

Public health challenges for controlling HCV infection

WHO informal consultation with VHPB
Geneva, May 13-14, 2002

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The Geneva meeting

This document is meant as a short introduction to the WHO informal consultation with the Viral Hepatitis Prevention Board (VHPB) on 'Public health challenges for controlling HCV infection,' Geneva, May 13-14, 2002.

The objectives of the meeting include:

- Review of the newest knowledge on hepatitis C virus infection and its epidemiology;
- Discussion of prevention and control strategies for HCV infection;
- Review of selected country experiences;
- Recommendations on public health action in the prevention and control of HCV infection.

The recommendations derived from this meeting will include amendments on points of view, guidelines, and existing recommendations issued by international organisations and institutes. A selection of them is listed in the next sections of this pre-meeting document, and is meant to be used as a basis for further discussion. In accordance with the VHPB tradition, the obtained information and points of view will be compiled and will appear in the next issue of *Viral Hepatitis*. Suggestions for further reading and additional sources are included in the reference list.

Hepatitis C

Hepatitis C is a blood borne liver disease, caused by the hepatitis C virus (HCV). First identified in 1989, the disease was initially known as 'non-A, non-B hepatitis'. The hepatitis C virus belongs to the Flaviviridae family of viruses, and is spread primarily through direct contact with the blood or bodily fluids of infected individuals. HCV infection is a leading cause of chronic liver disease, including cirrhosis of the liver. With an estimated 3% of the world's population currently infected with hepatitis C, and approximately 170 million persons at risk of fulminant hepatitis disease, the WHO recognizes hepatitis C as a global health problem. The high prevalence of hepatitis C, and the need to understand its epidemiology, warrants global surveillance of the disease in order to determine specific health care measures for disease prevention and control.

1. The virus

The hepatitis C virus is a small, enveloped, RNA virus of the Flaviviridae family. Although humans are the only known reservoir of HCV, the virus has been successfully transmitted to chimpanzees in experimental settings. Given its high rate of mutation, at least 6 distinct clades of HCV, and more than 100 subtypes, have been identified by nucleotide sequencing. Clades 1-3 have a worldwide distribution; clades 4 and 5 are found largely in Africa; and clade 6 is confined largely to Asia. Individual isolates consist

of closely related yet heterogeneous populations of viral genomes (quasispecies). Probably as a consequence of this genetic diversity, HCV has the ability to escape the host's immune surveillance, leading to a high rate of chronic infection. Comparing the genomic nucleotide sequences from different HCV isolates enables classification of viruses into several genotypes and many more subtypes (at least 6 distinct clades of HCV, and more than 100 subtypes, have been identified by nucleotide sequencing). The extensive genetic heterogeneity of HCV has important diagnostic and clinical implications, perhaps explaining variations in clinical course, difficulties in vaccine development, and lack of response to therapy.

2. Primary modes of transmission

2.1. Blood

Because HCV is a blood borne virus, the transfusion of blood and blood products, as well as the transplant of organs that have not undergone viral inactivation, are all potential sources of HCV transmission. Today, standard screening procedures have reduced the risk of HCV transmission through blood in the developed world. However, the problem has not been dealt with as effectively in the developing world, where medical and health care facilities are limited. Parenteral exposure to contaminated blood is also a risk factor for transmission. Therefore, the sharing of needles among intravenous drug users, inadequately sterilized instruments used in medical procedures, tattooing, and body piercing, are all considered high risk activities in the context of HCV transmission.

2.2. Sexual contacts

Studies to date indicate that there is a marginal risk of HCV transmission involved in regular sexual contact, and that this risk increases noticeably in the case of an HCV-infected individual with multiple partners. The reasons behind this discrepancy are not known, but the frequency of sexual contact is likely to be one factor.

2.3. Vertical transmission

Mother-to-infant transmission of HCV has been observed globally, but the risk has typically been less than 5%, unless the mother is co-infected with the human immunodeficiency virus (HIV). There has been no association between HCV transmission and breast-feeding. From a public health perspective, no specific recommendations for preventing the vertical transmission of HCV been made. More research is needed to determine risk and outcome before public health guidelines may be put into effect.

2.4. Nosocomial infections

Nosocomial transmission of HCV is possible when disinfection and sterilisation techniques are inadequate, and contaminated equipment is shared among patients. In particular, studies have indicated the possibility of an HCV infection occurring among patients on hemodialysis, due to poor infection control, and the sharing of contaminated medical vials and supplies.

3. Clinical course

Data on the natural history of hepatitis C are limited, because the onset of infection is often unrecognized and the early course of the disease is indolent and protracted in many

individuals. Prospective cohort studies are few, are typically small, include relatively few subjects whose date of infection can be well documented (e.g., blood transfusion recipients and victims of accidental needle sticks), and have relatively short followup. The natural history of this disease appears to differ according to geography, alcohol use, virus characteristics (e.g., genotype, viral load), co-infection with other viruses, and other unexplained factors.

4. Acute infection

After initial exposure, HCV RNA can be detected in blood in 1-3 weeks. Within an average of 50 days (range: 15-150 days), virtually all patients develop liver cell injury, as shown by elevation of serum alanine aminotransferase (ALT). The majority of patients are asymptomatic and anicteric. Only 25-35 percent develop malaise, weakness, or anorexia, and some become icteric. Fulminant liver failure following HCV infection has been reported but is a rare occurrence. Antibodies to HCV (anti-HCV) almost invariably become detectable during the course of illness. Anti-HCV can be detected in 50-70 percent of patients at the onset of symptoms and in approximately 90 percent of patients 3 months after onset of infection. HCV infection is self-limited in only 15 percent of cases. Recovery is characterized by disappearance of HCV RNA from blood and return of liver enzymes to normal.

5. Chronic infection

About 85 percent of HCV-infected individuals fail to clear the virus by 6 months and develop chronic hepatitis with persistent, although sometimes intermittent, viremia. This capacity to produce chronic hepatitis is one of the most striking features of HCV infection. The majority of patients with chronic infection have abnormalities in ALT levels that can fluctuate widely. About one-third of patients have persistently normal serum ALT levels. Antibodies to HCV or circulating viral RNA can be demonstrated in virtually all patients.

Chronic hepatitis C is typically an insidious process, progressing, if at all, at a slow rate without symptoms or physical signs in the majority of patients during the first two decades after infection. A small proportion of patients with chronic hepatitis C - perhaps less than 20 percent - develop nonspecific symptoms, including mild intermittent fatigue and malaise. Symptoms first appear in many patients with chronic hepatitis C at the time of development of advanced liver disease.

In chronic hepatitis, inflammatory cells infiltrate the portal tracts and may also collect in small clusters in the parenchyma. The latter instance is usually accompanied by focal liver cell necrosis. The margin of the parenchyma and portal tracts may become inflamed, with liver cell necrosis at this site (interface hepatitis). If and when the disease progresses, the inflammation and liver cell death may lead to fibrosis. Mild fibrosis is confined to the portal tracts and immediately adjacent parenchyma. More severe fibrosis leads to bridging between portal tracts and between portal tracts and hepatic veins. Such fibrosis can progress to cirrhosis, defined as a state of diffuse fibrosis in which fibrous septae separate clusters of liver cells into nodules. The extent of fibrosis determines the stage of disease and can be reliably assessed. Severe fibrosis and necroinflammatory

changes predict progression to cirrhosis. Once cirrhosis is established, complications can ensue that are secondary to liver failure and/or to portal hypertension, such as jaundice, ascites, variceal hemorrhage, and encephalopathy. The development of any of these complications marks the transition from a compensated to a decompensated cirrhosis.

The rate of progression is highly variable. Long-term studies suggest that most patients with progressive liver disease who develop cirrhosis have detectable ALT elevations; these can, however, be intermittent. The relationship is inconsistent between ALT levels and disease severity as judged histologically. Although patients with HCV infection and normal ALT levels have been referred to as "healthy" HCV carriers, liver biopsies can show histological evidence of chronic hepatitis in many of these patients.

6. Cirrhosis of the liver

Chronic hepatitis C infection leads to cirrhosis in at least 20 percent of patients within 2 decades of the onset of infection. Cirrhosis and end-stage liver disease may occasionally develop rapidly, especially among patients with concomitant alcohol use.

7. Hepatocellular carcinoma (HCC)

Chronic infection by HCV is associated with an increased risk of liver cancer. The prevailing concept is that hepatocellular carcinoma (HCC) occurs against a background of inflammation and regeneration associated with chronic hepatitis over the course of approximately 3 or more decades. Most cases of HCV-related HCC occur in the presence of cirrhosis.

The risk that a person with chronic hepatitis C will develop HCC appears to be 1-5 percent after 20 years, with striking variations in rates in different geographic areas of the world. Once cirrhosis is established, the rate of development of HCC increases to 1-4 percent per year. Among patients with cirrhosis due to hepatitis C, HCC develops more commonly in men than in women and in older than in younger patients.

8. Extrahepatic manifestations of HCV

Patients with chronic hepatitis C occasionally present with extrahepatic manifestations or syndromes considered to be of immunologic origin, including arthritis, keratoconjunctivitis sicca, lichen planus, glomerulonephritis, and essential mixed cryoglobulinemia. Cryoglobulins may be detected in the serum of about one-third of patients with HCV, but the clinical features of essential mixed cryoglobulinemia develop in only about 1-2 percent of patients. Chronic hepatitis C may be a major underlying cause of porphyria cutanea tarda.

9. Mortality

After an average followup of 18 years, a prospective study of patients who received blood transfusions showed no difference in overall mortality between HCV-infected cases and noninfected controls. Liver-related mortality, although rare, was twice as high in the cases (3.2 percent vs. 1.5 percent). A recent European study showed that survival among hepatitis C patients with compensated cirrhosis was 91 percent after 5 years and 79

percent after 10 years. Among patients developing decompensated cirrhosis, however, 5-year survival was only 50 percent.

Viral Hepatitis Prevention Board (VHPB)

The Viral Hepatitis Prevention Board points of view concerning prevention and control of HCV infection were expressed at a VHPB meeting on 'Control of Hepatitis C virus infection and associated disease' in Barcelona, Spain, March 17-18, 1995. The principles of the consensus reached at this meeting were published in *Viral Hepatitis* in July 1995, and are given below.

Notwithstanding the promising results regarding the efficacy of the recent combination in the treatment of hepatitis C, major efforts to prevent HCV infection within the population are required. The principal components of a *control strategy* for HCV infection and associated disease are:

- (a) Measures to establish adequate public health and information systems addressing occurrence, distribution and costs of the infection, and trends in these over time;
- (b) Measures to interrupt transmission;
- (c) Measures to counsel and control disease in those already infected;
- (d) Further research.

1. Establishing public health and clinical information systems

Public health authorities need urgently to review current systems where these exist and to make plans for their establishment or development. Such systems should be designed to allow:

- (a) Targeting of interventions;
- (b) Monitoring of the occurrence and trends of infection;
- (c) Monitoring of the uptake of treatment, and coverage of interventions;
- (d) Assessment of the effectiveness of previous treatments and of intervention programmes.

2. Interrupting transmission

2.1. Prevention of parenteral transmission

Maintain and monitor the protection of the blood supply and other tissues used for medical procedures and dialysis equipment. Currently, effective serological assays are available to prevent HCV transmission from blood, blood products and other human tissues. However these tests are expensive and are unaffordable for some developing countries and transitional economies.

This will require:

- 2.1.1. The development of cheap screening tests and the implementation of affordable screening programmes in blood banks of all countries. This will require negotiations with manufacturers.

- 2.1.2. Continuation or institution of screening of all donors of tissue products or the products themselves for the presence of HCV using modern sensitive tests. Appropriate quality control systems must constitute an integral part of such screening programmes.
- 2.1.3. Continuation or institution of policies of self exclusion from blood and tissue donation.
- 2.1.4. The use of viral inactivation treatments for blood and tissue products where feasible and appropriate.

2.2. Prevention of transmission to health care workers through occupational parenteral exposure

The adoption by health care workers of universal precautions developed to prevent other blood-borne diseases should be a major priority. To achieve this will require:

- 2.2.1. Raising the awareness of the occupational risks of infection through appropriate staff training;
- 2.2.2. Recognition of clinical settings and clinical groups in which a high prevalence of infection may be expected, and institution of appropriate infection control procedures by clinical and laboratory staff against HCV transmission.

2.3. Prevention of transmission through injecting drug use

This will require programmes comprising:

- 2.3.1. Preventive efforts aimed at reducing the number of new and established injecting drug users;
- 2.3.2. Preventive efforts aimed at early harm reduction through reducing injection associated behaviours likely to carry risk of transmitting the infection.

These should include:

- (a) Provision of information and education (e.g. early prevention in schools) promoting the avoidance of drug use and, in particular, injecting drug use;
- (b) Access to disposable sterile injecting equipment and promotion of disposal (needle exchange programmes);
- (c) Promotion of hygiene in preparation of injectable drugs and discouraging the sharing of injecting equipment.

It is crucial that such measures should be fully integrated with and build upon the experience of programmes for the prevention of HIV transmission through injecting drug use.

2.4. Prevention of perinatal transmission

The risk of perinatal transmission appears to be very low, and at present no effective pharmacological, immunological or behavioural means are available to control transmission of infection from an infected mother to her child. In these circumstances there would not appear to be any obvious benefit to the child in routine screening of pregnant women for HCV infection. Pregnancies among HCV-positive women should not be discouraged.

2.5. Other modes of transmission: sexual transmission

This may require measures focused both on individuals who are known to be HCV infected or who are at high risk of infection and on the population at large.

2.5.1. Individuals HCV infected or at high risks

Counselling should be offered to such individuals which fully informs them of currently available information about the risks of sexual transmission of the virus and which promotes safer sex practice. Individuals should be supported in making their own decisions about appropriate safer sex strategies (including condom use) to reduce their risk of transmitting infection to others, in the context of their particular circumstances.

2.5.2. General population

Current measures to promote safer sex strategies for the prevention control of HIV transmission should continue to be supported.

3. Transmission to household contacts by individuals who are HCV infected or at high risk

Such individuals should be fully informed of currently available information about the low risk of this mode of transmission of the virus. General precautions in terms of not sharing tooth brushes, razors and avoid contact with bleeding wounds should be encouraged.

Measures to counsel and control disease in those already infected

As described in the previous section the majority of individuals who are infected with HCV are likely to be unaware of both their infection and potential infectiousness. Thus there are two distinct groups who could benefit from such measures:

- (a) Individuals already known to be HCV infected;
- (b) Individuals who are HCV infected but in whom this is unknown.

4. Priorities for research

Priorities for such research should be to:

- 4.1. Develop cheaper, simpler, but highly sensitive and specific tests for HCV infection;
- 4.2. Describe the distribution of prevalent and incident HCV infections in the wider community by geography, social, demographic and behavioural features and presumptive mode of acquisition of infection. Where possible a subset of this information should be strain type specific;
- 4.3. Describe the historical evolution of the epidemic over time in both blood transfusion recipients and injecting drug users;
- 4.4. Define the natural history of the infection in patients acquiring infection by different routes, and the host and viral determinants of this;
- 4.5. Elucidate the mechanisms and efficiency of transmission of infection through apparently non parenteral routes;
- 4.6. Better establish prevalence, risks and control strategies for occupationally acquired and nosocomial infection;
- 4.7. Develop models of the transmission dynamics of HCV infection in different populations and the empirical estimation of the important transmission factors;

- 4.8. Identify the clinical and consequent economic benefits of therapeutic interventions over adequate follow-up periods, and the virological and host correlates of successful therapy. Studies in injecting drug users are urgently required;
- 4.9. Identify the epidemiological and consequent economic benefits of therapeutic interventions, secured through a reduction in the infectivity of affected individuals.

WHO consultation in collaboration with VHPB

A WHO consultation was organised in collaboration with the VHPB on April 27-29, 1998, in Geneva, Switzerland. A group of international experts reviewed the public health issues related to HCV infection and hepatitis C, and formulated recommendations for prevention and control. The report of this consultation represents a crucial document for the current symposium. The abstract is given below. The full text is delivered as *a separate pdf file* accompanying the electronic version of the pre-meeting document and constitutes an integral part (see *Annex*) of the printed version.

Abstract - Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. *J Viral Hepat* 1999; 6:35-47 - Hepatitis C is a global health problem caused by infection with the hepatitis C virus. Although representative prevalence data are not available from many countries, available data indicate that approximately 3% of the world's population is infected with HCV. It is estimated that as many as 170 million persons world-wide may be infected with HCV. In many countries, the exact magnitude of the problem and the relative contribution of the various routes of transmission have not been defined with population-based studies. Wherever possible such studies should be performed to enable countries to estimate the burden of hepatitis C disease, to prioritize their preventative measures and to make the most appropriate use of available resources. To assess hepatitis C on a global scale, the World Health Organization (WHO) organized a consultation of international experts, in order to review the public health aspects related to hepatitis C infection and to make recommendations for its prevention and control.

National Institutes of Health (NIH)

The NIH issued a Consensus Development Conference Statement on 'Management of Hepatitis C' on March 24-26, 1997, to provide health care providers, patients, and the general public with a responsible assessment of current available methods to diagnose, treat, and manage hepatitis C.

The consensus panel derived the following conclusions:

1. Individuals who have a history of transfusions of blood or blood products prior to 1990, who are on chronic hemodialysis, who have a history of injection drug use, who have had multiple sexual partners, who are the spouses or close household contacts of

hepatitis C patients, and who share instruments for intranasal cocaine use should be tested for hepatitis C.

2. Hepatitis C is a common infection with variable course that can lead to chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma. The course of illness may be adversely affected by various factors, especially alcohol consumption. Therefore, more than one drink per day is strongly discouraged in patients with hepatitis C, and abstinence from alcohol is recommended. Those addicted to alcohol or drugs should be helped to obtain treatment for their addiction so that they might qualify for anti-HCV therapy.
3. An EIA test for anti-HCV should be the initial test for diagnosis of hepatitis C. In low-risk populations, a supplemental RIBA test and/or a qualitative PCR test for HCV RNA should be performed in those whose EIA test is positive. In patients with clinical findings of liver disease, HCV RNA by PCR can be used for confirmation.
4. Because of assay variability, qualitative and quantitative PCR testing for HCV RNA must be interpreted cautiously. Rigorous proficiency testing is recommended for clinical laboratories performing this assay. The branched DNA signal amplification assay for viral level has been standardized, but may fail to detect low titers of HCV RNA. Sequential measurement of HCV RNA levels (viral load) has not, to date, proven useful in managing patients with hepatitis C.
5. Liver biopsy is indicated when histologic findings will assist decision making regarding patient management. In patients who are not treated with antiviral therapy initially, liver biopsy can be considered to assess disease progression.
6. HCV genotyping and tests for HCV RNA levels (viral load) may provide useful prognostic information, especially regarding response to therapy, but at present must be considered research tools.
7. Currently available therapy for chronic hepatitis C is indicated for patients who have persistently abnormal ALT (greater than 6 months), a positive HCV RNA, and liver biopsy demonstrating either portal or bridging fibrosis and at least moderate degrees of inflammation and necrosis. Patients with milder histological disease, compensated cirrhosis, or who are under age 18 or over 60 should be managed on an individual basis or in the context of clinical trials. Patients with decompensated cirrhosis should not be treated with interferon but should be considered for liver transplantation. Patients with persistently normal ALT and minimal histologic abnormalities should not be treated outside clinical trials. Contraindications to treatment of patients with interferon that must be considered are a history of major depressive illness, cytopenia, active alcohol use or illicit drug use, hyperthyroidism, renal transplantation, or autoimmune disease. Therapy should not be limited by mode of acquisition, risk group, HIV status, HCV RNA level, or genotype.
8. Because 12-month regimens with interferon are more successful in achieving sustained responses, initial therapy with interferon alfa (or its equivalent) should be 3 million units three times weekly subcutaneously for 12 months.
9. Nonresponders to interferon therapy can be identified early by assessing the serum ALT level and presence of serum HCV RNA after 3 months of therapy. If the ALT level remains abnormal and the serum HCV RNA remains detectable, interferon therapy should be stopped, because further treatment is unlikely to produce a response. Nonresponders should not be retreated with the same regimen, but should

be considered for combination therapy or enrollment in investigational protocols using different dosages or agents.

10. Patients who have an end-of-treatment response to a 6-month course of interferon alfa, but then relapse, should receive retreatment with a 12-month course of interferon alfa or be considered for combination therapy with interferon plus ribavirin or other regimens, preferably in a clinical trial.
11. Hepatitis A and B vaccination is recommended for all HCV-positive patients.
12. Patient support groups should be encouraged, especially for those undergoing therapy, those who fail therapy, and also those recovering from addiction.

The following recommendations are made to avoid transmission of hepatitis C:

1. In health care settings, adherence to universal (standard) precautions for the protection of medical personnel and patients is essential.
2. HCV-positive individuals should refrain from donating blood, organs, tissues, or semen. In some situations, the use of organs and tissues from HCV-positive individuals may be considered. For example, in emergency situations the use of a donor organ in which the HCV status is either positive or unknown may be considered in a HCV-negative recipient after full disclosure and informed consent. Strategies should be developed to identify prospective blood donors with any prior history of injection drug use. Such individuals must be deferred from donating blood.
3. Safer sexual practices should be strongly encouraged in persons with multiple sexual partners, including the use of latex condoms. In monogamous long-term relationships, transmission is rare. Although HCV-positive individuals and their partners should be informed of the potential for transmission, there are insufficient data to recommend changes in current sexual practice in persons with a steady partner. It is recommended that sexual partners of infected patients should be tested for antibody to HCV.
4. In households with an HCV-positive member, sharing razors and toothbrushes should be avoided. Covering open wounds is recommended. Injection needles should be carefully disposed of using universal precaution techniques. It is not necessary to avoid close contact with family members or to avoid sharing meals or utensils. There is no evidence to justify exclusion of HCV-positive children or adults from participation in social, educational, and employment activities.
5. Pregnancy is not contraindicated in HCV-infected individuals. Perinatal transmission from mother to baby occurs in less than 6 percent of instances. There is no evidence that breast-feeding transmits HCV from mother to baby; therefore, it is considered safe. Babies born to HCV-positive mothers should be tested for anti-HCV at 1 year.
6. Needle exchange and other safer injection drug use programs may be of benefit in reducing parenterally transmitted diseases. Expansion of such programs should be considered in an effort to reduce the rate of transmission of hepatitis C.
7. It is important that clear and evidenced-based information be provided to both patients and physicians regarding the natural history, means of prevention, management, and therapy of hepatitis C.

Centers for Disease Control and Prevention (CDC)

These CDC recommendations for 'Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease' are an expansion of previous recommendations for the prevention of hepatitis C virus infection that focused on screening and follow-up of blood, plasma, organ, tissue, and semen donors (CDC. Public Health Service inter-agency guidelines for screening donors of blood, plasma, organs, tissues, and semen for evidence of hepatitis B and hepatitis C. *MMWR* 1991; 40{RR-4};1-17). The current recommendations provide broader guidelines for a) preventing transmission of HCV; b) identifying, counseling, and testing persons at risk for HCV infection; and c) providing appropriate medical evaluation and management of HCV-infected persons. Based on currently available knowledge, these recommendations were developed by CDC staff members after consultation with experts who met in Atlanta during July 15-17, 1998, and published in *MMWR* in 1998. This report is intended to serve as a resource for health-care professionals, public health officials, and organizations involved in the development, delivery, and evaluation of prevention and clinical services.

1. Primary prevention recommendations

1.1. Blood, plasma derivatives, organs, tissues, and semen.

Current practices that exclude blood, plasma, organ, tissue, or semen donors determined to be at increased risk for HCV by history or who have serologic markers for HCV infection must be maintained to prevent HCV transmission from transfusions and transplants. Viral inactivation of clotting factor concentrates and other products derived from human plasma, including IG products, also must be continued, and all plasma-derived products that do not undergo viral inactivation should be HCV RNA negative by RT-PCR before release.

1.2. High-risk drug and sexual practices

Health care professionals in all patient care settings routinely should obtain a history that inquires about use of illegal drugs (injecting and noninjecting) and evidence of high-risk sexual practices (e.g., multiple sex partners or a history of STDs). Primary prevention of illegal drug injecting will eliminate the greatest risk factor for HCV infection in the United States. Although consistent data are lacking regarding the extent to which sexual activity contributes to HCV transmission, persons having multiple sex partners are at risk for STDs (e.g., HIV, HBV, syphilis, gonorrhea, and chlamydia). Counseling and education to prevent initiation of drug-injecting or high-risk sexual practices is important, especially for adolescents. Persons who inject drugs or who are at risk for STDs should be counseled regarding what they can do to minimize their risk for becoming infected or of transmitting infectious agents to others, including need for vaccination against hepatitis B. Injecting and noninjecting illegal drug users and sexually active MSM also should be vaccinated against hepatitis A.

1.3. Prevention messages for persons with high-risk drug or sexual practices

Persons who use or inject illegal drugs should be advised

- to stop using and injecting drugs.

- to enter and complete substance-abuse treatment, including relapse-prevention programs.
- if continuing to inject drugs,
 - ◇ to never reuse or "share" syringes, needles, water, or drug preparation equipment; if injection equipment has been used by other persons, to first clean the equipment with bleach and water;
 - ◇ to use only sterile syringes obtained from a reliable source (e.g., pharmacies);
 - ◇ to use a new sterile syringe to prepare and inject drugs;
 - ◇ if possible, to use sterile water to prepare drugs; otherwise to use clean water from a reliable source (such as fresh tap water).
 - ◇ to use a new or disinfected container ('cooker') and a new filter ('cotton') to prepare drugs;
 - ◇ to clean the injection site before injection with a new alcohol swab; and
 - ◇ to safely dispose of syringes after one use.
- to get vaccinated against hepatitis B and hepatitis A.

Persons who are at risk for sexually transmitted diseases should be advised

- that the surest way to prevent the spread of human immunodeficiency virus infection and other sexually transmitted diseases is to have sex with only one uninfected partner or not to have sex at all.
- to use latex condoms correctly and every time to protect themselves and their partners from diseases spread through sexual activity.
- to get vaccinated against hepatitis B, and if appropriate, hepatitis A.

Counseling of persons with potential or existing illegal drug use or high-risk sexual practices should be conducted in the setting in which the patient is identified. If counseling services cannot be provided on-site, patients should be referred to a convenient community resource, or at a minimum, provided easy-to-understand health-education material. STD and drug-treatment clinics, correctional institutions, and HIV counseling and testing sites should routinely provide information concerning prevention of HCV and HBV infection in their counseling messages. Based on the findings of multiple studies, syringe and needle-exchange programs can be an effective part of a comprehensive strategy to reduce the incidence of bloodborne virus transmission and do not encourage the use of illegal drugs. Therefore, to reduce the risk for HCV infection among injecting-drug users, local communities can consider implementing syringe and needle-exchange programs.

1.4. Percutaneous exposures to blood in health care and other settings

Health care, emergency medical, and public safety workers should be educated regarding risk for and prevention of bloodborne infections, including the need to be vaccinated against hepatitis B. Standard barrier precautions and engineering controls should be implemented to prevent exposure to blood. Protocols should be in place for reporting and follow-up of percutaneous or permucosal exposures to blood or body fluids that contain blood.

Health care professionals responsible for overseeing patients receiving home Infusion therapy should ensure that patients and their families (or caregivers) are informed of potential risk for infection with bloodborne pathogens, and should assess their ability to use adequate infection-control practices consistently. Patients and families should receive training with a standardized curriculum that includes appropriate infection-control procedures, and these procedures should be evaluated regularly through home visits.

Currently, no recommendations exist to restrict professional activities of health-care workers with HCV infection. As recommended for all health-care workers, those who are HCV-positive should follow strict aseptic technique and standard precautions, including appropriate use of hand washing, protective barriers, and care in the use and disposal of needles and other sharp instruments.

In chronic hemodialysis settings, intensive efforts must be made to educate new staff and reeducate existing staff regarding hemodialysis-specific infection-control practices that prevent transmission of HCV and other bloodborne pathogens. Hemodialysis-center precautions are more stringent than standard precautions. Standard precautions require use of gloves only when touching blood, body fluids, secretions, excretions, or contaminated items. In contrast, hemodialysis-center precautions require glove use whenever patients or hemodialysis equipment is touched. Standard precautions do not restrict use of supplies, instruments, and medications to a single patient; hemodialysis-center precautions specify that none of these items be shared among any patients. Thus, appropriate use of hemodialysis-center precautions should prevent transmission of HCV among chronic hemodialysis patients, and isolation of HCV-positive patients is not necessary or recommended.

1.5. Routine precautions for the care of all hemodialysis patients

- Patients should have specific dialysis stations assigned to them, and chairs and beds should be cleaned after each use.
- Sharing among patients of ancillary supplies such as trays, blood pressure cuffs, clamps, scissors, and other nondisposable items should be avoided.
- Nondisposable items should be cleaned or disinfected appropriately between uses.
- Medications and supplies should not be shared among patients, and medication carts should not be used.
- Medications should be prepared and distributed from a centralized area.
- Clean and contaminated areas should be separated (e.g., handling and storage of medications and hand washing should not be done in the same or an adjacent area to that where used equipment or blood samples are handled).

1.6. Other settings

Persons who are considering tattooing or body piercing should be informed of potential risks of acquiring infection with bloodborne and other pathogens through these procedures. These procedures might be a source of infection if equipment is not sterile or if the artist or piercer does not follow other proper infection-control procedures (e.g., washing hands, using latex gloves, and cleaning and disinfecting surfaces).

2. Secondary prevention recommendations

2.1. Persons for whom routine HCV testing is recommended

Testing should be offered routinely to persons most likely to be infected with HCV who might require medical management, and testing should be accompanied by appropriate counseling and medical follow-up. In addition, anyone who wishes to know or is concerned regarding their HCV-infection status should be provided the opportunity for counseling, testing, and appropriate follow-up. The determination of which persons at risk to recommend for routine testing is based on various considerations, including a known epidemiologic relationship between a risk factor and acquiring HCV infection, prevalence of risk behavior or characteristic in the population, prevalence of infection among those with a risk behavior or characteristic, and the need for persons with a recognized exposure to be evaluated for infection.

2.2. Persons who should be tested routinely for HCV infection based on their risk for infection

- Persons who ever injected illegal drugs, including those who injected once or a few times many years ago and do not consider themselves as drug users.
- Persons with selected medical conditions, including
 - ◇ persons who received clotting factor concentrates produced before 1987;
 - ◇ persons who were ever on chronic (long-term) hemodialysis; and
 - ◇ persons with persistently abnormal alanine aminotransferase levels.
- Prior recipients of transfusions or organ transplants, including
 - ◇ persons who were notified that they received blood from a donor who later tested positive for HCV infection;
 - ◇ persons who received a transfusion of blood or blood components before July 1992; and
 - ◇ persons who received an organ transplant before July 1992.

2.3. Persons who should be tested routinely for HCV infection based on a recognized exposure

- Health care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood.
- Children born to HCV-positive women.

2.4. Persons who have ever injected illegal drugs

Health care professionals in primary-care and other appropriate settings routinely should question patients regarding their history of injecting-drug use, and should counsel, test, and evaluate for HCV infection, persons with such histories. Current injecting-drug users frequently are not seen in the primary health-care setting and might not be reached by traditional media; therefore, community-based organizations serving these populations should determine the most effective means of integrating appropriate HCV information and services into their programs.

Testing persons in settings with potentially high proportions of injecting-drug users (e.g., correctional institutions, HIV counseling and testing sites, or drug and STD treatment

programs) might be particularly efficient for identifying HCV-positive persons. HCV testing programs in these settings should include counseling and referral or arrangements for medical management. However, limited experience exists in combining HCV programs with existing HIV, STD, or other established services for populations at high risk for infection with bloodborne pathogens. Persons at risk for HCV infection through limited or occasional drug use, particularly in the remote past, might not be receptive to receiving services in such settings as HIV counseling and testing sites and drug and STD treatment programs. In addition, whether a substantial proportion of this group at risk can be identified in these settings is unknown. Studies are needed to determine the best approaches for reaching persons who might not identify themselves as being at risk for HCV infection.

2.5. Persons with selected medical conditions

Persons with hemophilia who received clotting factor concentrates produced before 1987 and long-term hemodialysis patients should be tested for HCV infection. Educational efforts directed to health-care professionals, patient organizations, and agencies who care for these patients should emphasize the need for these patients to know whether they are infected with HCV and encourage testing for those who have not been tested previously. Periodic testing of long-term hemodialysis patients for purposes of infection control is currently not recommended. However, issues surrounding prevention of HCV and other bloodborne pathogen transmission in long-term hemodialysis settings are currently undergoing discussion, and updating recommendations for this setting is under development.

Persons with persistently abnormal ALT levels are often identified in medical settings. As part of their medical work-up, health-care professionals should test routinely for HCV infection persons with ALT levels above the upper limit of normal on at least two occasions. Persons with other evidence of liver disease identified by abnormal serum aspartate aminotransferase (AST) levels, which is common among persons with alcohol-related liver disease, should be tested also.

2.6. Prior recipients of blood transfusions or organ transplants

Persons who might have become infected with HCV through transfusion of blood and blood components should be notified. Two types of approaches should be used: a) a targeted, or directed, approach to identify prior transfusion recipients from donors who tested anti-HCV positive after multiantigen screening tests were widely implemented (July 1992 and later); and b) a general approach to identify all persons who received transfusions before July 1992. A targeted notification approach focuses on a specific group known to be at risk, and will reach persons who might be unaware they were transfused. However, because blood and blood-component donor testing for anti-HCV before July 1992 did not include confirmatory testing, most of these notifications would be based on donors who were not infected with HCV because their test results were falsely positive. A general education campaign to identify persons transfused before July 1992 has the advantage of not being dependent on donor testing status or availability of records, and potentially reaches persons who received HCV-infected blood from donors

who tested falsely negative on the less sensitive serologic test, as well as from donors before testing was available.

- Persons who received blood from a donor who tested positive for HCV infection after multiantigen screening tests were widely implemented. Persons who received blood or blood components from donors who subsequently tested positive for anti-HCV using a licensed multiantigen assay should be notified as provided for in guidance issued by FDA. For specific details regarding this notification, readers should refer to the FDA document, Guidance for Industry. Current Good Manufacturing Practice for Blood and Blood Components: (1) Quarantine and Disposition of Units from Prior Collections from Donors with Repeatedly Reactive Screening Tests for Antibody to Hepatitis C Virus (Anti-HCV); (2) Supplemental Testing, and the Notification of Consignees and Blood Recipients of Donor Test Results for Anti-HCV.

Blood-collection establishments and transfusion services should work with local and state health agencies to coordinate this notification effort. Health-care professionals should have information regarding the notification process and HCV infection so that they are prepared to discuss with their patients why they were notified and to provide appropriate counseling, testing, and medical evaluation. Health-education material sent to recipients should be easy to understand and include information concerning where they can be tested, what hepatitis C means in terms of their day-to-day living, and where they can obtain more information.

- Persons who received a transfusion of blood or blood components (including platelets, red cells, washed cells, and fresh frozen plasma) or a solid-organ transplant (e.g., heart, lung, kidney, or liver) before July 1992. Patients with a history of blood transfusion or solid-organ transplantation before July 1992 should be counseled, tested, and evaluated for HCV infection. Health-care professionals in primary-care and other appropriate settings routinely should ascertain their patients' transfusion and transplant histories either through questioning their patients, including such risk factors for transfusion as hematologic disorders, major surgery, trauma, or premature birth, or through review of their medical records. In addition, transfusion services, public health agencies, and professional organizations should provide to the public, information concerning the need for HCV testing in this population. Health-care professionals should be prepared to discuss these issues with their patients and provide appropriate counseling, testing, and medical evaluation.

2.7. Health care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood

Individual institutions should establish policies and procedures for HCV testing of persons after percutaneous or permucosal exposures to blood and ensure that all personnel are familiar with these policies and procedures. Health care professionals who provide care to persons exposed to HCV in the occupational setting should be knowledgeable regarding the risk for HCV infection and appropriate counseling, testing, and medical follow-up.

IG and antiviral agents are not recommended for postexposure prophylaxis of hepatitis C. Limited data indicate that antiviral therapy might be beneficial when started early in the course of HCV infection, but no guidelines exist for administration of therapy during the acute phase of infection. When HCV infection is identified early, the individual should be referred for medical management to a specialist knowledgeable in this area.

2.8. Children born to HCV-positive women

Because of their recognized exposure, children born to HCV-positive women should be tested for HCV infection. IG and antiviral agents are not recommended for postexposure prophylaxis of infants born to HCV-positive women. Testing of infants for anti-HCV should be performed no sooner than age 12 months, when passively transferred maternal anti-HCV declines below detectable levels. If earlier diagnosis of HCV infection is desired, RT-PCR for HCV RNA may be performed at or after the infant's first well-child visit at age 1-2 months. Umbilical cord blood should not be used for diagnosis of perinatal HCV infection because cord blood can be contaminated by maternal blood. If positive for either anti-HCV or HCV RNA, children should be evaluated for the presence or development of liver disease, and those children with persistently elevated ALT levels should be referred to a specialist for medical management.

2.9. Postexposure follow-up of health care, emergency medical, and public safety workers for hepatitis C virus infection

- For the source, baseline testing for anti-HCV.
- For the person exposed to an HCV-positive source, baseline and follow-up testing including
 - ◇ baseline testing for anti-HCV and ALT activity; and
 - ◇ follow-up testing for anti-HCV (e.g., at 4-6 months) and ALT activity. (If earlier diagnosis of HCV infection is desired, testing for HCV RNA may be performed at 4-6 weeks)
- Confirmation by supplemental anti-HCV testing of all anti-HCV results reported as positive by enzyme immunoassay.

2.10. Persons for whom routine HCV testing is not recommended

For the following persons, routine testing for HCV infection is not recommended unless they have risk factors for infection.

Persons for whom routine hepatitis C virus testing is not recommended

- Health care, emergency medical, and public safety workers.
- Pregnant women.
- Household (nonsexual) contacts of HCV-positive persons.
- The general population.

2.11. Health care, emergency medical, and public safety workers

Routine testing is recommended only for follow-up for a specific exposure.

2.12. Pregnant women

Health care professionals in settings where pregnant women are evaluated or receive routine care should take risk histories from their patients designed to determine the need for testing and other prevention measures, and those health care professionals should be knowledgeable regarding HCV counseling, testing, and medical follow-up.

2.13. Household (nonsexual) contacts of HCV-positive persons

Routine testing for nonsexual household contacts of HCV-positive persons is not recommended unless a history exists of a direct (percutaneous or mucosal) exposure to blood.

2.14. Persons for whom routine HCV testing is of uncertain need

For persons at potential (or unknown) risk for HCV infection, the need for, or effectiveness of, routine testing has not been determined.

Persons for whom routine hepatitis C virus testing is of uncertain need

- Recipients of transplanted tissue (e.g., corneal, musculoskeletal, skin, ova, sperm).
- Intranasal cocaine and other noninjecting illegal drug users.
- Persons with a history of tattooing or body piercing.
- Persons with a history of multiple sex partners or sexually transmitted diseases.
- Long-term steady sex partners of HCV-positive persons.

2.15. Recipients of transplanted tissue

On the basis of currently available data, risk for HCV transmission from transplanted tissue (e.g., corneal, musculoskeletal, skin, ova, or sperm) appears to be rare.

2.16. Intranasal cocaine and other noninjecting illegal drug users

Currently, the strength of the association between intranasal cocaine use and HCV infection does not support routine testing based solely on this risk factor.

2.17. Persons with a history of tattooing or body piercing

Because no data exist in the United States documenting that persons with a history of such exposures as tattooing and body piercing are at increased risk for HCV infection, routine testing is not recommended based on these exposures alone. In settings having a high proportion of HCV-infected persons and where tattooing and body piercing might be performed in an unregulated manner (e.g., correctional institutions), these types of exposures might be a risk factor for HCV infection. Data are needed to determine the risk for HCV infection among persons who have been exposed under these conditions.

2.18. Persons with a history of multiple sex partners or STDs

Although persons with a history of multiple sex partners or treatment for STDs and who deny injecting-drug use appear to have an increased risk for HCV infection, insufficient data exist to recommend routine testing based on these histories alone. Health-care professionals who provide services to persons with STDs should use that opportunity to take complete risk histories from their patients to ascertain the need for HCV testing, provide risk-reduction counseling, offer hepatitis B vaccination, and, if appropriate, hepatitis A vaccination.

HCV-positive persons with long-term steady partners do not need to change their sexual practices. Persons with HCV infection should discuss with their partner the need for counseling and testing. If the partner chooses to be tested and tests negative, the couple should be informed of available data regarding risk for HCV transmission by sexual activity to assist them in making decisions about precautions (see section regarding counseling messages for HCV-positive persons). If the partner tests positive, appropriate counseling and evaluation for the presence or development of liver disease should be provided.

Testing for HCV infection consent for testing should be obtained in a manner consistent with that for other medical care and services provided in the same setting, and should include measures to prevent unwanted disclosure of test results to others. Persons should be provided with information regarding

- exposures associated with the transmission of HCV, including behaviors or exposures that might have occurred infrequently or many years ago;
- the test procedures and the meaning of test results;
- the nature of hepatitis C and chronic liver disease;
- the benefits of detecting infection early;
- available medical treatment; and
- potential adverse consequences of testing positive, including disrupted personal relationships and possible discriminatory action (e.g., loss of employment, insurance, and educational opportunities).

2.19. Persons with high-risk drug and sexual practices

Regardless of test results, persons who use illegal drugs or have high-risk sexual practices or occupations should be provided with information regarding how to reduce their risk for acquiring bloodborne and sexually transmitted infections or of potentially transmitting infectious agents to others (see section regarding primary prevention).

2.20. Negative test results

If their exposure was in the past, persons who test negative for HCV should be reassured.

2.21. Indeterminate test results

Persons whose HCV test results are indeterminate should be advised that the result is inconclusive, and they should receive appropriate follow-up testing or referral for further testing (see section regarding testing for HCV infection).

2.22. Positive test results

Persons who test positive should be provided with information regarding the need for a) preventing further harm to their liver; b) reducing risks for transmitting HCV to others; and c) medical evaluation for chronic liver disease and possible treatment.

- To protect their liver from further harm, HCV-positive persons should be advised to
 - ◇ not drink alcohol;

- ◇ not start any new medicines, including over-the-counter and herbal medicines, without checking with their doctor; and
- ◇ get vaccinated against hepatitis A if liver disease is found to be present.
- To reduce the risk for transmission to others, HCV-positive persons should be advised to
 - ◇ not donate blood, body organs, other tissue, or semen;
 - ◇ not share toothbrushes, dental appliances, razors, or other personal-care articles that might have blood on them; and
 - ◇ cover cuts and sores on the skin to keep from spreading infectious blood or secretions.
- HCV-positive persons with one long-term steady sex partner do not need to change their sexual practices. They should
 - ◇ discuss the risk, which is low but not absent, with their partner (If they want to lower the limited chance of spreading HCV to their partner, they might decide to use barrier precautions {e.g., latex condoms}); and
 - ◇ discuss with their partner the need for counseling and testing.
- HCV-positive women do not need to avoid pregnancy or breastfeeding. Potential, expectant, and new parents should be advised that
 - ◇ approximately 5 out of every 100 infants born to HCV-infected women become infected (This occurs at the time of birth, and no treatment exists that can prevent this from happening);
 - ◇ infants infected with HCV at the time of birth seem to do very well in the first years of life (More studies are needed to determine if these infants will be affected by the infection as they grow older);
 - ◇ no evidence exists that mode of delivery is related to transmission; therefore, determining the need for cesarean delivery versus vaginal delivery should not be made on the basis of HCV infection status;
 - ◇ limited data regarding breastfeeding indicate that it does not transmit HCV, although HCV-positive mothers should consider abstaining from breastfeeding if their nipples are cracked or bleeding;
 - ◇ infants born to HCV-positive women should be tested for HCV infection and if positive, evaluated for the presence or development of chronic liver disease (see section regarding routine testing of children born to HCV-positive women); and
 - ◇ if an HCV-positive woman has given birth to any children after the woman became infected with HCV, she should consider having the children tested.
- Other counseling messages
 - ◇ HCV is not spread by sneezing, hugging, coughing, food or water, sharing eating utensils or drinking glasses, or casual contact.
 - ◇ Persons should not be excluded from work, school, play, child-care or other settings on the basis of their HCV infection status.
 - ◇ Involvement with a support group might help patients cope with hepatitis C.
- HCV-positive persons should be evaluated (by referral or consultation, if appropriate) for presence or development of chronic liver disease including
 - ◇ assessment for biochemical evidence of chronic liver disease;

- ◇ assessment for severity of disease and possible treatment according to current practice guidelines in consultation with, or by referral to, a specialist knowledgeable in this area (see excerpts from NIH Consensus Statement in the following section); and
- ◇ determination of need for hepatitis A vaccination.

3. CDC comments on 'Consensus Statement on Management of Hepatitis C' (NIH)

The NIH 'Consensus Statement on Management of Hepatitis C' was based on data available in March 1997. Because of advances in the field of antiviral therapy for chronic hepatitis C, standards of practice might change, and readers should consult with specialists knowledgeable in this area.

3.1. Persons recommended for treatment

Treatment is recommended for patients with chronic hepatitis C who are at greatest risk for progression to cirrhosis, as characterized by

- persistently elevated ALT levels;
- detectable HCV RNA; and
- a liver biopsy indicating either portal or bridging fibrosis or at least moderate degrees of inflammation and necrosis.

3.2. Persons for whom treatment is unclear

Included are

- patients with compensated cirrhosis (without jaundice, ascites, variceal hemorrhage, or encephalopathy);
- patients with persistent ALT elevations, but with less severe histologic changes (i.e., no fibrosis and minimal necroinflammatory changes) (In these patients, progression to cirrhosis is likely to be slow, if at all; therefore, observation and serial measurements of ALT and liver biopsy every 3-5 years is an acceptable alternative to treatment with interferon); and
- patients aged less than 18 years or greater than 60 years (note that interferon is not approved for patients aged less than 18 years).

3.3. Persons for whom treatment is not recommended

Included are

- patients with persistently normal ALT values;
- patients with advanced cirrhosis who might be at risk for decompensation with therapy;
- patients who are currently drinking excessive amounts of alcohol or who are injecting illegal drugs (treatment should be delayed until these behaviors have been discontinued for greater than or equal to 6 months); and
- persons with major depressive illness, cytopenias, hyperthyroidism, renal transplantation, evidence of autoimmune disease, or who are pregnant.

4. Public health surveillance

The objectives of conducting surveillance for hepatitis C are to

- identify new cases and determine disease incidence and trends;
- determine risk factors for infection and disease transmission patterns;
- estimate disease burden; and
- identify infected persons who can be counseled and referred for medical follow-up.

Various surveillance approaches are required to achieve these objectives because of limitations of diagnostic tests for HCV infection, the number of asymptomatic patients with acute and chronic disease, and the long latent period between infection and chronic disease outcome.

4.1. Surveillance for acute hepatitis C

Surveillance for acute hepatitis C - new, symptomatic infections - provides the information necessary for determining incidence trends, changing patterns of transmission and persons at highest risk for infection. In addition, surveillance for new cases provides the best means to evaluate effectiveness of prevention efforts and to identify missed opportunities for prevention. Acute hepatitis C is one of the diseases mandated by the Council of State and Territorial Epidemiologists (CSTE) for reporting to CDC's National Notifiable Diseases Surveillance System. However, hepatitis C reporting has been unreliable to date because most health departments do not have the resources required for case investigations to determine if a laboratory report represents acute infection, chronic infection, repeated testing of a person previously reported, or a false-positive result. Historically, the most reliable national data regarding acute disease incidence and transmission patterns have come from sentinel surveillance (i.e., sentinel counties study of acute viral hepatitis). As hepatitis C prevention and control programs are implemented, federal, state, and local agencies will need to determine the best methods to effectively monitor new disease acquisition.

4.2. Laboratory reports of anti-HCV-positive tests

Although limitations exist for the use of anti-HCV-positive laboratory reports to identify new cases and to monitor trends in disease incidence, they potentially are an important source from which state and local health departments can identify infected persons who need counseling and medical follow-up. Development of registries of persons with anti-HCV-positive laboratory results might facilitate efforts to provide counseling and medical follow-up and these registries could be used to provide local, state, and national estimates of the proportion of persons with HCV infection who have been identified. If such registries are developed, the confidentiality of individual identifying information should be ensured according to applicable laws and regulations.

4.3. Serologic surveys

Serologic surveys at state and local levels can characterize regional and local variations in prevalence of HCV infection, identify populations at high risk, monitor trends, and evaluate prevention programs. Existing laboratory-based reporting of HCV-positive test results cannot provide this information because persons who are tested will not be representative of the population as a whole, and certain populations at high risk might be underrepresented. Thus, data from newly designed or existing serologic surveys will be

needed to monitor trends in HCV infection and evaluate prevention programs at state and local levels.

4.4. Surveillance for chronic liver disease

Surveillance for HCV-related chronic liver disease can provide information to measure the burden of disease, determine natural history and risk factors, and evaluate the effect of therapeutic and prevention measures on incidence and severity of disease. Until recently, no such surveillance existed, but a newly established sentinel surveillance pilot program for physician-diagnosed chronic liver disease will provide baseline data and a template for a comprehensive sentinel surveillance system for chronic liver disease. As the primary source of data regarding the incidence and natural history of chronic liver disease, this network will be pivotal for monitoring the effects of education, counseling, other prevention programs, and newly developed therapies on the burden of the disease.

5. Future directions

To prevent chronic HCV infection and its sequelae, prevention of new HCV infections should be the primary objective of public health activities. Achieving this objective will require the integration of HCV prevention and surveillance activities into current public health infrastructure. In addition, several questions concerning the epidemiology of HCV infection remain, and the answers to those questions could change or modify primary prevention activities. These questions primarily concern the magnitude of the risk attributable to sexual transmission of HCV and to illegal noninjecting-drug use.

Identification of the large numbers of persons in the United States with chronic HCV infection is resource-intensive. The most efficient means to achieve this identification is unknown, because the prevention effectiveness of various implementation strategies has not been evaluated. However, widespread programs to identify, counsel, and treat HCV-infected persons, combined with improvements in the efficacy of treatment, are expected to lower the morbidity and mortality from HCV-related chronic liver disease substantially. Monitoring the progress of these activities to determine their effectiveness in achieving a reduction in HCV-related chronic disease is important.

European Association for the Study of the Liver (EASL)

The EASL International Consensus Conference on Hepatitis C was organised in Paris, France, on February 26-29, 1999. A Consensus Statement was drawn up by a panel of experts. The resulting report was published in *J Hepatol* (1999).

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/1 00000 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 14% 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 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, endoscopic 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 aminotransferases, although 20% of them have significant liver disease.

In patients with established or suspected cirrhosis, screening for hepatocellular carcinoma (ultrasonography and alpha-fetoprotein) 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, extra-hepatic syndromes, compensated cirrhosis, non-responders to current therapy, patients with HBV or HIV co-infection), and the benefits of maintenance therapy in non-responders.

Robert Koch-Institut (RKI)

Representatives of the Robert Koch-Institut in Berlin, Germany, have formulated their points of view on hepatitis C epidemiology and prevention in 2001. These considerations have been published. The full text is available only in German only. The corresponding abstract and selected parts of the original report are given below.

Abstract - Schreier E, Höhne M. Hepatitis C - Epidemiologie und Prävention. Bundesgesundheitsbl - Gesundheitsforsch - Gesundheitsschutz 2001; 44:554-561 - Epidemiological studies have demonstrated a world-wide distribution of hepatitis C virus (HCV), which before its identification and molecular characterisation has been the most frequent infectious agent causing post-transfusion hepatitis. The rapid establishment of HCV antibody detection systems and HCV genome detection assays resulted in the

clearing up of those hepatitis cases which had been designated as non-A, non-B. According to epidemiological studies, around 3% of the world population are infected with HCV, with considerable regional differences. HCV prevalence also varies widely depending on the cohort investigated. From a molecular epidemiological point of view a geographical dominance of certain HCV genotypes/subtypes is observed. Regarding routes of transmission, only parenteral transmission is established beyond doubt. However, the cause of a high number of sporadic HCV infections remains obscure.

1. Übertragungswege/Risikogruppen (Routes of transmission/risk groups)

Bei dieser nicht unerheblichen Zahl von HCV-Infizierten stellt sich die Frage nach dem Übertragungsweg bzw. nach der Ursache für die HCV-Infektion. Gesichert ist heute nur die Übertragung auf parenteralem Wege durch das Eindringen von Blut einer infizierten Person in die Blutbahn der das Gewebe des Empfängers. Studien zum Infektionsrisiko bei 4659 HCV-Infizierten im Raum Hamburg bestätigten zum einen - und dies gilt auch heute noch - dass das genannte 'needle sharing', der Nadel- bzw. Spritzenaustausch unter i.v. -Drogenabhängigen Ursache einer HCV-Infektion sein kann.

Auch bei Strafgefangenen, unter denen sich ein beträchtlicher Anteil von Drogenabhängigen befindet, stellt die HCV Infektion ein durchaus ernst zu nehmendes Problem dar. Problematisch für die Bewertung von Übertragungsrisiken bleibt der Umstand, dass bei einem Großteil der HCV-Infizierten zum Zeitpunkt der Diagnose nicht mehr nachvollziehbar ist, was ursächlich zur HCV Infektion geführt hat. Auch wenn man in anderen Körperflüssigkeiten wie Speichel, Schweiß, Tränen, Muttermilch und Samenflüssigkeit mit einer sehr empfindlichen Nachweismethode wie der Nukleinsäureamplifikationstechnik (z.B. Polymerasekettenreaktion 'PCR') HCV-Genom nachgewiesen hat, muss aufgrund bisheriger Untersuchungen davon ausgegangen werden, dass eine Infektion über andere Körperflüssigkeiten als Blut nicht sehr wahrscheinlich ist und somit nicht für den hohen Anteil an sporadischen HCV-Infektionen (hier ohne erkennbare Infektionsquelle gemeint) verantwortlich sein kann.

2. Wie hoch ist das Risiko einer sexuellen Übertragung von HCV? (What is the risk of sexual transmission of HCV?)

Die Frage nach dem sexuellen Übertragungsrisiko für HCV gehört zu den am häufigsten gestellten. Mindestens 50 Artikel in medizinischen Fachzeitschriften und eine Unzahl von Letters-to-the-Editor beschäftigen sich mit dieser Frage. Dies weist schon darauf hin, dass die bisherigen Antworten nicht ganz eindeutig bzw. nicht ganz befriedigend sind.

Untersuchungen in Langzeitpartnerschaften monogamer heterosexueller Paare zeigen in der Regel nur ein geringes sexuelles Übertragungsrisiko. In größeren Studienkollektiven werden Übertragungsraten in einer Größenordnung von 1 bis 3% berichtet. Deutlich höhere Übertragungsraten bei heterosexuellen Paaren werden aus asiatischen Ländern berichtet, über die Gründe für diese Differenz lässt sich derzeit nur spekulieren.

Eine überdurchschnittlich hohe HCV-Prävalenz wird in einer Reihe von Studien bei

- Prostituierten,
- homosexuellen Männern,

- Klienten von STD-Behandlungseinrichtungen und
- Sexualpartner/innen von i.v.-Drogenabhängigen

festgestellt. Allerdings sind solche Befunde nicht konsistent (z. B. bei homosexuellen Männern), und es bleibt häufig unbefriedigend geklärt, ob, und wenn ja, welche anderen Risikofaktoren, wie i.v.-Drogenkonsum, medizinische Behandlungen, Tätowierungen etc., vorgelegen haben. Auch gibt es kaum Analysen, die versuchen, HCV-Infektionsrisiken mit bestimmten Sexualpraktiken zu korrelieren.

Eine Analyse möglicher Übertragungsrisiken in einer kanadischen Kohortenstudie bei sexuell aktiven homosexuellen Männern stellt hier eine Ausnahme dar: im Rahmen dieser Studie wurden neben dem i.v.-Drogengebrauch oral-anale Kontakte und insertives Fisting als Risikofaktoren für eine HCV Infektion identifiziert. Bei diesen beiden Praktiken ist vorstellbar, dass eine Übertragung durch Blut-Schleimhautkontakt der Blut-Wund-Kontakt stattfinden könnte. In einem 'Research letter' in der Fachzeitschrift *The Lancet* wurde vor kurzem über Ergebnisse von PCR Untersuchungen der Samenflüssigkeit HCV-positiver Männer berichtet. Die Wissenschaftler wurden im Ejakulat von acht der 21 untersuchten HCV-infizierten Männern fündig. Die nachweisbare Viruskonzentration in der Samenflüssigkeit war jedoch drei bis vier log-Stufen niedriger als im Plasma und betrug in allen Fällen weniger als 200 Virus-RNA-Kopien pro ml. Der Nachweis von Virus-RNA bedeutet noch nicht, dass es sich um infektiöses Virus handelt.

Auch diese Untersuchung kann als eine sexuelle Übertragung von HCV weder beweisen noch ausschließen, legt aber nahe, dass wenn ein Übertragungsrisiko besteht, dieses relativ gering ist. Ungeachtet der HCV-Konzentration in Genitalflüssigkeiten ist jedoch zu bedenken, dass es bei Sexualkontakten auch zu Verletzungen und Blutungen kommen kann - wie es ja auch die kanadische Studie nahe legt - und die HCV-Konzentration im Blut deutlich höher ist.

Besteht neben der HCV-Infektion eine HIV-Koinfektion, so wurden bei heterosexuellen Partnern signifikant höhere HCV-Durchseuchungen festgestellt.

3. Risikofaktoren für die Mutter-Kind-Übertragung des Hepatitis C Virus (Risk factors for HCV transmission from mother to child)

Eine Reihe von Studien in den vergangenen acht Jahren hat sich mit der Frage der Häufigkeit der Mutter-Kind-Übertragung einer HCV-Infektion und der Identifizierung entsprechender Risikofaktoren beschäftigt. Konsistent über alle Studien hinweg war der Befund, dass Mutter-Kind-Übertragungen nur bei Müttern mit nachweisbarer HCV-RNA zum Geburtszeitpunkt beobachtet wurden. Bei diesen beträgt das durchschnittliche Übertragungsrisiko etwa 5% (17 bis 25). Als potenzieller Risikofaktor für eine Übertragung wurde in vielen Studien die Höhe der HCV-Viruslast im Blut der Mutter zum Zeitpunkt der Geburt analysiert. Zwar liegt in allen Studien die mittlere Viruslast bei den HCV-übertragenden Müttern höher als bei den nicht übertragenden, aber nur in einem Teil der Studien sind die Unterschiede signifikant.

Die Frage, ob eine HIV/HCV-Koinfektion einen Risikofaktor für eine vertikale HCV-Übertragung darstellt, wird durch die vorliegenden Studienergebnisse nicht ganz

eindeutig beantwortet, aber mehrheitlich wird die HIV-Koinfektion als zusätzlicher Risikofaktor für eine HCV-Übertragung angesehen. In einer neueren Studie wird in einem Kollektiv von 370 anti-HCV-positiven Schwangeren unter den 15 HIV/HCV-koinfizierten Frauen keine Übertragung gefunden, wobei aber alle 15 während der Schwangerschaft mit antiretroviralen Medikamenten behandelt wurden. In einer britisch-irischen Studie hingegen war das HCV-Übertragungsrisiko bei den HIV-koinfizierten Schwangeren 3, 8 mal höher als bei den nur mit HCV infizierten. Angaben zur retroviralen Therapie bei den HIV-infizierten Schwangeren werden in der Publikation nicht gemacht.

4. Zeitpunkt der Übertragung (Time of transmission)

Aufgrund der steigenden Nachweisbarkeit von HCV-RNA bei infizierten Neugeborenen in den ersten Wochen nach der Geburt wird vermutet, dass zumindest ein Teil der Übertragungen erst spät in der Schwangerschaft bzw. unter der Geburt stattfindet. Bisher publizierte Studien geben keinen Hinweis auf eine HCV-Übertragung durch das Stillen, in Muttermilch wurde auch kein infektiöses Virus nachgewiesen.

Die Datenlage dazu, ob die Kaiserschnittentbindung einen präventiven Effekt auf die HCV-Übertragung hat, ist nicht schlüssig. Die Situation erinnert an die lange Zeit kontrovers diskutierte Rolle der Sektioentbindung bei HIV-infizierten Schwangeren. Dort war die Datenlage ebenfalls lange Zeit widersprüchlich und erst eine Differenzierung zwischen elektiver primärer Sektio und sekundärer Sektio aus geburtshilflichen Gründen ergab einen statistisch deutlich erkennbaren Schutzeffekt für die primäre elektive Sektio.

Die bereits erwähnte britisch-irische Studie deutet in dieselbe Richtung: dort zeigt sich kein statistisch signifikanter Unterschied zwischen vaginaler Entbindung und Sektio wegen geburtshilflicher Komplikationen (7,7% bzw. 5,9% Übertragungsrate), aber ein deutlicher Unterschied zur elektiven Sektio (keine Übertragung bei 31 Fällen). Sofern eine nachträgliche Differenzierung zwischen elektiver primärer und sekundärer Sektio in früheren Studien und eine entsprechende Metaanalyse nicht möglich sein sollte, wäre eine prospektive randomisierte Studie der schnellste und sicherste Weg, diese Frage zu klären. In Untersuchungen an Kindern HCV-positiver Mütter, die 1978/79 in der DDR durch die Gabe von HCV-kontaminierten Immunglobulinpräparaten im Rahmen der Anti-D-Prophylaxe (bei Rhesusunverträglichkeit) zur Verhinderung der Neugeborenen-gelbsucht eingesetzt wurden, fand sich nur ein geringes Übertragungsrisiko (Anti-D Studie). Bezogen auf diese Anti-D-Studie waren innerhalb der betroffenen Familien nur selten HCV-Infektionen bei Angehörigen nachgewiesen worden (< 1%).

5. Andere potenzielle Übertragungswege (Other potential routes of transmission)

Obwohl sich zum gegenwärtigen Zeitpunkt nicht abschätzen lässt, welche Rolle z. B. Tätowierungen, Piercing der auch Akupunktur bei der HCV-Durchseuchung spielen, wurde in wenigen Studien gezeigt, dass HCV-Übertragungen dabei möglich sind. Es sollte beachtet werden, dass gerade Tätowierungen, Piercing der Ohrlochstechen in der Regel von medizinisch nicht geschultem Personal durchgeführt werden.

Beruflich bedingte HCV-Infektionen, beispielsweise im medizinischen Bereich, können zwar insbesondere beim invasiv tätigen medizinischen Personal nicht ausgeschlossen werden, jedoch scheint das Übertragungsrisiko im Vergleich zur akuten der chronischen Hepatitis B geringer zu sein. Es gibt Berichte, dass nach Nadelstichexposition über HCV-infizierte Patienten 2 bis 8% HCV Infektionen aufgetreten sind. Die Wahrscheinlichkeit einer HCV-Infektion nach Nadelstichverletzung lag in prospektiven Erhebungen bei ca. 2%. Mehrere internationale Studien haben gezeigt, dass die Durchseuchung unter Ärzten, Zahnärzten und sonstigen Beschäftigten im Gesundheitswesen nicht signifikant höher ist als die der Allgemeinbevölkerung. In einer Analyse, die 65 000 Beschäftigte im Gesundheitsdienst aus 16 Ländern umfasste, wiesen 1,8% HCV-Antikörper auf.

Was das Übertragungsrisiko von HCV durch medizinisches Personal auf Patienten angeht, so muss vermerkt werden, dass es in der wissenschaftlichen Literatur nur wenige Fallberichte gibt. Die Fälle betrafen Thoraxchirurgen, gynäkologische Operateure und Anästhesisten. Eine prinzipielle Risikobewertung einer HCV-Übertragung von infizierten medizinischen Mitarbeitern auf Patienten allein aus derartigen Fallberichten abzuleiten, wird dadurch erschwert, dass über 80% der HCV-Infektionen anikterisch verlaufen. Somit ist nach gegenwärtigem Kenntnisstand eine Aussage über das tatsächliche Risiko einer nosokomialen HCV-Übertragung erschwert, da in der Regel nur dann ein Zusammenhang z. B. zwischen einer Operation und einer Hepatitis hergestellt wird, wenn Krankheitssymptome auftreten. Tätigkeitseinschränkungen für HCV-Infizierte, insbesondere invasiv tätige Ärzte und Zahnärzte, haben sich natürlich daran zu orientieren, dass Übertragungen des HCV verhindert werden. In Deutschland versucht man derzeit Regelungen zu finden, die sich eng an nordamerikanische und britische Richtlinien anlehnen. Dies verlangt, dass für jeden konkreten Einzelfall durch ein Expertengremium, dem Ärzte differenter Fachgebiete angehören, geklärt wird, inwieweit Tätigkeitseinschränkungen notwendig sind.

Im Falle einer beruflichen HCV-Exposition (z. B. nach Nadelstichverletzungen) ist derzeit keine Postexpositionsprophylaxe angezeigt. Es empfiehlt sich aber, neben einer Nullprobe im Abstand von ca. vier Wochen nach Exposition über drei Monate auf HCV-RNA mittels einer Nukleinsäureamplifikationsmethode zu untersuchen. Zusätzlich ist auf HCV-Antikörper zu testen.

6. Blut und Blutprodukte (Blood and blood products)

Eine sehr hohe HCV-Prävalenz (50 - 90%) findet man in der Gruppe der Hämophilen, die multitransfundiert wurden bzw. über viele Jahre Blutprodukte erhielten. Die zur Substitution der fehlenden Gerinnungsfaktoren in der Vergangenheit ein gesetzte Präparate führten bis ca. 1985 zu einer beträchtlichen Zahl von HCV Infektionen. Bei über 80% der Patienten, die Präparate ohne Virusinaktivierung erhielten, ließen sich HCV-Antikörper nachweisen.

Als wichtigste präventive Maßnahme ist die Untersuchung von Blutspenden und Blutprodukten auf HCV-Antikörper und HCV-RNA bzw. die Verwendung virusinaktivierter Blutprodukte der gentechnologisch hergestellter Präparate anzusehen. Blut und Blutprodukte sind erheblich sicherer geworden. Eine weitere Optimierung der

Testmethoden und -strategien wird durchgeführt. Den noch sollten zelluläre Blutprodukte wie z. B. Erythrozyten- oder Thrombozytenpräparate nur nach strenger Indikationsstellung eingesetzt werden.

Bei i.v.-Drogenabhängigen (IVDUs) kommt es insbesondere durch die Benutzung derselben Nadel der Spritze durch verschiedene Personen (needle sharing) sehr schnell, d. h. meist schon einige Monate nach Beginn des Drogenkonsums zu einer HCV-Infektion. Weltweit sind zwischen 50 - 95% aller IVDUs mit dem Hepatitis C Virus infiziert. In den USA haben Studien ergeben, dass seit 1992 etwa zwei Drittel aller HCV-Neuinfektionen auf Drogengebraucher entfallen.

7. Molekulare Epidemiologie (Molecular epidemiology)

Aus der Sicht der molekularen Epidemiologie ist der Nachweis wichtig, dass sich das HCV in Genotypen und Subtypen differenzieren lässt, denn die Kenntnis der Verteilung solcher Genotypen/ Subtypen - sei es weltweit oder aber z. B. in bestimmten Risikogruppen - berücksichtigt auch evolutionäre Aspekte dieser Erkrankung. Durch die molekulare Charakterisierung von Hepatitis C Virus-'Isolaten' - in Europa, Amerika, Asien der Afrika - erhielt man in den letzten Jahren Detailinformationen zur genetischen Heterogenität des HCV. Aus der Kenntnis der verfügbaren kompletten Genomsequenzen lassen sich die Hepatitis-C-Viren in derzeit sechs Genotypen (mit den Ziffern 1 bis 6 bezeichnet) und eine Vielzahl von Geno-Subtypen (bezeichnet mit den Buchstaben a, b usw.) differenzieren.

Wir wissen heute, dass gewisse Genotypen wie 1, 2 und 3 eine breite weltweite Verteilung zeigen, während andere Genotypen wie 4, 5 und 6 in spezifisch begrenzten geografischen Regionen gefunden werden. So findet man in Westeuropa und Süd- und Nordamerika relativ häufig die Genotypen 1 - 3, während in Nord- und Zentralafrika Genotyp 4, in Vietnam und Thailand Genotyp 6 dominant sind.

Neben der geografischen Vorherrschaft bestimmter Genotypen/ Subtypen sind bestimmte Subtypen auch auffällig häufig in bestimmten Risikogruppen anzutreffen. So findet man überproportional häufig Genotyp 3a unter i.v.-Drogenabhängigen.

Insgesamt ist derzeit der Stellenwert einer Genotypisierung mehr in der epidemiologischen Information zu sehen, als in Verbindung mit Therapiekonzepten, auch wenn Genotyp 1-Infizierte auffallend schlechter auf eine Interferon/ Ribavirin-Therapie ansprechen als z.B. Genotyp 3-Infizierte.

Summary of the RKI points of view on prevention

Eine Schutzimpfung gegen Hepatitis C ist bisher nicht verfügbar. Der Nachweis von Anti-HCV-Antikörpern im Serum bedeutet keine protektive Immunität. In etwa 80 % der HCV-Antikörper-positiven Probanden ist mit der NAT HCV-Genom nachweisbar. Nicht beantwortet werden kann derzeit, inwieweit eine ausheilende Hepatitis C (kein HCV-Genom nachweisbar) eine bleibende Immunität hinterlässt.

Hepatitis C-infizierte Patienten, die serologisch keine Zeichen einer durchgemachten Hepatitis A- und Hepatitis B-Infektion aufweisen, sollten gegen diese beiden Viren geimpft werden, da eine Infektion mit diesen Viren bei bereits bestehender chronischer HCV-Infektion zu schwereren Krankheitsverläufen führt.

Besondere Aufmerksamkeit muss weiterhin der Risikogruppe der i.v. Drogenabhängigen gelten. Bemühungen, das gemeinsame Benutzen von Nadeln zu verhindern, sollten ebenso fortgesetzt werden wie die Propagierung des Kondomgebrauchs bei wechselnden Partnern. Medizinisches Personal sollte, entsprechend den Empfehlungen der 'Richtlinie für Krankenhaushygiene und Infektionsprävention', Anlage zu Ziffer 5.1 'Anforderungen der Hygiene an die Infektionsprävention bei übertragbaren Krankheiten', Vorsorge treffen für eine Vermeidung der HCV-Übertragung bei der Behandlung und Pflege von Patienten. In diesem Zusammenhang empfiehlt es sich, ähnliche Hygieneregeln zu beachten wie sie auch zur Verhütung einer HIV- oder HBV-Infektion empfohlen werden: Bei möglichem Kontakt zu virushaltigen Körperflüssigkeiten müssen Schutzhandschuhe getragen werden. Mundschutz und Schutzbrille sind zu benutzen, wenn virushaltige Aerosole entstehen können (z. B. bei der zahnärztlichen Behandlung). Scharfe oder spitze Gegenstände, die mit Blut oder anderen Körperflüssigkeiten in Berührung gekommen sind, müssen sicher entsorgt werden.

Als wichtigste präventive Maßnahme ist die Untersuchung von Blutspenden und Blutprodukten auf Anti-HCV-Antikörper und HCV-RNA bzw. die Verwendung virusinaktivierter Blutprodukte oder gentechnologisch hergestellter Präparate anzusehen. Blut und Blutprodukte sind erheblich sicherer geworden. Eine weitere Optimierung der Testmethoden und -strategien wird durchgeführt. Dennoch sollten zelluläre Blutprodukte wie z. B. Erythrozyten- oder Thrombozytenpräparate nur nach strenger Indikationsstellung eingesetzt werden.

Die Zulassung nach einer Erkrankung an Hepatitis C zu einer Gemeinschaftseinrichtung (z. B. Kindereinrichtung, Schule) kann erfolgen, sobald das Allgemeinbefinden den Besuch der Einrichtung wieder erlaubt, unabhängig davon ob der Erreger zu diesem Zeitpunkt im Blut noch nachweisbar ist. Sinngemäß gilt dies auch für HCV-Träger (Carrier) unter den Beschäftigten oder den Kindern einer Einrichtung. Eine Ausnahme von dieser Regel stellen nur Personen mit ungewöhnlich aggressivem Verhalten (Beißen), einer Blutungsneigung oder einer generalisierten Dermatitis dar. In diesen Fällen muss die Entscheidung über die Zulassung zu einer Gemeinschaftseinrichtung durch das Gesundheitsamt individuell getroffen werden.

Deutsches Hepatitis C Forum (Hepatitis C Forum International)

1. Hepatitis C is a common infection with variable course which can lead to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The course of illness may be adversely affected by various factors, especially alcohol consumption. Therefore,

more than one drink per day is strongly discouraged in patients with Hepatitis C and abstinence from alcohol is recommended.

2. EIA-2 should be the initial test for the diagnosis of hepatitis C. In low-risk populations, supplemental RIBA-2 and/or HCV RNA PCR testing should be performed. In patients with clinical findings of liver disease, qualitative HCV RNA PCR can be used for confirmation.
3. Liver biopsy is indicated when histologic findings will assist decision making regarding patient management. In patients who are not to be treated with antiviral therapy initially, liver biopsy can be repeated to assess disease progression.
4. HCV genotyping may provide useful prognostic information, but at present must be considered a research tool.
5. Because of assay variability, HCV RNA PCR testing must be interpreted cautiously. Rigorous proficiency testing of clinical laboratories performing this assay is recommended.
6. Currently available therapy for chronic hepatitis C is clearly indicated for patients who have persistently abnormal ALT (>6 months), a positive HCV RNA, and liver biopsy evidence of septal fibrosis and/or moderate to severe necroinflammatory changes. Patients with milder histological disease, compensated cirrhosis, or age under 18 or over 60 should be managed on an individual basis or in the context of clinical trials. Patients with decompensated cirrhosis should not be treated with interferon, but should be considered for liver transplantation. Patients with persistently normal ALT should not be treated outside of clinical trials. Treatment with interferon is contraindicated in patients with major depressive illness, cytopenia, active alcohol use or illicit drug use, hyperthyroidism, renal transplantation, or autoimmune disease. Therapy should not be limited by mode of acquisition, risk group, HIV status, HCV RNA levels, or genotype.
7. Since 12 month regimens with interferon are more successful in achieving sustained responses, initial therapy with interferon alfa (or its equivalent) should be 3 million units thrice weekly subcutaneously for 12 months.
8. Nonresponders to interferon therapy can be identified early by assessing the serum ALT level and presence of serum HCV RNA after 3 months of therapy. If the ALT level remains abnormal and the serum HCV RNA remains detectable, interferon therapy should be stopped, as further therapy is unlikely to produce a response. Nonresponders should not receive further therapy with interferon alone, but should be considered for combination therapy or enrollment in investigational protocols.
9. Patients who relapse should receive retreatment with their original therapy or combination interferon-ribavirin therapy, preferably in a clinical trial.

10. Patient support groups should be encouraged.
11. Hepatitis A and B vaccination is recommended for all HCV positive patients.
12. In health care settings, adherence to Universal precautions for the protection medical personnel and patients is essential.
13. HCV-positive patients should refrain from donating blood or semen. Strategies should be developed to identify prospective blood donors with any prior history of IVDU. Such individuals must be deferred from donating blood. In some situations, the use of organs and tissues from HCV-positive individuals may be considered.
14. To avoid transmission in persons with multiple sexual partners, safe sexual practices, including the use of latex condoms, should be strongly encouraged. In monogamous long-term relationships transmission is of low likelihood and therefore no changes in sexual practices are recommended. In such cases an individual's decision to modify sexual practices should follow a discussion of the potential risks of transmission. It is recommended that sexual partners of infected patients should be tested for HCV antibody.
15. In households with an HCV-positive member, the sharing of razors and toothbrushes should be avoided. Covering of open wounds is recommended. It is not necessary to avoid close contact with family members or to avoid the sharing of meals or utensils.
16. Pregnancy is not contraindicated in HCV-infected individuals. Perinatal transmission from mother to baby occurs in less than 6% of instances. Breast feeding is considered safe. Babies born to HCV-positive mothers should be tested for anti-HCV at 1 year.
17. Needle exchange programs are of proven benefit in reducing parenterally transmitted diseases. Expansion of such programs should be considered in an effort to reduce the rate of transmission of hepatitis C.

Hepatitis C Manual

Hepatitis C is a chronic disease and lifestyle modifications are important to improve the patient's sense of well being, to give the patient a feeling of control over the disease process and to prevent further hepatic damage through other agents.

1. Alcohol and hepatitis C

Alcohol has an additive effect on liver inflammation, increasing the progress to fibrosis though not to hepatocellular carcinoma. Patients with HCV often find they cannot tolerate alcohol. It may cause an exacerbation of their symptoms, fatigue or liver pain or it may make them nauseated. It is important to explore the patient's alcohol intake and if necessary refer them to a drug and alcohol counsellor.

2. Dietary advice

The liver plays a central role in metabolism and nutrition. Liver dysfunction gives rise to a variety of nutrient imbalances. The degree of deficiency is related to the severity of the disease.

Hepatitis C may cause gastrointestinal symptoms such as loss of appetite, nausea, reflux or diarrhoea, which may contribute to nutrient deficiency. Fatty foods often increase gastrointestinal symptoms. Diet should be tailored to the patient's needs and the severity of the disease.

Reduce alcohol intake to 1 standard drink per day. If this is impossible, use low alcohol drinks and avoid binge drinking.

3. Dietary guidelines

3.1. Maintain and improve nutritional status through the provision of adequate energy and nutrients:

- high complex carbohydrate intake;
- if fat is reduced substitute other energy food.

3.2. Promote liver regeneration

- high protein intake for liver repair and to replenish protein stores if malnourished.

3.3. Prevent and correct weight loss.

3.4. Reduce gastrointestinal symptoms

- small frequent meals;
- adequate fluids;
- avoid spicy foods;
- high energy drinks if poor intake;
- reduce smoking;
- avoid fatty and oily foods.

3.5. Vitamin supplements

- the most common deficiencies are folate, B12 and thiamine;
- fat malabsorption reduces A, D & E;
- iron deficiency may be present in women.

3.6. Protein restriction in hepatic encephalopathy.

4. Prescribed drugs

Drugs metabolised or known to be toxic to the liver may not be appropriate in hep C positive patients.

5. Hepatitis A and B vaccination

Should be offered to reduce the risk of further liver damage.

6. Stress

Stress often causes an increase in symptoms in patients with HCV. Patients should be encouraged to improve their stress management.

7. Prevention of spread

- Do not donate blood or other tissue;
- Do not share needles or any other injecting equipment;
- Advise health care workers and dentists of HCV status;
- Do not share toothbrushes, razors and other personal articles;
- Wipe up blood spills with bleach and paper towels;
- Cover cuts and wounds with waterproof dressings;
- Dispose of blood stained articles in a plastic bag before placing in the garbage;
- Practice safe sex avoiding blood contact during intercourse (during menstruation, with coexistent STDs or traumatic intercourse). Condoms should always be used for anal intercourse. There is no evidence that HCV is transmitted by kissing.

8. Counselling IDUs

Studies suggest that after one year of injecting drug use, 40% are hepatitis C antibody positive and after a few years 80-90% of users are positive. Counselling IDUs about hepatitis C is vital, not only for their own sakes, but to prevent the further spread of this disease which is already a major public health problem

8.1. Avoidance of illicit drug use

While this is the preferred option it may not be the choice of the patient. Advice should be given about drug and alcohol counselling, and detox and rehabilitation facilities. Information about local methadone clinics and prescribers should be offered.

8.2. Change to routes other than parenteral

Although the same dose may have a slower and reduced effect, smoking, snorting or taking drugs orally carries a much lower risk of infection.

8.3. Reduce risks if using intravenously

Needles, syringes and other users' equipment should not be shared. This includes avoiding sharing needles, syringes, swabs, filters, spoons, water, utensils and tourniquets. Information about local needle exchanges and safe disposal of needles should be offered.

8.4. If sharing needles, reduce risk by cleaning in bleach

This is not very effective at killing HCV but does reduce the risk of transmission.

8.5. Sharing needles with someone else with hepatitis C is not safe

Being HCV antibody positive does not protect a patient from reinfection. A person who has contacted HCV and does not have active disease may become infected with the same or another genotype. A person with active disease may become coinfecting by another genotype and develop more severe disease. Different genotypes are associated with varying severity of disease, infectivity and response to antiviral therapy.

8.6. Safe disposal of needles

This is vital to the prevention of spread of HCV.

National Institute for Clinical Excellence (NICE)

NICE has issued a 'Guidance on the use of ribavirin and interferon alpha for hepatitis C' in October 2000. Selected chapters are reproduced below.

1. Guidance

- 1.1 Interferon alpha and ribavirin as combination therapy is recommended for the treatment of moderate to severe hepatitis C (defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation), at standard doses for patients over the age of 18 years as follows:
 - 1.1.1 All treatment-naïve patients (that is, those who have not previously had interferon alpha monotherapy or combination therapy) and all patients who have been treated with interferon alpha monotherapy, and have had some response but have since relapsed. Such treatment should be continued for 6 months for all patients.
 - 1.1.2 A further 6 months combination therapy is recommended only for patients infected with hepatitis C virus of genotype 1, who respond to therapy by becoming clear of circulating viral RNA as detected by polymerase chain reaction (PCR) in the first 6 months.
 - 1.1.3 Those in whom liver biopsy poses a substantially increased risk (such as patients with haemophilia) may be treated on clinical grounds without histology.
- 1.2 Therapy involving either or both of these drugs is not in general recommended for patients who are continuing intravenous drug users. Only where the prescribing clinician can be reliably assured that re-infection, compliance and drug interactions pose no problems should patients in this group be considered for combination therapy. Former intravenous drug users including those on oral maintenance therapy need not be excluded from therapy.
- 1.3 Therapy involving either or both of these drugs is not in general recommended for patients who are heavy users of alcohol, because of an increased risk of exacerbation of liver damage.
- 1.4 There is insufficient evidence for making recommendations on combination therapy for patients less than 18 years of age. There is also insufficient evidence for making recommendations for using combination therapy after liver transplantation.

- 1.5 Interferon alpha monotherapy should be considered only when ribavirin is contraindicated or not tolerated. The recently licensed pegylated interferon monotherapy has not been considered in this guidance.
- 1.6 These recommendations are consistent with the European Association of the Study of the Liver (EASL) guidelines with the exception that (see para. 1.1.1), those who relapse after initially successful treatment by monotherapy are recommended for 6 months of combination therapy without the necessity of a viral load test after three months.

2. Clinical need and practice

- 2.1 Chronic hepatitis C is a disease of the liver caused by the hepatitis C virus (HCV). Six major genetic types of the hepatitis C virus have been found; these are of different virulence, and at least 40% are genotype 1; of the remainder the majority are genotypes 2 and 3. Generally the virus is transmitted parenterally but the natural history of the disease is not completely understood. It is acquired commonly through intravenous drug use and the sharing of needles. It was also spread through blood transfusion prior to the introduction of screening in 1991, as well as through blood products before the viral inactivation programme in the mid-1980s. There is a small risk of HCV infection associated with tattooing, electrolysis, ear piercing and acupuncture. Infection through sexual intercourse can also occur. There is a transmission rate of about 6% from mother to child if the mother is an HCV carrier. Concomitant HIV infection is thought to increase the risk of transmission.
- 2.2 After exposure to the virus, patients are often asymptomatic, however about 20% will develop acute hepatitis, some of whom will experience malaise, weakness and anorexia. Up to 85% of those exposed fail to clear the virus and go on to develop chronic hepatitis C. The ability of patients to rid themselves of the virus is partly related to the genotype of the virus, which affects the ability of the immune system to mount an effective response. The rate of progression of the disease is slow and variable, over 20-50 years. About 20-30% of those infected develop advanced liver disease or cirrhosis within 20 years and a small percentage of these develop hepatocellular carcinoma. A third of all those infected may never progress to cirrhosis or will not progress for at least 50 years. Patients with cirrhosis develop severe symptoms and complications. Patients with end stage liver disease or hepatocellular carcinoma may require liver transplantation.
- 2.3 Many individuals with HCV infection do not display symptoms. However, non-specific symptoms including fatigue, irritability, nausea, muscle ache, anorexia, abdominal discomfort, and right upper quadrant pain have been reported even in the absence of secondary pathology. If cirrhosis develops, patients may suffer severe symptoms and complications.
- 2.4 Estimates of prevalence for hepatitis C in England and Wales vary considerably, from 200,000 to 400,000. There is also great variation in prevalence between certain subgroups of the population: 0.04% in blood donors, 0.4% in antenatal attenders (in

London), 1% in genito-urinary clinic attenders and up to 50% in intravenous drug users.

3. The technology

3.1 The primary aims of treatment of patients with chronic hepatitis C are to achieve acceptable alanine aminotransferase (ALT) levels and clearance of hepatitis C virus (defined as undetectable HCV-RNA in the serum), with both sustained for at least 6 months after treatment cessation; in order to result in an improved quality of life for patients, a reduced risk of cirrhosis and hepatocellular carcinoma.

3.2 Until recently, interferon alpha was the only licensed treatment for chronic hepatitis C. The precise antiviral mode of action of interferon is unknown. However, it appears to alter host cell metabolism. There are several meta-analyses that review the effectiveness of interferon alpha in chronic hepatitis C. Approximately 47% of patients respond when treated with interferon alpha alone (monotherapy). More than half of these relapse within six months of stopping treatment. Treatment with interferon alpha is usually at the dose of 3 million units three times per week by subcutaneous injection. Injections may be administered by clinical staff or by the patient after adequate training. Patients who respond usually do so within three to four months, but some have had to continue with this dose of interferon alpha for 12 months.

3.3 Ribavirin (Rebetol, Schering-Plough) is currently licensed for use in combination with interferon alpha 2a (Roferon A, Hoffmann La Roche) and interferon alpha 2b (Viraferon, Schering Plough) for treatment of HCV in:

3.3.1 adult patients with histologically-proven, previously-untreated hepatitis C, without liver decompensation, who are positive for serum HCV-RNA and who have fibrosis or high inflammatory activity and

3.3.2 adult patients with chronic hepatitis C who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha but subsequently relapsed

3.4 Ribavirin is a nucleoside analogue with a broad spectrum of antiviral activity against RNA viruses. It is administered orally at a dose of either 1000mg (for patients weighing less than 75kg) per day, or 1200 mg (for patients weighing over 75kg), divided into 2 doses. Regular monitoring of full blood count to detect haemolytic anaemia is required in order to judge whether to reduce or cease ribavirin treatment.

3.5 Adverse effects related to combination therapy are similar in type and frequency to those of interferon alpha monotherapy and include influenza-like symptoms (fatigue, headache, fever), decreases in haematological parameters (anaemia, neutrophil count, white blood cell count, platelet), gastrointestinal complaints (anorexia, nausea), dermatological symptoms (alopecia), psychiatric disturbances (depression, anxiety) and hypo- or hyperthyroidism.

- 3.6 For patients considered for combination therapy, standard haematological tests and blood chemistry (i.e. full blood count and differential platelet count, liver function tests, uric acid, serum bilirubin and serum creatinine) are necessary for all patients before initiating therapy. Liver biopsy should be undertaken, where there are no increased risks, in order to assess liver scarring and necro-inflammation according to an accepted severity scale such as the Knodell. This is important in determining the need for treatment in those with significant fibrosis and necro-inflammation. Patients should be seen weekly for the first four weeks, and then monthly for 6 months, to check for haemolysis and changes in thyroid activity. The genotype of the hepatitis C virus with which the patient is infected should also be determined for all candidates for combination therapy.
- 3.7 A four-week cycle of interferon alpha at 3 million units 3 times a week costs around £200, and four weeks of ribavirin costs about £550. Six months of combination therapy costs around £4800 (excluding monitoring, counselling and other infrastructure costs). Genotype testing, viral load measures and other pre-treatment services are estimated to cost a further £200 per patient.
- 3.8 In terms of other options for the treatment of chronic hepatitis C, a longer acting version of interferon alpha, pegylated interferon, is currently being evaluated in dose-ranging studies in combination with ribavirin. Preliminary results indicate that it has a similar tolerance profile to current combination therapy. A licence has been granted to Schering Plough by the EMEA for monotherapy with ViraferonPeg and a licence is currently pending to Hoffmann La Roche for monotherapy with Pegasys.

4. Evidence

4.1 Clinical effectiveness

- 4.1.1 In total, nineteen published RCTs involving 3765 patients and two meta analyses were identified that compared ribavirin and interferon alpha ('combination therapy') versus interferon alpha alone ('monotherapy').
- 4.1.2 Since it is not possible in the short term to measure directly the effectiveness of treatment in reducing progression to cirrhosis and hepatocellular carcinoma, three surrogate markers have been used in trials: hepatic histology; circulating virological loss of hepatitis C virus-RNA (by quantitative polymerase chain reaction (PCR)); and alanine aminotransferase (ALT) levels.
- 4.1.3 The single most useful factor in predicting effectiveness of combination therapy is viral genotype. Results from the pooling of two multicentre trials (involving 1744 individual patients) show that 67% of patients infected with hepatitis C virus (HCV) other than genotype 1 respond on a sustained basis to combination treatment within 24 weeks. There is no further gain from a further 24 weeks of treatment. Only 17% of those infected with HCV of genotype 1 respond on a sustained basis after 24 weeks of combination treatment; 28% have a sustained

response after 48 weeks' treatment. Infection with genotypes 4, 5 and 6 is relatively rare in Britain, and therefore occurs infrequently in randomised trials.

- 4.1.4 Other patient factors which favour eradication of HCV are baseline viral load of less than 3.5 million copies/ml, favourable minimal hepatic histological abnormality on liver biopsy (i.e. no or minimal portal fibrosis), female gender, and age less than 40 years. However, no tests of interaction between these four factors or viral genotype appear to have been undertaken, so that any differential effect of combination therapy has not been addressed.
- 4.1.5 The effectiveness of combination therapy compared with monotherapy in patients being treated with interferon alpha for the first time, can be judged from the pooled results of two multicentre trials (see 4.1.3 above). The sustained virological responses rates were 33% (95% CI 29-37%) for patients on combination therapy compared with 6% (95% CI 3-10%) on monotherapy, based on 24 weeks treatment. The corresponding 48-week results were 41% (CI 36-45%) for combination therapy compared with 16% (CI 13-19%) for monotherapy. Biopsy and ALT results were consistent with a benefit of combination therapy in these patients.
- 4.1.6 The effectiveness of combination therapy in comparison with interferon monotherapy for relapsed patients (who responded to interferon alone but relapsed in the 6 months following initial treatment) was examined in a trial of 345 patients. Sustained virological response rates were 49% (95% CI 42-57%) on combination therapy compared with 5% (95% CI 2-9%) on monotherapy, for 24 weeks treatment. Biopsy and ALT results were consistent, with a benefit of combination therapy in relapsed patients.
- 4.1.7 The trials indicate that discontinuation of treatment (10-20%) is more frequent for combination therapy than for monotherapy. The most common reason either for study withdrawal or for dose reduction for combination therapy was related to haematological side effects. Treatment with combination therapy is frequently unpleasant and this may affect compliance.
- 4.1.8 Treatment of people who continue to use drugs intravenously is often not indicated due to the high probability of re-infection, presumed likelihood of relatively high levels of non-compliance and the possibility of drug interactions. Cessation of intravenous drug use before starting antiviral treatment is therefore important. Combination therapy is not contra-indicated for former intravenous drug users whose drug use has been stabilized on oral methadone or other products such as buprenorphine.
- 4.1.9 Evidence is currently lacking on the treatment of patients with mild/minimal changes on liver biopsy. The current consensus is that treatment is not necessary, though evidence as yet unpublished suggests that this strategy may need formal review.

- 4.1.10 Treatment of undecompensated cirrhosis with combination therapy appears to be much more successful than with monotherapy in which sustained response is very low. Treatment is more hazardous if the cirrhosis is decompensated and so is contra-indicated.
- 4.1.11 Evidence on whether non-responders to monotherapy respond to combination therapy is sparse and equivocal. Further research is necessary to determine whether it is either effective or cost-effective to treat this group.

4.2 Cost effectiveness

- 4.2.1 There have been a number of economic evaluations of the cost effectiveness of combination versus monotherapy.
- 4.2.2 For interferon alpha naïve patients, the incremental cost/QALY gained from treatment with combination therapy for 6 months in comparison with monotherapy has been estimated to be £7,000. For patients who have relapsed after a previous course of interferon alpha, the incremental discounted cost/QALY gained from 6 months of combination therapy compared with monotherapy has been estimated to be £3,050. Recent results comparing 6 months of combination therapy with 12 months of monotherapy show a cost per discounted QALY of about \$US3,500 (£2,500) overall, the highest subclass figure being \$US11,600 (£8,200) for genotype 1.
- 4.2.3 The incremental cost/QALY of treating for an additional six months (i.e. from 6 to 12 months) with combination therapy has been estimated to range from £5,000 to £36,000. Patients with genotype 1 who take longer to respond to treatment are a relatively cost-effective sub-group to treat for this additional period, but there is no additional benefit from the extra 6 months of treatment for genotypes 2 and 3. (While not all discounting of QALYs has been performed at the UK Treasury standard of 6% for costs and 1.5% for benefits, the effect is to make the estimates somewhat lower than appear above.)

5. Implications for the NHS

- 5.1 The total budget impact of combination therapy depends on a number of factors: prevalence, proportion of patients diagnosed, proportion of these who attend for assessment, and proportion considered suitable for treatment. If the prevalence of chronic hepatitis C is 0.4%, if a quarter of these are diagnosed, if half of those diagnosed are under specialist care, if half of these have had a biopsy, and if a half of those biopsied are treated, then there will be about 7,000 patients in England and Wales treated in the first instance. Assuming that treatment of these patients is spread out over three years, that all receive 6 months' treatment and two-thirds receive 12 months' treatment, the drug cost would amount to about £55 million, or about £18 million per year. Testing (including viral genotyping), monitoring (including viral load tests) and counselling will need to be substantially increased above present levels, and their costs would be in addition to this sum. Moreover, as

knowledge of the disease and its treatment becomes more widespread, it is also likely that more people than otherwise will be diagnosed and will seek treatment. However, significant costs of treatment downstream from liver-related conditions, including transplantations, together with drug costs for those already on combination therapy, must be subtracted. In the longer run, when the "backlog" of cases from a number of years has been cleared, and assuming an incidence rate of 10% of the prevalence (i.e. 0.04%), the annual continuing drug cost would be about £5 million. However, it is most likely that rates of diagnosis, referral to specialists, biopsy and acceptance of the therapy will all increase, so this estimate of annual costs after three years is likely to be an underestimate.

- 5.2 The importance of ready access to appropriate health care infrastructure, including viral genotyping and other laboratory testing, and adequate counselling, particularly about the side effects of treatment, is recognised. Confidential HCV testing and counselling should be made available whether or not treatment is initiated.
- 5.3 While the recommended treatments should all be performed as a specialist activity in hospital, and therefore should have little implication for Primary Care workload, prescribing and budgets, it is nevertheless likely that there may be a transfer of activities to primary care, particularly in counselling, in which staff may require additional education and training.

6. Further research

- 6.1 The prognostic value of monitoring viral load at one and three months with the aim of reducing the length of therapy for those patients whose viral load becomes undetectable should be investigated further.
- 6.2 Biopsy rates in diagnosed HCV carriers should be audited.
- 6.3 The largest single identifiable group of those infected with HCV is that of intravenous drug users. The majority of clinical trials performed on this technology have omitted this group of patients. Research related specifically to their treatment is therefore also needed.
- 6.4 Further research is also required to determine whether combination treatment of mild to moderate HCV patients and asymptomatic HCV carriers is clinically effective and cost-effective.
- 6.5 For patients who have not responded to interferon alpha monotherapy, research should be initiated to determine whether they respond to newer forms of therapy.

National Hepatitis C Resource Centre

It was decided in the planning stage that if the Mainliners 6th International Hepatitis C Conference, Lisbon, February 7-8, 2002, made recommendations which were endorsed by delegates, that this could be a powerful tool not only to assist in information dissemination, but also to influence policy development cross Europe. The Chairperson of each of the main streams of the Conference was asked to summarise the central points and produce key recommendations. These recommendations were presented back to the delegates at the end of the conference for agreement and there was concurrence that recommendations did accurately reflect events. European governments should consider the recommendations at local and national level when developing and implementing future hepatitis C strategies.

The recommendations will form the basis of a review at the 7th International Conference as a means of gauging progress across Europe. Please note that these recommendations are the result of the input by all the speakers and delegates at the conference, and do not necessarily represent the views of Mainliners or the National Hepatitis C Resource Centre.

1. Therapy

1.1. Therapy for patients with genotypes 2/3 should be biopsy independent

There is overwhelming evidence now indicating that genotypes 2/3 respond very well to therapy. Liver biopsy has been used to decide whether therapy is warranted or not. It is therefore recommended that consideration be given to changing the guidelines for patients with genotypes 2/3, such that therapy is received regardless of biopsy findings.

1.2. Guidelines should be widened to include more diverse patient groups

At present guidelines suggest that continued IVD users should not be treated. Chaotic life style, depressed pre-morbid state have all been used as reasons for not treating. IVD use is now the single most important risk for HCV transmission and will continue to be. By ignoring this group and the prison population, another reservoir for infection, policies are missing the very groups who, if treated with adequate support systems, will benefit the most and ultimately aid in the reduction of onward transmission to other groups. The conference recommended that Guidelines should be widened to include more diverse patient groups.

1.3. Patients must be involved in decision making processes at all levels

Each patient is an individual with individual needs and only those living with HCV can fully appreciate the burden of this disease. If adopted interventions are to be relevant and sensitive, personally, socially and culturally, decisions that influence the management of HCV should reflect the views of those living with HCV. The conference thus recommended that patients must be involved in decision making processes at all levels.

2. Prevention

2.1. Consistent, high-quality needle exchange programmes

The standards of practice within needle exchange schemes are variable both within and between EU states. While it is right that we campaign for increased provision of services, it is also vital that we maximise the quality and value for money of existing needle exchange services in reducing needle-sharing and related HCV risk behaviours by developing and working to agreed standards of good practice. With specific reference to low-threshold access to antibody testing, the importance of ensuring "informed consent" within all services was particularly highlighted. Promotion of up-to-date, evidence-based pre- and post-test counselling protocols was proposed as a way to ensure this.

It was noted that quality standards within needle exchange are also likely to relate to other associated activities such as overdose prevention. Ensuring that this happens is the responsibility of everyone from practitioners and expert needle exchange practice groups to policy makers.

2.2. Needle exchange provision must be monitored and coverage optimised

There is evidence to suggest that coverage of needle exchange in the UK (rates of provision of injecting equipment per injector per day) and HCV prevalence may be related. Although existing EU data on coverage are poor they suggest that coverage is insufficient in most countries. Valuable efforts are being made to develop these by the EMCDDA. It is important to support such efforts to understand the coverage in different EU states and the way this relates to HCV prevalence and prevention. This may become a valuable lobbying point for promoting equitable, effective and sufficient needle exchange provision across Europe.

2.3. Prisoners have the right to equivalent service provision as other members of society

It was widely acknowledged that prisoners are entitled to equivalent standards of healthcare as members of the general community. Despite some progress - notably the recent requirement in Spain that all prisoners should have access to needle exchange from the beginning of 2002 - this is still far short of happening in most EU states. Prison is an important risk environment for HCV acquisition and it is essential to continue efforts to lobby for HCV prevention work that compares with that for injectors in the general community. It was suggested that prisoners who can evidence that they have acquired HCV in prison, and where prevention measures were deficient in this way, may have legal redress against the relevant responsible authority.

2.4. The modest risk of sharing cocaine sniffing paraphernalia is reduced

There is limited evidence that sharing cocaine sniffing paraphernalia may constitute a low risk for HCV transmission and that risk behaviours that could, in theory, transmit HCV between cocaine sniffers are also common among some sub-groups of drug users such as more drug-involved 'clubbers'. Without distracting people from the importance of avoiding needle sharing - which is overwhelmingly the most important, persisting risk behaviour and target for prevention efforts - opportunities to economically raise awareness and prevent this easily avoidable risk should be sought and taken.

3. Patient involvement

3.1. Patient groups should have professional input and should be empowered to influence policy

Evidence shown from the U.K. and across Europe suggests that there is a need for education for health care professionals to enable them to assist in the facilitation of self help support groups for different client groups affected by HCV. This would in turn benefit those HCV individuals who wish to be involved in enabling self-help groups to become service providers, and educating group members on their rights to assist them to influence policy.

3.2. PCTs should provide resources to facilitate disease self management groups

Although the Department of Health in the U.K. is now channelling funds into Disease Self Management, delegates had a number of questions around this issue, one of these being; where should the responsibility lie for providing resources to allow HCV individuals to have access to this service? There was a unanimous decision that the primary health care trust should be encouraging health care professionals to empower HCV patients to effectively self manage HCV. This would suggest that this is an area that needs to be developed to benefit both those who are living with and those who are working with HCV.

3.3. Public enquiry into contamination of blood products should be held to prevent any repeat

The successful lessons learned from the campaigning carried out by the Haemophilia Society should be used to benefit those who had been infected not only by HIV but also HCV. Campaigning should be on-going to make sure that the human rights of those who have received contaminated blood products are recognized and not ignored.

3.4. Nationwide access to multidisciplinary specialists to assess patient as well as health needs

It has emerged from those who are living with co-infection of both HIV and HCV, that there are numerous difficulties faced by them with regards to their health care. One of the main difficulties faced is when a number of clinical specialists are involved in their care, such as Infectious Disease Consultant, Haematologist, Hepatologist, and G.U Consultant. Patients are not only coping with stress of living with two blood borne viruses, but their quality of life is also affected due to the fact that they are having to spend a lot of time at different hospital appointments.

4. Social care

4.1. Establish a structure for expanding advocacy across Europe

The success of the UK Assembly on Hepatitis C should provide the catalyst for greater co-operation among advocacy groups across Europe. It is clear that advocacy groups provide not just the front line view of what is the actual impact on the lives of those living with the virus, but are increasingly providing the political will to bring about changes. The establishment of a European structure based on the need to share lesson and experiences will become more urgent as we move toward a global strategy for improving social care.

4.2. Standardise good practice on education and information

It is well established that where there are a range of conflicting practices, information and education material this bring difficulties in terms of effective social care. Key institutions involved in advice on social care needs to agree on a minimum standard of training and education to health care professionals which will result in patients having the confidence to know that regardless of the starting point and modes of transmission, discrimination and stigmatisation will have no impact on their basic level of treatment and care.

4.3. Build alliances with all blood borne virus groups to eliminate discrimination

There is already a strong, well established, politicised HIV lobbying movement, originating in self-help in the early '80's. Currently, there is a high profile UK-wide campaign highlighting the issues of stigma and prejudice against people living with HIV. The Australian and UK Hepatitis C Discrimination hearings have both shown widespread discrimination, from healthcare workers, to dentists, to leisure centres and family and friends. There remains little public awareness around hepatitis C, and by joining forces with other blood-borne viruses, we are not only working towards reducing stigma attached to a specific condition, but we are also utilizing the knowledge and resources that already exist.

4.4. Establish a framework for co-ordinated application of pressure

There should be a commitment to the continual formal gathering of evidence, citing cases of discrimination, utilising existing mechanisms, such as one-to-one interactions, user groups etc. This evidence should be fed into a central point via forums such as Drug Action Teams (DATs), where a framework should exist in terms of guidance, ways of taking it forward and instigating change.

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Annex*

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* This article is not enclosed in the pdf version of the pre-meeting document. Please consult the WHO web site at <http://www.who.int/emc/diseases/hepatiti/jvh139.pdf> .