Hepatitis C: diagnosis and management issues

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Abstract

- Hepatitis C virus (HCV) is one of the main causes of chronic liver disease and hepatocellular carcinoma.
- The commonest means of transmission is intravenous drug use. Transmission by blood transfusion is now very low, and sexual transmission is low. Although there are reports of transmission between health care workers and patients, the risk is low. Infected surgeons do not need to stop work.
- People with known exposure should be tested by screening for anti-HCV antibodies, HCV RNA, and serum aminotransferase levels.
- Therapy is generally recommended for everyone 18 years or older who has no contraindications, an abnormal serum ALT level and a liver biopsy showing chronic hepatitis and significant fibrosis.
- We recommend that all chronically infected patients in the Australian Defence Force should be considered for treatment, as cure is possible.

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IN THE PAST 50 YEARS, enormous advances have been made in our understanding of infectious diseases that predominantly affect the liver (Box 1). The first observations were made in the 1950s that the common epidemic form of hepatitis, which affected large numbers of troops in World War II, must be different from the hepatitis observed after administration of blood transfusion and blood products. The incubation periods were different (15–49 days for epidemic hepatitis; 60–180 days for post-transfusion hepatitis). The discovery of a new antigen in an Australian Aboriginal in the 1960s, originally named the "Australia antigen" and later renamed "Hepatitis B surface antigen" gradually led to the identification of the hepatitis B virus.

Once a diagnostic test had been developed for hepatitis B surface antigen (in 1963), steps were taken to eliminate use of infected blood and blood products. However, elimination of blood products contaminated with hepatitis B did not eliminate post-transfusion hepatitis; it became obvious that there were other causative agents for what became known as "non-A non-B hepatitis". In the 1980s, researchers from the US Centers for Disease Control (CDC) and Dr Houghton from the Chiron Corporation identified a new virus named hepatitis C. By 1989, a commercially usable test identifying antibodies to this virus was developed, and this test was refined in the next few years to become extremely reliable for identifying exposure to the virus of hepatitis C. This antibody does not eliminate the virus and is positive in people with chronic infection. It was soon established that 90%–95% of patients with non-A non-B hepatitis were infected with the hepatitis C virus (HCV). Once blood could be tested for HCV antibody, the risk of acquiring post-transfusion hepatitis fell to 0.001%.

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Virology

HCV is a member of the *Hepacivirus* genus in the *Flaviviridae* family. HCV has been classified into genotypes and subtypes, and the genotype a patient is infected with has important implications for the success of treatment.

Prevalence

In 1998, the Hepatitis C Projections Working Group estimated there would be about 210 000 people infected by hepatitis C in Australia by 2001.[1] However, the HCV prevalence has been calculated to be about three times that of cumulative HCV notifications.[2] There is evidence that the number of new infections is now decreasing, probably because of safer sex practices.[3]

1 Landmarks in hepatitis C

1957: Discovery of interferons alfa, beta and gamma, which have antiviral properties.

1963: "Australia Antigen" (Hepatitis B surface antigen) identified.

1980–1990: Identification of hepatitis C virus in chimpanzee blood.

1991: First interferon alfa treatment approved for hepatitis C.

1998: US Food and Drug Administration approves use of ribavarin in hepatitis C as a coagent with interferon alfa.

2001: Pegylated interferon with ribavarin found to greatly improve response of chronic hepatitis C disease to treatment.

2003: Pegylated interferon alfa-2a and alfa-2b approved for treatment in conjunction with ribavarin for treatment of hepatitis C disease.

2005: Studies published comparing fixed and weight adjusted dosage schedules, and comparisons between interferon alfa-2a and alfa-2b.

Transmission[4]

Intravenous drug use

The commonest method of acquiring the virus is intravenous drug use; 60% of diagnosed patients have had exposure to intravenous drugs in the previous 6 months.[5] Among 178 intravenous drug users receiving opioid replacement in 2002–2003, the prevalence of HCV was 75%, and it increased with age from 61% among those aged 19–30 years to 93% among those older than 40 years.

Blood transfusion

Before the ability to screen blood for HCV, one transfused patient in 10 was likely to acquire the disease in the US. The risk at present is estimated at 1:100 000, presumed to be due to the donor having been infected recently and giving blood before hepatitis C antibodies have appeared. This will decrease further with the use of nucleic acid testing (testing for HCV genetic material in blood donors).[6]

Sexual or household contact

The risk of sexual or household transmission is very low to nil, but reliable figures are not available. There are cases of stable monogamous partners both being HCV antibody positive, but with HCV viruses of different genotypes, indicating transmission had not occurred between the partners. Other studies estimated the risk at 0.1% annually. The risk of sexual transmission may be greater if the index case is coinfected with HIV.

Perinatal transmission

Perinatal transmission to infants born to women who are HCV RNA positive is 5%. Precautions at present are not recommended. Breastfeeding seems to carry no risk. Infants of mothers with HCV antibodies will carry antibodies passively, and diagnosis of disease transmission requires HCV RNA testing.[5,7]

Health care workers

The incidence in health care workers appears to be 1%, which is the same as in the general population. The problem of needlestick injuries remains, and is an independent predictor of HCV infection. The average risk of acquiring the infection by subcutaneous exposure to blood from an HCV-positive patient is calculated at 1.8%, although rates up to 10% have been reported. There are no present recommendations for treatment at the time of the needlestick injury, but treatment may be worthwhile if acute hepatitis C develops. There are no reports of transmission by mucous membrane or non-intact skin exposure.[8,9]

The risk of transmission from infected health care workers is extremely low. As there is no vaccine, there is no public health justification to monitor health care workers. A computer model has calculated the risk of transmission from a health care worker to a patient as 0.014% ±0.002%.[10] No surgeon needs to stop work if HCV-positive. The risk of transmission to a single patient from an HCV-positive surgeon performing 5000 operations over 10 years is estimated at 50%.[10] Nevertheless, an infected surgeon should undergo treatment.

Other sources

In some patients, the cause of infection cannot be traced. High rates have been found in people with chronic alcohol dependence even in the absence of other risk factors.

2 Who to test for hepatitis C

- Everybody after any needlestick injury.
- Everybody who has ever received possibly contaminated blood products.
- Everybody who handles casualties or equipment soiled with blood.
- All blood donors.
- All donors of tissue for transplantation.
- Everyone with a history of intravenous needle use and possibly recreational drug use.
- Patients with elevated serum levels of aminotransferases (although many will have other forms of liver disease).
- Patients with diseases often associated with hepatitis C.

Note: The disease is frequently asymptomatic.

Contaminated equipment can be a cause. One case report implicated transmission at colonoscopy. Commercial barbers may spread infection occasionally. Procedures in traditional and folk medicine, tattooing and body piercing may be responsible for a few cases.[5]

Diagnosis

Box 2 summarises who should be considered for testing for HCV. After known exposure, the following testing schedule is recommended:

- test for hepatitis C RNA by polymerase chain reaction (PCR) immediately and after 4 and 8 weeks
- test for anti-HCV antibody by enzyme-linked immunosorbent assay (ELISA) immediately and after 12 weeks
- measure serum levels of aminotransferases immediately and after 4 and 8 weeks.

Clinical markers

Anti-HCV antibody

The preliminary diagnosis is generally made by detecting anti-HCV antibodies by ELISA. This test will not distinguish people who are chronically infected from those who have cleared the infection. This test will generally not be positive earlier than 8 weeks after exposure, and antibodies may appear only much later in some people with subclinical infection.[9]

HCV RNA

HCV RNA may appear in the serum a few days to 8 weeks following exposure. The test is useful to diagnose acute HCV infection after any needlestick injury.[11]

Serum aminotransferases

Serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) tend to rise at about 6–12 weeks, but may return to normal in many people. They may be normal despite progressive disease. The levels in active disease are rarely high (less than three times normal) and tend to fluctuate. Normalisation of serum aminotransferase levels after treatment does not indicate cure of the infection.

Clinical features and natural history of hepatitis C

Acute infection

New infection with HCV can result in a recognisable acute illness, but such clinical manifestations are rare. In the acute phase, the HCV RNA is detectable by PCR within days to 8 weeks, depending on the size of the inoculum. If there are symptoms, these consist of mild nausea, malaise and right hypochondrial pain. Serum aminotransferase levels may become elevated at 6–12 weeks. The acute illness lasts about 2–12 weeks. Fulminant disease is very rare, but may occur in patients with coexistent hepatitis B virus infection.

3 Factors that may influence progression of hepatitis C disease

- Host factors: genetic factors may affect progression of fibrosis, and this may become of practical importance in the future.
- Acquisition of the disease after the age of 40 years may be associated with more rapid progression.
- Children may have a lesser risk of disease progression.
- Transfusion-acquired hepatitis C may be more aggressive.
- A high body mass index (obesity) and liver steatosis may have a detrimental effect.
- Alcohol intake (even modest amounts).
- Marijuana use may have a detrimental effect.
- Viral factors: coinfection with more than one serotype may be detrimental
- Coinfection with HIV results in more severe hepatitis C disease.

Chronic infection[4,12,13]

Overall, 80%–100% of acutely infected patients become chronically infected, 80%–100% remain HCV RNA positive and 60%–80% have persistently elevated serum aminotransferase levels (ALT and AST). The rate of spontaneous clearance of the virus is very low (in one series, 14%). HCV is highly variable; in the liver and in the serum in a single patient, slightly genetically different virus particles (quasi-species) can be found. This variability is believed to be the reason that the development of antibodies does not usually prevent persistence of the virus and chronic disease.

Symptoms

Symptoms are variable and may be minimal. The commonest symptom is fatigue. Myalgia, arthralgia, nausea and anorexia occur, and weight loss may occur, but rarely. The severity of symptoms does not reflect disease activity.[14]

Serum aminotransferases

About 30% of patients have normal serum levels of ALT and AST. The rest have modest elevations (2–3 times normal), but elevations greater than 10 times normal are rare. There is poor correlation of serum AST and ALT levels with histology. The one exception is that reversal of the usual ALT/AST ratio to greater than one is often a marker of established cirrhosis.

Natural history

Chronic hepatitis C is the most common cause of chronic liver disease, and the commonest indication for liver transplantation. Not everyone progresses to chronic liver disease; the outcome is probably driven by both host and environmental factors (Box 3).[13,15-18]

There are many studies of the natural history and the results vary. In a French study, the mean time to cirrhosis was 30 years. In a cohort of soldiers found to have positive HCV antibodies, only two out of 11 developed liver disease. (This was a very large cohort of over 5000 soldiers; 17 were HCV antibody positive and 11 HCV RNA positive.) In several studies, cirrhosis developed in up to 55% after 20 years. It appears that there is little progression of the liver disease in those abstaining from alcohol in the first 15 years. The incidence of liver damage rises precipitously in those who consume alcohol; this applies to even those consuming relatively moderate amounts.

A role for direct liver cell damage by the virus is possible, particularly when high viral loads are present. An immune mechanism is probably important; infected liver cells are attacked by the host's immune system. An autoimmune mechanism has been postulated.

Cirrhosis and hepatic decompensation

Cirrhosis occurs after 20 years in about 50% of patients. This can be quite silent; some will have hepatosplenomegaly, but hepatomegaly alone is rare. Hepatic decompensation follows the development of cirrhosis. In one series this occurred at a rate of about 4% per year. The manifestations are the usual ones of ascites, variceal bleeding, encephalopathy and jaundice, in that order.

Hepatoma

Hepatoma (hepatocellular carcinoma) occurs almost exclusively in those who first become cirrhotic. In contrast to hepatitis B virus, HCV does not seem to be itself oncogenic; it is cirrhosis that is the predisposing factor. About 30% of all hepatomas are related to preexisting HCV infection.

Extrahepatic manifestations[19-21]

In addition to liver inflammation and progressive fibrosis, HCV causes several extrahepatic diseases.

Essential mixed cryoglobulinaemia

This is a lymphoproliferative disease leading to deposition of immune complexes in small to medium-sized blood vessels. Manifestations are palpable purpura, arthralgia and weakness, but peripheral neuropathy, brain and renal involvement can occur. HCV appears to be the main cause of essential mixed cryoglobulinaemia. Hepatitis C treatment may or may not cure symptoms of cryoglobulinaemia.

Auto-antibodies

Auto-antibodies are common in HCV infection. These include antinuclear antibodies, anticardiolipin antibodies and smooth muscle antibodies. The presence of such antibodies in the presence of arthralgia and other systemic symptoms may result in diagnostic difficulties. These antibodies may only appear after commencement of interferon treatment.

Some patients with liver/kidney antibodies have low viral loads but a disproportionally severe inflammatory activity, and may respond to prednisone, thus behaving as autoimmune hepatitis.

Anti-thyroid antibodies may be detected in 5%–17% of patients. Hypothyroidism is commoner than expected in the general population in patients with HCV infection. More significant is the development of thyroid disease in patients with HCV treated with interferon; 1%–5% develop painless thyroiditis. Graves disease and permanent hypothyroidism is also commoner in treated patients than in untreated controls. Therefore, all patients in interferon need to be monitored for thyroid disease. Treatment can be continued in presence of hypothyroidism which is being treated, but hyperthyroidism will usually necessitate cessation of interferon.

Immunological diseases

Sialoadenitis often associated with other features of Sjogren syndrome can occur. Idiopathic thrombocytopenic purpura, myasthenia gravis (possibly interferon-induced) and sarcoidosis have been reported.

Renal diseases

This occurs mostly in association with cryoglobulinaemia; membranous or proliferative glomerulonephritis may occur.

Skin diseases

Porphyria cutanea tarda caused by reduction of hepatic uroporphyrinogen decarboxylase activity results in photosensitivity and bullae. All patients with suspected porphyria cutanea tarda need screening for HCV. Leucocytoclastic vasculitis producing palpable purpura can occur. Necrolytic acral erythema is a psoriasis-like itchy skin condition, and in one series all had HCV antibodies.

The effect of treatment is variable on extrahepatic manifestations.[22]

Treatment of hepatitis C

Acute hepatitis C

The treatment of acute infection is not fully agreed upon. Patients are rarely diagnosed in this phase. Furthermore, this is the group more likely to clear the virus spontaneously. It is impossible to summarise the trials published in this brief space. A recent consensus statement from the US National Institutes of Health in 2002 states that treatment of acute HCV infection is warranted because of the high response rate, but

that the timing of therapy and the type of regimen remain to be determined.[22-24]

The best results have been with interferon monotherapy (5 million units subcutaneously daily for 4 weeks followed by 5 million units subcutaneously three times weekly for 20 or more weeks). It may be reasonable to switch to pegylated interferon plus ribavarin in patients who continue to be HCV RNA positive after 3 months of treatment.

As symptomatic patients with acute hepatitis are most likely to spontaneously clear the disease, one could wait and not treat. Asymptomatic patients with acute disease are most likely to become chronically infected and early treatment may be preferable if recent exposure is recognised.

4 Contraindications to antiviral treatment of hepatitis C

- Major uncontrolled depressive illness
- Recipients of renal, heart or lung transplants
- Autoimmune diseases (especially hepatitis) known to be aggravated by interferon
- Untreated hyperthyroidism
- Pregnancy and noncompliance with contraception
- Severe comorbidities
- Hypersensitivity to the drugs used

Chronic hepatitis C

Only a brief survey of the treatment of chronic hepatitis C can be attempted in this article. The recent greatly improved results with pegylated interferon plus ribavarin treatment have been very welcome.[22,25,26]

General measures

Counselling about risks of transmission, course and natural history of the disease, and complications of treatment are paramount. Abstinence from all alcohol is essential. Marijuana is probably detrimental. No other dietary measures are necessary. Any medications needed for coexisting diseases need not be adjusted and can be taken. Paracetamol should probably be restricted to 2 g/day. Patients lacking hepatitis A and B antibodies should be vaccinated against both viruses.

Factors affecting response rates

Genotype and to a lesser extent viral load are important. Patients infected with genotype 2 and 3 have the best response compared with genotype 1 (and 4). Patients with viral loads less than 2×10^6 copies/mL (800 000 IU/mL) do better than those with a high viral load.

Who to treat?

Therapy is generally recommended for everyone 18 years or older who has no contraindications, an abnormal serum ALT level, and a liver biopsy showing chronic hepatitis and significant fibrosis.

Contraindications are listed in Box 4. Relative contraindications include coinfection with HIV, chronic renal disease, decompensated liver disease, and recipients of a liver transplant. These patients should be referred to centres doing clinical trials for these subgroups.

In the past, treatment was often withheld in patients with a normal serum ALT level and no or minimal fibrosis on biopsy who acquired the disease before age 35 years, on the basis that these patients often had very slow progression of their disease.

We recommend that all chronically infected patients in the Australian Defence Force should be considered for treatment, as cure is possible. Thus, all patients with hepatitis RNA in the serum (especially those who have raised serum ALT levels) are candidates for treatment if there are no strong contraindications. Patients with normal ALT levels with positive hepatitis RNA on PCR should be treated especially if the liver biopsy is abnormal.

Treatment decisions should be individualised,[27] and will also be affected by coinfection with HIV and other coexisting diseases (eg, thrombocytopenia or anaemia).

Patients who have not responded to treatment need referral to a unit specialising in hepatitis C treatment. Patients with advanced cirrhosis should be referred for assessment for liver transplantation.

Do all patients need have to have a liver biopsy?

Generally, liver biopsy is extremely useful. It will determine the stage and the prognosis of the liver disease. Patients with cirrhosis require periodic screening for a hepatoma, and endoscopic examination for oesophageal varices. Concomitant other liver disease can be excluded with a biopsy. Possibly patients with low viral loads, and those with genotypes 2 and 3 (who tend to respond well), in whom other causes of liver disease have been excluded, could be treated without prior liver biopsy.[25]

Drug therapy for chronic HCV infection

Combination therapy with pegylated interferon alfa-2a or alfa-2b plus ribavarin is the most effective treatment at present. Ribavarin is best administered in a dosage dependent on weight (less than 75 kg, 1000 mg; more than 75 kg, 1200 mg per day). The usual dose of interferon alfa-2 is 1.5 mg/kg. There are differences between the two available preparations, interferon alfa-2a and alfa-2b. These may or may not be of clinical significance, but they are also pegylated with different size molecules, and this may affect absorption at receptor sites.

Patients with HCV genotypes 2 and 3 respond best and can be treated with lower dose ribavarin (800 mg/day) and shorter courses of treatment (24 weeks), especially those who clear viral RNA at 4 weeks. Genotypes 1 and 4 require 48 weeks treatment to achieve acceptable viral response rates. Clearance of virus at 4 weeks indicates a good prognosis. Persistence of viral RNA at 12 weeks has been considered a marker of non-response. These patients should be enrolled

5 Side effects of antiviral therapy used for hepatitis C

Interferon and ribavarin both have side effects, which in many ways overlap.

Interferon

- Fatigue
- Anaemia, neutropenia, thrombocytopenia
- Autoimmune diseases (especially thyroid)
- Depression
- Dyspeptic symptoms (see manufacturer's information leaflet)

Ribavarin

- Haemolysis
- Fatigue
- Depression
- Anorexia
- Insomnia
- Vertigo

into a clinical trial in clinics with a special interest. Maintenance pegylated interferon is an option being tested.

Summarising a number of trials, virological response rates are 40% for genotypes 1 and 4, and nearly 80% for genotypes 2 and 3. These are much better results than were previously available, and much work is going on to improve treatment.

Ondansetron[28] may alleviate fatigue, but is expensive, unreliable and causes constipation.

There are a number of complications of treatment (Box 5). These may necessitate reducing the dose of one or the other of the medications, or discontinuing treatment.

Treatment guidelines in Australia

Treatment in Australia is affected by the restrictions imposed by Section 100 of the Pharmaceutical Benefits Schedule, which determines which patients can be treated free of charge. These regulations are regularly updated. Approval for treatment with pegylated interferon and ribavarin has required initial liver biopsy (except in people with coagulation disorders preventing safe liver biopsy). From April 2006, liver biopsy will no longer be mandatory; the decision is left to the attending hepatologist. Patients must also fulfil the following criteria:

- abnormal serum ALT levels
- fibrosis of more than stage 1 on liver biopsy
- documented chronic hepatitis C (HCV antibody and RNA positive).

There are a number of exclusion criteria, including pregnancy, breastfeeding, and requirements for effective contraception during therapy.

Treatment efficacy has to be demonstrated at 12 weeks with at least a 2-log drop in HCV RNA on PCR in the same laboratory using the same test. Treatment length is determined by HCV genotype: 24 weeks for types 2 and 3, and 48 weeks for other genotypes.

Conclusions

Hepatitis C is a major public health problem which has been aggravated by the fashion of recreational intravenous drug use. Much has been learnt in the past 20 years about the biology of the virus and the clinical problems it poses; reasonably effective treatment is available, but we still lack a vaccine. At present, treatment is expensive and prolonged, and has side effects. However, infected ADF personnel should be considered for therapy. Significant further advances can be expected.

Competing interests

None identified.

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