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Hepatitis C Virus Infection (RE9733)

AMERICAN ACADEMY OF PEDIATRICS

Committee on Infectious Diseases

ABSTRACT. Hepatitis C virus (HCV) has become the most significant cause of chronic liver disease of infectious etiology in the United States. The recognition that HCV can be transmitted perinatally or through blood transfusions warrants particular attention by the pediatrician. The American Academy of Pediatrics recommends screening infants born to HCV-infected mothers and persons with risk factors for HCV infection such as injection drug use, transfusion of ≥ 1 U of blood or blood products before 1992, or hemodialysis should be screened for anti-HCV. Also, persons who received clotting factor concentrates before 1987, when effective inactivation procedures were introduced, also should be screened. Guidelines for counseling families of HCV-infected children are provided.

ABBREVIATIONS. HCV, hepatitis C virus; ALT, alanine aminotransferase; anti-HCV, antibody to HCV; HIV, human immunodeficiency virus; PCR, polymerase chain reaction.

Most cases of blood-borne non-A, non-B hepatitis have been proven to be caused by hepatitis C virus (HCV) infection, one of the most common causes of chronic hepatitis in developed societies. The identification of the etiologic agent responsible for this infection and the recognition that infection can occur in mothers and their children have raised numerous questions.

CLINICAL DISEASE

The incubation period of hepatitis C infection averages 6 to 7 weeks, with a range of 2 weeks to 6 months.¹ The clinical picture of disease in children is indistinguishable from hepatitis A- or B-associated disease. Most pediatric patients are asymptomatic. Symptomatic infections usually are mild and insidious in onset. Jaundice occurs in only 25% of patients, and elevations in alanine aminotransferase (ALT) generally are lower than those in hepatitis B virus infection. Fulminant hepatitis occurs but is extremely uncommon. With chronic disease, autoimmune complications are common (eg, autoimmune hepatitis, arthritis, serum sickness, and erythema multiforme). Children with an underlying immunodeficiency disorder have a higher and more rapid rate of disease progression.² Hepatocellular carcinoma develops in a small proportion of patients who have chronic hepatitis, but the true rate of this complication is unknown. It is not known whether the risk of chronic disease and subsequent complications is higher for patients infected as newborns than for patients infected at an older age. Persistent infection develops in at least 85% of infected newborns, even in the absence of biochemical evidence of liver disease.^{3,4} Chronic hepatitis occurs in ~70% of patients and cirrhosis in ~20%.¹

THE ETIOLOGIC AGENT

HCV is a small, single-stranded RNA virus in the family *Flaviviridae*. The HCV exhibits substantial heterogeneity as a result of mutations occurring during viral replication.³ This rapid mutation appears to be a mechanism that allows the virus to escape immune surveillance by the host and to maintain persistent infection. Because antibodies elicited by one virus type do not recognize other virus types, previous infection does not protect against reinfection with the same or different genotypes of the virus.³⁻⁵

EPIDEMIOLOGY

Prevalence

The seroprevalence of HCV infection is 1.8% in the general population of the United States (Centers for Disease Control and Prevention, unpublished data), with global distribution of infection. **Among children in the United States, the seroprevalence is 0.2% for those <12 years of age and 0.4% for those 12 to 19 years of age (Centers for Disease Control and Prevention, unpublished data).**

However, the seroprevalence of infection is highly variable in population subgroups.¹ The highest rates of antibody to HCV (anti-HCV) are found among those with large or repeated direct percutaneous exposures, such as injection drug users and patients with hemophilia who have received multiple blood transfusions (60% to 90%); moderate rates are found among those with smaller but repeated direct or inapparent percutaneous exposures, such as hemodialysis patients (20%); and lower rates are found among those with inapparent parenteral or mucosal exposures, such as persons with high-risk sexual behaviors and sexual and household contacts of infected persons (1% to 10%), as well as among those with sporadic percutaneous exposures, such as health care workers (1%). The lowest rates of anti-HCV are found among those with no high-risk characteristics, such as volunteer blood donors (<0.5%). Seroprevalence rates of 1% to 2% have been found in pregnant women.⁸⁻¹²

Transmission

Exposure to Blood and Blood Products

The most efficient transmission of HCV is through direct percutaneous exposure to infectious blood, such as through transfusion of infected blood or blood products or transplantation of organs or tissues from infectious donors, and sharing of contaminated equipment among injection drug users.¹ For these latter individuals, HCV infection usually occurs shortly after the onset of intravenous drug use. In the United States before 1986, transfusion-associated hepatitis occurred in 5% to 13% of recipients.¹ From 1986 to 1990, this rate decreased to 1.5% with the exclusion of high-risk individuals from the donor pool and with the introduction of surrogate testing of donors.¹² After the introduction of anti-HCV screening in 1990, the rate decreased initially to 1.0% and subsequently to $\leq 0.1\%$ per recipient (0.01% to 0.001% per unit transfused).^{13,14} A more sensitive second-generation test became available in 1992.¹⁵ Some transfusion-associated HCV infections continue to occur because assays currently available (second-generation) do not detect anti-HCV in $\sim 5\%$ of infected persons, and rare donations of blood are made by persons during the period between acquisition of infection and seroconversion. Hemodialysis patients and health care workers also are at risk as a result of exposure to infectious blood. For most infected children and adolescents, no specific source for their infection can be identified.

In 1994, the first outbreak of HCV infection associated with a licensed intravenous immunoglobulin was reported in the United States.^{16,17} According to the US Public Health Service, this outbreak involved recipients of a single product, Gammagard, also called Polygam (Baxter Healthcare Corporation, Glendale, CA), received between April 1, 1993, and February 23, 1994, when this specific product was withdrawn from the market. Presently, Gammagard is processed by a solvent/detergent treatment, rendering it noninfectious for HCV. Similar outbreaks have been reported from other countries among recipients of products manufactured in Europe.¹⁸ Intramuscular immune globulin has not been associated with the transmission of any infectious disease in the United States. To ensure their safety, all immune globulin products that are currently available commercially in the United States must undergo an inactivation procedure or be HCV RNA-negative before release.

Sexual Transmission

Among sexual partners of persons with chronic HCV infection who apparently had no other risk factors for infection, the average prevalence of anti-HCV was 5% (range, 0% to 15%).¹ Two studies have found a higher anti-HCV prevalence among the female partners of positive men compared with the male partners of positive women.^{19,20} Evaluations of the sexual contacts of partners coinfecting with

human immunodeficiency virus (HIV) have found similar rates of anti-HCV. However, in some studies, anti-HCV was found in both partners only when the male was coinfecting with HIV and HCV. In sexually active populations, the transmission of HCV has been associated with having multiple partners and failure to use a condom.¹

Maternal-Infant Transmission

According to studies of infants born to anti-HCV-positive women, an average of 5% (range, 0% to 25%) of infants acquired HCV infection based on second-generation anti-HCV testing.²¹⁻²⁸ Use of polymerase chain reaction (PCR) for the detection of HCV RNA did not result in a greater number of infections identified. In studies that followed up infants born to women coinfecting with HCV and HIV, the average rate of perinatal infection (14%; range, 5% to 36%) was higher than that among infants born to women with HCV infection alone.^{22,23,27-29} This difference may be attributable to higher titers of HCV in coinfecting women, because two studies have suggested that the risk of perinatal transmission is related to the maternal titer of HCV RNA.^{24,25}

Acquisition of HCV infection from human milk has not been documented,^{30,31} although HCV RNA has been detected in human milk. The overall rate of maternal-infant HCV transmission among breastfed infants has been the same as that among bottle-fed infants.^{23,26,28-30} HCV infection of the mother is not a contraindication to breastfeeding according to the most recent Public Health Service guidelines, although data are limited.³²

Household Contact With an Infected Individual

Epidemiologic studies have suggested that household contact with an infected person may be associated with nonsexual transmission of HCV.^{33,34} Seroprevalence studies have found an average anti-HCV rate of 4% (range, 0% to 11%) among household contacts with no other apparent risk factors for infection.¹ If person-to-person transmission of HCV does occur in the household, it is most likely the result of direct contact with blood, and the risk appears to be extremely low.

DIAGNOSTIC TESTS

Two major types of tests are available for the laboratory diagnosis of HCV infection: 1) detection of antibody to various HCV antigens, and 2) molecular methods to detect and quantitate the nucleic acid of the virus. Antigen-detection tests are not available. HCV antibody testing is analogous to antibody testing for human HIV infection. First, a screening enzyme immunoassay is performed, with repeat positive results confirmed by a recombinant immunoblot assay or other supplemental antibody test.³⁵ Both assays detect IgG anti-HCV antibody; no IgM tests are available. The second-generation enzyme immunoassay and recombinant immunoblot assay tests are 95% sensitive and 97% specific.³⁵ Negative antibody test results early in the course of acute disease do not rule out infection with HCV. In patients with acute HCV infection, a prolonged interval may occur between onset of clinical illness and seroconversion, although 80% of patients will be anti-HCV-positive within 5 to 6 weeks after onset of clinical hepatitis.^{35,36}

Although highly sensitive PCR assays for detection of HCV RNA and other nucleic acid-based amplification assays for quantitation of HCV RNA are available from several commercial laboratories on a research-use basis, they are not standardized and the cost is high. Both false-positive and false-negative results can occur from improper handling or storage or from contamination of the test samples. In addition, the detection of HCV RNA may be intermittent, and the meaning of a single negative PCR test result is not conclusive. The value of the nucleic acid-based assays outside of the research setting is not yet established, but such assays have been used to monitor patients receiving

antiviral therapy, diagnose early infection, and identify infection in infants early in life, when passively acquired maternal antibody interferes with the ability to detect antibody produced by the infant.

TREATMENT

Interferon-alpha is the only product licensed for the treatment of chronic HCV infection in adults, and only 10% to 15% of patients treated have a sustained response.³⁴ Most pediatric patients with chronic HCV infection are asymptomatic.^{36,37} No controlled trials of interferon therapy in children with chronic hepatitis C have been conducted, and interferon is not approved by the Food and Drug Administration for use in individuals <18 years of age. Although uncontrolled pilot trials of interferon in children with chronic HCV infection closely mirror the experience with adults, several factors need to be considered, including the lack of documented long-term beneficial effects on symptoms or disease progression and the side effects and cost of therapy.^{36,37} Children with symptomatic disabling disease or histologically advanced pathologic conditions (bridging necrosis or active cirrhosis) should be referred to a specialist experienced with HCV infection in children.

MANAGEMENT OF EXPOSED PERSONS

Immune globulin is manufactured from plasma that is anti-HCV-negative; it does not prevent infection or disease³⁸ and is not recommended by the Advisory Committee on Immunization Practices for prophylaxis.³⁹

No vaccine exists for the prevention of HCV infection. Successful immunization against HCV infection will be difficult for several reasons. There are at least six different genotypes of the virus, presumably with different immunogenic epitopes as well as sequential mutations that occur within infected individuals. HCV has not yet been grown to high titers in vitro, so antigens must be produced using recombinant DNA technology. Natural infection does not protect against reinfection with the same or different genotypes of the virus, either in patients or in experimentally infected chimpanzees. Much more investigation will be required before a successful vaccine can be expected.

RECOMMENDATIONS

Screening

Individuals Who Have Risk Factors for HCV Infection

Persons with risk factors for HCV infection, such as injection drug use, transfusion of ≥ 1 U of blood or blood products before 1992, or hemodialysis, should be screened for anti-HCV.³² Also, persons who received clotting factor concentrates before 1987, when effective inactivation procedures were introduced, also should be screened.

Pregnant Women

Routine screening of all pregnant women for HCV infection is *not* recommended. Physicians and other health care providers should become knowledgeable about the known and potential risks for HCV infection and obtain high-risk exposure histories on all of their patients.³²

Infants Born to HCV-Infected Women

Screening of all children born to previously HCV-infected women is recommended because ~5% will acquire the infection. The length of time passively acquired maternal antibody persists is unknown, but it is unlikely to be >12 months in most children. Therefore, testing for anti-HCV should be performed

after 12 months of age. PCR testing is generally not available or recommended for routine use in these children.

Recipients of Intravenous Immunoglobulin

The US Public Health Service has recommended that persons who received Gammagard or Polygam (Baxter) between April 1, 1993, and February 23, 1994, be offered screening (ALT and anti-HCV) for HCV infection.¹⁶ Because of concerns that anti-HCV may not be detectable in persons who are immunocompromised, PCR testing for HCV RNA is recommended for persons with elevated ALT levels who are anti-HCV-negative on repeated testing. Screening of children who have received other intravenous immune globulin products is not indicated.

Children With Clinical Hepatitis

Children who have had clinical hepatitis found not to be hepatitis A or B should be tested for anti-HCV.

Adoptees

Neither national or international adoptees are at increased risk of HCV infection; thus, routine screening is not indicated. However, a decision to test should be individualized if the child is born to a woman at known high risk for HCV infection (eg, child of an injection drug user).

Counseling and Management for HCV-Infected Children and Adolescents

Counseling

Patients with HCV infection should be counseled to avoid hepatotoxic medications and alcohol. All anti-HCV-positive patients should be considered infectious and informed of the possibility of transmission to others.³² Patients who are anti-HCV-positive should refrain from donating blood, organs, tissues, or semen. Among household contacts, toothbrushes and razors should not be shared. Exclusion of children infected with HCV from the child care center is *not* justified. Infected persons should be informed of the possible risk of sexual transmission to sexual partners. Persons with multiple partners should be advised to reduce the number of partners and take precautions to prevent the exchange of body fluids.

Hepatitis Vaccinations

All children should receive the hepatitis B vaccine and those with chronic HCV infection also should receive hepatitis A vaccination to prevent additional liver damage.

Clinical Management

Infected individuals should be followed at regular intervals by a physician familiar with tests required to monitor for evidence of chronic hepatitis. Children infected with HCV are at risk for development of serious liver diseases with advancing age, including hepatocellular carcinoma. All children who are known to be chronically infected with HCV should receive periodic screening, but definitive recommendations on what types of screening tests (liver transaminase, serum alpha-fetoprotein concentration, and abdominal ultrasonography) and the frequency of screening are precluded by a lack of data on screening (including the cost effectiveness of screening) in children. Children with persistently elevated serum transaminase levels (concentrations exceeding twice the upper limits of normal) as well as those with elevated alpha-fetoprotein concentrations or an abnormal abdominal ultrasonography finding should be referred to a gastroenterologist for additional evaluation and management.

Breastfeeding by HCV-Infected Mothers

According to current Public Health Service guidelines, maternal HCV infection is not a contraindication to breastfeeding, although the data are limited. Thus, HCV-infected women who wish to breastfeed their infants should be counseled that although there appears to be no increased risk of transmission, HCV RNA has been detected in breast milk, and the data are limited. A decision to breastfeed should be individualized after informed discussion between the mother and health care provider, as indicated in the most recent guidelines.³²

FUTURE DIRECTIONS

HCV infection is the most common reason for liver transplantation in the United States. As a consequence, intense efforts have been devoted to developing antiviral therapeutics. Recent advances in knowledge of unique viral enzymes (eg, proteases) will likely result in the testing of several drugs within the next few years.

Committee on Infectious Diseases, 1996 to 1997

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