedites linkage to care, counseling regarding high-risk behavior, and timely interventions to reduce virus transmission and liver disease progression.

- undiagnosed acutely-infected persons may be at greater risk of transmitting HCV to their presumably seronegative contacts than would be expected by chance.

- The diagnosis of acute hepatitis C can only be made confidently if recent seroconversion to anti-HCV antibodies can be documented, since there is no serological marker which establishes that HCV infection is in the de novo acquired acute phase.

- Not all patients with acute hepatitis C will be anti-HCV antibody-positive at diagnosis.
- In these cases, acute hepatitis C can be suspected if the clinical signs and symptoms are compatible with acute hepatitis [ALT] level >10 times the upper limit of normal, and/or jaundice in the absence of a history of chronic liver disease or other causes of acute hepatitis, and/or if a likely recent source of transmission is identifiable.

- In all cases, HCV RNA (or HCV core antigen) can be detected during the acute phase, although their levels may vary widely and there may be interludes (up to several weeks) of undetectable HCV RNA (or HCV core antigen).

- Thus, HCV RNA-negative (or HCV core antigen-negative) individuals should be retested for HCV RNA (or HCV core antigen) 12 and 24 weeks after a negative result to confirm definitive clearance.

- The best laboratory evidence to support a diagnosis of acute HCV infection is:

(1) a positive HCV RNA test in the setting of a negative HCV antibody test (identification during the seronegative window period) , or

(2) a positive HCV antibody test after a prior negative HCV antibody test (seroconversion).

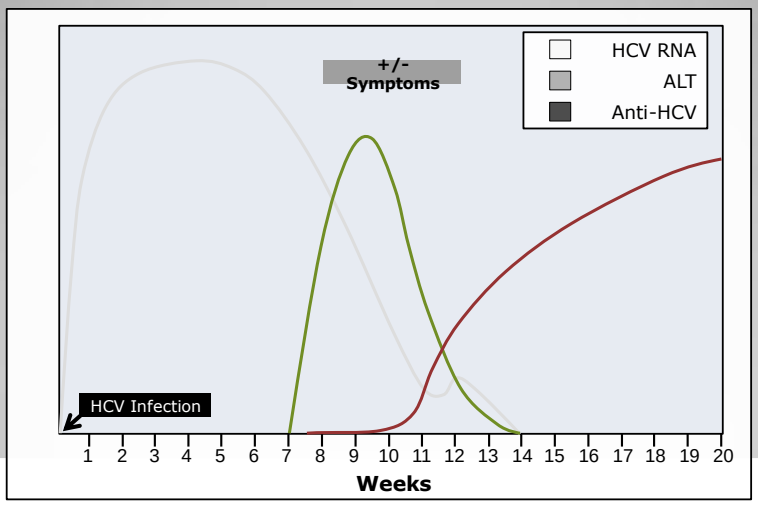
- There are rare instances in which these approaches may be misleading, such as in immunosuppressed individuals with impaired antibody production.

- In the case of suspected acute hepatitis C, in immunocompromised patients and in patients on haemodialysis, HCV RNA testing in serum or plasma should be part of the initial evaluation.

TEST	INTERPRETATION FOR DIAGNOSIS OF ACUTE HCV
HCV Antibody	Test may be negative during the first 6 weeks after exposure. Seroconversion may be delayed or absent in immuno-suppressed individuals. Presence of HCV antibody alone does not distinguish between acute vs chronic infection. A low signal-to-cutoff ratio may be present during acute HCV infection or represent a false-positive result.
HCV RNA	Viral fluctuations >1 log10 IU/mL may indicate acute HCV infection. HCV RNA may be transiently negative during acute HCV infection. Presence of HCV RNA alone does not distinguish between acute vs chronic infection.
ALT	Fluctuating ALT peaks suggest acute infection. ALT may be normal during acute HCV infection. ALT may be elevated due to other liver insults, such as alcohol consumption.

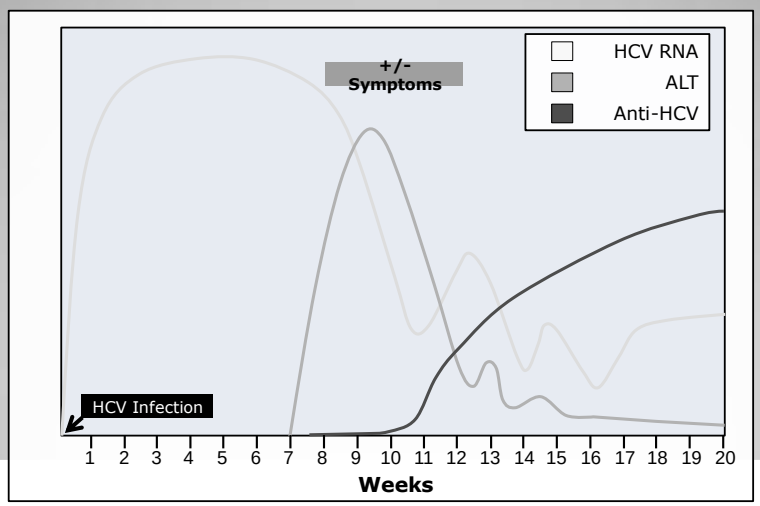
- HCV core antigen in serum or plasma is a marker of HCV replication.
- Core antigen detection can be used instead of HCV RNA detection to diagnose acute or chronic HCV infection.
- HCV core antigen assays are less sensitive than HCV RNA assays (lower limit of detection equivalent to approximately 500 to 3,000 HCV RNA IU/ml, depending on the HCV genotype.
- As a result, the HCV core antigen becomes detectable in serum or plasma a few days after HCV RNA in patients with acute hepatitis C.

Spontaneous Clearance of HCV after Acute Infection



Source: www.hepwebstudy.org

HCV Persistence after Acute Infection



Source: www.hepwebstudy.org

Treatment of acute hepatitis C

- Most patients with acute hepatitis C are asymptomatic, but a high rate of chronicity is expected (50–90%).
- Symptomatic disease with jaundice, female gender, a young age, and genetic polymorphisms in the region upstream of the IL28B (recently renamed, IFNL3) gene have been associated with spontaneous viral clearance, but none of these parameters accurately predicts spontaneous resolution at the individual level.

- Patients with acute hepatitis C should be considered for antiviral therapy in order to prevent progression to chronic hepatitis C.
- Indeed, immediate treatment of acute hepatitis C with DAAs improves clinical outcomes and was shown to be highly cost-effective compared with deferring treatment until the chronic phase of infection.
- The ideal time point for starting therapy has not been firmly established.

- The ideal duration of treatment of acute hepatitis C with IFN-free regimens remains unknown.
- The combination of sofosbuvir and ribavirin for either 6 or 12 weeks was not sufficient to achieve high SVR rates in patients with acute or early chronic hepatitis C.

- Patients with acute hepatitis C should be treated with a combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 and 6) or a combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1b) for 8 weeks (B1).

- Based on similarities to chronic hepatitis C, patients with acute hepatitis C may be treated with a combination of sofosbuvir and velpatasvir (all genotypes), a combination of glecaprevir and pibrentasvir (all genotypes), or a combination of grazoprevir and elbasvir (genotypes 1b and 4) for 8 weeks (C2).

- SVR should be assessed at 12 and 24 weeks post-treatment, because late relapses have been reported (B2).

- There is no indication for antiviral therapy as post-exposure prophylaxis in the absence of documented HCV transmission (B1).