Hepatitis C

Synonyms: HCV; 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 6 and 9 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:

- Parenteral route, especially intravenous drug use, but also 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; sexual transmission is low (less than 1% per year of a relationship) but the rate increases when an individual is also infected with HIV.\(^2\)
- Needlestick injuries in the healthcare setting result in a 3% risk of HCV transmission.
- Perinatal transmission from an infected mother.

Epidemiology\(^3\)

- 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: \(^4\)
  - Genotypes 1 and 3 are the most common subtypes of hepatitis C in England and Wales. People who have genotype 1 usually require a longer duration of treatment and tend to have a worse prognosis than people who have genotype 3.

- Patients can be infected by more than one genotype.

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 breast-feeding:
- Mother to baby (before or during birth); transmission rate from mother to child is about 6%. However, this is increased to around 14-17% when there is co-infection with HIV.
- Breast-feeding 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.

Presentation[4]
- 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.[2]

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
- About 75 of patients infected with hepatitis C will develop chronic disease. The remaining 25% clear the virus spontaneously at the acute stage.[1]
- It is indicated by persistently elevated or fluctuating liver enzyme levels.
- Chronic infection often goes unrecognised for 10-20 years unless identified when a patient volunteers for blood donation or has LFTs performed (aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT).
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. HCV-related liver disease is continuing to rise. Risk factors for more aggressive disease include:
- Obesity.
- Alcohol.
- Diabetes.
- Male.
- Older age of acquiring infection.
- Co-infection with HIV/hepatitis B.

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.

See Public Health England's reference 'Hepatitis C: guidance, data and analysis' for further information about the management of occupational exposure.

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.
- Ongoing infection is confirmed in those with positive serology by testing for HCV RNA. A negative test, despite positive serology, suggests non-viraemic infection, transient absence of viraemia or recovered infection, a level of viraemia below the detection limit of the assay, or may reflect a nonspecific ELISA result.
- The quantitative measurement of HCV RNA concentrations in serum and the determination of HCV genotype are recommended and should be used in helping to determine the duration of treatment.
- Spontaneous resolution of acute hepatitis C results in the loss of HCV RNA within the first two months. Only those HCV RNA-positive for more than two months need to be treated.
- Antibodies stay in the body lifelong, regardless of treatment.
- Assessing severity of disease:
  - Liver biochemistry is insensitive at predicting disease severity and normal results do not exclude progressive liver disease or cirrhosis.
  - Baseline ultrasound should be performed to look for focal lesions, splenomegaly (a marker of portal hypertension) or frank features of cirrhosis, although normal findings on imaging do not exclude cirrhosis.
  - Liver biopsy has largely been replaced by non-invasive investigations such as transient elastography (Fibroscan®).
  - Non-invasive methods for assessing fibrosis are evolving and include using serum markers (eg, macroglobulin, haptoglobin, apolipoprotein A1, GGT and total bilirubin) or with transient elastography, in which a shear wave is generated and tracked through the liver using ultrasound.
Liver biopsy can be valuable to provide an histological assessment of the severity of liver inflammation, potential progression of fibrosis and the presence or absence of cirrhosis (LFTs correlate poorly with both necro-inflammatory and fibrosis scores found on liver biopsy).

HIV testing should be considered in all patients with HCV. Patients should also be tested for serological evidence of previous infection with hepatitis A or B, and immunisation offered to those without evidence of previous infection.

Patients should also be assessed for other risk factors for liver disease (eg, alcohol, obesity) and given appropriate lifestyle advice and medical treatment.

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

Clinical Editor's notes (July 2017)

Dr Hayley Willacy recognises that treatments for hepatitis C infection have changed substantially since the development of HCV protease inhibitor therapies in 2011. 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.

Early diagnosis is essential for effective patient care. Refer to a specialist with a particular interest in HCV. The aim of treatment is to prevent cirrhosis, liver failure or hepatocellular carcinoma developing.

The management of uncomplicated acute viral hepatitis is largely symptomatic. However, early treatment of acute hepatitis C with interferon alfa (unlicensed indication) may reduce the risk of chronic infection.

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.

The risk of sexual transmission is small - maximum of 5%, but possibly much less. There is insufficient evidence firmly to recommend barrier contraception in stable monogamous relationships but is strongly advised for HCV-infected patients with multiple sexual partners.

Patients should be advised that excess alcohol consumption appears to hasten the progression of disease. Abstinence from alcohol is essential.

Drug therapy should be considered for all patients with hepatitis C.

Drug treatment

The effectiveness of treatment is related to the genotype of the virus. In trials for people with moderate or severe hepatitis C, about 75-85% of people with HCV genotype 2 or 3 had a sustained virological response six months after finishing a course of treatment with peginterferon alfa and ribavirin, compared with 40-50% of people with genotype 1, and somewhere in between these response levels for the three less common genotypes (4, 5 and 6).

- Weekly subcutaneous peginterferon alfa-2a (or alfa-2b) and daily oral ribavirin can be prescribed in line with current National Institute for Health and Care Excellence (NICE) guidelines.
- Combination therapy with peginterferon alfa-2a (or alfa-2b) and ribavirin can achieve a sustained virological response in approximately half of patients.
NICE has recommended boceprevir and telaprevir as options for the treatment of people with genotype 1 chronic hepatitis C, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or in whom previous treatment has failed.\cite{8, 10}

Both boceprevir and telaprevir work by inhibiting the activity of the NS3/4A serine protease. This protease is essential for viral replication and may be partially responsible for the ability of HCV to evade clearance by the host immune system.\cite{11}

Boceprevir and telaprevir will revolutionise the management of hepatitis C genotype 1 patients and will, most likely, decrease the burden of end-stage disease worldwide.\cite{12}

Current recommendations are to use combination therapy for varying times according to genotype:
- Treatment of genotypes 1, 4, 5, and 6 requires 48 weeks of pegylated interferon and ribavirin and leads to sustained viral response rates of between 38-50%.
- Treatment of genotype 2 and 3 requires 24 weeks of pegylated interferon and ribavirin and leads to sustained viral response rates of between 75-80%.
- A minimum of a 100-fold drop in viral load is required to continue treatment beyond 12 weeks. If this is not achieved then treatment is stopped early, as further therapy is likely to be futile.

Second or subsequent courses of treatment are not recommended for people who have been treated with a first course of either combination therapy or monotherapy with peginterferon alfa if they have not had an early response (as indicated by reduction in viral load at 12 weeks).

There is insufficient evidence to recommend combination therapy or monotherapy with peginterferon alfa for people with mild chronic hepatitis C who are under the age of 18 years or for those who have had a liver transplant.

Treatment is contra-indicated in women who are pregnant or breast-feeding. Adverse effects of treatment are common and can affect compliance.

NICE recommends sofosbuvir in combination with peginterferon alfa and ribavirin only for:\cite{13}
- Adults with genotype 1 HCV.
- Adults with genotype 3 HCV who are treatment-experienced (not adequately responded to interferon-based treatment). Only recommended for treatment-naive if they have cirrhosis.
- Adults with genotype 4, 5 or 6 HCV only if they have cirrhosis.

NICE recommends sofosbuvir in combination with ribavirin only for:\cite{13}
- Adults with genotype 2 HCV if treatment-experienced. Only for treatment-naive if intolerant to or ineligible for interferon.
- Adults with genotype 3 HCV only if they have cirrhosis and are intolerant to or ineligible for interferon.

Simeprevir, in combination with peginterferon alfa and ribavirin, is recommended by NICE as an option for treating genotype 1 and 4 chronic hepatitis C in adults.\cite{14}

Daclatasvir is licensed for:\cite{7}
- Use in combination with sofosbuvir for the treatment of chronic hepatitis C infection of genotypes 1 or 4, with or without compensated cirrhosis. The addition of ribavirin should be considered for patients with advanced liver disease or with other negative prognostic factors, such as prior treatment experience.
- Use combination with sofosbuvir and ribavirin for the treatment of chronic hepatitis C infection of genotype 3 in patients who are treatment-experienced, with or without compensated cirrhosis, and in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C infection of genotype 4.
- Daclatasvir must not be given as monotherapy.

Children\cite{15, 16}
- 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.\[17\]

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.\[4\]
• 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.\[4\]

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\[4\]
• The rate of progression of the disease is slow but variable.
• Approximately 50-85% of patients infected with HCV become chronic carriers.
• Type 1 genotype is more likely to clear spontaneously but leads to more severe chronic infection.\[2\]
• The chronic carrier state rarely resolves spontaneously.
• 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 to confer a worse prognosis.

Prevention
• No vaccine is currently available for HCV.\[18\]
• 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.

• Current public health actions include:
  • Prevention of new infections.
  • Increased awareness of infection.
  • Increased diagnosis of HCV.
  • Ensuring individuals with HCV have the appropriate treatment and care.

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
- Daclatasvir 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

1. Hepatitis C; NICE CKS, March 2010 (UK access only)
3. Hepatitis C; guidance, data and analysis; Public Health England, April 2013
5. Management of co-infection with HIV-1 and hepatitis B or C virus; British HIV Association (2010)
6. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C; AASLD (American Association for the Study of Liver Disease) and IDSA (Infectious Disease Society of America) (2017)
8. Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C; NICE Technology Appraisal Guideline, September 2010
9. Boceprevir for the treatment of genotype 1 chronic hepatitis C; NICE Technology Appraisal Guideline, April 2012
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11. Rowe IA, Mutimer DJ; Protease inhibitors for treatment of genotype 1 hepatitis C virus infection. BMJ. 2011 Nov 10;343:d6972. doi: 10.1136/bmj.d6972.
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14. Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C; NICE Technology Appraisal Guideline, February 2015
15. Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people; NICE Technology Appraisal Guideline, November 2013
16. Management of hepatitis C; Scottish Intercollegiate Guidelines Network - SIGN (July 2013)

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| Author: Dr Colin Tidy | Peer Reviewer: Prof Cathy Jackson |
| Document ID: 2252 (v27) | Last Checked: 24/04/2015 | Next Review: 22/04/2020 |

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