Hepatitis C

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Abstract

Hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease. Over 150 million people worldwide have chronic HCV infection and are at risk of developing its life-threatening complications. Acute infection is usually asymptomatic, with most patients unaware that they have contracted the virus. Some patients clear the virus spontaneously, but most become chronic carriers. If carriers are identified, they can be treated with antiviral therapy, the main goal being prevention of cirrhosis, liver failure and hepatocellular carcinoma by eradicating the virus. During the past decade, there has been impressive progress in the efficacy and tolerability of therapy, with modern treatment regimens able to eradicate the virus in >90% of cases with minimal adverse effects. However, therapy is costly, many infected individuals are unaware that they carry the virus, and for many there are barriers preventing them from accessing medical care. In the future, HCV could be eliminated, but to achieve this strategies to increase screening for infection and improve the uptake of treatment are needed.

Keywords Cirrhosis; directly acting antiviral agents; elimination; hepatitis C virus; hepatocellular carcinoma; MRCP; people who inject drugs

Key points

- Chronic hepatitis C infection is a significant global health problem
- Many patients are unaware that they carry the virus and are at risk of liver disease
- Most chronic carriers remain healthy, but 20–30% develop cirrhosis over a 20-year period
- Sustained viral eradication can be achieved in >90% of treated patients
- The World Health Organization has set a target for the global elimination of hepatitis C by 2030
- Targeted testing and treatment services should be more accessible – particularly to people who inject drugs

Introduction

Hepatitis C virus (HCV) was identified in 1989 and is an important cause of parenterally transmitted hepatitis. Chronic HCV infection is a major cause of liver disease and mortality worldwide.[1] More than 100,000 people in the UK and 150 million worldwide (approximately 2% of the global population) are chronic carriers of the virus, most being unknowingly infected. In developed countries, marked variations in prevalence exist: 0.04% in healthy blood donors, 1% in people attending genitourinary clinics and up to 50% in people who inject drugs (PWID).

Directly acting antivirals (DAAs) can now effectively cure the virus and prevent the associated complications of liver disease. The development of DAAs has also led to a global elimination goal for HCV by 2030.[2] However, under-recognition of infection, poor accessibility to the drug-using population and barriers to accessing medical care present major challenges to this being met. In the UK, case-finding initiatives with treatment outreach programmes are care priorities.

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The virus

Virology

HCV is an enveloped virus of the Flaviviridae family, with six major genotypes (1–6) and >50 subtypes. The viral genome is a single-stranded, positive RNA molecule consisting of a single open reading frame coding for all the structural and non-structural proteins of the virus (Figure 1). Replication is via a negative-strand RNA intermediate and is controlled by an RNA-dependent RNA polymerase that lacks proof-reading ability; this allows the generation of many mutant viruses, or quasi-species, within a single host. This diversity contributes to the ability of the virus to evade the host immune response and poses challenges to the development of an effective vaccine.

Transmission

In developed countries, recreational drug use is the dominant mode of HCV transmission. Sharing needles is the main risk factor, but infection can also occur from paraphernalia used to prepare drugs and participants of needle-exchange programmes are still at risk. The advent of effective screening of blood products in 1992 has dramatically reduced transmission by this means. In developing countries, poorly sterilized medical and dental equipment as well as infected blood products are also important sources of infection.

Sexual transmission of HCV is infrequent, and individuals in long-term monogamous relationships are generally at low risk of transmitting the virus. Those with multiple sexual partners, particularly those engaging in traumatic sexual activity, are at higher risk. Outbreaks of HCV have been reported in HIV-positive homosexual men in a number of cities in Europe. Perinatal transmission leads to infection in approximately 5% of infants born to HCV-infected women, and this risk is increased in

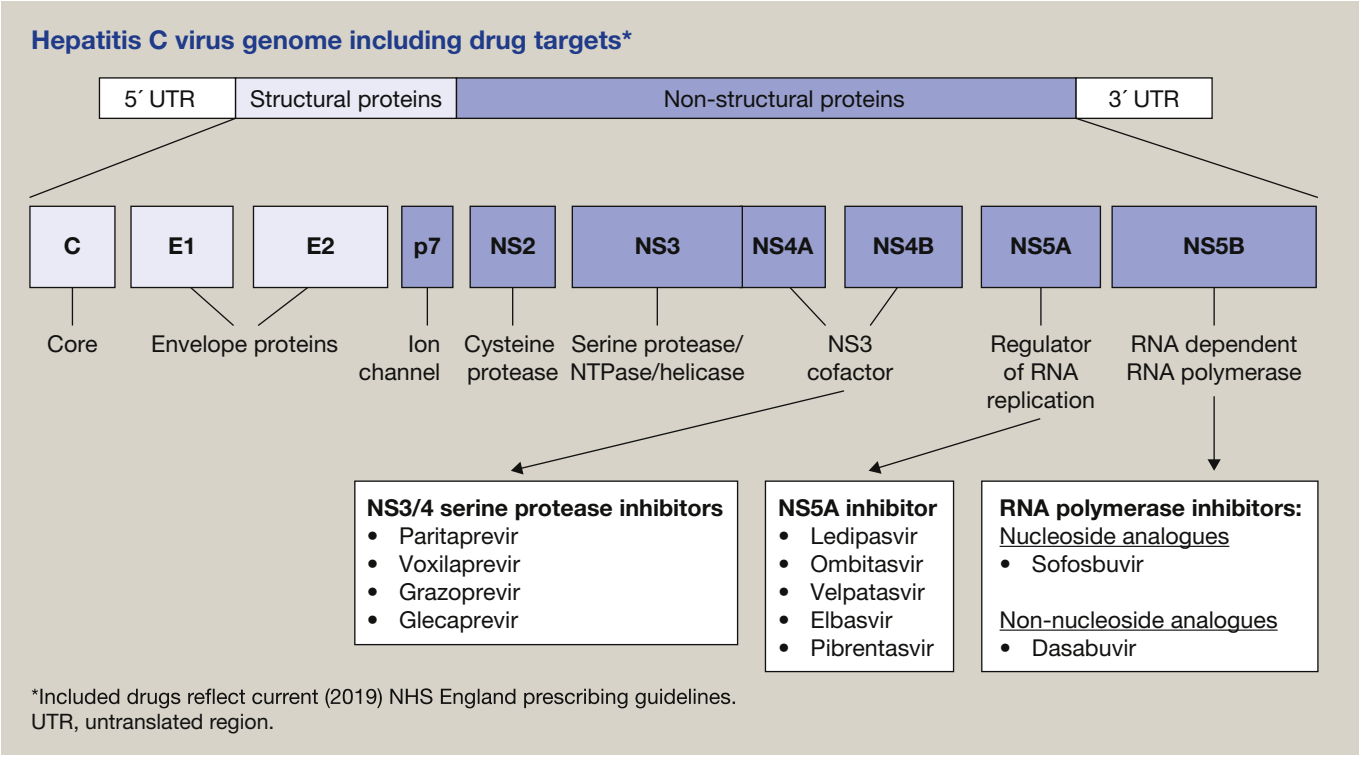

Figure 1

mothers co-infected with HIV. Breastfeeding and close household contact do not appear to transmit the virus.

Natural history of infection (Figure 2)

Acute HCV infection is usually asymptomatic and thus goes unrecognized, but if detected is highly amenable to treatment. A few patients clear the virus spontaneously but most (60–85%) become chronically infected. Whereas most chronic carriers do not develop significant liver disease, approximately 20–30% develop cirrhosis over a 20-year period. This variable clinical course depends on a number of host factors: more aggressive disease progression is predicted by alcohol consumption, obesity, diabetes mellitus, male gender, older age at infection and co-infection with HIV or hepatitis B.

Once cirrhosis has developed, the risk of developing liver failure is 2–5% per year. HCV infection is associated with an increased risk of hepatocellular carcinoma (HCC), primarily in individuals with cirrhosis, in whom the incidence is 1–4% per year. Chronic HCV infection is also associated with a number of extrahepatic manifestations (Table 1).

Evaluation of the patient

Clinical evaluation involves assessing both hepatic and virological aspects of infection. Progression of liver disease often occurs silently, with patients only reporting vague symptoms such as fatigue. Physical examination is usually normal until patients have advanced cirrhosis, so a high index of suspicion is required to identify patients who might have infection.

Virological assessment

Serological assays: serological testing is recommended for screening in individuals with risk factors for disease and patients found to have abnormal liver biochemistry (Table 2). Anti-HCV antibody is detected via enzyme immunoassay. Antibodies stay positive for life regardless of therapy. False-negative serological results may be seen in acute infection, immunocompromised patients or those with end-stage renal disease, and further RNA-based testing should be considered in these instances.

Molecular assays: active infection is diagnosed by detecting HCV RNA in the blood by a polymerase chain reaction-based assay. Highly sensitive quantitative commercial assays are available for detecting virus and for monitoring responses during and after treatment.

Genotyping assays: antiviral treatment decisions can be influenced by knowledge of the viral genotype because this can affect treatment response and duration. Commercial assays are available to determine the genotype by direct sequencing of the virus. Unless there is reinfection, genotypes do not change during the course of infection and need not be tested again.

Non-venepuncture tests: a variety of testing approaches have been validated that do not need conventional venepuncture, including dry-blood spot testing and point-of-care tests such as oral mouth swabs. This has increased the range of professionals able to test for HCV and has had a particular impact in high-risk

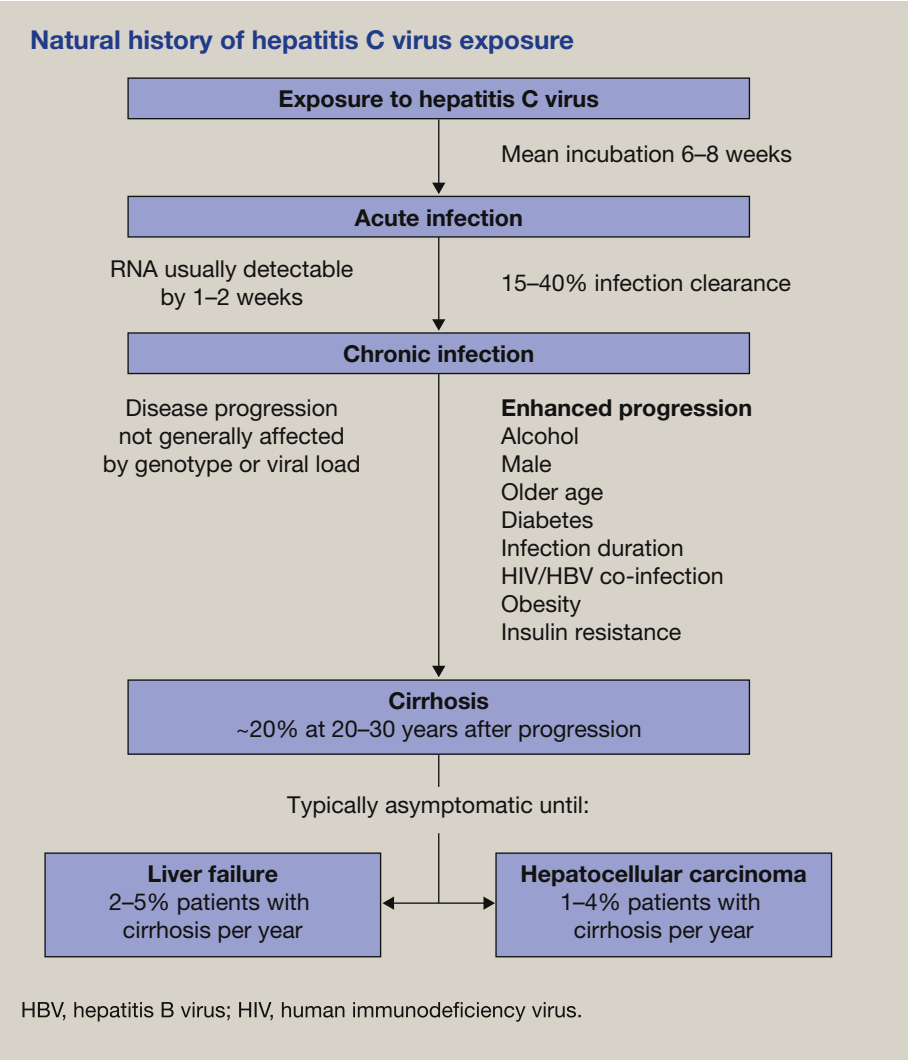

Figure 2

populations such as PWID and prisoners, where venepuncture can be difficult.

Liver assessment

When assessing a patient with HCV, it is important to determine whether they have significant liver fibrosis or cirrhosis. This has implications for their future risk of developing complications and can determine which treatment regimen the patient requires.

Liver biochemistry: liver function tests are insensitive for predicting liver fibrosis or cirrhosis. Serum alanine aminotransferase can be elevated in patients without significant histological abnormality. Similarly, normal values do not exclude progressive liver disease or cirrhosis.

Liver ultrasound: ultrasonography may demonstrate a coarse echotexture or a nodular margin to the liver if there is significant fibrosis; splenomegaly may indicate portal hypertension. However, a normal ultrasound scan does not exclude cirrhosis.

Extrahepatic manifestations of HCV infection

Autoimmune	Thyroid disease
	Siloadenitis
	Immune thrombocytopenic purpura
Haematological	Cryoglobulinaemia
	Monoclonal gammopathy
	Lymphoma
Ocular	Dry eyes
Pulmonary	Fibrosis
Renal	Membranoproliferative glomerulonephritis
Skin	Porphyria cutanea tarda
	Lichen planus
	Leucocytoclastic vasculitis
Bone	Osteosclerosis

Table 1

Individuals who should be considered for HCV screening

Persons who have ever injected illicit drugs[a]
Recipients of transfusions or organ transplants before 1992[b]
Healthcare workers who sustain a needlestick injury or mucosal exposure[c]
Haemophiliacs who were given factor concentrates before 1987
HIV-positive individuals
Children born to HCV-positive mothers[d]
Patients who have ever undergone haemodialysis
Persons with unexplained elevated serum alanine aminotransferase

[a] Use of intranasal cocaine has been associated with acquisition of HCV; infection can be acquired from sharing contaminated equipment even in those who deny sharing needles.
[b] HCV antibody testing was introduced in 1992.
[c] Incidence of seroconversion after needlestick injury is 3–4%.
[d] Testing can be performed although treatment as a child is uncommon and babies can carry their mother's antibodies until 18 months of age.

Table 2

Non-invasive assessment of fibrosis: several tests are available to assess for underlying liver fibrosis or cirrhosis in patients with HCV. These include composite serum markers based on routine and non-routine blood tests and novel imaging modalitities. One widely used modality is transient elastography, in which a shear-wave is passed into the liver to assess 'liver stiffness', used as a surrogate marker for underlying fibrosis. Transient elastography is now widely used and validated for assessment in patients with HCV. For an overview of the different methods available and how they compare to one another, see Houot et al.[3] and the European Association for the Study of the Liver guidelines.[4]

Liver biopsy: liver biopsies to assess the severity of liver disease have been largely replaced by non-invasive methods. Liver biopsies are still used in cases where there is diagnostic uncertainty about the underlying cause of liver disease.

Additional considerations

All patients should be screened for HIV and hepatitis B virus infections as their presence accelerates progression to cirrhosis and increases the risk of HCC. Patients without serological evidence of previous hepatitis A or B should be offered vaccination against these viruses. Patients should be assessed for other risk factors for liver disease (e.g. alcohol use, obesity, diabetes mellitus) and given appropriate lifestyle advice and medical intervention.

Treatment

Why treat?

Successful treatment of HCV is indicated by a sustained loss of viral RNA (SVR). SVR brings huge benefits: it is associated with a 70% reduction in risk of liver cancer, a 90% reduced risk of mortality related to liver disease, a resolution of symptoms and a reduced risk of transmission to the wider community.

Who should be treated?

Treatment with DAAs is now widely available in high-income countries, and few patient groups have contraindications to therapy. However, treatment remains contraindicated in pregnancy and lactating women, because of the potential teratogenic effects, and children should be referred to paediatric units for management. Because of the high treatment costs, there may in some settings be a need to ration therapy to individuals at greatest risk of complications from HCV. These include patients with cirrhosis, advanced fibrosis or debilitating extrahepatic manifestations, and liver transplant recipients.

For many years, clinicians were wary of treating prisoners and PWID. However, evidence shows that their response to therapy is similar to that of other patients; in addition, modelling studies show that treating PWID is likely to have a benefit to the wider community by preventing onward transmission.[5] The treatment of PWID is now recommended in international guidelines.[4]

Directly acting antiviral therapy

Until 2011, the standard of care for HCV was combination therapy with pegylated interferon-α by subcutaneous injection once weekly and oral ribavirin daily. Unfortunately, the treatment duration was long; it required intensive secondary care supervision and was associated with adverse effects and contraindications that affected uptake and accessibility.

However, the development of cell culture systems that supported complete HCV replication improved the basic understanding of viral replication and led to the identification of specific viral targets and antiviral compounds. Since 2011, DAAs with vastly improved efficacy across the viral genotypes have dramatically changed the treatment landscape (see Figure 1). Combinations of these agents can eradicate viral infection within 8–12 weeks in >90% of patients with few or no adverse effects. Treatment appears to be tolerated even in those with liver decompensation, a group that was previously ineligible for treatment with interferon-containing regimens.

Follow-up

All patients found to be HCV carriers should be referred to a hospital or community outreach treatment service so that their liver disease can be staged and therapeutic options discussed. Patients who undergo treatment and achieve SVR can be discharged if their liver disease is mild, but patients with cirrhosis require continued follow-up to detect complications (e.g. HCC, oesophageal varices). If SVR is not achieved after the completion

Potential barriers preventing PWID from accessing the HCV care pathway

Service factors	Social factors	Clinical factors
Inadequate staff expertise	Homelessness	Severe medical co-morbidities
A lack of community testing programmes	Lack of social support	Drug–drug interactions
Lack of a local HCV treatment centre	Incarceration	
Inflexible hospital appointments	Language barriers	
Hospital attendance policies	Drug addiction	
Limited drug commissioning	Private financial concerns	
	Social stigmatization	

Table 3

of therapy, second-line treatment options should be offered. If a decision is made not to treat, patients should undergo regular (i.e. annual) clinical assessment to review their liver disease.

Screening and prevention

Early detection and treatment of HCV has the potential to result in better health outcomes and to save costs by preventing future advanced liver disease. Identifying HCV carriers could also prevent further transmission. The greatest barrier to patients being given HCV treatment is a lack of awareness that they have infection, and there are barriers preventing patients, especially the drug-using population, from accessing treatment (Table 3). The importance of addressing this has been reflected in National Institute for Health and Care Excellence guidance. In the UK, pilot studies have demonstrated benefits from screening in pharmacies and drug treatment units, and such strategies are being more widely adopted as professionals work towards the international elimination target.

Several strategies are already in place to reduce new infections in developed countries. Organs and blood products are screened for the virus, and factor concentrates used to treat haemophilia are heat-inactivated, reducing but not eliminating the risk of acquiring the virus by these routes. The availability of needle-exchange programmes and improved education has reduced needle-sharing among drug users. Development of an effective vaccine is a difficult challenge because of the variability in HCV RNA, the lack of a simple protective antibody response, and the fact that an induction and maintenance of strong T cell immune responses against multiple HCV epitopes is necessary for protection against the virus. Recent HCV research has prioritized drug development and a vaccine is not on the horizon; arguably, this would have more impact globally as the burden of disease is predominantly in countries where the costs of drug treatment remain prohibitive. ◆

KEY REFERENCES

1 Stanaway JD, Flaxman AD, Naghavi M, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet* 2016; **388:** 1081–8.

2 World Health Organization. Combating hepatitis B and C to reach elimination by 2030. 2017, http://www.who.int/hepatitis/publications/hep-elimination-by-2030-brief/en/ (accessed 7 November 2016).

3 Houot M, Ngo Y, Munteanu M, Marque S, Poynard T. Systematic review with meta-analysis: direct comparisons of biomarkers for the diagnosis of fibrosis in chronic hepatitis C and B. *Aliment Pharmacol Ther* 2016; **43:** 16–29.

4 Pawlotsky J-M, Negro F, Aghemo A, et al. EASL recommendations on treatment of hepatitis C 2018. *J Hepatol* 2018; **69:** 461–511.

5 Innes H, Goldberg D, Dillon J, Hutchinson SJ. Strategies for the treatment of hepatitis C in an era of interferon-free therapies: what public health outcomes do we value most? *Gut* 2015; **64:** 1800–9.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 27-year-old man presented to the hepatitis C outreach clinic in the local drug support centre. He was injecting heroin on a daily basis, was not taking opiate substitution therapy and was drinking 30 units of alcohol per week. A dry-blood spot test taken 6 months ago has confirmed the presence of hepatitis C antibody and RNA.

What is the most important factor in determining progression to liver cirrhosis?:

A. Excessive alcohol intake
B. Co-infection with HIV
C. Male gender
D. Regular use of heroin
E. His age at the time of hepatitis C infection

Question 2

A 52-year-old-female presented to the hepatology clinic with hepatitis C for assessment.

Which of the following would be the most appropriate assessment modality for significant liver fibrosis or cirrhosis in a patient with hepatitis C?

A. Serum alanine aminotransferase concentration
B. Serum aspartate transferase/alanine aminotransferase ratio
C. Liver ultrasonography
D. Liver biopsy
E. Transient elastography

Question 3

A 34-year-old male, with a history of injecting drug use, underwent repeat testing for hepatitis C and was confirmed to have genotype 3a and an RNA titre of 4×10^4 IU/ml.

What conditions (if any) should be met before he is started on antiviral treatment?

A. No conditions
B. RNA $>1 \times 10^6$ IU/ml
C. Presence of cirrhosis
D. Abstinence from alcohol
E. On opiate substitution programme