PRELIMINARY DRAFT STATEMENT
June 12, 2002

NATIONAL INSTITUTES OF HEALTH
CONSENSUS DEVELOPMENT CONFERENCE STATEMENT
Management of Hepatitis C: 2002
June 10–12, 2002

NIH Consensus Statements are prepared by a nonadvocate, non-Federal panel of experts, based on (1) presentations by investigators working in areas relevant to the consensus questions during a 2-day public session; (2) questions and statements from conference attendees during open discussion periods that are part of the public session; and (3) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

Introduction

The hepatitis C virus (HCV) is the leading cause of known liver disease in the United States. It is the most common cause of cirrhosis and a common cause of hepatocellular carcinoma (HCC); it is also the most common reason for liver transplantation. At least 4 million people in this country are believed to be infected with this virus. Following the identification of hepatitis A and hepatitis B, this disorder was categorized in 1974 as "non-A, non-B hepatitis." In 1989, the hepatitis C virus was discovered and was found to account for the majority of those patients with non-A, non-B hepatitis. In March 1997, a Consensus Development Conference was held at the National Institutes of Health (NIH) regarding management and treatment. This led to an important, widely distributed NIH Consensus Statement that, for several years, was broadly accepted as the standard of care.

Now 5 years later, knowledge of hepatitis C has increased dramatically, leading to the need to reexamine the approaches to management and treatment. Accordingly, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has convened a Consensus Development Conference with the aim of reviewing the most recent developments regarding management, treatment options, and the widening spectrum of potential candidates for treatment and of updating the 1997 Consensus Statement.

This NIH Consensus Development Conference on Management of Hepatitis C: 2002 convened June 10–12, 2002. The primary sponsors of this meeting were the NIDDK and the Office of Medical Applications of Research (OMAR) of the NIH. The cosponsors were the National Institute of Child Health and Human Development (NICHD); the National Cancer Institute (NCI); the National Center for Complementary and Alternative Medicine (NCCAM); the National Institute on Alcohol Abuse and Alcoholism (NIAAA); the National Institute on Drug Abuse (NIDA); the National Institute of Allergy and Infectious Diseases (NIAID); the National Heart, Lung, and Blood Institute (NHLBI); the Centers for Medicare & Medicaid Services (CMS); the Centers for Disease Control and Prevention (CDC); the U.S. Food and Drug Administration (FDA); and the U.S. Department of Veterans Affairs (VA).

The Agency for Healthcare Research and Quality (AHRQ) provided support to the NIH Consensus Development Conference on Management of Hepatitis C: 2002 through its Evidence-based Practice Center program. Under contract to AHRQ, the Johns Hopkins University Evidence-based Practice Center developed the systematic review and analysis that served as a reference for discussion at the Conference.

This two-and-a-half-day conference examined the current state of knowledge regarding the management of hepatitis C and identified directions for future research.

During the first day-and-a-half of the conference, experts presented the latest hepatitis C research findings to an independent non-Federal panel. After weighing all of the scientific evidence, the panel drafted a statement, addressing the following key questions:

- What is the natural history of hepatitis C?
- What is the most appropriate approach to diagnose and monitor patients?
- What is the most effective therapy for hepatitis C?
- Which patients with hepatitis C should be treated?
- What recommendations can be made to patients to prevent transmission of hepatitis C?
- What are the most important areas for future research?

On the final day of the conference, the panel chairperson read the draft statement to the conference audience and invited comments and questions. A press conference followed to allow the panel and chairperson to respond to questions from the media.

The consensus panel's draft statement was posted to the Consensus Program Web site—http://consensus.nih.gov—on Wednesday, June 12, 2002.

1. What is the natural history of hepatitis C?

The Virus

HCV is an RNA virus of the Flaviviridae family. There are 6 HCV genotypes and more than 50 subtypes. These genotypes differ by as much as 30 to 50 percent in their nucleotide sequences. The virus also has a high propensity to mutate. The lack of a vigorous T-lymphocyte response appears to promote a high rate of chronic 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. Genotype 1 accounts for 70 to 75 percent of all HCV infections in the United States and is associated with a poorer response to treatment.

HCV replicates preferentially in hepatocytes but is not directly cytopathic, leading to persistent infection. During acute infection, the level of viral genomes/mL of plasma or serum has been reported to range from 10^5 to 10^7. Chronic HCV RNA levels are quite variable from person to person and generally range from 50,000 to 5 million. However, within the same individual, RNA levels are relatively stable.

Epidemiology

According to the National Health and Nutrition Examination Survey (NHANES) of 1988–1994, 3.9 million Americans were infected with hepatitis C, and of this group, 2.7 million are estimated to have chronic infection. However, NHANES is a population-based household survey that largely excludes groups with a substantially increased prevalence of infection, such as persons who are incarcerated, homeless, or institutionalized due to mental illness.

Although difficult to assess accurately, the incidence of HCV infection declined sharply in the late 1980s. Transmission from blood products was virtually eliminated by the introduction of a more sensitive test for anti-HCV antibodies in mid-1992. Currently, approximately 35,000 acute HCV infections are estimated to occur each year. Because of the high rate of persistent infection, a fourfold increase in the number of persons with chronic HCV infection is projected to occur from 1990 to 2015. The prevalence of HCV is presently believed to be at least 1.8 percent, making HCV the most common blood-borne infection in the United States. Persons aged 40 to 59 years have the highest prevalence of HCV infection, and in this age group, the prevalence is highest in African-Americans (6.1 percent).

HCV transmission occurs primarily through exposure to infected blood. This exposure exists in the context of injection drug use (IDU), blood transfusion, solid organ transplantation from infected donors, unsafe medical practices, occupational exposure to infected blood, birth to an infected mother, multiple heterosexual partners, and high-risk sexual practices. High HCV seroprevalence rates (from 15 to 50 percent) have been observed in specific subpopulations, such as the homeless, incarcerated persons, and hemophiliacs, with the highest rates (70 percent to more than 90 percent) reported in IDUs.

Acute Infection

After initial exposure, HCV RNA can be detected in blood in 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 percent of patients at the onset of symptoms, increasing to approximately 90 percent of these patients after 3 months. Within an average of 2 to 8 weeks, liver cell injury is manifested by elevation of serum alanine aminotransferase (ALT). Acute infection 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.

Chronic Infection

Chronic HCV infection is diagnosed by the detection of HCV RNA at least intermittently in the blood by either qualitative or quantitative tests for a period of at least 6 months. In general, prospective studies have shown that the majority of HCV-infected persons develop chronic infection. Factors associated with spontaneous clearance of HCV infection appear to include younger age, female gender, and certain major histocompatability complex genes. African-American men appear to be least likely to spontaneously clear the virus.

The most important sequelae of chronic HCV infection are progressive liver fibrosis leading to cirrhosis, end stage liver disease (ESLD), and HCC. Estimates of the proportion of chronically infected persons who develop cirrhosis 20 years after initial infection have been substantially higher from retrospective studies (17 to 55 percent) than from prospective studies (7–16 percent). The actual risk of progressive disease at 20 years is now considered to be closer to the estimates from prospective studies. There is little evidence that the risk of progression of liver disease is affected significantly by virologic factors, including viral load, viral genotype, and quasispecies diversity. However, many host factors are observed to increase this risk, including older age at time of infection; male gender; and an immunosuppressed state, such as HIV infection. Hepatitis B appears to increase the risk of progressive liver disease. Alcohol use plays an important role in increasing the risk of progressive liver disease, with strong evidence for the detrimental effects of 60 g/day in men (equivalent to six beers, four glasses of wine, or three mixed drinks) and 40 g/day in women, but there is suggestive evidence that lower amounts

can also increase the risk of liver damage associated with HCV. Other factors, including iron overload, nonalcoholic fatty liver disease, schistosomal coinfection, potentially hepatotoxic medications, and environmental contaminants, may also have important effects.

In the United States, deaths associated with chronic HCV are currently more likely to be due to ESLD than to HCC. Data from death certificates in 1999 found that approximately 4,000 deaths were attributed to HCV infection, but this is likely to be an underestimate. The only treatment option for persons who have developed ESLD (decompensated cirrhosis) is transplantation. Currently, HCV is the primary reason for liver transplantation in the United States. Little is known about the clinical course and risks of HCV-related complications in persons who have been infected longer than two decades.

HCV accounts for an estimated one-third of HCC cases in the United States. HCC rarely occurs in the absence of cirrhosis or advanced fibrosis. The incidence of HCV-related HCC is continuing to rise in United States and worldwide, in part because of the increasing numbers of persons who have been chronically infected for decades, the presence of comorbid factors, and the longer survival of persons with advanced liver disease due to improved management of complications. Risk factors for HCC in persons with chronic HCV infection are largely the same as those for the development of ESLD.

Extrahepatic Manifestations of HCV

Patients with chronic HCV can present with extrahepatic manifestations or syndromes considered to be of immunologic origin, such as rheumatoid symptoms, keratoconjunctivitis sicca, lichen planus, glomerulonephritis, and essential mixed cryoglobulinemia. Cryoglobulins have been detected in the serum of up to one-half of patients with chronic HCV, but the clinical

features of essential mixed cryoglobulinemia are less frequent. Chronic hepatitis C is also related to porphyria cutanea tarda.

2. What is the most appropriate approach to diagnose and monitor patients?

Various tests are available for the diagnosis and monitoring of hepatitis C infection. Tests that detect antibody against the virus include the EIAs, which contain HCV antigens from the core and nonstructural genes, and the recombinant immunoblot assays (RIBAs). The same HCV antigens are used in both EIAs and the RIBAs. Targeted amplification techniques using either polymerase chain reaction (PCR) or transcription-mediated amplification (TMA) have been developed to detect HCV RNA. Liver biopsy can provide direct histologic assessment of liver injury due to HCV but cannot be used to diagnose HCV infection.

HCV Serologic Assays

EIA tests are reproducible, inexpensive, and FDA-approved for use in the diagnosis of HCV. They are suitable for screening at-risk populations and are recommended as the initial test for patients with clinical liver disease. The very high sensitivity and specificity of the third-generation EIAs (sensitivity greater than 99 percent, specificity 99 percent) obviate the need for a confirmatory RIBA in the diagnosis of individual patients, particularly those with risk factors for HCV. A negative EIA test is sufficient to exclude a diagnosis of chronic HCV infection in immune competent patients. Rarely, patients on hemodialysis and patients with immune deficiencies may have falsely negative EIAs. Conversely, falsely positive EIAs may occur in patients with autoimmune disorders. In these patients, assays for HCV RNA are necessary for diagnosis. RIBA remains a useful supplemental assay in the setting of large-scale HCV screening of blood products.

Qualitative HCV Assays

Persistent HCV infection in a patient with a positive EIA test should be confirmed by a qualitative HCV RNA assay. The automated, FDA-approved, qualitative HCV PCR assay has a lower limit of detection of 50 IU/mL. More recently, a transcription-mediated amplification assay has been developed with a lower limit of detection comparable to the qualitative PCR assay. This latter assay has yet to be approved for use by the FDA. The specificity of these assays exceeds 98 percent. A single positive qualitative assay for HCV RNA confirms active HCV replication, but a single negative assay does not prove that the patient is not viremic. A followup qualitative HCV RNA should be performed to confirm the absence of active HCV replication. Once HCV infection is confirmed, repeat testing for qualitative HCV RNA by qualitative PCR is not helpful in the management of untreated patients. Almost all patients remain viremic, and a negative result may merely reflect a transient decline in viral titer below the level of detection of the assay.

Quantitative HCV Assays

Testing for HCV RNA level (or viral load) by a quantitative assay, either quantitative PCR (qPCR) or branched DNA signal amplification assay (bDNA), can provide accurate information on HCV viral titer. An HCV RNA standard has been introduced to permit normalization of reported viral titers in international units (IU). The reported IU does not represent the actual number of viral particles in a preparation. Significant variability exists between available assays. The dynamic range of each assay needs to be observed, and appropriate dilutions of sample material should be performed to obtain accurate quantitative results. The clinical utility of serial HCV viral titers in a patient is predicated on continued use of

the same specific quantitative assay used in the initial determination of the viral titer. While there is little correlation between disease severity or disease progression with the absolute titer of HCV RNA, quantitative determination of the HCV titer provides important information in assessing response to treatment.

Testing for serum ALT levels is the most inexpensive and noninvasive means of assessing disease activity. However, a single determination of ALT levels gives limited information about the severity of the underlying liver disease. In most studies, a weak association exists between the degree of ALT elevation and severity of the histopathological findings on liver biopsy. Serial determinations of ALT levels over time may provide a better means of assessing liver injury, but the accuracy of this approach has not been shown. 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 resolution of elevated ALT levels with antiviral therapy appears to be an important indicator of disease response. Serial determinations of ALT levels can be recommended as the general means of monitoring patients but is not adequate to assess progression to cirrhosis.

Various noninvasive tests have been examined for monitoring patients with chronic hepatitis C infection. These include routinely available laboratory tests, such as liver-associated chemistries, platelet count, and prothrombin time, as well as specific serum markers of fibrosis and inflammation that are not currently widely available or well validated. No single test or panel of serologic markers can provide an accurate assessment of intermediate stages of hepatic fibrosis. Similarly, quantitative tests of liver function and radiologic imaging of the liver are

sensitive for diagnosing advanced cirrhosis but are not useful in assessing hepatic fibrosis and early cirrhosis.

Liver Biopsy

Liver biopsy yields information on fibrosis and histology assessment that is not obtainable by any other means. Various noninvasive methods based on biochemical or serologic tests have been evaluated in several studies. Liver enzymes have shown little value in predicting fibrosis. Extracellular matrix tests do predict severe stages of fibrosis but cannot consistently classify intermediate stages of 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 toward cirrhosis. It is unusual for unexpected etiologies of liver disease to be discovered on liver biopsies from patients undergoing evaluation of chronic hepatitis C. The information obtained on liver biopsy does allow affected individuals to make more informed choices with regard to initiation or postponement of antiviral treatment. Adult or pediatric patients with persistently normal or slightly elevated ALT and minimal or no fibrosis on liver biopsy may be reassured of a favorable prognosis and decide to defer antiviral therapy. Since a favorable response to current antiviral therapy in patients infected with genotype 2 or 3 occurs in 80 percent, the necessity of routine pretreatment liver biopsy in these patients requires further study. Baseline assessment of liver histology offers the standard by which subsequent comparisons may be made. There is little information, however, on the appropriate interval for subsequent evaluations.

Hepatocellular Cancer 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 percent per year. Few studies examine specific screening strategies for HCC in patients with advanced HCV. Alpha fetoprotein (AFP) and ultrasound every 6 months were used in a single study of patients with cirrhosis secondary to HCV. Identification of HCC was not significantly increased in the screened population. Additional studies identifying new markers and testing specific screening protocols are warranted.

3. What is the most effective therapy for hepatitis C?

Since the 1997 NIH Consensus Development Conference on the Management of Hepatitis C, several important therapeutic advances have occurred, particularly with the introduction of PEG-interferon with ribavirin therapy. Combination therapy results in better treatment responses than monotherapy. The highest response rates have been achieved with PEG-interferon in combination with ribavirin. Genotype determinations now influence treatment decisions. Methods of genotyping include PCR-based techniques and, more recently, less expensive serotyping (antibody) assays. Sustained viral response (SVR), defined by the absence of detectable qualitative HCV RNA in the serum by RT-PCR 24 weeks after the end of treatment, is currently the best indicator of effective therapy.

Treatment of Naïve Patients

Three large pivotal trials have examined the efficacy of PEG-interferon plus ribavirin in the treatment of chronic HCV infection. These trials excluded patients with decompensated

cirrhosis and other comorbid conditions. Overall, PEG-interferon plus ribavirin is more effective than standard interferon-ribavirin combination or PEG-interferon alone. SVRs were similar with both forms of PEG-interferon (alpha 2a and alpha 2b) when used in combination with ribavirin. Factors associated with successful therapy include genotypes other than 1, lower baseline viral load, and less fibrosis or inflammation on liver biopsy. In all three trials, an SVR of 42 to 46 percent was achieved for genotype 1 using a higher dose of PEG-interferon and ribavirin for 48 weeks. An SVR of 76 to 82 percent was achieved for patients with genotypes 2 and 3. It appears that 24 weeks of treatment and a lower dose of ribavirin is adequate for genotypes 2 and 3. Early viral response (EVR), defined as a minimum 2 log decrease in viral load during the first 12 to 24 weeks of treatment, has been identified as predictive of SVR. Those who fail to achieve an EVR have only a small chance of achieving a SVR even if therapy is continued for a full year.

Although SVR has not yet been correlated with improved survival because of the necessity for long-term followup, the absence of a detectable serum HCV RNA has been correlated with resolution of liver injury, reduction in hepatic fibrosis, and a very low likelihood of recurrent HCV infection. Additionally, in two large recent studies from Japan, interferon treatment was associated with a reduction in the development of hepatocellular carcinoma, a finding that was more pronounced among patients with SVR.

Re-treatment of Patients

Patients who may benefit from re-treatment include those whose HCV infection failed to achieve SVR. Decisions regarding re-treatment should be based upon: (1) previous type of response, (2) the previous therapy and the difference in potency of the new therapy, (3) the

severity of the underlying liver disease, (4) viral genotype and other predictive factors for response, and (5) tolerance of previous therapy and adherence.

Relapsers achieve an initial end of treatment response (ETR) for their HCV disease, but it is not sustained over time (i.e., no SVR). Nonresponders never achieve an EVR, ETR, or SVR. Among the nonresponders, there is a subset of persons who have a substantial reduction of HCV RNA (1 to 2 log units or more) during therapy, and who can be categorized as partial responders. Even in the absence of SVR, treatment may be associated with improved histology.

Preliminary results suggest that overall only 15 to 20 percent of nonresponders treated with standard interferon/ribavirin combinations achieved an SVR on re-treatment using PEG-interferon with ribavirin. Patients with genotypes 2 or 3 have better response rates to re-treatment than genotype 1.

The ability to achieve SVR following re-treatment with PEG-interferon/ribavirin in patients who relapsed following interferon monotherapy or standard interferon/ribavirin therapy is currently being evaluated. However, in cases where the same regimen has been used for re-treatment, virtually all patients relapse again after treatment is stopped. Extending the duration of re-treatment without changing the dose or regimen may reduce the relapse rate, but this has not yet been proven prospectively.

Patients whose HCV infection does not respond to the current optimal therapy with PEG-interferon and ribavirin present a significant problem, particularly in the presence of advanced fibrosis or cirrhosis. The possible role of maintenance therapy with PEG-interferon alone in preventing further progression of cirrhosis, clinical decompensation, or development of hepatocellular carcinoma is currently the focus of a large-scale, multicenter United States trial,

HALT-C. Until the results of HALT-C or similar studies are available, the role of long-term, continuous therapy with PEG-interferon (or ribavirin or both) for nonresponders must be considered experimental.

Knowledge of the severity of the underlying liver disease is important in recommending re-treatment. Patients with advanced fibrosis or cirrhosis are at increased risk for developing hepatic decompensation and should be considered for re-treatment, especially if they were originally treated with interferon monotherapy. For the re-treatment of patients with intermediate degrees of fibrosis and disease activity, clinicians should consider the factors enumerated above.

Side Effects of Treatment

In the registration trials of PEG-interferon and ribavirin, significant side effects were noted that resulted in discontinuation of treatment in approximately 20 percent of subjects. Major side effects of combination therapy include influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms. The education of patients and caregivers about side effects and their prospective management is an integral part of treatment. Frequent monitoring of HCV therapy is necessary. Antidepressants, such as selective serotonin reuptake inhibitors, may be useful in the management of less severe depression associated with antiviral therapy. Treatment of cytopenias with hematopoietic growth factors may be useful and may prevent dose reduction or drug discontinuation. Severe hemolysis may occur in patients with renal insufficiency. Lactic acidosis may be a rare complication of combination therapy in patients undergoing therapy for HIV and HCV.

4. 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 who are at increased risk for progression to cirrhosis. These patients are characterized by measurable HCV RNA, a liver biopsy with portal or bridging fibrosis, and at least moderate inflammation and necrosis; the majority have persistently elevated ALT values. In some patient populations, the risks and benefits of therapy are less clear and should be determined on an individual basis or in the context of clinical trials.

Many patients with chronic HCV have been ineligible for trials because of injection drug use (IDU), alcohol abuse, age, and a number of comorbid medical and neuropsychiatric conditions. Efforts should be made to increase availability of the best current treatment to these patients. Because a large number of HCV-infected persons in the United States are incarcerated, strategies should be developed to better prevent, diagnose, and treat these individuals.

Normal ALT

Approximately 30 percent of patients with chronic HCV have normal ALT levels, and another 40 percent have ALT levels less than two times the upper limit of normal. Although most of these patients have disease that is histologically mild, some patients may progress to advanced fibrosis and cirrhosis. Experts differ on whether to biopsy and treat these patients.

Numerous factors must be considered in recommending treatment, including favorable genotype, presence of hepatic fibrosis, patient motivation, symptoms, severity of comorbid illness, and the patient's age. SVR rates do not differ in patients with normal or mildly elevated

ALT when treated with interferon monotherapy. Studies of PEG-interferon with ribavirin have not been completed in patients with normal ALT levels.

Mild Liver Disease

In patients with persistent ALT elevations, but with no fibrosis and minimal necroinflammatory changes, progression to cirrhosis is likely to be slow; these patients should be monitored periodically.

Advanced Liver Disease

Data on safety and efficacy of interferon (standard or pegylated) with or without ribavirin in patients with advanced fibrosis or compensated cirrhosis have been largely derived from subgroup analyses of larger trials. SVR is lower in patients with advanced liver disease than in patients without cirrhosis. An important goal of treatment in advanced liver disease is to delay histological disease progression, which is being evaluated in the NIH-sponsored HALT-C trial.

Patients with decompensated cirrhosis should be referred to clinical trials until safety and efficacy data of treatment are established, or they should be considered for liver transplantation. In patients with ESLD, the main treatment option is liver transplantation. There are ongoing studies of antiviral therapy of patients awaiting liver transplantation, but this approach may be limited by potentially life-threatening side effects of antivirals.

Recurrence After Transplantation

Hepatitis C frequently recurs following liver transplantation, and disease progression is accelerated compared to immunocompetent patients with HCV disease. Once cirrhosis develops

in the allograft, the risk of complications is higher than in immunocompetent cirrhotic patients. Recurrence of hepatitis C after transplant correlates with HCV RNA level at the time of transplantation, the age of the organ donor, and the degree of immunosuppression in the post-transplantation period.

Children

Few data are available on the treatment of children and adolescents, and further research is needed. Studies of interferon monotherapy in children have been largely uncontrolled, with small numbers of highly selected patients. SVR rates are similar to or even better than those in adults, ranging from 33 to 45 percent (26 percent for genotype 1 and 70 percent for other genotypes). Several studies of combination therapy in children are under way. Promising new therapies should also be studied in children.

Acute Hepatitis C

Acute hepatitis C is uncommonly recognized and diagnosed. Studies of interferon treatment for acute hepatitis C have been very heterogeneous and limited by small sample size, lack of randomization, variability in the timing of therapy after onset of infection, dose and schedule, and endpoints and followup. Although high SVRs have been seen in small uncontrolled trials with interferon monotherapy, recommendations on whether treatment is necessary, the timing of therapy, and which regimen to use remain open.

Injection Drug Users

Recent experience has demonstrated the feasibility and effectiveness of treating HCV in people who use illicit injection drugs (known as injection drug users or IDUs). This is important

because IDUs comprise the largest group of hepatitis C patients in the United States, and successful treatment may reduce transmission. Management of HCV-infected IDUs is enhanced by linking IDUs to drug-treatment programs. Efforts should be made to promote collaboration between experts in HCV and substance-abuse providers. HCV therapy has been successful even when the patients have not been abstinent from continued drug use or are on daily methadone. Few data are available on HCV treatment in active IDUs who are not in drug treatment programs.

HIV Coinfection

All HIV infected persons should be screened for HCV. Patients with chronic hepatitis C and concurrent HIV infection may have an accelerated course of HCV disease. Therefore, although there are no HCV therapies specifically approved for patients coinfected with HIV, these patients should be considered for treatment. Thus far, studies have enrolled only patients with stable HIV infection and well-compensated liver disease. In coinfected persons, an SVR can be achieved with HCV treatment. Preliminary data suggest better responses to PEG-interferon with ribavirin than to standard interferon with ribavirin. Although treatment of HCV has not jeopardized control of the HIV infection, additional data are needed.

Alcohol and HCV

Alcohol is an important cofactor in the progression of HCV liver disease to cirrhosis and HCC. A history of alcohol abuse is not an absolute contraindication to therapy; however, continued alcohol use during therapy adversely affects the response to treatment. Treatment of HCV should be performed in conjunction with efforts to treat alcohol abuse or dependence.

Heavy alcohol consumption of >80 g/day seriously compromises HCV treatment. Safe levels of alcohol consumption are still unclear.

5. What recommendations can be made to patients to prevent transmission of hepatitis C?

The large global 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 IDU accounts for over two-thirds of all new infections. Needle and syringe exchange programs and comprehensive risk-modifying educational programs that are highly effective in preventing HIV transmission are likely to be useful for decreasing HCV transmission. HCV is rarely transmitted by transfusion of blood products or transplantation of organs or tissues in the United States and other countries where screening tests exclude infectious donors.

The majority of other cases can be attributed to sexual transmission and occupational exposures to blood, although the actual risk of transmission through these routes is low. Data regarding transmissibility by sexual contact have been confounded in part by other exposures, including IDU, that can increase the risk of transmission of HCV. HCV genotypes appear to have no impact on the risk of transmission.

In the United States, the estimated seroprevalence of HCV is 2 to 3 percent among partners of HCV-infected persons who are in long-term monogamous relationships and is 4 to 6 percent among persons with multiple sex partners, sex workers, and men who have sex with men (those at risk for sexually transmitted diseases). For heterosexual, discordant monogamous couples, the risk of transmission is estimated to be 0 to 0.6 percent annually, with the risk to females being threefold greater than to male partners. Because of the low risk of HCV

transmission, couples need not use barrier protection (condoms); however, couples should be advised that the use of condoms may decrease the risk of HCV transmission. Based on studies in persons at risk for sexually transmitted diseases, HCV transmission is approximately 1 percent annually. 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. The sharing of common household items, such as razors and toothbrushes, is another potential source of transmission of HCV. 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.

Health care workers may have a slightly higher prevalence of HCV infection than the general population, although they may have acquired infection from nonoccupational sources. Transmission from health care workers to patients has also been documented, but it is rare and is confounded by other risk factors.

The risk of HCV infection from needle sticks is estimated to be 2 percent. At this time, antiviral prophylaxis is not recommended following needle stick exposure. It is recommended that the source and exposed individual should be tested for antibody to HCV. If the source individual is HCV EIA positive, an HCV RNA assay should be done. The exposed individual should be tested for HCV antibody and ALT at exposure and repeated at 4–6 months. If seroconversion occurs, recommendations for persons following acute HCV infection should be followed.

Percutaneous exposures, such as body piercing and tattooing, are other potential sources of transmission if contaminated equipment or supplies are used. However, the rates of transmission are less than 1 percent, and these data are confounded by other risk factors.

Perinatal transmission has been documented. Higher maternal HCV RNA load appears to be associated with a greater risk for HCV transmission to the infant. The risk of transmission is approximately 2 percent for infants when the mother is HCV seropositive; this risk increases up to 7 percent when a pregnant woman has two positive assays for HCV RNA. HCV transmission may be increased to approximately 10 percent with maternal injection drug use and up to 20 percent in women coinfected with HCV and HIV. There are no prospective studies evaluating the use of elective Cesarean section for the prevention of mother-to-infant transmission of HCV. There are currently no data to determine if antiviral therapy reduces perinatal transmission. Ribavirin and interferons are contraindicated during pregnancy.

Breast-feeding does not appear to transmit HCV. Children and personnel should not be excluded from daycare centers because of hepatitis C infection. Standard universal precautions should be used in any situation where blood or blood products are used.

6. What are the most important areas for future research?

- The development of reliable, reproducible, and efficient culture systems for propagating the HCV virus is considered to be of the highest priority. This goal is deemed essential not only for vaccine development but also for progress in fundamental aspects of HCV biology, hepatic tropism and viral replication. Furthermore, this development will assist in new drug discovery, as well as enhance understanding of the mechanisms of drug resistance.

- The role of genetic factors in the pathogenesis of HCV, including immune responses to infection, reasons for spontaneous resolution and variations in natural history, and responses to therapy, need further examination.

- Priority should be given to developing less toxic therapies and molecular-based agents that specifically inhibit viral replication and/or translation of viral RNA.

- Hepatic fibrosis is the principal complication of chronic HCV infection leading to the development of cirrhosis and ESLD. Directed investigation examining the development and progression of fibrosis is therefore essential for effective management of these patients. Studies also are needed to examine fundamental mechanisms of fibrosis in response to HCV. Studies are needed to define rates of progression of fibrosis in patients with prolonged duration of HCV infection. Similarly, the natural history of fibrosis in special populations including children, HIV-coinfected patients, the elderly, African-Americans, and HCV-infected patients with normal ALT levels needs to be determined. Evaluation of progressive fibrosis will best be accomplished with noninvasive tests capable of discriminating intermediate stages of fibrosis. Research into the development of noninvasive dynamic measures of hepatic fibrosis is strongly encouraged.

- Given the growing epidemic of chronic HCV, the large number of untreated patients, and a compelling number of important areas for future research, we recommend that NIH establish a Hepatitis Clinical Research Network. The goal of this network should be the conduct of research related to the natural history, prevention, and treatment of hepatitis C.

- Randomized controlled trials (RCTs) need to be carried out in special populations of patients not represented in current trials to determine the applicability of currently accepted treatment to these subgroups and to determine optimal doses and duration of therapy. These include children, patients with acute hepatitis, hemophiliacs, IDUs in drug treatment programs, active drinkers who demonstrate medication compliance, patients with depression stabilized with selective serotonin reuptake inhibitors and other antidepressants, as well as institutionalized patients and those coinfected with HIV. Therapies need to be developed for difficult treatment groups, including patients whose HCV infection does not respond to or relapse after current therapy, patients with decompensated cirrhosis, transplant patients, and patients with renal disease.

- Little information exists to describe the natural history of HCV viremia of prolonged duration of 20 years or more. Studies are needed to examine the pattern of HCV disease progression in persons infected for at least two decades.

- Natural history studies are needed in special groups, such as minorities, children, those older than 65, HCV-HIV coinfected patients, IDUs, and persons with normal ALT levels. More investigation is needed into the prevalence and clinical significance of extra hepatic manifestations of HCV.

- There is a need to assess the effectiveness of infection control strategies, including practices in hemodialysis units and safe injection practices. Better understanding of the risk of specific sexual practices and the effectiveness of risk reduction counseling are needed. The effect of elective Cesarean section on mother-to-infant transmission should be assessed.

- Trials are needed in combination therapy nonresponders or intolerant patients that compare combinations of antifibrotic and anti-inflammatory agents, as well as immunomodulatory drugs and drugs that are directed specifically at HCV replication. Studies are also needed to assess efficacy of alternative and nontraditional medicines.

- Because studies of acute hepatitis C are small in number, greater numbers of patients need to be included in clinical trials. Evidence-based proof is needed to determine whom to treat and when to start therapy. Delays in treatment for 2 to 3 months seem reasonable to identify cases that spontaneously resolve. Weekly monotherapy with PEG-interferon should be studied.

- Provision of educational programs for grades K–12 is necessary, as well as enhanced information related to risk factors for HCV for dissemination to the general public and the medical profession.

- There is a need to assess the effectiveness of supportive therapy to ameliorate the side effects of antiviral therapy.

- There is a need to more clearly establish the role of liver biopsy in the therapeutic management of patients with chronic hepatitis C. Studies are needed that more clearly describe biopsy techniques and side effects during trials. The relationship of pretreatment histology to treatment outcomes needs better definition. The value of liver biopsy in patients with normal liver function tests also needs evaluation as does the need and timing for followup biopsies in patients with stage 0–1 fibrosis when treatment is deferred. The relationship of pretreatment histologic characteristics, including steatosis, iron deposition, and the pattern of fibrosis to clinical outcomes

including progressive fibrosis and response to medical therapy, must be better defined. In addition, the requirement for direct assessment of hepatic histology by liver biopsy in the setting of nongenotype 1 infection should be critically evaluated. In the absence of sensitive noninvasive markers of fibrosis, liver biopsy remains essential for direct assessment of the degree of hepatic fibrosis. However, the precise interval for monitoring progression of fibrosis in HCV-infected patients, in particular those populations most at risk for rapid progression, needs to be evaluated.

- International standardization of viral RNA titers is needed along with a critical assessment of the utility of measuring viral kinetics as valid prognostic indicators of SVR and other clinically meaningful responses to therapy.

- Randomized controlled trials are needed to assess screening tests in patients at greatest risk of HCC for predicting this complication.

Studies are needed to assess whether there are safe levels of alcohol consumption in patients with HCV. Investigations into the role of fatty liver, obesity, diabetes, and hepatic iron stores on the natural history and responses to therapy are needed. Studies are needed in HIV coinfected patients to determine treatment outcomes and duration, maintenance therapy, treatment safety, and pathogenesis.

Conclusions

The incidence of HCV-related disease has diminished in the United States since testing for HCV has been widely applied in blood-banking practices. The virus is transmitted by blood and now occurs primarily through IDU, high-risk sexual practices, and occupational exposure.

The majority of infections become chronic, and, therefore, the prevalence of HCV infections has increased over the past decade with more than 4 million Americans now estimated to be infected. HCV now accounts for the majority of cases of liver disease resulting in cirrhosis and in HCC in the United States. The disease spectrum associated with HCV infection varies greatly and has become increasingly better characterized: Various studies have suggested that 3 percent to 20 percent of clinically infected patients will develop cirrhosis over a 20-year period. Older individuals, patients with continuous exposure to alcohol, and those coinfected with HIV or HBV demonstrate accelerated progression to more advanced liver disease. Conversely, many young European women with documented perinatal HCV exposure have no symptoms, little or no disease progression, and nearly normal liver findings over several decades.

The diagnosis is often suggested by abnormalities in ALT levels and is established by EIA followed by confirmatory determination of HCV RNA. Several sensitive and specific assays are now automated for the purposes of quantitating the viral load. Although there is little correlation between viral load and disease manifestations, this assay has proven useful in identifying persons at higher risk of transmission, in identifying those patients most likely to benefit from treatment, and particularly in demonstrating successful eradication, defined as SVRs. Liver biopsy is useful in defining baseline abnormalities of liver disease and in enabling patients and health providers to reach a decision regarding antiviral therapy. Noninvasive tests do not currently provide the information that is obtained through liver biopsy. A diagnostic test with prognostic importance is the genotype of the virus. Genotype 1, most commonly found in the United States, is less amenable to treatment than other genotypes. Clinical trials of antiviral therapies, therefore, require genotyping information for appropriate stratification of subjects.

Recent therapeutic trials in defined, selected populations have clearly shown that combinations of interferons and ribavirin are more effective than monotherapy. Moreover, trials using PEG-interferons have yielded improved SVR rates and fewer neuropsychiatric side effects. The results continue to show lower SVR rates in genotype 1 infections, in the presence of higher baseline HCV RNA levels, and with more advanced stages of fibrosis. Specifically, genotype 1 infections require therapy for 48 weeks, whereas shorter treatment is feasible in genotype 2 and 3 infections. Early virologic response (> 2 log decreases in HCV RNA) is associated with achieving clinical improvement. SVR is lower in patients with advanced liver disease than in patients without cirrhosis.

Ongoing trials are exploring the usefulness of combination therapy among various populations. Preliminary experience in IDUs, individuals coinfected with HIV, children, and other special groups suggest similar responses are achievable in these populations. In the presence of acute hepatitis C, recommendations for antiviral treatment must await further evaluation of the rate of spontaneous clearance of the virus and determination of the optimal time to initiate treatment.

Preventive measures beyond blood-banking practices include prompt identification of infected individuals, awareness of the potential for perinatal transmission, implementation of safe-needle practices, and implementation of education to modify risk behavior. Some of these measures have been successfully implemented in the control of HIV infections, and it stands to reason that they may be applicable to reducing HCV transmission.

Future advances in the diagnosis and management of hepatitis C require continued vigilance concerning the transmission of this infection, extending treatment to populations not formally evaluated in treatment trials, and the introduction of more effective therapies.

Recommendations

- Educate the American public on the transmission of HCV in order to better identify afflicted individuals and institute preventive measures.

- Develop reliable, reproducible, and efficient culture systems for propagating HCV and expand basic research in the pathogenic mechanisms underlying hepatic fibrosis.

- Promote the standardization and wide availability of diagnostic tests for HCV infection and its complications, leading to early diagnosis and the implementation of appropriate treatment practices.

- Expand the delineation of disease manifestations, noninvasive tests, and the role of the liver biopsy, so that the application of current treatment practices may be refined.

- Establish a Hepatitis Clinical Research Network for the purpose of conducting research related to the natural history, prevention, and treatment of hepatitis C.

- Organize RCTs to extend treatment to special populations not represented in current clinical trials and to determine the applicability of accepted antiviral drug combinations to populations such as children and adolescents, patients with acute hepatitis, hemophiliacs, IDUs in drug treatment programs, alcohol abusers, patients with stabilized depression, those with coinfection with HIV, patients with

decompensated cirrhosis and HCV infections in transplant recipients. Such an effort should lead to decreased morbidity and mortality from the disease, as well as a decrease in the reservoir of disease.

- Evaluate strategies to interrupt mother-to-infant transmission of HCV.

- Evaluate new therapies in nonresponders to current treatments, to include not just antiviral agents but also combinations of antifibrotic drugs, immunomodulatory agents, and alternative therapies.

- Encourage a comprehensive approach to promote the collaboration between health professionals concerned with management of addiction with specialists involved in various aspects of HCV and its complications in order to deal with complex societal, medical, and personal issues occurring in IDUs afflicted by the disease.

- Seek appropriate support from governmental agencies and the private sector to address urgent research questions concerning epidemiology and treatment of this disease.

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