Healthcare Improvement Scotland

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SIGN 133 • Management of hepatitis C

A national clinical guideline

July 2013

Evidence

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}

GOOD PRACTICE POINTS

✓	Recommended best practice based on the clinical experience of the guideline development group

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Scottish Intercollegiate Guidelines Network

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Scottish Intercollegiate Guidelines Network
Gyle Square, 1 South Gyle Crescent
Edinburgh EH12 9EBA

www.sign.ac.uk

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Contents

1 Introduction

1.1 THE NEED FOR A GUIDELINE

The hepatitis C virus (HCV) was first identified in 1989 and HCV infection has become a major health problem worldwide.[1] Approximately 0.8% of the Scottish population are thought to be chronically infected with HCV (around 37,500 individuals). The prevalence of infection varies between population groups, ranging from 50% in injecting drug users (IDU) to less than 0.04% among new blood donors.[1]

Up to 80% of patients infected with HCV become chronically infected and most of these patients will show evidence of chronic hepatitis.[2]

Hepatitis C is usually slowly progressive over a period of many years. Five to fifteen per cent of patients with chronic hepatitis may progress to liver cirrhosis over 20 years.[3] Four to nine per cent of patients with cirrhosis will develop liver failure; and two to five per cent of patients with cirrhosis will develop hepatocellular carcinoma (HCC) per annum.

In the UK the two major routes of transmission of HCV have been sharing of drug injecting equipment by IDU and transfusion of infected blood or blood products. Virus inactivation treatment of blood products began in 1987 and from 1991 blood has been screened for hepatitis C, virtually eliminating blood products as a source of HCV infection.

HCV infection can be effectively treated with combination drug therapy (pegylated interferon alfa and ribavirin) with sustained viral response (SVR) rates in 50-80% of patients. Although there are existing guidelines for the selection of patients for treatment[4-7] there are no national guidelines for screening, testing, diagnosis, service configuration, care during treatment or post-treatment follow up in adults or children.

1.1.1 UPDATING THE EVIDENCE

This guideline updates SIGN 92: Management of hepatitis C to reflect the most recent evidence around protease inhibitor treatment as an adjunct to current standard dual therapy treatment.

This update was limited in scope and covered treatment of chronic hepatitis C (CHC), provision of information for patients and carers and several other minor updates (*see section 1.2.3 and Annex 1*. In the sections not updated text and recommendations are reproduced verbatim from SIGN 92. The original supporting evidence was not re-appraised by the current guideline development group.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

The guideline provides evidence based recommendations covering all stages of the patient care pathway; screening, testing, diagnosis, referral, treatment, care and follow up of infants, children and adults with, or exposed to, HCV infection. The remit encompasses prevention of secondary transmission of the virus but specifically excludes primary prevention of HCV infection. Primary prevention of hepatitis C infection is an important public health concern but is outwith the remit of this guideline. The principles and evidence for the prevention of blood borne viruses are generalisable and while reviewing this large body of evidence would have been beyond the capacity of the guideline development group, reviewing the HCV evidence alone would have produced a distorted view.

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of interest to all health professionals in primary and secondary care involved in the management of people with hepatitis C infection.

1.2.3 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

2	Key recommendations	New
4	Prevention of secondary transmission	Minor update at 4.1
6	Children and hepatitis C	Minor update at 6.4
8	Assessment of liver disease	Minor update at 8.2
10	Treatment of chronic hepatitis C	Completely revised at 10.1, 10.2, 10.3.1, 10.3.3, 10.3.4, 10.3.6, 10.6.2, 10.6.4, 10.6.10 and 10.7.1
11	Treatment of advanced infection	Minor update at 11.1.1
13	Provision of information	Completely revised
14	Implementing the guideline	Minor update

1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.3.1 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off label' use.

Medicines may be prescribed off label in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally the off label use of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience. [8]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability". [8]

The General Medical Council (GMC) recommends that when prescribing a medicine off-label, doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF). [8] The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers. [9]

1.3.2 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

Healthcare Improvement Scotland processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Care Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice relevant to this guideline is summarised in section 14.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation. The grade of recommendation relates to the strength of the supporting evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

2.1 TREATMENT OF CHRONIC HEPATITIS C

A **All treatment-naive patients infected with HCV genotype 1 should be considered for treatment with pegylated IFN and weight-based ribavirin with the addition of a protease inhibitor as triple therapy.**

A **All treatment-experienced patients infected with HCV genotype 1 should be considered for treatment with pegylated IFN and weight-based ribavirin with the addition of a protease inhibitor as triple therapy.**

B **Treatment-naive patients co-infected with HIV and HCV genotype 1 who are unsuitable for treatment with a regimen which includes HCV protease inhibitors should be considered for treatment with pegylated IFN and weight-based ribavirin for 48-72 weeks depending on viral response.**

The recent availability of protease inhibitors to use with pegylated IFN and ribavirin in triple therapy, has significantly improved the SVR rates for patients with genotype 1 HCV infection with the prospect of reducing the overall length of treatment depending on response to therapy. Genotype 2 and 3 HCV infected patients continue to achieve high SVR rates with pegylated IFN and ribavirin dual therapy. These combination treatments should be discussed and offered as standard of care to all suitable patients with HCV infection.

2.2 CHILDREN AND HEPATITIS C

A **Children infected with all genotypes of hepatitis C with evidence of moderate or severe liver disease should be considered for treatment with pegylated IFN and ribavirin.**

B **Children infected with HCV genotypes 2 and 3 should be considered for treatment with pegylated IFN and ribavirin irrespective of disease stage.**

C **In children with mild disease and infection with other genotypes, benefits of treatment need to be balanced against risks of side effects.**

The outcome in children after treatment with pegylated IFN and ribavirin is equivalent to that in adults.[10] Side effects of treatment are seen with similar frequency and weekly injections cause distress. The advantages of achieving SVR early in life, eliminating the risk of onward transmission (particularly before girls reach child bearing age) and before the onset of chronic liver disease, will outweigh these disadvantages in many children infected with favourable genotypes. However, for those with less favourable genotypes and no evidence of chronic liver disease, it is appropriate to wait until more effective and acceptable treatment becomes available.

2.3 TESTING

D **Dried blood spot testing should be considered as a convenient and cost-effective method of accessing some target populations.**

D **There should be consideration given to methods to raise awareness and highlight information regarding hepatitis C amongst at-risk groups and the general public. The targeting of awareness campaigns to particular audiences is recommended. Staff should have access to appropriate training.**

D **Anyone who has a negative test but remains at risk of infection should be offered further testing on an annual basis.**

D **Testing for HCV should be offered to migrants from countries with a medium or high prevalence of HCV.**

The NICE guidance *Hepatitis B and C: Ways to promote and offer testing to people at increased risk of infection* [11] contains a number of key recommendations on testing. Although designed for the NHS in England and Wales it has direct applicability to Scotland on testing for HCV.

3 Testing

3.1 CLINICAL AND COST-EFFECTIVE TESTING FOR HEPATITIS C VIRUS

National and international guidelines recommend that individuals who have an excess risk of being infected and might benefit from knowing their HCV status should be offered an HCV test.[5, 12-14] This recommendation is based primarily on the need to diagnose an often silent infection, allowing the initiation of prompt antiviral treatment if appropriate.[15] Since treatment cannot be offered unless a diagnosis of chronic HCV infection is made, the offering, and uptake, of testing among populations at risk of HCV will convey a degree of clinical benefit. **4**

Further benefits of diagnosing people infected with HCV include the opportunity to convey information aimed at slowing the rate of HCV disease progression (such as advice about the dangers of excess alcohol consumption) and reducing the chances of infection being transmitted to others. No robust, consistent evidence to indicate the effectiveness of these interventions was identified.

UK guidelines consistently recommend that people who may convey an HCV risk to patients in the healthcare setting should undergo HCV testing.[5, 12-14] Several instances of healthcare worker to patient and blood/organ donor to recipient transmission of HCV have been recorded.[16, 17] **4**

Controlled trials or cohort studies to gauge the cost effectiveness of offering an HCV test to different population groups have not been undertaken. Limited evidence from economic modelling work indicates that offering an HCV test to former injecting drug users (IDU) in drug treatment and perhaps other settings would convey cost-effective clinical benefits.[18] Former IDU are more likely to have a higher prevalence of HCV and comply with therapy than current IDU. Models of best practice for the identification and testing of former IDU have not been developed and evaluated. Expert opinion suggests that general practices, particularly those that serve areas with a high prevalence of drug use, may constitute environments where focused, well supported testing initiatives might be successful. Prisons may also offer similar opportunities.[19] Targeted and generalised HCV awareness/testing campaigns have been conducted but no evaluations of their success in encouraging people (including former IDU) at high risk of HCV to engage with services have been reported. **4**

In populations where prevalence of HCV is low (eg genitourinary medicine clinic attendees), economic modelling indicates that universal testing does not convey cost-effective clinical benefit.[18] **4**

D **The following groups should be tested for HCV:**

- **blood/tissue donors**
- **patients on haemodialysis**
- **healthcare professionals who intend to pursue a career in a specialty that requires them to perform exposure prone procedures.**

D **The following groups should be offered an HCV test:**

- **patients with an otherwise unexplained persistently elevated alanine aminotransferase**
- **people with a history of injecting drug use**
- **people who are human immunodeficiency virus (HIV) positive**
- **recipients of blood clotting factor concentrates prior to 1987**
- **recipients of blood and blood components before September 1991 and organ/tissue transplants in the UK before 1992**
- **children whose mother is known to be infected with HCV**
- **healthcare professionals following percutaneous or mucous membrane exposure to blood which is, or is suspected to be, infected with HCV**
- **people who have received medical or dental treatment in countries where HCV is common and infection control may be poor**
- **people who have had tattoos or body piercing in circumstances where infection control procedure is, or is suspected to be, suboptimal**
- **people who have had a sexual partner or household contact who is HCV infected.**

The NICE guidance *Hepatitis B and C: Ways to promote and offer testing to people at increased risk of infection* [11] contains a number of key recommendations on testing. Although designed for the NHS in England and Wales it has direct applicability to Scotland on testing for HCV. | **4**

D **Dried blood spot testing should be considered as a convenient and cost-effective method of accessing some target populations.**

D **There should be consideration given to methods to raise awareness and highlight information regarding hepatitis C amongst at-risk groups and the general public. The targeting of awareness campaigns to particular audiences is recommended. Staff should have access to appropriate training.**

D **Anyone who has a negative test but remains at risk of infection should be offered further testing on an annual basis.**

D **Testing for HCV should be offered to migrants from countries with a medium or high prevalence of HCV.**

3.2 HEPATITIS C VIRUS DIAGNOSTIC TESTING

3.2.1 PRINCIPLES OF TESTING

Detection of viral ribonucleic acid (RNA) by nucleic acid tests (NAT, usually using reverse transcriptase polymerase chain reaction; RT PCR) indicates current infection. Detection of antibodies indicates resolved or current infection. The testing algorithm suggested in Figure 1 is based on:

Diagnostic assays are most reliable when used on plasma or serum.[20] | **2++**

Assays for antibody in saliva are very sensitive if optimum salivary collection devices and modified enzyme linked immunosorbent assays (ELISA) are used, but NAT for viral RNA is unreliable.[20-22] | **2++**

Nucleic acid testing sensitive enough to detect 50-100 IU/ml of virus must be performed to detect current infection.[23] | **2+**

Viral RNA can be detected as early as one to two weeks after infection, whereas antibody can be detected at seven to eight weeks after infection.[24] | **4**

Antibody to infection may not be generated, particularly if the individual is immune-suppressed.[25] | **4**

Following acute infection, HCV RNA may oscillate between positive and negative for several months. Results from samples taken at this time may be misleading.[24] In an individual positive for HCV antibody, but negative for HCV RNA, a second sample should be tested to confirm the initial diagnosis, especially as the date of infection is unknown in most cases. **4**

Individuals with a positive HCV antibody test and repeatedly negative RNA do not require further active management of hepatitis C infection.[25] **4**

Since hepatitis C is a serious communicable disease, after an initial laboratory diagnosis, a second sample should be taken from the patient to confirm correct identification of the original sample.[26] **4**

Genotyping of individuals with proven HCV infection is required to determine likely response to treatment. Those with genotype 1 infection require longer duration of treatment than those with genotype 2 and 3 (*see section 10.2.1*).[27] **1++**

Expert guidance suggests that healthcare professionals who have, or might have, sustained an occupational exposure to HCV should be offered RNA testing at 6, 12 and 24 weeks, with anti-HCV testing at 12 and 24 weeks.[28] **4**

B **Diagnostic testing for HCV should be performed on serum or plasma where possible.**

D **HCV genotyping should be undertaken if antiviral therapy is being considered.**

D **Following an isolated acute percutaneous exposure to blood infected, or strongly suspected of being infected, with HCV, healthcare professionals should be offered HCV RNA testing at six, 12 and 24 weeks and anti-HCV testing at 12 and 24 weeks.**

4 Prevention of secondary transmission

Secondary transmission is defined as the onward transmission of infection from individuals who are known to be HCV infected.

4.1 TRANSMISSION THROUGH SEXUAL AND HOUSEHOLD CONTACT

Observational studies indicate that there is a very small risk of people with diagnosed HCV infection transmitting infection to their family, or close contacts, and sexual partners. Cohort studies of couples discordant for HCV indicated an HCV incidence of 0-2 per 1,000 years of sexual contact.[29-31] Those with HIV co-infection, particularly men who have sex with men, may be more likely to transmit HCV to their sexual partners.[32, 33] The findings suggest that transmission may occur through exposure to blood as a consequence of, for example, the sharing of razors and toothbrushes (ie activities which might result in percutaneous or mucous membrane exposure to infected blood), and through unprotected sexual intercourse. **2+ 1-**

No studies were identified to ascertain if interventions such as educational initiatives, including the promotion of condom use, aimed at people diagnosed with HCV infection, are effective in reducing the frequency of such risk behaviours and/or preventing associated secondary transmission of HCV. Expert opinion suggests that people infected with HCV should be advised that the use of condoms and the avoidance of activities which could lead to percutaneous or mucous membrane exposure to infected blood will eliminate the albeit very small risk of them transmitting the virus to others.[14, 34] **4**

✓ After being advised of the low risk of HCV being transmitted sexually, individuals infected with HCV should be asked to consider using condoms for sexual intercourse if they are men who have sex with men or if either partner is infected with HIV.

D **Individuals co-infected with HIV/HCV should be advised always to practice safe sex and use condoms.**

D **Individuals infected with HCV should be advised to avoid activities which could result in percutaneous or mucous membrane exposure to their infected blood, such as the sharing of razors and toothbrushes.**

4.2 TRANSMISSION THROUGH INJECTING DRUG USE

The sharing of injecting equipment by drug users is the principal means through which infection is transmitted in developed countries.[14, 34] Observational data demonstrate that interventions such as needle and syringe exchange and methadone maintenance therapy are likely to have reduced, though not controlled, HCV transmission among IDU in a number of countries including Scotland.[35] Studies of interventions aimed specifically at preventing IDU known to be infected with HCV transmitting their infection to others through the sharing of injecting equipment, were not identified. **2+**

No robust consistent evidence on the influence of knowledge of HCV infection status among IDU on their injecting risk behaviour was identified. Expert opinion suggests that advising current IDU with chronic HCV on how to prevent transmission of their infection to other IDU, through for example safe injecting practice, may be an effective intervention.[14,34] **4**

D **Injecting drug users known to be infected with HCV should be given advice on how they can prevent transmission of infection to other injecting drug users.**

4.3 TRANSMISSION BETWEEN HEALTHCARE PROFESSIONALS AND PATIENTS

4.3.1 RISK OF HEALTHCARE PROFESSIONAL INFECTION

Expert opinion suggests that infection control precautions should be standard and universal and not determined by knowledge of patients' blood borne virus status.[36] **4**

Estimates of transmission risk following needlestick injury vary, with one large prospective study of 4,403 exposed healthcare professionals 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.[16, 37] The relative risk is higher when injuries are deep and from blood filled needles. Risk arising from superficial or mucocutatenous exposures is likely to be much lower, though difficult to quantify, while transmission from solid needles is extremely unlikely.[37] Transmission occurs only from RNA positive sources. **2+ 4**

✓ Standard infection control precautions against blood borne virus transmission should be undertaken by all healthcare professionals regardless of the patient's known or suspected infective status.

✓ Healthcare professionals 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.

4.3.2 RISK OF PATIENT INFECTION

Several reports have shown that HCV can be transmitted from healthcare professionals to patients.[17] 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%.[38-40] UK health departments advise that healthcare professionals who are HCV RNA positive should not undertake exposure prone procedures.[17, 41] **3 4**

D **Healthcare professionals who are aware they are HCV RNA positive should not undertake exposure-prone procedures.**

5 Referral

Referral to specialist care should be considered for all patients with active HCV infection (HCV RNA positive) and not be restricted to potential candidates for antiviral therapy. Specialist clinics are often a source of information for patients and relatives, including health promotion and methods of avoiding secondary transmission of the virus.

Modelling suggests that 90% of individuals with HCV in Scotland are current or former IDU.[1] Factors associated with injecting drug use (eg poverty, chaotic lifestyle, comorbidity, including alcohol dependence) can be obstacles to individuals navigating their way through and remaining in investigation, referral and treatment pathways.[15, 19] Expert consensus suggests that uptake of services may be improved by integrated multidisciplinary care which also addresses, for example, individuals' alcohol and drug use problems simultaneously with their HCV specialist care.[15] **4**

No evidence was identified supporting the view that investigation and treatment of current IDU with HCV infection should not be promoted because they are unlikely to have progressed to at least moderate hepatitis, or are unlikely to adhere to such care.

Two observational studies and one five-year follow-up study have shown that IDU, described as active at the time of enrolment and undergoing management of their drug problem, adhered to antiviral treatment to the same degree as those who had never injected drugs.[42-44] These studies were small and no details of participants' injecting behaviour were provided. **2**

All patients with acute HCV should be referred to specialist care immediately as treatment given during the acute phase is more likely to be successful (*see section 7.3*).[45] **1++**

Ideally the specialist clinic should be integrated with other services by means of outreach clinics so that the patient journey is seamless, especially for those who find it difficult to access medical care. Such integration should encourage agencies such as drug problems services and prison medical services to positively and repeatedly address the issue of HCV infection.

D **Individuals, including injecting drug users, diagnosed with chronic HCV should be offered integrated multidisciplinary care as it can maximise their uptake of, and retention in, services.**

A **Patients with acute HCV infection should be referred to specialist care immediately.**

✓ Current injecting drug users infected with HCV should not be excluded from consideration for HCV clinical management, including antiviral therapy, on the basis of their injecting status.

✓ All patients should be referred to a setting that periodically reassesses the state of infection and the progression of liver disease, to determine if further interventions or therapies are needed.

6 Children and hepatitis C

6.1 MOTHER TO CHILD TRANSMISSION

Pregnant women who are HCV RNA negative do not pose a risk of transmission to their child.[46,47] 2+

The risk of women who are HCV infected and RNA positive transmitting infection to their babies in utero or during parturition is approximately 5%; the rate is twice as high for those co-infected with HIV.[48] The baby's risk of acquiring HCV from a mother infected with HCV is not increased by mode of delivery or breast feeding.[48] One prospective study has indicated that fetal scalp monitoring may increase the risk of mother to child transmission.[49] A large retrospective study did not demonstrate any excess risk.[48] Vaginal delivery may increase the risk of HCV transmission if the mother is co-infected with detectable HIV viral load.[48] 2++

B **In pregnant women knowledge of HCV RNA positive status should not influence obstetric management or standard advice regarding breast feeding.**

6.2 HCV TESTING IN CHILDREN AND INFANTS

The aim of testing infants born to women with hepatitis C is not primarily to identify all children to whom the virus has been transmitted, but to identify those at risk of persistent infection and its long term consequences.

Infants born to women who are HCV antibody positive will test positive for HCV antibody at birth.[50] Infants who are not infected become negative for HCV antibody between six and 20 months of age. Around 80% will be negative by 12 months of age.[46, 51] Positive results for viral RNA by NAT may be obtained in the early months of life in children who subsequently become negative and lose HCV antibody.[51-54] Some infected infants may not become HCV RNA positive until 12 months of age or older.[54] One study indicates that the sensitivity of a positive reverse transcriptase polymerase chain reaction (RT PCR) result obtained on two occasions between two and six months of life in predicting infection is 81% (95% confidence interval; CI 58 to 97%).[55] 2+

Infants of mothers with HIV co-infection who are consistently positive for viral RNA may have negative HCV antibody tests between 12 and 18 months of age.[56] 3

B **Infants born to women who are HCV antibody positive and HCV RNA negative do not need to be tested.**

B **In children born to women infected with HCV, an HCV antibody test should be performed at 12 months of age or older to identify the minority of children who are infected.**

B **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.**

B **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.**

6.3 NATURAL HISTORY OF HCV INFECTION IN CHILDREN

Cross-sectional studies indicate that 20-40% of children who are HCV antibody positive after 18 months of age have undetectable HCV RNA, suggesting spontaneous clearance.[57,58] In those with chronic infection who remain HCV RNA positive, subsequent spontaneous clearance is rare (3.5%).[59] **3**

Levels of alanine aminotransferase (ALT) twice the upper limit of normal are found in 50% of infected children.[59] **3**

D **Children infected with HCV should be monitored to identify the minority who are at risk of progressive fibrosis during childhood, and who may be candidates for treatment.**

✓ Children infected with HCV should be assessed clinically every 6-12 months, and have blood taken for tests of liver function. Those with clinical or ultrasound abnormalities, or with serum ALT persistently twice the upper limit of normal should be considered for liver biopsy.

6.4 TREATMENT OF CHILDREN WITH HEPATITIS C

Response rates to treatment in children are of a similar magnitude to, and show the same influences of genotype, as adults (*see section 10*).[60] Combination treatment with interferon (IFN) and ribavirin gives an overall SVR of 50-60%.[60-63] There is potential for effects on thyroid function and growth problems.[62, 63] **3**

Combination therapy with pegylated IFN and ribavirin is superior to pegylated interferon alone, and results in outcomes similar to that in adult studies (*see section 10*).[10] **1+**

Combination treatment with interferon and ribavirin gives an SVR rate of 80-93% in children with genotype 3 infection, but only 47-59% in those with genotype 1 disease, which is similar to those in adult studies.[10, 64, 65] **2+**

A **Children infected with all genotypes of hepatitis C with evidence of moderate or severe liver disease should be considered for treatment with pegylated IFN and ribavirin.**

B **Children infected with HCV genotypes 2 and 3 should be considered for treatment with pegylated INF and ribavirin irrespective of disease stage.**

C **In children with mild disease and infection with other genotypes, benefits of treatment need to be balanced against risks of side effects.**

✓ Treatment of children with genotype 1 disease using protease inhibitors should only be considered as part of a clinical trial.

✓ Children infected with HCV should be managed in consultation with a paediatric service with specialist expertise in hepatitis C.

7 Acute hepatitis C

7.1 NATURAL HISTORY

The incidence of hepatitis C is unknown but can be estimated from the prevalence of chronic hepatitis C (CHC).[66] Acute hepatitis C infection is usually asymptomatic.[67] The full clinical spectrum of acute hepatitis C symptoms can occur but is rare (<15% patients).[68] The mortality of acute hepatitis C is very low (0.1% or less) and chronic infection is the most common outcome.[67-69] **3**

Laboratory diagnosis should start with testing for anti-HCV but in early cases HCV RNA may be the only marker of infection (*see section 3.2*).[70] **2+**

Spontaneous recovery occurs in 30-50% of patients with symptomatic infection, usually within three months of diagnosis. This is most common in females with an icteric illness.[66, 67, 71, 72] **3**

D **Patients with acute hepatitis C virus infection require clinical and laboratory monitoring** (looking for spontaneous viral clearance) **for the initial three months following diagnosis as they will often have a self limiting illness.**

7.2 POST-EXPOSURE PROPHYLAXIS

No trials were identified that show whether or not immunoglobulin, IFN based therapies or antiviral agents are effective at preventing transmission when given immediately post-exposure. Two reviews which considered older studies of immunoglobulin did not establish efficacy and concluded that immunoglobulin and IFN based therapies are not recommended after HCV exposure.[28, 73] **4**

7.3 TREATMENT OF PATIENTS WITH ACUTE HEPATITIS C

7.3.1 TIMING OF TREATMENT

Most patients who spontaneously clear hepatitis C do so within 12 weeks of diagnosis.[66, 72] There are no data to suggest that delaying treatment from three to six months post-diagnosis compromises treatment response, whilst allowing for spontaneous clearance to occur.[45] Delaying treatment to one year post-acquisition compromises a sustained viral response.[45] **3** **1++**

D **Treatment should start between three and six months after diagnosis of acute hepatitis C, if the infection has not resolved spontaneously.**

7.3.2 CHOICE AND DURATION OF TREATMENT

Two systematic reviews examined the effectiveness of non-pegylated IFN for the treatment of patients with acute hepatitis C.[74, 75] In one study participants in the treatment groups had higher sustained viral response rates (62%) than those in untreated groups (12%).[74] A Cochrane review demonstrated that increasing the dose of non-pegylated IFN during the induction phase of treatment was associated with higher sustained viral response.[75] There are no data on the influence of genotype on response to treatment for acute hepatitis C infection. **1++**

No randomised controlled trials (RCTs) of pegylated IFN versus conventional IFN for patients with acute hepatitis C were identified. A case series treated 16 patients, who had not seroconverted by three months, with pegylated IFN alone for 24 weeks, and reported a sustained viral response of 94%.[66]

3

A **Patients with acute HCV infection should be treated with IFN therapy if the infection does not resolve spontaneously.**

D **Patients can be treated with either pegylated IFN or non-pegylated IFN.**

D **Patients with acute HCV infection should be treated with IFN therapy for 24 weeks irrespective of genotype.**

8 Assessment of liver disease

8.1 CLINICAL ASSESSMENT

Clinical assessment of the severity of liver disease in patients with chronic hepatitis C is inaccurate and tends to underestimate the severity of change seen on liver biopsy.[76] **3**

8.2 FIBROSIS MARKERS

Studies of non-invasive prediction of the severity of liver disease using combinations of clinical and biochemical scores have found that it may be possible to distinguish patients with cirrhosis from those with mild disease. Intermediate stages are not distinguishable.[77] **2++**

A systematic review demonstrated that surrogate markers of fibrosis either reflecting disordered liver function (alanine aminotransferase, platelets) or fibrosis metabolism (eg tissue inhibitor of matrix metalloproteinase 1, hyaluronic acid) cannot be used individually to predict fibrosis. In individual patients such markers used alone cannot differentiate the stage of fibrosis reliably. Used in panels they can determine whether an individual has high or low levels of fibrosis. The 14 studies in the systematic review used 10 different panels of markers, none of which was superior to any other in statistical comparisons. The tests were compared against the gold standard of liver biopsy as part of their validation, although liver biopsy may potentially be inaccurate due to sampling error. Comparison of surrogate markers and liver biopsy to clinical outcomes would be more relevant.[78] **2++**

B **Biochemical markers should not be used as an alternative to liver biopsy for staging of intermediate grades of fibrosis.**

B **Biochemical tests may be used as an alternative to liver biopsy to diagnose cirrhosis or to direct screening for complications of fibrosis.**

✓ Measurement of liver stiffness may be useful as a non-invasive assessment of liver fibrosis.

8.3 LIVER BIOPSY

A liver biopsy needs to be at least 25 mm long in order to report stage of fibrosis with 75% accuracy.[79] The mortality rate of liver biopsy is between 0.13 and 0.33% and the rate of significant morbidity is about 5.9%.[80] **3**

8.3.1 WHEN TO BIOPSY

Liver biopsy of patients with CHC infection can reveal additional diagnoses such as alcoholic liver disease or steatosis (10% patients) and may influence management decisions in five per cent of patients.[81] Repeat liver biopsies may be useful in identifying individuals for treatment; one third of patients with mild CHC show one stage of fibrosis progression on the Ishak scale (0-6) at a median of 30 months.[82] The frequency and timing of liver biopsy should be tailored to individual patients as progression of fibrosis is non-linear. **3**

Advanced fibrosis or cirrhosis on liver biopsy compared with milder disease predicts a modest reduction in SVR after antiviral therapy.[83] **1++**

Liver biopsy before and after successful antiviral therapy (median 20 months interval) has shown both improvement in fibrosis (277 out of 1,094 patients) and downgrading of stage in cirrhosis (75 out of 153 patients).[84] **1+**

D **Liver biopsy should be performed if there is concern about additional causes of liver disease.**

D **Repeat liver biopsies should be considered in patients with mild disease who remain untreated, if progression of liver fibrosis would influence the decision to opt for antiviral therapy.**

✓ In patients with congenital bleeding disorders liver biopsy should be performed in consultation with a haemophilia specialist.

8.3.2 BIOPSY AND GENOTYPE

The sustained viral response rate after pegylated IFN and ribavirin therapy for patients with genotype 2 and 3 infection is 76-82% and is 41-51% for patients with genotype 1 infection.[7] The UK Health Technology Assessment Centre has recommended that pre-treatment liver biopsy in patients with genotype 2 and 3 may not be required.[7]

4

D **Liver biopsy should not be considered an essential test prior to using antiviral therapy, especially in patients with genotype 2 and 3 disease.**

9 Progression of untreated disease

Chronic hepatitis C infection is associated with a significant risk of progression to cirrhosis and hepatocellular carcinoma (HCC).[3, 85] Quantifying the magnitude of risk of progression to cirrhosis and HCC with time is difficult as reported outcomes are strongly influenced by study design and the characteristics of the population sampled.[3, 85] **2++**

A systematic review of 57 studies (both cross-sectional and longitudinal) which included liver clinic, post-transfusion, blood donor and community based patients, calculated the following estimates for the risk of progressing to cirrhosis after 20 years:[3] **2++**

- liver clinic: 22% (95% CI 18 to 26%)
- post-transfusion: 24% (95% CI 11 to 37%)
- blood donor: 4% (95% CI 1 to 7%)
- community based: 7% (95% CI 4 to 10%).

Due to the selection biases inherent in the cross-sectional liver clinic data, the community based cohort studies may be the most representative of true disease progression at a population level. The community based cohorts indicate that in those who acquire HCV infection in young adulthood, less than 10% will develop cirrhosis within 20 years. Older age at HCV acquisition, male gender and heavy alcohol consumption were associated with more rapid disease progression.[3] **2++**

The mean time from HCV infection to the development of HCC also shows considerable variation between studies, ranging from nine to 31 years in one systematic review.[85] Virtually no cases of HCC occur during the first decade of HCV infection, most are detected after 20 years of infection.[85] **2++**

Patients with established HCV related cirrhosis have a seven per cent risk of developing HCC by five years follow up.[86,87] **2+**

Patients with established CHC related cirrhosis are also at risk of complications such as ascites, gastrointestinal bleeding and hepatic encephalopathy.[86,87] The cumulative probability of all forms of decompensation in cirrhotic patients who remained tumour free was 18% at five years in one study, with an overall five-year survival rate of 91%.[87] **2+**

9.1 AGE, GENDER AND ETHNICITY

Increasing age at time of infection with HCV is associated with more rapid progression of liver fibrosis and reduced time from infection to cirrhosis.[88-90] Age over 40 years at time of infection is particularly associated with more rapid progression.[89, 90] **3**

Three cohort studies reported that men infected with HCV are more likely to progress to advanced stages of hepatic fibrosis than women.[89,91,92] **3**

Variations in disease progression have been observed in patients of different race. Two cohort studies demonstrated that disease progressed less rapidly in African-American than non African-American patients.[93, 94] The likely rate of progression in these patients should be considered when deciding whether to proceed with antiviral therapy. **2+**

D **When estimating the likely rate of progression of liver disease age at infection, gender and ethnicity should be considered.**

9.2 BODY WEIGHT

Studies have identified body mass index (BMI) >25 as being associated with hepatic steatosis (*see section 12.1.3*).

9.3 TOBACCO SMOKING

Smoking is an independent risk factor for the progression of hepatic inflammation and fibrosis in patients with CHC.[95,96] No data were identified on the impact of stopping smoking. **3**

D **Patients with CHC should be advised that smoking tobacco can accelerate progression of liver disease.**

9.4 ALCOHOL

Heavy alcohol consumption in patients infected with CHC is associated with more severe liver disease including cirrhosis, endstage liver disease and HCC.[97, 98] Average alcohol intake of more than six UK units per day is associated with more rapid progression of liver fibrosis.[88, 89, 92] Even moderate amounts of alcohol (within government recommended guidelines) have been associated with increased liver fibrosis compared to those who abstain.[89, 99] **2+** **2++**

Patients who are aware of their HCV status are more likely to heed advice on reducing alcohol intake than those who perceive themselves to be uninfected.[100] **2++**

B **Patients with CHC should be advised that drinking alcohol** (even in moderation) **can accelerate progression of liver disease.**

9.5 ALANINE AMINOTRANSFERASE

Approximately 25% (range 10-40%) of patients with CHC have persistently normal serum alanine aminotransferase (PNALT). Such patients are more likely to be female and have mild disease.[101] Although there is a substantial overlap between patients with PNALT and patients with mild liver disease, the terms are not synonymous and the groups are regarded separately for treatment purposes (*see sections 10.3.1 and 10.3.3*). The definition of 'persistently normal' varies in the literature with ALT measurements made every two to three months for time periods ranging between six and 18 months.[101] Flares in ALT have been reported in 21.5% of patients after being normal for 12 months.[102] There is no association with hepatitis C genotype or viral load.[101] **1-** **2-**

Progression of liver fibrosis is slower in patients with PNALT than in patients with elevated ALT.[103] In patients with untreated mild liver disease the progression to moderate or severe disease during follow up of 5.6 years is 5% in patients with PNALT and 24% in patients with elevated ALT. **2++**

Routine liver biopsy is not believed to be indicated unless specific information is required in selected patients.[101] **1+**

D **When defining PNALT serum ALT measurement should be undertaken every two to three months to ensure that flares in ALT are not missed.**

✓ The duration of follow up to define PNALT should be 12 months.

✓ Liver biopsy should only be considered if there are clinical or other concerns about the individual patient.

9.6 HIV CO-INFECTION

There is an increased rate of progression to end-stage liver disease in patients with HIV and HCV co-infection compared to those with HCV mono-infection (relative risk; RR 6.14, 95% CI: 2.86 to 13.2).[104] Median time to cirrhosis in patients with co-infection is 26 years, compared to 38 years in those with HCV mono-infection.[104] Patients with HCV infection with mild immunodepression as a result of HIV also have more severe liver disease than those with HCV mono-infection.[105] There is a marked increase in liver related mortality in patients with CHC and HIV co-infection (RR 17.5).[106] **1+ 2+**

Effective anti-HIV therapy and the associated immune recovery may limit HCV liver disease progression.[107] **2++**

B **The increased rate of progression to decompensated liver disease in patients with HCV and HIV co-infection should prompt early consideration of antiviral therapy.**

9.7 CO-INFECTION WITH HEPATITIS A OR B VIRUSES

Vaccination against hepatitis A and B is recommended in people with HCV.[108] A consensus report on the treatment of hepatitis recommended vaccination for hepatitis B virus (HBV) but not hepatitis A.[109] One case study of patients with HCV who contracted hepatitis A reported a very high level of fulminant hepatitis.[110] **4**

Antibody response to hepatitis B vaccination is reduced in patients with chronic HCV.[111] **3**

D **Vaccination against hepatitis A and B should be considered for patients infected with hepatitis C.**

Patients who are infected with HCV who have serological evidence of current or past infection with HBV are more likely to have advanced liver disease.[91, 112, 113] **3**

D **When estimating the likely rate of progression of liver disease as a result of hepatitis C infection, active or previous hepatitis B virus infection should be considered.**

✓ Patients infected with HCV should be tested for evidence of active or previous HBV infection.

9.8 IRON STATUS

Patients with CHC can have elevated iron stores, but there is debate over whether this has any influence on the disease. Serum ferritin and transferrin saturation are increased in 20-60% of patients and correlate with serum ALT, suggesting they are markers of inflammation.There is a poor correlation with hepatic iron concentration (HIC).[114] HIC is rarely significantly elevated in pre-cirrhotic patients.Twenty to fifty per cent of patients with cirrhosis will have elevated HIC but this is also a common finding in patients with cirrhosis due to hepatitis B and alcoholic liver disease.[114] **4**

It is uncertain whether hepatic iron excess as a single factor has any influence on response to treatment with IFN alone.[114] **4**

No evidence was found that iron depletion (by venesection) has any influence on the virus or the activity of liver disease.[114] There is some evidence from four small RCTs that venesection on selected patients with markers of iron excess prior to IFN monotherapy may improve the SVR.[114, 115] **4 1-**

D **Modest iron loading does not justify specific intervention prior to antiviral therapy as it is unlikely to be of clinical importance.**

D **Patients with significant iron retention require further investigation for additional conditions known to result in iron overload.**

9.9 HCV GENOTYPE

No consistent link between HCV genotype and disease progression has been demonstrated in several cohort studies.[88, 91,92, 116,117] **2+**

9.10 CRYOGLOBULINAEMIA

A poor quality meta-analysis of the influence of cryoglobulinaemia suggested that cirrhosis is diagnosed more frequently in patients with cryoglobulinaemia.[118] **1-**

10 Treatment of chronic hepatitis C

10.1 ANTIVIRAL THERAPY

Several meta-analyses and systematic reviews confirm that a combination of pegylated IFN and ribavirin dual therapy is effective in treating patients with CHC, leading to high levels of sustained viral response (SVR).[7, 119-121] All patients should be considered as candidates for treatment. **1+**

A **All patients with chronic HCV infection should be considered for antiviral therapy.**

10.1.1 SUSTAINED VIRAL RESPONSE

Sustained viral response has become the accepted objective of treatment programmes for CHC and is currently achieved in 41-51% of patients with genotype 1 disease and 73-82% of patients with genotype 2 and 3 disease who have received a course of combination therapy with pegylated IFN and ribavirin.[122, 123] Data are available on long term outcomes after SVR but are limited in number, quality and length of follow up:

- viral relapse is uncommon after SVR (1-13% of patients)[124-126] **1+**
- mortality is reduced after SVR[127] **2+**
- patients with an SVR have a reduced risk of developing cirrhosis and primary hepatocellular carcinoma[124,128] **2++**
- occult hepatitis C may persist in macrophages, lymphocytes to hepatocytes in some patients who have achieved an SVR. There may be a small risk of future relapse in this event.[129,130] **3**

B **Sustained viral response should be used as a marker for viral clearance.**

An SVR of 80% is achieved in patients who take 80% of the dose of both pegylated IFN and ribavirin dual therapy for more than 80% of the duration. This compares with 33% in less adherent patients.[131] **2+**

10.2 TREATMENT VARIATION BY GENOTYPE

10.2.1 GENOTYPE 1 AND DURATION OF TREATMENT

A systematic review assessed adjunct treatment with the protease inhibitors boceprevir and telaprevir in patients with genotype 1 hepatitis C. In both treatment-naive and treatment-experienced patients, sustained viral response rates were achieved more often with the protease inhibitors boceprevir or telaprevir in combination as triple therapy with pegylated IFN and weight-based ribavirin compared with pegylated IFN and weight-based ribavirin alone. Both medications were well tolerated, with anaemia presenting as the most treatment-limiting adverse effect.[132] Figures 1 and 2 show treatment algorithms for patients with genotype 1 HCV infection. **1+**

Three RCTs reviewed in two systematic reviews found that telaprevir administered for at least 12 and up to 48 weeks in combination with pegylated IFN and weight-based ribavirin as triple therapy was effective in the treatment of previously untreated or treatment-experienced adults with genotype 1 chronic hepatitis C infection. The trials included treatment-experienced adults who were non-responders, partial responders and relapsers following pegylated IFN and weight-based ribavirin. Sustained viral responses were significantly better than pegylated IFN and weight-based ribavirin dual therapy alone.[133,134] **1+**

Two systematic reviews found that boceprevir administered for 24-44 weeks as triple therapy in combination with pegylated IFN and weight-based ribavirin for up to 48 weeks was effective in the treatment of previously untreated or treatment-experienced adults with genotype 1 chronic hepatitis C infection. These trials included treatment-experienced adults who were either partial responders or relapsers following pegylated IFN and weight-based ribavirin but did not include previous non-responders. Sustained virological responses were significantly better than with pegylated IFN and weight-based ribavirin dual therapy alone; 66% for fixed duration triple therapy versus 63% for response guided triple therapy versus 38% for control group receiving standard dual therapy.[134,135] **1+**

A regimen including boceprevir requires a four week lead-in of pegylated IFN and weight-based ribavirin, whereas this is not required for telaprevir. A lead-in with boceprevir, however, does not reduce SVR. The response to the lead-in period can indicate likelihood of SVR in both treatment-naive and experienced patients.

A **All treatment-naive patients infected with HCV genotype 1 should be considered for treatment with pegylated IFN and weight-based ribavirin with the addition of a protease inhibitor as triple therapy.**

A **All treatment-experienced patients infected with HCV genotype 1 should be considered for treatment with pegylated IFN and weight-based ribavirin with the addition of a protease inhibitor as triple therapy.**

✓ In treatment-experienced patients with a lower likelihood of SVR, benefits of treatment need to be weighed against potential risks and side effects.

A **Response-guided therapy can only be used in treatment-naive patients and previous treatment relapsers who are not cirrhotic.**

No direct comparison studies of boceprevir and telaprevir were identified, therefore neither drug can be recommended over the other.

No evidence was identified suggesting that a particular pegylated IFN should be used in combination with a particular protease inhibitor.

Figure 1: Algorithm for the use of protease inhibitors in treatment-naive HCV genotype 1 infected patients.

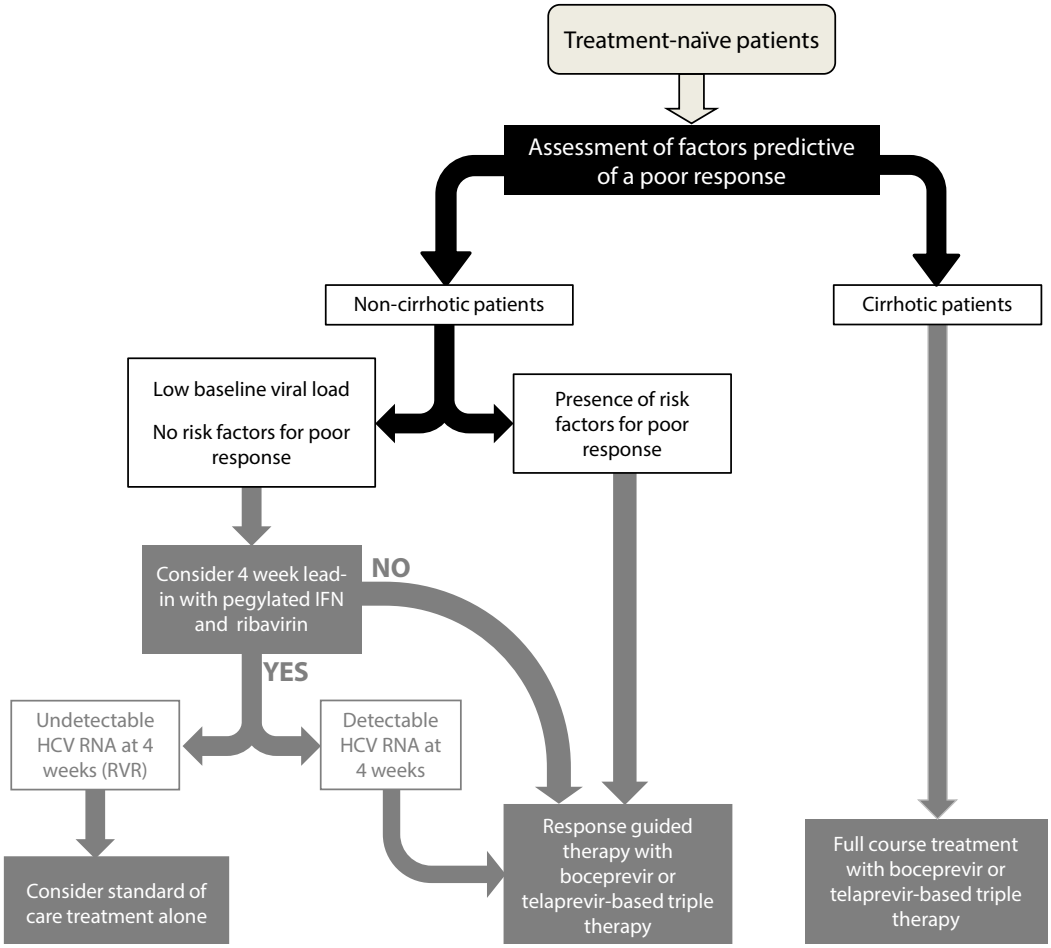

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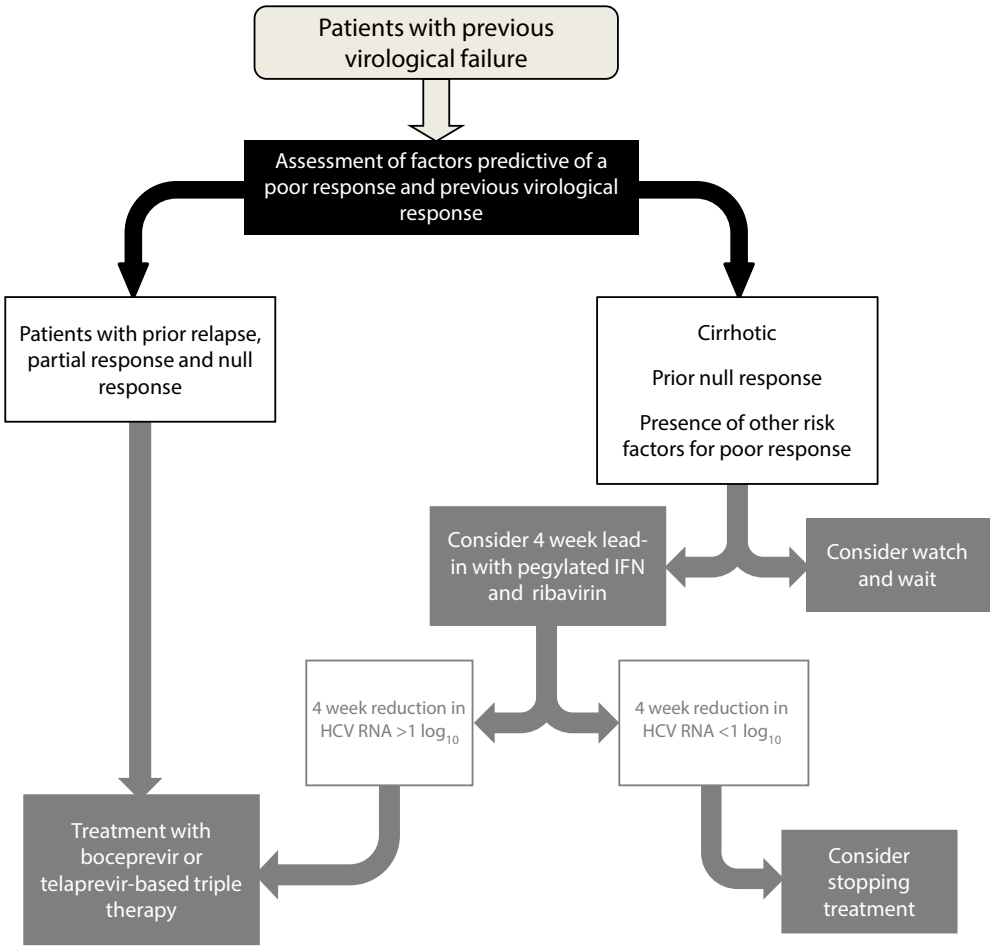
Figure 2: Algorithm for the use of protease inhibitors in HCV genotype 1 infected patients who have had prior viralogical failure on treatment.



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10.2.2 GENOTYPE 1 AND DURATION OF TREATMENT FOR PATIENTS UNSUITABLE FOR PROTEASE INHIBITORS

The optimal duration of treatment for patients with genotype 1 hepatitis C is 48 weeks.[7,119,120] **1++**

Patients with genotype 1 infection who fail to achieve an early viral response (EVR) at 12 weeks have a less than five per cent chance of achieving a SVR.[136] Of those genotype 1 patients who failed to achieve an EVR but continued on therapy and were still HCV RNA positive at 24 weeks, none had an SVR.[137] Following careful clinical assessment some patients infected with genotype 1 HCV may be considered unsuitable for treatment with a regimen which includes a protease inhibitor. This includes patients with potentially dangerous drug-drug interactions with prescribed or illicit medications, and those with co-morbid conditions that may impair adherence to therapy thus reducing the effectiveness of triple therapy and increasing the risk of developing drug resistance.[134] **1+**

The registration studies for telaprevir and boceprevir both demonstrate in post hoc analysis that patients with low viral loads, treated with pegylated INF and weight-based ribavirin and who achieve a rapid viral response (RVR), have the same SVR rate as those treated with the addition of a protease inhibitor.[138] A meta-analysis looked at shortened therapy for those treated with pegylated INF and weight-based ribavirin. Including all patients, relapse rates were significantly higher in patients with genotype 1 RVR if the treatment duration was reduced to 24 weeks with an overall reduction in SVR of -13.6% (95% CI -22.8% to -4.4%, p=0.004). If the viral load was less than 400,000 IU/ml there was no statistical significant reduction in SVR with 24 weeks of treatment with a mean difference of -3.1% (96% CI -8.6% to 2.4%). [138] **1+**

A
- **Patients with genotype 1 infection should be tested for an EVR at 12 weeks.**
- **Patients with genotype 1 infection who fail to achieve an EVR at 12 weeks should be considered for cessation of treatment.**
- **Patients with genotype 1 infection with an EVR at 12 weeks should continue treatment for 48 weeks. Those who are still HCV RNA positive at 24 weeks should discontinue treatment.**

B
Following informed discussion, treatment-naive patients with genotype 1 infection and:
- **minimal or no fibrosis**
- **low viral load** (less than 400,000 IU/ml)
- **who achieve an RVR following a lead in with pegylated IFN and weight-based ribavirin for four weeks can be considered for 24 weeks of treatment without the addition of a protease inhibitor.**

10.2.3 GENOTYPE 2 AND 3 AND DURATION OF TREATMENT

The optimal treatment for patients with genotype 2 and 3 infection is pegylated INF and weight-based ribavirin.[7, 119, 120] The primary outcome of one meta-analysis was comparison of SVR rates in patients with either genotype 2 or 3 infection. After 24 weeks of therapy, SVR rates were 74% and 69% respectively with an OR of 1.49 (95% CI 1.23 to 1.80) however the percentage difference was not significant (p=0.90). Among those with higher viral loads, the SVR rate in genotype 2 infection (75%) differed from genotype 3 infection (58%) with an OR of 2.36 (95% CI 1.80 to 3.09). The percentage difference of 24.9 % (95% CI 12.8 to 37.0; p=0.07) was not significant. In patients with low viral loads respective rates were 79% and 75% with an OR of 1.50 (95% CI 1.08 to 2.09) again with a non-significant difference (p=0.84). As a secondary outcome shortened therapy in patients with RVR treated for 12–16 or 24 weeks was analysed. SVR rates in genotype 2 infected patients were 83% and 84%, respectively, and in genotype 3 infected patients 84% and 86%. In patients without RVR treated for 24 weeks, the SVR was higher in those with genotype 2 infection, with a 17.8% weighted difference (95% CI: 8.7 to 27.0) and a pooled OR of 2.06 (95% CI 1.40 to 3.02). The authors concluded that 24 weeks of therapy should remain the standard duration for patients with genotype 2 or 3 infection. However, in patients who achieve an RVR, those with genotype 3 HCV respond to shortened treatment as well as those with genotype 2, irrespective of basal viraemia.[139] **1++**

The aim of a second meta-analysis was to determine the optimal length of treatment in patients with HCV genotypes 2 and 3. The results for these two genotypes were pooled. Pooled SVR data were higher for standard treatment in RCTs that randomised at baseline, with an RR of 0.88 (95% CI 0.76 to 1.01) favouring standard therapy over shortened therapy. The pooled proportion of SVR rates of RCTs that randomised at RVR were similar in the shortened treatment group (82%) and in the standard treatment (83%), with the pooled effect given by an RR of 1.00 (95% CI 0.92 to 1.09). The authors' conclusions should be treated with caution given the lack of detail about the methodology and a high level of heterogeneity between the included studies. The authors conclude that based on baseline characteristics all patients should be treated for 24 weeks with dual therapy. However patients who achieve an RVR at four weeks can have their therapy shortened to between 12-16 weeks of dual therapy with pegylated IFN and weight-based ribavirin. They found no difference between 12 or 16 weeks but numbers were small. Numbers of patients with cirrhosis were too small to allow any inference about that group. Weight-based ribavirin achieved higher SVRs than low fixed dose ribavirin.[140] **1+**

Evidence from two studies suggests that patients with genotype 2 or 3 infection who achieve a rapid viral response (HCV RNA negative) at four weeks can receive 12 or 16 weeks of pegylated IFN and weight-based ribavirin therapy with similar results to 24 weeks of treatment.[141, 142] **1+**

A
For patients with HCV genotype 2 or 3 standard treatment should be pegylated IFN and weight-based ribavirin for 24 weeks.

B
Non-cirrhotic patients, with genotype 2 or 3, who achieve an RVR at week 4 of therapy, could be considered for shortened duration of therapy of 12 to 16 weeks.

10.2.4 GENOTYPE 4, 5 AND 6 AND DURATION OF TREATMENT

The optimal duration of treatment for patients with genotype 4 hepatitis C is 48 weeks.[7, 119, 120] 1++

A meta-analysis of two large phase three/four prospective randomised clinical trials conducted in Belgium in patients with chronic hepatitis C (n = 1,073) compared the response to antiviral therapy of those with HCV genotype 5 with that of those with other HCV genotypes. The study found that genotype 5 infection responds to therapy in a similar way to genotype 1, however the genotype 5 population is older, more likely to have acquired infection by blood transfusion and more likely to have cirrhosis. The meta-analysis recommended treating patients with genotype 5 infection for 48 weeks with dual therapy.[143] 1+

A systematic review found very few studies of treatment of patients with HCV genotype 6 infection. Treatment with pegylated IFN and weight-based ribavirin is effective, with SVR rates around 70% after 48 weeks of therapy. SVR rates are similar in patients with HCV genotype 6 infection who receive 24 weeks of pegylated IFN and weight-based ribavirin, although additional studies are needed before recommending 24 weeks as the optimal treatment duration for these patients.[144] 1+

A **For patients with HCV genotype 4, 5 or 6 infection, standard treatment should be 48 weeks of pegylated IFN and weight-based ribavirin.**

10.3 PATIENT SUBGROUPS

10.3.1 PATIENTS WITH MILD CHRONIC HEPATITIS

In patients with mild CHC the efficacy and safety of non-pegylated IFN and ribavirin combination therapy is similar to that in other patients with hepatitis C. Liver biopsy to exclude patients with mild disease is therefore not required prior to considering antiviral treatment.[145] 1++

B **Patients with mild CHC should be considered for treatment.**

10.3.2 PATIENTS WITH CIRRHOSIS

See section 11.1.1 for information on patients with cirrhosis.

10.3.3 PATIENTS WITH PERSISTENTLY NORMAL ALT LEVELS

The efficacy and safety of pegylated IFN and ribavirin combination therapy in patients with CHC and persistently normal ALT level is similar to that seen in patients with elevated ALT levels (*see section 9.5*).[146] 1+

A **Patients with chronic hepatitis C and normal ALT should be considered for treatment.**

10.3.4 PATIENTS WITH HIV CO-INFECTION

Pegylated IFN and ribavirin for 48 weeks is effective in treating patients with HCV-HIV co-infection, leading to sustained viral response in 60% of patients with genotype 2 and 3 and 14-29% in patients with genotype 1. For patients with genotype 1 infection and low HCV viral load (<800,000 IU/ml), the sustained viral response rate is around 60%.[147-149] 1+

Ninety eight per cent of patients with HIV-HCV co-infection who did not have an EVR at week 12 did not achieve an SVR at week 48.[149] 1+

Patients co-infected with HIV and HCV genotypes 2 and 3 with undetectable HCV-RNA at week 4 did not benefit from prolonging therapy beyond 24 weeks.[150] 1+

Pegylated IFN plus weight-based ribavirin for the treatment of HCV was more effective than standard IFN plus weight-based ribavirin in achieving a sustained viralogical response in patients co-infected with HIV: 55% versus 26% overall, 46% versus 18% in genotype 1 and 4 and 71% versus 43% in genotype 2 and 3. The differences between cohorts were HCV-genotype dependant during the first 12 weeks of pegylated IFN therapy, regardless of HIV status. Among patients with HCV genotype 2 or 3, the study found a significantly sharper decrease in HCV RNA in HCV mono-infected patients compared with HCV-HIV co-infected patients 1+

only at week 4, whereas significant differences among patients with HCV genotype 1 were observed only after 12 weeks of therapy. Overall, longer duration of treatment (48-72 weeks) showed better treatment responses irrespective of genotype than shorter duration (24-48 weeks).[150-152] 1+

The expert opinion of the guideline development group was that recommendations could be made for treatment of patients co-infected with HIV and HCV genotype 1 by extrapolating from HCV genotype 1 mono-infected patient treatment regimens which include protease inhibitors.

A **All patients co-infected with HCV and HIV should be considered for HCV treatment.**

A **For patients with HCV genotype 1 infection and HIV, who do not achieve an EVR, treatment should be stopped.**

A
- **Co-infected non-genotype 1 patients who are considered suitable for treatment should be offered treatment with pegylated IFN and weight-based ribavirin for 48 weeks.**
- **Co-infected genotype 2 or 3 patients who achieve an RVR may be considered for 24 weeks of treatment.**

C **All patients co-infected with HIV and HCV genotype 1 should be considered for treatment with a regimen which includes an HCV protease inhibitor.**

B **Treatment-naive patients co-infected with HIV and HCV genotype 1 who are unsuitable for treatment with a regimen which includes HCV protease inhibitors should be considered for treatment with pegylated IFN and weight-based ribavirin for 48-72 weeks depending on viral response.**

✓ Genotype 1 co-infected patients who are not cured of their HCV infection should be monitored for disease progression.

10.3.5 PATIENTS WITH HEPATITIS B CO-INFECTION

Treatment outcomes with a combination of non-pegylated IFN and ribavirin in patients co-infected with chronic hepatitis B and C are similar to those achieved in patients with HCV mono-infection.[153,154] No trials were found examining pegylated IFN and ribavirin in patients co-infected with chronic hepatitis B and C. 2++

No evidence was identified to make a recommendation on treatment with protease inhibitors for patients who are genotype 1 and co-infected with hepatitis B as these patients were excluded from clinical trials.

C **Patients with chronic hepatitis B and C co-infection should be considered for treatment with pegylated IFN and weight-based ribavirin.**

✓ Patients with chronic hepatitis B and C genotype 1 co-infection could be considered for combination treatment with pegylated IFN and weight-based ribavirin with the addition of a protease inhibitor on an individual basis in centres with an expertise in management of hepatitis B.

10.3.6 PATIENTS IN DRUG TREATMENT PROGRAMMES

In patients with CHC 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-outs occur early, within the first eight weeks. After eight weeks adherence to treatment is similar to other groups.[44,155] 2+

Recent studies suggest active drug users have comparable treatment outcomes to non-drug users.[156-158] 2+ 1+

B **Patients with CHC who are on a drug treatment programme should be considered for treatment.**

✓ Active drug users should be engaged in efforts to address their healthcare needs and in harm reduction.

✓ Active drug users should have a comprehensive assessment of their psychological needs and of their likely adherence to antiviral treatment.

10.4 FACTORS INFLUENCING EFFECTIVENESS

10.4.1 AGE, GENDER AND ETHNICITY

Antiviral therapy is less effective in patients over the age of 40 and men are less likely than women to achieve a sustained viral response.[7,119,120] Variations have been observed in the response of patients of different race to antiviral therapy. A meta-analysis of ethnic differences showed that patients of African-American or Hispanic origin had lower SVRs than Caucasian or Asian groups (16% and 24% versus 32% and 59% with genotype 1 achieved SVR).[159] **1+**

A **Patients should be advised that older age at the time of treatment leads to a lower sustained viral response.**

B **Patients should be advised about the likelihood of sustained viral response according to their ethnic origin.**

10.4.2 BODY WEIGHT

Three systematic reviews report that in patients with CHC whose weight is greater than 75 kg, treatment with a combination of pegylated IFN and ribavirin leads to a lower SVR than in patients weighing less than 75 kg.[7,119,120] Dosage of pegylated IFN and ribavirin in these studies was given at a cut-off point of 75 kg and not weight related, therefore caution should be taken when extrapolating results. Weight and diet are discussed in section 12. **1+**

10.4.3 ALCOHOL

Treatment studies in patients continuing to use alcohol are limited. Two cohort studies have shown that response rate to standard IFN treatment was inversely proportional to the amount of alcohol ingested.[160, 161] A six month abstinence from alcohol did not offset previous lifetime alcohol intake.[162] **2+**

✓ Patients should be advised that drinking alcohol (even in moderation) can reduce the response to treatment with pegylated IFN and ribavirin.

10.5 CONTRAINDICATIONS

10.5.1 PREGNANCY AND RISK OF PREGNANCY

There are no studies on the effects of antiviral therapy on human pregnancy. Studies in animals have shown that ribavirin therapy, at well below the recommended human dose, causes malformations in the fetus. The incidence and severity of the teratogenic effects increased with escalation of the ribavirin dose. Survival of the fetus and the offspring was reduced.[163] Further animal studies have shown abnormalities in sperm.[163]

There are no data on the use of pegylated IFN in pregnant women and it is not known whether pegylated IFN or ribavirin are excreted in human milk.

✓ Pegylated IFN and ribavirin must not be prescribed to women who are pregnant.

✓ Treatment with pegylated IFN and ribavirin should not be initiated until pregnancy has been excluded.

✓ Couples, with one partner receiving pegylated IFN and ribavirin, should use two forms of contraception during treatment and for six months after therapy has ended.

10.5.2 PATIENTS WITH RENAL FAILURE

Ribavirin causes a dose-dependent haemolytic anaemia and the degree of haemolysis is dependent on the severity of the renal failure.[164] Treatment with pegylated IFN monotherapy at a dose of 135 µg subcutaneously per week for patients on haemodialysis may be considered but patients need to be closely monitored.[165] **1+ 3**

D **Patients with CHC and renal failure may be treated with IFN monotherapy, with careful monitoring required.**

10.5.3 PATIENTS WITH MENTAL HEALTH PROBLEMS

Patients with mental health problems respond equally well to IFN and ribavirin therapy but their psychiatric symptoms should be managed carefully, particularly in the first four weeks of treatment.[166,167] **2+ 3**

B **Patients with stable mental health problems should not be excluded from treatment for CHC.**

B **Patients with mental health problems should have their psychiatric symptoms monitored prior to and throughout IFN treatment.**

✓ Formal psychiatric assessment should be considered for selected patients if necessary.

10.5.4 PATIENTS TAKING OTHER MEDICINES

The protease inhibitors telaprevir and boceprevir are both inhibitors and substrates of the metabolising enzyme, cytochrome P450 (CYP) 3A4. Co-administration of either telaprevir or boceprevir with drugs metabolised by this enzyme can result in clinically significant and possibly life threatening drug-drug interactions. Due to the potential for toxicity and/or suboptimal treatment particular care should be taken to ensure a full drug history and medication review of all patients (including prescribed medication, over-the-counter products, herbal and/or illicit drugs).[134,168] An assessment should be made to ensure that co-administration will not result in any clinically significant alteration to drug metabolism. Reference sources such as the summary of product characteristics for each drug and University of Liverpool Hepatitis C drug interaction website should be consulted as the main sources of information;[169] however, all possible sources of reliable information should be used to prevent problems with drug interactions. In patients with complex medication regimens, referral to a specialist pharmacist should be considered to ensure that complex interactions are explored adequately. Primary care providers should be alerted to the potential for interactions by communicating the results of the medication review. In patients whose concurrent prescribed or illicit medicines are contraindicated with protease inhibitors, treatment should be with pegylated IFN and ribavirin only after consultation with the local multidisciplinary team.[134] **4**

Caution should be taken if co-prescribing protease inhibitors with drugs known to prolong the QT interval. Prescribing information for individual drugs provides directions on ECG monitoring. Other mechanisms for drug metabolism may be involved but not yet identified and prescribers should remain vigilant. Caution and close monitoring should be adopted when co-prescribing other medicines.

D **Patients should have a full drug history taken including prescribed, over-the-counter and illicit drugs.**

D **The co-administration of any drugs should be assessed to ensure there is no unacceptable potential for toxicity or suboptimal efficacy of either agent.**

✓ Patients with complex polypharmacy may benefit from input of a specialist pharmacist.

✓ Patients should be made aware of potentially dangerous interactions between over-the-counter medicines, illicit drugs and HCV therapy, even if they are not known to use illicit drugs.

10.6 MANAGEMENT OF ADVERSE EFFECTS

10.6.1 FLU-LIKE SYMPTOMS

Virtually all patients taking pegylated IFN and ribavirin will experience flu-like symptoms such as fever, myalgia, rigors, arthralgia and headache. These tend to become less severe after the first month of treatment.[170] Simple interventions such as paracetamol use and increased fluid intake and rest can minimise these effects.[170, 171] **4**

D **Patients experiencing flu-like side effects from pegylated IFN and ribavirin can be advised to use paracetamol within manufacturers' guidelines.**

D **Patients should be advised to maintain an adequate fluid intake throughout treatment with pegylated IFN and ribavirin.**

D **Patients should be advised to coordinate their injections of pegylated IFN and ribavirin with periods of reduced activity, such as weekends and holidays.**

10.6.2 ANAEMIA AND NEUTROPENIA

In clinical trials the use of erythropoietin (EPO) in patients who developed anaemia (haemoglobin level ≤120g/l) while on pegylated IFN and ribavirin therapy improved the anaemia and lessened the need to reduce the dose of ribavirin. It also improved quality of life.[172,173] There is no direct evidence that this results in an increase in the SVR. None of the erythropoietins are currently licensed for this indication. **1+**

Haemoglobin levels should be maintained at a level that prevents a need for dose reduction or discontinuation of pegylated IFN and ribavirin therapy as this can cause a reduction in SVR.[174] Up to a third of patients receiving combination therapy develop anaemia and 13% progress to a haemoglobin of less than100 g/l. With the addition of protease inhibitors to pegylated INF and ribavirin treatment, anaemia can be more frequent and severe, occurring in the first few weeks of therapy.[174] An RCT compared the use of EPO as first line therapy to maintain haemoglobin, with ribavirin dose reduction in patients receiving boceprevir. This demonstrated that dose reduction of ribavirin maintained haemoglobin levels and provided similar SVR (71%) to patients whose treatment was supplemented with EPO. This finding was confirmed in patients with cirrhosis[175] and during phase three trials using telaprevir in triple therapy regimes.[176] **2+** **1+**

Granulocyte-colony stimulating factor (G-CSF) may relieve drug-induced neutropenia in patients receiving pegylated IFN and ribavirin therapy. It is most commonly needed in patients given antiviral therapy post liver transplant.[177] **3**

B **Erythropoietin should be considered in CHC patients receiving pegylated IFN and ribavirin therapy who develop anaemia, to prevent curtailment or dose reduction of ribavirin.**

B **For patients receiving a protease inhibitor in combination with pegylated IFN and ribavirin therapy, consider ribavirin dose reduction as an alternative to the addition of EPO for controlling anaemia.**

D **Granulocyte-colony stimulating factor should be considered on a case-by-case basis for patients who develop significant neutropenia while receiving treatment with pegylated IFN and ribavirin for CHC infection, to prevent curtailment or dose reduction of pegylated IFN.**

10.6.3 DEPRESSION

Depression is a commonly reported side effect of pegylated IFN and ribavirin therapy in both patients who have previously experienced depression and those who have not.[178] Antidepressants can be successfully used for treatment related depression and as a preventative measure prior to exposure to antiviral treatment.[166, 179] **1++** **1+** **3**

B **All patients receiving pegylated IFN and ribavirin should be monitored for signs of depression before, during and immediately post-treatment.**

B **Patients treated with pegylated IFN and ribavirin who experience depression should be considered for treatment with antidepressants and for referral to a specialist, if necessary.**

✓ A validated assessment tool (eg Hospital Anxiety and Depression score) should be used for monitoring depression.

10.6.4 SKIN REACTIONS

Severe skin reactions are uncommon during pegylated IFN or ribavirin therapy but dry skin, pruritus and diffuse eczematous lesions occur in approximately 20% of patients.[170] Psoriasis may also be exacerbated by treatment for CHC. Injection site reactions occur in over 50% of treated patients.[171] Skin lesions appear most commonly on the distal limbs and head and neck region, suggesting a predominance in sun-exposed areas.[180] Patients respond well to antihistamines, emollients and topical steroids, allowing continuation of treatment.[180] Discontinuation rates for dermatological side effects are approximately 3-4%.[181] **4** **3**

Three RCTs report on a potentially fatal rash, one of the principal adverse events of telaprevir treatment. This leads to discontinuation of telaprevir in 5-7% of patients. Once the medication is discontinued the rash resolves (although this may take several weeks). The rash is predominantly eczematous and pruritic. Fifty per cent of patients developing a rash do so within the first four weeks of treatment although it can occur at any time. Early intervention with topical steroids reduces the severity of rash. Rarely, telaprevir has been associated with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or Severe Cutaneous Adverse Reactions to Drugs (SCAR) syndromes, which includes Stevens Johnson syndrome and toxic epidermal necrolysis, and these should be monitored for and, if detected, therapy should be discontinued.[182-184] **1+** **1++**

D **All patients on pegylated IFN and ribavirin should be advised to ensure appropriate skin hygiene and hydration.**

D **Patients should be advised to avoid overexposure to sun.**

D **Patients should be advised to rotate injection sites.**

D **The use of emollients and topical corticosteroids can be considered for non-specific rashes.**

A **Patients taking telaprevir must be monitored closely for rash and treatment centres should have a rash management plan.**

✓ The use of antihistamines can be considered for pruritus.

✓ Severe dermatological reactions or those that do not respond to first line treatment should be referred for dermatological opinion.

✓ Patients taking telaprevir should be promptly assessed for severity according to the percentage of body surface area involved and the presence of systemic symptoms.

✓ Patients with a history of rash or skin problems should be considered for treatment with boceprevir rather than telaprevir.

10.6.5 THYROID DISFUNCTION

IFN therapy is associated with the development of thyroid dysfunction (both hypothyroid and hyperthyroid) in up to 6% of those treated.[170] Females are more at risk, especially those with thyroid autoantibodies before treatment.[185] IFN is associated with the induction and enhancement of thyroid autoimmunity, which is not always reversible.[186,187] Pre-treatment autoantibodies are not universally predictive of thyroid dysfunction during treatment.[170]

4
1-
2+

D **Thyroid function should be monitored at baseline before IFN therapy, at week 12 of treatment and at any time where there is a suspicion of thyroid dysfunction.**

✓ Patients developing thyroid dysfunction should be referred to an endocrinologist.

10.6.6 WEIGHT LOSS

Chronic hepatitis C infection causes increased basal metabolic rate in non-cirrhotic patients.[188] Weight loss is commonly reported in patients on antiviral treatment.[170,171,189] Nutritional therapy of patients with HCV is discussed in section 12.1.

2-
4

10.6.7 DYSPNOEA

Dyspnoea is a rarely reported side effect of pegylated IFN and ribavirin therapy. It may occur as a result of treatment-related anaemia but may also be caused by more serious cardiovascular or respiratory conditions.[170, 171,190]

2-
4

D **Patients treated with pegylated IFN or ribavirin who report dyspnoea that is not related to anaemia should be urgently assessed medically for cardiopulmonary problems.**

10.6.8 RETINOPATHY

Retinopathy during pegylated IFN therapy is common but generally mild and transient. It resolves spontaneously on discontinuing IFN and treatment is seldom required. The long term consequences are unknown.[191] Patients with hypertension or diabetes are at greater risk of developing retinopathy.[171] Other ophthalmic side effects are uncommon.

1+
4

D **Patients with CHC and hypertension or diabetes should have an ophthalmic examination prior to commencing treatment, paying particular attention to cotton wool spots and retinal haemorrhage.**

D **Any patient reporting visual disturbance during treatment should be examined further by an ophthalmologist.**

D **IFN should be discontinued in any patient with visual disturbance until it has resolved or an ophthalmologist has confirmed there is no retinal injury.**

10.6.9 ALOPECIA

Alopecia is a relatively common reported side effect of IFN and ribavirin therapy. Hair will grow again on cessation of treatment.[170, 171]

D **Patients should be advised that treatment related hair loss is reversible on cessation of treatment.**

10.6.10 OTHER SIDE EFFECTS

Other reported side effects of protease inhibitors include insomnia, poor concentration, oral disease, anal/rectal discomfort, gastrointestinal problems, altered taste, nausea, and post-treatment withdrawal symptoms. No evidence on their effective management was identified.

Fatigue is one of the most commonly reported side effects of IFN or ribavirin treatment and may be multifactorial with anaemia, hypothyroidism, sleep disturbance and depression all contributing.[170, 171]

4

10.7 RELAPSE OR FAILED TREATMENT

10.7.1 IFN AND RIBAVIRIN

Retreatment with a combination of pegylated IFN and ribavirin is effective in patients with CHC who have had unsuccessful treatment with non-pegylated IFN with or without ribavirin, and leads to sustained viral response in a proportion of patients. The SVR is highest in patients who had received prior treatment with non-pegylated IFN monotherapy, those infected with genotypes 2 or 3, those who had relapsed rather than not responded to previous treatment, and those who were not cirrhotic at time of retreatment.[192] **3**

Two trials which addressed retreatment of patients with genotype 1 HCV, in whom treatment had been previously unsuccessful, showed that there was significant benefit in repeating treatment with a pegylated IFN and ribavirin regimen with the addition of a protease inhibitor.[134] For telaprevir triple therapy the overall SVR were 64% (without lead-in), 66% (with a four week lead-in) and 17% in the dual therapy control group, the differences of 47% (95% CI 37 to 57; p<0.001) and 50% (95% CI 40 to 60; p<0.001) between the triple therapy and control groups were significant.[193] For boceprevir triple therapy the overall SVR were 59% (32 week triple therapy), 66% (44 week triple therapy) and 21% in the control group. The differences of 38% (95% CI 25.7 to 49.1; p<0.001) and 45% (95% CI 33.7 to 56.8; p=0.001) between triple therapy and control groups were significant.[194] **1+**

D **Patients with CHC who have had unsuccessful treatment with non-pegylated IFN and ribavirin should be considered for pegylated IFN and ribavirin retreatment.**

A **Patients with genotype 1 CHC who have had any unsuccessful treatment should be considered for treatment with a protease inhibitor based regimen.**

✓ Patients with genotype 2 or 3 CHC who have undergone a suboptimal therapy could be considered for retreatment with pegylated INF and ribavirin for 48 weeks.

10.8 MONITORING PATIENTS WHO ARE NOT RECEIVING TREATMENT

10.8.1 CLINICAL REVIEW

No evidence was identified regarding effective practice in monitoring and advising patients who are not candidates for treatment or who have received unsuccessful treatment.

✓ Patients should be encouraged to continue attending follow-up clinics for review in order to monitor their condition and discuss new therapies as they emerge.

✓ Patients should have access to counselling and specialist nurse services to provide support on lifestyle issues relating to hepatitis C.

10.8.2 ROLE OF LIVER BIOPSY

Routine liver biopsy during or after antiviral treatment is not indicated unless specific information is required in selected patients.[101] **1-**

11 Treatment of advanced infection

11.1 ANTIVIRAL THERAPY

11.1.1 PATIENTS WITH CIRRHOSIS

Patients with cirrhosis are defined as having compensated or decompensated cirrhosis. Those with decompensation have deterioration with development of one or more of the following: jaundice, ascites, variceal bleeding or encephalopathy.

There are several large well conducted RCTs of IFN and ribavirin, pegylated IFN and ribavirin, and pegylated IFN monotherapy in patients with chronic HCV who have a high likelihood of progressing to end stage liver disease.[122, 123, 195, 196] Subgroups within these trials had cirrhosis or advanced fibrosis. Randomisation distributed them evenly between the interventions so that subgroup analysis was possible. Therapy appeared no more toxic to the patients with cirrhosis compared to those without cirrhosis, but was less effective. The SVRs achieved were 50-70% for genotype 2 and 3, and 20-30% for genotype 1. A further systematic review in patients with cirrhosis have confirmed reduced risk in hepatocellular carcinoma in those who achieve SVR (RR 0.25; 95% CI 0.14 to 0.46; p=0.00001).[97] **1+**

Whilst improved over previous therapies, SVR rates are likely to remain low in previously non-responding patients with cirrhosis, particularly in the context of a poor response to lead-in pegylated IFN and ribavirin. Treating these patients with protease inhibitors is also likely to increase development of drug resistant mutants, potentially jeopardising the use of future direct-acting antivirals. Therefore, careful consideration should be given to the best management option for this group. In patients with advanced fibrosis or cirrhosis there are non-significant trends towards better SVR rates with fixed duration therapy, but there is currently insufficient evidence for the use of response-guided therapy in patients with cirrhosis.[134] Further study of the efficacy of protease inhibitors in patients with cirrhosis would be beneficial as major trials on telaprevir excluded patients with a platelet count of <90,000/mm^3.[133] **1+**

No head-to-head trials of the different pegylated IFNs were identified. Studies of long term therapy for patients with cirrhosis are ongoing.

A **Patients with compensated cirrhosis should be considered for therapy, unless contraindicated.**

Treatment with weekly maintenance low-dose pegylated IFN in patients with cirrhosis showed no significant difference in slowing disease progression or reducing clinical outcomes compared to patients receiving no treatment. There were no differences in development of HCC, decompensation or transplantation.[198,199] **1++**

One RCT showed that 48 weeks of escalating pegylated IFN monotherapy in predominantly treatment-experienced patients with cirrhosis showed a reduction in all cause mortality and non-oncological morbidity; however this study was inadequately powered and not as yet reproduced by other researchers.[200] The prospectively defined sub-analysis in another RCT of patients with portal hypertension showed that pegylated IFN delayed significant portal hypertensive events such as variceal bleeding.[201] **1-** **1+**

A **Low-dose pegylated IFN maintenance monotherapy should not be used in patients with compensated cirrhosis.**

There was insufficient evidence on the treatment of patients with HCV and decompensated cirrhosis to make a recommendation.

11.1.2 PATIENTS REFERRED FOR LIVER TRANSPLANT

Several studies have addressed the benefits of antiviral therapy given in the period leading up to, or following, orthotopic liver transplantation (OLT).[177, 202-205] In the period before transplantation many patients are excluded from therapy because of contraindications. SVR rates are low. There is little evidence for treatment in the peri-transplant period (the time period immediately before, during and after transplantation). Post-transplant therapy is poorly tolerated, due to anaemia and leucopenia, but appears safe in regard to graft failure. In those patients able to tolerate full dose therapy, high SVRs are achieved. **3** **1+**

D **Patients in whom transplant is planned should not receive antiviral therapy in the pre-transplant or peri-transplant stages, except as part of clinical trials.**

D **Patients should be considered for antiviral therapy post liver transplant to achieve HCV clearance in cases of recurrence of HCV related liver disease.**

11.2 LIVER TRANSPLANTATION

In early studies of patients transplanted for HCV cirrhosis, the five- and 10-year survival rates were equivalent to patients after OLT for non-HCV causes (68% and 60%).[205] In an analysis of the United Network for Organ Sharing (UNOS) database outcomes were studied in HCV positive (n=5,640, 43%) and HCV negative recipients (n=7,386, 56.7%). In the HCV negative and the HCV positive recipient populations, five-year patient survival rates were 83.5% versus 74.6% ($p<0.00001$) and five-year graft survival rates 80.6% *v* 69.9% ($p<0.00001$), respectively. HCV infection reduces outcome following transplantation but this effect is not sufficient to deny an individual patient transplantation.[206] **2+**

Patients with HCV and transplantable hepatocellular carcinoma (one lesion <5 cm or fewer than three lesions <3 cm, on cross-sectional imaging) have no decrease in survival benefit up to 48 months post orthotopic liver transplantation when compared to patients with HCV alone.[205, 207] **2+**

Quality of life in patients post OLT for HCV is equivalent to patients with non-HCV at three years.[208] **3**

C **Patients with hepatitis C virus and concurrent operable hepatocellular carcinoma should be offered liver transplantation.**

C **Patients with HCV associated chronic liver failure should be considered for assessment for liver transplantation.**

No studies were found on the effectiveness of retransplantation in patients with graft loss due to HCV recurrence.

11.3 SCREENING FOR HEPATOCELLULAR CARCINOMA

The results of studies evaluating the sensitivity and specificity of serum alfa-fetoprotein for detection of HCC in individuals with HCV indicate that in isolation this marker is of limited value.[209] **1+**

Annual ultrasound scanning of patients with cirrhosis and HCV does not detect tumours at a stage that permits likely curative treatment.[210] Scanning on a six-monthly basis may result in the detection of tumours at a stage that permits curative therapy.[211] **2+**

Methods of screening and surveillance other than alfa-fetoprotein and ultrasound remain experimental.

The rate of development of HCC in patients with HCV who are non-cirrhotic compared with patients who are is extremely low (7.6% versus 92.4%).[212] **2+**

A **The measurement of alfa-fetoprotein should not be used in isolation for screening or surveillance of the development of HCC in patients with hepatitis C.**

D **Surveillance using ultrasound should take place at six-monthly intervals.**

C **Surveillance should be confined to patients with cirrhosis.**

12 Nutrition, supportive care and complementary therapies

12.1 NUTRITIONAL INTERVENTIONS

12.1.1 DIETARY INTERVENTIONS

Protein energy malnutrition is common in all patients with chronic liver disease and can lead to weight loss. Chronic hepatitis C infection increases basal metabolic rate in non-cirrhotic patients.[188] Malnutrition (either under- or overweight) negatively affects nutritional status, quality of life and survival. Nutritional assessment to identify patients at risk and provision of nutritional support (enteral and parenteral) to improve clinical outcome should play an important role in patient care.[213] **2- 4**

Weight loss is commonly reported in patients on antiviral therapy.[170, 171, 189] This is possibly a result of other side effects, such as fatigue and depression, which may have a negative impact on appetite.[170, 171] **2- 3**

D

- **Nutritional care for people infected with hepatitis C should involve promotion of optimal nutrition and prevention or treatment of malnutrition or deficiencies of specific nutrients.**
- **Patients should have a nutritional screen and if needed a nutritional assessment and appropriate advice from a dietitian.**

D **Patients with advanced liver disease should be given nutritional support to minimise malnutrition.**

✓ Antiviral therapy represents a high risk period for weight loss so patients should be monitored closely and given nutritional support, as required, during treatment.

A systematic review of 11 RCTs found no conclusive evidence to support any benefit of branched chain amino acids (BCCA) in patients with cirrhosis and hepatic encephalopathy.[214] It was unclear how many of the patients included in the study were HCV positive. BCCA improve serum albumin levels in the compensated stage of cirrhosis in patients with a branch chain tyrosine ratio (BTR) <4 and serum albumin level between 35-39 g/l.[215, 216] The methodology used in these studies gave little consideration to confounding variables. **1++ 1-**

Coffee may have a protective effect against the development of hepatocellular carcinoma in patients with liver disease when consumed in quantities of three or more cups per day. It is unclear which compound in coffee causes the effect.[217, 218] **2+**

12.1.2 VITAMINS AND MINERALS

There is little evidence that individual vitamins and minerals may influence the natural history of CHC.

Zinc supplementation of 34 mg/day may have some beneficial effect on sustained viral response in patients taking IFN therapy; with genotype 1b; with viral load lower than $5x10^5$ copies/ml.[219] **2-**

Vitamin K2 may be beneficial in the prevention of development of HCC in patients with hepatitis C.[220] **2-**

Vitamin E supplementation had no beneficial effect in patients taking pegylated IFN and ribavirin. It does not appear to prevent ribavirin haemolysis or enhance virological clearance.[221] **1-**

Iron restricted to <7 mg/day in conjunction with a controlled calorie intake of 30 kcals/kg, protein intake of 1.1-1.2 g/kg, and fat at 15% of dietary intake, reduces aminotransferase levels.[222] **4**

Vitamin C supplementation of 600 mg/day is not beneficial in the prevention of retinopathy associated with IFN therapy.[191] **1-**

✓ Patients with chronic hepatitis C should be encouraged to achieve the UK recommended nutrient intake of vitamins and minerals.[223] They should be advised that there is no identified evidence to support amounts in excess of this.

✓ Patients whose serum ferritin levels are consistently high should not be advised to reduce dietary iron intake.

12.1.3 OVERWEIGHT

Studies have identified BMI>25 as being associated with hepatic steatosis, which leads to more severe fibrosis.[89, 224] Liver fibrosis, steatosis and ALT level decrease with supervised weight loss programmes of diet and regular exercise, aiming at 0.5 kg weight loss weekly.[225] **2+** **3**

C **Patients who are overweight should be advised to lose weight, within a realistic weight loss target, as this may have a beneficial effect on the degree of liver damage associated with hepatitis C infection.**

✓ Weight loss should only be considered if the patient is stable in their management of hepatitis C. Interventions aimed at weight reduction during antiviral treatment are not recommended, as side effects may lead to excessive unintentional weight loss.

✓ Patients on weight loss programmes should receive regular follow up and support.

12.2 SPECIALIST NURSE INTERVENTIONS

Specialist nursing support is key to maintaining adherence to treatment in patients with psychiatric conditions.[226] Specialist hepatology nursing has a significant role to play in helping patients to attain and maintain SVR.[227] **2-**

✓ Clinical nurse specialists should be an integral member of the clinical team caring for patients with chronic hepatitis C.

12.3 PSYCHOSOCIAL INTERVENTIONS

Two studies on psychological interventions for patients with hepatitis C showed no evidence of benefit. One small non-randomised trial showed some benefit, but the other, an RCT which tested individually tailored interventions, showed no difference in outcome from standard care.[228, 229] **2-** **1+**

12.4 EXERCISE

Light to moderate exercise programmes have been recommended for patients receiving treatment for hepatitis C.[170] A small cohort study found that patients on antiviral therapy have a reduced exercise tolerance.[230] **4** **2-**

D **Patients with hepatitis C should be encouraged to take mild to moderate exercise. Those on antiviral therapy should be advised that they may find their capacity for exercise reduced.**

12.5 COMPLEMENTARY THERAPIES

Two meta-analyses have concluded that there is no evidence to support the use of complementary or alternative medicines in the treatment of patients with hepatitis C.[231, 232] **1++**

None of the trials identified ran for a long enough period to show the long term safety or harm of herbal remedies.

✓ Patients should be made aware that there is a potential for harm associated with some complementary preparations.

12.6 PALLIATIVE CARE

No evidence was identified looking specifically at palliative care for patients with HCV.

13 Provision of information

To find out patients' main information needs, interviews and focus groups were held with patients, and questionnaires sent to people with hepatitis C across the UK by the Scottish Hepatitis C support network and the UK Hepatitis C resource centre. The results have been translated into questions and suggested answers (*see section 13.2*), which could be used to encourage discussions between patients and health professionals. Several of the organisations listed in section 13.1 produce good-quality patient leaflets.

13.1 SOURCES OF FURTHER INFORMATION

British Liver Trust
Portman House
44 High Street
Ringwood BH24 1AG
Tel: 01425 463080 • Fax: 01425 470706
www.britishlivertrust.org.uk

The British Liver Trust provides a range of publications on individual liver conditions and offers support to patients with liver disease and those who care for them.

Haemophilia Scotland
4b Gayfield Lane
Gayfield Place Lane
Edinburgh EH7 4AB
Tel: 0131 557 5953
Email: dan@haemophiliia.org.uk

Haemophilia Scotland provides services for people with haemophilia and von Willebrand's affected by HIV and viral hepatitis.

Hepatitis C Trust
5 Charlotte Square
Edinburgh EH2 4DR
Tel: 0131 777 0989 • Helpline: 0845 223 4424
www.hepctrust.org.uk • Email: helpline@hepctrust.org.uk

The Hepatitis C Trust was set up by people with the illness and runs a range of services that provide support, information and representation for people with hepatitis C.

Hepatitis New South Wales
www.hep.org.au

This Australian website has a wealth of excellent interesting and helpful information and resources on hepatitis, however some resources are specific to Australian healthcare systems.

Hepatitis Scotland
1/91 Mitchell Street
Glasgow G1 3LN

Tel: 0141 225 0419 • Fax: 0141 248 6414
www.hepatitisscotland.org.uk • Email: enquiries@hepatitisscotland.org.uk

Hepatitis Scotland is the national voluntary sector organisation funded by the Scottish Government to help improve responses to viral hepatitis prevention, treatment and support.

13.2 INFORMATION ABOUT HEPATITIS C FOR PATIENTS AND CARERS

WHAT IS HEPATITIS C?

Hepatitis C is an illness caused by a virus which can be passed through blood from one person to another. It mainly affects the liver.

When your liver becomes inflamed it can become damaged and eventually has difficulty carrying out its various and vital functions. Over a long period of time, this can progress to serious liver damage (such as fibrosis and cirrhosis) or, in some people, liver cancer (hepatocellular carcinoma).

HOW DOES IT AFFECT PEOPLE?

Hepatitis C is a potentially life threatening condition that can affect you physically and emotionally. It can affect your quality of life. Treatment is available which can cure hepatitis C in the majority of people.

WHAT ARE THE SYMPTOMS OF HEPATITIS C?

Some people have no symptoms at all for many years while others may feel extreme tiredness, have sweats (especially at night), aches and pains, loss of appetite and concentration problems. Symptoms may come and go. In the later stages of the infection if the liver is more seriously damaged, there may be symptoms such as jaundice, itchiness, internal bleeding and a swollen abdomen.

HAVE I BEEN AT RISK?

Times when blood from someone infected with hepatitis C may get into the bloodstream of another person include:

- having a blood transfusion or surgical treatment abroad or in the UK before 1991, or blood products in the UK before about 1987 (transfusions and blood products are now safe from HCV infection in the UK);
- having medical or dental treatment in countries where hepatitis C is common and infection control may be poor;
- sharing any equipment when injecting or snorting drugs;
- sharing items such as razors, toothbrushes or any item that can scratch the skin;
- piercing, tattooing and cosmetic injection procedures (eg botox) if any equipment is reused;
- sexual activity, although the risk is low except where there is a risk of bleeding;
- being exposed to blood at work, for example, a needlestick injury, cuts, cleaning up blood, and dealing with violent incidents where blood is involved;
- transmission from mother to child around the time of birth.

SHOULD I BE TESTED?

If you think you may have been at risk, then you should get tested. The earlier treatment starts the more likely it is to provide a cure for the infection. If you know you are positive you can avoid infecting others.

WHAT DOES THE TEST TELL YOU ABOUT BEING POSITIVE OR NEGATIVE?

There are three types of test. The first type of test (the HCV antibody test) tells you if you have ever had the virus. Some people get rid of the virus naturally without medical help. The second type (PCR test) tells you if you still have the virus in your body (that is if you are infected with hepatitis C). If the PCR test is positive a further test will reveal the genotype (strain) of virus you have. The genotype will determine the treatment you receive.

WHAT ABOUT CONFIDENTIALITY?

Confidential testing is available in GP surgeries and at other sites. Your test results are confidential and will not be shared with others without your permission. GPs will only pass on information about positive tests to insurance companies if you have applied for insurance and given your consent for release of medical information. Negative tests will not be disclosed.

You can find information on hepatitis services across Scotland by visiting the Hepatitis Scotland website (*see section 13.1*)

ARE MY FAMILY AND FRIENDS AT RISK? SHOULD I TELL THEM?

The support of your family and friends is important and you should consider telling them about your diagnosis and what the effects and side effects of treatment are likely to be. You cannot infect your family and friends through everyday activities, such as sharing utensils, hugging or kissing.

To avoid infecting others,

- do not share items such as toothbrushes or razors
- clean up any blood spills with diluted bleach
- do not share any drug taking equipment (eg tooters, needles and syringes, water or cookers etc).

The risk of sexual transmission is very low in the absence of other complicating factors such as:

- blood from menstruation or anal sex
- ulcers or sores on your genitalia ie from a sexually transmitted infection such as gonorrhea, herpes or genital warts.

HOW WILL IT AFFECT MY JOB AND JOB PROSPECTS?

Many people stay well enough to work but you may have to make some adjustments to your routine if you have extreme tiredness or other symptoms.

You do not usually have to tell your employer that you have hepatitis C (unless you are a healthcare worker involved in procedures that may involve exposure to blood, for example some surgeries. However side effects of treatment may mean that you feel ill and unable to work for a period of time. It may be helpful to tell them that you are having treatment. For example, they may support you by changing your working hours or reducing any physical activities associated with your job during treatment.

HOW WILL A POSITIVE DIAGNOSIS AFFECT MY LIFE INSURANCE COVER?

In common with any serious health condition, a diagnosis of hepatitis C will have an impact when taking out life insurance. There are many types of life insurance cover so it is worth checking any policies you have as you may need to tell the insurer if you have a change in your health status. It is important to remember that any information you provide to your insurer forms part of a legal contract. If the information is inaccurate or untrue the agreement may be invalid.

If you are applying for insurance and consented for release of medical information, the person who tested you is legally obliged to pass on information about a positive test result if asked to by an insurance company.

You should read the small print on current or new insurance agreements before signing.

HOW WILL A NEGATIVE TEST AFFECT MY LIFE INSURANCE COVER?

Doctors do not need to give insurers any information about a negative test. Insurers can only ask for information where someone has had a positive test or is receiving treatment.

WHAT HAPPENS DURING TESTING?

Before you have a test a healthcare professional will discuss with you what happens. This will help you to understand the testing process, the test results and confidentiality.

Blood samples will be sent for laboratory testing. If your exposure to the virus has been in the last six months, you may be asked to return for a repeat test. This is because there is a 'window' period after exposure until the test becomes positive.

If your test is negative, the healthcare team will give you advice on how to avoid putting yourself at risk in the future. If your test is positive, they will explain what this means and refer you to a specialist clinic for assessment.

WHAT HAPPENS NEXT?

Assessment will include blood tests such as liver function tests (LFT), a genotype (strain of hepatitis C virus) test, an examination, discussions about lifestyle, other medical conditions and medicines you take, ultrasound scan, fibroscan and, in rare circumstances, a liver biopsy. A liver biopsy means taking a small piece of the liver for laboratory analysis. This is done under local anaesthetic but is not required before starting treatment.

When the assessment is complete, your healthcare team will talk to you about treatment. Treatment is very effective and side effects can be managed with good care and support. Your clinic should help you to find support as part of your care while on treatment. Treatment is not suitable for everyone and depends on other medical conditions or complications you may have.

While you or your partner are on treatment, and for six to 12 months afterwards, you should both use contraception to avoid pregnancy because these drugs may be harmful to an unborn baby.

LIVING WITH HEPATITIS C

There are a number of things that you can do for yourself that make living with chronic hepatitis C easier.

- Do not drink alcohol. Alcohol and hepatitis C damage the liver, and in combination cause damage at a faster rate. Professional support is available to help you reduce or stop drinking.
- Cut down on rich, fatty and sugary foods as a balanced diet is crucial. Losing excess weight puts less strain on your liver. However, weight loss can be a side effect of treatment and food supplements may be required. Professional help to reach a healthy balanced diet is available.
- If you have a poor appetite, try and eat smaller meals more often.
- Try to exercise regularly. It can reduce stress and depression, increase energy levels and help boost your immune system.
- Follow the dosage instructions for prescribed and over-the-counter medications. Both over-the-counter and illicit drugs are processed by the liver and may put extra strain on it. Illicit drugs may also contain impurities which are harmful.
- Stop smoking if you have hepatitis C. Stopping smoking reduces the risk of getting cancer. Help is available to stop smoking.
- Speak to your GP about vaccinations against hepatitis A and B. Other types of liver infection, especially when you already have hepatitis C, put much more strain on your liver and can slow or stop recovery for all types of hepatitis. You should also make sure you get the seasonal flu vaccination as an extra precaution when your immune system may be weakened.

There is very little evidence that complementary medicines are effective, but many patients find them helpful in dealing with the many different symptoms associated with this disease. It is important to get professional advice before starting these.

WHAT SUPPORT CAN I GET?

There are various specialist support services for people with hepatitis C, such as counselling, peer support from other people with hepatitis C, and support to help with making decisions.

Hepatitis C can make people feel very isolated and emotional support is important. You should expect:

- comprehensive team services providing good communication;
- good quality information;
- involvement at all stages of your care and treatment;
- access to specialist services as you require them, and
- regular assessment of your support needs.

14 Implementing the guideline

14.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

14.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations were identified as having significant budgetary impact.

14.3 AUDITING CURRENT PRACTICE

There are two mechanisms for auditing practice around the testing, treatment care and support provided by hepatitis C services in Scotland. The first is the Healthcare Improvement Scotland Hepatitis C Quality Indicators which are self audited by health boards. The second is the performance indicators contained within the Blood Borne Virus and Sexual Health framework which are audited nationally by the Scottish Government.

14.4 ADDITIONAL ADVICE TO NHS SCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

In September 2011, the Scottish Medicines Consortium (SMC) advised that boceprevir was accepted for use within NHSScotland for the treatment of CHC genotype 1 infection, in combination with pegylated IFN and ribavirin, in adult patients with compensated liver disease who have failed previous therapy or who have been previously untreated.

In September 2011, the Scottish Medicines Consortium (SMC) advised that telaprevir in combination with pegylated IFN and ribavirin, is indicated for the treatment of genotype 1 CHC in adult patients with compensated liver disease (including cirrhosis) who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders or patients who are treatment naive.

15 The evidence base

15.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2006-2012. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by one member of the group and one SIGN staff member using standard SIGN methodological checklists before conclusions were considered as evidence.

15.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to early management of patients with hepatitis C. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised and presented to the guideline development group.

15.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (*see Annex 1*). The following areas for further research have been identified:

- management of hepatitis C in children
- treatment in active drug users
- care pathways for the management of hepatitis C (older patients, prisoners, transplant patients, decompensated cirrhotic patients)
- testing and screening approaches.

15.3 REVIEW AND UPDATING

This guideline was issued in 2013 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

16 Development of the guideline

16.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in SIGN 50: A Guideline Developer's Handbook, available at **www.sign.ac.uk**

16.2 THE GUIDELINE DEVELOPMENT GROUP

Dr John Dillon *(Chair)*	*Consultant Hepatologist and Gastroenterologist, Ninewells Hospital, Dundee*
Dr Andrew Bathgate	*Consultant Hepatologist, Royal Infirmary of Edinburgh*
Dr Pete Bramley	*Consultant Gastroenterologist, Stirling Royal Infirmary*
Ms Katherine Davidson	*Senior Pharmacist (Liver Transplant), Royal Infirmary of Edinburgh*
Ms Pauline Dundas	*Nurse Specialist, Summerfield House, Aberdeen*
Dr Ray Fox	*Consultant Physician, Brownlee Centre, Gartnavel General Hospital, Glasgow*
Dr Andrew Fraser	*Consultant Physician in Gastroenterology, Summerfield House, Aberdeen*
Dr Rosie Hague	*Consultant in Paediatric Infectious Diseases and Immunology, Royal Hospital for Sick Children, Glasgow*
Mr Stephen Heller-Murphy	*Programme Manager/Health Services Researcher, SIGN, Healthcare Improvement Scotland*
Ms Fiona Marra	*Advanced Pharmacist HIV/HCV, Brownlee Centre, Gartnavel General Hospital, Glasgow*
Ms Kim McBeth	*Clinical Nurse Practitioner (Gastroenterology), Royal Infirmary of Edinburgh*
Mr Tom McEwan	*Specialist Clinical Pharmacist, Ninewells Hospital, Dundee*
Ms Pauline Morrison	*Specialist Pharmacist, Stirling Royal Infirmary*
Ms Joy Nicholson	*Pharmacist, Medicines Strategy, Healthcare Improvement Scotland*
Mr Walter Speirs	*Patient Representative*
Ms Jan Tait	*Clinical Nurse Specialist, Ninewells Hospital, Dundee*
Ms Petra Wright	*Scottish Officer, Hepatitis C Trust, Edinburgh*
Mr Leon Wylie	*Director, Hepatitis Scotland, Glasgow*
Dr David Yirrell	*Consultant Clinical Scientist (Virology), Ninewells Hospital, Dundee*

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive.

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interest and further details of these are available on request.

Mrs Karen Graham	*Patient Involvement Officer*
Mr Stuart Neville	*Publications Designer*
Miss Gaynor Rattray	*Guideline Coordinator*
Mr Campbell Reynolds	*Distribution and Office Coordinator*

16.2.1 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the development of SIGN 92: Management of hepatitis C, on which this guideline is based.

16.3 CONSULTATION AND PEER REVIEW

16.3.1 SPECIALIST REVIEWERS INVITED TO COMMENT ON THIS DRAFT

This guideline was reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Stephen Barclay	*Consultant Gastroenterologist, Glasgow Royal Infirmary*
Dr David Bell	*Consultant in Infectious Diseases, Brownlee Centre, Gartnavel General Hospital, Glasgow*
Mr. Charles Gore	*Director of the Hep C Trust*
Dr Magdalena Harris	*Lecturer, London School of Hygiene and Tropical Medicine*
Dr Carole Hunter	*Lead Pharmacist, Addiction Services, NHS Greater Glasgow and Clyde*
Professor William Irving	*Professor and Honorary Consultant in Virology, University of Nottingham and Nottingham University Hospitals NHS Trust.*
Dr Janice Main	*Reader and Consultant Physician in Infectious Diseases and General Medicine, Imperial College at St Mary's Hospital, London*
Dr Claire McIntosh	*Consultant Addiction Psychiatrist, Community Alcohol and Drug Service, Falkirk Community Hospital*
Dr Ewan Stewart	*Clinical Lead, Lothian Hepatitis MCN, NHS Lothian*

16.3.2 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of the SIGN Editorial group make yearly declarations of interest and further details of these are available on request from the SIGN Executive.

Professor Keith Brown	*Chair of SIGN; Co-Editor*
Dr Roberta James	*SIGN Programme Lead; Co-Editor*
Dr Sara Twaddle	*Director of SIGN; Co-Editor*

Abbreviations

ALT	alanine aminotransferase
BBV	blood borne virus
BCCA	branched chain amino acids
BMI	body mass index
BNF	British National Formulary
BTR	branch chain tyrosine ratio
CHC	chronic hepatitis C
CI	confidence interval
CYP	cytochrome P450
DDI	drug-drug interaction
DRESS	Drug Reaction (or rash) with Eosinophilia and Systemic Symptoms
ELISA	enzyme linked immunosorbent assay
EPP	exposure prone procedures
EPO	erythropoietin
EVR	early viral response
G-CSF	granulocyte-colony stimulating factor
GMC	General Medical Council
GUM	genitourinary medicine
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIC	hepatic iron concentration
HIV	human immunodeficiency virus
IDU	injecting drug users
IFN	interferon
IU	international units
LFT	liver function tests
MA	marketing authorisation
MTA	medical technology assessment
NAT	nucleic acid test
NICE	National Institute for Health and Care Excellence
OLT	orthotopic liver transplantation
PCR	polymerase chain reaction
PNALT	persistently normal serum alanine aminotransferase
QOL	quality of life
RCT	randomised controlled trial

RNA	ribonucleic acid
RR	relative risk
RT PCR	reverse transcriptase polymerase chain reaction
RVR	rapid viral response
SCAR	Severe Cutaneous Adverse Reaction to Drugs
SEM	standard error of the mean
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SVR	sustained viral response
UK	United Kingdom
UNOS	United Network for Organ Sharing

Annex 1

Key questions addressed in this update

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search strategy (*see section 15.1)*.

Key question
1. What is the evidence for treating patients with acute hepatitis C in terms of: • viral genotype • optimal timing of treatment • duration of treatment • choice of therapy – interferon versus pegylated interferon versus. pegylated interferon + ribavirin Outcome: sustained viral response/symptoms/Quality of Life (QOL)/adverse effects.
2. What is the evidence for the benefit of antiviral therapy (pegylated interferon + ribavirin) in patients with chronic hepatitis C in terms of: • viral genotype • duration of therapy • early viral response • viral kinetics Outcome: sustained viral response/symptoms/QOL/adverse effects How effective is treatment in the following subgroups? Consider: a) Age/age of acquisition b) Gender c) Different ethnic groups (South East Asian, Indian, Pakistani, Bangladeshi, Caucasian) d) Severity of disease – mild disease/cirrhosis e) Normal serum transaminases f) HIV co-infection g) Hepatitis B co-infection h) Obesity i) Smoking j) Alcohol intake above recommended guidelines k) Iron overload l) Viral genotype m) Active drug addiction or use n) Oral methadone/buprenorphine o) Patients with extrahepatic disease – fatigue, arthralgia, cryoglobulinaemia, glomerulonephritis, sicca syndrome, porphyria cutanea tarda, lichen planus, B cell non-Hodgkin lymphoma p) Non-response/relapse after previous interferon monotherapy or interferon/ribavirin combination therapy

3. What is the evidence that standard antiviral treatment is best avoided in the following subgroups (absolute and relative contraindications)?

   Consider:

   a) Pregnancy, breast feeding, inability to use effective contraception

   b) Chronic renal failure

   c) Age

   d) Alcohol intake above recommended guidelines

   e) Active drug addiction and use
      - ongoing injecting drug use
      - ongoing drug use (non-injecting)
      - substitute prescribing

   f) Mental health problems – depression, psychosis, learning disability

   g) Epilepsy or history of seizures

   h) Neoplasia

   i) Congestive cardiac failure/respiratory failure

   j) Psoriasis

   k) Haemolytic anaemia

   l) Anaemia, leucopenia, thrombocytopaenia

   m) Retinopathy – diabetic, hypertensive

   n) Obesity – body mass index ≥ 30

   o) Organ transplantation – liver, renal, bone marrow

   p) Autoimmune conditions – autoimmune hepatitis, hyperthyroidism

   q) Normal serum transaminases

   r) Mild chronic hepatitis C

   s) Relapse/non-response after previous antiviral therapy

   t) Hypersensitivity to interferon or ribavirin

   u) Other medications – immunosuppressants, myelosuppressants, theophylline, nucleoside reverse transcriptase inhibitors.

4. For patients who relapse following treatment or who are non-responders to standard antiviral treatment what evidence is there for additional drug therapies?

Consider:

Amantadine, thymosin, histamine, long term interferon treatment.

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Edinburgh Office | Gyle Square |1 South Gyle Crescent | Edinburgh | EH12 9EB
Telephone 0131 623 4300 Fax 0131 623 4299

Glasgow Office | Delta House | 50 West Nile Street | Glasgow | G1 2NP
Telephone 0141 225 6999 Fax 0141 248 3776

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