

# The increasing problem of hepatitis C virus infection

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## Abstract

The widespread incidence of hepatitis C (HCV) infection throughout the community is of concern. Although many of those infected will not suffer significantly from their infection, up to one-third will have liver disease, fatigue and oral health problems. General dental practitioners need to be aware of the precautions necessary in treating people with severe liver disease. This paper discusses the issues associated with treating patients who have HCV infection including the importance of preventive programs to reduce dental pathology and maximise oral health.

**Key words:** Hepatitis C, preventive programs, oral health, dental pathology.

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## Introduction

Hepatitis C virus (HCV) infection is an increasing issue of concern in health care in Australia and abroad. Major concerns are the high prevalence and incidence of the condition, the frequency of serious long-term health consequences of chronic HCV infection and the lack of an effective vaccine to protect healthcare workers and others at risk of exposure to the virus.

Approximately 200,000 Australians (0.5-1 per cent of the total population) are infected with HCV and there are estimated to be 8,000-10,000 new cases every year.<sup>1-3</sup> World-wide, 170 million people are infected, including 4 million people in the US and 5 million people in Europe.<sup>4</sup>

This paper discusses the issues associated with treating patients with HCV infection and aims to inform the general dental practitioner about the significant problem of HCV infection.

## Properties of the virus

HCV is a ribonucleic acid (RNA) virus. There is marked heterogeneity of the HCV genome as a

result of mutations that occur during viral replication.<sup>4-6</sup> Various genotypes and quasi-species of HCV have been identified. The genotype refers to genome heterogeneity found among different HCV isolates – the genotype varies according to the geographical area as well as the age of the infected person.<sup>4,6</sup> Quasi-species are populations of variants which develop from a single HCV isolate in an individual throughout the course of infection.<sup>6</sup> The humoral (antibody) response mounted against HCV fails to recognise the sequential changes in the virus throughout the course of infection and previously generated antibodies fail to neutralise the mutants.<sup>4</sup> Because of the extreme variability of the virus, the possibility of a vaccine for HCV in the near future appears remote.

## Health outcomes

The initial infection by HCV is often asymptomatic. The incubation period varies from two to 26 weeks, with an average of six-seven weeks.<sup>3,4,5</sup> Up to 40 per cent of adults may have acute symptoms, with jaundice occurring in 25-30 per cent of infected people.<sup>4</sup> Because of the relatively low frequency of symptomatic infections, the problem of 'hidden' disease in the community is substantial.

Spontaneous resolution of hepatitis C infection is rare, even though liver function tests may be normal. Persistent chronic infection develops in approximately 85 per cent of those infected, due to failure of the immune response to neutralise the virus. There are few symptoms in the first 20 years after infection and the course of infection runs for 40-50 years. Approximately 70 per cent of people with chronic HCV infection will develop chronic liver disease, cirrhosis of the liver being the most common liver disease (30 per cent). The high level of chronic infection following exposure to HCV may reflect both a defective humoral (antibody-mediated) immune response<sup>4,7</sup> and the virulence of the particular infective strain of HCV or its mutations over time.

In Australia, HCV infection is the leading cause of liver disease and the most common indication for

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liver transplantation.<sup>3</sup> In the US, 8,000-10,000 deaths occur each year from HCV-related liver disease.<sup>4</sup> While there are limited data for Australia, Thompson et al,<sup>8</sup> who evaluated the incidence of HCV in acute cases of hepatitis admitted to Fairfield Infectious Diseases Hospital in 1971-75, predicted the rapid increase in prevalence of HCV in the mid-1970s would translate into a rapid increase of HCV-positive people presenting with liver disease in the next 10 years.

Chronic HCV infection results in slowly progressive hepatic fibrosis which can be demonstrated by liver biopsy. When viral replication occurs, elevated levels of liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) occur. Cirrhosis is indicated when liver function tests show AST levels exceed ALT levels. For those who develop cirrhosis, there is a 19 per cent mortality rate within 10 years.<sup>3</sup> In addition to cirrhosis,<sup>3,4,9</sup> liver failure occurs in 5-15 per cent of chronically infected people. Children with chronic hepatitis C infection tend to present with mild disease with minimal fibrosis. However, the fibrosis increases with the duration of the disease and end-stage liver disease may therefore present in early adulthood for some infected children.<sup>10</sup>

There also is a small but significantly increased risk of developing hepatocellular carcinoma. Factors influencing progressive liver disease have been identified as alcohol, gender, age at infection, extent of immunodeficiency and HCV genotype.<sup>4,6</sup> Excessive alcohol intake is well recognised as a modifying factor in HCV liver disease, since this leads to more active replication of the virus.<sup>3,4</sup>

With chronic HCV infection, extra-hepatic disorders may occur, including keratoconjunctivitis sicca, arthralgia and lichen planus, however these are relatively uncommon manifestations of HCV infection. Liver cirrhosis is associated with increased risk for oral carcinoma.

### **Treatment of chronic HCV infection**

Limitation of alcohol consumption is by far the most effective natural therapy in influencing the outcome of chronic HCV infection.<sup>3</sup> Alternative therapies such as vitamins and herbal remedies show limited therapeutic benefit. Chinese herbal therapies can cause dose dependent hepatotoxicity, so care needs to be taken with the dietary intake of any therapeutic substance.<sup>3</sup>

Interferon-alpha 2b (IFN) therapy is only moderately effective in treating HCV.<sup>11</sup> The reported success rates vary widely from 15-20 per cent to as high as 50 per cent.<sup>4,5,9,11,12</sup> Several trials are underway to improve the efficacy of IFN treatment and dose and duration of treatment appear to be important variables in achieving a sustained response. The

success of therapy is much higher in those infected with genotypes 2 and 3 than genotypes 1 and 4.<sup>3,6</sup> Age at infection and duration of infection also affect the outcome of therapy.<sup>6,9</sup> Side-effects of IFN include a flu-like reaction with fever, myalgia, headaches, sweating and fatigue. Late side-effects include bone marrow suppression and neuropsychiatric disorders. Levels of platelets and neutrophils need to be monitored – levels of  $<50 \times 10^9/L$  and  $1 \times 10^9/L$  respectively indicate therapy should be ceased.<sup>9,13</sup>

Recent studies have evaluated combination therapy of IFN with ribavirin, with the aim of achieving a sustained response in more patients. Ribavirin, a synthetic nucleoside, is only available on a trial basis. Side-effects do not appear to be substantially worse than for IFN, and include dyspnoea, pharyngitis, pruritus, rash, nausea and anorexia.<sup>9</sup>

### **Screening for HCV**

While HCV is the major cause (>90 per cent) of viral hepatitis not related to the hepatitis A or B viruses (the so-called non-A, non-B hepatitis), the identification of HCV cases was hampered until 1992-93 by the lack of an effective serological test for antibody to HCV. Inability to screen donated blood led to inadvertent transmission of HCV by blood transfusions, particularly in the late 1980s and early 1990s.<sup>4</sup> Since the early 1990s, it has been common practice in Australia to routinely screen donated blood for antibodies to HCV, however instances of accidental administration of known HCV-positive blood to patients have occurred, with the predictable unfortunate consequences.<sup>14</sup>

The first enzyme-linked immunosorbent assay (ELISA) for antibodies to HCV, which was developed in 1990, produced variable results (particularly false positive results) and confirmatory tests were then not widely available. Since that time, assays have improved considerably, however even the current third generation ELISA will detect anti-HCV in only 95 per cent of infected people.<sup>4</sup> Testing is complicated by the fact that antibodies to HCV usually do not appear until after acute infection, with most people developing antibodies within one-three months but some taking as long as 12 months.

Confirmatory tests for HCV include Western blot and the detection of viral genetic material (RNA) by polymerase chain reaction (PCR).<sup>15</sup> The PCR assay for peripheral blood is hampered by the fact that viraemia is variable during the course of the disease and false negatives may occur as virus will not always be present. Nevertheless, the PCR assay has been useful for ascertaining the extent of chronicity and viral activity in people infected with HCV.

## Risk groups

Injecting drug users are the major at-risk group in the community.<sup>1,4-6,16-19</sup> While HCV is almost epidemic among long-term injecting drug users,<sup>15</sup> public health measures to address issues of injecting drug use, in combination with treatment and prevention programs for HCV, have not been a public health priority in Australia. Additional risk factors include body piercing and tattooing, use of cocaine (snorting with nasal straws),<sup>16</sup> transfusion (blood products pre-1990), sharing razors and toothbrushes and ineffective infection control. Healthcare workers who sustain sharps injuries from HCV carriers are another clearly identified risk group.

HCV has been isolated from saliva, with Chen et al<sup>20</sup> reporting recovery of HCV genetic material from the cellular fraction of saliva in 17 per cent of patients infected with HCV. Porter and Lodi<sup>21</sup> noted that HCV levels in saliva correlate to hepatic function. While there are documented cases of HCV infection following a human bite, transmission of HCV by saliva alone is a remote possibility unless the saliva is contaminated with blood. The epidemiology of HCV infection in the community argues against saliva and other non-parenteral pathways of transmission. No infections have been associated with mucous membrane or non-intact skin exposure, although there has been one report of a blood splash to the conjunctiva that apparently resulted in seroconversion.<sup>4</sup>

The precise epidemiology of HCV infection remains complex in that, in some communities, there is the suggestion of other modes of transmission. Intravenous drug use is the single dominant factor in many western societies, however in some countries this single risk factor plays a limited role. In Roffi et al's<sup>6</sup> study of a cohort of 1,368 HCV positive patients, there was a large proportion of sporadically acquired infections (61.9 per cent), with only 18.5 per cent related to transfusions and 19.6 per cent to a history of injecting drug use.

## Transmission of HCV to staff in the dental surgery

More than a decade ago, concern over transmission of HCV in the dental setting was identified as an important issue both for healthcare workers and their patients.<sup>22</sup> The dominant mode of transmission is blood-to-blood contact, with quoted transmission rates<sup>4,5</sup> of between 0-10 per cent (average: 1.8 per cent) in the situation where a healthcare worker sustains a sharps injury from an infected patient. While this is less than the comparable figure for hepatitis B virus (HBV), which has a transmission rate of 25-35 per cent, it should be remembered that healthcare workers can be immunised against HBV but not HCV.

In several investigations on the possibility that HCV was a major occupational risk to dentists, it was concluded that nosocomial transmission of HCV in dentistry is possible but relatively unlikely.<sup>5,21,23,24</sup> These assessments may need to be reviewed in the light of increasing prevalence of HCV in the community at large, taking into account more recent data on the risk of HCV transmission from sharps injury. It is currently believed the risk of occupational acquisition of HCV infection is greater for healthcare workers than the general community, particularly those healthcare workers in contact with seropositive patients, however the risk is small. Current data are relatively limited, but it appears the prevalence of HCV infection is not notably higher in dentists than in the general community. There is, however, an increase in prevalence with increasing years of practice and occupationally acquired HCV has also occurred in dental students.

Of note, HCV is more prevalent in oral surgeons than in general dentists and this may reflect not only exposure-prone procedures but also a higher rate of HCV infection in the patient groups treated. For example, in a survey of patients attending hospital oral surgery departments, 1.1 per cent of patients had anti-HCV antibodies, a considerably higher percentage than in the general community.<sup>25</sup>

## Transmission to patients

An increased prevalence of HCV has been documented in some populations of dental patients, implying cross-infection from patient to patient or staff to patient in the dental setting. This increased prevalence was first documented in Italy and Japan.<sup>26</sup> Hospitalisation and medical/dental care were implicated as risk factors for non-drug injecting people. Piazza et al<sup>27</sup> demonstrated dental treatment was the only risk factor in 9 per cent of cases of acute HCV infection. Through the use of the polymerase chain reaction (PCR) assay, the same researchers demonstrated HCV genetic material could be recovered from dental equipment, handpieces, burs and workbenches and extensive contamination of dental surgeries occurred following treatment of HCV-infected patients. Clearly, if sterilisation and decontamination procedures are inadequate, transmission of HCV in the dental surgery is a real possibility. Flamm et al<sup>17</sup> noted dental treatment may have been a risk factor for HCV before infection control precautions became commonplace.

## Dental management of the HCV-infected patient

The most significant problem to be faced with a patient suffering cirrhosis will be the likelihood of prolonged bleeding following dental procedures. This bleeding is caused by a lack of coagulation



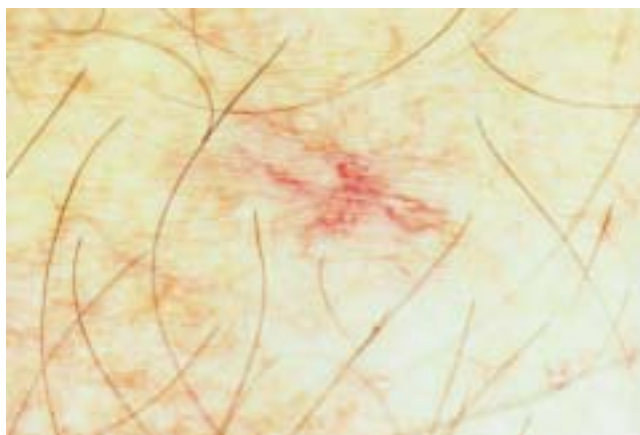


Fig 1. Spider naevi on the skin are an indication of poor liver function.



Fig 2. Petechiae on the soft palate should alert the dentist to potential bleeding problems that may be encountered during dental treatment.

factors and thrombocytopaenia<sup>28,29</sup> (Fig 1, 2). Consequently, any invasive dental treatment (extractions, surgery and extensive periodontal treatment) should be undertaken after consultation with the appropriate medical specialists. Simple treatment may be carried out utilising agents to establish local control of bleeding (for example, topical tranexamic acid).

There is a small but significant risk for a patient with severe cirrhosis that drug interactions and toxicity will burden an already stressed liver. The use of octapressin as a vasoconstrictor, for example, is contraindicated in someone with extensive liver dysfunction. Prescribing medications that are processed or excreted in the liver is also potentially hazardous. Drugs such as metronidazole, tetracyclines, erythromycin and paracetamol are contraindicated for people suffering liver failure.

In addition to medical complications arising from liver disease, problems in delivering dental treatment also exist for those undergoing HCV infection therapy. Drugs such as IFN, ribavirin and corticosteroids may lower resistance to infection and cause



Fig 3. Rampant dental caries can be present in HCV infection and, as a result, appearance may be affected.

bleeding, so invasive dental treatment should be postponed until therapy has ceased. Urgent dental treatment needs to be undertaken in consultation with the appropriate medical specialists.

Recent data<sup>30</sup> indicate people with HCV infection may be prone to extensive dental disease (Fig 3). This further complicates management for those who do suffer significant cirrhosis. The contributing factors to the dental disease burden are varied, but xerostomia is a notable feature of HCV infection and oral health is impacted by this factor (Fig 4). Farrell<sup>3</sup> reported a case of a man presenting with fatigue and irritability. Based on raised ALT and AST levels, HCV infection had been present undiagnosed for approximately 20 years. Clinically, the only symptom of disease was an enlarged parotid gland. Dentists need to be aware of the possible effects of a chronic viral infection on salivary gland function and institute appropriate preventive strategies to maintain dental health.

Several studies suggest a correlation between lichen planus and HCV infection. However, the reason for the correlation is unknown and although it has been proposed erosive lichen planus is an indication for serological testing for HCV infection,<sup>31,32</sup> this would seem to be unwarranted at this stage.



Fig 4. Xerostomia can increase the likelihood of oral infections such as candidiasis. In this patient, the candida infection is also related to the wearing of a partial denture.

Finally, alcoholism may be a problem for some patients and these individuals may show accelerated tooth wear from erosion.

## Conclusion

The widespread incidence of HCV infection is of concern. Although many of those infected will not suffer significantly from their infection, up to one-third will have liver disease, fatigue and oral health problems. Practitioners need to be aware of the precautions necessary in treating people with severe liver disease and the importance of preventive programs to reduce dental pathology and maximise oral health for individuals infected with HCV.

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