

Chronic hepatitis C infection: a review and update on treatment strategies

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HEPATITIS C VIRUS (HCV) is one of the leading causes of liver disease in Australia. It is a common cause of cirrhosis and hepatocellular carcinoma (HCC), as well as the leading reason for liver transplantation. At least 200 000 people in Australia are believed to have been infected with HCV.¹ Before the identification of this virus in 1989, this disorder was categorised as non-A, non-B hepatitis.

Natural history and clinical features of hepatitis C

HCV is an RNA virus of the Flaviviridae family.² There are six HCV genotypes and more than 50 subtypes.^{3,4} The lack of a vigorous T-lymphocyte response and the high propensity of the virus to mutate appear to promote a high rate of chronic infection. HCV replicates preferentially in hepatocytes, but is not directly cytopathic, leading to persistent infection. The extensive genetic heterogeneity of HCV has important diagnostic and clinical implications, perhaps explaining difficulties in vaccine development and the lack of response to therapy. Genotypes 2 and 3 account for a higher percentage of HCV infection in Australia (unlike the USA and Europe) and is associated with a higher rate of response to treatment.⁵ HCV is the most common chronic blood-borne infection nationally.¹ Currently, about 16 000 new HCV infections are estimated to occur each year in Australia.

HCV transmission occurs primarily through exposure to infected blood. This exposure exists in the context of injecting drug use, blood transfusion before 1992, solid organ transplantation from infected donors, unsafe medical practices, occupational exposure to infected blood, birth to an infected mother, high-risk sexual practices, and intranasal cocaine use. Transmission from blood products and organ transplants was virtually eliminated by the introduction of a more sensitive test for antibodies to HCV (anti-HCV) in mid-1992. High HCV seroprevalence rates have occurred in specific subpopulations, such as the homeless, incarcerated people, injecting drug users, and people with hemophilia who were treated with clotting factors before 1992. The highest seroprevalence rates (70% to more than 90%) have been reported in the last two of these groups.^{6,7}

After initial exposure, HCV RNA can be detected in blood within 1 to 3 weeks and is present at the onset of symptoms. Antibodies to HCV are detected by enzyme immunoassay (EIA) in only 50% to 70% of patients at the onset of symptoms, increasing to more than 90% after 3 months. Within an average of 4 to 12 weeks, liver cell injury is manifested by elevation of serum alanine aminotransferase (ALT) levels. Acute infection

Abstract

- ◆ Hepatitis C virus (HCV) is transmitted by blood and such transmission now occurs primarily through injecting drug use, sex with an infected partner or partners, and occupational exposure. Most HCV infections become chronic, so the prevalence of HCV infections is high.
- ◆ HCV is a leading cause of cirrhosis, a common cause of hepatocellular cancer (HCC) and the leading cause of liver transplantation in Australia. Studies suggest that 3%–20% of chronically infected patients will develop cirrhosis over a 20-year period, and these patients are at risk of HCC. People who are older at the time of infection, those continually exposed to alcohol, and those co-infected with HIV or hepatitis B progress more rapidly to advanced liver disease. Individuals infected at a younger age have little or no disease progression over several decades.
- ◆ The diagnosis of chronic hepatitis C infection is often suggested by abnormalities in alanine aminotransferase levels and is established by enzyme immunoassay, followed by confirmatory determination of HCV RNA. Liver biopsy is useful in defining baseline abnormalities of liver disease and to guide decisions regarding antiviral therapy. Viral genotypes 2 and 3, most commonly found in Australia, are more responsive to treatment than genotypes 1 and 4.
- ◆ Combination therapy with interferons and ribavirin is more effective than monotherapy. Trials using pegylated interferons have yielded improved sustained viral response (SVR) rates with similar toxicity profiles. However, the SVR rate is less in patients with genotype 1 infection, higher HCV RNA levels, or more advanced fibrosis. Genotype 1 infection requires therapy for 48 weeks, whereas shorter treatment is feasible in genotype 2 and 3 infection. In genotype 1, the lack of an early virological response (<2 log decrease in HCV RNA) is associated with failure to achieve a sustained viral response (SVR). The SVR is lower in patients with advanced liver disease than in patients without cirrhosis.
- ◆ In the military, unless specific contraindications exist, all personnel should be offered treatment after appropriate specialist workup.

ADF Health 2003; 4: 27-33

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can be severe but is rarely fulminant. Symptoms are uncommon, but can include malaise, weakness, anorexia, and jaundice. Symptoms usually subside after several weeks as ALT levels decline.^{8,9}

HCV replicates in the cytoplasm of hepatocytes, where it is not directly cytopathic. Persistent infection appears to rely on rapid production of virus and continuous cell-to-cell spread, along with a lack of vigorous T-cell immune response to HCV antigens.⁸ It is thought that HCV mutates antigenic epitopes, thereby escaping anti-HCV antibodies and cytotoxic T-cells, but the mechanisms responsible for the persistence of the virus are not clearly understood.

Persistence of HCV infection is diagnosed by the detection of HCV RNA in the blood for at least six months. In general, prospective studies have shown that 60%–85% of HCV-infected people develop chronic infection.^{10,11} Factors associated with spontaneous clearance of HCV infection appear to include younger age and female sex.

The most important sequelae of chronic HCV infection are progressive liver fibrosis leading to cirrhosis, end-stage liver disease and HCC. Estimates of the proportion of chronically infected people who develop cirrhosis 20 years after initial infection vary widely, from 2%–4% in studies of children and young women to as high as 20%–30% in middle-aged transfused subjects.^{12,13} The actual risk is probably between these two ranges, perhaps 10%–15%. There is little evidence that viral load, viral genotype or quasi-species diversity significantly affects the risk of progression of liver disease (Box 1). However, many host factors increase this risk, including older age at time of infection, male sex, and an immunosuppressed state, such as that associated with human immunodeficiency virus (HIV) infection (Box 1).¹⁴ Concurrent chronic hepatitis B also appears to increase the risk of progressive liver disease.^{15,16} Coinfection with hepatitis B and C or B, C and delta viruses results in severe chronic liver disease and responds poorly to interferon- α treatment.¹⁷

In addition, higher levels of alcohol use play an important role in promoting the development of progressive liver disease, with strong evidence for the detrimental effects of 30 g/day in men and 20 g/day in women.^{18,19} Lesser amounts of alcohol may also increase the risk of liver damage associated with HCV. Other factors, including iron overload, non-alcoholic fatty liver disease, diabetes, schistosomal coinfection, potentially hepatotoxic medications, and environmental contaminants, may also have important effects.¹² There has been recent interest in the possibility that cigarette smoking might play a role in the development of cirrhosis in people with hepatitis C. A single study has found smoking to be strongly associated with increased fibrosis.²⁰

I: Factors affecting disease progression

Adverse effect

Alcohol consumption
> 30 g/day (men) or
> 20 g/day (women)

Co-infection with hepatitis
B or HIV

Male sex

Age of acquisition > 45
years

No effect

Viral genotype

Viral load

Serum AST/ALT levels

Mode of transmission

Most patients with chronic hepatitis C have few if any symptoms, the most common being fatigue, which is typically intermittent.⁸ Right upper quadrant pain (liver ache), nausea, and poor appetite occur in some patients. Serum ALT levels are usually continuously or intermittently elevated, but the height of elevation correlates poorly with disease activity and at least a third of infected people have persistently normal ALT levels.²¹ In patients with persistently normal serum ALT levels, the underlying disease is usually, but not always, mild and non-progressive.²²

Little is known about the clinical course and risks of HCV-related complications in people who have been infected for longer than two decades. HCV accounts for an increasing number of HCC cases in Australia.²³ HCC rarely occurs in the absence of cirrhosis or advanced fibrosis.²⁴ The incidence of HCV-

related HCC continues to rise worldwide, in part because of the increasing numbers of people who have been chronically infected for decades, the presence of comorbid factors, and the longer survival of people with advanced liver disease due to improved management of complications. Risk factors for HCC in people with chronic HCV infection are largely the same as those for developing decompensated cirrhosis.²⁵ Some but not all studies suggest that treatment with interferon alone, or combination treatment with interferon and ribavirin, may reduce the risk of developing HCC in HCV patients with cirrhosis, but more data are needed.²⁶

Patients with chronic hepatitis C can present with extrahepatic manifestations or syndromes considered to be of immunological origin, such as rheumatoid symptoms, keratoconjunctivitis sicca, lichen planus, glomerulonephritis, lymphoma, and essential mixed cryoglobulinaemia.²⁷ Cryoglobulins have been detected in the serum of up to half of patients with chronic hepatitis C, but the clinical features of mixed cryoglobulinaemia are uncommon. HCV-related cryoglobulinaemia is the most common extrahepatic complication. Cryoglobulinaemia is marked by various combinations of symptoms, including fatigue, skin rash, purpura, arthralgia, renal disease and neuropathy. Blood tests show the presence of globulins that precipitate in the cold — rheumatoid factor, complement and complexes of HCV RNA and anti-HCV. Frank symptomatic cryoglobulinaemia is uncommon, probably occurring in less than 1% of patients with chronic HCV infection. The natural history of HCV-related cryoglobulinaemia has not been well defined, but it can lead to progressive renal disease and severe vasculitic complications.

Chronic hepatitis C is also related to porphyria cutanea tarda.^{27,28} It is unclear whether these conditions are directly caused by HCV infection or are consequences of the underlying liver disease or immune stimulation caused by the

chronic infection. Porphyria cutanea tarda occurs in patients with many liver diseases.

Psychological disorders including depression have been associated with chronic HCV infection in up to 30% of cases.

Diagnostic approaches to HCV infection and monitoring of infected patients

Various tests are available for the diagnosis and monitoring of HCV infection. Tests that detect antibodies against the virus include the enzyme immunoassay (EIA) and the recombinant immunoblot assay. The same HCV antigens from the core and non-structural genes are used in both assays. Target amplification techniques using polymerase chain reaction (PCR) have been developed as a qualitative test for HCV RNA. Target amplification (PCR) may be used to measure HCV RNA levels. Liver biopsy can provide direct histological assessment of liver injury due to HCV but cannot be used to diagnose HCV infection.

HCV serologic assays

EIA is suitable for screening at-risk populations and is recommended as the initial test for patients with clinical liver disease. The very high sensitivity and specificity of the third-generation EIAs (eg, Murex and Abbott) (sensitivity of greater than 99%, specificity of 99% in immunocompetent patients) obviate the need for a confirmatory immunoblot assay in the diagnosis of individual patients with clinical liver disease, particularly those with risk factors for HCV infection. A negative EIA result is sufficient to exclude a diagnosis of chronic HCV infection in immunocompetent patients.

Qualitative HCV RNA assays

Acute or chronic HCV infection in a patient with a positive EIA result should be confirmed by a qualitative HCV RNA test (ie, to detect the presence or absence of viraemia). However, confirmation may be unnecessary in a patient who has evidence of liver disease and obvious risk factors for HCV infection. The specificity of these assays for detecting HCV RNA exceeds 98%. A single positive qualitative assay for HCV RNA confirms active HCV replication, but a single negative assay does not exclude viraemia and may reflect only a transient decline in viral level below the level of detection of the assay. A follow-up qualitative HCV RNA test should be performed to confirm the absence of active HCV replication, usually six months later.

Quantitative HCV RNA assays

Testing for HCV RNA level (or viral load) with a quantitative assay such as a quantitative PCR assay provides accurate information on HCV viral levels. While there is little correlation between disease severity or disease progression with the absolute level of HCV RNA,

quantitative determination of the HCV level provides important information on the likelihood of response to treatment in patients undergoing antiviral therapy.

HCV genotype

The HCV genotype is an intrinsic characteristic of the transmitted HCV strain(s) and does not change during the course of the infection. HCV genotypes form six clades or types (numbered 1 to 6) and are themselves subdivided into a large number of subclades or subtypes identified by lower-case letters (1a, 1b, 1c, etc).²⁹

Serum alanine aminotransferase

Testing for serum ALT levels is the most inexpensive and non-invasive (but relatively insensitive) means of assessing disease activity. A single determination of ALT level gives limited information about the severity of the underlying liver disease. Serial determinations of ALT levels may provide a better means of assessing liver injury, but the accuracy of this approach has not been well documented. Patients who initially have a normal ALT level should undergo serial measurements over several months to confirm the persistence of normal ALT levels. Although loss or reduction in HCV RNA is the primary indicator of response to antiviral therapy, the lowering of raised ALT levels with antiviral therapy appears to be an important indicator of treatment response. ALT levels are insensitive in detecting disease progression to cirrhosis.

Liver biopsy

Liver biopsy provides a unique source of information on fibrosis and assessment of histology. Liver enzymes have shown little value in predicting fibrosis. Moreover, only liver biopsy provides information on possible contributions of iron, steatosis, and concurrent alcoholic liver disease to the progression of chronic hepatitis C to cirrhosis. Liver biopsies from patients undergoing evaluation of chronic hepatitis C rarely reveal unexpected aetiologies of liver disease, but the information obtained by biopsy allows affected individuals to make more-informed choices about antiviral treatment. Patients with persistently normal or slightly elevated ALT levels and minimal or no fibrosis on liver biopsy may be reassured of a favourable prognosis and, with information about the side effects of treatment, they may decide to defer antiviral therapy.

Hepatocellular carcinoma screening

HCC complicates cirrhosis secondary to HCV. It is estimated that HCC occurs after the development of cirrhosis at a rate varying from 0 to 3% per year. As the prevalence and longevity of the epidemic of chronic hepatitis has not yet peaked, we believe that the incidence of HCV-related HCC will increase over the next 15 years. Few studies have examined specific screening strategies for HCC in patients with advanced HCV.

The value of screening for alfa fetoprotein (AFP) is uncertain, as there are no available data to demonstrate the clinical impact of this screening on the management of HCC or associated mortality. Studies of the performance characteristics of AFP and hepatic ultrasound show that AFP has poor sensitivity and a high rate of false-positive reactions.³⁰ Hepatic ultrasound is more sensitive than AFP testing but is also more expensive, and it can lead to invasive and unnecessary evaluations of lesions (eg, regenerative nodules, hemangiomas, hepatic cysts) that are not HCC. Despite the lack of evidence, screening for HCC with AFP testing and hepatic ultrasound at six-monthly intervals is a common practice in Australia. However, such routine AFP or imaging screening should not be performed in patients with hepatitis C in the absence of cirrhosis, as HCC is so rare in this group.

HIV and HBV screening

Significant overlap exists for risk factors for HCV, HIV and HBV infections. Therefore, patients with documented HCV infection should be routinely screened for HIV and HBV infection.

Treatment for hepatitis C

The goal of therapy is a sustained fall in serum ALT and HCV levels, and histological improvement. Long term follow-up of patients who have experienced a sustained response to interferon therapy indicates that more than 90% will maintain normal ALT values and non-detectability of HCV-RNA over one to six years of follow-up. In such patients histological activity markedly improves.³¹ Currently, the best indicator of effective treatment is a sustained viral response (SVR), defined by the absence of detectable HCV RNA in the serum 24 weeks after finishing treatment. Whether this represents a “cure” of hepatitis C, with permanent eradication of the virus, remains uncertain, although this view is increasingly accepted by experts in the field.

Several important therapeutic advances have occurred in recent years, particularly interferon–ribavirin combination therapy^{32,34} and the introduction of pegylated interferons.

The exact mechanism of action of interferon in ameliorating chronic HCV infection has yet to be confirmed. Interferon has cytotoxic, cytostatic, antiproliferative antiviral and immunomodulatory effects that may all play a role. In chronic hepatitis C, interferon most likely has a direct antiviral effect that possibly disrupts viral replication. There is evidence that interferon has direct antiviral actions via induction of 2-5A oligoadenylate synthetase and ribonuclease L. Interferon also has immunomodulatory actions that enhance the expression of MHC class I proteins on the hepatocyte surface and activate the cellular immune system.

2: Factors favouring a positive response to antiviral therapy

HCV genotypes 2 and 3
Minimal fibrosis on biopsy
Female sex
Age < 40
Low viral load at baseline

Combination therapy with interferon and ribavirin results in better treatment responses than monotherapy with interferon, but the highest response rates have been achieved with pegylated interferon in combination with ribavirin.³⁴ Genotype determinations influence treatment decisions. Currently the best indicator of effective treatment is a sustained viral response (SVR), defined by the absence of detectable HCV RNA in the serum at 24 weeks after the end of treatment.

Pegylation is the process by which an inert molecule of polyethylene glycol is covalently attached to a protein, giving it a higher molecular weight and thus causing an effective increase in serum half-life (from a few hours for standard interferon to several days for the pegylated product).

Ribavirin is a synthetic nucleoside analogue with activity against some RNA viruses. The exact mechanism of action in combination with interferon therapy is unknown. Ribavirin alone is ineffective against chronic hepatitis C.

Treatment of previously untreated patients

Recent studies have examined the efficacy of pegylated interferon plus ribavirin in the treatment of chronic HCV infection.³⁴ These trials excluded patients with decompensated cirrhosis and comorbid conditions. Overall, pegylated interferon plus ribavirin was more effective than standard interferon–ribavirin combination or pegylated interferon therapy alone. SVR rates were similar with both forms of pegylated interferon (alfa-2a and alfa-2b) when used in combination with ribavirin. Factors associated with successful therapy included genotypes other than 1, lower baseline viral levels, less fibrosis or inflammation on liver biopsy, and lower body weight or body surface area. Among patients with genotypes 2 or 3, SVRs with standard interferon and ribavirin were comparable to those with pegylated interferon and ribavirin, and thus standard interferon and ribavirin could be used in treating patients with these genotypes. In two trials using pegylated interferon and ribavirin, SVR rates of 42% to 46% were achieved in patients with genotype 1, compared with rates of 76% and 82% in patients with genotypes 2 and 3.³⁵ In a recent, as yet unpublished, study, a 24-week course of pegylated interferon and ribavirin was found to be as effective as a 48-week course in patients with genotypes 2 and 3 (SVR rates of 73% to 78%), but not in patients with genotype 1 (SVR rates of 41% with 24 weeks and 51% with 48 weeks of treatment). Similarly, a reduced ribavirin dose of 800 mg daily appeared to be adequate for patients with genotypes 2 and 3, but the higher, standard dose of 1000–1200 mg daily yielded better response rates in patients with genotype 1.

Thus, 24 weeks of treatment and an 800 mg dose of ribavirin appears to be sufficient for people with genotype 2 and 3, while patients with genotype 1 need 48 weeks of treatment and standard doses of ribavirin. Interestingly,

pegylated interferon treatment appears better tolerated than interferon-2b.³⁵

Early viral response, defined as a minimum 2 log decrease in viral load during the first 12 weeks of treatment, is predictive of SVR and should be a routine part of monitoring patients with genotype 1 infection. Patients who do not have an early viral response at week 12 of treatment have only a slight chance of SVR, even if therapy is continued for a full year. Treatment need not be extended beyond 12 weeks in these patients. Although SVR is difficult to correlate with improved survival because of the necessity for long-term follow-up, the absence of detectable serum HCV RNA has been associated with resolution of liver injury, reduction in hepatic fibrosis, and a low likelihood of a relapse of the HCV infection.

Retreatment of patients

Selected patients who do not have an SVR may benefit from retreatment with pegylated interferon-based regimens. Studies are currently being conducted with pegylated interferon and ribavirin therapy in patients with recurrent disease after interferon monotherapy or standard interferon and ribavirin therapy. However, most patients relapse again when they are re-treated with the same regimen as used originally. Knowledge of the severity of the underlying liver disease is important in recommending re-treatment. Patients with advanced fibrosis or cirrhosis have an increased risk of hepatic decompensation and should be considered for re-treatment, especially if they were originally treated with interferon monotherapy.

Side effects of treatment

Major side effects of combination therapy include influenza-like symptoms, hematological abnormalities, and neuropsychiatric symptoms. Educating patients, families and caregivers about side effects and their prospective management is an integral part of treatment. Frequent monitoring of neuropsychiatric side effects, cytopenia, and adherence to HCV therapy is necessary.

Psychological conditions, particularly depression, are common among people with hepatitis C and are frequent side effects of interferon. Patients' mental health should be assessed before beginning antiviral therapy and monitored regularly during therapy. Antidepressants such as selective serotonin reuptake inhibitors may be useful in the management of depression associated with antiviral therapy.

In selected patients who develop persistent cytopenia despite dose reductions, treatment with haematopoietic growth factors may be useful to reduce symptoms and maintain adherence to antiviral therapy.

Supportive factors and treatment

There is an increasing view (supported by our experience) that good treatment outcomes are facilitated by appropriate

supportive care. This usually occurs in the setting of a specialist liver clinic. There is an important role for the hepatitis C nurse, who is able to provide support to patients between medical visits, assist with monitoring of side effects and their treatment, and facilitate better and more efficient treatment. In view of the high prevalence of comorbid psychiatric disease in this patient group, as well as the neuropsychiatric adverse effects of interferon, access to psychiatric care is frequently needed.

Which patients with hepatitis C should be treated?

All patients with chronic hepatitis C are potential candidates for antiviral therapy. Treatment is recommended for patients at increased risk of developing cirrhosis. These patients are characterised by detectable HCV RNA, a liver biopsy showing portal or bridging fibrosis, and at least moderate inflammation and necrosis. Most also have persistently elevated ALT levels. In some patient populations, the risks and benefits of therapy are less clear and should be determined on an individual basis.

Most HCV treatment in Australia is prescribed and funded through the S100 system. The S100 criteria require a minimum finding of fibrosis with inflammation on histology. The situation is somewhat different in the military, where no evidence of current bloodborne infections is permitted in any personnel. Thus chronic viral infections are not tolerated, and all HCV infections require treatment with a view to viral eradication (SVR).

All patients with chronic hepatitis C should be vaccinated against hepatitis A, and seronegative people with risk factors for hepatitis B virus (HBV) should be vaccinated against hepatitis B. Patients with hepatitis C are considered to have compromised hepatic function that may acutely (in the case of coinfection with hepatitis A) or chronically (hepatitis B) result in further hepatic decompensation.

Normal ALT levels

About 30% of patients with chronic HCV infection have normal ALT levels, and another 40% have ALT levels less than two times the upper limit of normal. Although most of these patients have histologically mild disease, some may progress to advanced fibrosis and cirrhosis.^{36,37}

In general, numerous factors must be considered in recommending treatment, including favourable genotype, presence of hepatic fibrosis, patient motivation, symptoms, severity of comorbid illness, and patient age (Box 2).

Mild liver disease

Progression to cirrhosis is likely to be slow in patients who have persistently elevated ALT levels but no fibrosis and minimal necroinflammatory changes.³⁷ Other than in a military setting, these patients may not need treatment and should be monitored periodically.

Acute hepatitis C

Acute hepatitis C is uncommonly recognised and diagnosed because most patients do not develop symptoms at the time that the infection is acquired. Studies of interferon treatment for acute hepatitis C have been heterogeneous and limited by small sample size, lack of randomisation and variability in the timing of therapy after onset of infection, dose, schedule, endpoints, and follow-up. High SVR rates (83%–100%) have been reported by small, uncontrolled trials with interferon monotherapy.³ Accordingly, treatment of acute hepatitis C is warranted, but the timing of therapy and the type of regimen to use remains to be determined from future trials.

Alcohol and hepatitis C

Alcohol is an important cofactor in the progression of HCV liver disease to cirrhosis and HCC.^{39,40} A history of alcohol misuse is not a contraindication to therapy, but continued alcohol use during therapy adversely affects response to treatment. Abstinence from alcohol is strongly recommended before and during antiviral therapy. Efforts to diagnose and treat alcohol abuse or dependence should be made in conjunction with treatment of HCV. Heavy alcohol consumption of > 80 g/day seriously compromises HCV treatment.⁴¹ Furthermore, safe levels of alcohol consumption are still unclear, and even moderate levels of consumption may accelerate disease progression in some patients.

Recommendations to prevent transmission of hepatitis C in infected individuals

The large reservoir of individuals infected with HCV provides a source of transmission to others at risk. Direct percutaneous exposure is the most efficient method for transmitting HCV, and injecting drug use accounts for more than two-thirds of all new infections in Australia. Most cases not attributed to injecting drug use can be attributed to other factors, including occupational exposures to blood and high-risk sexual practices, although the risk of transmission through these routes is low. The estimated seroprevalence of HCV is 2%–3% among partners of HCV-infected people in long-term monogamous relationships and 4%–6% among people with multiple sex partners, sex workers, and men who have sex with men (those at risk for sexually transmitted diseases).⁴² Sexual partners of male and female patients with hepatitis C should be tested for this infection. For heterosexual monogamous couples in which one partner is infected, the risk of transmission is estimated to be only 0 to 0.6% annually.⁴²

3: Strategies to prevent transmission of hepatitis C

Practise universal precautions to prevent transmission of infections in healthcare settings

Screen blood and organ donations

Intravenous drug users must practise “safe injecting” (ie, use sterile equipment, not share injecting equipment)

Avoid sharing toothbrushes or razor blades

Tattooing and body piercing require sterile equipment

Sexual transmission of hepatitis C is infrequent and will be avoided by safe sex practices recommended for avoiding other sexually transmitted diseases.

Because of the low risk of HCV transmission, monogamous couples do not need to use barrier protection (condoms), although they should be advised that condoms may reduce the risk of transmission. However, HCV-infected individuals with multiple sexual partners or in short-term relationships should be advised to use condoms to prevent transmission of HCV and other sexually transmitted diseases. Sharing common household items that may be contaminated

with blood, such as razors and toothbrushes, is another potential source of transmission of HCV that should be avoided. There is no evidence that kissing, hugging, sneezing, coughing, food, water, sharing eating utensils or drinking glasses, casual contact or other contact without exposure to blood is associated with HCV transmission.

Healthcare workers should use standard universal precautions to prevent transmission. The risk of HCV infection from a needlestick injury is estimated to be 2%.⁷ At this time, immune globulin or antiviral prophylaxis is not recommended following needlestick exposure. It is recommended that the source and exposed individual should be tested for antibodies to HCV. If the source individual is HCV EIA positive, an immunoblot or HCV RNA assay should be done in the exposed individual. Since HCV RNA is first detected in the blood two weeks after transmission, the exposed individual should be tested for HCV antibodies, HCV RNA, and ALT at exposure and again between two to eight weeks after injury. If seroconversion occurs, such people should be referred to a specialist for consideration of treatment.

Body piercing and tattooing are other potential sources of transmission if contaminated equipment or supplies are used. However, transmission through these activities is rare and frequently confounded by other risk factors.

The risk of perinatal transmission is about 2% for infants of anti-HCV seropositive women.⁴³ When a pregnant woman is HCV RNA positive at delivery, the risk increases to 4%–7%.^{43,44} Higher HCV RNA levels appear to be associated with greater risk. HCV transmission increases up to 20% in women co-infected with HCV and HIV.⁴⁴

Conclusions

Hepatitis C virus is transmitted by blood and transmission now occurs primarily through injecting drug use, sex with an infected partner or partners, and occupational exposure. Most infections become chronic. Various studies have suggested that 3% to 20% of chronically infected patients will develop cirrhosis over a 20-year period, and these patients are at risk for

HCC. The diagnosis of chronic hepatitis C infection is often suggested by abnormalities in ALT levels and is established by EIA, followed by confirmatory determination of HCV RNA. Liver biopsy is useful in defining baseline abnormalities of liver disease. Recent therapeutic trials in defined, selected populations have clearly shown that interferon-ribavirin combination therapy is more effective than monotherapy. Moreover, trials using pegylated interferons have yielded improved SVR rates without higher toxicity profiles. However, results continue to show that the SVR rate is lower in patients with genotype 1 infection, higher HCV RNA levels, or more advanced stages of fibrosis. Genotype 1 infection requires therapy for 48 weeks, whereas shorter treatment is feasible in genotype 2 and 3 infection. In genotype 1, the lack of an early virological response (<2 log decrease in HCV RNA) is associated with failure to achieve SVR.

References

- Howe M. Rising hepatitis C infections put increasing burden on Australia. *Lancet Infect Dis* 2002; 2: 712.
- Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001; 345: 41-52.
- Robertson B, Myers G, Howard C, et al. Classification, nomenclature, and database development for hepatitis C virus (HCV) and related viruses: proposals for standardization. *Arch Virol* 1998; 143: 2493-2503.
- Bukh J, Miller RH, Purcell RH. Genetic heterogeneity of hepatitis C virus: quasispecies and genotypes. *Semin Liver Dis* 1995; 15: 41-63.
- Liang TJ, Rehermann B, Seeff LB, Hoofnagle JH. Pathogenesis, natural history, treatment and prevention of hepatitis C. *Ann Intern Med* 2000; 132: 296-305.
- Batey RG. Hepatitis C: where are we at and where are we going? *Med J Aust* 2002; 176: 361-362.
- Alter MJ. Prevention of spread of hepatitis C. *Hepatology* 2002; 36 (5 Suppl 1): S93-S98.
- Hoofnagle JH. Course and outcome of hepatitis C. *Hepatology* 2002; 36 (5 Suppl 1): S21-S29.
- Orland JR, Wright TL, Cooper S. Acute hepatitis C. *Hepatology* 2001; 33: 321-327.
- Muir AJ. The natural history of hepatitis C viral infection. *Semin Gastrointest Dis* 2000; 11: 54-61.
- Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA* 2000; 284: 450-456.
- Seeff LB. Natural history of chronic hepatitis C. *Hepatology* 2002; 36 (5 Suppl 1): S35-S46.
- Alberti A, Chemello L, Benvegna L. Natural history of hepatitis C. *J Hepatol* 1999; 31 Suppl 1: 17-24.
- Marcellin P, Asselah T, Boyer N. Fibrosis and disease progression in hepatitis C. *Hepatology* 2002; 36 (5 Suppl 1): S47-S56.
- Tsai JF, Jeng JE, Ho MS, et al. Independent and additive effect modification of hepatitis B and C virus infection on the development of chronic hepatitis. *J Hepatol* 1996; 24: 271-276.
- Pontisso P, Gerotto M, Benvegna L, et al. Co-infection by hepatitis B virus and hepatitis C virus. *Antivir Ther* 1998; 3: 137-142.
- Weltman MD, Brotodihardjo A, Crewe EB, et al. Coinfection with hepatitis B and C or B, C and delta viruses results in severe chronic liver disease and responds poorly to interferon-alpha treatment. *J Viral Hepat* 1995; 2: 39-45.
- Westin J, Lagging LM, Spak F, et al. Moderate alcohol intake increases fibrosis progression in untreated patients with hepatitis C virus infection. *J Viral Hepat* 2002; 9: 235-241.
- Ostapowicz G, Watson KJ, Locarnini SA, Desmond PV. Role of alcohol in the progression of liver disease caused by hepatitis C virus infection. *Hepatology* 1998; 27: 1730-1735.
- Pessione F, Ramond M-J, Njapoum C, et al. Cigarette smoking and hepatic lesions in patients with chronic hepatitis C. *Hepatology* 2001; 34: 121-125.
- Conry-Cantilena C, Van Raden M, Gibble J, et al. Routes of interferon, viremia, and liver disease in blood donors found to have hepatitis C virus infection. *N Engl J Med* 1996; 334: 1691-1696.
- Puoti M, Magnini A, Stati T, et al. Clinical, histologic, and virological features of hepatitis C virus carriers with persistently normal or abnormal aminotransferase levels. *Hepatology* 1995; 21: 285-290.
- Law MG, Roberts SK, Dore GJ, Kaldor JM. Primary hepatocellular carcinoma in Australia, 1978-1997: increasing incidence and mortality. *Med J Aust* 2000 16; 173: 403-405.
- El-Serag HB. Hepatocellular carcinoma and hepatitis C in the United States. *Hepatology* 2002; 36 (5 Suppl 1): S74-S83.
- Dutta U, Byth K, Kench J, et al. Risk factors for development of hepatocellular carcinoma among Australians with hepatitis C: a case-control study. *Aust N Z J Med* 1999; 29: 300-307.
- Gramenzi A, Andreone P, Fiorino S, et al. Impact of interferon therapy on the natural history of hepatitis C virus related cirrhosis. *Gut* 2001; 48: 843-848.
- El-Serag HB, Hampel H, Yeh C, Rabeneck L. Extrahepatic manifestations of hepatitis C among United States male veterans. *Hepatology* 2002; 36: 1439-1445.
- Gumber SC, Chopra S. Hepatitis C: a multifaceted disease. Review of extrahepatic manifestations. *Ann Intern Med* 1995 15; 123: 615-620.
- Pawlotsky JM. Use and interpretation of virological tests for hepatitis C. *Hepatology* 2002; 36 (5 Suppl 1): S65-S73.
- National Institutes of Health Consensus Development Conference Statement: management of hepatitis C: 2002 — June 10-12, 2002. *Hepatology* 2002; 36 (5 Suppl 1): S3-S20.
- Boyer N, Marcellin P, Duchtalle V, et al. Sustained response after α interferon therapy in patients with chronic hepatitis C. *Hepatology* 1995; 22: 291A.
- Saracco G, Olivero A, Ciancio A, et al. A randomized 4-arm multicenter study of interferon alpha-2b plus ribavirin in the treatment of patients with chronic hepatitis C relapsing after interferon monotherapy. *Hepatology* 2002; 36: 959-966.
- Barbaro G, Di Lorenzo G, Soldini M, et al. Ribavirin-Interferon in Chronic Hepatitis Italian Group Investigators. Evaluation of long-term efficacy of interferon alpha-2b and ribavirin in combination in naive patients with chronic hepatitis C: an Italian multicenter experience. *J Hepatol* 2000; 33: 448-455.
- Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet* 2001; 358: 958-965.
- Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alpha-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347: 975-982.
- McCormick SE, Goodman ZD, Maydonovitch CL, Sjogren MH. Evaluation of liver histology, ALT elevation, and HCV RNA titer in patients with chronic hepatitis C. *Am J Gastroenterol* 1996; 91: 1516-1522.
- Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet* 1997; 349: 825-832.
- Jaecckel E, Cornberg M, Wedemeyer H, et al. Treatment of acute hepatitis C with interferon alpha-2b. *N Engl J Med* 2001; 345: 1452-1427.
- Wiley TE, McCarthy M, Breidi L, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology* 1998; 28: 805-809.
- Bellentani S, Pozzato G, Saccoccio G, et al. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study. *Gut* 1999; 44: 874-880.
- Ohnishi K, Matsuo S, Matsutani K, et al. Interferon therapy for chronic hepatitis C in habitual drinkers: comparison with chronic hepatitis C in infrequent drinkers. *Am J Gastroenterol* 1996; 91: 1374-1379.
- Norah A, Terrault. Sexual activity as a risk factor for hepatitis C. *Hepatology* 2002; 36 (5 Suppl 1): S99-S105.
- Yeung LT, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. *Hepatology* 2001; 34: 223-229.
- Dore GJ, Kaldor JM, McCaughan GW. Systematic review of role of polymerase chain reaction in defining infectiousness among people infected with hepatitis C virus. *BMJ* 1997; 315: 333-337.

(Received 7 Jan 2003, accepted 9 Feb 2003)

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