

Guidance for the prevention, testing, treatment and management of hepatitis C in primary care

Includes appendices on: hepatitis A and B vaccination guidance, hepatitis B and HIV

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The
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Disclaimer

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Executive summary

Introduction

1. Hepatitis C infection is an under-diagnosed (five out of every six people infected are undiagnosed) and under-treated important cause of morbidity and mortality.
2. Hepatitis C is a common and potentially curable disease, but only 1 to 2% of infected people are currently receiving National Institute of Clinical Excellence (NICE) recommended therapy.
3. Every general practitioner is likely to have between 8 to 18 infected individuals per GP, based on an average list size of 1,800 and, partly depending upon local population demographics. Many of these patients may not be diagnosed and knowledge about HCV in population and primary care remains low but improving.
4. Prevalence of the hepatitis C virus (HCV) is estimated to be between 0.4 to 1% of the United Kingdom (UK) population, equating to be between 250,000 to 600,000 sufferers. Worldwide there are an estimated 170 million people, about 3% of the world's population, who are chronically infected with HCV.
5. HCV is a blood-borne ribonucleic acid (RNA) virus that exists as a number of different strains (genotypes) and an important cause of liver disease. The effects of the infection vary from one individual to the next. Some people will remain symptom free, some will develop cirrhosis and others will develop liver failure or hepatocellular (primary liver) cancer.

Transmission and prevention

1. Unlike hepatitis A and B, there is no vaccine but infection is avoidable through strategies that reduce transmission.
2. Major route of transmission in the UK is sharing injecting equipment. Other risk factors include: blood transfusion (prior to 1991) or blood products (prior to 1987) and born or spent a significant amount of time in a high risk country. This may include health care given in early childhood so those born in the developing world may be at increased risk. A small but important number of infected people have acquired their infection through the use of non-sterile surgical equipment. This is most likely in those who have received health care in the developing world, including East Europe and Africa.
3. Practical suggestions to help prevention in primary care:
 - a) *Provide hepatitis A and B vaccinations in all patients using drugs and other high risk groups such as men who have sex with men.*
 - b) *Provide clear information about safer injecting and safer sex including condoms.*
 - c) *Ensure that all patients using drugs have easy convenient access to local needle exchanges, which provide injecting paraphernalia as well as needles and syringes and advise about safer smoking and snorting of drugs.*
 - d) *Advise injectors of strategies how to move away from injecting.*
 - e) *Run a needle exchange in the surgery.*
 - f) *Discuss alcohol with all patients, advise to stop and treat or refer on any alcohol problem.*
 - g) *Provide drug treatment including substitute medication or refer to secondary agency for help.*
 - h) *Monitor weight and provide help with weight reduction (risk of non-alcoholic fatty liver disease which causes cirrhosis irrespective of any other causes) and provide nutrition advice and support people who are HCV positive to optimise their nutrition.*
 - i) *Advise all patients to stop smoking and explain to people who are HCV positive that smoking can increase progression.*

Executive summary

Testing

1. As HCV is under diagnosed, testing in general practice is important, after ideally assessing all patients for risk factors – make no assumptions.
2. Ensure the patient understands the condition and the test before taking blood for:
 - a) HCV antibody blood test, to check if patient has been exposed to the hepatitis C virus.
 - b) HCV RNA (usually by a polymerase chain reaction (PCR)), to check if the infection is active or not.

Disease outcomes and symptoms

1. **Acute infection is usually asymptomatic but jaundice and malaise may occur.** The incubation period of acute hepatitis C infection is usually between six and nine weeks, with the specific antibody usually present by three months from infection, although in some cases it may take up to six months before the antibody is detected. Most people who become infected with hepatitis C are unaware of it at the time. Around 25% of those infected with hepatitis C infection will clear the virus at the acute stage.
2. **Chronic hepatitis C infection is a slowly progressive and often asymptomatic disease of the liver caused by the hepatitis C virus.** Early studies in patients infected for up to 20 years indicated that the prevalence of cirrhosis was very low suggesting the disease progressed at a very slow rate. However recent studies suggest the disease does not progress in a linear fashion and that mild disease may accelerate with time so careful surveillance of all infected patients is important.
3. **Many with chronic hepatitis C infection will have no symptoms, while others will feel unwell to varying degrees.** Symptoms, though not common, may include mild to severe fatigue, muscle aches, nausea, depression or anxiety, pain or discomfort in the liver and poor memory or concentration.

Treatment

1. **Early referral is advantageous.** It is now thought that chronic HCV does not progress in a linear fashion and that the disease accelerates with ageing so most patients with HCV may develop cirrhosis long term. Furthermore therapy is more effective when administered in the early stages of the disease and hence early referral is advisable.
2. **The most recent NICE guidance advocates treatment for all that want it including:**
 - a) active injectors
 - b) for **mild** to moderate hepatitis C (previous NICE guidance was only for severe disease).
3. **The current treatment is combination therapy with pegylated interferon and ribavirin.** This treatment is successful in clearing the virus (defined as no detectable virus) six months after treatment has ceased) in between 40 to 80% of those treated, according to genotype.
4. **Where treatment is provided from a hospital base: primary care can continue to play an important role in the patient's treatment by providing ongoing General Medical Services (GMS) to support the patient through the treatment process, supporting patients on therapy and giving practical advice to them on managing side-effects such as paracetamol for pyrexia, anti emetics if nauseated and moisturisers and steroid cream for itchy skin along with ongoing harm reduction information, support regarding drug dependency and monitoring of mental health, especially depression.**

Why this guidance?

This guidance has been produced to aid medical practitioners and others in the management of hepatitis C infection in primary care. Hepatitis C virus (HCV) was first identified in 1989 and rapidly emerged as a significant world public health problem.¹

The true prevalence of chronic hepatitis C (CHC) is unknown. Estimates remain vulnerable to the lack of information of the 'ever' and current IDU population at risk of CHC, leading to wide ranges around best guesses.² The prevalence of HCV is estimated to be between 0.4 to 1% of the United Kingdom (UK) population, equating to be between 250,000 to 600,000 sufferers.^{3, 4, 5, 6} Injecting drug users account for a large proportion of cases. Britain has a poor record in treating patients with chronic HCV, and out of the total population infected fewer than 17% have been diagnosed⁷ and it is estimated that only about 1 in 20 of those who are diagnosed are treated each year.⁸ Of the total number infected the treatment rate is less than 2%.^{2, 8}

According to The Health Protection Agency report on hepatitis C in 2005, 'deaths, transplants and hospital admissions for HCV-related end stage liver disease continue to increase...'⁹ The low rates of therapy for HCV infected patients in the UK are likely to lead to further increases in the late complications of CHC.^{5, 9} This has led many to describe hepatitis C as a 'public health time bomb' and said this 'failure to address hepatitis C is not acceptable that may cost the NHS up to £8 billion over the next 30 years as increasing numbers of people suffering cirrhosis, liver failure and liver cancers present for therapy.'¹⁰

Every general practitioner is likely to have between 8 to 18 infected individuals, with an average list size of 1,800, partly depending upon the local population demographics. However many of these patients may be undiagnosed. Therefore up-to-date, accurate knowledge about transmission, diagnosis, testing and treatment etc of HCV in primary care is essential. As part of *The Hepatitis C Action Plan* (released by The Department of Health (DH) in 2004)⁷ an educational booklet about HCV was sent to all general practitioners (GPs) in England and Wales. However independent follow up questionnaire assessments of GPs understanding of HCV suggest that knowledge remained poor.¹¹ This is compounded by the current poor understanding of HCV in the general population and professionals and by patients not coming forward for testing etc.¹² Further awareness campaigns for hepatitis C have been launched (the latest on-going campaign called 'FaCe It', commenced in 2004) with additional input to GPs.¹³ However no evaluation has been published and anecdotal evidence indicated that the knowledge base in general practice was still poor.

However a new report from the Health Protection Agency⁵ shows that the number of people newly diagnosed with hepatitis C has increased; from 2,116 in 1996, to 7,580

in 2005, but this is still a small fraction of the total infected population. New figures also show that testing for hepatitis C has increased overall, for example, in GP surgeries, testing has increased by almost 60% between 2002 and 2005.⁵ The report goes on to say that the latest estimates on the number of adults infected with hepatitis C showed there were around 231,000 in 2003. Many of these infected people do not realise they have the virus as it can take years or even decades for symptoms to appear. Early treatment, however, is effective at clearing the virus in the majority of people. It is therefore important that individuals at risk are tested by their GP, drug service or other health services.

The National Treatment Agency (NTA) have recently introduced targets to drug treatment services to offer HCV testing to and immunisation against HBV to 100% of patients in recognition that improvements need to be made in prevention and diagnosis.¹⁴

In a majority of people hepatitis C is a curable disease and therapy is recommended by the National Institute for Clinical Excellence (NICE).^{15, 16} This guidance has recently been updated (2006) and NICE now recommend treatment for mild to moderate disease, as well as severe disease.^{15, 16} However treatment rates in the UK remain low despite the on-going patient awareness campaigns, NICE recommendations and pressure from informed clinicians and their patients. Diagnosed individuals in France are 6 to 12 times more likely to enter treatment programmes.⁸

It seems probable that lack of awareness in primary care contributes to the low treatment rates in the UK and the purpose of this guidance is to provide clinical information about the management of hepatitis C infection in primary care that, hopefully, will lead to increased prevention of HCV transmission along with improved testing, diagnosis and treatment for patients who are already infected. This guidance is only one tool and should be accompanied by appropriate training.

It has also been shown that general practice has an important role in the care of people at risk of hepatitis C and when appropriately supported can effectively implement current best practice.¹⁷

This guidance is part of a series, which also includes the use of buprenorphine in opioid dependence treatment, treatment of cocaine users, hepatitis vaccination schedules (which have now been incorporated in this document as *Appendix 5*) and methadone in opioid dependence treatment.^{18, 19, 20, 21} These documents are available online at www.smmgp.org.uk and www.rcgp.org.uk

Who is the guidance for?

This guidance is aimed at all general practitioners, practice nurses and other clinicians working in primary care. Also for all clinicians and others involved in the care of drug using patients. It has been developed specifically to increase knowledge about HCV, increase testing, prevention, referral for treatment and support the management of chronic hepatitis C in primary care.

What is hepatitis C?

Hepatitis C infection is a slowly progressive and often asymptomatic disease of the liver caused by the hepatitis C virus. HCV is a blood-borne ribonucleic acid (RNA) virus that exists as a number of different strains (genotypes) that are defined by molecular analysis of the viral genome.

HCV is a blood-borne virus that causes liver and systemic disease. The effects of the infection vary from one individual to the next. Many people will remain symptom free, some will develop cirrhosis and a few will develop liver failure or primary liver cancer. Unlike hepatitis A and B, there is no vaccine but infection is preventable through strategies that reduce transmission.

Epidemiology

The prevalence of hepatitis C in the UK is between 0.4 to 1% equating to between 250,000 to 600,000 sufferers.^{3, 4, 5, 6} The Health Protection Agency (HPA) estimate that in England the prevalence of hepatitis C in the general population is around 0.5%.^{3, 5, 9} In Scotland the estimate is 0.8%.²² From their figures the HPA also predict that of these positive people: 31% will be in current injectors, 57% in ex-IDU and 12% in non-IDU population.⁵

Worldwide there are an estimated 170 million people, about 3% of the world's population, who are chronically infected with HCV.¹ In some parts of Europe and the Indian Sub-continent the prevalence of HCV infection is between 3 to 5%.¹ Patients being born or receiving health care in childhood in a high-risk countries are likely to have a higher prevalence of HCV.²³

Risks for infection in the UK include injecting drug use (past or current), receipt of blood transfusion (prior to 1991) or blood products (before about 1987), and receipt of health care abroad, including health care given in early childhood, or being born in the developing world may be at increased risk.²³ Other risk factors include sexual exposure, vertical transmission and renal failure requiring haemodialysis.²⁴ Of all cases of hepatitis C infection in the UK, injecting drug use accounts for transmission in most cases.

Natural history of HCV

The understanding of the natural history of hepatitis C has changed over the last few years. Early studies in patients infected for up to 20 years indicated that the prevalence of cirrhosis was very low suggesting the disease progressed at a very slow rate.²⁵ However recent studies suggest the disease does not progress in a linear fashion and that mild disease may accelerate with time. Thus a long history of hepatitis C that is associated with minimal liver fibrosis should **NOT** be interpreted as evidence that the disease will always be mild and referral for treatment, careful follow up or intervention is required to detect/avoid disease acceleration associated with aging.

Further, it has recently become clear that individuals with HCV infection are at higher risk of both all-cause and liver-related mortality than standard populations emphasising the importance of careful surveillance of this group.²⁶

Signs and symptoms of hepatitis C

Acute hepatitis C

The incubation period of acute hepatitis C infection is usually between six and nine weeks, with the specific antibody (antiHCV) usually present by three months from infection, although in some cases it may take up to six months before the antibody is detected. Detection of viral HCV RNA usually using PCR test may be the only marker in early infection. Most people who become infected with hepatitis C are unaware of it at the time hence the incidence of acute hepatitis C is unknown. Only between 25 to 35% show symptoms in the early stages and severe symptoms are rare. Some people may briefly feel unwell, with a mild flu like illness or may have nausea and vomiting and, rarely, jaundice. Between 30 to 50% patients with symptomatic infection spontaneous recover usually within three months.²⁷

Chronic hepatitis C

Most patients will pass on to chronic hepatitis C without knowing they have it and they are at significant risk of cirrhosis and hepatocellular carcinoma (HCC). Many people will have no symptoms, while others will feel unwell to varying degrees. Most people will remain well and without symptoms for a number of years and this makes the infection difficult to recognise. Disease progression and severity is very variable and patients may not become symptomatic until their liver disease is advanced.

Symptoms, though not common, may include mild to severe fatigue, muscle aches, nausea, depression or anxiety, pain or discomfort in the liver and poor memory or concentration. Symptoms tend to affect much more than just the liver and there is increasing evidence about the effect on the brain and hence the quality of life.²⁸

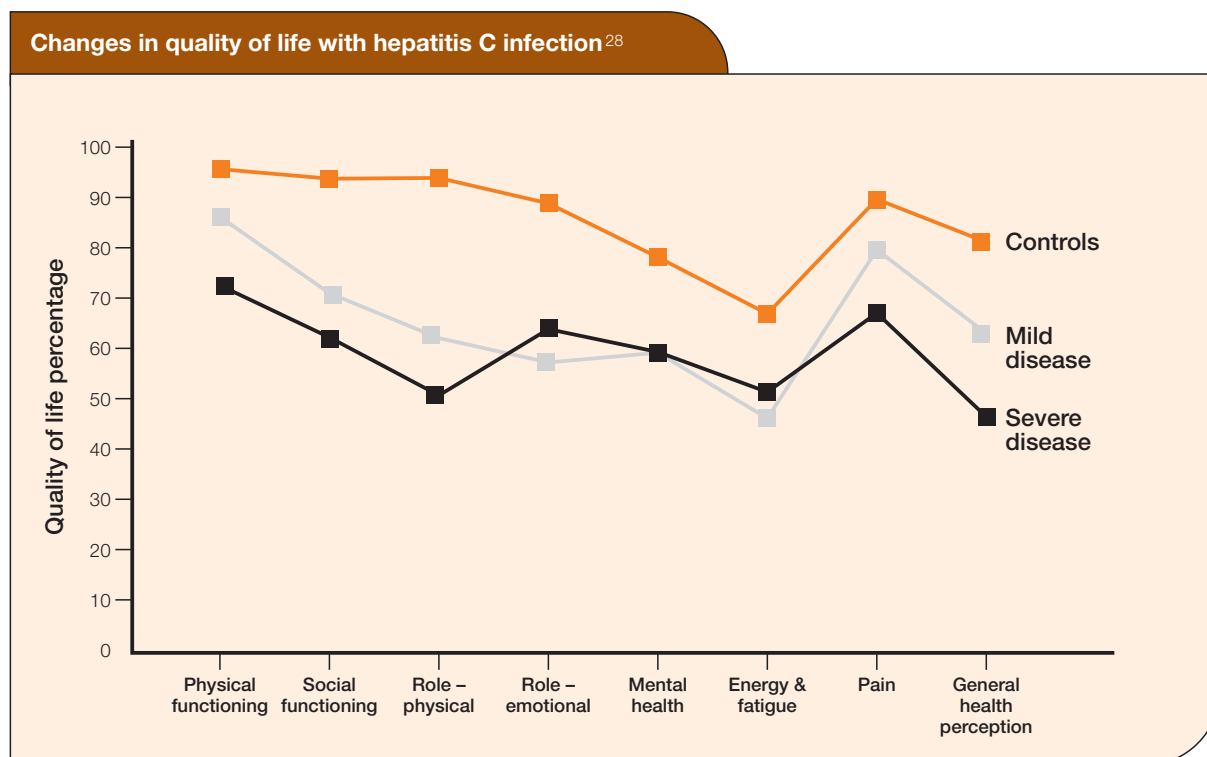


Figure 1

Many of these symptoms may come and go and symptoms may be wrongly diagnosed as due to on going drug use or occasionally as due to a chronic fatigue syndrome.

It should be noted that the severity of symptoms does not necessarily equate to the extent of liver damage. Some patients will report quite severe symptoms with no clinical signs of liver disease, while cirrhosis can be present without any obvious symptoms.

Individuals in whom the disease has progressed to cirrhosis may present with complications of decompensated liver disease, including oesophageal varices, ascites, bleeding and hepatic encephalopathy. Cirrhosis can also lead to hepatocellular carcinoma, a type of liver cancer. It has a high mortality rate. Screening using alfa fetoprotein (not very specific) and six-monthly ultrasounds should be undertaken in patients with cirrhosis.

Long-term outlook for the patient

Current evidence suggests that: around 25% of those infected with hepatitis C infection will clear the virus at the acute stage.²⁹ Of the 75% who do not:

- Some will remain well, and never develop liver damage.
- Many will develop only mild to moderate liver damage (with or without symptoms).
- Most will progress to cirrhosis of the liver over a period of 20 to 40 years. The outcome for those infected for more than 20 years is not yet clear but most studies indicate that a significant increase in the proportion with cirrhosis is likely with increasing age.
- A proportion of those with cirrhosis will progress to liver failure or HCC, approximately 5% per year will develop a life-threatening event.

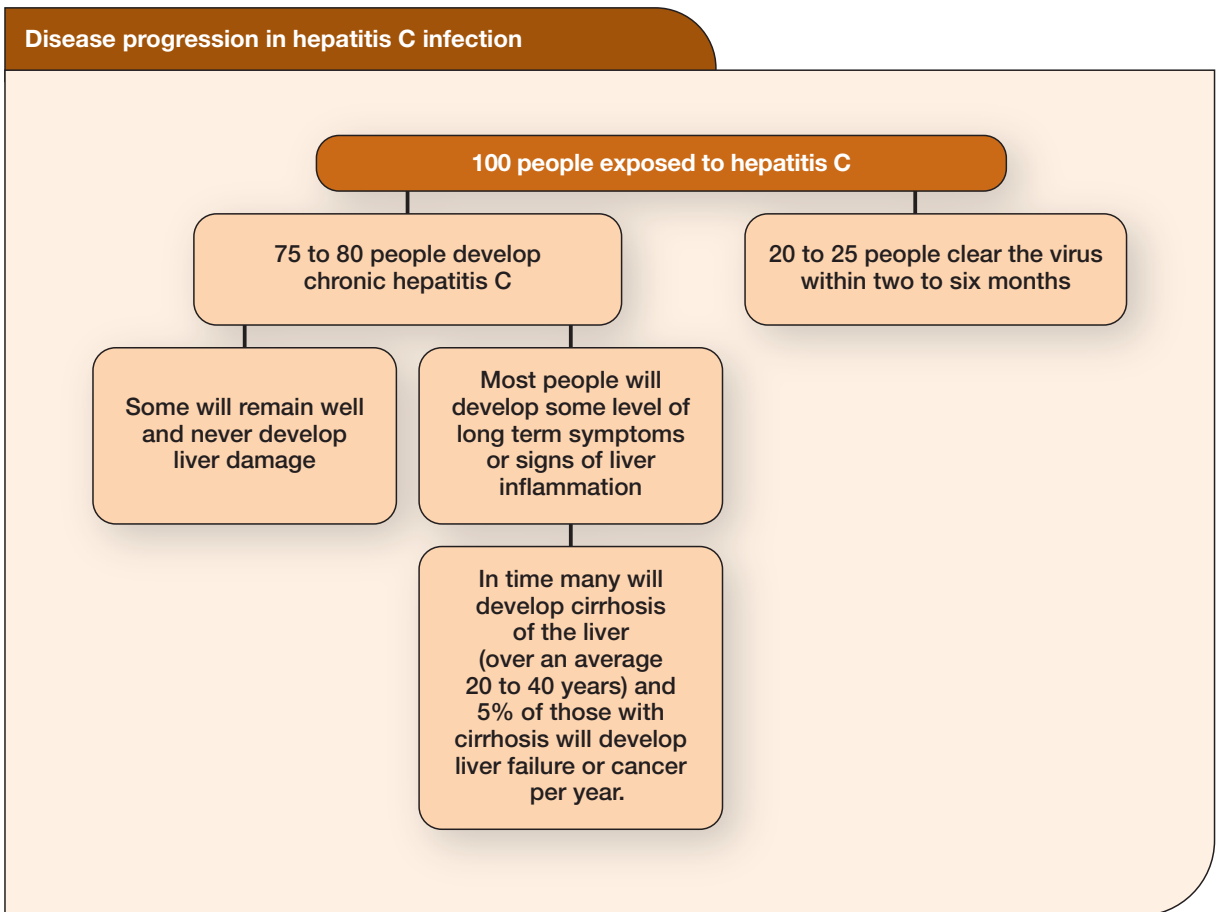


Figure 2

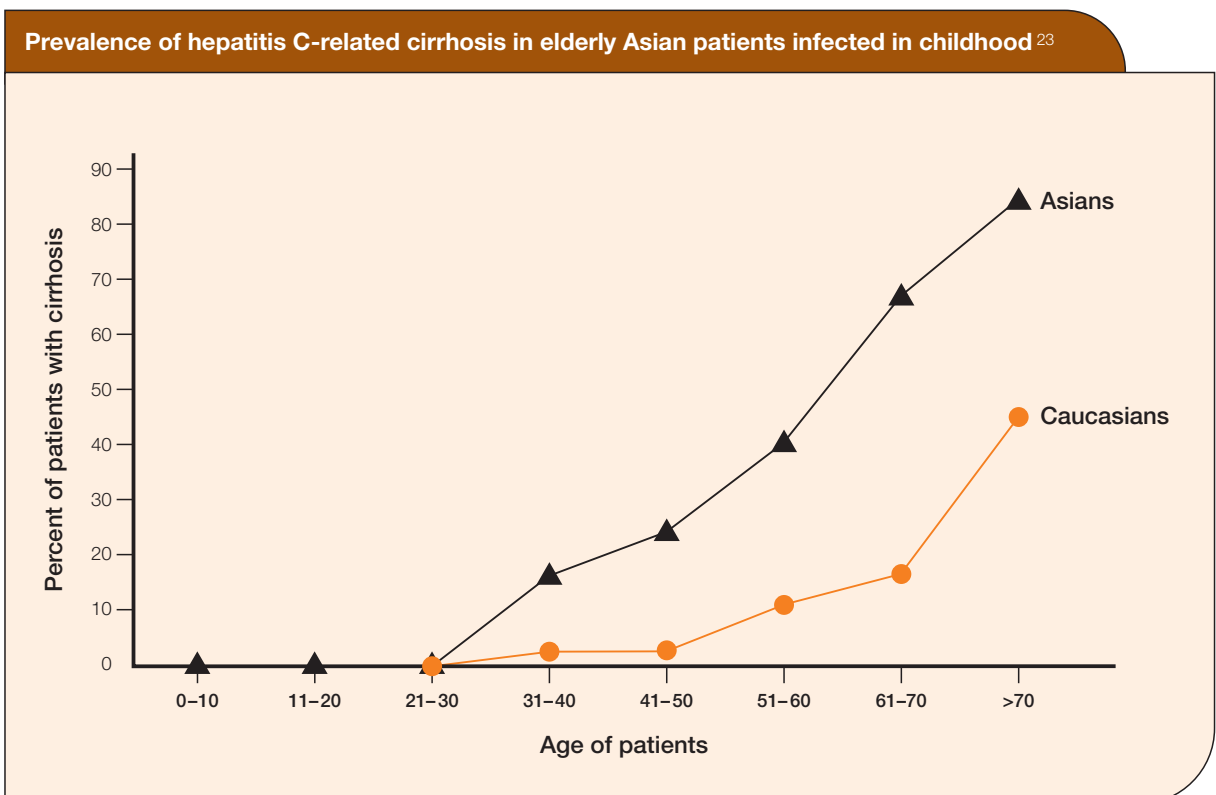


Figure 3

Predictors of HCV disease progression

Numerous studies have attempted to determine predictors of disease progression to cirrhosis. These studies indicate that some factors influence this progression, including:

Alcohol consumption³⁰

- Alcohol is strongly associated with increased likelihood of progression to severe liver complications.
- Progression to cirrhosis is higher in those who drink excessively.
- Faster progression is found in those who have previously drunk more than 50 units of alcohol a week for more than five years.

Age at infection³¹

- Those who acquire hepatitis C at an older age have a more rapidly progressing disease and reduced time from infection to cirrhosis.

Gender⁶

- Studies indicate that men are more likely to progress to cirrhosis than women.

Ethnicity

- In patients of different race there has been noted variations in disease progression. CHC appears to progress less rapidly in African-American patients than non African-American patients.³²
- Early reports suggest the disease may be worse in Asian patients. In one study of elderly Asian patients with chronic HCV nearly all those over the age of 60 had cirrhosis.²³

Co-infection with human immunodeficiency virus (HIV) or hepatitis A and/or B

- Those who are also co-infected with either HIV and/or hepatitis B and/or A are likely to progress to serious disease more rapidly.^{6, 33, 34, 35, 36}

Viral genotype

- Has no effect on disease progression but different genotypes have different sensitivities to therapy.^{6, 31}

Weight

- Body mass index above 25 has been associated with hepatic steatosis and, in some studies, more rapid disease progression.³⁷

Smoking

- Smoking is an independent risk factor of hepatic inflammation in patients with chronic hepatitis C (CHC).³⁸

Transmission of hepatitis C

The hepatitis C virus is carried in the blood and has been detected in other body fluids. However, blood has been identified as the only vehicle of infection and blood to blood contact is a very effective way of transmitting HCV.³⁹

Sharing injecting and other drug paraphernalia

The major route of HCV transmission in the UK is believed to be by sharing equipment for injecting drug use, mainly via blood-contaminated needles and syringes. Spoons, water and filters may also be vehicles of infection.

It is estimated that between 30 to 80% of all current injectors have been infected with hepatitis.⁴⁰ The corresponding rate for past injectors is thought to be higher. Sharing pipes for smoking and straws for snorting can also transmit HCV, particularly if there are cuts or damage to the lips or nose and blood present.

Blood transfusions and blood products

Prior to the introduction of screening of all blood donations in 1991, there was a risk to recipients of blood. A heat treatment process to protect blood clotting factors (used in the treatment of haemophilia) against hepatitis C and other viruses was introduced in the mid-1980s (treated Factor IX available in 1985 and Factor VIII in 1987). There is a high prevalence of hepatitis C in people with haemophilia who received untreated clotting factors before these dates.⁴¹ However, HCV should still be considered in patients from overseas or who have travelled abroad, who have had blood transfusions or surgery.

Mother to baby transmission

Mother to baby transmission does occur in women who are HCV and PCR positive, either in utero or at the time of birth, but appears to be uncommon, with upper estimates of 6% across the UK.⁴² There seems to be no reduction if caesarean section is performed.⁴³ Transmission does not occur if the woman is HCV RNA negative. However, this is increased to around 15 to 20% when there is co-infection with HIV. There is no association proven between breastfeeding and transmission of hepatitis C infection and mothers with only this infection should not be advised against breastfeeding.^{42, 43}

Sexual transmission

Sexual transmission of hepatitis C is possible but uncommon.⁴⁴ The prevalence of hepatitis C among attendees of genitourinary clinics who are either heterosexuals (non-injecting) or men who have sex with men, is relatively low, 0.3 to 0.8%.⁴⁴

There is a 3% lifetime risk of transmission if the partner is positive.⁴⁴ In men who have sex with men recent changes in sexual practices may have led to a number of cases of HCV infection. Several hundred such infections have been seen in London and Brighton over the last few years and, although the precise risk factor is not yet understood, it is probable that traumatic anal sex may carry an above average risk of HCV transmission.

The issue of sexual transmission is difficult and a consensus is not available. It is felt by some that figures of 3% are in large part due to shared risk factors and this view is supported by the article in *American Journal of Gastroenterology* which analysed over 8,000 patient years in 800 heterosexual couples and did not find a single instance of sexual transmission of HCV.⁴⁵

Generally patients can be advised that they are low risk of sexual transmission of HCV but they should consider using condoms. When HCV positive patients are co-infected with HIV they are more likely to transmit HCV to their sexual partners and they should be advised always to use condoms and practice safer sex.⁴⁶

One unit, in Nottingham, England, generally advises that there is no evidence to support the need for barrier methods of contraception (unless co-infected with HIV) within a stable relationship but that such devices should, of course, be used outside this context. This unit does not regard sexual partners as at high risk but will screen at request.

Endemic in some countries

There is a higher rate of infection in some countries, probably due to sexual transmission, unsafe obstetric practice, childhood inoculations, childhood rituals, shaving children, use of unsterilised needles and the widespread practice of needle re-use in many countries. There are prevalence rates of 1.7% in Americas, 5.3% in Africa, 4.6% in Eastern Mediterranean, 1.03% Europe, 3.9% in South-east Asia, and Western Pacific in 2.15%.¹

The prevalence among the Pakistani population (born abroad) in East London appears to be around 4%.⁴⁷

A further risk factor is frequent travel abroad (e.g. those visiting families in developing countries).

Procedures abroad

Transmission can occur through medical and dental procedures abroad, including therapeutic injections, blood transfusions, circumcisions where infection control may be inadequate.

Tattoos and/or body piercing

There is a risk from tattooing, ear piercing, body piercing and acupuncture with unsterile equipment in the UK or abroad. Examples may be homemade piercing in prison using re-used equipment.

Household contact and sharing toiletry items

There is some evidence that a very small amount of transmission may occur through the sharing of toothbrushes, razors and other personal toiletry items that could be contaminated with blood.⁴⁸ There is no risk of HCV transmission from everyday social contact such as holding hands, hugging or kissing or through sharing toilets, crockery and kitchen utensils.

Healthcare workers and others

Healthcare workers (and, to a lesser extent, other workers, such as police, prison staff and social workers) may be at risk of hepatitis infection from occupational injuries, for example needlestick injuries.⁴⁹ Estimates of transmission risk following needlestick injury vary, with one large prospective study of 4,403 exposed healthcare workers finding an overall transmission rate of 0.31%, whilst a review of 25 smaller studies reported a combined rate of 1.9% from 2,357 exposures.^{50, 51} The relative risk is higher when injuries are deep and from blood-filled needles. Risk arising from superficial or mucocutaneous exposures is likely to be much lower, though difficult to quantify, while transmission from solid needles is extremely unlikely.⁵¹ Transmission occurs only from HCV RNA positive sources.

Making the diagnosis

Many cases of hepatitis C remain undiagnosed.^{5, 12} In order to improve this situation it is important to obtain from all new patients a detailed past medical history, which should include history of previous and current drug and alcohol use, where they were born, transfusion abroad and of body-piercing and/or tattoos. Testing for hepatitis C has increased, however there is still much work to be done as a significant number of individuals remain undiagnosed.⁵ If the patient does not know they have it, they can't do anything about it. General practice and drug services need to develop strategies to increase testing.

Also, all current registered patients, whether they are currently injecting, snorting and/or smoking drugs or not, should also be questioned appropriately (unless previously interviewed). Make no assumptions about patient's histories. In the case of drug users, an offer of a test to a patient receiving drug treatment should be recorded on the National Drug Treatment Monitoring System (NDTMS) (with the patient's consent) by general practice / drug worker, even if the offer is not taken up by the patient.¹⁴

All patients currently or previously in treatment for drug and/or alcohol problems also need a full assessment of their past and current injecting, smoking and snorting techniques and a history of their injecting practices, particularly the sharing of any injecting equipment, not just needles and syringes. Paraphernalia which is often shared indirectly through lack of understanding includes the sharing of spoons, filters, water, burners, straws and tourniquets. It is important to ensure that this group of patients have been vaccinated against hepatitis A and B and that their tetanus vaccinations are up to date. If the patient is a current drug user, advice on good injecting and snorting techniques is also advised to prevent potential onward transmission and if not infected will help to protect self from infection.

NB: examples of useful leaflets regarding this can be found in resources section.

Testing in general practice

What to test

Initial HCV Antibody test

Blood needs to be taken for **an initial HCV antibody blood test** and this will indicate whether a person has ever been exposed to HCV. About 25% of people who become infected with HCV will clear the virus at the acute stage: however, these people will still have positive antibody results.²⁹ Blood should also be taken at the same time for hepatitis A and B and HIV antibody tests (after appropriate pre-test discussion – see *Appendix 4*).

Detection of HCV RNA by nucleic acid tests, usually using PCR test

If the **HCV antibody test is positive then further tests, including a polymerase chain reaction (PCR) test which is detecting hepatitis C viral RNA (HCV RNA) is required** to establish if the virus is still present, hence indicates current circulating virus. More sophisticated tests can then identify the amount (viral load) and the genotype of the virus. As the very act of venepuncture can be difficult in some previous or current injectors, some laboratories in England and Wales, and all in Scotland will accept two samples at the same time, the first asking for HCV antibody test and the second requesting that if this is positive for HCV, then they will undertake HCV RNA testing.

HCV positive and HCV RNA negative

If the **HCV RNA is negative, patients should undergo a second test after six months**, particularly as the date of infection may not be known and they may be in the window period and, if still negative, the patient can be told that they have cleared the virus. These patients who are antibody positive, but HCV RNA negative, do not need treatment but need further discussions around preventing re infection, alcohol intake, injecting behaviour etc. These patients can be well managed in primary care. They can be referred on to secondary care for specialist help, if requested. If the patient continues to engage in high risk behaviour e.g. injecting drug use, then repeat HCV RNA testing should be done 6 to 12 monthly to exclude re-infection and time to re-enforce risk reduction management.

HCV antibody test equivocal

If the test is equivocal, there are abnormal liver function tests and/or symptoms suggestive of chronic HCV then further investigation is indicated.

HCV and HCV RNA positive

All patients who are positive for both tests need further assessment and some of these investigations can be undertaken in primary care but usually means specialist hepatitis referral to hepatologists, gastroenterologists or infectious disease physicians, dependant upon the local arrangements.

The test result of a patient receiving drug treatment should be recorded on NDTMS (with the patient's consent) by general practitioner / the drug worker.

Why test

- Testing can allay anxiety even if the result is positive.
- A positive test allows early monitoring and intervention if required.
- Opportunity to immunise against hepatitis B and A. (co-infection significantly worsens prognosis).
- Testing can encourage the patient to change patterns of behaviour such as injecting drug use or excessive drinking whether the result is positive or negative. For example, continuing to share injecting equipment risks infection with another strain of HCV or another virus and alcohol use increases the rate of disease progression and liver damage.^{30, 31}
- There is now evidence that knowledge of HCV positive status has been shown to alter behaviour to avoid onward transmission (reduction in sharing).⁵²
- In light of recent improvements in treatment outcomes, testing offers a realistic possibility of cure.
- Testing promptly following recent exposure may identify acute infection, which responds to therapy in almost 100% of cases.²⁷

From diagnosis to treatment¹³

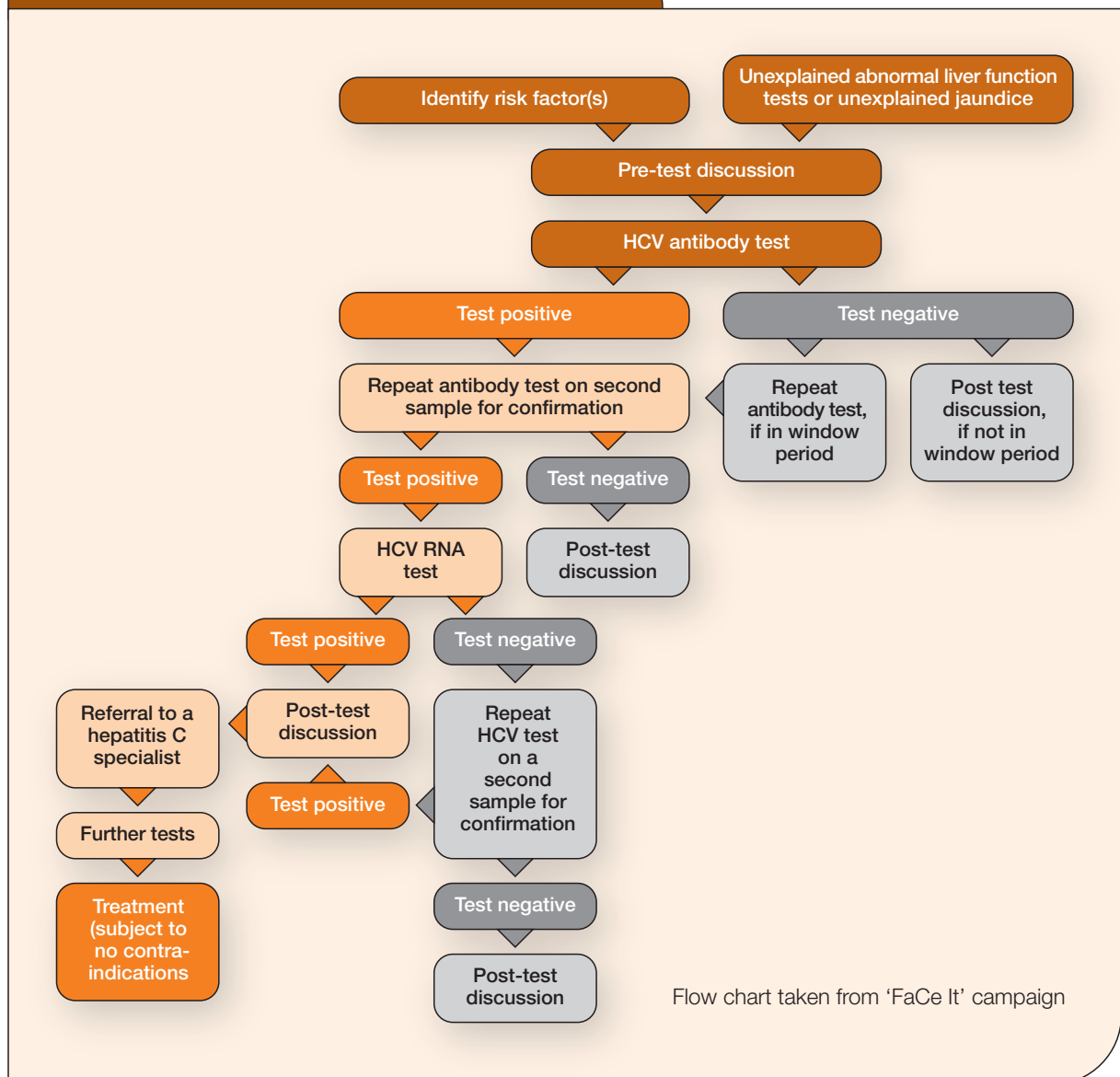


Figure 4

Who should be tested

The following people should be offered a HCV antibody test. It is good practice to offer HIV, HAV and HBV testing along with HCV after the appropriate discussion (see also *Appendix 4*):

1. Anyone who has ever injected drugs. It is very important that ex-injecting drug users are offered an HCV test as there is a high probability that many will have been infected for several or many years. Never assume a person has not used drugs in their past without asking, particularly if they present with a range of vague symptoms.
2. Current injecting drug users.
3. People who have or are currently snorting or smoking drugs such as cocaine, particularly if they have shared pipes or straws.
4. Recipients of blood (before 1991) or blood products (before 1986 in UK) and/or organ transplants (before 1992).
5. People from countries where hepatitis C is endemic (e.g. Bangladesh, Egypt, India, Japan and Pakistan).
6. People who may have had unsterile medical or dental procedures abroad.
7. People involved in high risk sexual practices with a person who is HCV positive (Regular sexual partners are at low risk and can be tested if requested).
8. People who are positive for hepatitis B and/or HIV.
9. People who may have had ear piercing, body piercing, tattooing or acupuncture with unsterile equipment. Particularly tattooing before the mid 80s or tattooing abroad as pre HIV awareness many tattoo parlours had inadequate sterilising facilities.
10. Children born to mothers with HCV who are HCV RNA positive.
11. There is some remote risk of social transmission through sharing of contaminated items such as razors or toothbrushes.
12. Consider any patient with abnormal liver function tests (LFT), especially elevated alanine aminotransferase (ALT).
13. Healthcare workers who have been accidentally exposed or needlestick injury.

Risk of transmission by routes other than those listed above is remote.

The following people should be tested for HCV (as well as HIV, HAV and HBV):

1. Anyone going to donate blood or tissue.
2. Healthcare workers who perform invasive techniques, such as surgeons.
3. People on dialysis.

What information do patients need

Before testing

Pre-test discussion

When antibody testing is undertaken it is important that the fears and anxieties of patients are discussed. Patients should also be made aware of the implications of both a positive and a negative result so that they are able to give informed consent to the process. This can be made straight forward and should not be allowed to become a barrier to prevent testing.

Health care professionals, including GPs, drug workers, practice nurses etc should be competent to carry out pre and post test discussions with patients:

Prior to antibody testing, practitioners should consider the following issues:

- Does the patient clearly understand the testing procedure?
- Is the patient able to give informed consent?
- Do they understand about the transmission of the virus?
- Any changes you would recommend they make to their lifestyle or activities to reduce their risk of future infection (or co-infection) to themselves and others?
- Do they understand that the antibody test is a test of exposure only and further tests are needed to see if the virus is active or not?
- They will need a HCV RNA after the antibody test to see if the HCV is 'active' or not (which is often taken at the same time as the initial test to avoid two separate blood tests).
- Does the patient have enough information about the disease to understand the long-term implications of a positive result.
- If the antibody test is positive test indicates that they have been infected at some time and 75% of them will continue with active infection but the other 25% will clear the virus for themselves.
- Does the patient understand the window period for testing using the HCV antibody test i.e. testing within six months of exposure may be inaccurate and a follow-up test is required at six months.
- Does the patient understand that since the updated NICE guidance a liver biopsy may not be required before treatment.¹⁶
- How are they going to cope while waiting for the result?
- What support does the patient have, particularly after the receipt of a positive test result?
- Does the patient understand that treatment has been markedly improved?

- Is the patient assured of confidentiality?
- Life insurance and mortgage issues:
 - A negative HCV test has no impact on ability to get life insurance or a mortgage and does not need to be reported.
 - A positive test or history of injecting drug use may make it more difficult to get life insurance policy or mortgage linked to a life policy but it is still possible to take out but may be more expensive. It will depend on the person's history, symptoms, liver function and treatments.
 - Giving false information will make the policy invalid.
- Explain the extent to which alcohol accelerates disease progression and the real difference they can make to empower them to make a change to their drinking habits.
- For regular travellers and foreign nationals, advice on the potential risks of medical treatment overseas is advisable.
- Encourage proper management of cuts and blood spills in both the home and work environment.
- Understand the sexual risk is low but not nil.
- Does the individual understand the risks of body piercing and tattooing abroad.
- Try to put any fears they have regarding the possibility they may also have infected their family and/or children into context as required and consider discussing transmission in the household setting to reduce anxiety.
- Does the patient understand the longevity of the disease and the long-term prognosis without treatment?

Patient education before testing

Before testing is an important opportunity for patient education and harm reduction advice. Does the individual understand about harm reduction such as HCV spread by sharing injecting equipment such as spoons, swabs and filters as well as needles and syringes and sharing straws when snorting drugs? Advice can be given about safer injecting and not sharing equipment or drugs. Information also needs to be given about dangers of alcohol, safer sex and condom use.

Potential disadvantages of testing

- Is the timing right? Negative result could give false reassurance if sample is taken within window period. Are there issues behind request for a test that should be dealt with first e.g. worries about drug use, relationships?

- Anxiety whilst awaiting the result.
- Coping with a positive result will require adaptation. The uncertainty of the prognosis of HCV, even with treatment, social stigma and concerns of transmitting the infection to others can cause depression and anxiety leading to risk of increased drug use, relationship problems. Rehearse with them how they will feel if result is positive or negative.

After testing

Getting the result

Implications of a positive test

Ideally the result should be given in person by the person who has done the test. The patient may want to have someone with them when they receive their result.

Giving the result

Every effort should be made to give the patient their result. It is better if the return appointment is made at the time of the test, depending on how long results take in your area. Explain that results are always done in person whether they are positive or negative. If they do not attend for their result, they should be actively sought out. As many as one in five patients do not receive their test results, which has implications for them and continued virus transmission and every attempt should be made to contact them to give their result.⁵³ If the test was undertaken in drug services or prison it may be the person has left treatment or been released before they get their result. It is wise to inform people that if this is the case the results will be sent on to their GP.

Negative results

Where antibody test results are negative, any continued risky behaviour should be discussed that may lead to infection in the future.

Repeat testing is advised if the patient is believed to have been exposed to the virus in the last three to six months, since HCV antibodies can take up to six months to develop.

Positive results

In the event of a positive antibody test, it is important that the patient clearly understands the result, and that further tests are required to establish if the HCV infection is active or not and identify the extent of any disease.

If the result is positive review the patient's understanding of the information given at the pre-test discussion. Then suggest that the HCV RNA is checked to look for active infection. This can be accompanied by several other tests (see later) or referral to specialist can occur at this point. The patient may need support to come to terms with a positive test result and potential future implications. Consider return appointments(s), referral to a local support group and the provision of national helpline numbers as appropriate during each consultation.

If current HCV infection has been diagnosed, patients should be advised:

- To ideally stop alcohol, as it is known continued alcohol consumption is the most important predictor for disease progression.³⁰
- This may be incredibly difficult for many patients who are heavy drinkers and they may need specialist alcohol support, counselling, in-patient detoxification and/or rehabilitation. Consideration should be given to out or inpatient alcohol detoxification whilst remaining on opioids if they are being prescribed.
- Reducing the amount of alcohol is helpful but any alcohol remains a risk to increased liver damage and to reduce intake having been dependent is almost impossible.
- They must not donate blood or carry an organ donor card.
- They need to be re-informed about not sharing any injecting or snorting equipment, and about the risks of hepatitis B virus (HBV), HIV and HCV re-infection.
- Although sexual transmission is very rare in a stable heterosexual or homosexual relationship, it can occur through risky sex and they need to be informed about condoms and safer sex to reduce this risk.
- Advised not to share razors or toothbrushes or any toiletry equipment that nicks or cuts as these could have been contaminated with blood which is still a risk whether it's fresh or dried blood, remembering transmission in the home environment is a real anxiety for most patients and is rare.
- Make sure they're fully immunised against the hepatitis A virus (HAV) and hepatitis B virus (HBV). The offer of HBV immunisation to a patient receiving drug treatment should be recorded on NDTMS (with the patient's consent) by General Practice/the drug worker, even if the offer is not taken up by the patient. Take up of the immunisation should also be recorded (see *Appendix 5* on vaccination schedules).
- Encouraged to inform injecting and sexual contacts so they too can be offered testing.
- If testing doctor is also the GP for a sexual or injecting partner, it is important to be aware of the potential moral issues of knowing the HCV status of a patient.

Other investigations to consider in general practice, before referral, if hepatitis C antibody positive

Baseline standard investigations

Baseline standard investigations which are worthwhile doing on all positive patients before referral. But these can be done by specialists, if practitioner prefers or problems with venopuncture:

1. HCV RNA to test for active infection in the blood.
2. Full blood count (FBC) including differential to check for anaemia, neutropenia etc, low platelets and signs of high alcohol consumption etc.
3. Urea and electrolytes (U+E), creatinine and calcium.
4. Liver function tests (LFT) especially alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) to test state of liver, although they are not a good indicators of liver damage and they do not indicate the severity of the HCV infection.
5. Glucose.
6. Thyroid function tests (TFT) for baseline as treatment with interferon can cause thyroid dysfunction (hyper or hypo thyroidism).
7. Ferritin to test iron stores as it can be elevated in patients with CHC.
8.
 - a) Hepatitis B surface antigen (HBsAg, also known as Australian Antigen, which signifies presence of HBV);
 - b) Hepatitis B core antibody (HBcAb or Anti-HBc, which indicates acute or chronic infection);
 - c) Hepatitis B surface antibody (HBsAb or Anti-HBs which indicates antibodies to the surface and if positive means that the person is immune to hepatitis B (from either having had the disease or from having been given the vaccine); and
 - d) Antibodies to 'e' (Anti-HBe) which indicates low infection rate and probable recovery.
9. Hepatitis A, if not done previously as any other form of hepatitis can be detrimental to hepatitis C.
10. HIV antibody test, **even if they previously tested negative** as HIV is currently increasing in injecting drug users.⁵⁴

More advanced tests worth considering to do by experienced practitioners before referral

These can be very helpful to further inform the patient before referral but some specialist centres may well repeat them which could mean the patient has an extra round of blood tests. If you undertake them always include a full copy of all the results with the referral.

1. *Genotype*: there are different strains (genotypes) of hepatitis C with numerous subtypes. These vary from country to country. The most common in the UK, Europe and USA are genotypes 1, 2 and 3, with 1 being the most common in UK. There are a few genotypes 4, 5, and 6, most of which have been acquired abroad. Subtypes are labelled a, b and c. The different genotypes do not appear to result in different patterns of disease but are important in relationship to length and response to treatment. Genotypes 2 and 3 are more responsive to treatment and genotype 1, 4, 5 and 6 are less responsive and need longer treatment (see later section on treatment).
2. *Viral load*: more useful for seeing response to treatment – can go up and down in response to many things.
3. *Clotting studies* – may be compromised if liver damage.
4. *Alfa fetoprotein (AFP)* – is raised if hepatocellular damage e.g. cirrhotic nodules. Above 500, most likely to be a hepatocellular carcinoma (HCC), but AFP is not sensitive or specific to HCC, so a small rise in AFP does not exclude malignancy.
5. *Immunoglobulins (IgGs)*.
6. *Autoantibodies (ANA)*, which is a marker of the immune process and if raised is a non-specific marker for a variety of auto-immune diseases.
7. *Mitochondrial cell antibodies*.

Other things to consider before referral (and continue working on post-referral):

1. Encourage abstinence from alcohol as:
 - a) leads to faster progression; and
 - b) many centres will not treat if actively drinking.
2. Injecting is no longer a reason to prevent treatment but patients may manage the treatment better if stabilised on substitute medication.
3. If needing help with a drug problem provide or refer and if also requires substitute medication start or refer on for starting drug treatment and get stabilised before referral for HCV treatment.
4. Ensure that if injecting the patient has access to all clean equipment and/or advice on moving away from injecting.
5. Provide help and support for other drug problems, especially cocaine injecting.
6. Assessment for depression and start treating if required. This is important as antiviral treatment can cause or increase depression.
7. They (and you) are fully aware of what is going to happen when they arrive at the clinic. This will help to reduce real anxiety on the part of the patient and encourage attendance at their first specialist appointment.
8. Encourage them to take someone (friend or buddy) to their first appointment or support in the interim period, particularly leading up to their first appointment with the specialist.

Prevention

There is currently no vaccine against hepatitis C, so prevention of new infections (primary prevention) is particularly important. The effectiveness of antiviral therapy has made a significant contribution to secondary prevention (eradicating the virus from those infected) and tertiary prevention (preventing complications from the virus in those infected). However unlike HIV infection, the prevalence of hepatitis C remains high amongst injecting drug users and therefore primary prevention of hepatitis C remains an important public health challenge. There has been a worrying recent increase in HIV which may be related to cocaine injecting.⁵³

Primary prevention

Needle exchange programmes

(distributing needles, syringes and other injecting paraphernalia).

Historically the evaluation of the effectiveness of needle exchange programmes (NEPs) at reducing the risk of blood-borne viruses has been limited because:

- It has been deemed unethical to use randomised controlled trial methodology to evaluate needle exchanges.
- Quantifying the direct effect of NEPs is difficult as often there is an interaction with other factors causing a reduction (e.g. provision of bleach or counselling); or the effect of secondary exchange.

In the USA (the country that conducts the most health orientated research) the use of federal funds for the provision or evaluation of needle exchange programmes was banned for a period of time.^{55, 56}

There is some evidence to suggest that NEP reduces the incidence of hepatitis C, however not as effectively as they are in reducing the prevalence of HIV. A number of studies conducted in the mid-1990s compared prevalence of anti-HCV for the periods before during and after introduction of NEPs.^{57, 58, 59, 60}

Generally speaking, following NEP introduction there was a reduction in anti-HCV prevalence of the order of 10 to 15% to a prevalence of approximately 50% amongst injecting drug user populations. One USA based case control study found that a practice of not using a NEP was associated with a seven-fold greater risk of anti-HCV seroconversion.⁶¹

Whilst not studying the outcome of anti-HCV incidence, two large observational studies conducted in the United States demonstrated that the introduction of NEPs leads to a self-reported reduction in sharing when associated with an increase in distribution. Encouragingly such increase in distribution does not lead to either an increase in the prevalence of injecting drug use or a switch from non-injecting to injecting practice.^{62, 63}

However NEPs have been much more effective at reducing the prevalence of HIV and this needs to be borne in mind when considering the cost effectiveness of NEPs. Also co-infection with HIV significantly worsens the prognosis of HCV and therefore it could be argued that needle exchanges have had a significant impact upon reducing the risk of becoming co-infected.

Easily accessible drug treatment including substitute prescribing

Whilst methadone maintenance therapy has been successful in reducing the incidence of HIV, the evidence for its effectiveness in reducing HCV incidence is less convincing. An Italian study of 263 HCV negative injecting drug users showed an incidence rate of 28.6 per 100 person years. However compared to those taking methadone maintenance, the adjusted odds ratio for 'lack of methadone treatment' (in the six months prior to testing) was only of borderline significance.⁶⁴ These findings concur with the results of a USA based study of 716 injecting drug users in treatment services. Multivariate analysis showed a non-statistically significant lower incidence of HCV seroconversion in those who remained in methadone maintenance treatment compared to those who had left, though the reduction did not reach statistical significance due to insufficient numbers in the study.⁶⁵

However the studies in this field have not reported the mean methadone doses that may affect the reduction in anti-HCV incidence. This may be important as some commentators have argued that under-dosing would reduce the effectiveness of MMT at reducing unsafe injecting behaviour.⁶⁶

Using behavioural programmes to reduce the risk of HCV transmission

Behavioural interventions work within a framework of psychological theory and can be delivered at the individual or group level. There do not appear to be any studies that have evaluated such an approach with the specific goal of reducing incidence of hepatitis C. Therefore in keeping with many aspects of primary care it would appear that there is gain when 'talking therapies' are provided alongside other medical or health interventions (e.g. prescribing).⁶⁷

Distribution of bleach, when and where required

The issue of whether to distribute bleach to injecting drug users has at times been contentious.⁶⁸

Some commentators argue that training drug users to clean syringes with bleach provides the user with false re-assurance regarding the risk of re-using injecting equipment.

Unfortunately there appears to be limited evidence to inform best practice. There was only one study conducted in the USA on this topic and unfortunately it was not sufficiently powered to obtain a definitive answer. Findings were encouraging in reporting a statistically non-significant reduction trend of lower anti-HCV seroconversion for those who used bleach all the time, compared to those who used it some of the time, to those who did not use it at all.⁶⁹ Whilst not providing the definitive answer, the study would at the very least suggest that there is merit in conducting larger trials in the real-world setting of needle exchanges to evaluate the effectiveness of bleach distribution. On current evidence it would be difficult to support a policy of not distributing bleach.

Drug consumption rooms

The evidence base for drug consumption room effectiveness is still evolving but to date they are not available in UK. They are legally sanctioned and supervised facilities designed to reduce the health and public order problems associated with illegal injection drug use. Recently drug consumption rooms have opened in Australia, Canada and several European countries. The evidence base for their effectiveness is still developing and to date there has only been one evaluation of a drug consumption room that specifically studied anti-HCV conversion as an outcome. The evaluation was a time series statistical analysis though for the outcome of anti-HCV conversion descriptive data only was presented. This showed no change in the incidence of notifications of hepatitis C infections among local users during the 18-month trial period, despite an increase in notifications from neighbouring areas.⁷⁰

Prevention of needlestick injuries or other occupational injuries

Standard infection control precautions against blood borne virus transmission should be undertaken by all healthcare workers regardless of the patient's known or suspected infective status. Healthcare workers sustaining needlestick injuries from HCV infected sources should be advised that: the overall risk of transmission is probably less than 2% and may be much lower the risk is higher from deep injuries and from blood-filled needles transmission from solid needles is very unlikely. ^{49, 50, 51}

Prevention of healthcare worker to patient infection

Several reports have shown that HCV can be transmitted from healthcare workers to patients.⁷¹ Most of these occurred after exposure prone procedures, usually after deep-cavity surgery. Estimates of transmission rates to patients in two retrospective analyses involving infected cardiothoracic surgeons were 2.3% and 0.36%, whilst the risk of transmission from an infected gynaecologist was only 0.04%.⁷² UK health departments advise that healthcare workers who are HCV RNA positive should not undertake exposure prone procedures (EPP).^{71, 73}

Healthcare workers who are aware they are HCV RNA positive should not undertake exposure prone procedures.

Mother to foetus/child transmission

There are currently no proven methods to prevent the small risk of vertical transmission from mother to child/foetus (see *Special groups* on page 15).

Travelling abroad

Prevention of transmission through blood or blood product transfusion and medical intervention when travelling abroad where screening programmes are not in place.

What practical things can be done to help primary prevention in primary care

1. Provide hepatitis A and B vaccinations in all patients using drugs (see *Appendix 5* for vaccination regimes) and other high risk groups such as men who have sex with men.
2. Provide clear information about safer injecting and safer sex including condoms.
3. Ensure that all patients using drugs have easy convenient access to local needle exchanges, which provide injecting paraphernalia as well as needles and syringes and advice safer smoking of drugs such as glass pipes for smokers and clean straws for snorting.
4. Advise injectors of strategies how to move away from injecting.
5. Run a needle exchange in the surgery.
6. Discuss alcohol with all patients, advise to stop and treat or refer on any alcohol problem.
7. Provide drug treatment including substitute medication or refer to secondary agency for help.
8. Monitor weight and provide help with weight reduction (risk of non-alcoholic fatty liver disease which causes cirrhosis irrespective of any other causes and provide nutrition advice and support people who are HCV positive to optimise their nutrition).
9. Advise all patients to stop smoking and explain to people who are HCV positive that smoking can increase progression.

Table 1

Special groups

Mother to baby (vertical transmission)

Pregnant women who are chronically infected with hepatitis C may transmit their infection to their infants at or around the time of birth. The risk of transmission has been estimated at between 5 to 6%.⁹ Transmission is largely restricted to women who have hepatitis C viraemia during pregnancy or delivery and mainly in women with high levels of the virus.

The baby's risk of acquiring HCV from a HCV infected mother is not increased by mode of delivery or breast feeding.⁴¹

Additional risk factors for vertical transmission among vaginal deliveries include, a reduction in umbilical cord blood pH, the occurrence of perineal or vaginal laceration or prolonged rupture of membranes.^{74, 75}

Therefore for women who are infected with hepatitis C only, elective caesarean section is not indicated. However in mothers who are co-infected with HIV, the rate of transmission of HCV to their infants can be increased by three to four times. Therefore elective caesarean section is indicated for mothers who are co-infected.⁴²

Although hepatitis C has been isolated from breast milk, the role of breast feeding in transmitting HCV from mother to infant is unclear and a number of studies have recorded that for those mothers who are only HCV infected there are no significant differences in transmission rates between breast fed and bottle fed babies.⁷⁵ However, mothers coinfected with HIV are three to four times more likely to transmit HCV from mother to infant. Breastfeeding should therefore be avoided in those co-infected with HIV.⁴² SIGN recommend 'in pregnant women, knowledge of HCV RNA positive status should not influence obstetric management or standard advice regarding breast feeding.'²²

There are currently no drugs that can be offered during delivery to reduce the risk of transmission of HCV. Antenatal testing is still controversial but in the absence of a proven safe and effective intervention to prevent infant infection and limited evidence about the treatment of children infected with HCV antenatal testing for HCV it is not recommended.

Children

Infants born to women who are HCV antibody positive and HCV RNA negative do not need to be tested. In children born to women infected with HCV, an HCV antibody test should be performed at 12 months of age or thereafter to identify the majority of children who are not infected.

In children whose mothers are co-infected with HIV, and in infants found to be HCV antibody positive after 12 months, an HCV RNA test should be performed, and if positive, confirmed on a second sample.

If information regarding the risk of HCV infection in an individual child is required before 12 months of age, an HCV RNA test and retest can be performed after two months of age. Further testing is still required to make a definitive diagnosis.

Prisoners

All prisons are now working with PCTs to carry out a joint health needs assessment for the local prison population and to formulate health improvement plans.

All prisoners should have access to clinical investigations, NHS treatment and care for hepatitis B, C and HIV infections. Responsibility for combination drug treatment for hepatitis C should fall to the PCT of residence of the prisoner. Hepatitis C services for prisoners should include pre and post test discussion and the provision of psycho social support. Those testing positive should be referred to local NHS specialists.⁹

However in many prisons and for many prisoners HCV is not on the agenda. In one study in 2003 in Parkhurst of 1618 prisoners, 137 (8.5%) accepted testing; 41 (30%) had HCV but only 3 (2.1%) received therapy.⁷⁷

Referral – what will happen next?

1. **Early referral is advantageous.** It is now thought that chronic HCV does not progress in a linear fashion and that the disease accelerates with aging so most patients with HCV may develop cirrhosis long term. Furthermore therapy is more effective when administered in the early stages of the disease and hence early referral is advisable.¹⁵

This makes sense for all kinds of reasons, although the MRC early treatment study didn't provide very impressive figures. The Trent Group have recently shown this very clearly (Thomson BJ *et al.* on behalf of the Trent Group, response rates to combination therapy for chronic HCV infection in a clinical setting and derivation of probability tables for individual patient management). This paper, however, has been submitted for publication but not yet accepted. Also, even if patient does not want treatment they can be given information and support. Acute HCV should be referred immediately and given treatment.⁷⁸

2. Currently there is a high non attendance rate for most hepatology appointments, so it is vital to provide good quality information and support before and through referral which can help increase the attendance rate, and help more patients access the treatment they need.⁷⁹
3. **Ultrasound:** Most HCV infected patients will undergo an ultrasound scan of their liver. Ultrasound is not a primary tool to establish the diagnosis or determine the prognosis in chronic hepatitis C infection. Neither can ultrasound accurately assess the degree of inflammation or fibrosis in the liver. However ultrasound is an excellent test for the detection of liver masses such as tumours or cysts and may detect cirrhosis (if present). It is normally performed after referral to the specialist centre.
4. **Liver biopsy:** In the past all patients with HCV underwent a liver biopsy and early NICE guidance stated that the decision of whether to treat or not was dependent on a liver biopsy to determine disease stage.¹⁵ The need for a pre-treatment liver biopsy has recently been reviewed and the updated NICE guidelines allows treatment to start for some patients without this additional investigation.¹⁶

The impact of the new NICE guidelines is unknown at present but as many patients fear the liver biopsy it is probable that the number of patients who request antiviral therapy will increase.

However liver biopsies are still useful in patients with HCV as they remain the best current method of assessing the extent of liver damage, such as inflammation, fibrosis or cirrhosis and are often recommended for reasons unrelated to the decision to initiate treatment.⁸⁰

Biopsy is also helpful in ruling out other causes of liver disease such as alcoholic features, non-alcoholic steatohepatitis, autoimmune hepatitis, medication induced, co-infection with HBV, HIV or iron overload and may identify patients with cirrhosis who have an increased risk of liver cancer. Hence patients may be offered a liver biopsy but it is no longer a mandatory investigation prior to therapy.

Treatment

Who to treat?

Anyone who is hepatitis C positive and has given informed consent can be treated. The most recent NICE guidance advocates treatment for mild to moderate hepatitis C. The discussion should include current knowledge of disease progression and success of treatment and will allow the patient to make informed choices about treatment. The approach that – ALL patients with chronic HCV (irrespective of the stage of the disease) should be considered for therapy is endorsed by NICE.¹⁶

It is important to note that therapy for active injectors is also approved by NICE and is recommended for those who wish to receive therapy and those who have appropriate support.¹⁶ Active injectors who are receiving therapy can be given advice on not sharing or reusing injecting equipment and information on how to access needle exchange programmes.

Before initiating therapy with former injectors, it is also advisable to discuss any connotations or support they may need in using 'injecting' as a form of administration and how any side-effects requiring painkillers may be managed if the use of opioid based medications is not feasible.

When to treat?

Therapy should be considered for all patients with hepatitis C and all patients should have an opportunity to discuss therapy. In general compliance with therapy is best when patients are given a chance to choose the timing of their treatment. Some patients may choose to defer therapy and adopt a policy of 'watchful waiting' in the hope that new, more 'user friendly' drugs will become available in the future. Such a decision should only be made by the person after a fully informed consultation with a responsible clinician.

Where to treat?

It is important that all practitioners are aware of their local care pathways into treatment. The Hepatitis C Action Plan states that 'Chief executives of primary care trusts and NHS hospital trusts should be able to demonstrate that there are adequate services and partnerships at local level to enable models of best clinical practice to be followed.'⁷

Recent NICE Guidance suggests that the decision to treat should be based upon clinical need and not lifestyle choices.¹⁶ Local commissioning structures and treatment provision should reflect this.

What is the treatment for hepatitis C?

The current treatment is combination therapy with pegylated interferon and ribavirin. This treatment is successful in clearing the virus (with no detectable virus six months after treatment has ceased) in between 40 to 80% of those treated, accordingly to genotype. There are two commercially available products:

1. Peginterferon alfa-2b (ViraferonPeg) available in a pen and ribavirin (Rebetol) (Schering-Plough Ltd); and
2. Peginterferon alfa-2a (Pegasys ®) available in a pre-filled syringe and ribavirin (Copegus ®) (Roche Ltd);

but there have been no trials comparing them.

Interferon

Interferon is a manufactured drug that mimics the naturally occurring interferon produced as part of the body's immune response to a viral infection. The aim of the drug is to prevent the virus from multiplying and causing further liver damage but one side-effect is that it is like giving the patient a viral illness, sometimes severe.

Ribavirin

Ribavirin is a direct antiviral agent and is used against a range of viruses. It is teratogenic so it is essential to provide effective contraception for both men and women during treatment and for six months after completing treatment.

The treatment generally lasts for 24 to 48 weeks and involves self-administered subcutaneous injection of pegylated interferon once a week, plus a daily dosage of oral ribavirin. Pegylated interferon can maintain therapeutic drug levels over longer periods than previous interferon and, in combination with ribavirin and is much more successful in clearing the virus than conventional interferon and ribavirin.

Contraindications and cautions

1. Pregnancy and risk of pregnancy

Ribavirin is thought to be teratogenic and cause abnormalities in the sperm (although there are no human studies), and should not be prescribed to pregnant women or women who are trying or may be pregnant. Two forms of contraception for men and women are recommended during treatment and for at least six months after it has finished.

2. Patients with mental health problems

Patients who have mental health problems should receive treatment in the normal way as they respond equally well but their mental health problem should be managed carefully, particularly in the first four weeks of treatment. Those with depression need treatment and careful monitoring before commencing treatment.

Anti depressants are helpful and selective serotonin reuptake inhibitors (SSRIs) can work well. If insomnia is an issue a small dose of tricyclic such as trimipramine 20 mg can be taken at night. The doses need to be carefully monitored and doses higher than routine maintenance may be needed. Psychosis may re-emerge, in the presence of a history of psychosis. They and their carer should be warned that the onset can be rapid. This is treatable and they should be given a range of contact details for weekday and out of hours psychiatric support. Treatment for depression should be started early and psychosis managed with antipsychotics

3. Patients with renal failure

Can be treated but need to be carefully monitored because of the risk of ribavirin causing haemolytic anaemia.

Drug interactions

1. Interferon inhibits the metabolism of theophylline and concomitant use of vaccines is not recommended.
2. Ribavirin: possibly inhibits the effect of stavudine and zidovudine, used in HIV treatment.

Unwanted and adverse effects of treatment

Unwanted and adverse effects are numerous and troublesome and include lethargy, flu-like symptoms, headaches, nausea, anaemia, other cytopenias, oral disease, insomnia and depression. These can vary enormously between individual patients but need help and treatment.

Management of unwanted and adverse effects

1. **Flu-like symptoms:** Almost all will experience these and include fever, rigors, aching joints and muscles and headache. It could be said the treatment is provoking an acute viral infection. This can be helped by information, paracetamol, increased fluids and rest.
2. **Anaemia:** Is common and needs to be checked for regularly. It needs treatment to avoid a dose reduction which leads to a reduction in response. Erythropoietin has been found to be helpful in some people and improve the anaemia (see personal story page 30).
3. **Depression:** Mental state needs to be assessed before treatment and monitored during treatment.
4. **Skin reactions:** Dry skin, eczema and pruritis are common and affect about 20% of patients and need to be managed with emollients, antihistamines and topical steroids as required and psoriasis may deteriorate. Severe skin reactions are uncommon.
5. **Thyroid dysfunction:** Either hyperthyroid or hypothyroid can result in about 6% of those receiving treatment and thyroid function should be monitored during treatment and dysfunction referred and/or treated.
6. **Fatigue:** Probably related to several things including sleep disturbance, anaemia, depression etc – advise on rest and sleep hygiene.
7. **Insomnia:** Is reported and can be very detrimental to health. Advice on sleep hygiene needs to be given.
8. **Weight loss:** Is common and may need nutritional support.
9. **Dyspnoea:** Is rare and may be related to anaemia but if anaemia not present needs to be investigated urgently.
10. **Alopecia:** Is relatively common and will grow back after completing treatment.

Factors influencing response to antiviral therapy for hepatitis C

Nonadjustable factors

Viral genotype: Viral genotype is the major viral factor which determines likelihood of achieving a sustained virologic response (SVR), the indicator used to monitor treatment progression, following a complete course of antiviral therapy for hepatitis C. All studies, whether employing standard or pegylated interferon, given with or without ribavirin, indicate that patients most likely to respond to therapy are those infected with genotype 2 and slightly less so, those with genotype 3. Unfortunately, the majority of individuals world wide are infected with less responsive genotypes, namely genotypes 1 and 4.

Viral load: Viral load plays an important role in determining whether the outcome of therapy is successful or not. The influence of viral load has diminished with the development of more effective therapies but it remains a significant determinant of treatment outcome.

Gender and ethnicity: Men are less likely than women to achieve a SVR. Response varies in different ethnic groups and a meta-analysis of ethnic differences showed that patients of African-American and Hispanic origins had lower SVRs than Caucasian and Asian groups.^{32, 81}

Degree of hepatic fibrosis and cirrhosis: Consistently across all published trials the greater the degree of hepatic fibrosis the lower the response to antiviral therapy, hence the current advice to consider early treatment before significant fibrosis has developed. But therapy doesn't appear to be more toxic in patients with or without cirrhosis, although less effective and therefore those with hepatic fibrosis need to be considered for treatment.

Age: Treatment is less effective when over 40 years old. The likelihood of a SVR diminishes by about 5% per decade. Thus it has been suggested, that treatment be considered sooner rather than later, so as to not reduce the chance of achieving an SVR, particularly in those who are difficult to treat because they are infected with genotypes 1, 4, 5 or 6. There is no pharmacologic explanation for this age effect.

Adjustable factors

Weight and/or body mass index: Recent data indicates that both the degree of fat within hepatocytes (hepatic steatosis) and body mass index influence treatment response. Weight loss in those who are obese may significantly improve response to therapy.

Alcohol consumption: Retrospective analyses have shown that alcohol consumption both prior to and during treatment may influence the outcome of therapy, above and beyond the effects of alcohol in causing more rapid disease progression and influencing adherence.³⁰ Thus, it is recommended that patients abstain from alcohol prior to and during antiviral therapy for hepatitis C. But information about treating people who continue to drink is limited but it appears that response to treatment was inversely proportional to the alcohol ingested. Unfortunately stopping alcohol for six months did not correct for a life time of drinking.⁸²

Combination therapy according to genotype:

The impact of treatment is developing rapidly – current recommendations are to use combination therapy with pegylated interferon and ribavirin for varying times according to genotype:

- Treatment of genotype 1, 4, 5, and 6 requires 48 weeks of pegylated interferon and ribavirin and leads to SVR rates of between 38 to 50%
- Treatment of genotype 2 and 3 requires 24 weeks of pegylated interferon and ribavirin and leads to SVR rates of between 75 to 80%
- A minimum of a 100 fold drop in viral load is required to continue treatment beyond 12 week. If this is not achieved then treatment is stopped early as further therapy is likely to be futile.

Drug dose and treatment regimen to be followed for combination therapy with peginterferon alfa-2a or -2b plus ribavirin

Peginterferon alfa-2a (Pegasys®) available in a pre-filled syringe and ribavirin (Copegus®) (Roche Ltd.)	Peginterferon alfa-2b (ViraferonPeg) available in pen and ribavirin (Rebetol) (Schering-Plough Ltd.)
Genotypes 1, 4, 5 and 6: 48 weeks (for patients who exhibit a virological response at week 12) treatment with peginterferon alfa-2a, 180 µg once weekly, plus ribavirin, 1,000 mg/day (for those under 75 kg) or 1,200 mg/day (for those above 75 kg).	Genotypes 1, 4, 5 and 6: 48 weeks (for patients who exhibit a virological response at week 12) treatment with peginterferon alfa-2b, 1.5 µg/kg/week, plus ribavirin, 800 mg/day (for those under 65 kg) or 1,000 mg/day (for those above 65 kg) or 1,200 mg/day (for those above 85 kg).
Genotypes 2 and 3: 24 weeks' treatment with peginterferon alfa-2a, 180 µg once weekly, plus ribavirin, 800 mg/day.	Genotypes 2 and 3: 24 weeks' treatment with peginterferon alfa-2b, 1.5 µg/kg/week, plus ribavirin, 800 mg/day (for those under 65 kg) or 1,000 mg/day (for those more than 65 kg) or 1,200 mg/day (for those above 85 kg).
All genotypes: monotherapy with peginterferon alfa-2a monotherapy, where combination treatment with ribavirin is inappropriate.	All genotypes: monotherapy with peginterferon alfa-2b, 0.5 or 1.0 µg/kg/week, where combination treatment with ribavirin is inappropriate.

Table 2

Reducing time of treatment for genotype 2 and 3 patients

There is now some information appearing which shows treatment for genotype 2 and 3 patients can be shorter with 12 weeks of pegylated interferon and normal dose ribavirin, when there is an early virological response (EVR).⁸³ These new regimes are now under careful evaluation. This is useful when the patient is experiencing severe side-effects. Current opinion still favours treatment for 24 weeks and shorter treatment is not recommended yet while trials continue.

Improving treatment for genotype 1, 4, 5 and 6 patients

By increasing the dose of ribavirin and extending the length of treatment the response rates may be improved in those patients who have a slow, initial response to therapy.⁸⁴ There is some data suggesting that patients who are PCR negative at week four can successfully stop therapy after 24 weeks with very good sustained response rates (although this is not yet approved by NICE).

Adherence to treatment: Achieving an early virologic response (EVR)

The factor that has the greatest effect on the outcome of antiviral therapy remains the ability of the patient to maintain full dose or close to full dose therapy for the prescribed duration. In studies of pegylated interferon and ribavirin it has been calculated that individuals who are able to maintain at least 80% of the doses required have an 80% chance of achieving an early virological response.⁸⁵

There are many factors which play a role in facilitating adherence to hepatitis C treatment:

1. **Time of initiation of therapy:** needs to be optimal for the patient. Avoid initiation during the time of a major life event or when an individual is psychologically unprepared due to overwhelming social, medical or relationship complexities. Discuss the timing for starting treatment with the patient explaining the advantages and disadvantages to enable them to make an informed choice. It should ultimately be the individual's decision to go ahead at that time or delay for a period.
2. **Pre-emptive treatment of side-effects:** Predictable side-effects may be minimised. Of greatest benefit to the patient is for their ongoing treatment to be closely monitored by an individual who has the time to interact and support them throughout treatment. Specialist nurses best perform this role. They can support the patient by providing the time the patient needs to talk. Pyrexia associated with interferon can be managed with paracetamol. For fuller discussion of management of unwanted effects see previous on page 18.
3. **Appropriate dose reduction of interferon and/or ribavirin:** Dose reduction is most often required because of adverse laboratory events particularly a fall in haemoglobin and/or absolute neutrophil count. Sometimes symptoms, particularly overwhelming fatigue and shortness of breath, may occur when the haemoglobin is not very low but the haemolysis caused by ribavirin has been particularly rapid. Under these circumstances, it may be necessary to reduce ribavirin and/or interferon dosage for a short period of time.
4. **Drug dependency support and counselling:** A recent study of antiviral therapy given to patients with hepatitis C indicated that adherence rates could be easily maintained in individuals stable on methadone. But in those who were former injecting drug users, but not on methadone, the drop out rate was higher and hence SVR rates were much lower.⁸⁶ Unfortunately, methadone is only useful in injecting drug users who are addicted to opioids, and there is no substitute medication to help cocaine or other drugs users. Antiviral treatment can be successful in current injecting drug users in whom safety can be maintained by their regular attendance at appointments.⁸⁷
5. **Use of support groups and specialist hepatology nurses:** Joining a support group and talking to the specialist nurse can help adherence by educating and helping with side-effects, reducing isolation and stigma. The specialist nurse can also help prepare well for the start of therapy, emphasis the need to keep appointments and run a support group (see *Appendix 7* for further details).

Referral pathway/clinical networks

Once a positive test result is obtained, primary care teams should have a clear pathway of referral to a specialist team within a geographically accessible managed clinical network (see *Appendix 7*). Specialist services are most commonly based within hospital settings, due to the requirements of running a specialist service.¹²

Sadly this is not always happening and there tends to be a high fall out rate at several points along the patient pathway, in the network. One study looked at the clinical pathways for newly diagnosed patients with hepatitis C to see what actually happened. They found from all the laboratory hepatitis C results, 256 (2.3%) were positive but only 125 (49%) of these positive results were appropriately referred: 64.3% of those from primary care were referred compared to 18.4% from prison, 42.4% from drug and alcohol services and 62.6% from secondary services. Of the 125 (49%) referred, 68 (27%) attended, 43 (17%) underwent liver biopsy and only 26 (10%) started treatment.⁵³

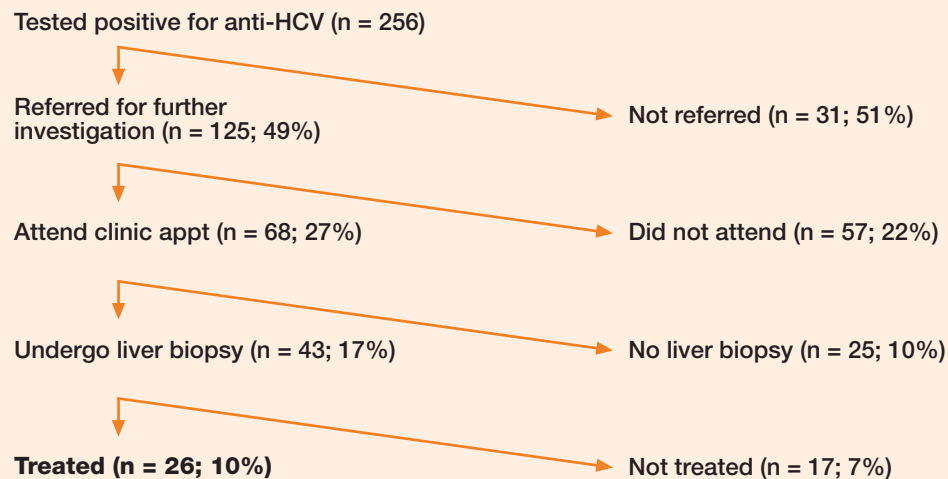
Patient journey from diagnosis to cure: complex and slow⁵³

Table 3

Patient groups in treatment**1. Injecting drug users**

In patients with chronic hepatitis C who are on a stable drug treatment programme, management with a combination of pegylated IFN and ribavirin is effective, leading to high levels of sustained viral response, whilst drop-out rates are higher than in other cohorts. The drop-out from treatment occurred early, within the first eight weeks. After eight weeks compliance is similar to other groups.^{87, 88} One study found that 43% of the former addiction group versus 14% of the methadone group discontinued treatment for their hepatitis C, thought to be on the basis that interferon's side-effects feel like opiate withdrawal so risk of relapse for former opiate users is high.⁸⁸ This could also be an issue for other substances of dependence including alcohol, given that there is significant crossover for symptoms and signs of withdrawal.

2. Co-infection with HIV

This is a hard group to treat and traditionally, they have not been treated, as there were too few responders and too many side-effects. However following the improved survival of patients with HIV due to the success of combination therapy, many HCV and HIV infected individuals are developing end stage liver disease and HCV is now recognised as a major cause of mortality in patients with HIV. This has led many to recommend that co-infected patients be considered for therapy. Trials have shown encouraging response rates in patients who are co-infected with HIV and HCV, leading to SVR in 60% of genotype 2 and 3 and between 14 to 29% in genotype 1.⁸⁹

3. Co-infection with hepatitis B

There have been no trials in co-infected patients with hepatitis B and C but they should be considered for treatment.

4. Patients with mild chronic hepatitis

Response is similar to other patients with hepatitis C so liver biopsy is no longer always necessary.¹⁶

5. Patients with advanced liver disease including cirrhosis

Individuals with HCV induced cirrhosis potentially have the most to gain in the short, and possibly the long term, were they to be successfully treated for their hepatitis C infection. Therapy appears no more toxic but it is less effective with SVR rates in genotype 2 and 3 of between 50 to 70% and 20 to 30% for genotype 1 cirrhotic individuals. Both early and long-term follow-up liver biopsy data indicates that regression of hepatic fibrosis may be observed following antiviral therapy. A significant benefit in terms of reduction in HCC is disputed, although this may occur in Japanese patients.⁹⁰ There are reports that following successful antiviral therapy the rate of hepatic decompensation is reduced in both Japanese and Caucasians, but all the data to date is from observational studies, where the less severe patients tend to be those treated. Hence therapy is recommended for patients with cirrhosis although patients should be aware that the response rate may be less than in patients with less severe disease.

Patients with cirrhosis should be aware that, although successful therapy may reduce the risk of liver cancer it may not abolish it completely and therefore life long screening for cancer and end stage liver disease will be required even if therapy is successful.⁹⁰

6. Relapses or failed treatment

One of the big issues in the treatment of patients with chronic hepatitis C is what to offer patients who are non-responders or relapsers after a first course of treatment. Should a patient fail after a first or second course of treatment the following options are available:

1. Re-treatment with peg interferon alpha and ribavirin for patients who received interferon alpha and ribavirin, or interferon alpha alone for their first course of treatment.
2. Re-treatment with peg-interferon alpha at a higher dose and/or for a longer duration, with ribavirin.
3. Enrolment in approved clinical trials of novel compounds.

At present there is insufficient data to make firm recommendations and those who have failed to respond to therapy should be advised by an individual with up-to-date information on the options that are available. Non-responders need to be kept under regular review to monitor for advancing liver disease, HCC and other complications and offered re-treatment when new treatments become available. There are some new drugs on the horizon however commercial availability for new compounds may be some way off (at least five years). But most of these are going to face retriels fairly imminently.

Ongoing care

Monitoring patients who are HCV RNA positive but are not receiving treatment

It is important to continue to review patients who have chosen not to have treatment, who are not suitable for treatment or who have received unsuccessful treatment in order to monitor their disease, discuss new therapies as they develop and to continue to support behaviour changes.

Ongoing care during treatment, usually in hospital

They must also be undertaken if patients have declined referral. Need the regular review of:

1. Blood tests (for comparison with earlier and later tests) including: Viral load, FBC, TFT, LFT and pregnancy test.
2. Ongoing advice regarding injecting medication.
3. Ongoing support including referral to counselling, psychotherapy and/or psychiatry; referral to hepatitis C support groups and referral to support for benefits advice.

Ongoing review/care after treatment.

At the end of treatment.

Qualitative PCR to see if virus is detectable.

Three months after end of treatment.

Qualitative PCR to make sure virus remains undetectable.

Six months after end of treatment.

Qualitative PCR to make sure virus remains undetectable.

If the virus is undetectable at this point, this is a SVR.

In general practice

Where treatment is provided from a hospital base, primary care can continue to play an important role in the patient's treatment by:

- Provision of ongoing General Medical Services (GMS) to support the patient through the treatment process.
- Supporting patients on therapy and giving practical advice to them on managing side-effects such as paracetamol for pyrexia, anti emetics if nauseated and moisturisers and steroid cream for itchy skin.
- Ongoing harm reduction information.
- Support regarding drug dependency. Doses of substitution medication may need changing.
- Monitoring of mental health, especially depression.
- Ongoing support with remaining alcohol free.

It is therefore important to continue to have good communication pathways between primary and secondary care. The following can improve the communication between primary and secondary care services:

- Development of a referral proforma to ensure the transfer of good quality and standardised information at the time of referral.
- Patient's address and mobile phone number rechecked at the time of referral (and regularly thereafter). Many were not receiving appointments due to changing address frequently, or having an insecure postal address, or being functionally homeless, in which case the practice's address could be used for correspondence.
- Improvement of communication from the hospital services. The hepatology department offers an appointment within four weeks of receiving a referral, i.e. while the patient is well motivated. The hospital informs the practice of the date and time of the appointment, so that they can encourage the client to attend.

- Continue communication post referral with a 'partnership' letter as a basis for shared care during treatment. Clearly most of the service will be provided by the hospital, but an informed GP, providing informed support and feeling able to prescribe, if necessary, for nausea/pyrexia/insomnia/mild depression etc can make an extremely positive contribution.

Where treatment is provided from primary care

There are also a small but growing number of examples of treatment being offered from primary care by specialist hepatitis C nurses employed by hospital specialist teams. Whilst the responsibility for the treatment lies with the specialist doctor based in the hospital, some GPs are taking an increased role in overseeing and monitoring the patient with the support of the specialist nurse.

Where this is the case, it is important that there is agreement on clear care pathways between primary and secondary care, including clinical governance arrangements.

The advantages of providing hepatitis C treatment from a primary care setting include:

- A more accessible service for the patient in terms of locality.
- Increased rates of attendance, and involvement in treatment plans.
- Access to GMS as well as hepatitis C treatment.
- GP will often already have a relationship with the patient.
- Access to both hepatitis C and drug treatment services from the same medical practice.

Additional support to treatment

Nutrition

Nutrition: protein malnutrition is common in all patients with chronic liver disease hence nutritional advice and support is important. Weight loss is common in people on antiviral therapy.⁹¹ This can be made worse by side-effects such as depression and lethargy.

Supplementary vitamins and minerals have generally not been shown to help HCC, except vitamin K may be beneficial in the prevention of HCC in patients with hepatitis C.⁹²

Complimentary therapies

There is no evidence that complementary or alternative medicine can help in the treatment of patients with hepatitis C, however many people report finding it useful with symptoms and during treatment.⁹³

Care Pathways – example of good practice

In January 2005, collaboration between the secondary care specialist service and an inner city practice in Nottingham specialising in substance misuse enabled a unique community clinic to be established. This specialist hepatology nurse-led service was constituted with three broad aims:

- to proactively test all patients who attended shared care clinics in the practice for HCV and other blood borne viruses;
- to identify clients who could be safely treated with pegylated interferon and ribavirin and to initiate and monitor treatment in the practice; and
- to facilitate consultant review of those with likely cirrhosis and for whom treatment was being considered.

By January 2007, 111 HCV PCR positive patients have been identified at this single GP practice who had not been treated at the local hospital. 35 (31.5%) of these have been identified as suitable to treat safely with antiviral therapy: 14 have been commenced on pegylated interferon and ribavirin; a further four are due to start treatment in prison; one will be treated at hospital due to complicated medical history, and the remaining 16 do not want to undergo treatment at present. The most common reason for withholding treatment was the ongoing consumption of excessive amounts of drugs and/or alcohol.

The patient's tolerance and outcomes on pegylated interferon and ribavirin do not appear to differ from those of the hospital-based population. Active HCV management has also played a key role in re-engaging some clients with opiate substitution treatment (Jack K, Thomson B, Willott S. January 2007, data on file)

Developments are now in place to extend this model of care to other GP with Special Interest who participate in the shared care treatment of substance misusers.

Table 4

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Appendix 1

Further reading and useful resources

Further Reading

NHS public/patient leaflets

Health Protection Agency (HPA) Hepatitis C Report. December 2006

Scottish Intercollegiate Guidelines Network Management of hepatitis C (SIGN) A national clinical guideline December 2006 © Scottish Intercollegiate Guidelines Network

HPA – Eye of the Needle. November 2006

Shooting Up Report Health Protection Agency Report. October 2006

APPHG Expanding The Options. October 2006

Scottish Action Plan. 26 9 06

National Institute for Health and Clinical Excellence (NICE). Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. NICE technology appraisal guidance 106. August 2006. www.nice.org.uk

Hepatitis C Strategy for England August 2002 London, Department of Health

Hepatitis C Strategy for England Action Plan Department of Health

Hepatitis C Essential information for professionals 2002

Department of Health Hepatitis C – guidance for those working with drug users London: Department of Health. 1999

Useful resources and links – hepatitis C specific

NHS hepatitis C website

www.hepc.nhs.uk

'FaCe It' campaign to provide information of hep C and how to prevent it

Department of Health

www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/HepatitisC/fs/en

Hepatitis C Trust

27 Crosby Row, London SE1 3YD
Tel: 020 7089 6220 Helpline 0870 2001200
www.hepcuk.inf

Set up by people with the illness and run a range of services that provide information, support and representation for people with hepatitis C is a resource for all infected or affected by hepatitis C in UK

British Liver Trust

2 Southampton Road, Ringwood BH24 1HY
Tel: 0870 770 8028
e-mail: info@britishlivertrust.org.uk
www.britishlivertrust.org.uk

The British Liver Trust (BLT) is concerned with raising awareness and providing information and education on all forms of liver disease. The charity produces a number of publications.

Health Protection Agency

www.hpa.org.uk/infections/topics_az/hepatitis_c/

UK Hepatitis C Resource Centre, Mainliners

195 New Kent Rd, London SE1 4AG
Tel: 0870 242 2467 (UK Hepatitis C information line)
e-mail: info@hepccentre.org.uk
www.hepccentre.org.uk

Provides resources, information and support services for professionals and the public. Works to raise awareness and facilitate information exchange to progress treatment, care and support for hepatitis C.

The Health Tool

Interactive software which delivers education, raises awareness and provides a referral pathway for healthcare professionals. Further details can be obtained at www.thehealthtool.org

Other useful links

The Alliance

www.m-alliance.org.uk

Exchange Supplies

www.exchangesupplies.org

Royal College of General Practitioners (RCGP)

www.rcgp.org.uk

Substance Misuse Management in General Practice (SMMGP)

www.smmgp.org.uk

UK Harm Reduction Alliance

www.ukhra.org

Appendix 2

Definitions and abbreviations

Definitions (Adapted from SIGN Management of Hepatitis C)

Acute hepatitis C

There is no generally accepted definition of acute hepatitis C infection but for purposes of investigations and treatment of acute hepatitis C, the following criteria have been used: a clear point of exposure and a positive HCV RNA within six months or a significant rise in serum alanine aminotransferase or seroconversion in which antibody and/or HCV RNA is absent from a first and present in a second sample.

Chronic hepatitis C

Ongoing infection with hepatitis C virus beyond the acute phase.

Mild liver disease

Mild disease is present when inflammation of the liver tissue is absent or largely confined to the portal tracts with no evidence of fibrous tissue extending between the portal tracts.

Moderate liver disease

Moderate liver disease is described when there is significant inflammation and/or liver cell damage associated with increased fibrous tissue extending beyond the portal tracts but not resulting in nodule formation.

Severe liver disease

Severe disease occurs when patients have developed bridging fibrosis or cirrhosis (histologically proven or otherwise) of the liver, whether there are clinical signs of liver dysfunction or not.

Genotypes

Many different strains of HCV have been recognised by virological testing. These have been grouped into six categories known as genotypes 1 to 6. There are significant geographical variations in the prevalence of the different genotypes in different parts of the world. In the UK genotype 1 is the most common, followed by genotype 3 and then genotype 2. There are small numbers of patients in the UK infected with hepatitis C virus of genotypes 4, 5 and 6, most of whom acquired the infection overseas.

Sustained viral response

Sustained viral response (SVR) is defined as undetectable HCV RNA in the patient's serum using sensitive nucleic acid detection techniques, six months after the end of a period of antiviral therapy.

Early viral response

Early viral response (EVR) is either a negative HCV RNA or a two log drop in quantitative HCV RNA levels after starting antiviral treatment. It is measured at 12 weeks for patients with genotype 1.

Rapid viral response

Rapid viral response (RVR) is a negative qualitative HCV RNA measured four weeks after antiviral treatment for patients with genotype 2 or 3.

Non-responder

A non-responder is a patient who after antiviral treatment for HCV has detectable HCV RNA at the end of treatment.

Relapser

A relapser is a patient who after antiviral treatment for HCV has no detectable HCV RNA at the end of treatment, but who does have detectable HCV RNA six months after the end of a period of antiviral therapy.

Exposure prone procedures

Exposure prone procedures (EPP) are those where there is a risk that injury to a healthcare worker may result in the exposure of a patient's open tissues to the blood of the worker. These procedures include those where the worker's gloved hands may be in contact with sharp instruments, needle tips and sharp tissues (spicules of bone or teeth) inside a patient's open body cavity, wound or confined anatomical space where the hand or fingertips may not be completely visible at all times.

Abbreviations

AFP	Alfa foetal protein
ANA	Autoantibodies
CHC	Chronic hepatitis C
ELISA	Enzyme linked immunosorbent assay
EPP	Exposure prone procedures
EVR	Early viral response
FBC	Full blood count
GGT	Gamma-glutamyl transferase
GMS	General Medical Services
HAV	Hepatitis A virus
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDU	Injecting drug users
IFN	Interferon
IgGs	Immunoglobulins
LFT	Liver function tests
NICE	National Institute for Health and Clinical Excellence
NTA	The National Treatment Agency
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
SVR	Sustained viral response
TFT	Thyroid function tests
U+E	Urea and electrolytes
UK	United Kingdom

Appendix 3

Patient information and personal story of treatment

Part A

Thinking about being tested leaflets

There are a number of good leaflets available for patients. Examples are from 1. Hepatitis C Trust 'Have you got a clue?' 2. Exchange and 3. Department of Health.

Part B

Patient information leaflet about being diagnosed hepatitis C positive

If you have just been diagnosed with hepatitis C, you need to know what this means and what happens next. You may be frightened or confused or unsure exactly what you have been told. Luckily you have time to let the diagnosis sink in and find out about the options open to you, including treatment, because hepatitis C is a slow disease. It is caused by a virus that primarily damages the liver but it does so over many years.

Although it is a serious disease and the damage caused can eventually stop your liver working properly, it is not a death sentence. Nor is it highly infectious in the way a cold is. The virus is carried round the body in the blood so infection occurs through blood to blood contact, not through hugging, kissing or sharing knives and forks or cups and glasses.

You are not alone. Hepatitis C is much more common than people think. It is estimated that between 250,000 and 600,000 people in the UK are infected but, unfortunately, the vast majority have not yet been diagnosed.

Testing for hepatitis C

There are usually two blood tests for hepatitis C. The first test looks for antibodies, which are produced by your body to fight the hepatitis C virus (HCV), and is known as an antibody or anti-HCV test. Antibodies remain in your blood so a positive test only means that you were infected at some point. It does NOT necessarily mean you are still infected now. One in four people get rid of the virus themselves but the likelihood is that you have hepatitis C. So the best thing is to assume you do and look after yourself and your liver.

A second test, called a PCR or RNA test, is needed to see if the virus is still in your blood. This is a more complicated and expensive test which is why an antibody test is almost always done first. Both of these tests can be undertaken by your GP or they may refer you to a specialist for the second test

How important is it to know how you were infected?

Unless there was a particular time when you know you came into contact with infected blood, it is probably very hard to be certain when you were infected. Some people have no idea how they could even have been at risk. More important is deciding what to do about it now and being safe so as not to infect anyone else.

Who to tell?

The two main reasons for telling someone you have hepatitis C are: to get support for yourself or because you think they should get tested. But you can tell them when you are ready. You may need time to come to terms with your diagnosis or to get more information. You do not have to tell other people and before deciding to tell, say, your employer you may find it useful to talk to someone else with hepatitis C to see who they told and when and how they did it.

What happens next?

Once you have had a positive PCR or RNA test, you should be sent to see a specialist, who may be working in general practice or at a hospital. There you will have another blood test to check which strain of the virus you have (there are six different HCV strains or genotypes; genotypes 1, 2 and 3 are the most common in the UK). The specialist will then talk to you about whether you want treatment. To help make this decision, sometimes you will need to undergo a liver biopsy to give the doctor more information about the state of your liver but this is no longer always necessary.

What you can do

There is a lot you can do to help support your liver and your immune system and you may also find this helps reduce your symptoms. Almost everything you eat, drink, smoke, swallow or absorb through your skin goes through the liver so the less toxic that is, the less your liver has to cope with. In particular, try to:

- stop all alcohol if possible, or reduce it as much as possible because alcohol causes the hepatitis C to damage your liver much more quickly. This is the single most beneficial thing you can do.
- drink plenty of water.
- eat less food that is fatty, fried, processed or high in chemical additives.
- eat more food that is high in anti-oxidants such as fresh fruit and vegetables.
- manage your energy and stress levels by getting enough rest and taking moderate exercise.
- ask for support when the disease or the symptoms get you down.

Many people find that complementary medicines such as acupuncture, massage and herbs are helpful in managing their hepatitis C but people are different and what works for someone else may not necessarily work for you. It is important to go to a qualified practitioner with experience of treating hepatitis C because some complementary medicines can damage the liver.

Treatment

The current treatment for hepatitis C is a combination of two drugs – pegylated interferon, which is injected, and ribavirin, taken as a pill. It is successful in getting rid of the virus in about 80% of people who have genotype 2 or 3 and about 50% of those with genotypes 1, 4, 5 or 6. In general, it works less well the longer you have been infected, the more damaged your liver is and the more overweight you are. Treatment usually lasts for six months for those with genotypes 2 and 3 and a year for genotypes 1, 4, 5 and 6 and most people have some side-effects. So it is important to talk to your doctor and also people who have done treatment to help you decide whether to do it.

Many new drugs are in development to treat hepatitis C but it is unclear how well they will work or how soon they will become available.

What are the symptoms?

You may have been tested because you had symptoms but many people with hepatitis C have no symptoms or their symptoms are vague. Different people are affected differently. Even if you do feel very unwell, this does not necessarily mean that your liver is badly damaged but, equally, you can feel fine even with a lot of liver damage.

There are a lot of symptoms connected with hepatitis C, partly because the liver is involved in so many different functions of the body and partly because hepatitis C affects not just the liver. The symptoms may include:

- fatigue
- digestive problems
- nausea
- loss of appetite and/or weight
- aching joints or muscles
- flu-like symptoms such as sweats and chills
- pain in the liver area
- depression and/or mood swings
- difficulty concentrating
- blurred vision
- itchy skin
- red palms
- little red spider-shaped marks on chest

It may be a relief to know that some symptoms you have can be explained by your hepatitis C but, because there are so many, it can be tempting to blame everything on your hepatitis C. This may not be safe because they may be caused by something else and it is better to run through your symptoms with your doctor.

There are also some symptoms associated with severe liver disease. If damage to the liver becomes irreversible it is called cirrhosis. In advanced or decompensated cirrhosis key liver functions may stop working and produce the following symptoms:

- swelling of the stomach or back or ankles caused by water retention.
- black stools caused by internal bleeding.
- severe mental confusion caused by the liver's failure to clear poisons from the blood.
- jaundice (a yellow tinge to the skin and whites of the eyes) caused by poor liver function.

If you have hepatitis C and notice any of these symptoms, you should see your doctor immediately.

Prevention

To infect someone else your blood has to get into their bloodstream so, rather than being paranoid about it, you just need to take common sense precautions, such as:

- cleaning thoroughly with undiluted bleach any surface that you bleed onto and safely disposing of any cloths used.
- carefully dressing any cut or graze you have so that you don't bleed without knowing it.
- not sharing anything that is inserted through your skin including earrings, piercing jewellery, acupuncture needles and, of course, needles for injecting drugs or steroids.
- not letting anyone else use anything that could have come into contact with your blood. This means anything that could have cut you or caused you to bleed such as razors, toothbrushes, even nail clippers. It also means anything you could have bled onto, such as a straw or note for snorting drugs.
- never sharing anything used for injecting drugs, meaning water, spoons, filters as well as the syringes and needles themselves

Can it be transmitted sexually?

No-one is completely sure but it seems to be extremely rare that hepatitis C is passed on during sex if there is no blood involved, but blood, even in tiny amounts, can be present for example in anal sex or rough sex or during a women's period. There is some evidence that it may happen if you or your partner has a sexual infection or a damaged immune system (for example as a result of HIV) but this is not certain.

The best advice is: unless you are in a stable heterosexual relationship not involving anal or rough sex or sex during the woman's period, it is safer to use a condom.

Getting more information and support

You are likely to need more information and you can find this in books, on the internet and from talking to other people with hepatitis C, either on the phone, at support groups or in online discussion forums. Talking to others with the disease is also a useful form of support.

Part C

Living and dealing with the side-effects of treatment – a personal story

Like many others before and many others since, I recently became aware that I had contracted the hepatitis C virus. I assume that I have lived with it for many years but with no perceptible symptoms.

The day came when diagnostic tests sounded the alarm. I already knew that I had the nastier genotype 1 and liver function tests results that were unacceptable. The biopsy told a fuller story. Damage to my liver, although moderate, had started. Even though I felt fine, was a complete workaholic and went to the gym every day it was time to do something or suffer the consequences of this invading basic life form.

No one *wants* to have to go through the treatment: drugs such as interferon and ribavirin are notoriously bad company – particularly together. Nonetheless, these were the allies with whom I was going to have to join forces in a biochemical battle against the HCV. They were my equalizers; tough guys, no manners and tediously single-minded, I was going to have to live with them for the next year.

So: what is it like to undergo HCV treatment? They say it varies from one person to another. Those who enjoy it appear thin on the ground and I have certainly never met one. So how is it for me? Well, it feels like I'm the battleground for a biological and chemical struggle that is being waged by microscopic combatants. Sometimes I feel like scorched earth or a toxic dump where intercellular warfare is taking place.

I suppose the people of an occupied country must feel rather like this as their liberators arrive and start scrapping with the occupying forces. Like France in WW2, I guess: these powerful armed forces that are blasting the internal environment of my body with explosives and anti-personnel weapons are *on my side*. It's hard to believe it sometimes, but that's the truth. The occupier, the virus, will not leave without a good fight, and the good guys are going to cause me no little suffering while they take on the well-entrenched defences of those occupying viral elements. I must always remind myself who my allies are when the going gets tough. And it does!

My therapeutic regime consists of weekly shots of pegylated interferon; backed up by twice-daily doses of ribavirin tablets. And what is the collateral damage of this campaign of chemical bombardment? The physical side for me mainly consists of breathlessness due to anaemia, itchy skin rashes, mouth ulcers, mouth thrush, aching joints, insomnia and headaches. In psychological terms, mostly mood swings, difficulty in concentrating, excessive and overly critical self-examination, and finally *irritability*, a word that covers a multitude of sins!

Anything that can be done to alleviate symptoms is likely to increase compliance with the regime. I was surprised how little specific information was available. With a little research I stumbled on to several things that have helped me a great deal. During the first three months, I had those nasty cracked crusty mouth corners, the ones that would split when you yawn or laugh (not that often!). Fed up with being told to rub in Vaseline, I found out that by applying nystatin cream and 1% hydrocortisone cream to the angular cheilitis (that's what it's called) – it was completely gone within a few days. My advice is to get the separate creams apply the nystatin, wait an hour and then the hydrocortisone.

When my skin gets so itchy that I want to rub it with a cheese grater – I apply some Betnovate cream and regularly use a moisturising cream – there's a cheap one in a big pump called Diprobase.

With the daily gym visit having been such a key part of my life and something I had used effectively to manage stress and mood – the anaemia was particularly tough. Forget running – gasping after a few stairs has become the norm.

My friend Jerry in Los Angeles, who had also been through the treatment, said to me “get your doctor to put you on the Procrit.” This was the same guy who called me the Spartan warrior for long haul flying and working while on treatment – flattery like this can be very helpful too! Anyway, I did a little research and found that Procrit was a trade name for erythropoietin (EPO) – the drug athletes use to illicitly boost their endurance. It is being used successfully in the USA to help ensure compliance with HCV treatment in those patients where anaemia is serious. My own EPO dose involves three shots taken together on a weekly basis – it is an expensive drug so one has to put forward a very persuasive case. It was seven months into treatment when I started the EPO and although I am still very anaemic – without question it has helped a great deal. While it appears to make little medical sense – the weekly batch of unpleasant mouth ulcers and mouth thrush also stopped soon after I started the EPO.

Sleep deprivation in battle scenarios will wear you down – particularly if you have to get up and go to work. Negotiate with your doctor on which sleeping tablets work for you – changing them around works for me. For aches and pains, I find changing painkillers around to also be effective – paracetamol, aspirin and ones containing members of the codeine family.

The two days after having my interferon shot are the worst of my week. I started by taking it on Friday but soon moved this to Saturday night – hell, one might as well make Saturday the best day of the week. Taking the ribavirin tablets at noon and midnight seems to best fit my schedule and cause me the least problems.

Beyond that, there are a few general points that I would want to try to pass on to anyone else who find themselves in this unenviable position:

- Keep to the regimen, or ‘just keep taking the tablets.’ Seriously, perseverance with each item on your schedule is vital. Keep on keeping on, even when – especially when – you're having trouble remembering why on earth you ever embarked on this titanic struggle.
- Let some other people in; talk to them and tell them about your little war; those around you who care about you the most, allow them to help you and carry some of your load. Make sure that your partner is briefed, as you will behave in bizarre ways, well I certainly do.
- Try to maintain a sense of humour. There is a great tradition of gallows humour amongst human beings enduring in the face of one or other form of disaster. Keep hanging in there.

Finally, you may well have noticed a military theme permeating throughout – thinking of it as a fight has helped me get through the tougher times. With that in mind...

Forget the 80%/80%/80% rule because it sets a lower threshold for taking our two medications.

- Take 100% of the interferon shots, 100% of the ribavirin tablets for 100% of the time. Well try...
- Take power – get informed.
- Take lots of water.

Five weeks to go...

1 October 2006

Sebastian Saville

Executive Director – www.release.org.uk
Drugs, the Law and Human Rights

Appendix 4

Hepatitis B and C and HIV test proforma

This proforma is designed to record and prompt appropriate discussion prior to hepatitis B and C and HIV testing. It can be used to design your own template.

Name: Date of birth: Date of interview:

Reason for test discussion

- Patient request (give reason for concern)
- Risk behaviour
- Antenatal
- Investigation of illness
- Other (specify):

Risk assessment (see 'Who should be tested?' on page 9)

Nature of risk:

.....

Timing of risk:

.....

Patient knowledge and awareness checklist

- What these initial tests can tell us
- Antibodies take three (HIV) to six (HBV and HCV) months to develop – repeat test required?
- If any are positive what further tests may be needed (HCV PCR if antibody positive, CD4 count if HIV positive)?
- Natural history and disease progression – impact of treatment
- Monitoring and treatment – hepatitis B and C can be cured but HIV is a chronic illness but no cure
- Harm reduction – safer sex, safer injecting and stopping alcohol
- Life assurance and mortgage issues including confidentiality
- Patients understanding of risk factors
- Pregnancy issues

Immunisation

Hepatitis A 1st..... 2nd.....

Hepatitis B 1st..... 2nd..... 3rd..... 4th..... (4th dose after 1 year for accelerated courses)

NB Twinrix (combined hepatitis A and B vaccine) reduced response compared to separate vaccines

Support and coping considerations

How would you feel if you were positive? What would be the worst thing?

Who would you tell? Is this the right time for a test?

Who can offer you support whilst waiting for result and if you get a positive result?

Taking the tests

Window period? Yes No

Advised to repeat any test? Yes No

Appointment for result:

Support whilst awaiting result (partner, friend, GP, agency)

Appendix 5

Hepatitis A and B vaccination in primary care

Introduction

Groups at increased risk of acquiring hepatitis B in the UK include injecting drug users, men who have sex with men (MSM), sex workers, health care workers (from sharps injury) and people who have sex abroad or with a partner from countries where hepatitis B is common.¹ It is estimated that 21% of injecting drug users in England and Wales have evidence of past or current hepatitis B infection.² Hepatitis B disease can be prevented by vaccination. IDUs have been targeted for vaccination since 1988 and the Department of Health has made MSM a particular target in the last five years.³ Both the availability of vaccination and uptake by IDUs are recognised to be poor in the UK.^{4,5} Proactive provision of hepatitis B vaccination through widely available services is critical for protecting this difficult to reach target group.

Practices who opt to provide a National Enhanced Service to patients with drug misuse problems under the new GMS contract will be expected to undertake six-monthly audits of hepatitis B screening and immunisation data of this patient population.⁶ This appendix contains guidance on how screening and immunisation should be carried out and suggests criteria to facilitate audits.

Availability and accessibility

Hepatitis B vaccination should be considered an essential component of the care offered to drug users, MSM, sex workers, health workers and other high risk groups in primary care. Some of these groups may have poor patient attendance which is often reported as a major barrier. To address this issue, vaccination needs to be carried out opportunistically at the time when the patient makes contact with the practice, e.g. at the time of methadone prescribing for drug users. Practices should keep a stock of hepatitis B vaccine.

Pre-vaccination testing

It has been standard practice in many settings to advise that clinicians wait for hepatitis B test results before giving the first dose of vaccine, although most GUM clinics have had a policy of vaccinating all those at risk on their first visit for the last ten years or more.⁷ The rationale for the 'wait and see' advice was to prevent unnecessary vaccination of those who have already been infected or previously vaccinated.

Due to poor uptake of vaccination, current expert advice is to focus on protection through vaccination rather than testing. The Department of Health has dispensed with routine pre-vaccination testing in the national hepatitis B immunisation programme for prisons⁸ and for all patients in the new 'Green Book' Immunisation against infectious disease.⁹

Pre-testing should never act as a barrier or delay to vaccination. People should have access to vaccination without testing if desired. If someone wishes to be tested, the first dose of vaccine should be offered at the same time.^{4,10} Delaying vaccination can do harm because a patient may become infected before the next visit or may not return.⁴

The aims of testing need to be considered to ensure that it is of benefit. Anti-core antibody (anti-HBc), if used as the primary screening test, will indicate previous exposure to hepatitis B if positive. In those who are positive it should be routinely followed by surface antigen (HBsAg) testing to differentiate between chronic carriers and those who are naturally immune. Someone who is anti-HBc negative will need vaccination. Those who are anti-HBc positive but HBsAg negative are probably immune, although some would do anti-HBs testing to make sure and vaccinate if anti-HBs negative.¹⁰ Patients who are HBsAg positive need to be appropriately investigated for liver disease.

HBsAg is recommended as a screening test instead of anti-HBc by the Department of Health, but only as a means of detecting people who are chronic carriers. If HBsAg is used as the primary test, anti-HBc will have to be measured in all who are negative if testing is being used as a means of identifying people who do not need vaccination.^{7,9}

Primary vaccination schedule

A pragmatic approach to vaccination schedule is recommended. Every time a patient contacts the practice, the healthcare worker should consider whether hepatitis B vaccination should be offered. Emphasis needs to be placed on giving as many doses as possible. Lack of certainty of vaccination status should not act as a barrier to vaccination and reliance on recall of history of vaccination is not advised.

Accelerated schedules (0, 1 and 2 months or 0, 7 and 21 days) are now widely recognised as the most appropriate for people at high risk including drug users.^{7,9} A study of homeless drug users at an inner city primary care centre found a seven times higher completion rate with the 0, 7 and 21 day schedule compared with the conventional 6 month schedule.¹¹ The 0, 7 and 21 day schedule is being promoted by the Department of Health for prisons⁸ and GUM clinics. Even incomplete vaccination schedules offer some protection.⁶ The interval between vaccine doses is not critical for an immune response and it has been found that doses spread as far apart as four years still work.¹⁴

Practices and drug services need to ensure that there is a robust system for recall for very high risk groups such as IDUs.

Booster doses

Current best practice is to give a booster at 12 months if an accelerated schedule is used.¹⁵ Again, a flexible pragmatic approach is advisable for people who are often not in sustained contact with services. When someone presents to services, the healthcare worker should consider whether this is an opportune time to offer a booster dose.

Post-vaccination testing

An alternative approach is to test for antibodies to the hepatitis B surface antigen (anti-HBs) at least one month after the primary course and make a decision about whether a booster dose is needed depending on the antibody levels (table 1).¹⁶ Current evidence suggests that all those people who are immune competent and have responded to vaccine with any level of antibody are probably immune for life and do not need further testing or vaccination.¹⁶ Routine post-vaccination testing is not recommended for drug users as a group because of the practical difficulties with follow-up.¹⁶

5 to 10% of healthy people will not mount an effective antibody response after vaccination.¹⁷ Some of these apparent non-responders may still be protected against clinically significant infection⁹, but it is unsafe to assume this. Current evidence suggests that immune-competent people are protected if antibody levels are > 10 iu/l and do not need a booster if levels are in the range 10 to 99 iu/l.¹⁸ People with an immune disorder, e.g. due to HIV infection, are at higher risk of failing to respond and may need regular testing for anti-HBs and a booster injection when the level falls below 100 mIU/ml.¹⁶

Promotion of vaccination

Prominent display of posters and use of leaflets promoting hepatitis B vaccination may be helpful. Promotion of vaccination is dependent on motivated knowledgeable staff. GPs and practice nurses may also need training and awareness sessions to ensure greater uptake of vaccination. In drug services, uptake rates have been found to be higher where staff training and confidence were better.²⁰

Vaccination of partners and children of high risk or HBV-infected patients

The partners and children of high risk or infected patients may also be at risk of hepatitis B infection but their need for vaccination is often overlooked. Hepatitis B can be transmitted through sexual and other contact e.g. sharing razors.^{7,9} Children infected with hepatitis B have a higher risk of chronic infection than adults.

Organising the vaccination of families may not be straightforward. Families may not be registered with the same practice as the patient. Some people may be reluctant to disclose the risk to their partners. Healthcare workers need to work with drug users to advise them of the risks and promote the routine offering of vaccination to partners and children.

Post vaccination antibody testing and actions to consider^{16, 17, 19}

Antibody level (miu/ml)	Status	Action
<10	Non-response	Screen for markers of present or past infection (HBsAg, antiHBc). Give additional dose. Consider repeating full course.
10–100	Poor response	Give additional dose if immune compromised e.g. HIV+
>100	Protective	No further action needed if immunocompetent.

Table 1

Hepatitis A vaccination

People at higher risk of hepatitis A infection include IDUs, due to poor living conditions with spread probably occurring through faecal contamination of drugs or injecting paraphernalia²¹ and blood to blood spread through needle sharing during viraemia is also possible. Hepatitis A is also seen in people travelling outside of northern Europe and the USA.²² In the UK outbreaks occur in closed communities such as army barracks and boarding schools and amongst men who have sex with men.²³

Hepatitis A vaccination of people infected with hepatitis C and/or with chronic liver disease has been recommended for many years because of the risk of more serious illness if they became infected.¹⁹ The Public Health Laboratory Service Advisory Committee on Vaccination and Immunisation expanded this recommendation in 2001 to include all IDUs.²⁴

As for hepatitis B, it is advisable to offer drug users a hepatitis A vaccine without pre-testing because of the risk that the opportunity to vaccinate may be lost, e.g. due to the drug user not returning.¹⁴ MSM who are at risk should also be offered vaccination.^{7, 9} There is no validated test that can be used to measure vaccine response.

Hepatitis A vaccine is available as a single component vaccine or combined with hepatitis B vaccine (table 2). Using them as separate vaccines is recommended as one dose of hepatitis A vaccine confers greater protection against hepatitis A than one dose of the combined vaccine because the combined vaccine only has half the amount of hepatitis A antigen than the single component vaccine.

Monitoring

Local information on vaccine uptake and completion is crucial in order to judge the quality of the service and plan achievable improvements. The minimum information required is the number of vaccinations received.²⁵ An easy recording system is needed.

Suggested criteria for audit

Criteria for audit should be kept simple. The minimum criteria should be:

- The number and percentage of at-risk people who have received one dose of hepatitis B vaccine (HBV).
- The number and percentage of at-risk people who have received two doses of HBV.
- The number and percentage of at-risk who have received three doses of HBV.

Other criteria to consider include:

- The number and percentage of at-risk who have been offered hepatitis B vaccination.
- The percentages of at-risk who have received one and two doses of hepatitis A vaccine.

Summary of recommendations

- Vaccinate all drug users (non-injectors may become injectors), men who have sex with men, sex workers, health care workers (from sharps injury) and people who have sex abroad or with a partner from countries where hepatitis B is common against hepatitis B.
- No need to carry out pre-vaccination testing.
- Use accelerated 0, 7 and 21 day schedule in most circumstances.
- Offer hepatitis B vaccination to partners and children.
- Vaccinate all injecting drug users and MSM against hepatitis A.
- Single component hepatitis A vaccine preferable to combined hepatitis A and B vaccine.
- Devise and use an easy recording system to enable audit.

Recommended schedules of hepatitis A and B vaccines¹⁵

Hepatitis vaccines	Schedule
Single A	Two doses with second dose after 6–12 months. Second dose may be delayed for up to three years.
Combined A and B	Routine: 0, 1, 6 months. Accelerated: 0, 7, 21 days with booster ideally at 12 months.

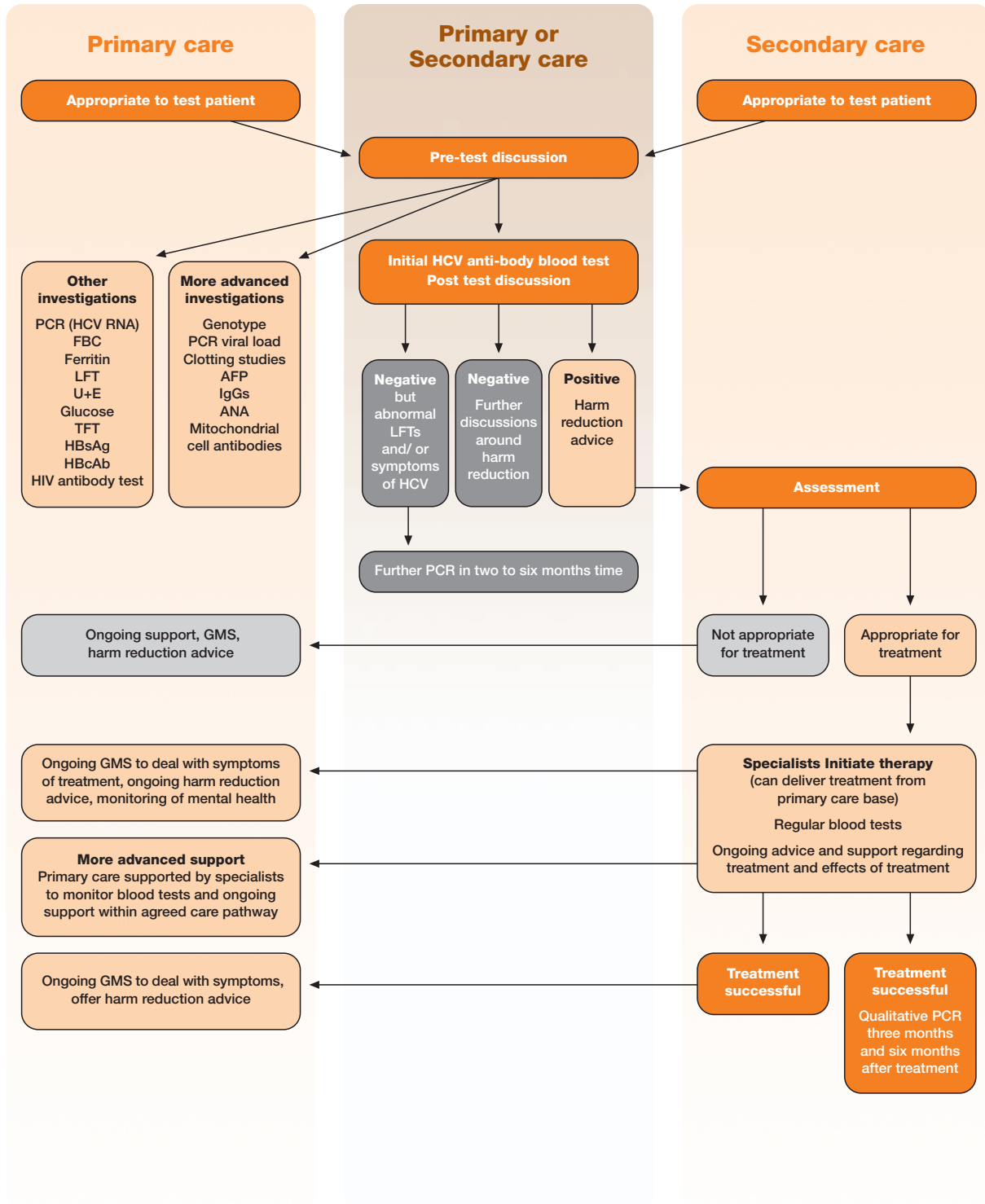
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Appendix 6

Testing and treatment care pathway in primary care



Appendix 7

Structure of viral hepatitis nursing service

Suggested model for a viral hepatitis nursing service includes three elements:

1. Facilitation of a viral hepatitis support group

The heart of a hepatitis C nursing service is hepatitis A Support Group. Support groups can provide support, information, empowerment, and political strength. It can assist with acceptance of diagnosis and adherence to treatment.

2. Nurse led hepatitis C treatment integrated care pathway

A nurse led hepatitis C treatment integrated care pathway allows assessment and provision of treatment by a suitably experienced and trained Specialist Nurse. It commences when a client is referred from the consultant to the Nurse Specialist for treatment. It allows a full assessment of the patient before treatment, examining all aspects of care relating to hepatitis C treatment, including improvements in the Liver Biopsy pathway.

By predicting problems and by referring on to other agencies where required, the patient can be helped through the difficult treatment.

3. Creation of a clinical Nurse Specialist role within the drug agency

The role of the Nurse Specialist within the drug agency is:

- To train generic substance misuse care co-ordinators to undertake test for hepatitis C, including pre and post test counselling.
- To supervise hepatitis C testing to all clients who inject or have ever injected drugs. This is a harm reduction target set by the National Treatment Agency.¹
- The Nurse Specialist should contribute to the local immunisation training and ensure that all nurses within the substance misuse agency have been trained in immunisation skills and have signed a patient group directive allowing them to vaccinate against hepatitis A and B.
- To provide onward referral for those who have hepatitis C to the hepatitis C treatment specialist.

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Appendix 8

Testing models in a drug service

Increasing hepatitis C (HCV) testing amongst drug users is a priority. Testing informs clients so that they can change behaviour regarding injecting practice and lifestyle.^{1,2} It also allows them to be assessed for treatment. There are four possible models of hepatitis C testing: passive or opt-in, compulsory testing, opt-out and active.

Passive or opt-in

The passive or opt-in model is based on the Hepatitis C Strategy.³ All clients are offered a test and an appointment is made with a specialist in blood borne viruses, such as a secondary care hepatitis nurse, running a clinic within a drug agency. The problem is that the specialist carrying out HCV testing has HCV knowledge, but may have poor substance misuse knowledge. There is poor attendance from client because the client does not know/trust the specialist, the client has many competing pressures on their time and there is no methadone prescription to use as a carrot.

Compulsory testing

The second model, compulsory testing, has been advocated by the National Treatment Agency. However it ignores the right of drug users to 'autonomy' and their right to make decisions about their own health. It may harm clients, giving them results of test they are not ready for and may discourage clients from entering drug treatment.

Opt-out

The opt-out model is gaining ground in HIV after research and debate. It has, for example been accepted according to Centre for Disease Control and Prevention⁴ guidelines in the USA and has been proposed by World Health Organization/UNAIDS⁵ for high prevalence countries. All clients who enter the service are routinely tested, with the client given an option to 'opt-out' of the test. They are offered pre-test discussion, but it is not mandatory. It is, however, a controversial development in HIV testing, and the result of debate and research. There is no body of research and ethical evidence that this is a good model in HCV testing. It may harm clients, giving them results they are not ready for and it may discourage clients from entering drug treatment.

Active model

The final mode, the active model, is our preferred option. The whole service actively encourages clients to have the HCV test, and testing available whenever and wherever client attends. To achieve this the testing is done by trained and supported drug workers. The drug worker does not have specialist HCV knowledge but knows the client, and can use treatments as carrot for attendance. HCV testing is part of all client care plans. The drug workers are trained to test for hepatitis C, and are supported and supervised by a Specialist Nurse. A leaflet is given as part of pre-test discussion. Oral mucosal transudate swabs used which saves appointments with a phlebotomist. Specialist Nurse makes a referral to the Consultant. There should be frequent campaigns to increase testing. The training should include the ethics of testing, the meaning of informed consent and breaking bad news.

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Appendix 9

Hepatitis B

General

1. Hepatitis B is a potentially fatal liver disease caused by the hepatitis B virus (HBV). HBV infection can cause both acute and chronic disease.
2. Acute hepatitis B (a notifiable disease) is liver inflammation lasting one to six months, which, occasionally can lead to liver failure.
3. Chronic hepatitis B (CHB, not a notifiable disease) comprises a lifelong infection characterized by liver inflammation and damage that can lead to morbidity and in some cases mortality from cirrhosis and liver cancer.
4. Accordingly to a report by the Foundation for Liver Research, October 2004,¹ HBV is second only to tobacco as a human carcinogen, causing 50% of primary liver cancer in the world and patients with CHB are 100 times more likely to develop hepatocellular carcinoma than those not infected.
5. NICE estimate that 180,000 people (0.3% of the UK population), are chronically infected with hepatitis B.² About 1,300 new cases of acute hepatitis B and 7,700 new cases of chronic hepatitis B are reported in the UK each year.¹ Of the new chronic cases, 96% are found in people who have entered the UK from areas of high prevalence.¹
6. The World Health Organisation³ state that young children who become infected with HBV are the most likely to develop chronic infection and about 90% of infants infected during the first year of life and 30 to 50% of children infected between one and four years of age develop chronic infection. The risk of death from HBV-related liver cancer or cirrhosis is approximately 25 percent for those who become chronically infected during childhood.

Transmission of hepatitis B

HBV can be transmitted in a variety of ways and is thought to be 100 times more infectious than HIV.¹ The virus is found in the blood and other bodily fluids and may survive in dried blood for up to a week.¹ The main route of transmission in the UK is via unprotected sex and injecting drug use and the transmission profile is similar to HIV which means that many people in high risk groups may be co-infected. Worldwide the most common route of infection is transmission from mother to child at birth.¹

Other routes of transmission include needlestick injuries in healthcare professionals, transfusion of infected blood products in countries with inadequate screening, piercing and tattooing with unsterilised equipment.¹

Prevention and vaccination

An effective vaccine to prevent HBV infection has been available since 1982 and the World Health Organisation recommends that 'routine vaccination of all infants against HBV infection should become an integral part of national immunization schedules worldwide.' The UK does not offer universal HBV vaccination at birth or in childhood. Other methods of prevention are also important including safer sex and safer injecting information and provision of condoms and clean injecting equipment.

Symptoms

Acute HBV may not cause symptoms, even though these patients may be infectious and capable of transmitting the infection. In patients who do develop symptomatic acute hepatitis, the symptoms can include: nausea, anorexia, fatigue, low grade fever, abdominal pain, rash and joint pains. Around 30% develop jaundice with a yellowish discolouration of the skin and whites of the eyes, dark urine and pale stools.¹

Many people chronically infected with HBV have no symptoms, they may also have normal or fluctuating liver function test results and often feel healthy, meaning that the infection may be undetected. Without treatment, chronic HBV can lead to liver scarring (cirrhosis), liver cancer, liver failure (and the need for liver transplantation) and ultimately, death.

Diagnosis

Diagnosis is based on a combination of symptoms and diagnostic tests, which may include:

- HBsAg (hepatitis B surface antigen) is detectable in the blood during acute and chronic infection and persists until the infection is resolved and antibodies develop.
- HBeAg (hepatitis B 'e' antigen) correlates with high levels of virus replication and a high risk of transmitting the virus. However it is now known that many patients who lack HBeAg also have high levels of virus and are at risk of developing liver damage. This HBeAg negative form of hepatitis is caused by a mutated virus and is now the commonest form of hepatitis B in many parts of the world. Hence the old classification based on HBeAg status is now obsolete and all patients with HBsAg (with or without HBeAg) need assessment and, possibly, therapy.

- Liver function tests can be used to measure liver enzyme levels, for example ALT levels are raised in both acute and chronic infection.
- Liver biopsy offers the only way to accurately assess the extent of liver damage.
- Measuring HBV DNA in the blood is the most accurate measurement of viral load.

Chronic hepatitis B

Chronic hepatitis B is defined as persistence of HBsAg for six months or more after acute infection. Currently, two types of CHB are recognized – HBeAg-positive and HBeAg-negative.¹ E antigen is a viral protein secreted by HBV-infected cells. Its presence is often associated with a high amount of virus in the blood. Between 8% and 15% of patients with CHB develop antibodies (anti-HBe) against HBeAg and a loss of HBeAg each year.¹

Generally, once HBeAg seroconversion has developed, levels of viral DNA drop substantially, liver inflammation is reduced and the risk of disease progression is limited. However many patients who seroconvert go on to develop active disease – HBeAg negative disease. HBeAg-negative disease is becoming increasingly common worldwide and these patients have a high risk of disease progression.¹

Treatment

Acute hepatitis B is often self-limiting and usually only requires relief of symptoms. Treatment of CHB aims to prevent progression to hepatocellular carcinoma or cirrhosis.²

The first drugs to be licensed for the treatment of CHB were alfa interferons. Interferons are natural proteins which activate the immune system in response to viral infection. Treatment is by subcutaneous injection three times a week. For four to six months.² The recent introduction of long acting pegylated interferons has led to thrice weekly standard interferon therapy being replaced by weekly injections of a pegylated interferon and pegylated interferon therapy for chronic HBV is now approved by NICE.

Lamivudine is a nucleoside analogue which works by blocking viral replication. It reduces inflammation, prevents liver damage and slows disease progression. It is taken orally once daily.

Adefovir dipivoxil is a nucleotide analogue, which produces sustained reductions in viral load and ALT levels. It is recommended by NICE as an option if treatment with interferon alfa or peginterferon alfa-2a has been unsuccessful, poorly tolerated or a relapse has occurred after initial successful treatment. Adefovir dipivoxil is not normally given before treatment with lamivudine although recent studies showing that lamivudine therapy is often associated with resistance have led many units to commence therapy with both lamivudine and adefovir to reduce the risk of long term treatment failure.

NICE recommends peginterferon alfa-2a (once weekly injection) as an option for the initial treatment of adults with chronic hepatitis B. Peginterferons are formed by attaching strands of polyethylene glycol (PEG) to the interferon molecules, which slows the rate of absorption.

The NICE Guidance states that 'drug treatment with peginterferon alfa-2a or adefovir dipivoxil should be initiated only by an appropriately qualified healthcare professional with expertise in management of viral hepatitis. Continuation of therapy under shared-care arrangements with a general practitioner is appropriate.'

Entecavir is a new nucleoside analogue which selectively inhibits HBV DNA polymerase and was licensed in the UK in 2006.

Telbivudine is a novel L-nucleoside with potent, specific activity against HBV and is expected to receive licensing authorization in the UK and EU during 2007.

There is considerable concern about viral resistance in the long-term treatment of chronic hepatitis B and future research may look at combination therapy with antiviral drugs in reducing the development of resistance to treatment.²

Monitoring can be with blood tests and annual liver ultrasound.

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Appendix 10

HIV infection

General¹

1. Human immunodeficiency virus (HIV) is a retrovirus that causes acquired immunodeficiency syndrome (AIDS), a condition in which the immune system begins to fail, leading to life-threatening opportunistic infections.
2. The UK is a relatively low prevalence country for HIV infections. Nevertheless HIV prevalence continues to rise steadily in the UK, and at the end of 2005 there were an estimated 63,500 people over 15 years of age living with HIV infection.
3. In the UK HIV has a higher incidence in men who have sex with men and in people who have lived or been born abroad, especially in Southern Africa, the Far East and Eastern Europe.
4. The increased number of people living with HIV in the UK is due to a number of factors, including people living longer with HIV due to advances in treatment, sustained levels of newly acquired infections in gay men, further diagnoses among heterosexuals who acquired their infection in Africa, and cases being picked up earlier.
5. But it is estimated that between 27 to 33% are unaware of their infection.²
6. HIV remains a life-threatening condition. The introduction of drug therapies has improved the lives of many people infected with HIV, but there is still no cure. Since 1995 the use of Highly Active Antiretroviral Therapy (HAART) in the UK has resulted in a 2/3 reduction in deaths from AIDS.³
7. The benefits of testing patients and knowing the diagnosis are now clear. Late diagnosis, when patients are ill with HIV disease or have a CD4 count below 200, is now the single largest cause of mortality in patients with HIV.⁴
8. Patients who are diagnosed late are seven to ten times more likely to die within a year of their HIV diagnosis compared to those with higher CD4 counts. Substantial potential exists for reducing mortality associated with late diagnosis through opportunistic and targeted HIV testing in primary care.
9. Every general practitioner is likely to have a few known HIV positive patients and a few more who are undiagnosed.
10. Since the epidemic began in the early 1980s 17,161 deaths in HIV infected individuals are known to have occurred in the UK.
11. A non specific flu-like illness may occur soon after a person acquires HIV infection. Thereafter the infection may be asymptomatic for many years. As many of those who are infected do not know that they have acquired HIV, complex methods of surveillance are needed to estimate the number of people with HIV infection.)

Transmission

Since the beginning of the pandemic three main transmission routes for HIV have been identified:

■ Sexual route

The majority of HIV infections are acquired through unprotected sexual intercourse. Sexual transmission can occur when infected sexual secretions of one partner come into contact with the rectal, genital or oral mucous membranes of another.

■ Blood or blood product route

This transmission route can account for infections in intravenous drug users, haemophiliacs and recipients of blood transfusions (though all transfusions are checked for HIV in the developed world) and blood products. It is also of concern for persons receiving medical care in regions where there is prevalent substandard hygiene in the use of injection equipment, such as the reuse of needles. Health care workers such as nurses, laboratory workers, and doctors, have also been infected, although this occurs more rarely. People who give and receive tattoos, piercings and scarification procedures can also be at risk of infection.

■ Mother-to-child transmission (MTCT)

The transmission of the virus from the mother to the child can occur in utero during the last weeks of pregnancy and at childbirth. In the absence of treatment, the transmission rate between the mother and child is 25%. However, where drug treatment and Caesarian section are available, this can be reduced to 1%. Breast feeding also presents a risk of infection for the baby.

Prevention

Preventing spread of HIV sexually can be reduced by the use of condoms and using all clean equipment for injecting drug users. Currently there is no vaccine.

Diagnosis and testing

Diagnosis is made via an HIV antibody test but should be thought of in all people who are at a sexual or injecting risk and they should be offered a test and anyone who requests one. HIV should also be thought of in otherwise healthy people who present with unusual infections such as: rash and flu-like illness (seroconversion illness), severe seborrhoeic dermatitis, oral candidiasis, HSV, shingles, atypical pneumonia.⁵ Seeing a new patient with HIV is not common, but it must be thought about.

The HIV antibody test is taken first to see if positive or negative. If positive further tests such as CD4 count, can either be undertaken in general practice or the patient can be referred on. The CD4 count is a marker of the state of the immune system. A CD4 count within the last three months which is above 500 means any acute condition is less likely to be related to HIV. A CD4 count of below 200, or previous illnesses, indicates a higher likelihood of HIV related illness and greater vigilance is required. Patients with CD4 counts of below 200 require prophylactic treatment against PCP (pneumocystis carinii pneumonia) – co-trimoxazole 480 mg daily. As the CD4 count falls other prophylactic treatments may be required. Routine vaccination against pneumococcus, haemophilus and influenza is also recommended.

Treatment

Is with a combination of antiretrovirals, at least 3 and sometimes four. If the CD4 is below 200 then co-trimoxazole for PCP (pneumocystis carinii pneumonia) prophylaxis should be taken. Also routine vaccination against pneumococcus, haemophilus and influenza is recommended.

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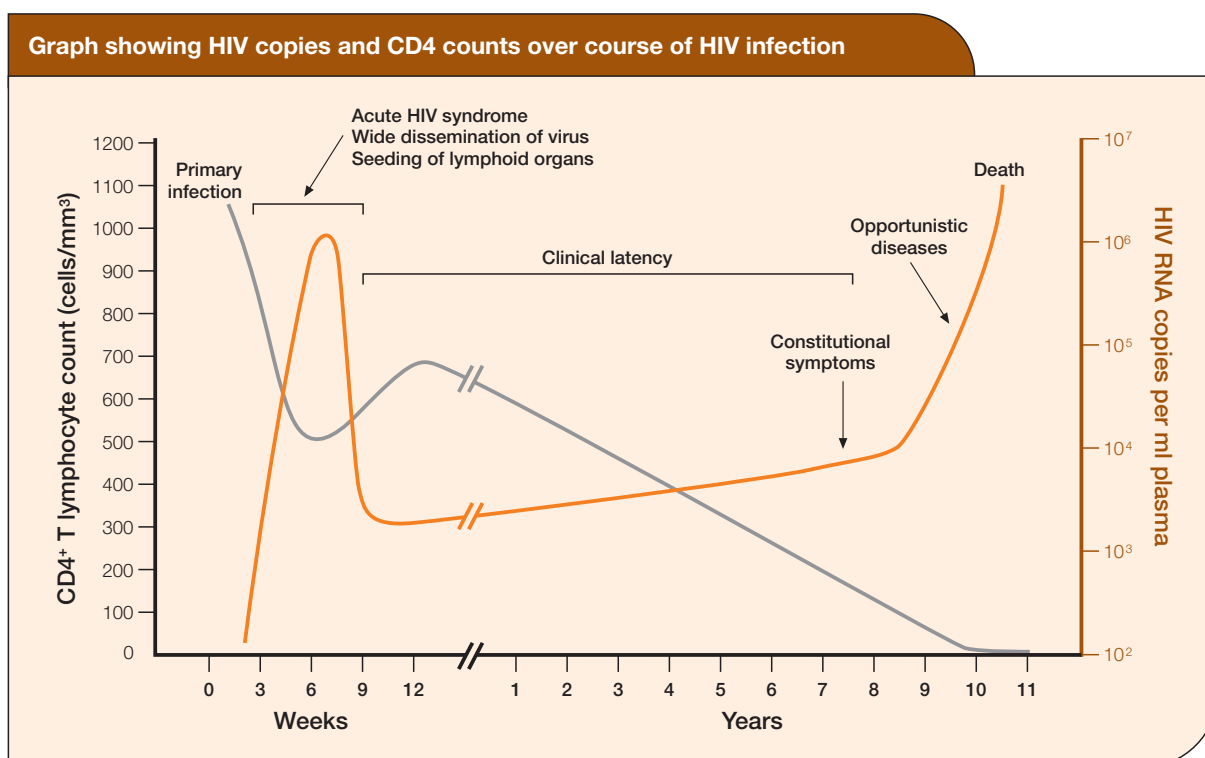


Figure 1

For additional copies, and for further information about training on hepatitis C and other issues relevant to primary care based drug and alcohol treatment, please contact

RCGP Substance Misuse Unit
Royal College of General Practitioners
Office 314
Frazer House
32–38 Leaman Street
London
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020 7173 6090
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This guidance, and other resources including an interactive discussion forum, are available on the SMMGP website at www.smmgp.org.uk