



Viral hepatitis in the 1990s, part III: hepatitis C, hepatitis E, and other viruses

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■ Acute hepatitis can be caused by a number of viruses, especially A, B, C, E, delta, Epstein-Barr virus, and cytomegalovirus. Hepatitis A and B have been discussed previously in this series. The virus responsible for most cases of what commonly has been referred to as non-A non-B hepatitis has been tracked, and antibodies to certain proteins of this virus have been identified. This virus is now referred to as hepatitis C. The possible clinical outcomes after acute hepatitis C virus infection are similar to those for hepatitis B virus infection, except that hepatitis C is far more likely to become chronic. Clinical testing for hepatitis C virus infection is in its infancy and has certain limitations. Successful treatment of at least some cases of hepatitis C is possible. Hepatitis E has recently been described, primarily in third-world countries. It causes an acute hepatitis that may be particularly lethal for pregnant women. Herpesviruses may also cause hepatitis, particularly in the newborn or the immunocompromised. Exotic viruses causing acute hepatitis are enumerated.

□ INDEX TERMS: HEPATITIS, VIRAL, HUMAN; HEPATITIS, VIRAL, NON-A, NON-B; INFECTIOUS MONONUCLEOSIS; CYTOMEGALIC INCLUSION DISEASE □ CLEVE CLIN J MED 1992; 59:595-601

RECOMBINANT DNA TECHNOLOGY has brought the medical world to a new era in research on non-A non-B hepatitis. The cloning and sequencing of portions of the hepatitis C virus (HCV) genome and the development of serologic assays to detect antibodies to portions of the virus are major breakthroughs in the long search for the specific causative agent of non-A non-B hepatitis. In the previous parts of this series^{1,2} we discussed hepatitis A, B, and delta hepatitis. In this final article, we highlight hepatitis C and provide a brief overview of other viruses that may produce hepatitis.

HEPATITIS C VIRUS

The major cause of non-A non-B hepatitis (also known as posttransfusion hepatitis), the hepatitis C virus is a positive-stranded RNA virus and appears to be distantly related to the flavivirus subgroup of togaviruses. In 1989, a somewhat nonspecific antibody to the virus responsible for most cases of parenterally acquired hepatitis was described.^{3,4} This antibody is nonneutralizing and develops late after acute HCV infection and appears to be a good marker of persistent viremia.⁵ A more detailed discussion of tests for HCV is presented later.

Blood donors infected with HCV can be detected using this assay. For example, anti-HCV antibodies were detected in six of seven human sera that were shown previously to transmit non-A non-B hepatitis to chimpanzees.⁴ Anti-HCV activity was detected in at least one unit of blood given to 9 of 10 patients who developed non-A non-B hepatitis after blood transfusions. Moreover, the sera of all 10 patients converted

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from anti-HCV-negative to anti-HCV-positive.^{4,6} A high incidence of anti-HCV antibodies are seen in patients with non-A non-B hepatitis from Italy, Germany, and Spain.^{4,7,8} In addition, 58% of non-A non-B hepatitis patients from the United States are positive for HCV antibody.^{4,6} These data support HCV as a major cause of non-A non-B hepatitis throughout the world.

Epidemiology

Transmission of hepatitis C seems to be largely parenteral. Individual risk for contracting hepatitis C from blood products is a function of the number of blood products received.⁹ Although other routes may occasionally be responsible, nonparenteral spread of hepatitis C is very inefficient. Epidemiologic studies indicate that an additional risk factor may include sexual contact with multiple heterosexual partners.¹⁰ Current evidence suggests that household contacts and sexual partners where a stable monogamous relationship exists are not at increased risk for development of hepatitis C. In these important ways, then, the spread of hepatitis B and C are quite different. Perhaps this relates to differences in the presence of virus in body fluids. A recent study searching for evidence of HCV in cell-free semen and in saliva failed to find evidence of virus.¹¹ Other investigators did detect significant levels of HCV-specific antigen from semen that had not first been rendered cell-free.¹²

Clinical course

The clinical course of hepatitis C is variable. The incubation period has a wide range, from 14 days to 6 months, with a mean of 7 to 8 weeks.^{13,14} When compared with posttransfusion hepatitis B, the clinical course of acute hepatitis C is generally less severe. More patients are asymptomatic. In some respects, this disease behaves like hepatitis B, but it is far more likely to become chronic. Persons with chronic HCV infection can remain infectious for years.^{9,15} Only 5% to 10% of individuals infected with hepatitis B, but at least 50% of those with HCV, develop chronic disease.^{4,7,16-18} Recent reports link HCV with the subsequent development of hepatocellular carcinoma.¹⁹ Additional observations from Japan and Italy confirm a high prevalence of anti-HCV in patients with primary hepatocellular carcinoma, even in patients without detectable markers for coexisting hepatitis B.¹⁹

Laboratory diagnosis: current status

Identification of HCV infection on clinical grounds

is sometimes quite difficult. Until recently, diagnosis rested upon symptoms together with raised serum transaminases. However, symptoms are absent more often than not, and even the liver enzymes may be normal because of the characteristic fluctuation in enzyme levels seen with this disorder. The alanine aminotransferase (ALT, SGPT) level is more likely to be raised than the aspartate aminotransferase.²⁰

Diagnostic precision has been enhanced by the development of a number of methods for detecting antibodies to HCV. The first is an enzyme-linked immunosorbent assay (ELISA) that detects the presence of antibody directed against the C100-3 protein of HCV. Using this test, anti-HCV antibodies are found in up to 85% of patients with posttransfusion non-A non-B hepatitis and in implicated blood donors.⁵ The frequency of anti-HCV in blood donors increases proportionately with the donor ALT level and also with the presence of hepatitis B core antigen (anti-HBc), indicating that those who are at risk for hepatitis B are also at risk for hepatitis C.²¹ Anti-HCV antibodies have been reported in 60% to 80% of patients with hemophilia receiving replacement clotting factors, in 60% to 70% of those with chronic active hepatitis or cirrhosis with a history of blood transfusion, and in 50% to 70% of intravenous drug abusers.^{4,6,8,18} Surprisingly, anti-HCV antibodies are also found in more than 40% of patients with autoimmune chronic hepatitis and in nearly as many with primary biliary cirrhosis, alcoholic cirrhosis, and cryptogenic cirrhosis. None of these patients had a history of blood transfusion.^{8,15} It seems clear that false-positive reactions to the ELISA for anti-HCV are frequent, particularly in those with liver disease. Thus, this test may be useful in screening blood in a blood bank, but positive results need to be interpreted with great caution in the patient with liver dysfunction.

This first-generation test has been available commercially since mid-1990. As mentioned above, its utility has been limited by frequent false-positive reactions.^{22,23} A second-generation ELISA has been introduced which incorporates new epitopes, including the core protein C22. This ELISA (developed by Abbott Diagnostic Laboratories) recently won US Food and Drug Administration (FDA) approval and is used as a screening test for anti-HCV in most clinical laboratories today. Evidence suggests that this second-generation ELISA is more sensitive²⁴ and specific²⁵ than the first-generation test. Nevertheless, false-negative reactions can still be observed.²⁵

A radioimmunoassay (RIBA) has been

developed for use as a supplemental assay to detect antibodies to a panel of specific HCV antigens. As currently formulated, it detects the presence not only of antibody directed against protein C100-3, but also to antibodies against three additional HCV-related proteins. A reaction is considered positive when two or more antibodies are present. It has been shown that a number of patients with autoimmune chronic active hepatitis who tested positive to the first-generation anti-HCV ELISA test negative with the RIBA.²⁶ Although the RIBA has not yet been licensed by the FDA, it is available through many regional laboratories. This test may be negative in some patients who are found to have HCV RNA in their serum.²⁵

Anti-HCV antibodies frequently do not emerge until many months after exposure.⁵ In those with acute non-A non-B hepatitis *not* acquired through transfusions (sporadic or community-acquired), about half are positive for anti-HCV within 6 weeks of illness, and another 40% have detectable antibody 6 months later.²⁷ Thus, with currently available assays, at least 6 months and probably 12 are required before all seroconversions will have occurred. Those who remain negative for anti-HCV may have another virus or another cause for liver test abnormalities.²⁸ On the other hand, they may have hepatitis C but without an immune response. The resolution of these issues and a more timely diagnosis of acute HCV infection must await the development of new and more sensitive serologic assays. Most important, markers for the presence of viral antigens are sorely needed. Recent research into techniques that amplify the minute amounts of HCV RNA in serum or tissue are promising in this regard; one such technique employs a polymerase chain reaction. For the first time, it is possible to differentiate between those who harbor antibodies but may have cleared infection and those who harbor actively replicating virus who may or may not test positive for antibodies. Unfortunately, the polymerase chain reaction is technically demanding and may not be clinically available for a few years.²⁹

Treatment of acute HCV infection

Since no specific treatment exists for acute HCV infection, treatment is directed at symptoms. Modified activity with increased rest, as dictated by fatigue, is all that is needed in the majority of cases. About one half will recover. Interferon alpha, which will be discussed at length as treatment for chronic hepatitis C, has been little studied in the treatment of acute disease. A recent report suggests that interferon therapy *may* be useful in

TABLE
TREATMENT OF CHRONIC HEPATITIS C VIRUS INFECTION
WITH INTERFERON ALPHA

Dosage	Normal	ALT* level after treatment	
		Near normal	Combined
3 million units	36%	7%	46%
1 million units	16%	12%	28%
Control	4%	4%	8%

*ALT, alanine aminotransferase, was formerly SGPT, serum glutamic pyruvic transaminase

decreasing the severity of hepatitis and hastening resolution. However, there was no reduction in the incidence of chronic cases.³⁰ Interferon is not indicated in the treatment of acute viral hepatitis.

Those who develop chronic HCV infection, even if asymptomatic, are at risk for the development of cirrhosis. Attempts at interruption of the disease seem reasonable, but no truly satisfactory treatment is available. Interferons show promise, but they are expensive, require parenteral injections over a long time, and are associated with numerous troublesome side effects.³¹ These problems have been addressed more fully.³² Lower doses of interferon usually suffice in the treatment of hepatitis C compared with hepatitis B.

A number of large trials of interferons in the treatment of chronic hepatitis C have been reported.^{33,34} In one typical multicenter trial, dosages of 1 million units three times a week and 3 million units three times a week were compared with no treatment. All patients had liver biopsies before therapy and after 24 weeks of therapy. Those with either chronic active or chronic persistent hepatitis were admitted, as were those with well-compensated cirrhosis. The best strategy proved to be a dosage of 3 million units. In those so treated, the liver enzymes became normal or nearly so after 6 months of therapy in slightly less than one half of cases. Nearly all responders showed a response within 12 weeks of initiating therapy (Table). Nearly half of the responders maintained their response even after treatment was stopped.³³ To summarize, about one quarter of patients with chronic hepatitis C appear to obtain lasting benefit from treatment with interferon. Only much longer term follow-up will allow us to learn if this improvement represents a cure.

It is encouraging, in this regard, that recent studies have demonstrated that HCV RNA, as detected by reverse transcriptase and nested polymerase chain reaction, disappears from the serum after 4 to 8 weeks

of therapy and remains undetectable after treatment is stopped in those whose liver enzymes remain normal, but returns in those who relapse.³⁵

Many questions about the treatment of chronic hepatitis C remain unanswered. Should mild cases (eg, those with only chronic persistent hepatitis) be treated? Can those with decompensated cirrhosis be safely treated with lower dosages, and to what purpose? Can interferon help in post-liver transplantation chronic hepatitis C? Does control of hepatitis C reduce the potential for development of hepatocellular carcinoma? What can be done for the majority of patients who obtain no lasting benefit from a 6-month course of interferon? The answers to these and other questions will require years of additional study. Newer agents with some activity against viral hepatitis, such as ribavirin and thymosin, need to be studied in chronic hepatitis C patients.

Prevention

Unfortunately, no active vaccine for hepatitis C is available yet. Interruption of blood-borne disease is extremely difficult in a culture in which intravenous drug use is common. Screening blood donors by use of anti-HCV antibody, ALT, and anti-HBc testing has already been discussed. However, since only a small percentage (less than 10%) of cases of acute hepatitis C appear to come from blood transfusions, elimination of hepatitis C from blood banks will have only a modest effect on the hepatitis C problem in this country. Prevention of hepatitis C in other settings (eg, intravenous drug use, tattooing with dirty needles) will be essential if major reduction in the frequency of new cases is to be realized. Since over 40% of those with acute hepatitis C have no identifiable risk, prevention may also depend upon a more accurate understanding of modes of spread of this disease. For the sake of patient and family well-being, it is also important to reiterate that family members and monogamous sexual partners do not appear to be at risk. The Centers for Disease Control (CDC) recommendations are as follows: (1) For individuals with a stable monogamous sexual relationship, no change in sexual practice is recommended; (2) For individuals with multiple sexual partners, "safe sex" practices should be followed.³⁶

As for passive immunization, older studies using gamma globulins are difficult to interpret because no suitable identifying markers for hepatitis C were available. There is a suggestion that administration of 5 cc to each buttock 1 week before and 1 week after blood transfusion may reduce episodes of posttransfusion

hepatitis by as much as two thirds in open heart surgery cases.³⁷ Military personnel assigned to Korea were found to have a lower incidence of icteric hepatitis C if they received immune serum globulin. This protective effect was apparent for 6 months.³⁸ It is hard to make confident public health policy recommendations, considering the dearth of appropriate studies. The CDC equivocates about the use of gamma globulin after percutaneous exposure to non-A non-B hepatitis. For persons with percutaneous exposure to blood from a patient with parenterally transmitted non-A non-B hepatitis, it may be reasonable to administer immune globulin (0.06 mL/kg) as soon as possible after exposure. In other circumstances, no specific recommendations can be made.³⁹

ENTERICALLY TRANSMITTED NON-A NON-B HEPATITIS

More than 50% of cases of acute hepatitis in some developing countries appear to be unrelated to infection by either hepatitis A virus (HAV) or hepatitis B virus (HBV). Accumulating evidence suggests that a high proportion of this non-A non-B hepatitis is *enterically* transmitted. This was first documented in New Delhi, India, in 1955, when 29,000 cases of icteric hepatitis were identified following widespread fecal contamination of the city's drinking water.⁴⁰ These were originally attributed to HAV, but analysis of paired serum samples from documented cases revealed neither HAV nor HBV.⁴¹ This waterborne hepatitis virus, inferred from epidemiologic studies of outbreaks, is also referred to as endemic non-A non-B hepatitis.

Contaminated drinking water—particularly likely to occur after monsoon rains or other natural occurrences that lead to fecal contamination of drinking water—are the usual setting in which outbreaks of epidemic non-A non-B hepatitis occur. Young adults are most likely to be affected. The Indian subcontinent, South East Asia, Africa, and Mexico have all experienced outbreaks. The apparent incubation period is 22 to 60 days (mean 40). Most cases are benign, and it has a self-limited course resembling that of HAV infection. Some outbreaks have been associated with a very high (about 20%) mortality rate in infected pregnant women.⁴²⁻⁴⁴ To date, cases in Western countries have been related to travel to endemic areas.

Virus-like particles have been identified in the stool, and a serologic response to these particles has been demonstrated by several investigators. Molecular cloning of viral genome of these 32- to 34-nm virus-like

particles has been carried out. The virus is probably a single-stranded, polyadenylated RNA and appears to be a calicivirus, a family with similar characteristics to the picornaviruses.⁴⁵ In view of the combined data linking this virus-like particle to enterically transmitted non-A non-B hepatitis, it is suggested that this agent now be called hepatitis E virus.^{42,45}

MISCELLANEOUS CAUSES OF VIRAL HEPATITIS

Common herpesviruses such as cytomegalovirus (CMV), herpes simplex, and Epstein-Barr virus (EBV) may cause mild hepatitis in individuals with normal immunity but may cause life-threatening hepatitis in those with depressed cell-mediated immunity.

Epstein-Barr virus

EBV infection can be acquired at any age. Primary infection in childhood is usually asymptomatic. In adolescence, infectious mononucleosis occurs in roughly half of those with primary EBV infection.⁴⁶ Twenty-five to 80% of US college students have detectable EBV antibodies.⁴⁷ Liver involvement occurs in 90%.⁴⁸ The distinctive signs and symptoms of infectious mononucleosis (profound fatigue, sore throat, fever, tender enlarged lymph nodes) often overshadow signs and symptoms referable to the liver. Jaundice is uncommon. The SGOT and SGPT will be elevated, often strikingly. The diagnosis can be confirmed by any of a number of acute phase reacting (immunoglobulin M) antibodies. The Paul-Bunnell-Davidsohn test or the Monospot test is positive for 3 to 4 months after the onset of illness.

In adults over age 40, atypical presentation with abdominal pain and fever mimicking biliary tract disease has been described.^{49,50} The hemophagocytic syndrome can also be associated with EBV infection,²⁹ as with other herpes viruses. This can masquerade as fulminant hepatic failure, and disseminated intravascular coagulation is a prominent feature. The pathognomonic features on bone marrow analysis include hemophagocytosis and benign lymphohistiocytic proliferation. Interferon therapy has been tried.

Cytomegalovirus

Like EBV, CMV is acquired most frequently by intrauterine, perinatal, intrafamilial, or sexual transmission. It may also follow blood transfusion or transplantation of a solid organ. Eighty percent of those over age 40 harbor antibodies to CMV, proving its ubiquitous nature.⁴⁷ In otherwise healthy adults, CMV infection is

usually asymptomatic. An occasional patient may have a heterophile-negative mononucleosis-like illness. Only seldom does hepatitis overshadow other features of the disease. In such cases, lymphadenopathy and atypical lymphocytosis are usually present. Immuno-compromised patients—those with cancer, organ transplant patients on immunosuppressive drugs, or patients with other infections such as human immunodeficiency virus are likely targets for severe or disseminated disease. The virus may be isolated in many body secretions, including saliva, urine, blood, and semen. It is also present in a number of organs, including lung and liver, where it produces typical cytoplasmic inclusions in infected cells.

In renal allograft recipients, CMV causes up to half of reported hepatitis episodes.⁵¹ About half of liver transplant patients develop CMV infection (primary or recurrent), although not all are symptomatic. Of potential risk factors for CMV following liver transplantation, positive CMV serology in the donor appears to be the most important factor implicated in the development of CMV in the recipient.⁵²

Neonates with congenital infection may have hepatosplenomegaly and raised serum transaminases. Jaundice may be exacerbated by hemolysis. Hepatic fibrosis with fatal cirrhosis has been reported following congenital CMV infection.⁵³

A significant rise in complement-fixation antibody titer is quite suggestive of CMV infection. Diagnosis in neonates is confounded by the presence of maternal antibodies⁵⁴ and by the relative inability of the immature immune system to mount an immune response.⁵⁵ CMV should be sought by one of the rapid cell culture confirmation methods which are now widely available.⁵⁶ Biopsy of the affected liver (or other organs) should reveal typical inclusions, a hallmark of the disease.

Treatment of CMV with antiviral agents is now possible, although not always necessary. CMV is self-limited in most adults. For severe or worrisome cases, particularly in those with impaired cell-mediated immunity, therapy should be initiated. Acyclovir is ineffective for established cases.⁵⁷⁻⁵⁹ Ganciclovir is effective, although significant toxicity (eg, bone marrow suppression) may occur.⁶⁰ Use of gamma globulin as prophylaxis seems to be effective in reducing the incidence of disseminated CMV disease in liver transplant recipients.⁵²

Other viruses

An occasional allograft recipient has been reported

with adenovirus hepatitis.⁶¹ Exotic viral infections are prevalent in particular geographic regions, and the liver often is involved. Examples are the yellow fever virus (Africa, Central and South America), Lassa fever virus, Marburg virus, Ebola virus infection, Rift Valley fever virus (enzootic hepatitis), Congo-Crimean hemorrhagic fever.⁶²⁻⁶⁹ In travelers returning to US communities from these areas, these infections must be considered.

CONCLUSIONS

Acute hepatitis can be caused by a number of viruses, especially A, B, C, E, delta, EBV, and CMV. Whereas the outcome is favorable in the majority of cases of hepatitis A, B, and C, pregnant women with E virus infection often have a worse outcome. Only a few patients with acute hepatitis A will die from it, and

none develop chronic liver disease. The fatality rate for acute HBV and HCV infection is similarly very low. Fewer than 5% of people with HBV infection develop chronic disease, but at least 50% of those with HCV do. Treatment of all forms of acute viral hepatitis is nonspecific, unless the infection is fulminant, in which case intensive care management and emergency liver transplantation are needed. Promising treatment for chronic forms of HBV and HCV infection are now available.

Active immunization against hepatitis C is not possible at the present. The value of passive immunization with immune globulin is unclear but is sometimes recommended. Major research efforts in hepatitis during the coming years will be the development of safe vaccines for protection against hepatitis C. Improved treatment strategies for established chronic viral hepatitis are needed as well.

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