Hepatitis C

Synonym: non-A, non-B (NANB) hepatitis

This disease is notifiable in the UK; see NOIDs article for more detail.

Hepatitis C virus (HCV) was first identified in 1989. It is an enveloped RNA virus in the Flaviviridae family with a narrow host range (humans and chimpanzees).

- HCV is blood-borne and, based upon differences in molecular structure, a number of different strains (genotypes) have been described.
- The incubation period of acute hepatitis C is usually between six and nine weeks [1].
- HCV infection may be acute or chronic. Acute hepatitis C is usually asymptomatic and often does not come to light until some years after infection. Hepatitis C is often diagnosed after routine blood testing, with the onset of hepatic impairment, or when screening a person at risk or a blood donor.

Routes of transmission

Hepatitis C is transmitted via:

- Intravenous drug use.
- Blood transfusion received before September 1991 (since 1991 all blood used in the UK has been screened for HCV).
- Haemodialysis.
- Sexual contact with an infected individual.
- Needlestick injuries in the healthcare setting.
- Perinatal transmission from an infected mother.

The rate of transmission increases when an individual is also infected with HIV.

Epidemiology [2]

- The most recent national estimates suggest that around 214,000 individuals are chronically infected with HCV in the UK.
- Deaths, transplants and hospital admissions for hepatitis-related end-stage liver disease continue to rise.
- Worldwide, over 180 million people are infected.
- However, there is a very large number of undiagnosed cases and estimates of true prevalence are much higher.
- Six major genetic types of HCV have been found [3];
  - Genotypes 1 and 3 are the most common subtypes of hepatitis C in England and Wales.
  - Patients can be infected by more than one genotype.

Chronic HCV infection

- About 75% of patients infected with hepatitis C will develop chronic disease. The remaining 25% clear the virus spontaneously at the acute stage [1].
- Cirrhosis develops in 20-30% after 20 years.
- Around 1-4% of patients with cirrhosis develop hepatocellular carcinoma and 2-5% per year develop liver failure.
- The number of people affected by HCV-related liver disease is continuing to rise.

Risk factors

- Drug misuse:
  - Injecting drug use remains the single most important reported risk factor for acquiring hepatitis C infection.
  - The major route of HCV transmission in the UK is by sharing equipment for injecting drug use, usually via blood-contaminated needles and syringes. Other drug-injecting equipment (eg, spoons and filters) may also transmit the infection if it is contaminated with infected blood.

- Blood transfusions:
  - Receiving a blood transfusion before September 1991 has since been shown to account for the majority of cases of post-transfusion NANB hepatitis.

- Pregnancy and breastfeeding:
  - Mother to baby (before or during birth); transmission rate from mother to child is about 6% [3]. However, this is increased to around 14-17% when there is co-infection with HIV.
  - Breastfeeding is considered safe.
• Sexual intercourse:
  - Sexual transmission of HCV is possible but uncommon. Fewer than 5% of the regular sexual partners of people with HCV infection will become infected.
  - Studies have shown that individuals with multiple sexual partners have a slightly increased prevalence of hepatitis C compared with the general population.

• Other routes of transmission:
  - Needlestick injury is a significant risk for healthcare workers and other groups such as police, prison staff and social workers.
  - Worldwide, poorly sterilised medical and dental equipment as well as infected blood products are the primary sources of infection.
  - Tattooing, ear piercing, body piercing or acupuncture when performed with unsterile equipment.
  - Sharing razors or toothbrushes which are contaminated with blood.

• Certain factors are associated with more rapid progression to severe liver disease. These include:
  - Being over 40 years old at the time of infection.
  - Alcohol consumption.
  - Male gender.
  - Co-infection with HIV or hepatitis B:
    - As many as a third of patients with HIV also have HCV.
    - With increased survival in patients with HIV, the major burden of disease is becoming end-stage liver disease secondary to HCV infection with rapidly progressive fibrosis and cirrhosis.
    - Co-infection leads to earlier and more severe liver disease.
  - Immunosuppressive therapy.

**Needlestick injury**

See also the separate Needlestick Injury article.

• Risk of transmission is estimated at 3%.
• No post-exposure vaccine is currently available and neither immunoglobulin nor any antiviral agent has been shown to be effective.
• For healthcare workers exposed to a source known to be positive for anti-HCV or HCV RNA (or a source whose hepatitis C status is unknown but who is assessed to be at high risk), serum should be obtained from the healthcare worker at baseline, 6, 12, and 24 weeks after exposure.
• Serum should be tested for HCV RNA at 6 and 12 weeks and for anti-HCV at 12 weeks and 24 weeks.
• Early testing of the serum of the healthcare worker for HCV RNA will, if negative, give some reassurance at this stage.
• If the care worker seroconverts, they should be referred for specialist care.


**Risk factors for more aggressive disease include:**

• Obesity.
• Alcohol.
• Diabetes.
• Male.
• Older age of acquiring infection.
• Co-infection with HIV/hepatitis B.

**Presentation** [3]

• People infected with HCV are often asymptomatic.
• Many people who are chronically infected will experience nonspecific symptoms, including malaise, weakness and anorexia.
• Clinical features are worse if there is a high alcohol intake or other liver disease.

**Acute HCV infection**

• The majority are asymptomatic. 20-30% present with jaundice or deranged liver enzymes - alanine aminotransferase (ALT); and 20-30% have nonspecific symptoms such as anorexia, lethargy or abdominal pain.
• Average time from exposure to onset of symptoms is 6-7 weeks and, to seroconversion, 8-9 weeks (can take up to nine months).
• 15-25% of patients appear to clear the virus without sequelae (no detectable virus and normal LFTs; however, the remainder develop chronic infection.
Chronic HCV infection

- Chronic HCV is indicated by persistently elevated or fluctuating liver enzyme levels.
- Chronic infection often goes unrecognized for 10-20 years unless identified when a patient volunteers for blood donation or has LFTs performed - aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT).

Investigations

Investigations should include a full assessment for other possible causes of abnormal LFTs, hepatitis, cirrhosis or any other individual presentation.

Screening for HCV in general practice is recommended for unexplained abnormal LFTs and for any person in an at-risk group.

Patients with suspected HCV infection should be tested for anti-HCV serology. False negatives can occur in patients with acute infection, immunodeficiency or end-stage kidney disease. HCV serology is positive three months after exposure in 90% of cases but may take as long as nine months to become positive.

Testing for hepatitis C

- In immunocompetent people: antibodies to hepatitis C virus, indicating if a person has ever been infected with HCV.
- If the antibody test is positive, or in immunocompromised people: HCV RNA (to check if HCV infection is active) and genotype analysis.
- If the antibody test is negative, consider repeating it (especially if the person is at high risk of infection).
- Repeat the antibody test at an appropriate time if the last risk exposure occurred within the 3- to 6-month "window period" of the test, as it can take at least three months for antibodies to become detectable.
- Seek specialist advice if there is uncertainty about the optimal time to repeat the test.
- Repeat HCV RNA after 6/12 if antibodies are positive but HCV RNA is negative.
- Repeat HCV RNA if positive to confirm diagnosis.

Other initial baseline investigations

These should include:

- FBC, renal function and electrolytes, LFTs, clotting screen, HbA1c, TFTs, ferritin.
- Hepatitis A serology: hepatitis A immunoglobulin M (HAV-IgM).
- Hepatitis B serology: hepatitis B surface antigen (HBsAg) or antibody to hepatitis B core antigen (anti-HBc).
- HIV test.
- Also consider screening for other sexually transmitted infections, if hepatitis C infection is thought to have been sexually acquired.

Further investigations

Further specialist investigations to assess the state of infection and progression of liver disease may include:

- Blood tests: viral load to assess response to treatment; clotting studies; autoantibodies.
- Transient elastography can be offered to diagnose cirrhosis. If this is not suitable, liver biopsy can be offered.
- Liver ultrasound is used in people with advanced fibrosis or cirrhosis to screen for hepatocellular cancer. Ultrasound cannot accurately assess the degree of inflammation or liver fibrosis, or predict the prognosis.
- Liver biopsy may be considered in individual cases - for example, to assess the extent of liver damage caused by inflammation, fibrosis, or cirrhosis; to identify iron overload; and to exclude other causes of liver damage. However, liver biopsy has largely been replaced by non-invasive investigations such as transient elastography (Fibroscan®).

Associated diseases

There is an increased risk of developing diabetes mellitus in patients with HCV infection. There is also an increased risk of developing the following conditions:

- Sjögren's syndrome.
- Essential mixed cryoglobulinaemia.
- Polyarteritis nodosa.
- Autoimmune hepatitis.
- Thyroiditis.
- Membranous glomerulonephritis.
- Porphyria cutanea tarda.
- Lichen planus.
- Immune thrombocytopenia.

Management

Notify the local Health Protection Team of suspected cases of acute viral hepatitis by completing a notification form immediately. Provide sources of support and information about hepatitis C, including British Liver Trust and Hepatitis C Trust.
Acute HCV

- Arrange a same-day assessment or immediate specialist advice if suspected acute HCV (hepatitis C antibody positive with clinical features of acute hepatitis, and/or a likely recent source of transmission is identified).
- Acute HCV infection: specialist clinical and laboratory monitoring to check for spontaneous viral clearance for the initial three months following diagnosis, as they will often have self-limiting infection which will not require treatment.
- If needed, treatment with interferon started between 3-6 months after diagnosis is more likely to clear infection and reduces the risk of chronic HCV infection and progression of liver disease than if started later in the course of disease.

Chronic HCV

- Arrange urgent specialist referral if a person has suspected chronic hepatitis C infection (hepatitis C antibody positive and RNA positive with no clinical features of acute hepatitis).
- The diagnosis of chronic HCV is usually made by a specialist 4-6 months following the initial diagnosis of HCV infection if the virus has not spontaneously cleared in that timescale.
- Specialist assessment and monitoring to determine if further management is needed, including screening for hepatocellular cancer.
- Early treatment to eradicate HCV infection is associated with increased and sustained viral response rates, and can reduce the risk of complications such as end-stage liver disease and hepatocellular carcinoma.

Lifestyle advice

- Advise to stop drinking alcohol and stop smoking. Patients should be advised that excess alcohol consumption appears to hasten the progression of disease. Abstinence from alcohol is therefore essential.
- Maintain a healthy body weight and diet.
- Arrange counselling from a health carer with knowledge and experience of chronic HCV infection - on the implications of HCV positivity, the risks of passing on the infection and risk reduction. Patients with HCV should not donate blood, organs, tissues or semen. Nor should they share razors, toothbrushes or any other object which might be contaminated with blood.
- Advise about the risk of sexual transmission: rare in a stable relationship, but greater risk in people co-infected with HIV and with risky sexual practices, including anal sex. Advise those at higher risk of sexual transmission always to practise safe sex and use condoms.
- Encourage the person to inform injecting or sexual contacts, so they can be tested for hepatitis C.

People with hepatitis C infection should be offered immunisation against hepatitis A and B, as co-infection with hepatitis A can increase the risk of acute fulminant hepatitis, and co-infection with hepatitis B can lead to hepatic decompensation and a worse prognosis.

Advises the person that they may be eligible for financial compensation if they were alive on 29 August 2003, and have chronic hepatitis C that is attributable to NHS treatment with blood or blood products received before September 1991.

Specialist treatments

Antiviral combination therapy

- All people with chronic HCV infection should be considered for antiviral therapy (always initiated by a specialist). The treatment regime, duration of treatment, and effectiveness will depend on the HCV genotype and subtype, viral load, severity of liver disease, the person’s comorbidities, and ability to tolerate treatment.
- Combination dual drug therapy usually consists of weekly self-administered subcutaneous injections of pegylated interferon alfa and daily oral doses of oral ribavirin. The combination of ribavirin and interferon alfa is less effective than the combination of peginterferon alfa 2b and ribavirin. Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated.
- Daclatasvir, ombitasvir, sofosbuvir, ledipasvir are licensed for use in combination therapy. Sofosbuvir is also licenced in combination with velpatasvir and voxilaprevir.\(^4\)

Regular clinical and blood monitoring is needed to check for any medication adverse effects and response to treatment.

Couples, with one partner receiving dual or triple therapy, should use two forms of contraception during treatment and for six months after treatment has ended, due to the risks of teratogenicity.

As newly developed drugs become available over the next few years these changes are expected to continue. To provide healthcare professionals with up-to-date guidance as new therapies are available and integrated into HCV regimens, the Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD) have developed a ‘living document’ for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management.\(^5\)

Liver transplantation

Liver transplantation is the treatment of choice for people with end-stage liver disease. HCV recurrence due to graft infection is common after transplantation, and the life of the graft is reduced in people with recurrent HCV. The course of HCV-related liver disease is accelerated in liver transplant recipients, and about one third of people will develop cirrhosis within five years following transplantation.

Children\(^6,7\)

- Peginterferon alfa in combination with ribavirin is recommended, within its marketing authorisation, as an option for treating chronic hepatitis C in children and young people.
- Children infected with all genotypes of hepatitis C, with evidence of moderate or severe liver disease, should be considered for treatment with peginterferon alfa and ribavirin.
• Children infected with HCV genotypes 2 and 3 should be considered for treatment with peginterferon alfa and ribavirin irrespective of disease stage.
• In children with mild disease and infection with other genotypes, the benefits of treatment should be balanced against the risk of side-effects.

New generations of drugs need to be developed which address the genetic variability of HCV and also issues of viral resistance.

Further management
• After successful eradication of the virus, patients with substantial fibrosis or cirrhosis require long-term follow-up - eg, to monitor for complications such as hepatocellular carcinoma and oesophageal varices[3].
• Consideration should be given to entering patients with established cirrhosis into surveillance programmes for hepatocellular carcinoma (provided their general health is good enough that emerging cancers could be appropriately treated). Scottish Intercollegiate Guidelines Network (SIGN) recommends that all patients with HCV and cirrhosis should have a six-monthly ultrasound scan to screen for hepatocellular carcinoma.
• Some people with end-stage liver disease or hepatocellular carcinoma may need liver transplantation[3].

Complications

Patients who develop cirrhosis are at increased risk of hepatocellular carcinoma:

• Between 1% and 5% of those infected with HCV will develop primary liver cancer.
• Hepatocellular carcinoma is suggested by weight loss and raised alpha-fetoprotein level.

Prognosis[1]

The rate of progression of the disease is slow but variable. Approximately 50-85% of patients infected with HCV become chronic carriers. The chronic carrier state rarely resolves spontaneously.

Type 1 genotype is more likely to clear spontaneously but leads to more severe chronic infection. People with HCV genotype 1 typically have a longer treatment course than other genotypes. They may be considered for treatment with triple therapy involving the addition of a protease inhibitor which has improved treatment success rates compared with dual therapy.

HCV infection is cured in more than 99% of people who achieve a sustained viral response (SVR):

• HCV genotype 1 on dual treatment: SVR of 52%; increased to 70% for people on triple therapy.
• HCV genotypes 2 and 3: SVR rates of 76-82% on dual therapy.
• HCV genotypes 4, 5, and 6 on dual therapy: SVR of 71%.

About 30% of those who are infected develop cirrhosis within 20-30 years and a small percentage of these people are at a high risk of developing hepatocellular carcinoma. A third may never progress to cirrhosis or will not progress for at least 50 years.

Both co-infection with hepatitis B and alcohol abuse seem to confer a worse prognosis.

Prevention

• No vaccine is currently available for HCV[8].
• Patients and at-risk groups should be counselled to minimise transmission.
• Prevention strategies target those groups at greatest risk of infection (eg, intravenous drug users and in prisons) and include:
  • Improving education on illicit drug use.
  • Reducing initiation of injecting drug use.
  • Helping intravenous drug users to quit injecting.
  • Minimising harm for those who continue to inject.
  • Promoting the use of condoms, especially for those with multiple partners.

Further reading & references

• Recommendations on treatment of hepatitis C; European Association for the Study of the Liver (Apr 2014)
• Guidelines on hepatitis B and C testing; World Health Organization (February 2017)
• Ledipasvir–sofosbuvir for treating chronic hepatitis C; NICE Technology Appraisal Guidance, November 2015
• Dasabuvir for treating chronic hepatitis C; NICE Technology Appraisal Guidance, November 2015
• Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C; NICE Technology Appraisal Guidance, November 2015
• Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C; NICE Technology Appraisal Guidance, September 2010
• Boceprevir for the treatment of genotype 1 chronic hepatitis C; NICE Technology Appraisal Guideline, April 2012
• Telaprevir for the treatment of genotype 1 chronic hepatitis C; NICE Technology Appraisal Guidance, April 2012
• Sofosbuvir for treating chronic hepatitis C; NICE Technology Appraisal Guidance, February 2015
• Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C; NICE Technology Appraisal Guidance, February 2015

1. Hepatitis C; NICE CKS, February 2016 (UK access only)
2. Hepatitis C: guidance, data and analysis; Public Health England, April 2013
4. British National Formulary (BNF); NICE Evidence Services (UK access only)
5. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C; American Association for the Study of Liver Disease/Infectious Disease Society of America (2017)
6. Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people; NICE Technology Appraisal Guidance, November 2013
7. Management of hepatitis C; Scottish Intercollegiate Guidelines Network - SIGN (July 2013)

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