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Consensus Statement*

1. What are the Public Health Implications of Hepatitis C?

Hepatitis C is a major health problem. The global prevalence of chronic hepatitis C is estimated to average 3% (ranging from 0.1 to 5% in different countries): there are some 150 million chronic HCV carriers throughout the world, of whom an estimated 4 million are in the USA and 5 million in Western Europe. The prevalence seems to be higher in Eastern Europe than in Western Europe. In industrialized countries, HCV accounts for 20% of cases of acute hepatitis, 70% of cases of chronic hepatitis, 40% of cases of end-stage cirrhosis, 60% of cases of hepatocellular carcinoma and 30% of liver transplants.

The incidence of new symptomatic infections has been estimated to be 1–3 cases/100 000 persons annually. The actual incidence of new infections is obviously much higher (the majority of cases being asymptomatic). The incidence is declining for two reasons: (a) transmission by blood products has been reduced to near zero; (b) universal precautions have markedly reduced transmission in medical settings. Intravenous drug use remains the main mode of transmission; but, even here, the rate of transmission is diminishing due to a heightened awareness of the risk of needle sharing and, in some countries, the availability of needle-exchange programs.

2. What is the Natural History of Hepatitis C? What are the Factors Influencing the Disease?

Hepatitis C is a disease with various rates of progression. In general, its course is slowly progressive. About 15% of HCV-infected individuals recover spontaneously; an additional 25% have an asymptomatic illness with persistently normal aminotransferases and generally benign histological lesions; hence, about 40% of patients recover or have a benign outcome. In those with biochemical evidence of chronic hepatitis, the majority have only mild to moderate necro-inflammatory lesions and minimal fibrosis: their long-term outcome is unknown and, probably, most of them will not succumb to the liver disease. About 20% of patients with chronic hepatitis C develop cirrhosis in 10–20 years, and may die of complications of cirrhosis in the absence of liver transplantation. Thus, hepatitis C is a dichotomous disease in which a subset of patients will die from liver-related causes, but in which the majority will probably live out their normal life span.

Several cofactors play an important role in the development of cirrhosis: (a) the age at the time of infection (on average, patients who acquire the disease at an older age have a more rapidly progressing disease, while progression is slower in younger patients; (b) alcoholism (all studies show that alcohol is a very important co-factor in the progression of chronic hepatitis to cirrhosis); (c) co-infection with HIV; (d) co-infection with hepatitis B virus.

The incidence of hepatocellular carcinoma is 1–4% per year in patients with cirrhosis. This risk supports the necessity of regular monitoring by ultrasonography and measurement of alphafetoprotein in patients with established or suspected cirrhosis. Development of hepatocellular carcinoma is rare in patients with chronic hepatitis C who do not have cirrhosis.

3. Diagnostic Tests

ELISA tests are easy to use and inexpensive, and are the best tests for initial screening. These tests are reliable in most immunocompetent patients who replicate HCV. They are less sensitive in hemodialyzed and in immunocompromised patients.

In low-risk settings, such as blood banks and other

* This statement was drawn up by the Consensus Panel.

general screening situations where approximately 25% of ELISA positive results may be false, a supplemental specificity test, such as a strip immunoblot assay, is recommended to avoid unwarranted notification of false positives. Then, a qualitative HCV RNA test should be performed if anti-HCV positivity is confirmed.

In high-risk populations and in clinical settings where hepatitis C is suspected, a positive ELISA should be confirmed by a qualitative HCV RNA test.

In patients with acute hepatitis of unknown cause, an ELISA test should be performed first. If hepatitis A and B tests are negative, then a qualitative HCV RNA test must be performed.

In ELISA-negative patients with chronic hepatitis of unknown cause, particularly in hemodialyzed and immunocompromised patients, a qualitative HCV RNA test should be performed.

Genotyping and quantitative HCV RNA tests are only recommended prior to the treatment of patients.

4. Who Should be Screened for Hepatitis C?

General screening is not advisable. Screening should be limited to risk groups: (a) persons who have (or might have) received blood products prior to initiation (1991) of second-generation ELISA test; (b) hemophiliacs; (c) hemodialyzed patients; (d) children born to mothers who have hepatitis C; (e) current or previous users of intravenous drugs; (f) donors for organ or tissue transplantation.

5. How Can the Transmission of Hepatitis C be Prevented?

The two main sources of infection are intravenous drug use and administration of blood products. The latter source has almost completely disappeared since 1991.

Sexual transmission is very uncommon: the prevalence of HCV infection in stable partners of homosexual or heterosexual individuals infected with HCV is very low, but is higher in persons with multiple partners. The use of condoms in stable monogamous relationships is not justified; the use of condoms is strongly encouraged in patients with multiple partners.

Pregnancy is not contraindicated in HCV-infected women. Routine HCV screening is not recommended in pregnant women.

HCV vertical transmission is uncommon: the prevalence of transmission from mother to child is less than 6%. The risk of transmission appears to be greater in women with high levels of viremia or HIV co-infection. The mode of delivery (cesarean section/vaginal) does not appear to influence the rate of HCV transmission from mother to child.

There is no association between breast feeding and transmission of HCV infection from mother to child.

There are insufficient data concerning the risk of vertical transmission of *in vitro* fertilization in patients with hepatitis C to make recommendations at this time.

Nosocomial HCV infection is efficiently prevented by the observance of universal precautions.

6. Which Patients Should be Treated?

The decision to treat is a complex issue which must take into consideration numerous variables: age of the patients, general state of health, risk of cirrhosis, likelihood of response, and other medical conditions that may decrease life expectancy or contraindicate the use of interferon or ribavirin.

Does the decision to treat depend on the histologic lesions?

It is appropriate and important to obtain a percutaneous liver biopsy before beginning therapy. The liver biopsy provides an opportunity to grade the severity of necro-inflammation and to stage the progression of fibrosis, which may then be considered in relation to the supposed duration of the disease, clinical status and biochemical abnormalities to make therapeutic decisions. The biopsy also provides a baseline in individual patients. There is agreement that patients with moderate/severe necro-inflammation and/or fibrosis should be treated.

Does the decision to treat depend on the age of the patient?

The physiological age of the patient is more important than the chronological age of the patient. Factors to be considered in older patients include overall health status with a special assessment of the cardiovascular system to determine the potential risk of a decrease in hemoglobin level if treatment with ribavirin is being considered.

Does the decision to treat depend on the clinical manifestations?

In the early stages, in the absence of advanced cirrhosis, there is a poor correlation between the clinical manifestations and the histological lesions of the disease. Overall, clinical status may affect the decision to treat with regard to quality of life. Studies have shown the abatement of symptoms in patients in whom treatment has induced sustained loss of HCV RNA.

Does the decision to treat depend on the level of viremia?
Only patients who have detectable serum HCV RNA are candidates for therapy. It is widely recognized that patients who have higher levels of viremia (more than 2 million copies/ml) are relatively less likely to respond to therapy. However, the level of viremia should not be used as a reason to deny treatment.

Does the decision to treat depend on the genotype of the virus?
Although it is well-recognized that patients with genotype 1 respond to the treatment less well than patients with genotype 2 or 3, the genotype should not be used as a reason to deny treatment.

Should children be treated?
There are no large studies of the treatment of chronic hepatitis C in children. Available studies suggest that children have response rates to interferon monotherapy similar to adults. There are no data on combination therapy with interferon and ribavirin in children. The decision to treat a child must take into consideration the same factors as in adults. There may be additional factors that are unique to young children, in particular the effect of interferon on growth, which require further studies.

Should patients co-infected with HIV be treated?
Chronic hepatitis C is frequently found in HIV-infected subjects. It has been established that the progression of chronic hepatitis C is accelerated in co-infected patients. Treatment of hepatitis C may be indicated in those patients in whom treatment has stabilized the HIV infection. Consideration must be given to possible drug interactions and to additive blood abnormalities when treating these co-infected patients.

Should patients with compensated cirrhosis be treated?
Patients with compensated cirrhosis may be treated. Some potential benefits, such as the reduction in the development of hepatocellular carcinoma and decompensation, are not proven and should be assessed in future controlled studies.

Should patients with persistently normal aminotransferases be treated?
Patients who are HCV RNA positive and have persistently normal aminotransferase levels generally have mild disease and an uncertain response to therapy. At present, it is not recommended that these patients undergo therapy, but they should be followed up every 4–6 months or entered into clinical trials.

Should patients with HCV-related extrahepatic conditions be treated?
Consideration should be given to the treatment of HCV-related extrahepatic conditions, for example symptomatic cryoglobulinemia, glomerulonephritis or vasculitis. However, sustained remission is unlikely, and long-term maintenance therapy with interferon may be required. The efficacy of interferon and ribavirin combination therapy should be assessed.

Should patients with acute hepatitis C be treated?
Most experts are in favor of treating patients with acute hepatitis C. The timing and duration of the treatment have not been clearly established. Patients with acute hepatitis C should be informed of the 15% chance of spontaneous recovery, the 85% risk of chronic hepatitis C, and the side effects of therapy. Treatment decisions should be individualized and, ideally, patients should be entered into clinical trials. Combination therapy has not been evaluated.

Which patients should not be treated?
Given the relatively low efficacy and the side effects of the current treatment of hepatitis C, many patients with hepatitis C virus are not suitable candidates for therapy. In particular, patients with active heavy alcohol intake should not be treated because alcohol adversely increases viremia and interferes with the response to treatment. Active intravenous drug users should not be treated due to the risk of reinfection. In addition, compliance with treatment is poor in patients in whom alcoholism has not been interrupted and in whom drug addiction continues. It is potentially dangerous and there is no evidence that treatment is beneficial to patients with decompensated cirrhosis. The benefits of treating patients with histologically mild disease are uncertain, especially older patients, with co-morbid conditions.

7. What is the Optimal Treatment?

In naive patients, the combination of interferon and ribavirin should be offered to those without contraindications. The duration of therapy depends on the genotype and level of viremia. In patients with genotype 2 or 3, the duration is 6 months (regardless of the level of viremia). In patients with genotype 1, the current data suggest that 6 months is sufficient if the level of viremia is low (less than 2 million copies/ml); 12 months of treatment is recommended if the level of viremia is high (more than 2 million copies/ml).

Preliminary data suggest that, with combination therapy, 5–10% of patients with detectable HCV RNA

after 3 months of therapy may nevertheless clear HCV RNA after 6 months of treatment and develop a sustained response after treatment. There has been no consensus for recommending that therapy be discontinued if HCV RNA remains detectable after 3 months of treatment.

In naive patients in whom ribavirin is contraindicated, interferon monotherapy (3 MU or 9 μg thrice weekly) should be administered for 12 months, with HCV RNA testing after 3 months of therapy. Therapy should be continued only in patients in whom HCV RNA has disappeared. It is not proven that an increased dosage of interferon, or daily administration, or high-dose induction increases the sustained response rate.

Absolute contraindications to interferon are the following: present or past psychosis or severe depression; neutropenia and/or thrombocytopenia; organ transplantation except liver; symptomatic heart disease; decompensated cirrhosis; uncontrolled seizures. Relative contraindications to interferon are the following: uncontrolled diabetes; autoimmune disorders, especially thyroiditis.

Absolute contraindications to ribavirin are the following: end-stage renal failure; anemia; hemoglobinopathies; severe heart disease; pregnancy; no reliable method of contraception. Relative contraindications to ribavirin are the following: uncontrolled arterial hypertension; old age.

In patients who have relapsed after interferon monotherapy, two options can be considered: (a) treat with a combination of interferon and ribavirin for 6 months if there are no contraindications to ribavirin; (b) treat with a high dose (more than 3 MU or 9 μg thrice a week) of interferon for 12 months. In both options, HCV RNA should be checked after 3 months and therapy should be discontinued if HCV RNA remains positive.

In patients who have failed to respond to interferon monotherapy or combination therapy, there are no clear data to indicate that retreatment will be beneficial.

Liver transplantation is indicated in patients with life-threatening cirrhosis, and those with hepatocellular carcinoma on cirrhosis. Patients with cirrhosis should be considered for transplantation if they develop complications of their cirrhosis and have a life expectancy of 1–2 years without transplantation. This includes patients with recurrent or refractory ascites, Child-Pugh C cirrhosis, uncontrolled gastrointestinal bleeding after medical, endoscopical and TIPS (transjugular intrahepatic portacaval shunt) procedures, severe encephalopathy (spontaneous or after shunt), bacterial peritonitis.

Patients with hepatocellular carcinoma on cirrhosis can be considered for transplantation if there are less than 3 nodules of 3 cm and if there is no extrahepatic spread, including portal invasion.

After liver transplantation, HCV reinfection is almost constant. At 3 years, about 50% of the patients have a normal graft or mild lesions, 45% of the patients have chronic hepatitis and only 5% develop severe lesions. The 5-year rate of HCV-related cirrhosis on the graft is about 10%.

The 5- and 10-year patient survival rate in Europe is about 70% and 60%, respectively, which is comparable to that of patients transplanted for other non-malignant liver diseases. Patients should be informed of the risk of HCV recurrence and its potential consequences before transplantation.

8. How Should Untreated and Treated Patients be Monitored?

Laboratory tests are not very reliable in monitoring the progression of liver disease in hepatitis C patients. Nevertheless, checking blood counts, including platelet counts and liver enzymes every 6 months is recommended. Liver biopsy is necessary to assess progression of fibrosis and cirrhosis. In patients in whom treatment has not been initiated because of mild liver disease at the initial biopsy, repeat liver biopsy at intervals of 4–5 years is recommended.

In patients with normal aminotransferase levels at presentation, repeat aminotransferase testing is recommended every 6 months to identify patients who may develop elevated aminotransferase levels during follow-up. Liver biopsy is not routinely recommended in the patients with normal aminofransferases, although 20% of them have significant liver disease.

In patients with established or supected cirrhosis, screening for hepatocellular carcinoma (ultrasonography and alphafetoprotein) should be performed, although the cost-effectiveness of this screening program has not been established.

Prior to initiation of treatment, patients should have a liver biopsy and HCV genotyping. Quantitative tests for HCV RNA may help in predicting response to treatment and in guiding the duration of therapy in patients with HCV genotype 1. All patients should be tested for thyroid function. Older patients and those with risk factors should have their cardiac status assessed prior to treatment. Because of the risk of teratogenicity during ribavirin treatment, women with reproductive potential should have a negative pregnancy test prior to treatment.

During treatment, patients should have complete blood counts including platelets checked regularly. This should be performed weekly during the 4 four

weeks in patients undergoing ribavirin therapy, as a decrease in hemoglobin of 30–40 g/l may be observed. In addition, regular tests (every 3–6 months during treatment and then 6 months after treatment) for thyroid function should be performed. Emotional status, in particular depression, of patients must be regularly assessed because suicide attempts and successful suicides have been reported. Men and women with reproductive potential must practice strict contraception during and for 6 months after combination therapy.

Response to interferon monotherapy should be assessed by retesting HCV RNA after 3 months of treatment; treatment should be interrupted if HCV RNA is positive.

Response to combination therapy should be assessed by retesting HCV RNA after 6 months of therapy in patients with genotype I (and high pretreatment levels of viremia); treatment should be continued for an additional 6 months if HCV RNA is undetectable. There has been no consensus for recommending interim assessment of HCV RNA after 3 months of therapy.

Response at the end of treatment (monotherapy or combination therapy) should be assessed by testing for aminotransferases and qualitative tests for HCV RNA just before stopping therapy.

Sustained response should be assessed by testing for aminotransferases and qualitative tests for HCV RNA 6 months after the cessation of treatment. Repeat liver biopsy is not necessary to assess response. Patients with a sustained response should continue to be followed in clinics, as the long-term outcome in these patients remains unknown.

9. Main Unresolved Issues: Treatment, Vaccination

Hepatitis C is an enormous present and future health burden to the world. Even by the year 2010, and allowing for falling prevalence, a huge backlog of infected patients will still be progressing towards cirrhosis and hepatocellular carcinoma. Even if it were possible at the present time to treat all those infected and so slow down the progression towards chronic severe liver disease, the cost of such large-scale investigations and therapy would be enormous.

Progress in our understanding of HCV infection has depended on the support of the pharmaceutical industry, particularly in physician education and in evaluating therapy in large clinical trials. However, at the present time, the cost of combination therapy is too great for the large numbers of patients in Europe and other continents who will require it.

The cost of monitoring therapy must be considered. Detection of HCV RNA by PCR is the "gold standard" and has been recommended to monitor treatment. Genotyping and quantitation of viremia are useful but remain costly. These tests must be made more generally available.

The use of other combinations of drugs presently available is unlikely to achieve much better results than the combination of interferon and ribavirin. Antisense oligonucleotides targeted against the ribosomal-binding site of the 5′ non-translated region of the HCV genome are being investigated. A new ribozyme specific approach to treatment is also under study. Helicase inhibitors and protease inhibitors are not yet available.

HCV is a worthy adversary, changing continually to avoid immune surveillance by the host. A traditional vaccine is unlikely to become available in the foreseeable future. HCV infrequently induces an effective protective immune response. Neutralizing antibodies, CD4 and CD8 T-cells are poorly elicited by natural infection.

The difficulties of preparing a protective vaccine are: (a) only man and the chimpanzee are infected, and better animal models are needed; (b) HCV replicates poorly *in vitro*; (c) the viral envelope proteins (E1/E2) are highly mutable; antibodies against them fail to provide long-term protective immunity.

Other themes for the future might include the following: *In the field of diagnosis*: surrogate markers of fibrosis, the role of hepatocellular carcinoma screening, and standardization of HCV testing. *In the field of natural history*: the long-term outcome of patients with persistently normal aminotransferase levels, predictors of fibrosis, and predictors of hepatocellular carcinoma. *In the field of virology*: the development of *in vitro* models to assess HCV replication and to assess the effectiveness of new drugs, and the development of alternative animal models to study new antivirals and vaccines. *In the field of therapy*: the benefit of treatment in special groups (acute hepatitis, patients with normal aminotransferases, patients with mild disease, extrahepatic syndromes, compensated cirrhosis, non-responders to current therapy, patients with HBV or HIV co-infection), and the benefits of maintenance therapy in non-responders.

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