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PRACTICE

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CLINICAL UPDATES

Hepatitis C

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Infection with hepatitis C virus (HCV) presents as an acute illness (such as fatigue, arthralgia, jaundice) in about a third of patients, but most patients are asymptomatic. After acute infection, up to 45% of young healthy patients may develop a vigorous antibody and cell mediated immune response, which leads to the spontaneous eradication of the virus.[1] However, most infected patients fail to clear the virus. This results in chronic infection and progressive liver damage.

How common is it?

Hepatitis C seems to be endemic in most parts of the world. The total global prevalence is estimated to be about 1.6%, corresponding to 115 million previous viraemic infections, but there is considerable geographical and age variation in the incidence and prevalence of infection and of genotypes.[2 3] The prevalence may be as high as 5-15% in some parts of the world, and different regions have a different risk profile and age demographic.[4] The prevalence is higher in specific populations, such as people who are incarcerated or institutionalised.[5]

What causes it?

Hepatitis C virus (HCV) is an infectious, hepatotropic virus belonging to the *Flavivirus* family, and is transmitted by percutaneous blood exposure. The most common worldwide cause is unsafe injection practices during medical treatment.[6] Infection is also common in people who inject drugs. Less commonly, it is spread through sexual activity, perinatally, intranasal drug use, or after accidental blood contact (such as haemodialysis). Blood and blood products not screened for HCV have also been sources of infection. About 10% of people with HCV infection have no recognised risk factor.[7]

Some patients, particularly younger women, will spontaneously clear the virus, but most people will develop chronic infection.[8] Black people seem to be least likely to spontaneously clear HCV.[9]

How does it present?

Acute infection

After initial exposure to the virus, most patients are asymptomatic.[14] About 30% of patients have features such as fatigue, arthralgia, or jaundice, associated with a transient rise in serum aminotransferases, particularly alanine aminotransferase,[15] but fulminant hepatic failure is extremely rare.

Chronic infection

Chronic hepatitis C infection is generally defined as persistence of HCV RNA in the blood for at least six months. Patients are usually asymptomatic but may present with features of decompensated cirrhosis (such as jaundice, ascites, and hepatic encephalopathy) or hepatocellular carcinoma. Occasionally, patients may present with extrahepatic manifestations (such as vasculitis, renal complications, and porphyria cutanea tarda (see fig 1⇓)).

Factors that influence the development of chronic liver disease include older age at time of infection and male sex.[10] Concurrent chronic hepatitis B, HIV infection, or high alcohol intake may also increase the risk of progressive liver disease.[11] In a large prospective study of patients with advanced liver disease related to hepatitis C, regular coffee consumption was associated with lower rates of disease progression.[23] Caffeinated coffee consumption of more than two cups daily is associated with reduced histological activity (inflammation) in chronic HCV.[24] Daily cannabis use is strongly associated with moderate to severe fibrosis and steatosis.[12 13]

How is hepatitis C diagnosed?

Diagnostic tests for HCV are used to establish a clinical diagnosis, prevent infection through screening of donor blood, and make decisions regarding medical management of patients.

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What you need to know

- After acute exposure to hepatitis C virus (HCV), about 55% to 85% of patients develop chronic hepatitis C
- Most acute and chronic infections are asymptomatic; however, hepatic inflammation is often present and can lead to progressive hepatic fibrosis
- The goal of treatment is to eradicate the virus, achieve a sustained virological response, and prevent disease progression
- Interferon based treatment regimens are no longer recommended for HCV infection as oral, direct acting antiviral agents are now considered first line therapy
- Long term complications of chronic HCV infection include cirrhosis and hepatocellular carcinoma

Acute infection

HCV RNA testing is needed to diagnose acute infection. Nucleic acid tests include reverse transcription followed by polymerase chain reaction (PCR), branched chain DNA analysis, and transcription mediated amplification (TMA). A positive result indicates the presence of active infection.[25] No nucleic acid test is preferred, but TMA is the most sensitive. Most providers use PCR, however, because it is most readily available. It is important to remember that 15-45% of people exposed may ultimately clear the virus without treatment.[1] In these patients, the HCV antibody test will remain positive, but, because they are no longer viraemic, the nucleic acid test will become negative (see fig 2⇓).

Chronic infection

Antibody tests

Following exposure to the virus, it can take several weeks to develop anti-HCV antibodies (fig 2⇓). Also, patients may spontaneously clear the virus up to 12 weeks after an acute exposure (such as a contaminated needlestick injury). Therefore, a screening test such as an enzyme immunoassay (EIA) may be negative, and should be repeated in three months.[11] Every patient with HCV infection should have a viral genotype before treatment in order to determine the most appropriate treatment regimen.[26]

A screening test by EIA detects antibodies against the virus. The same nucleic acid tests used for acute infection are used to confirm viraemia in a patient with a positive EIA or assess the effectiveness of antiviral therapy. A positive result indicates the presence of active infection.[25] Occasional false negative EIA occurs in immunocompromised patients or those undergoing dialysis.[11] False positives may occur in patients with autoimmune disease. Suspicion of a false positive or false negative result should also lead to testing for HCV RNA.

Liver function tests

Physical examination or laboratory values alone may not indicate disease until it is advanced. Serum aminotransferases, particularly alanine aminotransferase, can be used to measure disease activity (fig 2⇓), although sensitivity and specificity are low.

Liver biopsy

Liver biopsy is not used to diagnose hepatitis C infection but is useful in staging fibrosis and the degree of hepatic inflammation. However, because direct acting antiviral therapy is now considered to be so effective, biopsy is rarely warranted. Another potential reason to obtain a biopsy is to evaluate the possibility of cirrhosis and thus begin a surveillance programme for hepatocellular carcinoma.

Other non-invasive tests

Non-invasive tests for prediction of fibrosis are becoming the standard of care compared with liver biopsy. In Europe, non-invasive tests such as elastography have been more accepted as replacements for liver biopsy. However, elastography may not be adequate on its own to rule in or rule out significant fibrosis.[27]

How is hepatitis C managed?

The goal of antiviral treatment is to clear the virus from the bloodstream. Treatment is also associated with stabilisation or even improvement in liver histology and clinical course. Other goals are symptom control and prevention of complications of progressive liver disease, including cirrhosis, decompensated liver disease, and hepatocellular carcinoma.

Acute infection

There is no specific treatment for acute exposure until viraemia is established. If both physician and patient decide that a delay in starting treatment is acceptable, the patient should be monitored for spontaneous clearance of the virus for a minimum of six months. If spontaneous clearance occurs, no antiviral treatment is necessary.[26]

Treatment during the first six months, if undertaken, should be the same as for chronic infection.

HCV RNA should be monitored for at least 12-16 weeks to allow for spontaneous clearance before treatment is started.[26] If HCV RNA is not detected within 12-16 weeks after the acute exposure, the patient is unlikely to have been infected or has cleared the virus spontaneously.

Chronic infection

The American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidelines recommend treatment for all patients with chronic HCV infection except those with a short life expectancy (for example, because of comorbid conditions). Studies demonstrate that treating at an earlier stage of disease is associated with improved outcomes compared with waiting for more advanced disease to develop.[26]

Interferon based treatment regimens are no longer recommended for HCV infection as oral, direct acting antiviral agents are now considered first line therapy.[28] Up to 30% of HCV infected patients receiving interferon therapy develop major depression. A 12 year, population based cohort study found that HCV infected patients with a history of interferon induced depression had a significantly higher risk for recurrent depression, even without further exposure to interferon alfa. The use of antidepressants during treatment with interferon alfa did not reduce the risk of recurrence.[29]

The recent rapid development of new antiviral agents has resulted in changes to treatment guidelines, and the mainstay

of treatment is now with directly acting antiviral agents (DAAs).[26] A specialist should be consulted before selecting the most appropriate treatment regimen. Specific regimens primarily depend on the HCV genotype and the presence or absence of cirrhosis.[26]Box 1 shows current treatments for HCV infection, and box 2 lists emerging treatments.

A Cochrane review in 2017 of 138 randomised clinical trials (25 232 patients) comparing DAAs with no intervention or placebo, alone or with co-interventions, found that DAAs have mainly been studied short term with sustained virological response as a surrogate outcome. Few or no data are available yet about the effect of DAAs on hepatitis C related morbidity or mortality.[32]

The introduction of DAAs into HCV treatment regimens means that there is an increased risk of drug interactions with other medications the patient may be taking (such as antiretrovirals, anticonvulsants, antifungals, corticosteroids, statins, antibiotics, and herbal medicines). There is also a small risk of reactivation of hepatitis B (see box 3)

What is the prognosis for those treated for chronic infection?

Mortality is increasing, and the number of HCV related deaths now exceeds the number of HIV/AIDS related deaths in the US. The number of deaths from HCV was 19 659 in 2014 (5 deaths per 100 000 population), mainly in patients aged 55-64 years (25 deaths per 100 000 population or 50.9% of all HCV related deaths). The mortality rate was approximately 2.6 times greater for men compared with women.[35]

Sustained virological response (SVR) is defined as undetectable virus in the serum three months after treatment completion, which correlates well with long term absence of virus. A systematic review found high SVR rates for all FDA approved treatment regimens. SVR rates were >95% in patients with HCV genotype 1 infection for most drug combinations and patient populations. Overall rates of serious adverse effects and treatment discontinuation were found to be low (<10%) across all patients.[36]

Abstinence from alcohol, maintaining ideal body weight, avoiding hepatitis A or B (via vaccination), and avoiding HIV via safe sex are prudent.

As with treatment naive patients, recommended options for treatment experienced patients vary by HCV genotype and the presence or absence of cirrhosis.[26] However, the recommended regimen also depends on the patient's previous regimen that resulted in treatment failure.

Can hepatitis C be prevented?

Clean needles and needle exchange for intravenous drug users have been shown to decrease the risk of HCV transmission.[37] Although sexual transmission of HCV is very inefficient, safe sex is a reasonable precaution in people with multiple partners and in people infected with HIV. Disposable medical and dental equipment should be used during medical and dental procedures. The risk of acquiring HCV from unsafe medical practices is very low in developed countries.

Should the general population be screened for hepatitis C?

Screening practices may be different between countries and, in particular, developed countries may have different practices from developing countries with limited medical facilities. Local guidance should be followed. For example, infants born in countries where there is a high risk of medical transmission should be tested. The US Preventive Services Task Force has recommended against routine screening for HCV infection but does now recommend screening for people at high risk for infection.[38] The US National Institutes of Health also recommends promoting the establishment of screening tests for groups at high risk of infection, including injecting drug users and incarcerated people.[11] The Centers for Disease Control and Prevention (CDC) also recommends that screening should be considered in refugees as part of the routine medical examination for new arrivals.[39]

In the US, there has been a recommendation of screening by birth cohort (such as screening all people born between 1945 and 1965), and this approach seems to be cost effective.[40-42] The CDC recommends the one time screening of any person born between 1945 and 1965, as this is a population with a disproportionately high prevalence of HCV infection and related disease.[43] This recommendation may not apply to other countries, as specific approaches to screening will depend on the local epidemiology.

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Box 1: Current treatments for hepatitis C infection

Drug regimen components (which may be given with or without ribavirin) include:

- Daclatasvir plus sofosbuvir
- Elbasvir/grazoprevir combination
- Ledipasvir/sofosbuvir combination
- Ombitasvir/paritaprevir/ritonavir combination with or without dasabuvir
- Sofosbuvir plus simeprevir
- Sofosbuvir/velpatasvir combination

Box 2: Emerging treatments for hepatitis C infection

- Sofosbuvir/velpatasvir/voxilaprevir combination
  A drug application was submitted to the Food and Drug Administration (FDA) in December 2016 for sofosbuvir/velpatasvir/voxilaprevir, a once daily, single tablet regimen for treatment experienced patients
- Glecaprevir/pibrentasvir combination
  A drug application was submitted to the FDA in December 2016 for glecaprevir/pibrentasvir. Glecaprevir is an HCV non-structural (NS) protein 3/4A protease inhibitor, and pibrentasvir is an NS5A inhibitor
- Second generation NS5a inhibitors
  Second generation NS5a inhibitors (other than velpatasvir) with pangenotypic activity as well as activity against resistant variants from first generation inhibitors are in development
- Alternative daclatasvir based regimens
  Daclatasvir plus asunaprevir (a nucleotide analogue protease inhibitor) is currently being tested in patients with HCV genotype 1b infection[30]

  Daclatasvir plus asunaprevir plus beclabuvir (a non-nucleotide polymerase inhibitor) is undergoing phase III trials.[31] This regimen will also have activity against genotype 1a infection.
- Other treatments
  Non-specific cytoprotective agents may be helpful by blocking the cell injury caused by the virus infection. Ongoing research is evaluating molecular approaches to treating hepatitis C infection, such as small interfering RNA particles (gene silencing).

Box 3: Reactivation of hepatitis B by directly acting antiviral agents

The Food and Drug Administration (FDA) has issued a warning about the risk of hepatitis B reactivation in patients who are treated with direct acting antiviral agents (DAAs) and who have current or previous hepatitis B infection.[33] Although the risk is low, hepatitis B reactivation has resulted in severe liver problems (requiring liver transplant) or death. All patients should be screened for evidence of current or previous hepatitis B infection (by testing for HBsAg, antibody to hepatitis B surface antigen, and antibody to hepatitis B core antigen) before initiating treatment with DAAs. Patients should also be monitored during and after treatment. The European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC) supports these recommendations.[34] Hepatitis B vaccination is recommended for all susceptible individuals.[26]

Sources and selection criteria

We searched PubMed up to October 2016 with the terms “hepatitis C” and “hepatitis C treatment,” targeting reviews and studies published in English since 1990. We searched the references of identified articles as well as our own files. The selection of references was made based on our assessment of relevance to the topic. Where relevant, we incorporated the guidance recommendations from the American Association for Study of Liver Diseases and Infectious Diseases Society of America website: http://hcvguidelines.org.

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Figures

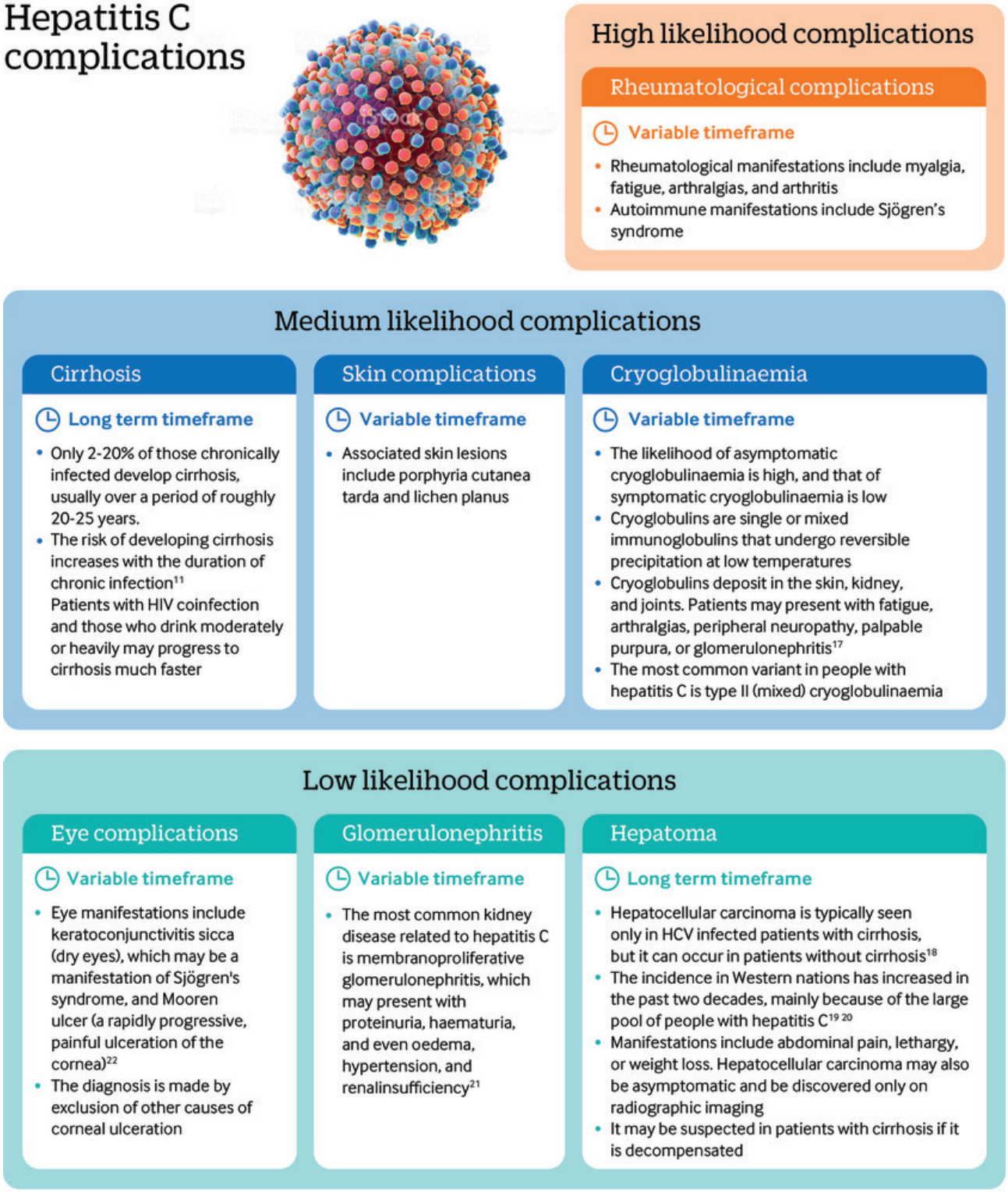

Fig 1 Complications of hepatitis C

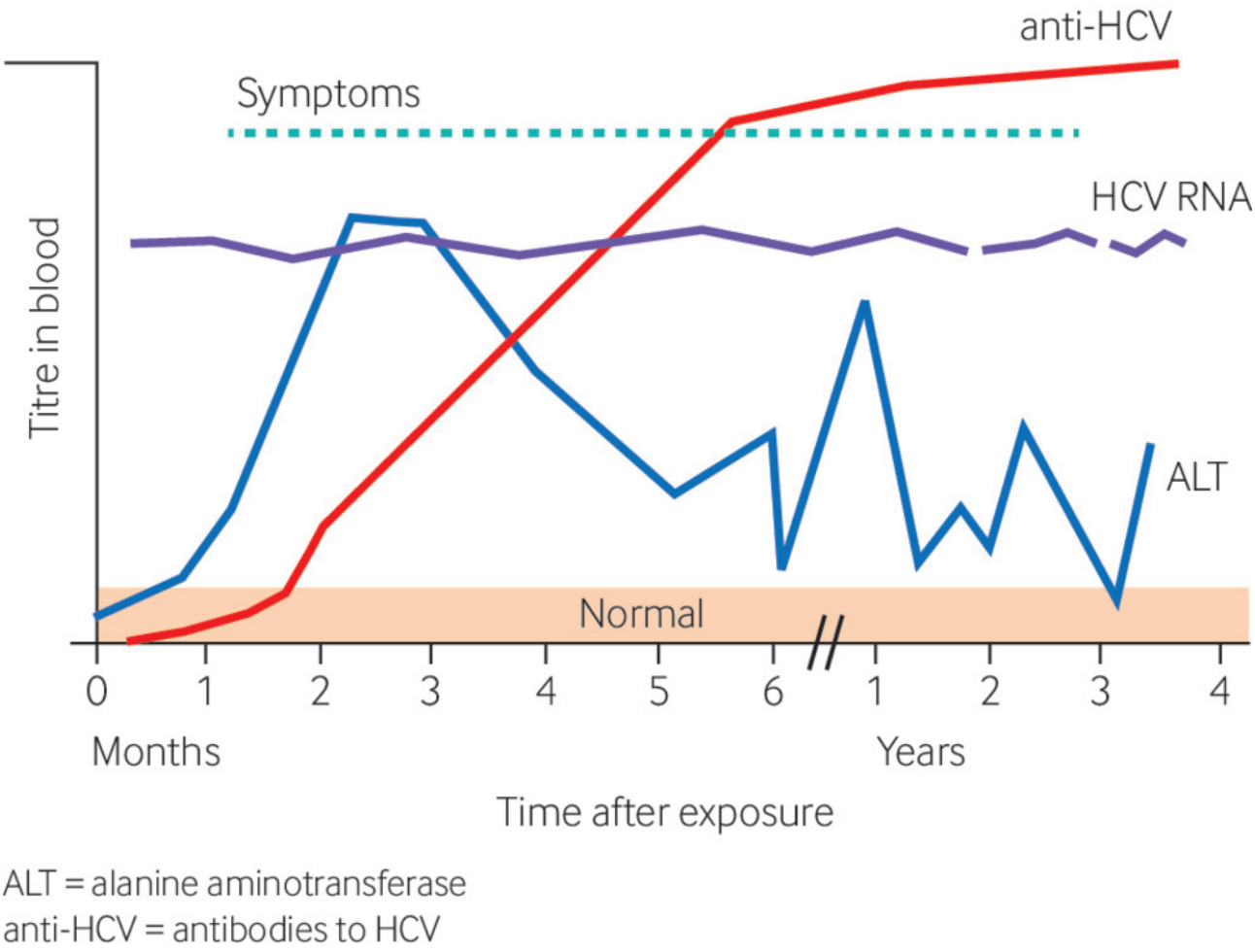

Fig 2 Changes in blood titres of markers of hepatitis C virus (HCV) infection over time. (Adapted from Newfoundland and Labrador Public Health Laboratory. HCV RNA (Hepatitis C virus RNA nucleic acid amplification test). http://publichealthlab.ca/reportingname/hcv-rna-hepatitis-c-virus-rna-nucleic-acid-amplification-test/)