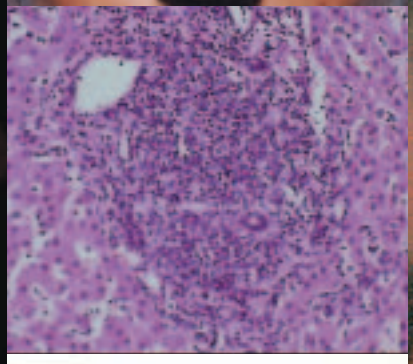
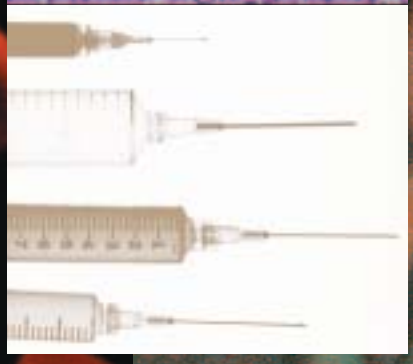
AUSTRALIAN
Family Physician

Hepatitis C

AN UPDATE





Hepatitis C and general practice: the challenge continues

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Why is hepatitis C so important in general practice? This serious chronic infection is now believed to affect over 200 000 Australians, including patients in your practice.

In 1999, The Royal Australian College of General Practitioners developed a then groundbreaking supplement on the primary care management of hepatitis C virus (HCV) infection – *Hepatitis C: A management guide for general practitioners* published by *Australian Family Physician*.

Due to ongoing demand, this issue of *AFP* presents eight updated chapters from the original guidelines and provides the opportunity to revisit hepatitis C four years on. The full version of the guidelines (including the updated chapters) is available from our website: http://www.racgp.org.au.

In an original editorial[1] in 1998, I stated that hepatitis C had become the new challenge for general practitioners in the 1990s. In 2003, hepatitis C remains an important challenge. While the pattern of the disease is changing, there is no evidence that any of the previously identified challenges have waned and there are now around 20 000 new cases of hepatitis C notified in Australia each year.[2]

Most GPs are now more familiar with hepatitis C management through ongoing contact with their own patients and many are now well experienced in the counselling issues facing these patients. We are also able to better understand the long term physical and psychological aspects of hepatitis C including chronic liver damage, reproductive issues, depression and anxiety. Our patients affected by hepatitis C continue to be a diverse group, including people from often marginalised groups such as injecting drug users, people from non-English speaking backgrounds, indigenous Australians and recipients of blood products. Hepatitis C remains a chronic, continuing condition well suited for initial diagnosis, management and ongoing monitoring in the general practice setting.

Significant numbers of our patients will develop long term complications of chronic hepatitis C including cirrhosis and hepatocellular carcinoma.[3] As GPs, we need to be aware of which patients will benefit most from advances in antiviral therapy and the best time to refer these patients.[4]

Testing with HCV PCR now attracts a Medicare rebate, and through a pilot training program by the Australasian Society for HIV Medicine, some New South Wales GPs are now prescribing interferon and ribavirin. General practitioners in other states may soon follow.

As GPs, we remain the health care workers still most likely to see cases of acute HCV infection. Around 80% of cases of hepatitis C have occurred through injecting drug use, and while the percentage of cases in other groups is smaller, the number of recorded cases in Australia (now over 180 000[2]) makes this number highly significant. While patient education for the prevention of HCV transmission has always been a large part of GP management of hepatitis C, the increasing numbers of people diagnosed, combined with the shift toward increasing management in the primary care setting, places an even larger public health responsibility upon us.

Australian GPs are responding to the needs of our patients, but we need access to up-to-date resources tailored to our specific clinical needs in the face of a still changing epidemic. It is in this spirit of commitment to quality care that our colleagues have authored the *AFP Hepatitis C update* for primary care management.

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Epidemiology of hepatitis C virus infection in Australia

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Australian HCV notifications: 1990–2001

From 1990 HCV infection became a notifiable disease in all Australian state and territory health jurisdictions, with notifications rising rapidly to reach a level of approximately 20 000 new diagnoses by 1994 (*Figure 1*). Since 1994, this level of newly reported HCV diagnoses has been maintained, with cumulative notifications over the period 1990–2001 above 180 000.[1] The vast majority of notifications have been 'unspecified' (prevalent) HCV cases, with 'incident' (newly acquired) HCV cases (anti-HCV antibody positive following a negative test within the previous 12 months, or acute clinical hepatitis with positive anti-HCV antibody and other causes of acute hepatitis excluded) constituting between 154 and 587 cases per year over the period 1997–2001.[1] The generally asymptomatic nature of newly acquired HCV infection, irregular HCV testing of many people at increased HCV risk, and the resource intensive nature of enhanced HCV surveillance are explanations for the relatively low number of reported newly acquired HCV cases.

The highest rate of HCV notifications is among young adults (20–39 years) and males (65%), with relatively low rates among children and the elderly.[1] HCV notifications in younger age groups have a higher proportion of females, particularly newly acquired HCV cases (*Figure 2*).[1]

Australian HCV transmission

Studies based on HCV notification data from 1993–1994,[2,3] and a 1995 survey of antenatal women[4] suggested that around 80% of all HCV infections in Australia had occurred through injecting drug use. Transfusion of blood products before 1990 was reported in 5–10% of HCV cases in these studies, although a higher figure was seen in early blood donor[5] and liver clinic series.[6] Other and 'sporadic' (unknown) modes of HCV transmission were reported in 10–15% of HCV cases notified,[2,3] but higher in blood donor[5] and liver clinic series. A large proportion of 'sporadic' cases are among people born in countries of relatively high HCV prevalence, such as Egypt and Vietnam.[6]

The virtual elimination of blood transfusion acquired HCV infection since the introduction of screening in 1990, and continuing high HCV incidence among injecting drug users (IDUs)[7] suggested that the proportion of IDU related parenteral HCV transmission would increase further. A recent analysis of newly acquired HCV cases in Australia over the period 1997–2000 in which approximately 90% were associated with a recent history of injecting drug use,[8] supports this.

Tattooing and body piercing are generally considered risk factors for parenteral HCV transmission[9] – more so when multiple and performed outside recognised parlours – but only tattooing has been epidemiologically linked to HCV infection in Australia.[5] Occupational needlestick exposure is a further recognised mode of parenteral HCV transmission.[10] However, its contribution to overall HCV transmission in Australia is likely to be small and HCV prevalence among health care workers approximates the estimated population prevalence.[11]

Currently, no proven intervention for mother-to-child HCV transmission is available. In Australia there are approximately 250 000 annual births,[12] and an estimated 1% of antenatal women are anti-HCV antibody positive.[4] Based on an estimated 50% HCV viraemia (HCV-RNA positive) among anti-HCV antibody positive antenatal women and a 6% mother-to-child HCV transmission from viraemic mothers,[13] approximately 75 children will be born with HCV infection each year in Australia.

The contribution of sexual transmission to overall levels of HCV infection remains controversial.[14,15] In the United States, the Center for Disease Control and Prevention (CDC) estimate that 20–25% of HCV transmission is associated with sexual contact.[16] In contrast, Australian stud-

ies that have included a detailed HCV risk factor assessment indicate that less than 2% of HCV infection is associated with sexual contact.[3,17] The proposed explanation for this contrasting picture is greater under reporting of injecting drug use in the USA compared to Australia, rather than different HCV transmission dynamics.[9]

Population groups with high HCV prevalence

There are several population groups in Australia who have clearly been demonstrated to be at higher risk of HCV infection.

People who inject illicit drugs

Australian studies indicate that the proportion of IDUs with HCV infection has been in the range 50–80% since the early 1970s.[7,18-23] Factors associated with HCV infection among IDUs include:

- older age
- longer duration of injecting
- imprisonment, and
- frequent sharing of injecting equipment.[18,22]

Based on cross sectional surveys (with dried blood spot HIV and HCV testing) in a network of needle and syringe program (NSP) sites throughout Australia, HCV prevalence among IDUs declined during the mid 1990s (63% in 1995, 51% in 1996, and 50% in 1997).[20] Furthermore, HCV prevalence among IDUs with less than three years duration of injecting declined from 22% in 1995 to 13% in 1997.[20] However, there is considerable evidence for ongoing and possibly increasing HCV risk among IDUs. Hepatitis C prevalence among IDUs with a duration of injecting less than three years in the NSP survey has increased from 13% in 1997 to 28% in 2001, with prevalence in female IDUs higher than male IDUs.[1] In addition to recent increases in HCV prevalence, the prevalence of injecting drug use has increased during the 1990s.[24] In the period 1988–1997, estimated dependent heroin injectors more than doubled, from approximately 33 000 to 70 000.[24]

People in prison

The prevalence of HCV infection in prison populations in Australia is extremely high. The explanation is almost certainly high levels of injecting drug use, but blood-to-blood contact in tattooing and physical and sexual assaults may play a role.[25] Studies in Melbourne[26] and Sydney[27] showed HCV prevalence among prisoners of 37–39%, with an increase to approximately 65% among prisoners reporting a history of injecting drug use.

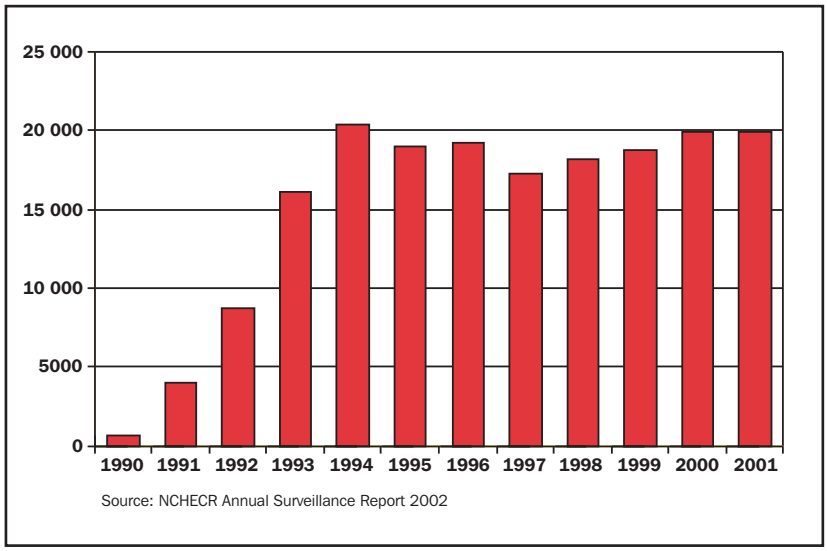

Figure 1. Hepatitis C notifications in Australia, 1990–2001

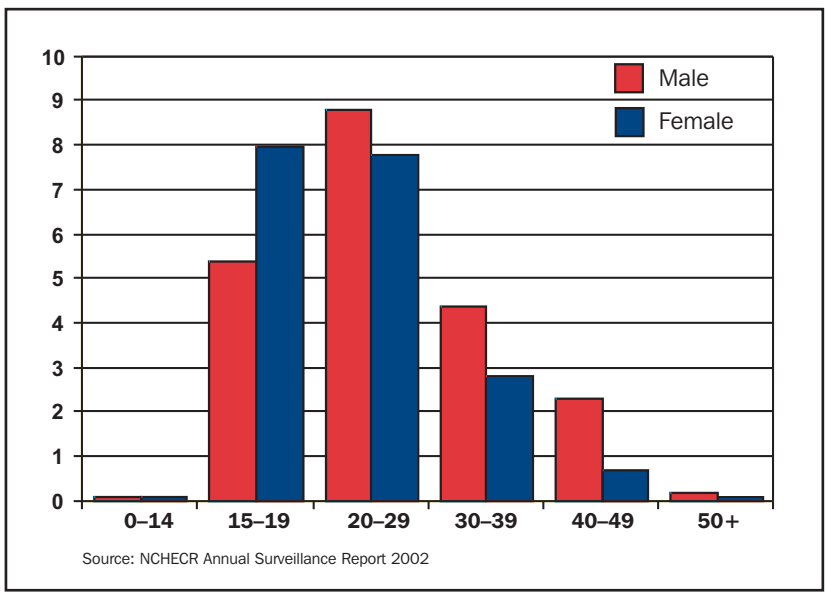

Figure 2. Rate per 100 000 of newly acquired hepatitis C, 2000

People who received blood products before HCV screening

People with a history of transfusion of blood products before the introduction of HCV screening in February 1990 were at risk of acquiring HCV infection. This risk was highest for those people (eg. male haemophiliacs) who received blood product transfusions from multiple donors. In 1990, an HCV prevalence of approximately 75% was reported among people with haemophilia in Melbourne.[28]

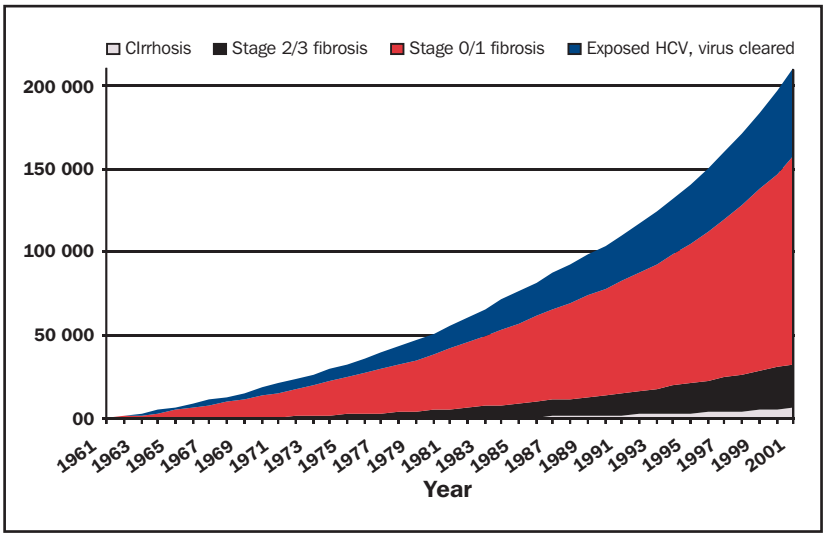

Figure 3. Estimates of hepatitis C epidemic in Australia

Since 1990, the risk of HCV related post-transfusion hepatitis has fallen dramatically. A recent study in Melbourne estimated the risk to be approximately one case per 250 000 donations.[29]

People born in high prevalence countries

Broadly, regions of high HCV prevalence (>1.0%) include Asia, the Middle East, southern and eastern Europe, and parts of South America and Africa.[30]

In these regions, a large component of HCV transmission has probably occurred through non-sterile medical, dental and other health care and traditional procedures that have involved blood-to-blood contact. In Egypt, where HCV prevalence is greater than 20% in many areas, unsafe injection practices related to mass schistosomiasis eradication campaigns from 1960–1987 appear to have contributed to rapid HCV spread.[31]

HCV genotype distribution

Several studies have documented the distribution of HCV genotypes within the Australian population.[32–36] Based on these studies, the most prevalent HCV genotype is genotype 1 (55%), followed by genotype 3 (33%), genotype 2 (8%), genotype 4 (3%), and other genotypes (1%). Associations with HCV genotype include younger age or more recent HCV acquisition (genotype 3), and country of birth (Egypt: genotype 4, Southeast Asia: genotype 6). Although HCV genotype appears to have a limited impact on liver disease progression rates, it has a strong association with response to interferon based antiviral therapy.[37,38]

Liver disease progression

Based on a recent review of the natural history of chronic HCV infection, risk of progression to cirrhosis is 7% and 20% after 20 and 40 years infection, respectively. Corresponding estimates for HCV related mortality are 1% and 4%.[39] However, liver disease progression is highly variable and certain subgroups of people with chronic HCV infection are at increased risk of advanced liver disease. Those groups include people with a heavy alcohol intake those who have co-infection with HIV or HBV, and those who have already progressed to moderate-severe hepatic fibrosis.[39]

HCV estimates and projections

An estimated 210 000 people in Australia were living with HCV infection at the end of 2001, with estimated HCV incidence increasing from 11 000 in 1997 to 16 000 in 2001.[40] The number of people estimated to be living with HCV related cirrhosis in 2001 was 5900, and without effective therapeutic intervention was projected to increase to 12 800 by 2010. In Australia, approximately 35 000 people are estimated to have chronic HCV infection and clearly progressive liver disease – evidence of at least moderate hepatic fibrosis (*Figure 3*),[40] and should be strongly considered for HCV antiviral therapy. The risk of advanced liver disease complications is considerable in this group,[41] therefore, a large proportion will need to access antiviral therapy in the near future if the burden of advanced disease over the next decade is to be limited in Australia.

Conclusion

The HCV epidemic in Australia continues to expand, fuelled by high levels of HCV transmission among IDUs. Despite the widespread introduction of harm reduction measures for IDUs in Australia since the late 1980s, HCV infection remains a constant risk, in particular among those who share injecting equipment, are imprisoned, or who are young. Although a minority of people with chronic HCV infection are estimated to progress to advanced liver disease complications, the expanding HCV epidemic is likely to lead to considerable increases in disease burden over the coming decades.

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Preventing transmission of hepatitis C

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This update describes the main strategies for preventing the transmission of hepatitis C virus (HCV) infection according to the main population groups affected (*Figure 1*).

Recipients of blood transfusions and body tissue

Post-transfusion HCV infection is relatively rare in developed countries since donors with risk factors for blood borne viral infections and donors with HCV antibodies have been excluded from donating blood or body tissue. In Australia, prevention of HCV transmission from blood transfusion and body tissue transplant is achieved by excluding blood, plasma, organ, tissue, or semen from donors with risk factors for blood borne viral infections or with serological markers for HCV infection.

People who inject illicit drugs

Prevalence and incidence of HCV infection are high among injecting drug users in Australia, with estimates of around 16 000 new infections in 2001.[1–3] Incidence of HCV remains high, around 20 per 100 person years in Sydney.[2] There has also been a trend of increased HCV infection among new and young injectors throughout Australia since 1998, probably reflecting recent transmission.[2]

The principal strategy for preventing HCV transmission among people who inject drugs has been preventing blood contact around injection. In particular, by not injecting or by using sterile needles and syringes for injection. Availability of needles and syringes through a variety of mechanisms has been central to this strategy. Methadone programs and peer based education have also been widely supported in Australia.

With the introduction and expansion of the Needle and Syringe Program in the late 1980s and early 1990s, there was a significant decrease in the reported re-use of another person's syringe. In 1985, more than 90% of respondents reported sharing syringes in the month before interview; 10 years later almost 90% reported that they had not shared syringes.[4] In recent years however, the level of syringe sharing has been stable, with around 15- 25% reporting re-use of another person's syringe in the month before survey.[2,4]

Needle and syringe programs, methadone maintenance and peer based education, have been successfully used to prevent transmission of HIV and might therefore be expected also to be effective in preventing spread of HCV infection. However, because HCV was endemic among people who inject drugs in Australia before implementation of measures to prevent HIV infection, occasional episodes of shared injecting equipment may have been sufficient to sustain high rates of HCV transmission among this population. In addition, anecdotal reports have suggested that not all infections occur through the shared use of needles and syringes. It is important therefore, that equipment such as tourniquets, spoons and solvents are not shared, and blood contact is avoided when injecting.

Exclusive use of sterile needles and syringes and avoiding blood contact during injection will prevent transmission of HCV among those who use drugs. However, because of the chaotic lifestyle associated with drug dependence, the illegality of drug injection and the consequent social stigma, injecting drug use often remains hidden and is carried out in situations where blood contact is difficult to avoid. Reducing injection behaviour through the use of other routes of administration such as methadone maintenance or other pharmacological therapies, and counselling should be encouraged.

Other factors associated with increased risk among those who inject drugs include history of imprisonment, opiate use (compared to stimulant use), frequent injecting and exposure to hepatitis B virus (HBV).[1,3] The influence of the type of drug injected is probably related to the frequency of injecting; opiates tend to be injected more frequently than amphetamines, and cocaine injectors

Prevention: reducing new infections

All patients

- Encourage all patients to discuss drug related concerns by listening and questioning in an open and nonjudgmental manner – accepting the reality of IDU within the community
- Inform patients of transmission modes and means of minimising risk from any potential blood-blood contact, eg. sharing injecting equipment, including water and spoons, nonsterile tattooing, piercing, sharing of razors and toothbrushes, etc

IDU patients

- Discuss/encourage:
  - use of new sterile injecting equipment and safe disposal, through needle and syringe programs
  - use of own filter, spoon, water, tourniquet, swab and noncontact with blood at all stages
- Discuss noninjecting routes of administration (swallowing, snorting, smoking, rectal insertion) particularly in high risk situations (eg. syringe reuse)

Harm reduction: reducing morbidity

Harm reduction strategies, in relation to HCV, aim to reduce morbidity associated with both HCV infection and IDU. Reducing the frequency of injecting will also reduce the risk of new infections. Harm reduction strategies include a full range of options, from choosing abstinence through to safer practices.

HCV infection

- Encourage lower alcohol intake (especially discourage binge drinking)
- Encourage patients, who wish to explore complementary therapies, to keep their GP informed
- Assess eligibility for antiviral therapy and refer, as appropriate
- Review tetanus immunisation status, HAV and HBV immunisation status and HBV and HIV sero-status. Recommend HAV and HBV vaccination
- Inform breastfeeding postnatal patients of the low risks of vertical transmission

IDU

- Encourage all patients to discuss drug related concerns by listening and questioning in an open and nonjudgmental manner – accepting the reality of IDU within the community
- Evaluate the severity and chronicity of drug use by exploring:
  - past and current drug use – which drugs, how much, how often?
  - future plans regarding drug use, ie. continue, reduce, stop?
  - psychosocial issues, eg. mental health, family, relationships, financial, housing, legal, etc
- Discuss safer injecting technique (to reduce vein damage and other related problems)
- Discuss effects of drugs (eg. alcohol, benzodiazepines) on compromised liver
- Discuss strategies to reduce or stop drug use and encourage patient to return at any time if they want to reduce or stop in the future
- Review tetanus immunisation status, HAV and HBV immunisation status and HBV and HIV sero-status
- Discuss treatment with methadone or buprenorphine and refer (as appropriate) to alcohol and drug services

Figure 1. HCV prevention and harm reduction

can inject as often as 10–15 times per day. Risk behaviour associated with injecting networks could also partly explain the association with the type of drug injected. However, there have been no reported cases of blood borne viral infection acquired from needlestick injury in public places.

Transmission in the prison setting

The prevalence of HCV infection is high in prisons. Prevention measures include diversion of drug offenders into drug treatment or minimising blood contact in prison. The latter includes reduced injecting drug use and unsafe tattooing and policies that reduce self harm and fighting. Availability of professional tattooing equipment, guidelines for infection control, counselling, education, syringe exchange, methadone maintenance and other pharmacological therapies to reduce drug use should also reduce transmission.

Tattooing and other skin penetration

Tattooing and other forms of skin penetration such as body piercing, acupuncture, electrolysis and ear piercing have been implicated as a transmission risk for HCV infection.[5–7] Tattooing involves penetration of the epithelium, bleeding, re-use of equipment and re-dipping of equipment into the dye solution. Consequently, there is potential for transmission of infection from client-to-client, from operator-to-client and from client-to-operator. With other forms of skin penetration the possibility of client-to-client transmission exists particularly when hollow bore needles are used and when skin piercing equipment is shared. In one American study, ear piercing in men (but not women) was significantly associated with HCV transmission.[5]

Professional tattooists and services offering body or ear piercing should follow infection control guidelines and adhere to standard precautions to prevent transmission of HCV infection. Sterile equipment (available from only a few needle and syringe programs) should be used for nonprofessional body piercing.

Accidental needlestick injuries most often occur in the health care setting but are occasionally the result of stepping on a needle in recreational areas. (See the chapter *Acute hepatitis C* by George Marinos and Jeffrey Post).

Transmission in the health care setting

Two studies of health care workers exposed to HCV infection through percutaneous exposure demonstrated that transmission is associated with viral load.[8,9] In fact, there was no HCV transmission among health care workers who reported needlestick injury when the source was negative for HCV RNA. The rates of transmission from a source with HCV polymerase chain reaction (PCR) detected were 2.5%[8] and 10%.[9] In addition to percutaneous transmission, there have also been three case reports of HCV infection following conjunctival splash; two in health care workers,[10,11] the other in a prison worker.[12]

In Australia, there is limited information on occupationally acquired HCV infection in health care workers. No cases of seroconversion have been documented in a national project monitoring occupational exposure to blood borne viruses in almost 60 hospitals.[2] In this project, prevalence of HCV infection among source patients tested following health care worker exposure was 5% in 1997.[2]

Transmission of HCV infection between five patients undergoing minor surgery in the one session was reported from an Australian hospital.[13] The actual path of transmission was not determined although the authors suggested that blood contaminated anaesthetic filters were involved, with possible inoculation through pharyngeal abrasion caused by airway devices.

Transmission to patients has also been reported from haemodialysis units. Cross sectional surveys of haemodialysis patients without history of blood transfusion have found HCV prevalence of 7%[14]

Table 1. Needlestick injury prevention[17]

- Minimise handling of sharps in clinical waste
- Do not bend or recap needles
- Do not remove needles from disposable syringes
- Provide rigid containers for disposal and a safe needle handling system
- Keep 'sharps' containers out of reach of toddlers
- Keep 'sharps' containers close to worksites to aid immediate disposal

and 18%.[15] Isolation of patients with HCV antibody into a separate area reduced the incidence of HCV infection in one unit.[16]

Persons at risk of occupational exposure to HCV, and persons living with people with HCV infection, should adhere to standard precautions to prevent percutaneous, mucosal or nosocomial transmission of HCV infection (*Table 1*).[17] Standard barrier precautions and engineering controls should be implemented to prevent exposure to blood. In addition, protocols should be in place for reporting and follow up of exposures to blood or body fluids that contain blood. NHMRC guidelines advise that health care workers should not perform exposure prone procedures if there is evidence of current/active HCV infection.[18] Diagnosis of active infection should be assessed clinically by an experienced physician over a reasonable period of time, rather than being based solely on testing for HCV infection.

Sexual transmission of HCV

There has been little convincing evidence that sexual contact is an important factor in HCV transmission. Cross sectional studies from France, the United States, and Australia show low prevalence of HCV antibody among long term sexual partners of people with chronic HCV unless there were shared parenteral risk factors.[19,20] There are no published studies that prospectively measure the rate of new HCV infection in people who are sexually exposed – the most reliable means of assessing the rate of sexual transmission.

In retrospective surveys of long term male sexual partners of women who acquired HCV following administration of anti-D immunoglobulin, no HCV RNA was detected among 94 partners in one study,[21] and in another study, three of 393 partners had anti-HCV detected.[22] In one of these cases, the result could not be confirmed by other serological assays, another had a history of blood transfusion and the third had not been evaluated for other risk factors.

Hepatitis C virus has been detected in semen from men and in the menstrual blood of women.[7] Even though the number of people tested in these studies was small, the presence of HCV in genital tract secretions demonstrates the theoretical plausibility of sexual transmission of HCV.

While sexual contact cannot be dismissed as a possible route of HCV transmission, the evidence from studies of sexual partners suggests that the efficiency of sexual transmission is, at most, very low,[23] and alternative risk factors account for many cases of apparent sexual transmission.

The risk of sexual transmission from a person with chronic HCV infection is probably negligible.[19] For this reason there are no recommendations for change in sexual practices. However, people with HCV infection should be informed that where there is potential for blood contact, barrier precautions should be used. In general, persons at risk for any sexually transmitted infections should be counselled with regard to number of sexual partners, protecting themselves and their sexual partners from sexually transmitted infection, and vaccination for hepatitis A and B.

Household transmission

Studies of transmission of HCV in households are limited by shared behavioural characteristics of household members that put them at risk of HCV infection. Some studies have found high prevalence of HCV in older populations relative to populations at low risk of infection. Studies of children have found rates similar to background prevalence. In addition, studies that reported increased prevalence were conducted in countries in which past exposure to contaminated equipment used in traditional and nontraditional medical practices and ritual blood exchange might have contributed to familial clustering of HCV infections.[23–25]

Person-to-person transmission in the household setting appears to be extremely uncommon and household contact other than percutaneous blood contact has not been shown to be epidemiologically important in transmission of HCV. Nevertheless, where the possibility of blood contact exists, toothbrushes, razors or other items should not be shared.

Mother-to-child transmission

A high level of maternal HCV RNA is the strongest risk factor for vertical transmission of HCV. A review of published studies that compared transmission rates among women with HCV RNA to rates among women without HCV RNA, reported HCV transmission from 0–42% (combined rate 6.2%; 95% CI: 4.6–7.8%) among women with HCV RNA.[26] No case of transmission was reported among children born to mothers without detectable HCV RNA. Coinfection with HIV is another important risk factor.[20,26]

Hepatitis C virus RNA has been detected in breast milk by some investigators[27] and not by others.[28] Another study suggested that HCV RNA is only found in breast milk when maternal viraemia is high.[29] No association between transmission and breastfeeding was found in one study, but another reported longer duration of breastfeeding in mothers whose infants became infected.[7] NHMRC (1997) and CDC (1998) recommendations do not discourage breastfeeding. However, women with cracked or bleeding nipples should be advised to express and discard milk from that breast until the lesion is healed.

Data regarding the relationship between delivery mode and HCV transmission are also limited and indicate no difference in transmission between infants delivered vaginally and infants delivered by caesarean section.[7,20] As there is no evidence that mode of delivery is related to transmission, determining the need for caesarean versus vaginal delivery should not be made on the basis of HCV infection status.

Conclusion

Direct percutaneous exposures such as transfusion of contaminated blood or blood products, shared equipment for drug injection, and needlestick injuries, are the most efficient methods for transmitting HCV infection. Other percutaneous routes of transmission include body piercing and tattooing. Nonpercutaneous routes of transmission such as sexual and perinatal transmission are relatively inefficient. Because no vaccine is available, prevention of transmission remains the most effective way to prevent HCV infection. In Australia, current and past injecting drug users comprise the largest group with HCV infection and people who inject drugs are now at greatest risk for ongoing transmission.

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Acute hepatitis C

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Hepatitis C virus (HCV) causes acute hepatitis, but most cases are subclinical and go unnoticed. Acute HCV is symptomatic in approximately 30% of cases.[1] The incubation period is usually 6–10 weeks (with a range of 2–21 weeks) and is shortest after a large inoculum such as following the administration of infected factor VIII.[2] Most people with acute HCV infection report injecting drug use as a risk factor for infection. The clinical features resemble those of other forms of acute viral hepatitis. The symptoms are malaise, nausea, right upper abdominal discomfort, pale stools, dark urine and jaundice. These symptoms are usually mild but, as in other forms of viral hepatitis, may be very variable. Fulminant hepatitis occurs rarely, and when it occurs it is usually in patients who are immunosuppressed.[3]

Investigations

Evidence of hepatocellular injury

Liver function tests

Hepatocellular injury is almost invariable in acute HCV. The most useful laboratory test for such an injury is the level of serum alanine aminotransferase (ALT). Over 80% of patients acutely infected with HCV have a greater than 10-fold elevation in ALT level. Following infection, the rise in ALT typically occurs after seven weeks, but can occur as soon as two weeks after exposure. The rise in ALT normally precedes the onset of symptoms. As the acute inflammation subsides, the serum ALT levels may fluctuate and become normal or near normal, making the determination of true convalescence difficult. A persistently normal ALT is likely to be associated with viral clearance, however it is possible for viral persistence to occur in this setting, and specific viral tests are required to establish whether viral clearance has occurred.

Liver biopsy

A liver biopsy is not required in the assessment of acute HCV as it does not change the management of the patient.

Specific diagnosis of acute HCV

Anti-HCV antibody test

The most commonly used diagnostic test for HCV infection is the detection of specific antibodies to the virus (anti-HCV). Anti-HCV antibodies can be detected in 50–70% of patients at the onset of symptoms and in approximately 90% of patients three months after onset of infection. Therefore, a negative anti-HCV result does not exclude acute HCV infection. With the current third generation anti-HCV tests, antibodies do not become detectable before 7–8 weeks after infection and may occasionally not develop in rapidly resolving infections.[4]

HCV RNA PCR

The ideal test of early infection with HCV is the detection in the serum of a specific viral marker of infection, hepatitis C virus RNA (HCV RNA), by polymerase chain reaction (PCR). HCV RNA can be detected in blood within 1–2 weeks of exposure.[5] In patients with an acute self limiting illness the HCV RNA may become undetectable within a few weeks of onset of symptoms indicating clearance of HCV RNA. Spontaneous viral clearance occurs in as many as 45% of people with HCV infection.[6] Persistence of serum HCV RNA, even with resolution of the acute symptoms and return of ALT levels to normal, indicates that the patient is chronically infected.

Tests of immunity to HCV

There are no clinically available tests of immunity against HCV. In fact, individuals may be re-infected with the same or different genotype of HCV. The persistence of detectable anti-HCV is indicative of acute, chronic or past resolved infection.

Treatment

General measures

Supportive measures are the mainstay of management with referral to hospital if markers of hepatic decompensation such as encephalopathy, coagulopathy or intractable vomiting develop.

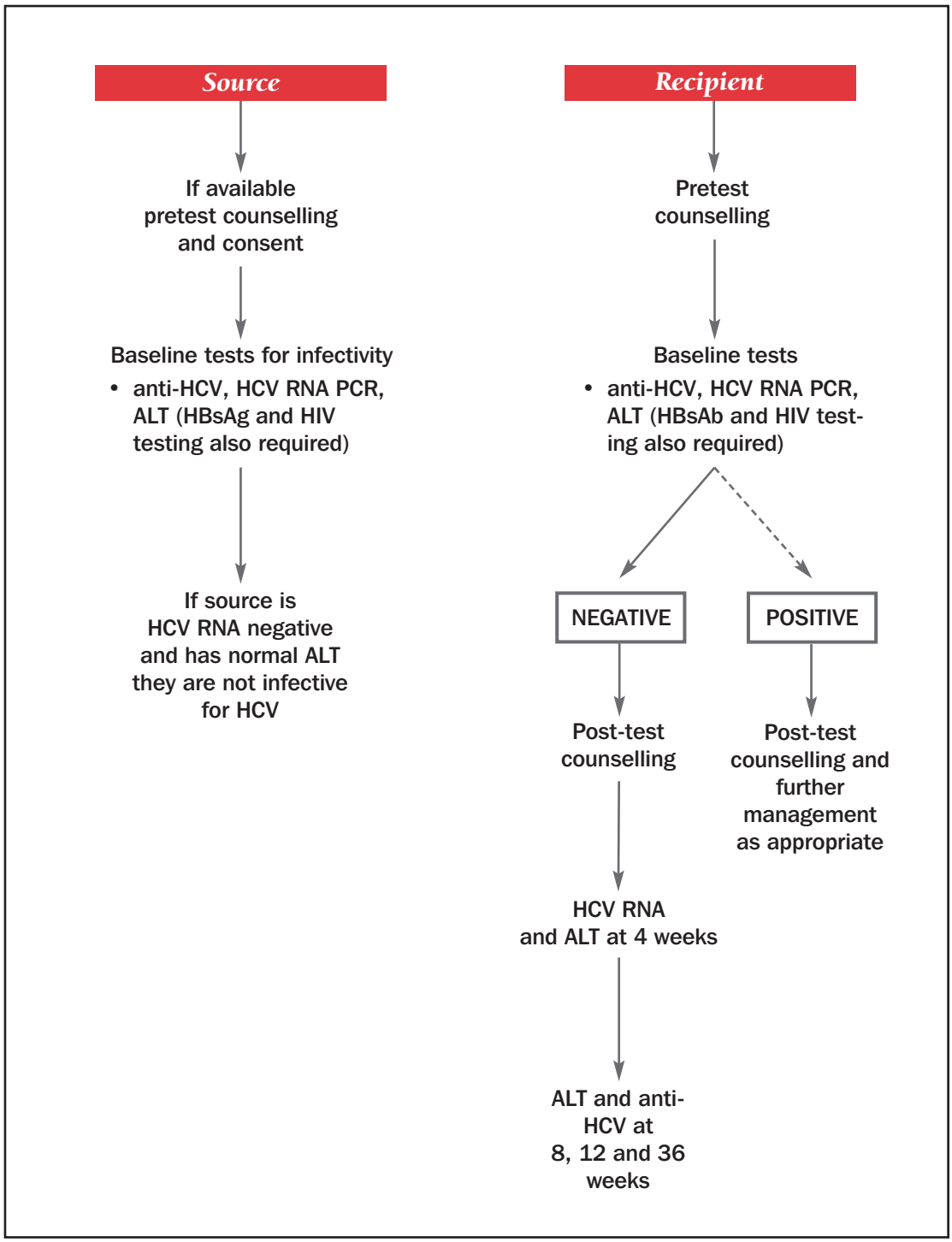

Figure 1. Needlestick injury management from HCV perspective

Appropriate counselling of the patient is important and is discussed below. In addition, patients should be advised to take adequate rest, a light balanced diet and to avoid alcohol. There is no evidence that strict bed rest or a certain diet will alter the clinical outcome. However, many patients feel more comfortable with a reduced fat intake.

Specific therapy

Meta-analyses have demonstrated that interferon therapy in acute HCV infection is associated with normalisation of ALT and elimination of HCV viraemia.[7,8] Most studies have used higher doses of interferon than those used to treat chronic HCV infection, with the attendant toxicity. It remains to

be seen whether treatment should be started immediately or delayed for a few months (or longer) after the onset of symptoms. Postponing therapy for 3–4 months appears not to affect the successful elimination of HCV. This delay has the advantage of identifying patients whose illness will resolve spontaneously and who therefore would not need to face the toxicity associated with interferon therapy. It is also unclear whether a strategy of early treatment is any more cost effective or safer than delaying therapy until chronic infection with histological progression occurs. It is also likely that new therapeutic agents will become available in the future that may allow less toxic therapy for patients with chronic and acute HCV infection.

Needlestick injuries

Transmission of HCV after accidental blood inoculation has been recorded and several studies on the occupational risk of HCV infection have been reported. The risk of HCV transmission after a needlestick injury is between 3% from an anti-HCV positive source[9] and 10% from a HCV RNA positive source.[10]

After exposure to HCV infected blood, the exposed person should have baseline studies including anti-HCV, HCV RNA PCR and ALT, to assess for any evidence of baseline infection. If available and willing to consent, the 'source patient' should be tested similarly to assess the level of infectivity. Persons who are HCV RNA negative with normal ALT do not transmit infection.[11] Follow up of the exposed worker should include HCV RNA and ALT at four weeks and anti-HCV at four, eight, 12 and 36 weeks after exposure (*Figure 1*).

There is no recommended postexposure management after exposure to HCV infected blood, other than usual first aid. Although meta-analyses and uncontrolled studies have shown a benefit of interferon therapy in acute HCV in terms of normalisation of ALT and clearance of HCV RNA from serum, this therapy has not been studied in patients before the onset of viraemia.

The risk of transmission from a needlestick injury from a discarded needle in the community is low, however these people should be followed serologically for nine months to exclude HCV seroconversion.

Occupational infection with HCV often has significant psychological morbidity and may have long term financial and medical implications including chronic liver disease and an attributable mortality. Health care workers who are viraemic with HCV should not perform exposure prone procedures. Some of the issues to consider when faced with a needlestick injury in the workplace are:

- confidentiality
- the need for review of work practices, and
- potential for litigation and compensation.

Meticulous documentation is essential.

Resource

National Needlestick Hotline:
1800 804 823 (for health care workers sustaining needlestick injury).

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AFP

Chronic hepatitis C

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Between 75 and 80% of all patients infected with the hepatitis C virus (HCV) develop chronic infection which is defined as infection persisting for more than six months, usually with a degree of hepatitis. The term 'chronic' relates specifically to the duration of infection not to the severity of the disease. While the mechanisms underlying the failure of viral clearance are unclear, the clinical significance is readily apparent. Chronic HCV infection leads to a wide spectrum of liver disease ranging from minimal damage (even after 30 years) through chronic hepatitis (mild, moderate, severe) to cirrhosis, liver cell cancer and liver failure. In discussing chronic HCV, it is appropriate to deal with the disease in Australia, aspects of diagnosis, clinical and laboratory evaluation and other investigations, and management including shared care protocols.

The size of the problem

It is estimated that there are 220 000 patients with chronic HCV in Australia but at present less than 180 000 have been demonstrated to be HCV antibody positive.[1] The vast majority of these patients will have chronic HCV infection. Incident cases of acute HCV are uncommon because most acute infections are subclinical.

Less than 20 000 Australians have received antivirals for chronic HCV. Thus, the vast majority of HCV infected individuals have not come forward or been referred for therapy. This may be because their symptoms and severity of liver disease do not warrant an aggressive approach to management, or because they elect not to have treatment for other reasons. It seems likely that some remain unaware of the place of antiviral therapy in elimination of chronic HCV infection and cure of the resultant liver disease. As the outcomes of antiviral therapy for HCV improve, an increasing number of patients are likely to present or be referred for consideration of treatment.

Evolution of chronic HCV

The full consequences of chronic HCV infection remain poorly defined. Furthermore, the natural history of chronic HCV infection in Australia may differ from that in regions such as North America or Egypt where there are different patterns of HCV genotypes (genotypes indicate major structural differences between HCV isolates). In Australia, 50–55% of infections are due to genotype 1 and approximately 40% to genotype 3. Other genotypes account for the remainder, with genotypes 2 (common in patients born in Italy and parts of Asia) and 4 (Middle East) being the next most frequent. In general, it is agreed that for every 1000 patients with chronic HCV infection in Australia:

- 70–100 will progress to cirrhosis over a mean of 20 years. This number will increase as follow up extends to 30 years[1]
- 50–100 of the cirrhotic group will develop hepatocellular carcinoma over a further 10 years
- at least 10% (overall) will progress to liver failure and require consideration for liver transplantation, and
- the remainder will experience varying degrees of liver injury and symptomatology.

In the last, most common group, some will have minimal symptoms but fibrosis will be evident on liver biopsy. The presence of hepatic fibrosis in chronic HCV indicates the potential to progress to more severe liver disease. On the other hand, other patients may have many and disabling symptoms but exhibit minimal changes on liver biopsy.

Diagnosis of chronic HCV

The diagnosis of chronic HCV infection requires the detection of anti-HCV (or more specifically, the presence of HCV RNA) in serum on two occasions over a period of six months or more.[2] To define chronic hepatitis more specifically, liver tests (ALT in particular) should be abnormal on several occasions over a six month period. In occasional patients hepatitis may be present histologically even with normal liver tests.

Having diagnosed chronic HCV, the physician needs to evaluate the patient's symptoms, physical signs and laboratory tests to estimate the likely severity of the condition before determining what management strategies need to be put in place.

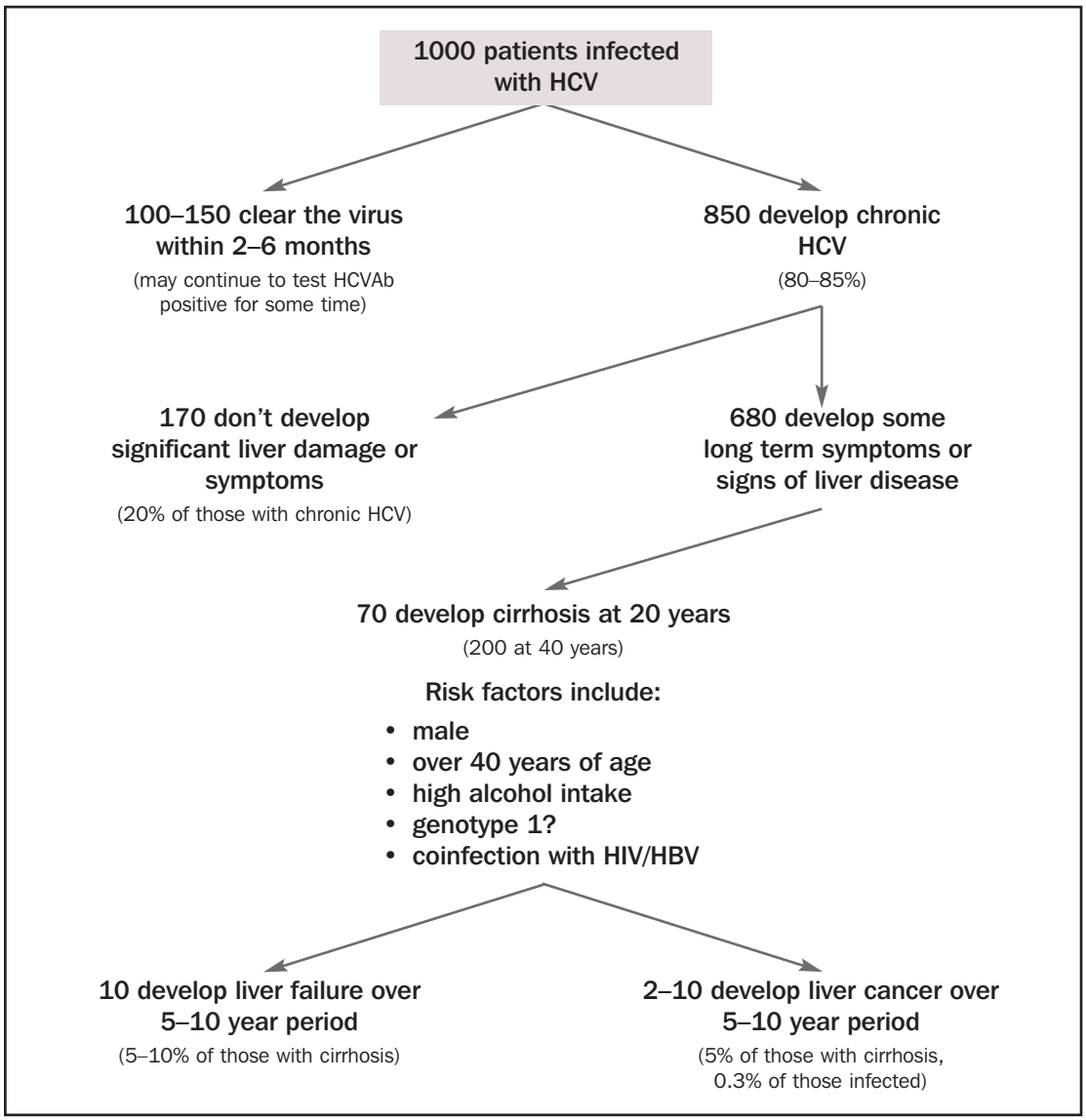

Figure 1. Natural history and prognosis HCV infection

Evaluation of chronic HCV

Patients who have evidence of chronic HCV infection will present with a very wide spectrum of symptoms, signs and clinical needs. Many patients will have no symptoms at all and will have no evidence of chronic liver disease on clinical examination and investigation. On the other hand, a significant minority will have evidence of significant liver disease. A detailed history, clinical examination and laboratory work up is essential in every patient before assessment can be deemed complete.

History and examination

In the patient who presents with chronic HCV it is important to establish when they may have contracted the disease and the likely source of infection. This is because determining the duration of infection gives some idea of the likely chance of the patient having established chronic hepatitis with or without fibrosis and perhaps cirrhosis. The natural history of HCV infection is outlined in *Figure 1*. Determining the source of HCV also influences outlook. Those infected in Egypt have a high incidence of cirrhosis as do older Italian patients who are likely to have contracted their infection in childhood from medical (needle/glass syringe) contamination.

In most cases it is impossible to pinpoint the exact time HCV was contracted, although it may be attributable to the time of a blood transfusion or a tattooing/body piercing episode. It is more dif-

Table 1. Extrahepatic manifestations of chronic hepatitis C

- Cryoglobulinaemia
- Glomerulonephritis (usually membranoproliferative)
- Polyarteritis nodosa
- Vasculitis
- Lichen planus
- Peripheral neuropathy
- Sjögren's syndrome
- Porphyria cutanea tarda
- Thrombocytopenia (this is more often a complication of portal hypertension)
- Non-Hodgkin's lymphoma
- Thyroid dysfunction

Table 2. Signs of liver disease in chronic hepatitis C*

Common

- Spider naevi
- Hepatomegaly
- Firm liver edge
- Liver palms (palmar erythema)

Less common, usually indicate severe liver disease

- Jaundice
- Hepatic flap (asterixis)
- Loss of body hair
- Gynaecomastia
- Hirsutism in females
- Hepatomegaly or shrunken liver from cirrhosis
- Splenomegaly
- Dilated veins on abdominal wall
- Ascites
- Peripheral oedema
- Hepatic bruits (a sign of liver cell cancer)

*Most patients (~60%) have no signs of chronic liver disease

Table 3. Staging of chronic hepatitis

Extent of fibrosis as determined by liver biopsy

Stage 0 = no fibrosis (normal)

Stage 1 = expansion of portal tracts

Stage 2 = early fibrotic septa

Stage 3 = linked fibrotic septa with early regenerative change

Stage 4 = cirrhosis (definite or probable)

ficult in those who have been born in a country of high prevalence. It is reasonable to assume that injecting drug users contracted the infection within the first 2–3 years of commencing a regular habit.[3]

Several studies have confirmed a deleterious effect of an alcohol intake greater than 40 g (four standard drinks) each day on the progression of chronic HCV.[4,5] Those who are over the age of 40 years at the time of infection have a more aggressive disease.[4]

Symptoms

Tiredness (fatigue) and lethargy (often to the point of exhaustion after a normal day's work) are very common in patients with chronic HCV. While these symptoms are often worse in those with more advanced liver disease, they can be quite marked in people with minimal evidence of liver damage. The symptom of fatigue is nonspecific, but its impact in individuals should be documented. Many patients will require assistance in claims for unemployment benefit based on the severity (level of incapacity) of their tiredness. In evaluating fatigue, it is helpful to enquire about effort tolerance compared with two years ago, time of retiring to bed, need for a rest during the day and problems with concentration. These changes can then be charted over ensuing visits. Tiredness may relate to central nervous system involvement with the HCV.

Other symptoms include discomfort in the right upper quadrant, nausea and anorexia, a tendency to fluid retention with oedema and abdominal swelling and signs of coagulation disorder (from impaired clotting factor production) such as bruising and epistaxis. Jaundice is seldom evident in chronic HCV until very late in the course.

Hepatitis C can rarely present with extrahepatic manifestations (*Table 1*). Symptoms of these extrahepatic manifestations should be sought. It is of interest that a high proportion of sporadic cases of porphyria cutanea tarda (PCT) are associated with chronic HCV.[2] The exact link between these two conditions remains unclear but porphyria needs to be considered in any patient with blistering skin lesions on photosensitive areas. Conversely among patients diagnosed with PCT, lichen planus or cryoglobulinaemia, anti HCV testing should always be performed.

Physical examination

Patients with chronic HCV infection should be evaluated for any signs of chronic liver disease and

for evidence of the extrahepatic manifestations indicated above. Spider naevi are the most sensitive sign of chronic hepatitis, but like all other signs of liver disease they are relatively nonspecific. The specificity of spider naevi for liver disease is less in women than in men.

Patients with chronic HCV often have no signs of chronic liver disease, partly because many individuals with chronic HCV infection do not develop cirrhosis and/or liver failure (*Table 2*). Perhaps 60% of those with chronic HCV will have minimal signs of liver impairment. A common feature is simply tender hepatomegaly with or without a few spider naevi. The presence of a firm liver edge gives rise to concern that fibrosis is present. This should lower the threshold for considering a liver biopsy. Splenomegaly is usually an indication of portal hypertension in this disease, and as such is a very important sign.

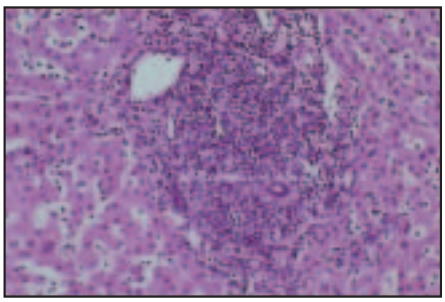

Figure 2. Portal inflammation in hepatitis C. The portal tract is infiltrated with inflammatory cells but the majority are confined to the portal tract area with no spill over into the lobule. This patient has no fibrosis and would receive a score of 1 to 2 for portal inflammation, 0 for lobular inflammation and 0 for fibrosis

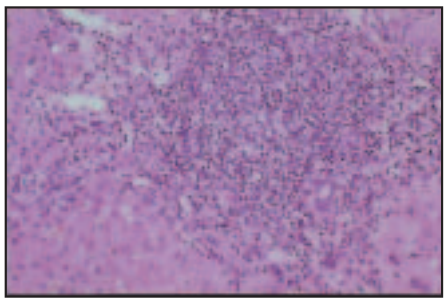

Figure 3. More advanced inflammation with portal cellular infiltrate now spilling into the lobule with some hepatocytes surrounded by inflammatory cells. A score of 3+ for portal inflammation, fibrosis is not evident in this biopsy

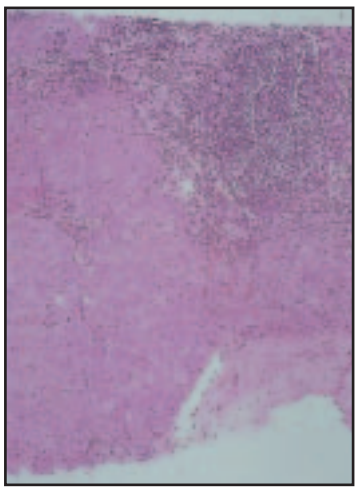

Figure 4. Portal and lobular inflammation can be seen in this section with a large vessel identified at the lower edge of the biopsy. Some expansion of inflammation along a possible fibrous tract is seen at the top of the biopsy. A score of 2 to 3 for portal inflammation, 2 for lobular inflammation and 1 for fibrosis

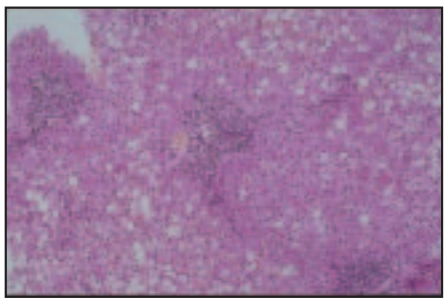

Figure 5. Marked steatosis is frequent in hepatitis C. The link between the fat and ethanol intake and viral infection remains to be more clearly defined. Portal inflammation is less than that seen in previous biopsies with a score of 1. Lobular inflammation is present, a score of 1. Fibrous bands are seen extending from the portal area in the centre of the biopsy, a score of 2

Laboratory evaluation

The presence of ongoing hepatitis should be documented with repeated liver tests. An appropriate interval is 2–3 monthly testing in the early evaluation of patients, decreasing to six monthly in stable patients not progressing to (or following) antiviral treatment. ALT elevations indicate ongoing hepatic inflammation but a proportion (up to 30%) of those with normal liver enzymes may have mild hepatitis on biopsy. Therefore, ALT levels cannot be used to predict the severity of liver disease,[6–8] but AST levels may be of value in conjunction with the platelet count in predicting significant hepatic fibrosis.

By paying attention to albumin, bilirubin and prothrombin time (which are true liver function tests) a truer assessment of the severity and progression of the disease can be gained. Any major changes in these tests indicate the need to move to treatment if this has been deferred. Serial platelet counts are of unusual value in chronic HCV; a progressive fall indicates progression of hepatic fibrosis, usually with cirrhosis and increasing portal hypertension.

Liver biopsy

Liver biopsy should be considered to define the severity (activity and stage) of chronic HCV in patients with infections for >5 years (*Table 3*). Patients may seek to avoid liver biopsy because of concern about discomfort and risk. They need to be informed that biopsy remains the only reliable test to document disease severity, by histological determination of necroinflammatory activity and particularly to allow quantitative analysis of hepatic fibrosis. In most settings in Australia, liver biopsy is carried out by physicians, gastroenterologists or hepatologists, with patients being admitted on a day only basis. Arranging this procedure, therefore, requires a link to a centre where this service is offered. Alternatively, in some centres liver biopsies are carried out by interventional radiologists. Liver biopsy is usually performed

under local analgesia. It causes minimum discomfort in the hands of experienced personnel. About one in 30 patients experience significant pain after the procedure. There is a small but definite risk of postprocedural bleeding (1/1000 biopsies), a complication that requires longer hospital stay and often intervention (hepatic arteriography with embolisation or aparoscopy). Other liver biopsy complications include inadvertant perforation of other organs, bile leak and pneumothorax. The risk of these is probably lessened by ultrasound sighting of the biopsy, a precaution that is available in major urban centres. The only common contraindication for liver biopsy is significant impairment of coagulation or severe thrombocytopenia. Thus, patients are required to have recent prothrombin time, activated partial thromboplastin time and platelet counts available at the time of the biopsy procedure.

A major requirement for maximising the value of a liver biopsy is that of a histopathologist with experience in liver disease. Biopsy evaluation is now based on scoring systems that have been developed to quantify portal and lobular inflammation and fibrosis in chronic hepatitis. Examples of increasingly severe liver damage are shown in *Figures 2–5*. The fibrosis score is of great importance in determining the response to interferon treatment.

Viral testing

It is emphasised here that serological tests for HCV antibody only indicate exposure to the virus, whereas the PCR test for HCV RNA indicates the active presence of the virus in serum. If HCV RNA is present, it is always helpful to have the genotype and viral load information as a guide to antiviral therapy. These tests are available (funded by Medicare) for patients who are being evaluated for treatment. At this stage, they need to be ordered by liver clinic staff, although with the project for GP prescribers in NSW, these doctors may be able to order the tests and have them funded by Medicare in the immediate future.

Other laboratory tests

Routine testing should include full blood count, thyroid function (usually TSH) and tests to exclude other forms of liver disease. Haematological changes (pancytopenia) can complicate cirrhosis when portal hypertension is present, and as indicated above, the platelet count may act as a surrogate indicator of cirrhosis in HCV. Baseline values are essential for subsequent monitoring of antiviral therapy. Tests for evidence of cryoglobulinaemia, renal disease and porphyria may be indicated if clinical signs and symptoms indicate the likely presence of these rarer complications of chronic HCV infection.

Imaging

In the early stages of evaluation, it may be appropriate to perform abdominal ultrasound to determine liver size and to look for evidence of portal hypertension. As many centres now perform an ultrasound before liver biopsy it is probably cost efficient to defer the first test until biopsy, if this is planned.

The complications of liver disease include liver cell cancer (hepatocellular carcinoma, HCC), which may first be identified on ultrasound investigation. Patients with stage 3 fibrosis or cirrhosis on liver biopsy, should have six monthly ultrasound and three monthly alpha fetoprotein as part of a screening program to detect early HCC development. Patients who are suspected of having portal hypertension (eg. splenomegaly, pancytopenia, ultrasonographic evidence) should generally undergo upper gastrointestinal endoscopy in order to diagnose complications such as gastroesophageal varices or portal hypertensive gastropathy.

Management

The management of patients with chronic HCV is a complex and prolonged process requiring the skills of specialist and generalist in almost all cases.

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AFP

Pretest counselling and diagnosis

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This update focusses on making a diagnosis of hepatitis C in general practice. The diagnosis of hepatitis C virus (HCV) is complicated but a clear diagnostic process helps to avoid potential misdiagnoses.

Who should be tested?

Patients may present with risk factors or symptoms suggestive of HCV, or may simply request HCV testing. Some may be referred from other sources, such as a blood bank for confirmatory testing after having been screened for HCV. In all situations, assessment of risk is the first step in diagnosing HCV infection followed by clinical examination and further laboratory tests.

People at high risk should be offered testing.[1,2] A history of injecting drug use is particularly important. Some practical guidelines in the approach to obtaining an accurate history of drug using behaviours are summarised in *Table 1*.

In those with a significant (although lower) risk of HCV infection, clinicians should consider the need for HCV testing, especially if symptoms or signs of HCV coexist. In lower risk populations, further research is required to determine the exact level of risk of transmission, and this uncertainty may cause some patient anxiety. This is particularly relevant for sexual transmission.

Some patients may have accurately assessed their personal risk of HCV infection as high, but hide their risk from the clinician for personal reasons such as the stigma associated with injecting drug use. Thus, when any person requests HCV testing it is appropriate that this be performed.

Signs and symptoms

The clinical signs and symptoms of chronic HCV are the commonest clinical findings of HCV related disease. Hepatitis C virus can occasionally present as an acute infection or rarely as a result of extrahepatic manifestations of infection.[1,2]

Many people have no symptoms or signs. Many of the signs and symptoms are nonspecific and common to many diseases, but the diagnosis of HCV becomes more likely in the presence of coexistent risk behaviour.

Acute HCV infection is often asymptomatic and is uncommonly diagnosed. Fulminant HCV is rare. However, HCV should be considered in the differential diagnosis in the acutely ill patient presenting with an illness suggestive of a hepatitis, with anorexia, nausea, jaundice or abnormal liver function tests (LFTs). A recent history of possible HCV exposure may require follow up testing if the initial tests are negative.

Chronic HCV infection should be considered in all people with any clinical evidence of liver disease, such as lethargy, hepatomegaly, spider naevi or other stigma of chronic liver disease, and raised alanine aminotransferase (ALT). It is particularly important to exclude HCV if there is a risk factor, or no other causes of liver disease are apparent. Even in the presence of another cause such as HBV infection, coinfection with HCV should be considered as these two viruses share some modes of transmission.

Pretest counselling

Counselling for HCV testing is based on the principles of testing for HIV infection, which are well documented.[4,5,6] Having identified risk behaviours, clinical features of hepatitis or a patient requesting HCV testing, informed consent is required before HCV testing is carried out. We advise counselling the patient before testing to:

- explain the benefits and risks of HCV testing
- educate the patient to reduce the risk of transmission, and
- ensure that appropriate support is available, especially in the event of a positive result.

The three Cs: counselling, confidentiality and consent

A thorough approach to counselling before HCV testing minimises potential adverse outcomes in the event of a positive diagnosis. Counselling not only involves giving information to patients so that they can make an informed choice about HCV testing, but is inextricably linked to education to

reduce the risk of HCV transmission. As well as ensuring privacy, reassurances of confidentiality increase the likelihood of disclosing illegal or stigmatised behaviours.

The level of patient fear attached to testing for blood borne viruses should not be underestimated and counselling also aims to assess and lessen the psychosocial impact of testing.

Assessing risk behaviours and educating patients for the reduction of risk

Considerable sensitivity is required to elicit transmission risk information from marginalised populations. For example, many patients will not readily reveal injecting drug use behaviours for fear of censure from health providers.

Overcoming discomfort in discussing alcohol and other drug use

Questions about drug use may be uncomfortable for both the patient and the doctor. Patients with drug related health problems may also fear discrimination upon disclosure of drug use and avoid accessing health services. Using exact, nonjudgmental language combined with a sincere concern for the patient's welfare helps to build the patient's trust. This should improve management and prevention outcomes.

Use accurate, nonjudgmental language

Accurate language also helps to estimate the level of risk of HCV transmission. The term 'intravenous' is particularly inaccurate as many patients at high risk of HCV infection inject intramuscularly or subcutaneously, such as steroid users and temazepam injectors.

Using terms such as 'drug addict' may not only be inaccurate, but may send signals to the patient that the discussion of injecting behaviours may result in discrimination with the potential to compromise treatment (*Table 1*). Occasional recreational and experimental injectors are also at high risk of acquiring HCV.

Language may also convey messages about disability that are inappropriately, albeit inadvertently, threatening to HCV infected persons.

Strategies for assessing drug use

One useful strategy for eliciting information on injecting drug use behaviours as a routine part of every medical assessment is to begin with questions about legal drug use and then gradually move to illegal use. Begin with questions about caffeine, smoking, alcohol and sedative use. Further nondirective questions such as: 'Any other drug use?' may elicit marijuana or other illegal drug use. If amphetamine use is disclosed, the question: 'Was that taken orally or injected?' is a gentle means of communicating that the clinician is prepared to discuss injecting behaviours. An additional question such as: 'Have you ever injected any other drugs?' may disclose opiate or other drug use. This gradual disclosure of information allows wary patients some control over the risk assessment process while they judge the reactions of the clinician. Once trust has been established, direct questions can be asked.

In our experience, assessment of drug history can be easier in new patients at the first presentation. Clinicians may feel hesitant in questioning familiar patients about sensitive issues, but patients understand the need for questioning about practices that may affect their health.

Table 1. Accurate assessment of drug related HCV risk

Choice of language when talking to patients

- Avoid the terms:
  - addict, addiction, drug addict, drug abuse, drug abuser, intravenous
- Use the terms:
  - injecting (rather than intravenous)
  - drug use (not abuse)
  - injecting equipment (not needles)
  - reused not shared (eg. have you ever re-used another person's injecting equipment?)
  - ask about the presence of withdrawal symptoms and/or dependence, not addiction
- Clarify meaning of any colloquial, subcultural terms associated with marginalised groups

Strategies to improve eliciting drug use practices

- Routinely include questions on drug use in general history taking
- Start with questions about legal drug use eg. caffeine, cigarettes and alcohol before asking about illegal drugs

Questions to include

- Do you or have you ever smoked?
- Do you or have you ever consumed alcohol?
- Do you or have you used any other drugs?
- Do you or have you ever injected drugs?
- Have you ever re-used another person's injecting equipment?
- When did you first inject drugs? Which drug(s) did you inject?
- Have you ever injected any other drugs?
- How often would you inject drugs?
- Have you ever been tested for hepatitis or HIV? When, and what were the results?

Prefacing sensitive questions with a remark such as: 'I need to ask a few sensitive questions because it may affect your treatment' can help prepare patients for potentially uncomfortable situations.

History and HCV testing

The time course of risk behaviours and testing provides information on the possible date of first exposure to HCV and duration of infection. A prior negative anti-HCV test may help establish the date of acquisition.

Education for risk reduction

Education for reducing the risk of HCV transmission usually occurs simultaneously with risk assessment. As each possible risk is examined, patients are given information on how HCV is and is not transmitted. Patients need to know what constitutes risk behaviour so that they can assess their own risks in their daily environment. This key issue is addressed in *Chapter 2*.

Education should be in words that the patient understands, which may require an interpreter if the patient's first language is not English.

Practical consequences of HCV infection

Patients need to understand about HCV and the nature of the HCV test—whether it is a test for antibodies or for the virus. Carefully explain the difference between a positive, negative or an indeterminate result. Some patients misunderstand the term 'positive', thinking that this is a good outcome. Explain how HCV causes the antibody test to turn positive, including the length of time required for this to occur.

Give accurate information about the possible medical consequences of HCV infection, including its prognosis and treatment. Questions about the vertical transmission of HCV are common, as many HCV infected people are of child bearing age.

Patients need to understand the possibility of discrimination in housing, medical and dental treatment, employment, insurance and the value in maintaining privacy about their potential diagnosis. Laws regarding notification of positive results to health departments should be told to patients before testing.

Clinicians may need to assist the patient to think through the repercussions of a positive, negative or indeterminate result. This essential aspect is considered in *Chapter 7*.

Laboratory tests for HCV

The routine test for HCV infection is an antibody test. A positive test usually indicates exposure to HCV but does not prove active infection. Polymerase chain reaction (PCR) testing may be carried out to determine if active infection is present in anti-HCV positive people with normal ALT levels. Accurate testing to detect the presence of HCV infection can be complicated due to current difficulties in serological and virological assays.

All tests need to be performed and interpreted within the context of a thorough clinical assessment, ALT levels and risk factors. Clinicians should not hesitate to contact their local pathology laboratory, or state or national reference laboratories, in the event of problems in interpreting HCV results. Difficulties in interpreting results may also require specialist referral.

This uncertainty around HCV testing can be a significant source of concern, but warning of this possibility during pretest counselling helps patients prepare for this outcome.

HCV RNA testing

The detection of HCV RNA is not a first line investigation in the diagnosis of HCV infection; it should not be viewed as a confirmatory test of serological status. The low level of viral HCV RNA requires highly sensitive detection systems such as PCR. This is important for monitoring disease during antiviral treatment.

Hepatitis C virus viraemia fluctuates over time, and may be undetectable even in the presence of active HCV infection. Therefore, a negative PCR result does not completely exclude HCV infection. There may be a supplementary role in diagnosing HCV in patients before the development of antibodies during seroconversion, or in immunocompromised patients. This is best done in a specialist setting.

Testing for HCV genotype and viral load

At present, HCV genotype and viral load testing is not required for the diagnosis of HCV, but is valuable in consideration of treatment. Its use is currently limited to specialist units.

Post-test counselling

Post-test counselling aims to minimise the psychological trauma of HCV testing and educate

Table 2. Anti-HCV EIA (enzyme immunoassay)

Possible results	Interpretation
Anti-HCV positive	• All initial reactive EIA tests confirmed (automatically by the laboratory) with a second EIA test using a different assay • Average time for the appearance of antibodies is 10 weeks, although this may vary from 2–26 weeks ('window period') • A positive antibody test result is no guide to the severity of hepatitis • HCVAb positive patients should be considered currently infected with HCV and therefore infectious • 80–85% of patients with acute infection remain infected, while 15–20% clear the virus. However, they remain HCVAb positive • False positive results are unlikely, especially in the presence of raised ALT and an identified risk factor • Children less than 12 months of age (occasionally up to two years) born to HCVAb positive mothers may reflect maternal antibody persistence
Anti-HCV negative	• Repeat EIA at six months if possibly within 'window period' • False negative results are possible if a patient is within the 'window period', especially in the presence of an identified risk factor • Immunocompromised patients (HIV/AIDS) may not produce HCV antibodies, but still be infected with HCV
Indeterminant	• Where initial reactive EIA test is not confirmed by second EIA test using different assay, HCV PCR test should be conducted (rebatable by Medicare under these circumstances). Refer to specialist if still in doubt

Table 3. Qualitative HVC RNA by PCR

The Medicare Benefits Schedule covers one qualitative HCV RNA PCR test per person per year for patients who:

- have tested HCVAb positive and who have had two normal liver function tests over the past six months
- have inconclusive HCVAb test results
- are immunocompromised and may not be producing antibodies to HCV
- may have acute HCV before seroconversion, eg. needlestick injury

Possible results	Interpretation
HCV RNA positive	HCV present in the body. Patient considered infectious
HCV RNA negative	HCV not detected in the body. The patient could have cleared the virus but does not completely rule out infection as viraemia may fluctuate

Within this context, the term 'counselling' includes listening for and addressing patient concerns in an encouraging, open and nonjudgmental manner, as well as the provision of information and advice, covering the following points. Refer NHMRC, *A Strategy for the detection and management of hepatitis C in Australia*

Pretest

- ☐ Explain the virus (HCV) and hepatitis C
- ☐ Describe the HCVAb test and possible results
- ☐ Explore psychosocial issues and support
- ☐ Obtain informed consent
- ☐ Investigate coinfection
- ☐ Provide prevention information/education
- ☐ Provide further information and support

Post-test

- ☐ Provide and explain the result in person
- ☐ Assess and address patient's psychosocial reaction

Negative result

- ☐ Explore need for repeat test
- ☐ Offer HAV/HBV vaccination
- ☐ Provide prevention information/education
- ☐ Discuss harm reduction options
- ☐ Provide further information and support

Positive result

- ☐ Describe natural history and discuss prognosis
- ☐ Discuss self management and harm reduction options
- ☐ Explain relevant legal issues
- ☐ Investigate coinfection
- ☐ Provide prevention information/education
- ☐ Provide further information and support

Indeterminate result

- ☐ Explain need for repeat testing
- ☐ Provide prevention information/education
- ☐ Provide further information and support

Figure 1. HCV test counselling checklist

patients about how to reduce the risk of HCV transmission. HBV and/or HIV results are often given in conjunction with HCV results and post test counselling should also be given for these.

Test results should always be given in person, and wherever possible by the individual who performed pretest counselling. Even a negative result may cause distress, and the need to be given the results personally should be emphasised in pretest counselling. Results should never be given over the telephone, even if patients are persistent in their demands. All clinic staff, including nursing and reception staff, should only inform patients via telephone as to whether test results have returned, not to disclose the actual result.

Possible test outcomes

Hepatitis C virus testing may result in positive, negative or equivocal results (*Table 2*). Post-test counselling and initial management of patients with a positive HCV result is detailed in *Chapter 6* and *Figure 1*.

The negative result

This provides an ideal opportunity for reinforcing harm reduction behaviours and lifestyle modification. Patients should be offered retesting if potential exposure to HCV has occurred within the past six months (2–26 weeks), especially if there are clinical symptoms or signs of acute HCV infection. These patients may need close monitoring. If patients continue to be at significant risk of HCV exposure, repeat the HCV test after 12 months.

Equivocal results[6]

Sometimes the anti-HCV result is neither clearly positive (high antibodies, reproducibly detected) nor negative. Examples include a positive result by one test kit, but negative by a second assay, or a weakly positive result by two assay systems. Such results are reported as 'indeterminate' or equivocal.

The uncertainty associated with receiving an indeterminate result is likely to cause major anxiety for patients. Some patients may actually be in the process of developing antibodies ('seroconverting') and this usually occurs in the presence of recent risk behaviour. Others have a false positive result; detection of anti-HCV is more likely to be a false positive if there are no known risk factors for HCV.

In each case, indeterminate results should be discussed with your laboratory or the National Serology Reference Laboratory to formulate the best approach for individual patients. The first step is to repeat the HCV antibody test, preferably with a different manufacturer's kit. Polymerase chain reaction testing for HCV RNA may be performed; this is best done in consultation with specialist centres (*Table 3*). If repeat antibody testing still yields indeterminate results, refer the patient to a specialist or liver clinic to resolve the issue.

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AFP

Post-test counselling and initial management

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The importance of a well informed general practitioner who meaningfully engages the hepatitis C virus (HCV) positive person cannot be overemphasised. The establishment of a strong patient–doctor relationship may well determine the success or failure of a patient's long term outcome and follow up.

This update describes the initial consultation between a GP and a person who is about to be told that he or she has a blood test result that is positive for hepatitis C antibodies (anti-HCV). There are a number of key issues that need to be addressed in this initial consultation. These are summarised in *Table 1*.

Pretest and post-test counselling

The importance of pretest counselling

No person should receive a positive diagnosis for HCV without having received counselling before testing to ensure that they understand the purpose and the implications of a positive result. (See previous chapters).

How to give the diagnosis

As stated, the results should be given in person, not over the telephone, and sufficient time should be allowed for the patient to respond to the diagnosis and to express their feelings. ('How do you feel about this news?') The GP will need to provide an adequate explanation to the patient of the meaning and implications of the test result and mention that appropriate referral and/or psychological support may be required. Patients with equivocal (or indeterminate) results should also be counselled with regard to the implications of such a result and the need for further testing.

Natural history and prognosis of HCV

It is important to ensure that patients understand the natural history and the variety of possible outcomes related to a diagnosis of HCV. ('What do you know about HCV?') The availability and knowledge of management options such as antiviral (interferon) therapy should be discussed. The need for future monitoring, especially during the next few months as the staging of the disease is determined, should also be discussed.

Prevention of transmission and the need for contact tracing

It is important that patients are aware of the potential routes of transmission and that they modify their lifestyle to minimise transmission. ('Do you know how people can catch hepatitis C?') Potential contacts should be identified and the GP should emphasise the need for these people to be informed that they are at risk of being infected already with HCV and to be offered testing.

The true prevalence of sexual transmission is not known but is generally regarded as low.[1,3,4] Although HCV is not regarded as a sexually transmitted disease, sexual acts that involve blood contamination may place individuals at risk. Sexual transmission risk may also be increased during acute HCV and this may have implications for the testing of sexual partners.

The prevalence of mother-to-child transmission as measured by HCV RNA varies between 0–9%.[4–7] Higher rates of transmission are also reported in mothers coinfected with HIV (up to 36%).[4,8,9] Limited studies on breastfeeding have not shown any increased rate of transmission.

Infants born to HCV infected mothers will acquire IgG antibodies transplacentally. These will be lost over the first year of life. It is therefore recommended to test these infants after 12 months of age.

Lifestyle assessment and health promotion[10]

Lifestyle modification should be discussed, in particular alcohol consumption and illicit drug use. Prevention of coinfection with other viruses such as hepatitis A and B can be achieved with appropriate vaccinations.

Advice to minimise cross infection

This includes the avoidance of sharing toothbrushes, razors or other grooming tools that might cause

skin abrasion or penetration. Care needs to be taken with blood spills and open wounds. For those who inject drugs, avoidance of all possible means of blood contamination should be addressed. These measures include safer routes of drug administration (if abstinence is not chosen or achieved), use of sterile injecting equipment, and avoidance of blood contamination during injection.

Alcohol

Alcohol intake has a synergistic effect on liver injury and alcohol intake should be minimised to not more than one standard drink per day.[10–13]

Illicit drugs and other medications

Injection of illicit drugs may impair health and indirectly affect liver function through associated malnutrition and/or alcohol intake. Certain prescribed medications may not be appropriate in HCV, including high doses of paracetamol (>2 g/day), as these may have a synergistic effect on liver injury. Drugs that are metabolised by the liver may need dose modification, particularly in those patients with significant impairment of liver function.

Many patients express concern about the possibility of their liver disease being worsened by concomitantly prescribed medications. There have been some reports of NSAID associated rashes in this population. The major risk of adverse drug effects relates to the severity of the liver disease rather than the HCV infection. Advice to these patients should be based on an assessment of the state of their liver function.

Smoking

Smoking cessation should be advised as, for many individuals, this is a greater risk to health than HCV infection.

Vaccination

Hepatitis A and hepatitis B vaccination should be offered to all patients with chronic HCV who do not have protective antibodies (anti-HAV and anti-HBs, respectively) to minimise the risk of decompensation of liver disease associated with a second hepatitis infection. There is an effective combination vaccine for those who have not developed immunity to HAV and HBV.

No effective vaccine has yet been developed to protect contacts of those infected with HCV. Immune serum globulin (ISG) does not confer protection.

Table 1. Issues to consider during the initial consultation with a person diagnosed with HCV

Pretest and post-test counselling
- The importance of pretest counselling
- How to give the diagnosis
- Explanation about the natural history and prognosis of HCV
- Explanation on prevention of transmission and the need for contact tracing
- Assessment of lifestyle and advice on how to minimise impaired health from HCV
- Assessment of supports and explanation of supports available for people with HCV

Clinical assessment and initial investigations
- Clinical assessment of symptoms and signs of liver disease
- Assessment of the severity of disease
- Initial investigations

Explanation of the need for monitoring and long term management
Referral of appropriate patients and shared care options
Notification requirements and other legal requirements
Follow up arrangements

Support for people with HCV

The GP should ascertain the availability of people to provide support to the patient at the time of diagnosis. ('Who are you going to tell today?') Psychosocial support for people with HCV, their families and other supporters should be offered. Empathy and understanding by the GP is necessary as the time of diagnosis is often a very traumatic experience. Community resources such as those provided by local HCV councils can be invaluable to patients and their families and other supporters.

Clinical assessment and initial investigations

Clinical assessment of liver disease

The patient should be assessed for symptoms of significant liver disease and physical examination should be undertaken to search for evidence of liver problems. Patients who demonstrate signs of portal hypertension and decompensation require prompt referral to a liver specialist. The absence of signs of chronic liver disease, however, does not exclude severe liver disease.

Initial investigations

Severity of liver disease is best assessed by hepatic synthetic function as measured by serum albumin

and international normalised ratio (INR) or prothrombin time. Serum alanine aminotransferase (ALT) levels are not reliable indicators of the severity of liver disease or the degree of inflammatory change.

The following tests are recommended at the initial consultation:

- repeat anti-HCV test (to confirm the diagnosis)
- ALT
- bilirubin
- albumin
- INR, and
- full blood count (especially platelet count).

Monitoring and long term management

People with active HCV infection will require regular monitoring to assess for signs of chronic liver disease, portal hypertension and complications of liver disease. Laboratory tests, in particular tests of synthetic function, will need to be monitored on a regular basis.

Referral of appropriate patients and shared care options

Not every person with a positive anti-HCV test result will require specialist referral. Indications for referral will include:

- when the diagnosis of HCV remains ambiguous; this may include a suspected false positive or a persistently indeterminate test result
- people who appear suitable for treatment and who state they may be prepared to undertake treatment
- people with signs or complications of liver disease
  - falling serum albumin levels
  - prolongation of prothrombin time
  - development of jaundice
  - development of other clinical signs (eg. peripheral oedema, ascites, muscle wasting)[10]
- people with suspected hepatocellular carcinoma including:
  - cachexia
  - worsening of liver disease
  - refractory ascites
  - raised alpha-fetoprotein
- people who may be suitable for liver transplantation, and
- anyone who requests referral.

There are a number of referral options available including referral to liver or hepatitis clinics in public institutions and referral to private hepatologists, gastroenterologists, infectious diseases physicians or other physicians with an interest in HCV. Some GPs also specialise in the care of people with HCV and may be prepared to receive referrals from other GPs.

Notification and legal requirements

- GPs are advised to contact their state or regional based public health units to ascertain local requirements.
- Patients need to be advised that their legal obligations include abstaining from donating blood, semen, ova, body tissues or organs.
- Failure to disclose their positive HCV status at the time of application may jeopardise life insurance cover.
- Standard precautions ensure protection for health care workers who may be exposed to body fluids. People with HCV are often advised to inform health care workers of their infection in order to improve treatment outcomes. However, many feel uncomfortable about disclosing their serostatus for fear of stigmatisation and discrimination.
- Discrimination is a major issue for people infected with HCV. Antidiscrimination legislation may apply to refusal of service, employment and medical or dental treatment on the grounds of an individual's HCV status.
- The Hepatitis C Council in each state can advise and refer individuals seeking legal advice.

Follow up arrangements

At the conclusion of the initial consultation, arrangements should be made for follow up. It is advisable to review people, with the results of initial investigations, within a week of informing them about their diagnosis. The GP should emphasise that she or he is available before this time, if the patient, their family or other supports have particular concerns that they would like to discuss.

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AFP

Ongoing management of hepatitis C

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The majority of patients infected with hepatitis C virus (HCV) who are encountered in general practice have chronic infection. Patients can be subdivided on the basis of clinical evidence of liver disease and alanine aminotransferase (ALT) results (*Figure 1, 2*). Although patients with consistently normal ALT levels may have histological evidence of significant hepatitis or even cirrhosis, disease activity is generally less severe. This group of patients may also be less likely to respond to current antiviral treatment regimens, although this is controversial.

When to refer for specialist assessment

Patients with clinical evidence of liver disease or with persistently abnormal ALT levels should be referred to a specialist with experience in HCV. The 'shared care' of patients starts at this point. A referral checklist is shown in *Table 1*. Before referral screen for other causes of chronic liver disease, including hepatitis B, haemochromatosis, autoimmune liver disease, Wilson's disease and α-1-antitrypsin deficiency. Patients with or without cirrhosis can sometimes be distinguished on clinical grounds, based on a hard liver edge, splenomegaly, ascites, features of hypersplenism, coagulopathy, thrombocytopenia or impaired hepatic synthetic function (low serum albumin). However, liver biopsy is the only way to establish the stage of liver disease with a high degree of certainty. Response to currently available antiviral agents is significantly influenced by the presence or absence of cirrhosis.

Approximately 20% of compensated cirrhotic patients develop decompensated liver disease over a 3–5 year period. Only patients with grade 3 or 4 fibrosis (developing or established cirrhosis) are at risk of hepatocellular carcinoma (HCC). HCC screening of patients with advanced fibrosis can be performed with serum alpha foetoprotein and hepatic ultrasound, but it is not yet clear how often the detection of HCC by screening alters the outcome. The excellent results of liver transplantaion as a management option for small HCC detected by screening favours the use of screening tools.

Coinfection with HIV, HBV or HGV

Coinfection of HCV infected persons with hepatitis B virus (HBV) or HIV and hepatitis G virus (HGV) is relatively common. The first step in management is to diagnose such coinfection, and to appropriately assess the activity of these infections and the disease that may ensue.

The presence of HIV infection has been clearly shown to accelerate the development of HCV related liver disease, probably on the basis of immune compromise. The incidence of cirrhosis is doubled and rate of decompensation increased six-fold in coinfected individuals, with 50% liver related mortality. High titres of HCV are generally present and the risk of transmission by perinatal or sexual spread is correspondingly greater. Treatment of HIV infection with antiretroviral therapy has precipitated hepatic decompensation in some cirrhotic HCV coinfected patients. Caution is therefore required in treating such patients. The use of alpha interferon and ribavirinin HIV/HCV coinfection has been shown to achieve lower long term responses compared to non HIV populations. This is largely due to reduced tolerability of treatment. Coinfected patients should be managed under the care of a specialist HIV/HCV clinic.

Coinfection with HBV also influences the progression of chronic liver disease. The presence of HCV usually suppresses HBV replication, and HBV coinfection may similarly suppress levels of HCV RNA in the coinfected patient's serum. Notwithstanding the ill understood complexities of virus interactions, the resultant liver disease is often severe. Results of conventional treatments for HBV and HCV have not been thoroughly evaluated but appear less satisfactory.

Coinfection with HGV is also frequent in

HCV infected individuals; in Australia it occurs in 20% of cases.[1] Occasional individuals also have concurrent HBV and/or HIV infection. In many studies, HGV/HCV coinfection has not altered outcome or treatment response compared to those infected with HCV alone.

Diet and alcohol

A well balanced diet should be recommended for all patients but there are no specific requirements. In particular, there is no need to routinely limit the fat content of the diet or to supplement the diet with minerals or vitamins unless nutrition is recognised to be inadequate. On the other hand, there is increasing evidence for interactions between HCV and obesity and type 2 diabetes (NIDDM).[2,3] Thus, overweight patients (BMI >25) should be counselled on a weight reducing lifestyle (diet and exercise).

Although it has been reasonably established that prolonged heavy intake of alcohol contributes to more advanced liver fibrosis, the level of alcohol consumption that aggravates HCV induced hepatic fibrosis has not been established. Patients consuming more than seven standard drinks (70 g) of alcohol per week respond less well to interferon treatment.[4] Such patients should be strongly counselled to reduce their alcohol intake to below this level although this is no longer a requirement for Section 100 funding of interferon/ribavirin antiviral therapy.

Specific issues for women

Safe sex advice should include avoidance of intercourse if there is ulceration of the genital tract, or during menstruation. The risk of sexual transmission of HCV is low unless there is blood contact during intercourse.

The risk of transmission of HCV in pregnancy and childbirth is low (3–6%) unless the person is coinfected with HIV. Thus, vaginal delivery is not contraindicated. There is no evidence for transmission of HCV with breastfeeding, but it is advisable to suspend breastfeeding if there are cracked nipples. Assessment during pregnancy is outlined in *Figure 2*. Oral contraceptives and oestrogen therapy is not contraindicated even in decompensated disease.

Women who are treated with interferon and ribavirin must avoid pregnancy during treatment and for six months post-treatment.

Table 1. Recommended investigations at time of initial specialist referral

- Full blood count including platelet count. This is to detect thrombocytopenia which may be associated with HCV, particularly in the presence of cirrhosis
- Alpha foetoprotein – baseline result for future screening for hepatocellular carcinoma
- Plasma thyroid stimulating hormone. There is an incidence of thyroid dysfunction in HCV infected patients and this can be exacerbated by treatment with alpha interferon
- HIV and HBV screen. Similar risk factors apply for these diseases as for HCV infection. In coinfection, the disease is more aggressive. Hepatitis B vaccination is recommended if exposure to HBV has not already occurred
- Ultrasound of liver and biliary tree. Examination for anatomical abnormalities before biopsy, plus evidence of cirrhosis or hepatocellular carcinoma

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Table 2. Herbal remedies and the liver

Plants and herbal remedies proven or suspected to be toxic to the liver

- Crotalaria
- Senecio
- Heliotropium
- Symphytum officinale (comfrey)
- Atractylis
- Callilepsis
- Teucreum chamaedrys (germander)
- Larrea (chapparal, creosote bush, grease wood)
- Cassia (senna) (chronic ingestion only)
- Chinese herbs (infrequent toxicity, responsible agent(s) not yet identified)
- Jin Bu Huan
- Pennyroyal oil
- Viscum (mistletoe)
- Scutellaria (skullcap)
- Valeriana (valerian)
- Sassafras
- Teucrium polium
- Mentha pulegium
- Berberis vulgaris
- Hedeoma pulegioides
- Azadirachza indica (margosa oil)
- Kombucha tea
- Black cohosh

Adapted from: Journal of Hepatology 1997; 26 (Suppl 1):47–51. Reproduced with permission: National Hepatitis C Management Guide for GPs

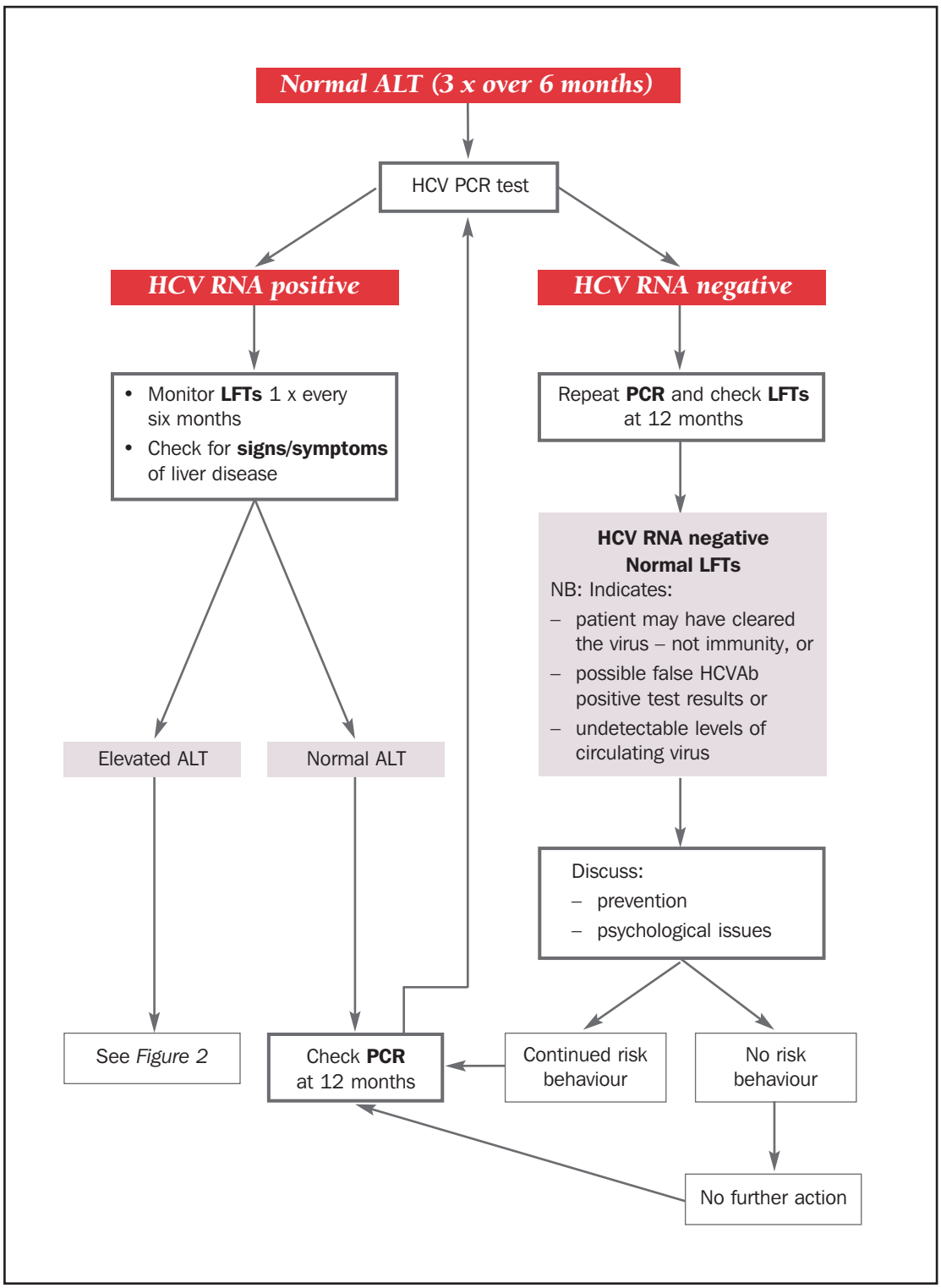

Figure 1. Normal LFTs (HCVAb positive) patient

People who inject drugs

Individuals chronically infected with HCV who use illicit drugs by injection require additional assessments. These include investigation for concurrent HBV and HIV infection. Immunisation for HBV and HAV is indicated if the individual is not immune. Some illicit injected substances may be hepatotoxic and can therefore cause

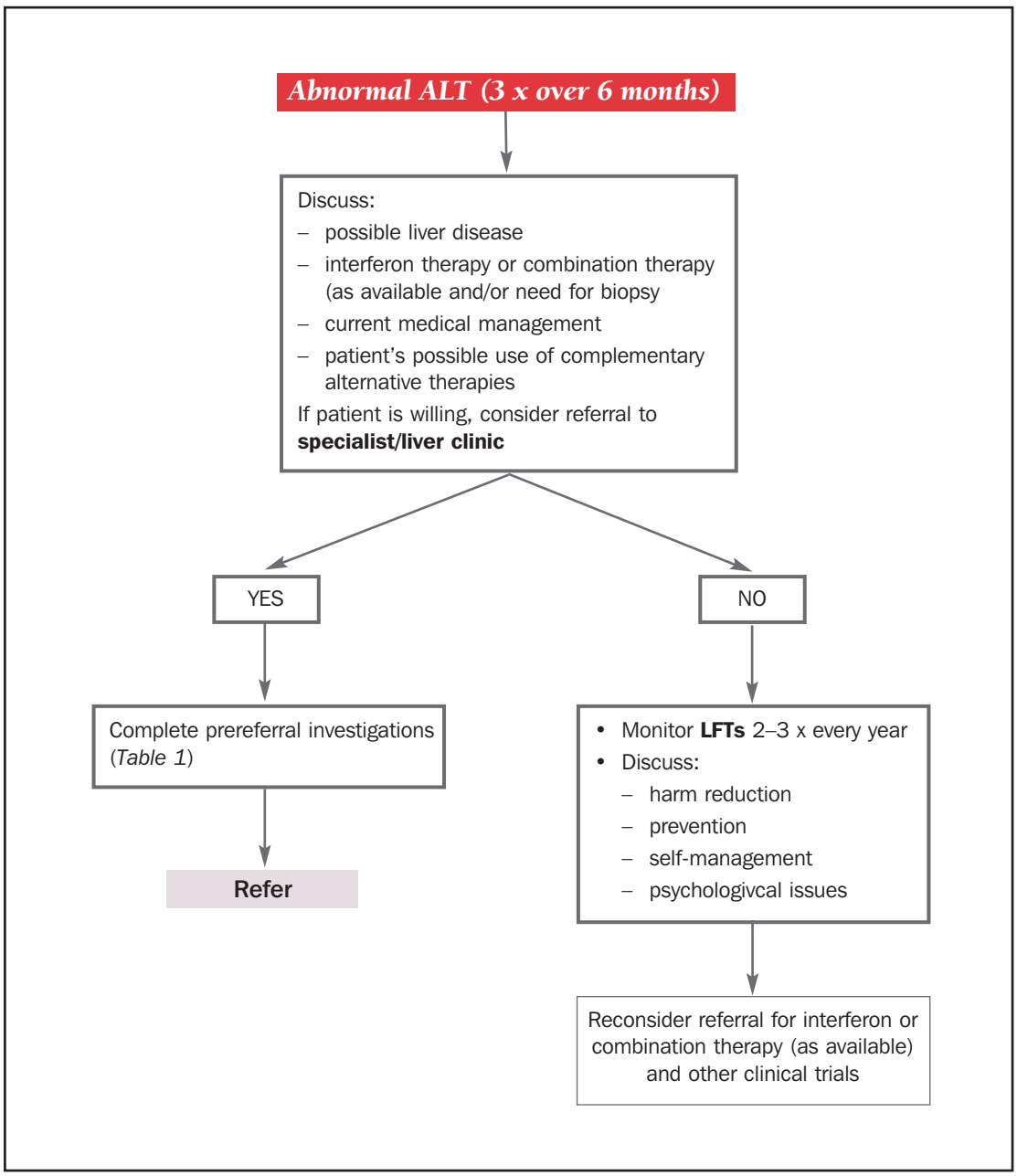

Figure 2. Abnormal LFTs (HCVAb positive) patient

alterations in liver function tests. The indications for liver biopsy are the same as for other HCV infected persons. The decision to proceed with antiviral therapy will depend upon the clinical assessment, the prospect of a high degree of compliance during treatment, and the wishes of the infected individual.

Adherence to antiviral therapy may be difficult for some people who are using substances of addiction but once this issue is resolved, alpha interferon and ribavirin therapy can be administered safely and successfully. Alpha interferon is not known to interact with methadone, amphetamines or heroin. There is no evidence of interaction between ribavirin and other drugs.

The presentation of a person who uses illicit substances by injection for the assessment of HCV infection is an opportunity for the medical practitioner to consider interventions that can prevent further complications of the injection drug usage, such as acquisition of other viral infections or transmission of HCV to others. It is

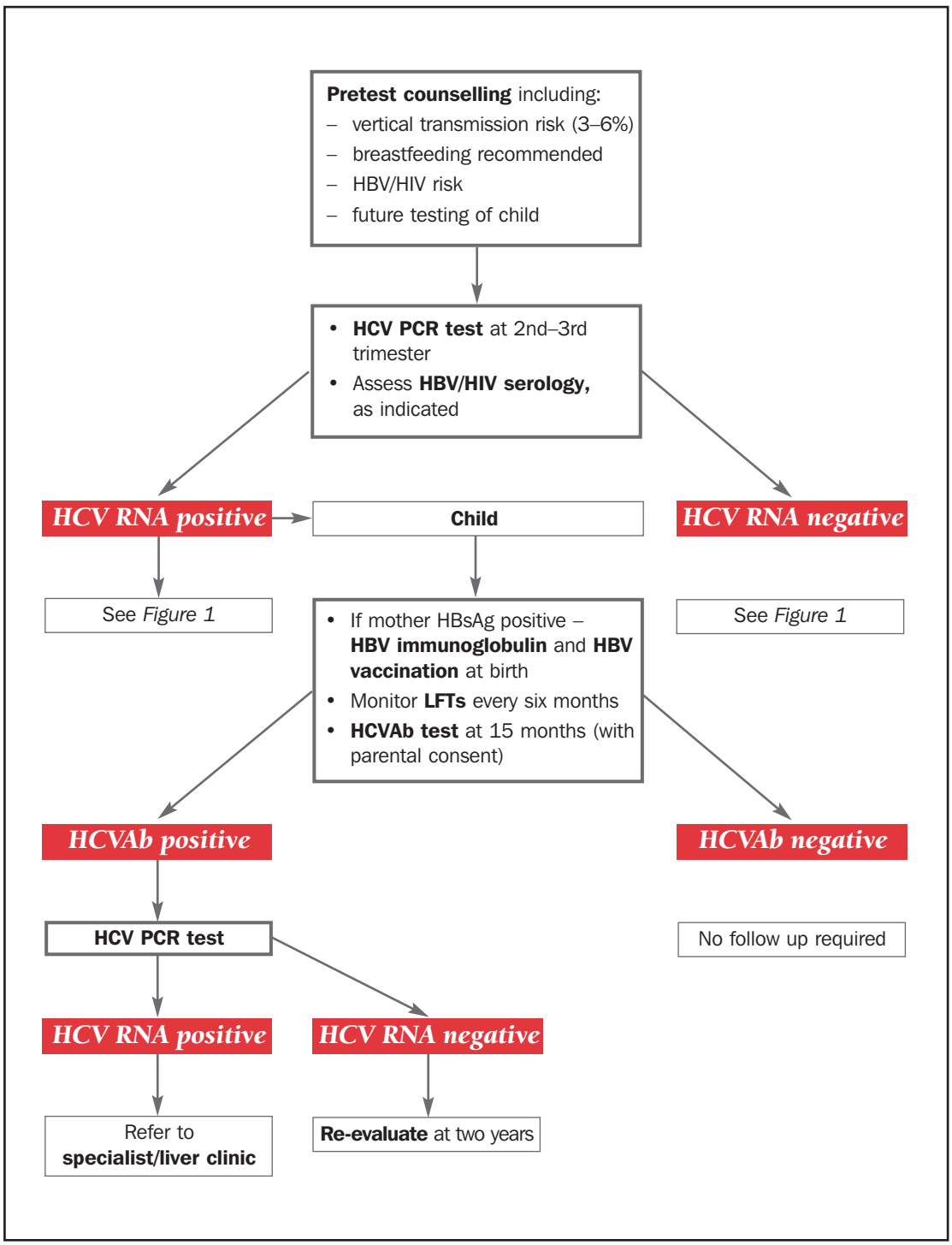

Figure 3. Antenatal (HCVAb positive) women
NB: Routine HCVAb screening without patient's consent is not appropriate

also important on follow up appointments to check for cellulitis and other complications at injection sites. The referral to treatment programs and provision of a supportive structure may reduce the risks of overdosage and death in this patient group.

Assessment by a psychiatrist may be warranted, as the prevalence of psychological problems is relatively high in HCV infected persons, particularly low self esteem, anxiety and depression. This is an important step before the administration of alpha interferon therapy.

Alternative therapies

There have been a number of strategies recommended in the management of chronic HCV. Very preliminary data on protease inhibitor drugs is promising. There are inconsistent data regarding the benefits of reducing hepatic iron stores before interferon therapy[5] and at present this is not recommended. Amantidine, cytokines, immunomodulatory drugs, ursodeoxycholic acid, nonsteroidal anti-inflammatory drugs and pentoxyfylline have been trialled but have not shown consistent benefit.

There has been considerable interest in the use of antioxidant drugs and Chinese herbal medicines, a number of which have antioxidant properties. Many patients with chronic HCV shun traditional medical care and favour natural or herbal remedies. There is very little objective evidence that can be shared with patients. An extract of 16 herbal medicines (exact constituents not recorded) was evaluated in a controlled study and demonstrated a significant fall in ALT levels in treated patients.[6] However, there was no histological assessment of hepatitis activity after treatment and no patient cleared HCV RNA during treatment. Milk thistle contains a naturally occurring antioxidant silymarin and is used by many patients. Oxymatrine, Bing Gan Tang and Yi Zhu decoction have been evaluated without compelling evidence of benefit. These herbal remedies are generally safe. It is important to discuss the potential risks of all herbal preparations. A list of potentially hepatotoxic remedies is given in *Table 2*.

Shared care

There is considerable scope for the shared care of HCV infected patients between primary care physicians and specialists involved. Patients value this cooperative approach to management. It is recommended that any general practitioner who is eager to be actively involved in the antiviral treatment of their patients should discuss this issue directly with the treating specialist and establish a shared care model that suits their own situation. Many shared care programs include comprehensive education programs for GPs to support their continuing involvement in the management of their patients with HCV.

All GPs should be aware of the availability of clinical trials for HCV in their local area. General practitioners who do not wish to take a major interest in HCV shared care still need to know the fundamentals of diagnosis, assessment and counselling. However, they may wish to establish a referral pattern to colleagues with a particular interest in this area.

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Antiviral therapy for chronic hepatitis C

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Over the four years since this article was first written, the response to therapy for chronic hepatitis C virus (HCV) infection has improved remarkably. Interferon monotherapy was then the standard treatment and sustained response rates were relatively low. The international standard of therapy now is the combination of pegylated interferon and ribavirin, which has been approved for use in Australia and is currently waiting government funding at the time of writing. Improved response rates are clearly related to more effective treatment but also to greater experience with interferon based treatments for both patients and clinicians. However, the aims of treatment have not changed and in the broadest sense, the short term aims of antiviral therapy for HCV are to stop viral replication and therefore limit infectivity and to reduce liver cell inflammation and necrosis so that progressive fibrosis does not occur. The primary long term objective is to prolong survival by decreasing the incidence of cirrhosis, liver failure and hepatocellular carcinoma (HCC). Clinicians must make an effort to identify the subset of patients most likely to benefit from currently available antiviral therapy and to avoid exposing patients who are unlikely to develop progressive liver disease to unnecessary treatment.

Predicting response and selecting patients for antiviral therapy

The natural history of chronic HCV infection reflects a complex interplay over many years between the virus and the host. Epidemiological studies have shown that age at the time of acquiring the infection; alcohol use, male gender, body weight and variability in immune response may all affect the extent of liver injury.[1,2] There may also be other significant viral, host and environmental determinants that have not yet been characterised. Current estimates are that only 20–30% of HCV infected patients will progress to cirrhosis over 30 years or more and some studies based on broad 'community based' populations have demonstrated even lower progression rates.[3,4] A proportion of those who do not develop cirrhosis will have chronic hepatitis with variable degrees of fibrosis. Thus, while every patient with HCV should be considered for antiviral therapy, it does not follow that all should be treated. So what are the factors to consider before undertaking a course of antiviral therapy?

Viral and host factors

Various viral and patient factors have been evaluated for possible correlations with the outcome of antiviral therapy. Hepatitis C genotype and viral load determinations provide the most reliable predictors of response.[5] Genotypes refer to subtypes of the HCV that are about 80% related at a genome level. The most common genotypes in Australia are 1, 2, 3, 4 and 6. However, recent studies have identified patients with genotypes 7, 8 and 9.[6] Patients with genotype 1 typically respond less often than non-1 genotypes to both standard interferon plus ribavirin therapy (30% compared to 70%) and to pegylated interferon plus ribavirin (45% compared to 80%). Similarly, patients with low baseline viral loads (under 2 million copies/mL or <800 000 IU/mL using polymerase chain reaction [PCR] based assays) are more likely to achieve a treatment response that patients with high baseline viral loads. Among host factors, the absence of bridging fibrosis or cirrhosis, age less than 40 years and female gender have been associated with better response to therapy. These predictors are not absolute and patients should not be denied therapy on the basis of an unfavourable genotype, viral load or degree of fibrosis determined before treatment.

Liver biopsy

Histological assessment of liver tissue has long been the standard for defining the degree of liver inflammation and fibrosis. The biopsy result, combined with an estimate of the duration of infection, can provide the clinician and the patient with the best possible estimation of the risk of fibrosis progression, ie. the natural history of HCV in an individual (assuming that fibrosis progression is

linear over time, although this notion is not universally accepted). The biopsy is unlikely to reveal additional or unsuspected causes for chronic liver disease; rather the usefulness of biopsy is based on indicating the risk of evolution to advanced liver disease. For patients with a long (>10 year) duration of infection with minimal fibrosis on liver biopsy, the likelihood of fibrosis progression is low and such patients might reasonably defer treatment until more effective therapy is available.[7] Alternatively, patients with established fibrosis and active inflammation on biopsy are at higher risk of developing advanced liver disease and should strongly consider antiviral therapy. The value of pretreatment liver biopsy may diminish if therapy for HCV eventually becomes better tolerated and more effective in a greater proportion of patients.

Indications for antiviral treatment

Consider recommending treatment to:

- Patients with active necroinflammatory changes on biopsy and significant hepatic fibrosis. This is the group most likely to develop progressive liver disease and therefore most likely to benefit if a sustained response is achieved
- Patients with compensated cirrhosis. While this group of patients generally experience a lower response to treatment than patients with less severe fibrosis recent data indicate that interferon treatment, with or without a sustained virological response, may be associated with less progressive fibrosis and a lower risk of developing HCC
- Patients coinfected with HIV. The majority of natural history studies show that co-existing HIV infection accelerates the progression of liver fibrosis in HCV infected patients and liver disease is now a major cause of death in this patient population.[8] Medical management is complex and requires expertise in both HIV infection and chronic viral hepatitis
- Patients with acute HCV infection. The rationale for treating patients with acute infection is based on studies suggesting lower rates of chronic infection in treated patients; however most studies have been small.[9] A recent German study showed high rates of viral clearance using a high dose interferon monotherapy regimen.[10] Many questions remain regarding the definition of acute infection and optimal timing and composition of treatment regimens. Currently patients with acute HCV infection do not fulfill Australian Commonwealth Section 100 criteria for treatment.

Consider recommending delaying or not having treatment if:

- Patients have minimal inflammation and no fibrosis on liver biopsy. The 1997 Consensus Development Conference on the management of HCV sponsored by the US National Institutes of Health suggested that an acceptable alternative to antiviral therapy in patients with no fibrosis on liver biopsy and minimal inflammatory changes would be 'observation, serial measurement of ALT and liver biopsy every 3–5 years';[11] although this recommendation has never been rigorously studied and reliable noninvasive methods to assess liver fibrosis, while not currently available, may alter the need for follow up biopsies in future[12,13]
- Patients have persistently normal ALT levels. A common definition for 'persistently normal' remains contentious, as does the natural history of this group, since a proportion of these patients may have bridging fibrosis or cirrhosis. The outcome of large randomised, controlled studies that will help to resolve the controversy should be available soon
- Patients with cirrhosis from HCV and signs of decompensation (ie. low serum albumin, prolonged prothrombin time, raised serum bilirubin, ascites, jaundice, or variceal haemorrhage). These patients should be considered for liver transplantation and should not be offered interferon.

Definition of treatment response

Response to antiviral therapy can be defined biochemically by normalisation of the serum ALT (rather than AST) and virologically by the disappearance of HCV RNA from serum using a sensitive method such as the PCR. A response at the completion of a course of treatment is defined as an 'end of treatment' response, or ETR, but the desirable goal is a sustained response (SR). A sustained virological response (SVR) is defined as undetectable HCV RNA at six months following the completion of treatment. Patients who develop abnormal ALT values or detectable serum HCV RNA following an ETR are defined as relapsed. Finally, the ALT may normalise (or viraemia become undetectable) initially but later become abnormal (or 'breakthrough')

Table 1. Effects of interferon (IFN) plus ribavirin (RBV) in producing a sustained virological response (SVR) in previously untreated patients with chronic HCV

	IFN + RBV for 48 wks	IFN + RBV for 24 wks	IFN + placebo for 48 wks
Poynard, et al[15]			
Overall			
ETR*	52%	57%	33%
SR	43%	35%	19%
SVR by genotype			
1 or 4	31%	18%	11%
2 or 3	64%	64%	33%
McHutchison, et al[16]			
Overall			
ETR	50%	53%	24%
SR	38%	31%	13%
SVR by genotype			
1	28%	16%	7%
non-1	66%	69%	29%

* ETR: End of treatment response

while still on treatment, or the virus may remain detected throughout treatment; both patterns are defined as nonresponse.

Therapeutic agents

Interferon

Interferons are naturally occurring antiviral proteins that act by stimulating the host immune response to produce an 'antiviral state' that results in the elimination of virally infected cells. The original report of the use of recombinant alpha interferon to treat non-A, non-B hepatitis was in 1986.[14] For many years the standard of treatment was interferon monotherapy and the usual regimen was 3 million units (MU) given three times per week over 12 months; a sustained biochemical response was seen in approximately 20–30% of patients. In 1998, two seminal studies were published showing that the combination of interferon plus ribavirin achieved superior SVR rates compared to interferon alone[15,16] (*Table 1*). Ribavirin is a guanosine analogue, which is ineffective in eradicating HCV when given alone but in combination with interferon reduces the relapse rate following the end of therapy and thus improves the overall sustained response rate. The precise mechanism of ribavirin's antiviral activity is unknown.

More recently two large studies were published on the outcome of therapy with pegylated interferon plus ribavirin showing improved response rates with the greatest benefit in patients with genotype 1.[17,18] Pegylation, or the addition of polyethylene glycol to the interferon molecule, delays metabolism so that a single weekly injection of pegylated interferon provides a sustained blood concentration and therefore greater exposure to the therapeutic effects of interferon. There are two commercially available pegylated interferons (α2a and α2b), which differ in the size of the peg molecule but appear similar in therapeutic efficacy and adverse events. The overall SVR rate to therapy with pegylated interferon and ribavirin is approximately 55%; patients with genotype 1 have lower response rates than patients with non-1 genotypes in a similar manner to response rates following treatment with unmodified interferon and ribavirin (*Table 2*).

The current recommendations for treatment with pegylated interferon and ribavirin, the international gold standard of therapy, vary primarily by genotype.[19] Patients with genotype 1 should receive treatment with either peginterferon α2a (180 μg weekly) or peginterferon α2b (1.5 μg/kg weekly) plus ribavirin 1000–1200 mg daily for 12 months. Patients with genotypes 2 and 3 should receive the same interferon doses plus weight based ribavirin for six months; recent data suggests that a ribavirin dose of 800 mg/day may be sufficient for these patients.[20] Unfortunately, there are few data to guide therapy for patients with other genotypes[4–9] although it is generally thought that patients with genotype 4 require 12 months therapy and patients with genotypes 6, 7, 8 and 9 may only require six months treatment.[6]

A decision to stop treatment is based on virological response at certain time points. If a qualitative PCR assay is used, then six months is the correct time to stop treatment if patients have detectable viraemia, since the likelihood of a response with further treatment is less than 2%. If a quantitative determination is made (ie. viral load is measured) then retrospective analysis of the two large pivotal trials of pegylated interferon and ribavirin suggest that patients who fail to demonstrate >2 log reduction in viral load at week 12 of treatment are unlikely to become sustained viro-

logical responders.[21] Application of these 'early stopping rules' will avoid exposing patients unnecessarily to the adverse effects of combination therapy. Since there are concerns based on reproducibility between laboratories in regard to the widespread use of quantitative testing; it is advisable that the same laboratory, using the same methodology, be used to determine the log reduction in viral load in an individual patient during a treatment course.

Monitoring therapy and side effects

Combination therapy with pegylated interferon plus ribavirin is associated with predictable adverse events that require close monitoring of patients during therapy (*Table 3*). A conscientious approach to side effect management is an important aspect of HCV treatment since some adverse events may lead to dose reduction or discontinuation and thus affect the outcome of therapy.[22] Counselling before therapy and continued support during treatment play an important part in helping patients to complete a treatment course and therefore adherence to therapy and avoidance of inappropriate dose reduction or discontinuation will provide the best chance of achieving a sustained virological response or cure. In the two large international registration studies of pegylated interferon and ribavirin, 10% of patients receiving peginterferon α2a plus ribavirin and 14% of patients receiving peginterferon α2b plus ribavirin had treatment stopped because of an adverse event or laboratory abnormality. These discontinuation rates are better than those reported in the original studies of unmodified interferon plus ribavirin and reflect a greater experience in dealing with drug toxicity.

Table 2: Effects of pegylated interferon (PEG) plus ribavirin (RBV) in producing a sustained virological response (SVE) in previously untreated patients with chronic HCV

Manns, et al[17]

	Higher dose PEG (1.5 μg/kg/wk) + RBV (800 mg/d)	Lower dose PEG (1.5/0.5 μg/kg/wk) + RBV (1000–1200 mg/d)	IFN 3 MU tiw + RBV (1000–1200 mg/d)
Overall			
ETR	65%*	56%	54%
SVR	54%*	47%	47%
SVR by genotype			
1	42%*	34%	33%
2/3	82%	80%	79%

* Significantly better than standard interferon plus ribavirin

Fried, et al[18]

	PEG 180 μg + RBV (1000–1200 mg/d)	PEG 180 μg + placebo	IFN + RBV (1000–1200 mg/d)
Overall			
ETR	69%*	59%	52%
SVR	56%*	29%	44%
SVR by genotype			
1	46%*	21%	36%
2/3	76%*	45%	61%

*Significantly better than both comparators
ETR: end of treatment response
IFN: interferon
MU: million unit

Adverse effects associated with interferon

Commonly experienced adverse events that occur early in interferon therapy are flu-like symptoms of fatigue, fever, lethargy, headaches and myalgias. These symptoms are most intense after the first few interferon injections and tend to abate thereafter, but some patients are plagued with such symptoms throughout treatment. Paracetamol (1 g administered two hours before interferon injection and again 2–3 hours after) may partly alleviate these unpleasant effects. Other side effects reported in 10–20% of treated patients include anorexia, malaise, alopecia, diarrhoea and weight loss. Alopecia is usually minor and reversible. Loss of greater than 10% of body weight is usually an indication to reduce the dose.

Interferon treatment has been associated with the development of potentially serious psychiatric complications such as anxiety and lability of mood, which includes hypomania and depression although severe depression is infrequent. Less commonly, acute brain syndrome and psychotic disorders may occur. Of particular concern are observed behavioural changes that are characterised by impulsivity, a tendency to return to addictive behaviours in a small minority of patients and an increased potential for violence and suicide.

Table 3. Side effects of HCV antiviral treatments

Interferon

Systemic
- malaise, nausea, fever, weight loss, diarrhoea, hair loss
- exacerbation of diabetes

Neurological
- loss of concentration, sleep disturbance, paraesthesiae, exacerbation of epilepsy, visual loss (rare), deafness (rare)

Psychological
- depression, irritability, psychosis

Myelosuppression
- neutropaenia, thrombocytopenia

Susceptibility to infection

Induction of autoimmunity
- autoimmune thyroid disease (hypothyroidism, thyrotoxicosis), haemolytic anaemia, thrombocytopenic purpura, worsening of psoriasis worsening of autoimmune hepatitis

Cardiac
- arrhythmia, congestive failure

Ribavirin

Haematological
- haemolytic anaemia

Respiratory tract
- cough, dyspnoea, pharyngitis, sinusitis

Dermatological
- alopecia, pruritus, rash

Teratogenicity

Potential for drug interaction with some antiretroviral agents

While a past history of psychiatric illness is not an absolute contraindication to treatment, it is important to recognise factors that may contribute to psychiatric illness. Patients with a history of substance abuse have an increased risk of psychiatric disorders that confers increased vulnerability during interferon treatment.

Depression and anxiety are the most common serious adverse effects of interferon therapy. They appear to be best managed with a selective serotonin reuptake inhibitor starting at a low dose. It may be necessary to withhold long acting (pegylated) interferon until a response to medication occurs. Psychiatric consultation should be considered before commencing interferon based treatment in patients with a history of severe depression, including prior suicide attempts or bipolar disorder, or in patients unresponsive to initial management efforts during treatment. Patients who develop psychotic illness should always be referred for psychiatric assessment and management.

The decision to withdraw interferon is made on an individual basis taking into consideration the risk of behavioural disturbance, particularly suicide, and the severity of the liver disease. In those patients with good insight and capacity for compliance and with relatively stable and supportive social circumstances, treatment with interferon and psychotropic medications, which may be commenced prophylactically, is often appropriate. In other cases, discontinuation of interferon is usually associated with rapid improvement in the mental state, although psychiatric disturbance precipitated by interferon may persist, requiring intervention.

Adverse effects associated with ribavirin

Two important side effects should be considered before commencing patients on treatment with ribavirin. The first is a predictable dose dependent haemolysis; most patients experience a decrease in serum haemoglobin between 20–40 g/L. This is an especially important consideration for older patients who may have significant but clinically silent coronary artery disease that may become symptomatic with a fall in haemoglobin. Second, ribavirin is a known teratogen and both partners should use adequate contraception during therapy and for six months following treatment cessation. Other side effects include skin rashes, which occasionally can be widespread and severe, and upper respiratory symptoms (cough, pharyngitis), which are usually mild.

Monitoring

Before commencing therapy, the following tests are recommended:
- full blood examination (FBE)
- thyroid stimulating hormone (TSH)
- antinuclear antibodies
- urea, electrolytes and creatinine
- fasting blood glucose
- serum or urine bHCG
- ophthalmological examination in patients with diabetes or hypertension.

During combination therapy, patients should be reviewed monthly with liver function tests and a full blood examination and periodic (eg. three monthly) testing of thyroid function. Those patients at risk of

retinal disease because of hypertension or diabetes should have an ophthalmological review prior to treatment or during therapy as clinically indicated. Patients should be reminded at each visit of the need for adequate contraception for themselves and their partners during therapy and for six months after ceasing ribavirin. Following completion of treatment, patients can be reviewed less often.

Neutropaenia and thrombocytopaenia

Myelosuppression is not uncommon in patients taking either unmodified or pegylated interferon; neutropaenia requiring dose reduction occurred in approximately 20% of patients in the registration studies for pegylated interferon and ribavirin. However, in general decreases in white cells and platelets are mild and not dose limiting except in patients with low pretreatment values. This is a particular problem in treating patients with cirrhosis in whom leucopoenia or thromboctyopenia may be complications of hypersplenism. An approach during treatment is to reduce interferon to 1.5 MU per day (for interferon α2b) or to decrease pegylated interferon doses by 50% for neutrophil counts below 0.75 x 10^9/L and to discontinue interferon for neutrophil counts less than 0.5 x 10^9/L. Neutrophil counts will usually recover in 1–2 weeks following treatment discontinuation.

Haemolytic anaemia

Ribavirin is concentrated up to 60-fold in erythrocytes and this leads to a degree of haemolysis in almost every patient, although the degree and the clinical impact of anaemia varies among patients. Ribavirin dose reduction is sufficient for patients without a history of coronary artery disease who experience a fall in haemoglobin to under 100 g/L although it should be discontinued if the haemoglobin is <85 g/L. Haemoglobin concentrations that trigger dose reduction and discontinuation are generally higher for patients with a history of stable heart disease. The use of haematopoietic growth factors to support patients during ribavirin-induced haemolysis is not yet widespread.

Thyroid abnormalities

Thyroid disorders, either hypothyroidism or hyperthyroidism, occur in around 2% of patients although some series have reported a higher incidence. The presence of thyroid autoantibodies before treatment is predictive of interferon induced thyroid disorders. It is recommended that serum levels of thyroid stimulating hormone (TSH) are determined before starting interferon, and repeated at three monthly intervals.

Relapse

Relapse, if it occurs, will usually be identified during the six month period after ceasing therapy. Lack of detection of HCV RNA by a sensitive method such as PCR six months following the end of treatment fulfils the definition of a sustained virological response. Late relapse is uncommon and patients who achieve a SVR are generally considered to have successfully eradicated HCV infection.[23]

Long term benefits of antiviral therapy

The ultimate anticipated benefit from combination therapy is improved survival and there are now indicative data that hepatic fibrosis may regress and that HCC may occur less often in treated patients. An intriguing study from Japan in 1995 followed 90 patients with cirrhosis from chronic HCV infection and found a lower incidence of hepatocellular carcinoma in interferon treated patients compared to untreated patients.[24] Two subsequent studies from Japan have shown similar degrees of risk reduction for HCC development in treated patients compared to untreated patients.[25,26] In a similar vein, histological improvement, measured as a reduction in stage of fibrosis, has been noted in several studies[27,28] even in patients who were deemed to be cirrhotic before treatment. A recent retrospective Japanese study concluded that liver related deaths were significantly less frequent in interferon treated patients.[29]

Generally patients who achieve a sustained virological response show the greatest benefit, but some improvement can be seen even in patients who remain viraemic. While it is tempting to conclude that cirrhosis can be reversed and survival improved, further long term prospective studies addressing the confounding issues of biopsy sampling error and short term follow up would be necessary to justify such a conclusion. Currently a number of large international trials are prospectively examining the role of maintenance interferon therapy in nonresponding, persistently viraemic patients; hopefully these data will guide us toward better treatment for the majority of HCV infected patients.

New treatment concepts

More effective and less toxic therapy is needed for patients who have not responded to the best available therapy and for those who might benefit from treatment but have elected to defer treatment because of possible adverse effects. Nonresponding patients to interferon have only a 15% SVR rate following retreatment with combination therapy.[29] Recent studies have suggested that high dose (induction dosing) interferon plus ribavirin with or without prolonged (>12 months) interferon therapy may be useful in patients who have not responded to standard regimens.[30,31] The efficacy of pegylated interferon plus ribavirin for nonresponders to standard combination therapy and the use of long term, low dose pegylated interferon monotherapy (maintenance therapy) to prevent progression of hepatic fibrosis are currently being studied in two large multi-centre trials (HALT-C and EPIC[3]).

While antiviral therapy is likely to remain interferon based for several years to come, there are exciting new therapies on the horizon that are specifically directed at HCV molecular targets. An HCV serine protease inhibitor was recently shown in phase 1 studies to be effective in suppressing viral replication over 48 hours.[32] Longer duration studies are required to demonstrate safety and efficacy, especially to explore the potential for viral resistance. Other strategies include targeting other viral proteins, gene silencing techniques using antisense oligonucleotides and RNA interference and the development of therapeutic vaccines. Two recent developments, an experimental model of in vitro HCV replication (the HCV replicon)[33] and early reports of a small animal model[34] have reinvigorated the search for new agents. The likelihood of translating these novel outcomes of basic scientific research into clinically relevant treatment outcomes for HCV infected patients seems very real indeed.

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Further information

The US National Institutes of Health Consensus Development Conference 'Management of Hepatitis C: 2002' is available online without charge at the following URL: http:hepatology2.aasldjournals.org. Click on 'current issue' to download individual chapters.

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AFP

Cirrhosis and liver cancer

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This chapter will address the issues relating to hepatitis C virus (HCV) associated cirrhosis and hepatocellular cancer (HCC).

Prevalence of cirrhosis

Progression from chronic hepatitis to cirrhosis in patients with HCV is a slow process. Although it is clear that cirrhosis may occur as quickly as 2–5 years post initial infection, various studies have estimated median times to cirrhosis of 20–40 years.[1] Progression to cirrhosis is not inevitable. At least 20–30% of HCV infected cohorts with evidence of chronic hepatitis show no significant progress despite 20 years of infection.[1] Conversely, up to 20–30% progress to cirrhosis over a 20–40 year period.[1] Factors that influence the progression to cirrhosis include duration of infection, gender, alcohol consumption and age of acquisition of HCV (*Table 1*).

In a cohort of HCV infected women (Irish women infected by antirhesus immunoglobulin), the prevalence of cirrhosis after 18 years was only 2.2%.[1] Furthermore, serum alanine aminotransferase (ALT) often normalises during pregnancy. It has thus been suggested that women may progress to cirrhosis more slowly than men.

It is clear that significant alcohol consumption in chronic HCV infection leads to an increased prevalence of cirrhosis,[2–4] but the role of alcohol consumed in moderation is less certain. The observation that age >40 years at acquisition of HCV is associated with a more rapid progression of liver injury is well documented but currently remains unexplained.[2]

Is there clinical evidence of cirrhosis?

The symptoms of compensated cirrhosis are essentially the same as those of chronic HCV infection itself. Although many patients with cirrhosis may be asymptomatic, profound lethargy and significant right upper quadrant discomfort are frequent symptoms. Physical examination may reveal a hard liver edge and splenomegaly.

There may also be clues from biochemical and haematological parameters that cirrhosis is present. These include a slightly low serum albumin, a slightly prolonged international normalised prothrombin ratio (INR), an aspartate aminotransferase (AST) level greater than ALT level and thrombocytopenia (*Table 2*). The latter presumably represents hypersplenism secondary to portal hypertension. However, it should be noted that some cases of 'true' idiopathic thrombocytopenic purpura (ITP) have been linked to HCV.

A liver ultrasound and/or CT scan may also detect early portal hypertension (*Figure 1*). An irregular outline of the liver on CT scan would imply that cirrhosis is present but increased echogenity on ultrasound does not, as it may reflect fat accumulation. Finally signs and symptoms of mixed cryoglobulinaemia (skin rash – palpable purpura on lower limbs, proteinuria) are more frequent in the presence of cirrhosis.

What is the role of antiviral therapy in cirrhosis?

Based on current treatment protocols, patients with cirrhosis are less likely as non cirrhotic patients to respond to interferon therapy. However, they are the group of patients who are at risk of decompensation and HCC and would seem more likely to benefit from pegylated interferon/ribavirin combination therapy.

Retrospective multivariant analyses have suggested that cirrhotic patients treated with interferon have a reduced risk of hepatic decompensation and liver cancer.[5] A difficulty in interpreting these studies is that relatively few have reported end of treatment response (ETR) rates and even fewer sustained response (SR) rates. Idilman et al recently reviewed the results from 26 published studies and reported ETR rates of 53% in noncirrhotic patients and 27% in cirrhotic patients.[6] Australian researchers originally made significant contributions to this area, demonstrating an ETR (based on serum ALT) in 32% of cirrhotic patients and a SR in 14%.[7,8] However, the data now with pegylated interferon and ribavirin suggests SVR of 40% ETR in cirrhotic patients with genotype 1 and 60–70% with genotype 3. Currently 24 week thera-

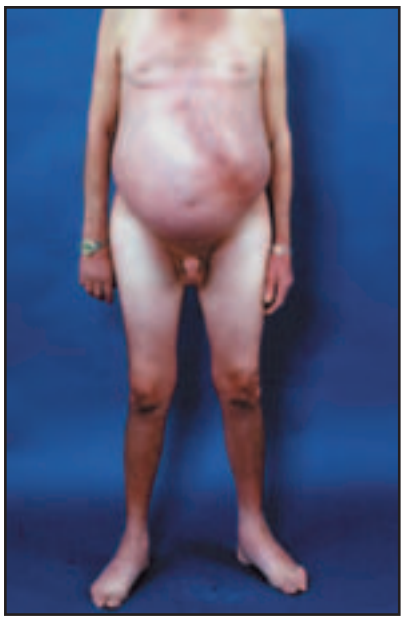

Figure 1. Signs of advanced cirrhosis ascites and muscle wasting. Note also dilated abdominal wall veins due to portal hypertension and gynaecomastia

Table 1. Factors that predispose to HCV related cirrhosis

- Age (>40 years) at acquisition of HCV
- Male gender
- Duration of HCV infection
- Hazardous alcohol intake (>4 standard drinks/day)
- Failure to respond to interferon therapy
- Viral co-infection (HBV, HIV)
- Immunosuppression

Table 2. Clinical features and laboratory results that suggest cirrhosis

Subtle features

- Hard liver edge and/or splenomegaly on physical examination
- Mild thrombocytopenia
- Slightly low albumin
- Slightly prolonged INR
- AST>ALT
- Nodular liver on CT/ultrasound
- Cryoglobulinaemia

More significant features

- Ascites, significant low albumin
- Muscle wasting
- Hepatic encephalopathy
- Upper gastrointestinal bleeding from oesophageal/gastric varices or portal hypertensive gastropathy
- Hypersplenism (thrombocytopenia, leucopenia)

py seems acceptable in this latter group. It should be noted that patients with only compensated cirrhosis are recommended for therapy.

What are the complications of cirrhosis?

The five year prognosis for patients with compensated cirrhosis is generally good. Fattovich et al in a retrospective study examined outcomes in a cohort of 384 European patients with hepatitis C and compensated cirrhosis followed for five years.[9] Hepatic decompensation occurred in 18% at five years, while 7% developed HCC. Overall, the five year survival for this cohort was 91%. Seventy percent of the patients with cirrhosis who died in this study did so from liver related causes, a much higher percentage than the controls or for all patients with hepatitis C.

The indications that a patient may be progressing from a state of compensated cirrhosis to liver failure include ascites, hepatic encephalopathy, gastrointestinal bleeding and the physical signs of splenomegaly and muscle wasting (*Figure 1*). The biochemical features include a low serum albumin and prolonged INR, while haematological features of hypersplenism (low WCC, thrombocytopenia) may also be found. Some of these parameters are used to 'score' the severity of cirrhosis according to the Child–Pugh criteria (*Table 3*). Patients with Child's C cirrhosis have a median survival of <1 year.

Ascites is best managed by salt restriction and the introduction of aldactone (initially 25 mg bid) as the diuretic of choice. If ascites continues to be a problem, increased doses and the introduction of frusemide therapy (40 mg daily) may be necessary. Close monitoring of patient weight, serum electrolytes and creatinine are necessary at this stage.

A clinical suspicion of spontaneous bacterial peritonitis (SBP) must always be entertained in patients with ascites. It may present as increasing ascites, but more commonly is associated with malaise, abdominal discomfort and tenderness; fever, signs of peritonism and leucocytosis may not be present. This is a medical emergency and requires hospital admission, examination of ascitic

Table 3. Child–Pugh criteria

	1 point	2 points	3 points
Bilirubin (mmol/L)	<40	40–60	>60
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
PT (sec prolonged)	1–3	4–6	>6
Ascites	none	slight	moderate
Encephalopathy (grade)	none	grade 1–2	grade 3–4

Grades: A=5–6 points; B =7–9 points; C = 10–15 points.

fluid and pre–emptive antibiotic therapy. Attacks of recurrent SBP may be prevented with oral antibiotic (quinolone) therapy.

There is evidence that prophylaxis of gastrointestinal bleeding in cirrhosis may be achieved by oral ß blocker therapy.[10–12] Thus upper endoscopy should be performed in patients with HCV associated cirrhosis and a clinical suspicion of significant portal hypertension. Therapy needs to commence at low doses with an aim to reduce the heart rate by 25%. Treatment is particularly effective in patients with large varices and endoscopic signs of potential bleeding. However, beta blocker therapy is not always well tolerated in cirrhosis and the role of prophylactic banding is increasingly under investigation.

Encephalopathy in cirrhosis is usually due to potential reversible events such as sepsis (particularly SBP), electrolyte imbalance, gastrointestinal bleeding, and concurrent medications particularly diuretics and sedatives. Thus these precipitating factors need to be carefully sought and recognised. It should also be realised that once the complications of cirrhosis begin to develop, it is important to consider liver transplantation. Chronic hepatic encephalopathy in cirrhosis can usually be managed with lactulose therapy. This should be administered at doses that give the patient two loosely formed bowel motions per day.

Hepatocellular carcinoma: the role of surveillance

The development of HCC is one of the major complications of chronic HCV infection. Although HCC does occur in non cirrhotic patients with hepatitis C, only a few cases have been reported. In patients with HCV related cirrhosis, the annual risk of developing HCC is 1–6%.[9,13] In a retrospective study of 384 patients with compensated cirrhosis, Fattovich et al[9] found an annual incidence of HCC of 1.4% while in prospective studies Bruno et al[13] found it to be 2.5%. Hepatocellular carcinoma occurs much more frequently in men than women and is more likely in patients >60 years of age with Child's B/C cirrhosis.

This means that patients with cirrhosis due to hepatitis C are at significant cumulative risk of developing HCC. Hence surveillance for early diagnosis and treatment seems logical.[14] Before the issue of surveillance can be addressed, however, the important issue of available therapies and their effectiveness needs to be addressed. Resection of HCC is limited to patients with Child's A cirrhosis, no evidence of significant portal hypertension and no evidence of metastases. Liver resection for other types of cases carries a significant chance of precipitating liver failure.

Only tumours ≤ 5 cm in diameter are suitable for resection. Another major problem with resection is that the 'precancerous' cirrhotic liver remains in place. The incidence of further HCC development over the next five years is up to 80%.[14] In patients where resection is not an option local therapies such as direct ethanol injection have been used to treat tumours <5 cm in diameter. Three year survival rates have been similar to surgical resection. There is increasing evidence, however, that patients with small tumours and significant portal hypertension and/or liver failure are best treated with liver transplantation. Therapies such as chemoembolisation and/or systemic chemotherapy for large tumours do not improve survival.

It follows that one of the major problems with the assessment of liver cancer screening programs is the limitation and availability of therapies once an HCC is diagnosed. As a consequence, it has been difficult to show improved survival in patients undergoing regular surveillance.[14]

Another issue in assessing the role of surveillance for HCC is the cost. Attempts have been made to determine the cost of surveillance programs.14 The type and frequency of surveillance testing will affect the cost. An isolated serum alpha fetoprotein (AFP) has low specificity but it is relatively cheap. Rising AFP levels are important and comprise an indication for hepatic imaging. Hence, the most widely used protocol is six

monthly ultrasound and AFP. This combined protocol is relatively low cost, sensitive and specific. Based on the doubling time of small asymptomatic HCCs, the six monthly interval means that most HCCs will be detected while they are potentially curable.[14] Reducing the surveillance time to three months substantially increases the cost per year of life saved. Using six monthly AFP and ultrasound, the cost per year of life saved appears to be significantly more than for breast, cervical or colonic cancer. To reduce this cost, surveillance should target high risk groups, such as older male patients and patients with already elevated AFP levels. It is reasonable to recommend six monthly surveillance in patients with HCV related cirrhosis in whom the detection of small hepatocellular cancers would lead to changes in management, such as, resection, ethanol injection or liver transplantation (*Table 4*).

Indications for liver transplantation

HCV cirrhosis is now the commonest reason for liver transplantation in Australian adults, with 30% of all adult transplantations for HCV associated cirrhosis. Liver transplantation should be considered when signs and/or symptoms of decompensation emerge (*Table 5*). Other factors influencing the decision to transplant include age, hazardous alcohol intake and continued opiate dependence. Patients are required to show significant insight into any problems associated with excessive alcohol use and be able to commit to long term abstinence. Patients who continue to inject drugs are not considered for liver transplantation and patients on maintenance methadone may be asked to consider methadone withdrawal. It is therefore important to foreshadow these issues during the long term follow up of patients with chronic HCV before advanced disease is established.

Although recurrence of HCV after liver transplantation is universal,[15] the medium term results are excellent *(Figure 2)*. However, 10% of allografts are lost in the short term due to HCV recurrence. Long term survival of patients beyond 10 years may be complicated by the development of recurrent HCV related cirrhosis. Therapies with pegylated interferon and ribavirin are currently under investigation in an attempt to improve outcomes.[16]

Table 4. Available therapies for primary liver cancer

	Therapy	Effectiveness
1.	Surgical resection	suitable for small tumours: 50–80% recurrence at 5 years
2.	Ethanol injection	suitable for small tumours, 50% survival at 3 years but 20–30% at 5 years
3.	Chemoembolisation	may decrease size of large tumours but no increase in survival
4.	Liver transplantation	suitable for small tumours* in patients with portal hypertension and/or liver failure
5.	Systemic chemotherapy/ tamoxifen	No proven benefit

*see *Table 5*

Table 5. Indications and suitability for liver transplantation in advanced hepatitis C

- Child B/C cirrhosis
- Small liver cancer in a patient with portal hypertension*
- No alcohol/drug dependence
- No significant extrahepatic disease
- Strong motivation, psychological support

*Tumours usually <5 cm diameter (single), <3 cm if multiple (<3), no extrahepatic spread

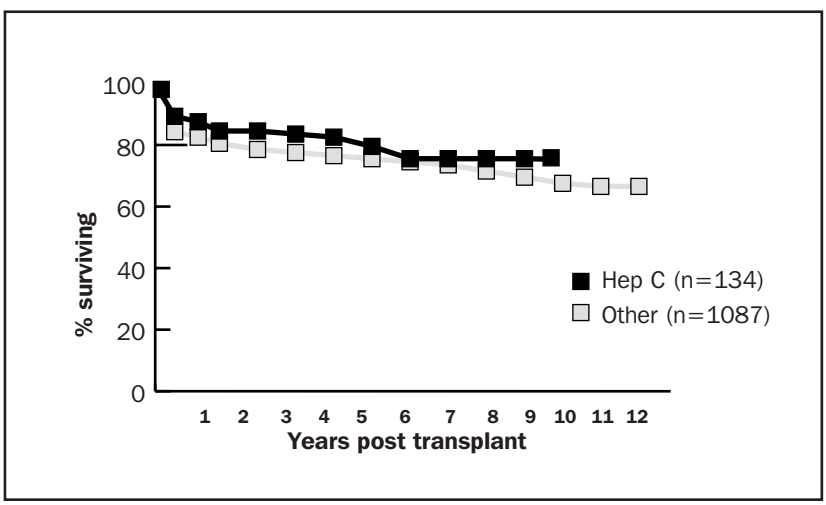

Figure 2. Liver transplant outcomes in patients with HCV associated cirrhosis. Source: National Liver transplant Registry

Shared care of patients with cirrhosis

It is clear that patients with signs or symptoms indicating cirrhosis and/or with HCC should be cared for in a close relationship between GP and specialist. Such care may need to be undertaken weekly to monthly depending on the situation. Patients with compensated cirrhosis (generally well, no jaundice or ascites, normal albumin) require regular review by specialists (1–2 years) but can be monitored more closely by GPs. In most cases GPs will be able to arrange six monthly ultrasound and AFP levels to screen for early HCC as well as liver enzymes, albumin, bilirubin, INR and full blood count.

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AFP

Meaning for the person

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Introduction and overview

In 1996 the hepatitis C councils across Australia carried out an analysis of needs faced by people living with hepatitis C.[2] A key finding was that discovering they had hepatitis C was shocking and traumatic for people. This was compounded if their treating doctor lacked the knowledge and skills to be able to counsel them about living with HCV. In November 1998, the New South Wales Legislative Council Standing Committee on Social Issues completed an 18 month inquiry into hepatitis C, and tabled their report entitled *Hepatitis C: The Neglected Epidemic*'.[3] Other reports also describe the needs of people with hepatitis C, and can serve as useful information sources for practitioners.[4]

The community based hepatitis C councils receive many thousands of calls each year, predominantly from people with hepatitis C, seeking information, support, counselling and advice about referral options. One could argue that the general practitioner is a better suited source for individually tailored advice and support, as it is often through a GP that the diagnosis of HCV is given. Thus the range of responses to the diagnosis of hepatitis C will depend, among other things, on the person's attitude to life and health at that time. A person who uses drugs very heavily may see HCV infection as the least of their concerns, perhaps through relief that the diagnosis is not of something more serious. A middle aged professional who dallied briefly with the needle years ago may be shattered by the discovery. A pregnant woman may have prime concern about the health of her unborn child. Health care workers contracting HCV occupationally, people with haemophilia or those who contracted HCV through blood transfusions may experience additional anger as a response. The GP is well placed to address the particular concerns of each person as they arise.

Personal and social impact of hepatitis C

Chronic HCV related illness can affect all aspects of a person's life. As one person noted in their submission to the NSW Parliamentary inquiry:[3]

> 'My illness has limited my capacity to work, seriously questioned my ability to be an effective parent, partner or friend, and prevented me from participating in my community. I feel isolated and often through that isolation, robbed of the necessary tools to combat negativity and hopelessness.'

Apart from the impact of fatigue, nausea, pain, feelings of general malaise and other outcomes of chronic HCV illness, the physical symptoms of chronic HCV infection lead, for many, to depression and mood swings, anxiety over the future, social isolation, loss of self esteem, the development of mild paranoia and acute stress regarding the decline of control over one's life. Many people describe their fears of death and their uncertainty, particularly about lifespan and the prospect of long periods of illness possibly leading to death from liver failure or cancer. Many are also concerned about passing on their infection to others.

Often, use of inappropriate terminology such as 'victim', 'plague', or 'junkie' can have a negative impact on a person's outlook on their lives. Even words such as 'sufferer' can sometimes act as a form of disempowerment and so possibly cause the person living with hepatitis C to view themselves in a negative light. Far better terms include: 'person with hepatitis C', and 'person who uses drugs illicitly'.

A positive diagnosis

The impact of a positive diagnosis, when given without adequate pre- or post-test counselling, can be devastating for a person.[2,5] It can add to the trauma of receiving news of being hepatitis C positive itself. Many people who received notification of their disease status in this manner continue to construct their perception of their illness in these helpless terms.

It is important, first, that a person gives their prior, informed consent to HCV testing. This is particularly true for pregnant women, who should be subjected to antenatal HCV screening only when there is a history of risk factors,[3] or if they request screening when counselled about relevant risk.

The GP can help to place the news of a positive

diagnosis in a meaningful context. It is vital that the GP affirms the fact that HCV infection can often persist for decades with no ill effect on the individual. However, even those who have no symptoms can develop considerable anxiety about what the future holds. Since the majority of people with hepatitis C do not progress to severe liver damage (*Chapter 6*) and long term prospective studies show no comparative reduction in longevity in people with HCV infection,[7] the GP can help to allay excessive concerns.

Anticipation of common concerns is invaluable. Counselling a person with HCV is time consuming but vital. A few facts, for example, that liver cancer does not usually occur unless cirrhosis is present, may not only help to maintain perspective, but may also encourage the person to become fully informed about their condition. For those with nonspecific symptoms such as malaise, fatigue or anorexia, it is imperative the GP seeks and excludes coexistent morbidity. In one study, up to 57% of HCV positive people who inject drugs had significant depressive symptomatology.[9] It is worthwhile pursuing treatable conditions before attributing all symptoms to HCV.

Treatment considerations

Treatment, for those who have tried it, can impact enormously on a person's life. It brings with it its own set of physical and psychological side effects. Fewer than 4% of Australia's estimated (at 1997) 190 000 HCV antibody positive people have tried interferon therapy.[9] Pharmaceutical treatment gives great hope to affected people. Expectations of success are high.

There are many information resources available, and it is recommended that in addition to being verbally briefed by a primary health care practitioner and specialist, written information is provided to the person with HCV.

As discussed in *Chapter 8*, it is also vitally important to adequately assess an HCV infected person's suitability for interferon (IFN) (or IFN/ribavirin) treatment in terms of their potential tolerance. Some people with a history of depression or other mental health problems can undergo such treatment, provided there is additional monitoring of psychological progress and possibly concurrent use of antidepressant medication. The capacity for IFN to have a significant psychological impact is great. Mood swings and depression have been known to cause suicides for people on interferon treatment.[10,11]

Appropriate counselling and support by an experienced and empathetic practitioner is especially important for a person considering treatment. A full explanation of the potential impact on that person, their family and possibly their employer is highly desirable. It may be appropriate for the person to consider making arrangements that could allow them to take some time off work at times when side effects are likely to be greatest (the first four weeks). This needs to be balanced against considerations of the person's confidentiality and their desire to disclose their HCV status or not.

No treatment

Many people with hepatitis C are not interested in undergoing currently available pharmaceutical therapies. This could be because the levels of toxicity, relatively low treatment success rates or significant side effects may combine to deter many from embarking on a course of treatment. Furthermore, others may have the opinion that HCV is not a serious illness, a view widely promoted in the early 1990s. For many of these people, a purely medical approach to their health monitoring and maintenance is neither appropriate nor helpful.

While medical treatment remains controversial and the long term effects of the newer antiviral therapies are unknown, GPs best serve their patients by supporting their choice of management. Realistic guidelines about alcohol management, diet and nutrition, stress management, appropriate referral to psychological or social support services and even just spending time with and providing support for a person with HCV are highly desirable and useful. Together with appropriate referral to available services and an acknowledgment and understanding of a person's loss of their previous optimum health status, the above are often all that is required to give an individual the tools they need to manage their own health and wellbeing more effectively.

Complementary therapies

Western herbs such as St Mary's thistle (*silybum marianum*), Chinese herbs such as the CH100 formula (subject of scientific trials in Newcastle and Northern Rivers in NSW and in WA) and raw Chinese herbs, homoeopathy, acupuncture, naturopathy and nutritional supplements are all widely used by people with hepatitis C, with varying results.

Frequently, with any treatment, people are given overly optimistic notions of the likely success of their treatment. Treatment failure, be it alternative or conventional, can be devastating. It can be even more harmful if the person feels they have burnt their bridges with their GP by having chosen alternative treatments.

The Hepatitis C Handbook is an excellent resource containing detailed information about complementary therapies and a complete overview of all aspects of HCV.[12]

Self management: alcohol, diet and stress management

The ideal course of action for anyone with HCV is to drink no alcohol and eat a balanced, regular diet. Often it is very difficult for someone to cut out alcohol entirely, especially if it is part of their social life or if there is an alcohol dependency. Referral to a support service may be appropriate but there are techniques people can use to help reduce, as far as possible, the amount of alcohol consumed (*Table 1*).

Effective stress management is often a very difficult aspect for people with HCV to come to terms with. Time spent just listening to someone talk about their worries, referrals to appropriate support services, counselling, or providing guidelines about gentle exercise and relaxation techniques can all be of immense benefit.

Medical acquisition of HCV

Those people who contracted HCV through blood transfusions or through receipt of blood products, and health care workers who contract HCV in an occupational setting often express additional emotions of anger, frustration, disbelief and bitterness at their diagnosis. Links made by society at large with injecting drug use can make their situations even more difficult.

Some blood banks have caused additional unnecessary harm by informing lookback program clients of an HCV positive diagnosis by letter, and additional support for these people is appropriate.

Rural communities

Particular additional problems of distance to health services, few resources, less support, fear of rejection by the local community, confidentiality, self employment problems and some small community attitudes are just some of the aspects of rural and remote life which have the potential to intensify the already existing problems for a person living with hepatitis C.

Table 1. Practical alcohol management guidelines for a person with hepatitis C

- Above all, binge drinking should be avoided
- Start off with a non alcoholic drink
- Alternate usual drinks with alcohol free or low alcohol drinks
- Switch to low alcohol drinks
- Break the habit of drinking in rounds
- Have at least two alcohol free days a week
- Note that alcohol itself is a cause of possible liver inflammation
- Refer to an alcohol information and support service if appropriate
- Support a person to achieve the single most important lifestyle change that can impact on their health
- It is no use just to tell someone with hepatitis C they have to give up drinking. They need to be provided with the tools and support to enable them to make that change.

Prisoners

Prisoners with HCV do not have the same access to information and support, or health services, as those in the general community. Additional support and referral services may be required by prisoners with HCV on their release.

Family relationships

Hepatitis C can impact on parenting and families in many negative ways. Fear of HCV transmission to children is one example, even though the risk is low. Another is the impact of symptoms on the ability to have the physical energy to look after, interact with and raise children. Single parents, extended families and parents with alcohol or other drug dependencies face additional burdens as a result of their hepatitis C illness.

Migrants and people from non-English speaking backgrounds

People who have acquired HCV in certain countries abroad may develop symptoms in later life. Without obvious risk factors, hepatitis C may be more difficult to diagnose. Apart from the clinical implications of rarer HCV genotypes, the information and support services available in Australia for people whose first language is not English are lacking. The issues surrounding hepatitis C in migrants

are explored further in *Chapter 12.*

Confusion with HIV, other viral hepatitides and sexual transmission

Unnecessary fear and hardship often result from the confusion between HIV and HCV. It is important to reassure people with hepatitis C that apart from certain shared political and public health responses to the epidemics of both HIV and HCV, and except in the case of coinfection, there are few other links. Some transmission routes and risk behaviours overlap, but clinical effects, communities affected, prognosis and treatments are all different. It is also important, where necessary, to assist a person with hepatitis C to distinguish between HCV and the other hepatitides, ranging from A through to G.

The close linkages with HCV and sexually transmissible viruses can cause confusion and upset for people with hepatitis C, particularly for those who have been in long term, stable relationships where couples have only had each other as sexual partners. While safer sex guidelines are certainly advisable where there is a risk of blood to blood contact during sex, or where a person has new or multiple sexual partners, there is usually no need for HCV positive people in long term, monogamous relationships to start using condoms when having penetrative sex.

Discrimination and stigmatisation

A keynote speaker summed it up well when he said at a major HCV conference that discrimination faced by people with hepatitis C was a secondary or underlying epidemic, just as prevalent, just as virulent and just as threatening as hepatitis C itself.[1] The NSW inquiry found and was greatly concerned about the extent of the discrimination and stigmatisation against HCV positive people by:

- health care workers including nurses, GPs, medical specialists and dentists
- friends of the person with hepatitis C, and
- the general community.

Additionally, at least two studies have documented discriminatory incidents experienced by those with hepatitis C.[13,14]

Calls to hepatitis C council lines and information from drug user community organisations provide disturbing amounts of evidence of discrimination.

Discrimination by health care and allied workers

Before diagnosis, a person with hepatitis C typically experiences fatigue related symptoms; prolonged periods of light to very serious unwellness and inability to cope despite having (if no HCV test is carried out) no adequate explanation or reason. This often results in implicit or explicit accusations of 'malingering' or hypochondriasis, largely by primary health care providers.

> 'When I became ill I was a postgraduate student with a bright future. I have had to face the possibility of never working again and this has been very difficult to accept, particularly when others have disparaged me as 'hypochondriac' and I myself have felt that my illness was psychosomatic or mere 'laziness'. Many people, myself included, find it difficult to accept the existence of 'invisible illness' such as hepatitis C.'[2]

Current or past drug use is often reported as a major obstructing factor in good relations with an HCV positive person's doctor or other health care worker. The marking or 'branding' of HCV positive people in health settings (eg. with yellow armbands or some other tag) is both unnecessary and likely to lead to public disclosure of HCV status and breach of confidentiality. Rigorous adherence to standard infection control guidelines will preclude the need for this.

Doctors advising women to terminate their pregnancies because they are HCV positive should know that this is inappropriate, illegal, and possible grounds for litigation. Consensus guidelines state that unless there is a risk of blood being present in breastmilk, in which case formula feeding could be substituted, the benefits of breastfeeding probably outweigh the low risk of HCV transmission.[3,15]

In Croft's study, 46% of discrimination cases against people with HCV occurred in health care settings.[14] Doctors who are unwilling to continue seeing HCV positive clients ought to explain this to their patient and give them a reliable referral to another GP or to hepatitis C telephone information and support services. Funeral workers are commonly known to refuse relatives to view or touch the body or even carry the coffin of deceased HCV positive people.[2,5,13]

Disclosure

Except in the case of certain health care workers in certain jurisdictions, there is no legal obligation for

anyone to disclose their hepatitis C status to anyone else. Often, though, people feel a moral obligation to inform others, only to find their trust breached when that knowledge gets into the public domain. Again, read the testimony of an HCV positive person:

> 'I constantly live in fear of someone discovering my secret and being automatically pre judged and stereotyped. The guilt I carry is soul destroying. It creates an added stressful burden that intensifies my illness and interrupts what could be a reasonably normal life.'[2]

Inadvertent disclosure of someone's HCV status is unnecessary and harmful. Often there are valid reasons for a person disclosing their status to a health care worker or some other person. But to pass that information on without a valid reason for doing so, and without the person's consent, is wrong.

Additional discrimination is faced by people with hepatitis C who use drugs illicitly. It is clear that a double stigmatisation of people with hepatitis C who inject drugs occurs with gloomy regularity. Often assumptions of illegal behaviour (and this labelling remains a great hurdle to effective health care and management) are made whatever the mode of HCV transmission or whether the patient used drugs years before.

People who currently use drugs illicitly often report disbelief and dismissal, on the part of health care workers, when genuine requests for pain relief or support are made. The labelling of drug users, or the more negative term 'junkie', can become barriers to people seeking help as they feel they will encounter these reactions from health care providers.

If someone with hepatitis C remains engaged in risk behaviours, such as drug injecting or tattooing, by informing them in a balanced and empathetic way of the true facts around HCV transmission routes, a doctor can make a significant impact in preventing secondary transmissions: a vital consideration when their patient can then pass on accurate information to their friends and contacts.

Discrimination by the general community

As one person from a rural area commented to the NSW inquiry:

> 'Combating the disease and the discrimination simultaneously and with so little public information or awareness at hand makes the condition almost unbearable.'

People with hepatitis C have an important role to play in the promotion of public understanding of the disease, its methods of transmission and prevention, but are often unable to make this contribution because of the public's response to them as infected people, or through lack of understanding of these issues themselves.

Financial impact

Many HCV positive people with serious symptoms are unable to continue working in their normal capacity, as the effects of chronic fatigue limit their ability to work full time. Self employed people, who are unable to work, frequently put already financially vulnerable businesses at risk especially in rural areas. Of all professions, the economic impact is possibly greatest upon those HCV positive people who are health care workers, especially where their line of work requires them to perform exposure prone procedures.

Inadequate, substandard or difficult to access housing is an additional burden for people with hepatitis C, particularly for the very many who already live in financial hardship. Difficulties accessing disability support pensions for those theoretically eligible add further psychological stress to their existing problems of coping with symptoms and reduction of income.

Referral and conclusion

In each Australian state and territory there is either a community based or government organisation providing information and support services. Hepatitis C councils and drug user consumer groups play vital roles, along with primary health practitioners and other health care providers in ensuring people with hepatitis C and the general public are better informed. Effective networking, cooperative partnerships and sharing of information and support resources will go a long way to ensuring the needs of people living with hepatitis C are better met, and will help bring this neglected epidemic under control.

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The meaning of hepatitis C for the community

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As with any new or newly discovered infection, hepatitis C virus (HCV) has developed a range of meanings for the Australian community. These vary widely between different interest groups and have evolved over time. Research elucidating the nature of the virus and its associated disease, and the availability and nature of treatment for chronic HCV infection, have set the agenda for these meanings. In many instances the pace of this research has been slow, leaving widespread uncertainties that have fuelled prolonged controversy and debate. Many such uncertainties remain, including less than perfect treatment, and these are mirrored in continuing confusion about the meaning of hepatitis C to the community.

It is reasonably clear that transmission of HCV occurs very largely through blood-to-blood contact. Issues of contagion have arisen from time to time, especially in the context of discrimination against people infected with HCV, but, in contrast to the early response to HIV, the HCV has never been seen as a threat to the whole community.

The early governmental response to evidence of high prevalence of HCV among those who inject drugs exacerbated confusion on the part of some segments of society. Harm reduction programs (especially needle and syringe exchange, expansion of methadone maintenance programs and peer education) had targeted HIV almost exclusively and their impact on other blood borne viruses, especially hepatitis B and C, had never been evaluated. Therefore, when HCV was shown to be present in very high prevalence even among injecting drug users (IDUs) who were clearly in contact with these programs, the initial response from government took the form of the syllogism: 'these programs are effective in stopping the spread of HIV; HCV is spread the same way as HIV; therefore the programs will be effective in stopping HCV'. This response was partly responsible for fostering the misconceptions that HCV is sexually transmitted (as is HIV), and that HCV is a deadly, AIDS like virus – these erroneous views are still commonly held. The continued spread of HCV among those who inject drugs placed harm reduction programs into question. However, several agencies inimical to these approaches concluded that they did not work, failing to appreciate the differences between HIV and HCV.[1]

Underlying these responses, and often commented on but poorly documented, was a belief that because HCV was only blood spread, and because the introduction of universal donor screening for HCV in 1990 had ensured the blood supply was protected, the major group at risk of HCV was IDUs. Given the common attitudes toward people who inject drugs as socially undesirable, there was therefore little perceived political priority for HCV control.

Stopping the hepatitis C epidemic

In terms of control of the HCV epidemic, generating political will has proven the greatest challenge. Because most people in the community perceive HCV as no threat to them, governments do not immediately see an urgency or a cost benefit in providing funding for control. HCV is effectively not sexually transmitted in the majority of cases, and is absolutely not contagious. To become infected with HCV, one must engage in injecting drug use, or to a much lesser degree other behaviours such as tattooing – behaviours that are not common in the general community, and are often highly stigmatised.

It has been estimated that there are 11 000 new infections with HCV per year, almost exclusively among IDUs – this is a sizeable epidemic.[2] Given the very high prevalence of HCV among those who inject drugs, and the relative lack of spread of HIV and some other blood borne viruses in the same groups,[3] there seems to be no clear path in targeting education strategies. Evidence suggesting that HCV is spreading between IDUs by blood

transfer in ways other than the sharing of needles and syringes further complicates development of control strategies.[4,5] A sense of futility pervades some quarters, including among many drug users: 'Everyone has got it, so why should I care?' Strategies proposed for control of HCV in Australia include the promotion of noninjecting routes of administration of illicit drugs. These have caused much debate in some quarters and lead to a consideration of an even more contentious issue, that of drug policy reform.

The main reason for the continued transmission of HCV among those IDUs would seem to be the vastly higher prevalence of HCV compared with HIV – the major mode of transmission is sharing of needles and syringes, a behaviour that must be virtually absent if HCV transmission is to be significantly curtailed. This implies major expansion of strategies for distribution and disposal of needles and syringes. Existing control measures for blood borne viruses are increasingly being seen as expensive, and governments do not have the resources to expand them in proportion to the size of the epidemic. Part of the current debate about the best way to control illicit drugs in the community is a backlash against harm reduction policies, despite their manifest success. In this atmosphere, it is becoming more difficult to maintain the partnerships between governments, the scientific and medical community and the affected community which have been so effective in controlling transmission of HIV.

Control of HCV transmission among those who inject drugs therefore remains problematic; it also raises the very thorny question of control measures in prisons. Control of HCV transmission in prisons is seen to be essential to control of HCV in the community, because of the role in promoting sharing of injecting equipment and mixing of at risk populations. This issue too is socially divisive, with calls for needle exchange programs in prisons by public health authorities being met with condemnation by some politicians and prison authorities.

Dealing with discrimination and stigmatisation

Hepatitis C has raised major issues related to discrimination and stigmatisation in the Australian community. Many of these issues are based on ignorance of the modes of transmission of HCV, resulting in fear of contagion; many are related to interactions of HCV infected people with the medical profession.[6] In some states, antidiscrimination authorities have responded to these issues to some extent, but the major part of this discrimination remains hidden; few antidiscrimination suits around hepatitis C have reached relevant tribunals to date. Impressively, despite the clear epidemiological picture, with the majority of those infected having a background of injecting drug use, when a case series of discrimination and stigmatisation related to HCV was collected in 1994, none of the cases was reported from someone with such a background.[5] It can be speculated that this was because those with a history of injecting drug use were not prepared to complain of the discrimination they had suffered, either because they were aware of the futility of such action or from fear of disclosure of their behaviour that would worsen their situation. Discrimination and stigmatisation on the grounds of hepatitis C status are inextricably linked with discrimination and stigmatisation against people with histories of injecting drug use; joint and separate action to diminish both is necessary.

One deleterious aspect of the realistic belief that the majority of those infected with HCV were or are IDUs, and the social stigma injecting drug use attracts, has been the stigma attached to hepatitis C as a disease of 'junkies'. This has had iniquitous effects on those infected with HCV through means other than injecting drug use, who are tarred with the same brush, and it has created several levels of difficulty in responding to the epidemic. First, portrayal of the epidemic as the serious public health threat that it is, so as to win government support for efforts to control it, has necessitated emphasis of the threat to the individual's health. This has created unnecessary fear in the minds of many people living with HCV, whose health may not actually be threatened, or at least not to a significant degree. Aggressive marketing on the part of companies selling treatments for chronic HCV infection has contributed to this unnecessary fear.

Second, divisions have sometimes arisen between people living with HCV in relation to the mode of acquisition. As happened with HIV, some in the community divide people living with HCV into 'innocent victims' and those who contributed to their own infection (for the most part, those who

inject drugs). This division has affected the hepatitis C 'community' as well, with conflicts between different community organisations – hepatitis C support groups on the one hand, and drug user peer groups on the other. In part, these distinctions, based on moral assumptions rather than science, have also underlain discriminatory attitudes toward treatment availability.

A further cause of division and tension has been the alliance of HCV with HIV in the national response. Rather than developing specific mechanisms to deal with HCV issues, HCV was simply added on to existing HIV structures as a 'related disease'. As well as dividing the affected communities, especially around priorities for the division of scarce funding, this strategy caused immense confusion among the general public and the media. While the strategy gave HCV a higher profile as an issue than it might have otherwise gained, it led to media references to HCV as 'Australia's most common HIV related condition', and to the groups most at risk of HCV being 'prisoners' and 'young people who don't use condoms'. This in turn has fed back into stigmatisation of people with HCV, conflated as it is in the public mind with HIV.

Treatment and care

Given the nature of the major affected group, HCV also raises questions about access to treatment and care. Injecting drug users suffer much discrimination; for instance, under conditions laid down by the first NHMRC Working Party on HCV, this group was denied access to treatment with alpha interferon. The reasons given for this were that IDUs do not care about their health, are noncompliant and might not complete treatment, and that even if cured they will simply become reinfected.

There are reasons for concern about treating all patients chronically infected with HCV with currently available treatments. Such treatment is effective only in a proportion of cases, and is associated with potentially major side effects (*Chapter 8*). Little is known about how to target treatment to those who will benefit most. High proportions of IDUs, the major group requiring treatment, have conditions such as depression that may contraindicate current therapies.[7] Until simpler, safer and more effective therapies for chronic HCV infection are available, decisions about treatment – both at the community and individual levels – will remain controversial.

Again, much of this controversy is fuelled by antagonistic or at best ambivalent attitudes toward the major risk group, injecting drug users, whose access to nondiscriminatory and appropriate health care is limited.

The cost to the community

Calculations of the potential cost to the community of the hepatitis C epidemic are limited. One such calculation concluded that for every 1000 new HCV infections, approximately $14.32 million would be added to Australia's direct health care expenditure. Given the estimated 11 000 new infections per year, this gives a total of around $150 million per year – 0.5% of the total commonwealth health budget in 1994 terms.[8] These calculations did not account for indirect costs generated by HCV, including loss of productivity through time off work and income replacement costs, nor the social costs of HCV including discrimination and family breakup.

A second estimation found that the total cost burden of HCV to the community – including costs of research, prevention, diagnosis, treatment and palliation – was approximately $75 million in 1996–1997, of which total treatment costs were about 60%.[9] This same analysis found that the average lifetime direct health care costs generated by each person with chronic HCV infection is around $13 000 in 1996 terms, for a total of about $13 million per 1000 new infections – very much in line with the above estimate.

Allocation of resources is therefore an issue of major debate, as it perennially is when limited resources are called upon for both treatment and prevention. Clearly where treatment is well targeted and effective, it both prevents further transmission and secondary, costly disease sequelae. Just as clearly, if the rate of transmission remains high, there will be far more people infected with HCV who will in the future require treatment.

Discussion

Just as the previous epidemic of HIV was characterised by the raising of many divisive and difficult public policy issues, so too is the current epidemic of HCV. Similarities between the two epidemics include the targeting of some of the most vulnerable and politically most disenfranchised groups, raising issues of discrimination, resource allocation

and priorities for preventive action. To most in the community, HCV is a disease of other people, requiring no action for their own protection. The people who are affected are often socially stigmatised; therefore by association hepatitis C itself has become socially stigmatised. There is no immediate political constituency for the major groups affected by HCV, IDUs and prisoners, so generating political will to combat its transmission is difficult.

However, today's IDU is often tomorrow's solid citizen, as is being observed in gastroenterology clinics where many of the patients with chronic HCV infection have hidden histories of injecting drug use from many years before. As well, every new HCV infection carries a chance of the need for expensive medical treatment at some time in the future, however infection occurs. If altruism does not convince, self interest should motivate action on the part of government to do everything possible to curb the HCV epidemic now.

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Hepatitis C infection in migrants Issues for GPs

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It is estimated that 170 million people worldwide are infected with the hepatitis C virus (HCV).[1] Studies of blood donors suggest the prevalence of anti-HCV antibodies is low in northern Europe, the USA and Australia, higher in southern Europe, the former USSR, the Middle East, Asia, South America, and highest in Africa.[2] The recent spread of the virus is thought to be due to receipt of blood products before the introduction of testing, poor infection control measures in some countries, and increase in injecting drug use (IDU) in western countries.

It is difficult to gauge the level of HCV infection among different ethnic groups within Australia from diagnostic testing. Hepatitis C is notified by laboratories, but these notifications do not contain information on the ethnicity of the patient. Generally, in New South Wales, unless a doctor reports an acute case, active follow up is not performed and therefore no information is obtained on ethnicity. As hepatitis C serology is not required for migration to Australia, positive serology cannot distinguish between an overseas and a locally acquired infection. To date there are few data published on hepatitis C seroprevalence among different ethnic groups in Australia. Therefore the only available information on HCV infection in ethnic groups comes from seroprevalence studies performed in the country of origin. Worldwide data on new and chronic infections are not optimal or are incomplete: most data come from blood donor studies or other limited epidemiological investigations and as such cannot be readily extrapolated to entire populations. These studies often do not include confirmatory testing and may include many false positives. They should therefore be viewed as only broadly indicative.

Higher prevalence of hepatitis C in some ethnic groups

The prevalence of hepatitis C varies from country to country. South East Asian studies found the prevalence of hepatitis C was 3.9% in Indonesia,[3] and 4–9% in patients with no known risk factors in Vietnam.[4] Studies from the Middle East indicate hepatitis C prevalence as 6% in Yemen,[5] 0.11% in Lebanon[6] and up to 21% in Egypt, where there is thought to be a strong association between HCV and parenteral therapy for schistosomiasis.[7,8]

Australia is a melting pot of different nationalities and within the past two years 85 752 new settlers have arrived.[9] Before migration into Australia, all immigrants and refugees undergo screening for tuberculosis and those 15 years and above are tested for HIV. In most states and territories, refugees are offered voluntary postarrival screening for diseases such as hepatitis B but hepatitis C screening is not generally included.

Hepatitis C in people from non-English speaking backgrounds (NESB) is not usually associated with IDU. In older NESB people, HCV infection is mostly associated with the use of unsterilised medical equipment in their country of origin. In countries such as Italy, it is generally thought that the spread of HCV may have occurred years ago through parenteral routes such as mass vaccination campaigns and injections for treatment of tuberculosis.[10] However, in younger NESB people HCV infection may be linked to injecting drug use.

In developing countries, transmission of HCV may still continue due to practices such as unscreened blood transfusions, inadequately sterilised hospital and injecting equipment, scarification and circumcision tools.[1,2] Modern hygiene and sterilisation measures, such as those used in Australia, have significantly controlled exposure to HCV infection which in the younger generations is mainly confined to high risk groups, such as persons who inject drugs.

Most current resources available for the prevention of hepatitis C target those in the latter risk group. As this is not usually the predominant way in which migrant cases contracted their disease, much of the information may appear irrelevant. In

addition, people may feel victimised and shamed by being inadvertently associated with drug use and the stigmatisation attached to it (*Chapter 10*). Written information on hepatitis C in other languages is not readily available.

Clinical assessment of hepatitis C in persons from a NESB

People from a NESB with hepatitis C may present with more advanced disease. Thus, a recent study found that persons with chronic HCV born in countries of high HCV prevalence had a considerably higher risk of cirrhosis compared to those born in low prevalence countries. This was thought to relate to longer duration of infection, which may have occurred at a younger age.[11] Therefore, hepatitis C screening is critical in older clients from NESBs who present with cirrhosis or elevated liver function tests, and should be considered in those with a nonspecific loss of good health. In addition to the nonspecific nature of symptoms in hepatitis C, the physical expression of signs of chronic liver disease may be less obvious in those from racial backgrounds associated with skin pigmentation. For example, spider naevi are easily missed in Melanesian people. There are also cultural differences in how illness is handled in families as discussed below.

Difficulties in accessing services for NESB people

It is important that people with hepatitis C are managed with sensitivity to their cultural and language needs. Some patients will travel significant distances to see a culturally appropriate GP, while others tend to change their GP frequently, making continuity of care difficult. Referral to specialist clinics is often difficult for these patients as they are unlikely to be reviewed by a clinician speaking their own language, and interpreter services are not always readily available. This client group often relies heavily on their children or other family members for medical management decisions and interpretation. Therefore, it is imperative that GPs understand these issues and ensure ongoing care for NESB people with chronic HCV. A GP who speaks the same language as the patient is often the best person to discuss aspects of management and prognosis with the family, especially when complex issues are involved, such as clinical trials of new treatment and life threatening complications.

Unemployment rates are higher, particularly in Vietnamese, Lebanese, Cambodian and Chinese migrants than in Australian born people.[12] This may lead to financial constraints and difficulty in paying medical expenses. Migrants and refugees may have to deal with numerous psychological problems such as communication barriers, isolation and lack of understanding of, and from, the medical system. Refugees in particular may be recovering from the trauma of conflict such as torture, injury, and loss of family and friends.

Infection control issues in relation to traditional practices

Some traditional practices performed in a person's homeland may place them at risk of acquiring blood borne viruses including HCV. Examples include ritual tattooing and female genital mutilation (FGM). These procedures are most often performed by traditional practitioners without medical training. In settings such as these, infection control procedures may be minimal or nonexistent. Some of these practices may be continued in Australia. Although FGM is illegal in Australia, it may still occur, though to date there have been no prosecutions. Some parents may, however, send their children to their homeland to have the ritual performed.

Some overseas born communities continue to utilise untrained and/or unregistered dentists ('backyard dentists'), who are unlikely to practise adequate infection control. Identification and prosecution of these practitioners is a difficult task.

A hepatitis C shared care project

There are substantial geographic differences in ethnic mix across Australia. South Western Sydney Area Health Service (SWSAHS) consists of one of Australia's most culturally diverse populations. Fairfield local government area is a striking example with 53.5% of the population born overseas. More than 35% of the SWSAHS population were born overseas compared to 23% across NSW; 37.5% of those over five years of age speak a language other than English at home.[12]

Under a demonstration program funded by the NSW Health Department, SWSAHS has initiated a hepatitis C shared care project specifically targeting NESB populations. This group is being targeted, as they are less likely to have contracted the

infection through IDU and therefore, derive less benefit from currently advocated prevention interventions. They also contribute greatly to the attendances of the two local hepatology clinics (80% at Bankstown and 50% at Liverpool). The project is utilising national shared care protocols modified to meet local needs aiming to involve and support GPs in the ongoing care of this client group. Educational workshops have been provided to government and nongovernment organisations that serve NESB clients with, or at risk of, HCV infection. In addition a hepatitis C manual and hepatitis C booklets translated into 16 languages have been made available to GPs and other service providers in SWSAHS.

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Test technology

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The so called first generation hepatitis C virus (HCV) antibody tests (anti-HCV) were based on recombinant proteins from the NS3/NS4 non structural region of HCV and were derived from the original clone.[1] This test became available in Australia in early 1990. In May, 1991, second generation assays incorporating a combination of core and other non structural antigens were introduced. Subsequently, many companies have marketed a variety of anti HCV assays. These tests tend to give concordant results with strongly reactive samples. However, subtle differences in sensitivity and specificity mean that discrepancies do occur between assays when testing some other samples.[2,3] More recently, third generation tests have been released. These tests contain additional antigens, such as NS5, and some of the other antigens have been reconfigured in an effort to increase sensitivity.

Sensitivity and specificity

The sensitivity of an anti HCV assay can be defined as its ability to detect reactivity in specimens from subjects who have been infected with HCV. The specificity is defined as the ability of the assay to show non reactivity in specimens from subjects who have never been infected with HCV. In reality, there is no accepted gold standard for confirming the presence or absence of antibodies, hence sensitivity and specificity can only be estimated.

Studies of blood donor and other low risk populations show that there has been a clear improvement in specificity from first generation to second generation tests, with specificities now exceeding 99%.[4] Third generation testing was shown to resolve the status of a high proportion of samples with indeterminate second generation serology. However, it also has generated a number of indeterminate results in previously negative individuals.[5] Apparent false reactivity has been documented in conditions associated with autoimmune disease, hyperglobulinaemia and alcoholic liver disease[3] but it also occurs in samples unrelated to these conditions. The cause of false reactivity is difficult to determine. It must be recognised that the antigens used in the assays are made by molecular means; the antigens are probably not in the native conformation produced by the natural viral infection.

While the development of the first generation tests was considered a major breakthrough it only detected 60–80% of infected individuals, and in acute cases it was up to 6 months before 90% of patients showed evidence of seroconversion. This improved considerably with the second generation assays, largely due to the inclusion of c22-3 (core antigen). This allowed detection of a further 12–20% of infected individuals and detected seroconversion 1–3 months earlier. Third generation assays have marginally increased sensitivity and further reduced the window period after acute infection. These improved characteristics appear to be mostly due to modifying the antigens and plate coating concentrations rather than the addition of the NS5 antigen.[3] Under the National Health and Medical Research Council strategy, a positive test must be confirmed before a report will be issued.[4] For diagnostic laboratories, this means those samples which are positive on initial testing are re-tested using a different assay which contains a different range of recombinant HCV antigens. If the second test is positive, then a positive result is issued. If there is a difference between the two test results, the sample is re-tested using the initial assay. If this remains positive, then the sample is referred to a reference laboratory for further testing.

The use of HCV anti HCV tests is the most widely used and cost effective method for diagnosing hepatitis C. The format for the test is similar to standard serological assays and it can be automated, which makes it suitable for the large scale screening required by blood banks. However, these assays are limited because there is no true confirmatory test for the diagnosis of HCV infection. Some discrimination can be obtained by supplementary tests such as immunoblots or by alternative assays such as viral nucleic acid tests.

Anti HCV supplemental assays

The most commonly used anti HCV supplemental assay is the recombinant immunoblot assay (RIBA). Instead of having the HCV antigens coating a bead or on the bottom of a plastic well, the proteins are blotted as individual bands onto a nitrocellulose or nylon strip. As with the plate based assays, several generations of immunoblots have been developed and third generation assays are currently available. A Western blot assay is also available in which the recombinant antigens have been separated on a gel and subsequently blotted onto the strip. These assays have the advantage of determining the specific reactivity of the patient's antibodies to the individual HCV proteins. Normally the result is deemed positive if there is reactivity with two or more bands, indeterminate with one band and negative for no specific reactivity. The strips contain appropriate controls, including one to control for reactivity to the proteins from the expression system and controls to estimate the intensity of reactivity. The latter allows for a qualitative assessment of the amount of HCV antibody present that can be reported as 1+ to 4+. The use of supplemental assays to aid diagnosis is controversial. Many believe that they contribute little to diagnosis and, as they are expensive, several laboratories prefer to use nucleic acid tests as an alternative.

Viral nucleic acid testing – detection of HCV RNA

In the absence of any suitable methods for direct detection of viral antigens, assays have been developed to detect the presence of HCV RNA in blood. The most common assay used is the polymerase chain reaction (PCR). This relatively new technology relies on amplification of a targeted piece of the viral genome to allow for easier detection. For HCV, the RNA must be first converted in vitro to DNA. There have been a number of difficulties in bringing what was essentially a research technique into the diagnostic laboratory but reproducibility and quality control problems have largely been overcome by the development of the semi-automated HCV COBAS AMPLICOR assay (Roche Diagnostics). Another form of nucleic acid amplification of HCV RNA, transcription-mediated amplification (TMA), is currently being used by the Australian Red Cross Transfusion Service. The assay relies on the generation of a large number of RNA transcripts from the original RNA using a DNA intermediate. The transfusion services favour the dual TMA HIV 1/HCV assay which can detect either HCV or HIV RNA. Molecular techniques based on PCR are also available for measuring viral load (Roche HCV Monitor). This test is less sensitive than the qualitative PCR and much more expensive. Prototype kits for so-called real time PCR are currently being evaluated (Roche Taqman HCV assay). Normally, PCR product is detected or quantified when cycling has been completed, so-called endpoint measurement. A more precise quantitative measure is during the exponential phase of amplification when the efficiency of the PCR reaction is at an optimum and not influenced by limitations of reagents and other thermal cycling parameters. Most real time PCR assays rely on fluorimetry based detection chemistry to detect PCR product as it is accumulating without having to physically remove the samples for analysis. Results are displayed as an amplification curve showing the increase in fluorescence during cycling. This newer PCR quantification technology offers a wider dynamic range and more accurate quantification of HCV RNA and will supercede the present MONITOR assay. Additionally, viral load can be measured by an alternative technology, branched chain DNA (bDNA, marketed by BAYER). This relies on chemiluminescent signal amplification. This method is less sensitive than the HCV Amplicor and Monitor tests but is not prone to problems with contamination as there is no amplified DNA.

One of the major uses for HCV RNA detection has been to monitor antiviral therapy, both to predict and determine response.[6] It also has some diagnostic applications. These amplification assays are capable of distinguishing past resolved infection from active infection, particularly useful in patients with normal liver function tests. In acute infection, patients may be PCR positive as early as 2 weeks post infection, well before the development of an antibody response. There is a common misconception regarding PCR as a substitute confirmatory assay. It is true that a valid PCR positive result does show that the patient is infected with HCV. However, there will also be patients truly anti HCV positive but PCR negative; such cases probably represent resolved infection.

Nucleic acid amplification testing for hepatitis C viral RNA has recently been included on the Pathology Services Table of the Medicare Benefits Schedule (MBS). However, testing is restricted to one test per year and defined criteria must be met; these are:

- seropositive patients who have had normal liver functions tests on two occasions 6 months apart;
- indeterminate serological status;
- determining the hepatitis C status in the immunocompromised/immunosuppressed; and
- detection of acute hepatitis C before seroconversion (eg. needlestick).

An extension of the PCR technology for HCV is genotyping. As nucleotide sequence data have been accumulated, it has been shown that HCV is genetically heterogeneous and phylogenetic analysis has allowed HCV to be arbitrarily classified into sets of distinct genotypes. Determination of genotype has been proven to be clinically useful as a predictor of response to treatment. Using combination therapy of interferon and ribavirin, it has been shown that treatment duration can be tailored according to the infecting HCV genotype.[7] For patients infected with HCV genotype 2 or 3, sustained response rates were not increased when therapy was continued beyond six months. In contrast, for patients infected with genotype 1, 12 months of therapy was necessary before higher sustained reponse rates were achieved. In Australia, HCV isolates are comprised predominantly of genotypes 1 and 3.[8] Genotyping can be determined by sequencing PCR product or by using PCR product with a commercially available line probe assay (LiPA from Innogenetics).

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The virus

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Although some aspects of the molecular biology of hepatitis C virus (HCV) are well defined, the same is not true of the basic virology, the mechanism of virus replication and the functions of some of the viral proteins. The same difficulties that delayed the discovery of the virus in the past now hinder work directed toward these goals: in general, these are the low level of viraemia and poor in vitro cell culture systems. Although HCV is reported to replicate in vitro in some cell types, the level of replication is too low to provide useful information. In addition, as the level of replication in vivo is similarly low, few data have been generated from the study of naturally infected liver samples.

It is not possible to detect viral antigens in the serum of HCV infected persons in a manner analogous to the detection of hepatitis B (HBV) virus surface antigen. Further, the only direct marker of HCV replication and viraemia is the detection of HCV RNA by reverse transcriptase polymerase chain reaction (RT-PCR). Approximately 80% of individuals who are infected with HCV develop persistent infection. The mechanism(s) for this are still unclear and many hypotheses have been advanced. However, it seems likely to be a strategy adopted by the virus because even in immunosuppressed individuals the levels of viraemia are low. In support of this, recent experiments performed in the HCV laboratory of the Sir Albert Sakzewski Virus Research Centre have detected feedback inhibition by a virus protein on HCV RNA replication.

The basic virology

Before the discovery of HCV, the non A, non B agent was considered to be a 30–60 nm particle with a lipid envelope.[1] More recent electron microscopic studies of virions, purified from the serum of HCV infected individuals, have confirmed HCV to be an enveloped virus of approximately 60 nm diameter.[2] Treatment of the virus with detergent increased the density of the particle, consistent with the removal of a lipid containing glycoprotein envelope and release of a 33 nm nucleocapsid.[3]

Physicochemical studies have identified two HCV populations with different densities. The low density population contains infectious virus associated with low density lipoproteins (LDL), while the high density fraction contains virus that is non-infectious because the particles are coated with antibody.[4] These results explained a discrepancy in the infectivity of different serum samples that contained similar levels of virus (by RT-PCR), and are consistent with immune complex diseases that are often associated with persistent HCV infection.

The HCV genome

The HCV genome is a positive sense, single strand RNA molecule of approximately 9500 nucleotides (nt) that contains a single long open reading frame (gene). This encodes a polyprotein of 3008–3037 amino acids, depending on the genotype, that is flanked by untranslated regions (UTR) at the 5′ and 3′ ends (*Figure 1*). As a result, HCV was classified as a separate genus in the Flaviviridae. The core and envelope (E1 and E2) proteins are structural proteins that form the virus particle, while the remainder, the non-structural (NS), proteins are required for virus replication. The proteins are discussed more fully below.

The nucleotide sequence of certain regions of the genome of different isolates has been shown to differ and, on this basis, six genotypes each containing a number of subtypes have been described.[5] Consequently, this results in the production of proteins that also differ in their degree of identity. However, HCV is typical of many RNA viruses in that the viruses that circulate in the blood of an infected individual usually include a major population of closely related viruses and variants, both derived from a common origin. This population is described as a quasispecies. The variants and the subsequent quasispecies arise as a result of random mutations in the genome during the process of RNA replication. In addition, the genome contains a region, known as hypervariable region 1 (HVR1) at the 5′ end of the E2 gene that has been shown to accumulate mutations at a rapid rate; the corresponding region in the E2 protein is thought to contain an epitope for neutralising antibody.

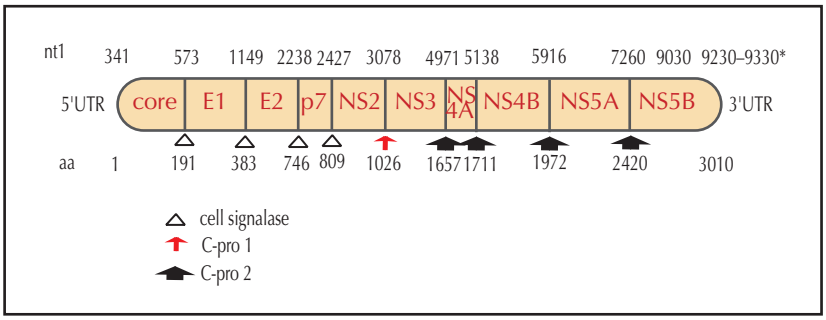

Figure 1. The HCV genome and polyprotein processing

* The length of the 3'UTR varies due to the variable nature of the poly U tract

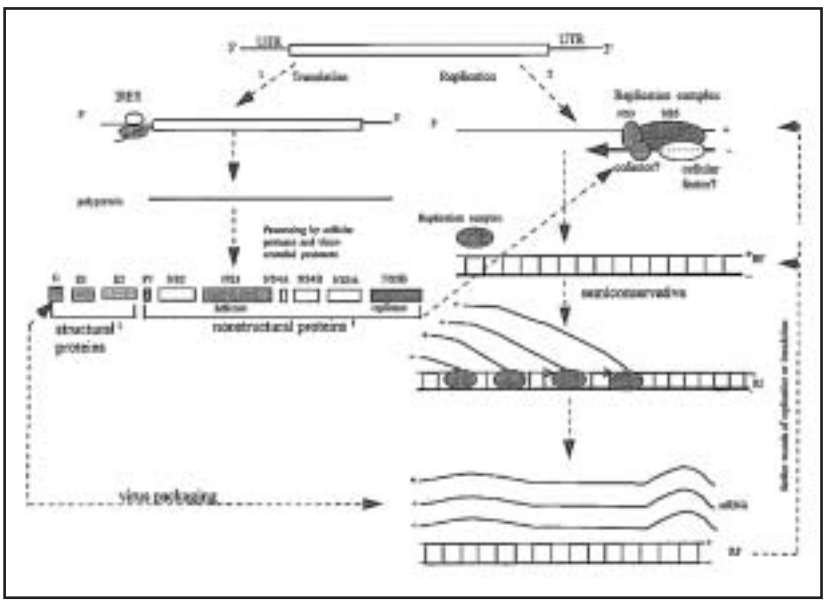

Figure 2. The replication of HCV

UTR=untranslated region; IRES=internal ribosome entry site; RF=replicative form; RI= replicative intermediate; ssRNA=single strand RNA.

This figure was modified from a figure produced by Dr Yunhao Gong (PhD Thesis, University of Queensland.

The 5′ and 3′ UTR are the most conserved regions in the genome, although the conservation in the 3′ UTR is limited to the 98 nucleotides at the extreme terminus. These regions are thought to be important for the control of RNA transcription/replication and/or protein translation. The 5′ UTR contains an internal ribosome entry site (IRES) which permits the translation of proteins from the genome in a cap independent manner. This contrasts with the cap dependent mechanism used by most cellular mRNA molecules. It is unclear why HCV uses such a mechanism for protein expression, but this feature represents a virus specific target that is the subject of intense research in the race to find novel HCV specific antiviral agents.

The viral proteins

The synthesis of a polyprotein which is co and post translationally processed into the mature individual polypeptides is common among viruses, and members of the Flaviviridae (prototype, yellow fever virus) and the Picornaviridae (prototype, poliovirus) provide established models. In vitro replication systems for HCV have not generated new information and our knowledge of HCV polyprotein processing is derived from artificial systems. The structural (S) proteins are cleaved into the mature polypeptides by a cell signalase which is probably located in the lumen of the endoplasmic reticulum, while the NS proteins are cleaved by one of two virus specific proteinases (*Figure 1*). Specific functions have been assigned to each of the proteins except p7, NS4A and NS5A.

The production of viral proteins by genetic engineering underpins the assays used to diagnose infection with HCV. The individual proteins are coated on a solid phase, typically an ELISA plate, and used as the antigen target in tests to detect anti HCV in individual serum samples. The viral proteins can also be detected in liver biopsy and autopsy samples. However, the levels of viral protein expression makes this a difficult task, and these procedures are not performed on a routine basis in the manner used to detect HBV surface and core antigens.

The NS3 and NS5 proteins have helicase/protease and RNA polymerase activities, respectively.[6] These activities are vital for virus replication and represent logical targets for antiviral agents. The protease activity of NS3 is likely to be a particularly suitable target in view of the phenomenal success of specific protease inhibitors which have revolutionised treatment for infection with HIV. NS5A contains a region, the interferon sensitivity determining region (ISDR), thought to influence the response of the virus to treatment with interferon. However, the importance of the ISDR has not been confirmed in other studies, and it is thought that interferon resistance may be multifactorial.[7] Nonetheless, NS5A interacts with and inhibits the double stranded RNA induced protein kinase (PKR), which is part of the immunological cascade leading to the production of interferon.[8]

Virus replication

In the absence of a reproducible cell culture system for HCV, very little is known about the mechanism

of virus replication. It has been suggested that the virus may bind to the hepatocyte as a consequence of the LDL component of the envelope binding to the cellular LDL receptor. More recently, the virus has been shown to bind to the CD81 molecule, and it has been proposed that this molecule represents the cellular receptor for the virus.[9] The other events of replication are equally ill defined, but by analogy with other members of the Flaviviridae, particularly the pestiviruses, it is possible to construct a model. After entry and uncoating, the virus RNA acts as mRNA for the synthesis of the virus polyprotein; this is co and post translationally processed to produce the mature viral proteins. The input RNA is then used as a template for the synthesis of nascent RNA in a replicative complex which is thought to contain NS5B and other NS proteins, initially by the synthesis of a negative strand which then base pairs with the input plus strand to form a double strand replicative form (RF), and then by the production of nascent plus strands from the RF. It is thought that the helicase function of NS3B is required to unwind the double stranded RF and/or to remove secondary structure from the plus strand to permit synthesis of the nascent strands. The nascent plus strands can then be used in one of three ways:

- as a template for the production of the polyprotein;
- as a template for the production of nascent negative strands; and
- encapsidated and exported from the cell as mature virus.

A scheme for the replication of HCV is shown in *Figure 2*. It is based on previous data derived by studies with the flavivirus, Kunjin,[10] and the pestivirus, bovine viral diarrhoea virus.[11] Consequently, the detection of negative strand HCV RNA is thought to be a marker of virus replication, although the detection of negative strand RNA by strand specific RT-PCR is fraught with difficulties.[12] It is thought that the replication complex is closely associated with internal cellular membranes in a similar manner to that proposed for flaviviruses.[10]

Conclusion

Despite the lack of an authentic reproducible cell culture system for HCV, tremendous advances have been made in our understanding of the molecular biology of the virus. Nevertheless, much is still not understood and the immediate challenge is to ensure that many of the results derived from artificial expression systems are applicable to the naturally infected hepatocyte.

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Summary of important points

Epidemiology

- The Australian HCV epidemic continues to expand, fuelled by the high transmission rate in injecting drug users (IDUs).
- An estimated 210 000 Australians were living with HCV at the end of 2001, 35 000 have chronic HCV and 5900 are living with HCV related cirrhosis.
- There were an estimated 16 000 new HCV infections in IDUs in 2001.
- Major risk groups for HCV are IDUs, prisoners and people born in countries of high prevalence, ie. Asia, Middle East, southern and eastern Europe, parts of Africa and South America.
- Since HCV screening was introduced in 1990, the risk of HCV infection from transfusion has decreased dramatically to 1 in 250 000 donations.
- Vertical transmission only occurs from women who are HCV RNA positive, ie. viraemic. The transmission rate is approximately 6%.
- Tattooing has been epidemiologically linked to HCV transmission.
- The risk of sexual transmission is controversial but is likely to be low.
- Household contact (other than percutaneous blood contact) has not been epidemiologically linked to HCV infection.

Prevention

- The principle of prevention in IDUs is to prevent blood contact around injection: needle and syringe programs, methadone maintenance and peer education are important.
- Shared injecting equipment, not just needles, can lead to HCV transmission.
- There is no evidence that mode of delivery affects vertical transmission.
- Breastfeeding should not be discouraged but it is advisable to express and discard milk when the mother has cracked or bleeding nipples.

Clinical

- Acute HCV is usually clinically mild or subclinical.
- 75–80% of patients infected with HCV develop chronic infection.
- Chronic HCV leads to a wide spectrum of liver disease from minimal to chronic hepatitis to cirrhosis.
- Chronic HCV is detected by the presence of HCV RNA in serum on two occasions over a period of six months.
- In chronic HCV hepatitis LFTs (esp. ALT) are abnormal on at least three occasions over six months.
- Liver biopsy should be considered in patients with persisting LFT abnormalities to determine the severity of disease.
- Progression to cirrhosis from chronic HCV is estimated to be 7% after 20 years and 20% after 40 years.

HCV testing and counselling

- Pre and post-test counselling is a vital part of HCV testing.
- Counselling, confidentiality and consent are prerequisites of HCV testing.
- Anti-HCV is the initial test and may be positive, negative or indeterminate.
- Indeterminate tests need to be repeated with a different assay and HCV RNA PCR performed.
- HCV RNA detects viraemia.
- HCV test results should always be given in person and never over the phone.
- Educating patients to reduce HCV transmission is a key component of diagnosis.

Antiviral treatment

- Current antiviral treatment is a combination of pegylated interferon and ribavirin.
- Antiviral treatment is recommended for patients with active necroinflammatory changes, compensated cirrhosis, HIV coinfection and acute HCV.
- Normalisation of ALT and disappearance of HCV RNA from serum by PCR indicates response to therapy.

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