The NIH 2002 Consensus Conference on Hepatitis C: What it Said and What it Means

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Infection with hepatitis C virus is a world-wide problem, and is a significant cause of cirrhosis and its complications, liver transplantation, liver cancer and death. As new knowledge about this infection and its management evolves rapidly, the National Institutes of Health of the United States have dedicated two consensus conferences to this topic, one in 1997 and the most recent one in June 2002. NIH Consensus Development and State-of-the-Science Conferences are organized to evaluate the available scientific evidence on a controversial and important issue in medicine. The consensus statement is the report of the process of receiving and reviewing the scientific evidence, the public testimony, and the audience response to the draft of the report (1). Although not meant to be a practice guideline, and not representing federal or NIH policy, this evidence-based statement carries considerable weight and influences the practice of medicine.

The Consensus Conference on the management of hepatitis C in 2002 studied six key questions. These addressed the following topics: the natural history of hepatitis C, the most appropriate approach to diagnose and monitor patients, the most effective therapy, which patients should be treated, recommendations to prevent transmission, and important areas for future research (2). The purpose of this review is to summarize the findings and recommendations of this Consensus statement, therefore setting the stage for new developments in this rapidly expanding field of knowledge.

What is the natural history of hepatitis C? Hepatitis C is an RNA flavivirus with 6 genotypes and more than 50 subtypes. The lack of a vigorous T cell response to infection with this virus and the high mutation rate account for the chronicity of the majority of infections. Acquisition is primarily through exposure to infected blood by injection drug use, blood transfusions before 1992, solid organ transplant from infected donors, unsafe medical practices, occupational exposure, high risk sexual practices and possibly intranasal cocaine use.

Thirty-five thousand new infections occur in the United States every year, with an estimate of 3.9 million infected and 2.7 million having chronic infection. Ten to twelve thousand deaths are related to hepatitis C each year. Prevalence in the general population is estimated to be at least 1.8 percent, slightly higher in African Americans and Hispanics, 15 to 50% in the homeless and incarcerated and 70 to 90% in drug users and hemophiliacs. A fourfold increase is expected in adults diagnosed with hepatitis C between 1990 and 2015.

The disease becomes chronic in 60 to 85% of those infected. Spontaneous clearance of virus occurs more frequently in young persons, females, and those with certain HLA genes. Male African Americans have a lower clearance rate. Progression to cirrhosis occurs in 10 to 15% of those infected, but is only estimated at 2 to 4% in children and young women, while it is 20 to 30% in middle-aged transfused adults. An increased risk of cirrhosis is associated to older age, male gender, an immunosuppressed state, and chronic hepatitis B infection. Higher levels of alcohol use (20 gm per day in females and 30 grams per day in males) have also been associated to a higher risk of cirrhosis. Other factors that may be associated to worse disease include iron overload, non-alcoholic fatty liver disease, Schistosomiasis, hepatotoxic medications and environmental contaminants.

What is the most appropriate approach to diagnose and monitor patients? Diagnostic tests include those that detect antibodies to hepatitis C virus and are used for screening, and those that detect presence of viral RNA and confirm active viral infection. Third generation enzyme immunoassays (EIA) are the initial tests used in a clinical setting and for population testing. They are over 99% sensitive and specific in immunocompetent persons. A negative HCV antibody test virtually excludes infection in an immunocompetent host. Qualitative tests for HCV RNA are the confirmatory tests of active viral infection. Testing by polymerase chain reaction (PCR) has a detection level of 50 to 100 IU/ml, while the transcription mediated

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amplification assay (TMA) has a detection level of 5 to 10 IU/ml and has been approved by the FDA since November 2002 (3). Quantitative tests of HCV RNA use either PCR or branched DNA technology. Reports should be in International units to standardize results and the same assay should be used for follow-up testing in a given patient. Low viral levels at baseline correlate with a positive response to therapy.

Alanine aminotransferase levels (ALT) are relatively insensitive markers of disease, and serial determinations are necessary before determining a patient has persistently normal ALT.

The liver biopsy offers a unique source of information on the presence of fibrosis and an assessment of the histology of the liver. It can detect iron deposits, steatosis and concurrent alcoholic liver disease. Knowledge of the extent of liver disease allows for more informed choices about therapy.

Good data on the value of screening for hepatocellular carcinoma is not available. In the absence of cirrhosis, screening for cancer is not indicated.

All patients infected with HIV should be screened for HCV; the converse, however is not necessary. Only patients with HCV at risk also for HIV should be tested for this infection.

What is the most effective therapy for hepatitis C? The highest response rates have been observed with pegylated interferon (alpha 2a and 2b) plus ribavirin. Sustained viral response (SVR) is defined as the absence of HCV RNA by a qualitative assay 24 weeks after the end of treatment. For patients who have not received any therapy (naive), the combination of pegylated interferon and ribavirin is best. Factors that correlate with a good response rate are genotypes other than 1, lower viral levels, less fibrosis or inflammation on biopsy, and lower body weight or body surface area. Patients with genotype 1 should be treated for 48 weeks with pegylated interferon plus ribavirin 1000 to 1200 mg daily. Patients with genotypes 2 and 3 exhibit a similar response when treated with standard interferon three times per week plus ribavirin when compared with pegylated interferon plus ribavirin. In these genotypes, 24 weeks of treatment at a dose of ribavirin of 800 mg per day is sufficient.

Early viral response (EVR) has been shown to predict SVR, and "should be a routine part of monitoring patients with genotype 1". EVR is defined as a drop from the baseline viral count of a minimum of 2 logs as determined 12 weeks after starting treatment. Patients not showing an EVR can be discontinued from therapy, as the probability of SVR is extremely low [1.6%., (4, 5)]. Sustained viral response is associated to resolution of liver injury, reduction in fibrosis and a low relapse rate. Whether it is also associated to a lower risk of hepatocellular carcinoma is not clear.

Retreatment should be considered in selected patients, considering previous treatment (monotherapy with interferon, or standard interferon plus ribavirin), previous response (relapser versus non-responder), severity of liver disease, genotype, factors predictive of response, and tolerance of therapy. Non-responders to standard interferon plus ribavirin show only a SVR of 15 to 20% with pegylated interferon plus ribavirin (higher for genotypes 2 and 3). Treatment of relapsers is under study and maintenance therapy is experimental.

Adherence to treatment is critical for obtaining the expected response rate, and the management of side effects requires patient education and monitoring. Since ribavirin is cleared by the kidneys, patients with renal disease may benefit from therapy with pegylated interferon alone.

Which patients with hepatitis C should be treated? All patients with chronic hepatitis C should be considered potential candidates for treatment. Therapy is currently recommended for those at an increased risk of developing cirrhosis. These include those with a positive HCV RNA, portal or bridging fibrosis and moderate inflammation or necrosis. Approximately 30% of patients with chronic HCV infection will have normal ALT. Of these, some will progress to advanced fibrosis or cirrhosis. There is currently no consensus on whether to biopsy or treat patients with normal ALT.

In patients with mild disease, progression is likely to be slow. These patients may not need treatment, but should be monitored periodically, and the decision to treat must be individualized.

Patients with advanced liver disease have a lower SVR. Further studies are needed in this area. Post-liver transplant patients with recurrent hepatitis C have an accelerated progression of their disease. Treatment of this group is currently experimental.

Children should be screened if the mother is HCV positive, they received blood before 1992 or have high risk behavior. The SVR seems to be better than adults, but more studies are needed.

Treatment seems to be warranted for acute hepatitis C, but the timing and regime is still undetermined. Active drug use in itself is not a contraindication for therapy, but should be combined with a drug treatment program. Alcohol use, on the other hand, adversely affects response to treatment, and abstinence is strongly recommended.

Patients co-infected with HIV exhibit an accelerated course of liver disease. However, SVR can be achieved, and treatment is recommended.

What recommendations can be made to patients to prevent transmission of hepatitis C? Percutaneous transmission from the large number of infected patients,

in particular through injected drug use, is the most important source of contagion. Drug treatment programs, needle and syringe exchange, access to sterile needles and syringes, and risk-modifying education are likely to be of help.

Sexual transmission is less frequent. Sex partners of infected persons should be tested. For monogamous relationships, no barrier methods are recommended; all others are advised to use condoms.

Transmission by body piercing and tattoos is rare, and needlesticks are associated to a 2% transmission rate.

Perinatal transmission is 2% in hepatitis C antibody positive mothers, 4 to 7% in mothers that are HCV RNA positive (with the risk proportional to the viral titers), and 20% in HCV/HIV co-infected mothers. No data supports the need for cesarean sections, and breast feeding does not seem to carry a risk of transmission.

What are the most important areas for future research? Areas identified for future investigation include the development of HCV culture systems, the role of genetic factors in hepatitis C, the development of less toxic molecular-based treatments, further studies in the pathogenesis of fibrosis, the institution of a NIH Hepatitis Clinical Research Network, and randomized clinical trials in special populations. Specific topics for research are the natural history of viremia after 20 years, the prevalence and clinical significance of extrahepatic manifestations, strategies for the control of infection and transmission, studies in non-responders, alternative and non-traditional medicines, other drugs, trials for acute hepatitis C, and educational programs for students. Studies in uninsured and publicly insured populations are necessary. The role of supportive therapy for side effects needs to be assessed, the role of the liver biopsy must be established, there must be an international standardization of viral RNA titers, and the usefulness of viral kinetics must be evaluated. Randomized trials on screening for hepatocellular carcinoma are needed. The safe level of alcohol consumption should be evaluated, as well as the role of fatty liver, obesity, diabetes and iron stores. Further research is needed in co-infection with HCV and HIV.

Conclusions

The NIH Consensus Conference on the management of hepatitis C reviewed and summarized the scientific evidence available in 2002 and identified areas for future research. Significant findings that impacted clinical practice included the establishment of pegylated interferon plus ribavirin as the best treatment for genotype 1- HCV; the predictive value of EVR; the contribution of liver biopsy to the management of the patient; the shorter treatment for genotypes 2 and 3; and the indications for treatment in HCV/HIV co-infected patients. Important clinical issues that need further clarification are the treatment of active drug users and patients with acute hepatitis C, normal ALT, advanced liver disease, post-transplant recurrence, or chronic renal disease.

The call for epidemiologic studies, particularly in uninsured and publicly insured populations, is of special significance to Puerto Rico, where a high prevalence of hepatitis C infection has been found in adults living in San Juan (6), and where more than half of the population is publicly insured. This research question should be high in our priority list.

References

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Author's Note

After this manuscript was submitted, the American Association for the Study of Liver Diseases (AASLD) published practice guidelines entitled "Diagnosis, Management and Treatment of Hepatitis C" (Strader, Wright,Thomas and Seef, Hepatology April 2003). These guidelines summarize the available evidence as well as expert opinions on hepatitis C, updating those presented in the NIH consensus conference, and making specific recommendations in areas such as acute hepatitis C, children, HIV/HCV co-infected, chronic renal disease among others. The reader interested in specific guidelines for therapy is referred to this excellent article, which has been endorsed by the AASLD and the Infectious Diseases Society of America.