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Assessment and management of chronic hepatitis C infection

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Clin Med JRCPL 2002;**2**:302–6

Hepatitis C infection

It is estimated that 0.5–1% of the UK population is infected with hepatitis C virus (HCV) and 170 million people worldwide. The commonest route of infection in the UK is injecting drug use, although there are still a significant number of people whose infection was contracted from infected blood products prior to the introduction of HCV screening in 1991. The virus is parenterally transmitted, so other risk factors include:

- vertical transmission during childbirth
- transmission during medical procedures
- tattooing
- body piercing, and
- sexual transmission[1].

Key Points

- **Hepatitis C is parenterally transmitted**
- **Hepatitis C virus (HCV) leads to chronic infection in 85% of those exposed**
- **Chronic hepatitis C causes progressive liver damage**
- **Liver damage is silent in the majority**
- **Liver biopsy is the most accurate way to assess severity of liver damage**
- **Antiviral treatment is recommended in most patients with progressive liver disease**
- **Antiviral treatment achieves viral clearance in 30-56% (depending on regimen)**
- **HCV genotypes 1 and 4 are more resistant to antiviral therapy than genotypes 2 and 3**

KEY WORDS: chronic hepatitis, hepatitis C virus, interferon, PEGylated interferon, ribavirin, viral hepatitis

Acute hepatitis C infection

In the vast majority of cases acute HCV infection is asymptomatic, leading to flu-like symptoms in some subjects and clinical jaundice in less than 20%. Acute hepatitis C is rarely diagnosed, but if encountered should be treated promptly, as recent evidence has shown sustained viral clearance rates in excess of 90%[2].

Chronic hepatitis C infection

Chronic infection is established in about 85% of those exposed and is often silent, which probably leads to underestimation of its prevalence. Common routes to diagnosis are:

- routine screening by the blood transfusion service
- direct request for testing from the patient
- incidental discovery of abnormal liver function tests during investigation of unrelated symptoms.

Chronic hepatitis C (CHC) infection is characterised by an immune-mediated hepatitis associated with progressive fibrosis. It is the severity and rate of progression of this fibrosis that dictates the mortality and morbidity associated with CHC. About one-third of patients have an indolent course to their disease lasting at least 30 years before significant fibrosis develops, but most of them will progress to significant liver fibrosis or cirrhosis within 20 years of infection[3].

The National Institute for Clinical Excellence (NICE) has recently issued guidance on the treatment of CHC[4]. These recommendations are consistent with guidelines from the European Association for the Study of the Liver[5] and the British Society of Gastroenterology[6]. Funding should now become more widely available for antiviral treatment in CHC. This article suggests a plan for the assessment and management of patients with HCV infection within the current healthcare climate.

Initial assessment of patients with chronic hepatitis C infection

When assessing a patient with CHC it is important to try to identify the duration of infection; this will give an indication of the rate of progression of the resultant liver disease.

History

A careful history obtained by an experienced practitioner (eg clinical nurse specialist) will usually reveal a likely risk factor. The history should assess symptoms attributable to CHC infection such as lethargy, malaise, abdominal and joint pains, in addition to symptoms of severe liver disease (eg encephalopathy, bruising, ascites). It is important to establish whether there is an ongoing risk factor for parenteral infections and/or any behaviour that would exacerbate the liver damage associated with CHC (eg excess alcohol consumption).

Concomitant disorders that might influence the course of disease or suitability for treatment should be sought at the time of initial assessment. These include a history of cardiovascular disease, autoimmune disorders and psychiatric illness (Table1).

Examination and investigations

Examination of patients with CHC should be directed at assessing their general health and identifying any stigmata of chronic liver disease.

Laboratory tests. Following clinical assessment, the diagnosis of HCV infection should be confirmed (Table 2). If the patient is polymerase chain reaction (PCR) negative, the antibody status should be confirmed by recombinant immunoblot assay; if antibody positive and PCR negative on repeat testing, reassurance should be given that HCV has previously been cleared and there is no long-term risk of HCV related liver damage unless re-infected. **It is, however, important to stress that they are not immune to future HCV infection.**

Most patients who are antibody positive will also be PCR positive. The further tests required to assess the severity of any associated liver damage are shown in Table 2. If CHC coexists with another liver disease, the pathologies can be synergistic. It is therefore usual to screen CHC patients for other common causes of liver disease. If there is evidence of cirrhosis, the patient should be regularly screened for primary hepatocellular carcinoma (HCC) as the risk is 3–5% per annum.

Liver biopsy. Liver biopsy plays an important role in the assessment of CHC infection. It is the only accurate way to assess the severity of liver damage attributable to HCV and also allows identification of any coexistent liver pathology. If liver biopsy is not contraindicated, it should be offered to all patients who would be considered candidates for antiviral therapy. The large multicentre randomised control treatment trials have included patients with moderate to severe liver damage, and the evidence base for treatment and response rates to therapy are based on this subgroup[7–9]. Patients in whom liver biopsy is contraindicated (eg haemophiliacs) must be assessed on clinical grounds alone.

Management of patients with chronic hepatitis C infection

Many hepatitis C patients are well informed and have expectations of how their disease should be managed, although some of the information available to the public on the worldwide web is inaccurate and misleading. Support and education are central to the management of these patients. For all patients attending a hepatitis C clinic, there should be a good source of accurate educational material available, such as leaflets from the British Liver Trust and trusted local support groups. The management of the patients should be multidisciplinary, with input from clinical nurse specialists, counsellors and addiction management experts when appropriate.

Harm reduction is necessary in all patients. This includes removal of risk factors for further infection and reduction of risk of transmission to their families, contacts and carers. In addition, any factor that could exacerbate the liver

Table 1. Possible contraindications to antiviral therapy in chronic hepatitis C infection (in order of significance).

Serious	Minor
History of serious mental illness (hospitalisation, suicide attempt, drug treatment)	Past history of depression
Autoimmune disease	Mild liver damage on biopsy
Decompensated cirrhosis	Compensated cirrhosis
Unstable ischaemic heart disease	Stable ischaemic heart disease
Uncontrolled hypertension	Raised blood pressure
Chaotic drug use or alcohol abuse	Continuing stable drug use
Serious respiratory disease	Excess alcohol consumption
Proliferative diabetic retinopathy	Poorly controlled diabetes mellitus
Ribavirin sensitivity	Age >70 years
Co-infection with HIV or HBV	Thrombocytopenia or neutropenia

HBV = hepatitis B virus.

Table 2. Tests used for the assessment of patients with chronic hepatitis C infection.

	Purpose of test	Nature of test
Initial tests	Anti-HCV antibodies	3rd generation ELISA
	HCV RNA	PCR
	General health	Full history and examination TFTs Chest X-ray and ECG
Further tests	Screening for other liver diseases	HBV serology HAV immunoglobulins HIV status (if appropriate) Anti-nuclear antibodies Anti-smooth muscle antibodies Anti-mitochondrial antibodies Ferritin (followed by Fe and TIBC if raised) β1-antitrypsin level Liver ultrasound
	Assessment of liver function	Prothrombin time ALT ALP Albumin Bilirubin
	Screening for HCC in cirrhosis	β-fetoprotein Liver ultrasound

ALP = alkaline phosphatase; ALT= alanine aminotransferase; ELISA = enzyme-linked immunosorbent assay; Fe = iron; HAV = hepatitis A virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; PCR = polymerase chain reaction; TFT = thyroid function test; TIBC = total iron binding capacity.

damage in CHC should be removed or minimised (ie venesection in iron overload, abstinence from alcohol).

Every patient should be considered for antiviral treatment if they wish and assessed for the presence of contra-indications, the majority of which are relative and should be appraised individually and regularly in each patient (Table 1).

Patients with mild liver disease may be considered for entry into clinical trials such as the NHS Health Technologies Assessment study which is examining response rates to combination therapy in mild liver disease. Otherwise, six-monthly or annual assessment is appropriate, allowing continuing education, support and re-appraisal. Re-biopsy may be useful 2–5 years after the initial biopsy to assess the rate of progression of the liver damage, but this is not essential.

Patients with decompensated cirrhosis should be seen more frequently in the clinic, as clinically indicated. It may be appropriate to screen them for HCC at 6-monthly intervals with liver ultrasound scan and serum alpha-fetoprotein[6]. A patient who is considered to be a possible candidate for liver transplantation should be referred to a transplant centre for assessment.

Antiviral therapy

The established current treatment for CHC is the combination of interferon (IFN) β and ribavirin[10,11]. NICE has recommended the use of this combination for the treatment of moderate to severe CHC liver damage in adults who:

- have not previously been treated with combination therapy or
- have previously responded to IFNβ monotherapy but have since relapsed.

Table 3. Common side effects of combination therapy in chronic hepatitis C infection.

Side effect	Frequency (%)	Comments	Management
Flu-like symptoms	70	Tolerance may develop over time	Paracetamol prn
GI symptoms	25	Often transient	Reassurance/symptomatic
Depression	32–36	May not be recognised by patient Need for continuity of care	SSRI or suitable antidepressant
Breathlessness	19	More common in smokers – check PFTs with transfer factor to exclude pulmonary fibrosis (very rare) or infiltrates	May require reduction in ribavirin dose if no evidence of lung damage, or IFN withdrawal
Cough	15	Dry cough	Reassure
Pharyngitis	10–20	Often transient	Reassure
Alopecia	30	Usually just general thinning	Reassure
Thyroid dysfunction	<5	May be hyper- or hypothyroidism, often transient	Manage as appropriate and consider IFN withdrawal
Pruritus	20	Often transient	Emollient cream
Rash	20–28	May require cessation of ribavirin	Emollients and occasionally topical steroid

GI = gastrointestinal; IFN = interferon; PFT = pulmonary function test; prn = as required; SSRI = selective serotonin reuptake inhibitor.

Table 4. Monitoring schedule for patients on combination therapy for hepatitis C virus (HCV) infection. (Visits represented in italics are relevant only for patients with genotypes 1 or 4 who are HCV RNA negative at 24 weeks. Treatment is stopped at 24 weeks in all other cases).

Week of therapy	Tests	Action
0	HCV genotype (and viral load if available), FBC, urea and electrolytes, LFTs, TFTs, BP, fundoscopy, urinalysis, chest X-ray, ECG, pregnancy test (if appropriate)	
1,2,4,6,8	FBC, LFTs, pregnancy test (if appropriate)	If Hb falls by >2 g/dl or there is a large rise in bilirubin, reduce ribavirin to 600 mg daily If platelets <75 or neutrophils <1.0, reduce IFN by 50% Both drugs may require transient withdrawal
12,*36*	FBC, LFTs, TFTs, pregnancy test (if appropriate)	
16,20,*28,32,40,44*	FBC, LFTs, pregnancy test (if appropriate)	
24, *48*	FBC, LFTs, TFTs, HCV PCR, pregnancy test (if appropriate)	

BP = blood pressure; FBC = full blood count; Hb = haemoglobin; IFN = interferon; LFT = liver function test; PCR = polymerase chain reaction; TFT = thyroid function test.

In patients who have a contraindication to ribavirin, polyethylene glycolylated (PEG) IFN is licensed for use as monotherapy, although this indication has not yet been considered by NICE. The efficacy of combination treatment is around 40% sustained virological response in all-comers. HCV exists as six different genotypes or strains, and subgroup analyses have shown that genotypes 2 and 3 are more sensitive to treatment[10,11]. PEGylated IFN monotherapy achieves sustained virological response rates of around 30%, again with genotypes 2 and 3 more responsive to therapy[12]. PEGylated IFNs in combination with ribavirin have achieved sustained viral response rates of over 55%, with subgroups ranging from 25–85% or higher[13]. In addition to their enhanced efficacy, the need for administration only once weekly represents a significant benefit over standard IFN. Undoubtedly, regimens incorporating PEGylated IFNs will become established as the preferred choice of antiviral therapy.

There are considerable side effects from these drugs, of which the patients must be fully informed before embarking on a course of treatment (Table 3).

Patients who fulfil the criteria for treatment and wish to proceed must have agreement from their local health authority to fund their treatment. The intention is to treat patients with genotype 1 or 4 for 48 weeks and all other genotypes for 24 weeks. In genotypes 1 and 4, if the PCR remains positive at 24 weeks of therapy, treatment is usually withdrawn as the chances of successful sustained virological response are negligible. (PCR negative at 24 weeks = sustained virological response.)

If there is no contraindication to therapy, the patient should be weighed to determine the required ribavirin dose (1,000 mg daily if <75 kg, 1,200 mg if >75 kg). It is important to inform the patient that ribavirin is teratogenic in expectant mothers and paternal sperm, and that two reliable forms of contraception should be used for the duration of treatment and the follow-up period. The initial dose of standard IFNβ is three million units thrice weekly subcutaneously. (It is important to note that the dose of PEGylated IFN may also be subject to weight-based adjustments.)

The patient should be taught to self-administer IFN and should be monitored closely whilst on treatment. A typical monitoring schedule is shown in Table 4. If blood tests or symptoms reveal problems, more frequent visits may be indicated.

Follow-up

After the end of treatment, the patient is seen at weeks 4 and 12 to ensure resolution of symptoms and side effects from therapy. If the patient was HCV PCR negative at the end of treatment, the PCR is repeated 24 weeks after treatment to assess whether there has been a sustained virological response.

Patients who are PCR positive at the end of treatment or 24 weeks later are classified as non-responders or relapsed responders. They should be followed in the clinic with regular reassessment of their liver disease, and may be offered further therapy if appropriate.

If there has been a sustained virological response, it is usual to follow the patient for at least a year after cessation of therapy and to confirm HCV negativity with further PCR tests and possibly a liver biopsy to assess histological change. It remains important to encourage these patients to avoid the risk of re-infection and to maintain a healthy lifestyle with low alcohol intake.

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Assessment and management of chronic hepatitis B

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Clin Med JRCPL 2002;**2**:306–10

Hepatitis B virus (HBV) infection is one of the most common viral infections in humans. It is estimated that more than two billion people worldwide have been exposed to the virus. Approximately 350 million people are chronic carriers of HBV[1,2], of whom 15–40% will develop serious liver complications during their lifetime[3]. Chronic HBV infection remains a leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). The distribution of patients with hepatitis B varies greatly throughout the world. It is thought to be uncommon in the UK, but the real prevalence of chronic hepatitis B surface antigen (HBsAg) carriers in the general population or amongst patients with chronic liver diseases is not known because only cases of acute hepatitis B infections are reported. Importantly, it is a preventable disease for which a safe and effective vaccine has been available for nearly 20 years.

Definitions and terminology in hepatitis B virus infection

Chronic infection with HBV is defined as persistence of HBsAg in a patient's serum for more than six months[4]. These patients, colloquially referred to as 'chronic HBsAg carriers', represent a heterogeneous group. Their precise characterisation includes three components:

1 *Virological:* detection of hepatitis B e antigen (HBeAg) or antibody to HBeAg (anti-HBe) in serum. The level of HBV replication is determined by quantification of serum HBV DNA.

2 *Biochemical:* serum alanine aminotransferase (ALT) levels.

3 *Liver histology:* assessment of the grade of hepatic inflammation and the stage of fibrosis (Table 1).

Table 1. Standardisation of terminology in chronic hepatitis B virus (HBV) infection (based on ref 4).

Terms	Diagnostic criteria
Chronic hepatitis B	1 Serum HBsAg positivity longer than 6 months 2 Persistent or intermittent elevation of ALT/AST levels 3 Serum HBV DNA >10^5 copies/ml 4 Liver biopsy with a necroinflammatory score O 4
Inactive HBsAg carrier	1 Serum HBsAg positivity longer than 6 months 2 HBeAg(-); anti-HBe(+) 3 Serum HBV DNA <10^5 copies/ml 4 Persistently normal serum ALT/AST levels 5 Liver biopsy* showing absence of significant inflammation (necroinflammatory score <4)
Resolved hepatitis B	1 Serum HBsAg(-); anti-HBc(+) 2 Normal serum ALT levels 3 History of known acute or chronic hepatitis B 4 Undetectable serum HBV DNA (hybridisation assays)**

* In these circumstances liver biopsy is optional.
** HBV DNA may be detectable using sensitive polymerase chain reaction assays.

ALT = alanine aminotransferase; anti-HBe = antibody to hepatitis B e antigen (HBeAg); anti-HBc = antibody to hepatitis B core antigen; AST = aspartate aminotransferase; HBsAg = hepatitis B surface antigen.