Managing hepatitis C virus infection

Kathryn L Nash,1 Ian Bentley,2 Gideon M Hirschfield3

Chronic infection with the RNA flavivirus hepatitis C is a major cause of liver disease.1 The Department of Health estimates that in the United Kingdom, chronic infection is present in 200,000 people—of whom 50% are unaware that they carry the virus—with variations in prevalence between different groups (0.04% in blood donors, 1% in people attending genitourinary clinics, and up to 50% in intravenous drug users). A general practitioner with an average list of 1800 can expect to have eight to 20 patients with hepatitis C infection. If such patients are identified and treated, the virus can be eradicated in more than half of them. We outline this area of hepatology, highlighting risk factors for acquisition, groups to screen, and specialist management of patients with chronic infection.

What is the natural history of hepatitis C infection?

In the UK the main mode of acquisition is recreational intravenous drug use; in developing countries transmission of blood products and exposure to unclean or unsterilised objects remains important—for example, during circumcision, scarification, and tattooing (box 1). Outcomes of infection are not uniform (fig 1).2 Acute infection is usually unrecognised, and 60-85% of patients progress to chronic infection with persistent detection of hepatitis C virus RNA.

The major complication of persistent infection is chronic hepatitis, which leads to advanced fibrosis and cirrhosis in about one in five patients over a period of 20 to 30 years. The infection is a leading indication for liver transplantation. Alcohol consumption, coinfection with HIV or hepatitis B virus, obesity, hepatic steatosis, diabetes, male sex, and older age at the time of infection predict more aggressive disease, and consequently complications.3 Patients with cirrhosis have an increased risk of hepatocellular carcinoma, which has an incidence of 1-4% per year in such patients.4 The association of hepatitis C infection with an increased risk of developing insulin resistance and type 2 diabetes, as shown by cross sectional and longitudinal studies, is noteworthy,5 as are rare extrahepatic autoimmune or lymphoproliferative manifestations such as cryoglobulinaemic vasculitis and B cell lymphoma.6 7 A systematic review supports the concept that patients with hepatitis C virus infection have clinically significant reductions in health related quality of life.6

How are patients assessed for hepatitis C infection?

Who to screen

Acute infection is usually not identified, unless investigation is prompted by symptomatic hepatitis. Chronic infection—for longer than six months—may be identified when evaluating abnormal liver biochemistry, thrombocytopenia (seen with portal hypertension), incidental imaging findings suggesting cirrhosis, or decompensated liver disease. Screening in general practice is recommended (www.dh.gov.uk/en/PublicHealthCommunicableDiseases/HepatitisC) for individuals in the following groups.

• Unexplained abnormal liver biochemistry tests
• Ever injected drugs
• Received blood transfusion in the UK before September 1991 or any blood products before 1986
• Received medical or dental treatment where infection control may be poor
• Children of infected mothers
• Sexual partners of infected people
• Exposed to blood where a risk of transmission exists
• Received tattoos, piercings, or acupuncture with poor infection control procedures.

How to test for infection

Screening identifies exposure to the virus through testing for specific antibodies. False negatives can occur in patients with acute infection, immunodeficiencies, or end stage renal disease. Ongoing infection is confirmed in those with positive serology by testing for hepatitis C viral RNA, and those with a positive result are usually referred for further assessment. In those who test positive for antibodies but negative for RNA, tests should be repeated once after six months. The features of the disease are similar across the genotypes, but treatment response and duration are related to genotype, with the best responses seen for genotypes 2 and 3.

How to assess the severity of liver disease

Liver biochemistry is insensitive at predicting disease severity; normal results do not exclude progressive liver disease or cirrhosis.8 Baseline ultrasound to look for focal lesions, splenomegaly (a marker of portal hypertension), or frank features of cirrhosis is appropriate, although normal findings on imaging do not
exclude cirrhosis. Traditionally biopsy was universally recommended, but it has limitations, including sampling error and patient reluctance. Biopsy is often used if treatment is to be deferred (for example, in patients with genotype 1 infection and mild fibrosis), if other cofactors may have contributed to liver disease (such as steatosis, iron overload, or alcohol), or if different non-invasive markers of fibrosis are discordant.

Non-invasive methods for assessing fibrosis are evolving and remain best at differentiating between extremes (normal or cirrhosis). Fibrosis can also be assessed using serum markers, as in the FibroTest (Biopredictive, Paris, France), which associates five biochemical tests—α2 macroglobulin, haptoglobin, apolipoprotein A1, gamma glutamyl transpeptidase, and total bilirubin—adjusting for sex and age. Alternatively, liver stiffness can be measured with transient elastography, in which a shear wave is generated and tracked through the liver using ultrasound. Simple calculations can also give an indication of advanced liver disease; for example, the aspartate aminotransferase to platelet ratio index, calculated as aspartate aminotransferase (U/l)/upper normal × 100/platelet count (10^9/l), for which scores greater that 1.5 have a positive predictive value for substantial fibrosis of 88%.

Other considerations
Non-randomised evidence points towards adoption of routine opt-out HIV testing in all patients with chronic viral hepatitis. In people without serological evidence of previous infection with hepatitis A or B, vaccination against these viruses is appropriate.

When should hepatitis C infection be treated?
Although all patients with chronic infection are candidates for antiviral therapy, the risks and benefits of therapy must be weighed carefully on an individual basis. Treatment is considered successful when hepatitis C viral RNA is undetectable six months after stopping therapy (sustained virological response), and even patients with cirrhosis can benefit, since long term viral
eradication is sometimes also associated with regression of cirrhosis.12,13 Evidence based guidelines developed by the National Institute for Health and Clinical Excellence (www.nice.org.uk/Guidance/TA106) and the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/pdf/sign92.pdf) are available, as are practice guidelines.14 All patients with moderate to severe fibrosis or cirrhosis should be considered for treatment to prevent disease progression; those with mild disease are also eligible for treatment, although some patients may opt to wait until disease reaches a moderate stage. For genotypes 2 and 3, treatment at the stage of mild disease, as well as at more severe stages, is cost effective in all patients. Treatment of mild disease is also cost effective in patients younger than 65 with genotype 1 (and probably 4), but in older patients with these less responsive genotypes treatment should probably be restricted to those with more severe fibrosis.15 Retrospective evidence shows that insulin resistance, along with advanced fibrosis and unfavourable genotype, are independent predictors of non-response to treatment.16 Difficult to treat populations such as prisoners17 or those with a history of substance misuse18 remain candidates for treatment. Psychiatric comorbidities can affect treatment, but are not absolute contraindications since tolerability and antiviral responses comparable to best practice can be achieved if tailored psychiatric input is available.19

**How is hepatitis C infection treated?**

The current treatment for chronic infection is combined peginterferon alfa by subcutaneous injection once weekly and oral ribavirin daily (fig 2). Pegylated interferon is formed by attachment of interferon, a naturally occurring cytokine with immunomodulatory, antiproliferative, and antiviral effects, to polyethylene glycol, which improves the pharmacokinetic profile and permits weekly dosing. Two preparations are available: peginterferon alfa-2b, given as a weight based dose of 1.5 μg/kg, and peginterferon alfa-2a, given as a fixed 180 μg dose. Ribavirin is a purine nucleoside that has antiviral effects against hepatitis C only when combined with interferon alfa, and its addition to treatment reduces rates of relapse. Combination therapy with peginterferon alfa and ribavirin achieves sustained virological responses in almost half of patients with genotype 2 infection and about four fifths of those with genotype 2 or 3 infection.20,21 Findings of randomised trials show that patients with genotype 1 need 48 weeks of peginterferon alfa therapy with daily ribavirin (1000-1200 mg) according to weight.22 Genotypes 4 to 6, which are uncommon in

<table>
<thead>
<tr>
<th>TIPS FOR NON-SPECIALISTS</th>
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<tr>
<td>A GP with an average list size of 1800 will have eight to 20 patients with hepatitis C, half of whom are probably undiagnosed</td>
</tr>
<tr>
<td>Identifying such patients requires a high index of suspicion with assessment for risk factors to which exposure may have occurred many years ago</td>
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<tr>
<td>Onwards referral to secondary care is advised to stage liver disease and consider the need for antiviral therapy in those with chronic infection (RNA positive)</td>
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<tr>
<td>Prevention of superimposed hepatitis A and B should be recommended through vaccination</td>
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<td>Once patients are on antiviral treatment the GP has a supportive role in diagnosis and aiding management of side effects (such as mood disorders, rashes, thyroid disorders, infections, gastrointestinal upsets)</td>
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<tr>
<td>After successful eradication of virus, patients with substantial fibrosis or cirrhosis still need long term follow-up (for example, to survey for complications such as hepatocellular carcinoma and varices)</td>
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**Box 3 Role of the clinical nurse specialist**

- Support and education of patients, often those with complex problems including substance abuse
- Nurse led clinics, in parallel with medical clinics, to provide continuity of care from initial referral through treatment, follow-up, and potential discharge to GP
- Preparing patients for possible side effects of treatment and supporting them through what can be a challenging time
- Liaising with drugs and alcohol agencies, homeless health care, GP, and mental health teams where needed

Elizabeth Burge, Southampton University Hospitals NHS Trust

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**Fig 2** Current treatment algorithms in routine practice

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Elizabeth Burge, Southampton University Hospitals NHS Trust
How is treatment monitored in hepatitis C infection?

Side effects of peginterferon alfa and ribavirin (box 2) are reported in over half of patients and range from mild, non-specific, influenza-like symptoms to major neuropsychiatric disturbance. Medical treatment in the form of antipyretics, haematological support, and antidepressants is common, and multidisciplinary teamwork, usually coordinated by nurse specialists, has developed as the standard of care, although data from trials are scarce to prove this model of care is better than others (box 3).

Patients must receive appropriate education before treatment (box 4), including techniques for self subcutaneous injection. In the first month a full blood count is checked weekly; if results are stable blood may then be checked at monthly reviews throughout treatment. Thyroid function needs to be checked before treatment and every three months (or if symptoms develop). Thyroid function needs to be checked before treatment and every three months (or if symptoms develop). Generally the need for dose reduction is based on marked falls in blood count (such as neutrophil count <0.7×10⁹/l; platelets <75×10⁹/l; haemoglobin <100 g/l or fall by >20 g/l in any four week period). Anaemia occurs in about 10-30% of patients, with interferon causing bone marrow suppression and ribavirin causing haemolysis. Reduction of ribavirin dose may reduce treatment efficacy; the aim should be to maintain a target dose greater than 80% of the original dose, and use of haematological growth factor for anaemia seems cost effective according to pooled data studies.

AdDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals
- World Health Organization (www.who.int/mediacentre/factsheets/fs164/en)—useful factsheet on hepatitis C
- Department of Health (www.dh.gov.uk/en/PublicHealth/CommunicableDiseases/HepatitisC)—UK Government webpage on hepatitis C
- Health Protection Agency (www.hpa.org.uk/webvHPAwebPage&HPAwebAutoListName/Page/1191942171144?p=1191942171144) —resources on hepatitis C
- Gastroenterology and Liver Diseases Specialist Library (www.library.nhs.uk/GastroLiver)—specialist collection of NHS evidence

Resources for patients
- The Hepatitis C Trust (www.hepctrust.org.uk)—national UK charity for hepatitis C
- British Liver Trust (www.britishlivertrust.org.uk)—national charity working to reduce the impact of liver disease in the UK
- NHS Choices (www.nhs.uk/healthibrary/HepatitisC)—patient orientated advice on hepatitis C
- American Liver Foundation (www.liverfoundation.org)—American organisation that aims to facilitate, advocate, and promote education, support, and research for the prevention, treatment, and cure of liver disease
- The Skipton Fund (www.skiptonfund.org/Eng/index.html)—UK-wide ex gratia payment scheme established to make payments to certain people who were infected with hepatitis C through treatment with NHS blood or blood products before September 1991

EUROPE AND NORTH AMERICA, are treated as for genotype 1. Care is guided by quantitative monitoring of viral RNA during treatment. Failure to achieve an early virological response (≥2 log₁₀ decline at week 12) is a good predictor of non-response and treatment should be discontinued. Patients with the more favourable genotypes 2 and 3 need be treated for only 24 weeks with pegylated interferon and ribavirin 800 mg daily.

In children, treatment is usually delayed until they reach adulthood. Treatment is poorly tolerated in patients with HIV infection, renal failure, haemophilia, or viral recurrence after liver transplantation. Specialised centres manage such groups.

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Box 4 Components of treatment management and monitoring
- Education of patients, usually by a nurse specialist, is paramount
- Careful pretreatment evaluation of medical, psychiatric, and social issues, with appropriate pre-emptive intervention
- Regular clinical and laboratory assessment of patients being treated, with easy access for the patient and their GP to the treatment team for any concerns arising
- Dose reduction only when absolutely necessary to manage anaemia, neutropenia, or thrombocytopenia, as treatment efficacy can be impaired

Box 5 Possible future directions of treatment

Modifications to existing regimens
- Interventions reducing insulin resistance such as exercise, weight loss, insulin sensitisers
- Weight based ribavirin
- Modified interferon (such as albuferon)
- Newer ribavirin (such as taribavirin)

Antiviral approaches in clinical trials
- NS3 protease inhibitors (telaprevir, bocepravir—in phase III clinical trials)
- NS5B polymerase inhibitors (valopicitabine, R1479, and NM107—in phase II and III trials)
- Cyclophilin inhibitors without immunosuppressive properties that regulate hepatitis C virus NS5B-RNA dependent RNA polymerase (such as Debio 025—in preclinical and early clinical trials)
- Thiazolides (such as nitazoxanide—in phase II/III studies)
- Al-trans retinoic acid (in vitro and preliminary clinical observation)
- Peptide vaccine

Preclinical research strategies
- Cell entry inhibitors targeting the structural protein E2
- NS5 helicase inhibitors
- Inhibition of the p7 ion channel
- Specific antiviral agents targeting viral RNA (such as small interfering RNA molecules, ribozymes, antisense RNAs)

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A PATIENT’S PERSPECTIVE

I had been feeling increasingly tired when a blood test following a sports injury revealed I had hepatitis C. I was concerned but assumed that the condition could be stabilised. I stopped drinking alcohol and began organising my life in order to spend a year taking a course of interferon and ribavirin. I found the treatment difficult: the need to inject myself was disturbing. I was short of energy and experienced a significant slowing of mental ability. I worked closely with a specialist nurse who monitored my medication and was available to provide information and support. The treatment unfortunately had no effect on the hepatitis C and was discontinued after six months. My condition was stable for five years, during which I had regular outpatient appointments and underwent blood tests and ultrasound scans. Eventually I became swollen with ascites and it became apparent that I needed a liver transplant. I was placed on the waiting list and nine months later I had a transplant. I still have hepatitis C as the virus infected my new liver but I am markedly better. I have great optimism that with continuing research, a cure for hepatitis C will eventually be possible.

Michael Baigent

What are the new approaches to treatment?

There is ongoing interest in optimising duration and dosage of current antiviral regimens to maximise virological response rates, shorten treatment duration in those predicted to be cured, and spare unnecessary cost and side effects if treatment is likely to fail (box 5). Retrospective and randomised studies show that a rapid virological response at four weeks is a better predictor of sustained response than is response at 12 weeks for all genotypes.24-26 Patients with genotypes 2 and 3 who have a rapid virological response may be cured with a shorter duration of treatment, 12-16 weeks, according to randomised controlled trial data.27 A randomised study in patients with genotypes 1 and 4 showed a similar likelihood for both genotypes of reducing treatment duration by half in those with a rapid virological response.28 Gene expression analysis has identified hepatic gene signatures for patients who do not respond to treatment, and eventually it may provide predictive tools.29 Randomised controlled trial data in genotype 1 patients also showed virological response rates at four, eight, and 12 weeks to have value in stratifying treatment duration to 24, 48, or 72 weeks, allowing therapy to be tailored without loss of efficacy.29 Another randomised controlled study, however, showed that long term therapy with peginterferon in those who do not respond to initial treatment is not clinically advantageous.30

An improved understanding of viral replication has allowed identification of specific viral targets and antiviral compounds.31 Hepatitis C specific enzyme inhibitors, including protease inhibitors (such as telaprevir and boceprevir) and nucleoside and non-nucleoside polymerase inhibitors, are being evaluated, with new agents presently being added to standard of care. Other drugs, such as the cyclophilin inhibitor Debio 025 and the thiazolidine nitazoxanide, have also shown antiviral activity in early studies. Direct antiviral therapies may lead to viral resistance,32-36 a concern not relevant with interferon based therapy.

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Competing interests: None declared.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent obtained.

SUMMARY POINTS

Chronic hepatitis C infection is a substantial global health problem

Strategies to prevent infection through provision of safe blood products and targeting intravenous drug users are essential

Many people are unaware that they carry the virus and are at risk of liver disease

Complications of liver disease related to hepatitis C infection are expected to increase over the next 10 years

Sustained viral eradication and prevention of disease progression is possible through antiviral therapy

Optimal treatment is peginterferon alfa and ribavirin tailored to genotype and response to therapy

New specific targeted antiviral therapies are being developed

dies.4-6 Eltrombopag, an oral thrombopoietin receptor agonist, increases platelet counts in patients being treated for hepatitis C infection.4-6

CORRECTIONS AND CLARIFICATIONS

Managing UK research data for future use
Because of an editorial error this article was wrongly titled and should have had the title “Sharing the raw data from medical research” (BMJ 2009;338:b1252, print publication 28 March 2009, pp 729-30).

High vitamin C intake may help prevent gout
In this Short Cuts item by Alison Tonks (BMJ 2009;338:b1078, print publication 21 March 2009, p 685) the units of vitamin C given in the first and final paragraphs should be in milligrams not grams. The labelling on the graph is correct.

Sexual violence must be treated as medical emergency, charity says
A digit (1) was missing from the start of two numbers cited in this article by Jacqui Wise (BMJ 2009;338:b8850, print publication 7 March 2009, p 560). The first sentence of the fifth paragraph should read: “MSF [Médecins sans Frontières] teams provided health care to 12 791 victims of sexual violence in 127 projects worldwide in 2007.”

Shaky foundations: compromising the NHS
In this Observations article by Nigel Hawkes (BMJ 2009;338:b789, print publication 28 February 2009, p 508), the following sentence about the compromise on top-up payments by the national cancer director, Mike Richards, should have stated: “This [the compromise] involves NHS patients [not private patients, as was stated] being allowed to pay for drugs that haven’t been recommended by the National Institute for Health and Clinical Excellence (NICE), so long as they are administered in another part of the hospital.” The whole point, of course, is that NHS patients are being allowed to pay for drugs privately.

Entanglement in Scotland
David R Ball and colleagues have alerted us to an error in their letter (BMJ 2009;338:b763, print publication 28 February 2009, p 494). In describing how often the anaesthetics departments held sponsored meetings, the authors should have said that four [not three, as stated] departments held less than one meeting a month.

Alzheimer’s disease
An error occurred in this Clinical Review by Alistair Burns and Steve Iliffe (BMJ 2009;338:b158, print publication 21 February 2009, pp 467-71). In the Treatment section, under the Pharmacotherapy subsection (p 470), the article stated that “all three cholinesterase inhibitors are available in patch form.” This statement is wrong: only rivastigmine is available in patch form. As the BMJ follows the BNF’s style for drug names we should also have referred to cholinesterase inhibitors as acetylcholinesterase inhibitors.

Does acupuncture relieve pain?
Because of an administrative error, Adrian White and Mike Cummings, the authors of this editorial (BMJ 2009;338:a2760; print publication 7 February 2009, pp 303-4), cited data from a previous version of the linked research paper. The standard mean difference between placebo acupuncture and conventional care was –0.42 (95% confidence interval –0.60 to –0.23), corresponding to a reduction of 10 mm (not 9 mm, as was stated) on a100 mm visual analogue scale. The difference between needling classic points and control points was –0.17 (–0.26 to –0.08), and the overall effect size of acupuncture in relation to usual care was 14 mm (not 12 mm) on a visual analogue scale.

Managing health problems in people with intellectual disabilities
In the “Additional educational resources” box in this clinical review by Henny M J van Schrojenstein Lantman-de Valk and Patricia Noonan Walsh (BMJ 2008;337:a2507, print publication 13 December 2008, pp 1408-12), “Beyond Words” should read “Books Beyond Words.” The article wrongly said that these books were available from the British Institute of Learning Disabilities. Relatives and care staff can, however, obtain information about Books Beyond Words and order them from the Royal College of Psychiatrists (at www.rcpsych.ac.uk/bbw).

Endgames: Acute breathlessness and metastatic cancer
As a result of an editorial processing error, the title of this case report (BMJ 2008;337:a1405, print publication 20 September 2008, p 699) was wrong: it should have been ”Breathless beyond obvious.” Additionally, we inadvertently omitted three authors from the authorship list. The full list should have been: Chloe I Bloom, L C Price, E F Bowen, and M E Roddie.


Shutt JD, Robathan J, Vyas SK. Impact of a clinical nurse specialist on patients [not private patients, as was stated] being allowed to pay for drugs privately. Ann Intern Med 2004;140:346-55.


