

Hepatitis C

Daniel Lavanchy MD, Pilar Gavinio MD

D Lavanchy, P Gavinio. Hepatitis C. Can J Gastroenterol 2000;14(Suppl B):67B-76B. Hepatitis C has been identified as the most common cause of post-transfusion hepatitis worldwide, accounting for approximately 90% of this disease in Japan, the United States and Western Europe. Hepatitis C is a major global public health problem. New infections continue to occur, and the source of infection includes transfusion of blood or blood products from unscreened donors; transfusion of blood products that have not undergone viral inactivation; parenteral exposure to blood through use of contaminated and inadequately sterilized instruments and needles used in medical, dental and 'traditional' medicine; procedures such as hemodialysis; high risk sexual practices; household or sexual contacts of hepatitis C virus (HCV)-infected persons; and infants of HCV-infected mothers. In many countries, the relative contribution of the various sources of infection has not been defined with population-based epidemiological studies. Such studies are necessary to enable countries to prioritize their preventive measures and to make the most appropriate use of available resources. Given the substantial morbidity and mortality attributable to HCV-related chronic liver disease, each country, irrespective of economic status, should develop a plan of HCV-related public health activities for the prevention of new HCV infections and the treatment of established chronic infections.

Key Words: *Hepatitis C; Hepatitis C virus prevention; Public health; Review*

L'hépatite C

RÉSUMÉ : L'hépatite C est reconnue comme la cause la plus courante d'hépatite post-transfusionnelle dans le monde entier, représentant environ 90 % des cas de cette maladie au Japon, aux États-Unis et en Europe de l'Ouest. L'hépatite C est un problème majeur et global de santé publique. De nouveaux cas d'infection continuent à apparaître, et les sources d'infection comprennent les transfusions de sang ou de produits sanguins provenant de donneurs non dépistés, les transfusions de produits sanguins qui n'ont pas été soumis à une inactivation virale; une exposition parentérale au sang par le biais de l'utilisation d'instruments et d'aiguilles contaminés et insuffisamment stérilisés qui sont utilisés en médecine « traditionnelle », allopathique et dentaire ; de techniques comme l'hémodialyse, de pratiques sexuelles à risque élevé, des contacts sexuels ou de l'entourage de personnes contaminées par le virus de l'hépatite C (HCV) et des enfants dont les mères sont infectées par le HCV. Dans de nombreux pays, la contribution relative des différentes sources d'infection n'a pas été définie par des études épidémiologiques basées dans la population. Ce type d'études est nécessaire pour permettre aux pays d'établir des priorités dans leurs mesures préventives et pour utiliser au mieux les ressources disponibles. Étant donné la morbidité et la mortalité substantielles liées à l'hépatite chronique, chaque pays, indépendamment de son statut économique, devrait développer un plan d'activités de santé publique reliées au virus de l'hépatite C pour la prévention des nouvelles infections à HCV et pour le traitement des infections chroniques avérées.

Hepatitis C is a viral infection of the liver that was referred to as parenterally transmitted or 'non-A, non-B' hepatitis until identification of the causative agent in 1989 (1). Since the discovery and characterization of the hepatitis C virus (HCV), the understanding of its primary role in post-transfusion hepatitis and its tendency to induce persistent infection has been widely documented. Viral hepatitis C is a major global public health problem. Accurate global figures regarding prevalence, incidence, and socioeconomic burden of acute and chronic hepatitis C are still lacking from many countries. In areas of high endemicity for viral hepatitis, acute HCV infection appears to be the cause of a significant proportion of acute liver disease (Table 1). New infections continue to occur, likely due to the use of un-

screened blood transfusions and failure to sterilize medical equipment adequately. Implementation of appropriate primary prevention measures could reverse these trends (2-4).

NATURAL HISTORY OF HCV INFECTION

HCV infection can be detected by tests screening for anti-HCV-specific antibodies and viral genomic RNA in serum. Acute HCV infection in general is relatively mild, with only 20% to 30% of infected persons developing symptoms or clinically evident acute hepatitis C. However, 70% to 80% of acute HCV infections do not resolve and result in a persistent viral infection (5-8).

The late sequelae of chronic HCV infection result in serious public health consequences that include chronic hepati-

World Health Organization (WHO), Communicable Diseases Surveillance and Response, Geneva, Switzerland

Correspondence and reprints: Dr D Lavanchy, World Health Organization (WHO), Communicable Diseases Surveillance and Response, CH-1211 Geneva, Switzerland. Telephone +41-22-791-2656, fax +41-22-791-4878, email lavanchyd@who.int

Received for publication September 16, 1999. Accepted September 27, 1999

TABLE 1
Prevalence rates for hepatitis C virus (HCV), based on published reports by country/area (1999)

Country	HCV rate (%)	Country	HCV rate (%)	Country	HCV rate (%)
Algeria	0.2	Guatemala	0.7	Portugal	0.5
Angola	1.0	Guinea	10.7	Puerto Rico	1.9
Argentina	0.6	Haiti	2.0	Qatar	2.8
Australia	0.3	Honduras	0.1	Republic of Korea	1.7
Austria	0.2	Hong Kong SAR of China	0.5	Republic of Moldova	4.9
Bangladesh	2.4	Hungary	0.9	Reunion Island	0.8
Belarus	1.4	Iceland	0.1	Romania	4.5
Belgium	0.9	India	1.8	Russian Federation	2.0
Belize	0.1	Indonesia	2.1	Rwanda	17.0
Benin	1.5	Iran	0.5	Saudi Arabia	1.8
Bhutan	1.3	Ireland	0.1	Senegal	2.9
Bolivia	11.2	Israel	0.4	Seychelles	0.8
Botswana	0.0	Italy	0.5	Sierra Leone	2.0
Brazil	2.6	Jamaica	0.3	Singapore	0.5
Bulgaria	1.1	Japan	2.3	Slovakia	0.4
Burundi	11.1	Jordan	2.1	Solomon Islands	0.9
Cambodia	4.0	Kenya	0.9	Somalia	0.9
Cameroon	12.5	Kiribati	4.8	South Africa	1.7
Canada	0.1	Kuwait	3.3	Spain	0.7
Central African Republic	4.5	Libyan Arab Jamahirija	7.9	Sudan	3.2
Chad	4.8	Luxembourg	0.5	Suriname	5.5
Chile	0.9	Madagascar	3.3	Swaziland	1.5
China	3.0	Malaysia	3.0	Sweden	0.003
Colombia	1.0	Mauritania	1.1	Switzerland	0.2
Costa Rica	0.3	Mauritius	2.1	Thailand	5.6
Croatia	1.4	Mexico	0.7	Togo	3.3
Cuba	0.8	Micronesia, Federal States of	1.5	Trinidad and Tobago	4.9
Cyprus	0.1	Mongolia	10.7	Tunisia	0.7
Czech Republic	0.2	Morocco	1.1	Turkey	1.5
Democratic Republic of Congo	6.4	Mozambique	2.1	Uganda	1.2
Denmark	0.2	Nepal	0.6	Ukraine	1.2
Dominican Republic	2.4	Netherlands	0.1	United Republic of Tanzania	0.7
Ecuador	0.7	New Zealand	0.3	United States of America	1.8
Egypt	18.1	Nicaragua	0.6	United Arab Emirates	0.8
El Salvador	0.2	Niger	2.5	United Kingdom	0.02
Ethiopia	0.8	Nigeria	1.4	Uruguay	0.5
Finland	0.02	Norway	0.1	Vanuatu	0.9
France	1.1	Oman	0.9	Venezuela	0.9
French Guiana	1.5	Pakistan	2.4	Vietnam	6.1
Gabon	6.5	Panama	0.1	West Bank and Gaza Strip	2.2
Germany	0.1	Papua New Guinea	0.6	Yemen	2.6
Ghana	2.8	Paraguay	0.3	Zambia	0.0
Greece	1.5	Peru	1.6	Zimbabwe	7.7
Grenada	1.1	Philippines	3.6		
Guadeloupe	0.8	Poland	1.4		

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tis, cirrhosis and hepatocellular carcinoma (HCC). The mechanism of liver injury in acute and chronic hepatitis C is unknown; however, because there is little evidence that HCV is cytopathogenic, damage to the liver is considered to be mediated by the host's cellular immune response to the infection. An undetermined proportion of chronic infections are asymptomatic, with normal liver enzymes and relatively normal liver histology. Most of these patients show little or no disease progression in contrast to those with elevated liver enzymes, who often progress to more serious disease (5,6,8-11).

It is generally agreed that the clinical disease and natural history are not influenced by geographic or demographic factors. Although only one species of HCV is recognized, more than one infection with HCV has been observed in humans and experimentally reproduced in chimpanzees (12-16).

Most persons with persistent HCV infection progress from mild to moderate to severe hepatitis, and ultimately to cirrhosis over a variable time frame (ranging from five to 50 years, average 20 to 30 years). However, a small proportion of infected persons may rapidly develop severe liver disease infection (5-8). Factors that influence the rate of progression of chronic hepatitis C to cirrhosis and HCC include alcohol abuse, being male, age at time of infection, severity of liver histology at initial biopsy and, possibly, viral titre. The role of other factors, such as viral genotype, coinfection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV), sex and immunogenetic factors, is less well understood.

HCC is one of the most serious sequelae of chronic hepatitis C, and HCV and HBV are the two most important causes of HCC. The geographic importance of the two viruses in the etiology of HCC differs from region to region. In areas where chronic HBV infection is highly endemic (ie, Asia and Africa) HBV remains the major cause of this cancer, with HCV accounting for approximately 15% of the cases. In countries with a lower endemicity for hepatitis B, such as Japan and Italy, over 50% of HCC are associated with chronic HCV infection. In countries with a low incidence of HCC, neither HBV nor HCV is dominant, but HCV (and alcohol) may be more important than HBV (17-29). In some countries, dual infection with HCV and HBV appears to potentiate the development of HCC (30,31). When patients with HCC are compared with those with HBV-associated HCC, male predominance is less striking, patients are usually older, and tumours are less acute in their presentation and exhibit a less sudden and severe course (20,32-34).

Chronic HCV infection has also been associated with a number of extrahepatic sequelae. Many of these appear to be immunologically mediated, with the development of autoantibodies and/or circulating immune complexes, and include essential mixed cryoglobulinemia and glomerulonephritis with or without the nephrotic syndrome. Other extrahepatic conditions thought to be associated with chronic hepatitis C but whose pathogenesis is unknown include cutaneous manifestations (sporadic porphyria cutanea

tarda and lichen planus), ocular lesions (ie, Mooren's ulcers), sialadenitis and B cell lymphoma (35).

DIAGNOSTIC APPROACH

Commercially available diagnostic tests are based on the detection of anti-HCV specific antibodies (anti-HCV enzyme immunoassay [EIA]) and the detection of circulating HCV RNA by amplification tests (eg, polymerase chain reaction [PCR], branched chain DNA [bDNA] assay). Third generation EIAs for anti-HCV can detect more than 95% of chronically infected patients, but the long window period between infection and the appearance of anti-HCV in most patients results in a lower frequency of detection (50% to 70%) during acute infection. Despite the high sensitivity and specificity of the EIA, the positive predictive value in a low prevalence population, such as blood donors, may only be 60% to 80%, resulting in a high false positive rate. Thus, confirmatory testing becomes invaluable in these settings.

Diagnostic tests for HCV infection can be used to prevent infection through screening of donor blood and plasma, and to assist the clinician in making better decisions regarding medical management of a patient (36-38).

A recombinant immunoblot assay (RIBA) that identifies antibodies that react with individual HCV antigens is often used for confirmation of a positive EIA result. The use of such a confirmatory test is not a requirement for routine blood screening in resource-limited settings.

Testing for HCV genomic RNA is also being used for confirmation of serological results as well as for assessing the effectiveness of antiviral therapy. Unfortunately, current molecular assays, such as reverse transcription (RT)-PCR and the bDNA assay, sometimes suffer from problems of sensitivity (bDNA assay) or specificity (RT-PCR). In addition, the genetic and associated serologic heterogeneity of HCV strains may not be detected with equal sensitivity by current diagnostic tests.

For resource-limited regions, the available enzyme immunoassays for anti-HCV are unaffordable. This often results in absent or erratic testing of blood donations and a lack of appropriate diagnostic testing for patients with acute or chronic liver disease. Such regions need rapid diagnostic (bedside) tests that are laboratory instrument-independent and can be performed at ambient temperatures. Similarly, RT-PCR assays and confirmatory tests (RIBA) are too expensive for use in these areas. As a result, the failure to test blood donations remains a critical issue in many settings, and the lack of patient screening withholds them from receiving appropriate follow-up and treatment.

Because of the complexity of HCV testing, including the low positive predictive value of the anti-HCV enzyme immunoassay when used for screening in low prevalence populations, there is a need to develop or strengthen national centres of expertise for diagnostic testing and to integrate practical training about test methods, quality control and interpretation of test results. HCV test technology should be developed that is more affordable, yet of adequate sensitivity

TABLE 2
Estimated hepatitis C virus (HCV) prevalence per region and number of infected population worldwide (1999)

WHO region	Total country population in millions (WHO 1996)	% HCV prevalence	Infected population (in millions)	Number of countries with no data available
Africa	602	5.3	31.9	12
The Americas	785	1.7	13.1	7
Eastern Mediterranean	466	4.6	21.3	5
Europe	858	1.03	8.9	19
South-east Asia	1500	2.1	32.0	3
Western Pacific	1600	3.9	62.2	11
Total	5811	3.0	169.7	57

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and specificity, preferably with minimal dependency on a cold chain.

HCV

HCV is a small enveloped RNA virus that belongs to the family Flaviviridae. Humans are the only known hosts of HCV, but the virus can be transmitted experimentally to chimpanzees. HCV can be classified into six major genotypes (designated 1 to 6) and approximately 100 subtypes (designated a, b, c, etc) based on the sequence heterogeneity of the genome (39). Genotypes 1 to 3 have a worldwide distribution. Genotypes 4 and 5 are found principally in Africa, and genotype 6 is distributed in Asia (40-51).

PREVALENCE

Acute hepatitis C infection is most often asymptomatic and, therefore, difficult to diagnose. The available diagnostic assays are expensive and not optimal for epidemiological studies. As many as 80% of infected people can become chronically infected after acute HCV infection and are at risk of serious long term clinical sequelae (7,52-54). Hence, representative prevalence data are not available from many countries and the relative contribution of the various sources of infection has not been defined with population-based epidemiological studies.

Well designed prevalence studies of the general population are needed in most countries in all regions of the world to arrive at an accurate estimate of the number of people infected and the disease burden. Such studies should be performed to enable countries to prioritize their preventive measures and to make the most appropriate use of available resources. Given the substantial morbidity and mortality attributable to HCV-related chronic liver disease (55), each country, irrespective of its economic status, should develop a plan of HCV-related public health activities for the primary prevention of new (incident) HCV infections. Additional information is needed to define preventive strategies in the most economic fashion.

Nevertheless, available data indicate that approximately 3% of the world's population is infected with HCV (Table 2). Thus, it is estimated that there may be as many as 170 million chronic carriers infected with HCV at risk of de-

veloping liver cirrhosis and/or liver cancer (56). This places HCV among pathogens of primary concern to humanity (5,57). In most populations living in Africa, the Americas, Europe and south-east Asia, the prevalence of anti-HCV is under 2.5%; rates for the western Pacific regions average 2.5% to 4.9%; and rates range from 1% to more than 12% for the Middle East (Table 2). These figures translate to an estimated 13.1 million infected people living in the Americas and 8.9 million in Europe. However, the vast majority of infected individuals live in Asia and Africa (32 million in Africa, 62 million in eastern Asia and 32 million in south-east Asia) (Figure 1) (56).

Published studies on the prevalence of hepatitis C in various subgroups of the population worldwide showed rates from 0% to 70% (56). In many countries the prevalence of HCV is very high among drug users (58-61).

PUBLIC HEALTH STRATEGIES

The source of HCV infection in developing countries includes transfusion of blood or blood products and organs from unscreened donors; transfusion of blood products that have not undergone viral inactivation; parenteral exposure to blood through the use of contaminated and inadequately sterilized instruments and needles used in medical, dental and various forms of 'traditional' medicine, and blood-contaminated objects in conjunction with circumcision and other surgery; injection drug users; health care workers exposed to contaminated needles or sharps; individuals undergoing procedures such as hemodialysis or who receive unsafe injections; persons who participate in high risk sexual practices; household or sexual contacts of HCV infected persons; and infants of HCV-infected mothers (2,62,63).

PRIMARY PREVENTION

A comprehensive primary prevention HCV strategy should include surveillance, prevention, detection and research of HCV, control of HCV-related chronic liver disease and evaluation of the effectiveness of prevention activities. Prevalence studies should provide information about populations who might be routinely tested for HCV infection.

Screening for hepatitis C: Screening for hepatitis C is a complex issue, and advice cannot be applicable in all regions of



Figure 1) Global prevalence of hepatitis C. Data from reference 111

the world. The cost-benefit and cost effectiveness of screening specific groups requires evaluation. In particular, screening for hepatitis C may not be advantageous if treatment is not envisaged. Ideally, there should be pretest counselling, and counselling when testing is performed and when results are reported. Post-test counselling for persons with positive results must include an interpretation of those results and a recommendation for medical follow-up when medical care is available.

HCV counselling programs for individuals tested for HCV should begin with public education of persons at highest risk who have access to sites for counselling and testing. The emotional consequences need to be dealt with. Individuals with positive results also should be counselled regarding further liver injury from alcohol. Behaviours that might lead to transmission of HCV to others should be identified. It is important to emphasize that discrimination against HCV-positive individuals must be avoided.

Prevention activities: Prevention activities should include screening hepatitis patients and chronic hemodialysis patients in public or private facilities, in order to permit identification of epidemics and monitoring of infection control practices in a high risk setting so that specific precautions designed to reduce transmission can be implemented. Routine screening is not recommended for pregnant women and health care workers.

Blood transfusion: Before the introduction of routine screening of blood and blood production in the early 1990s, the transmission of HCV through contaminated blood or blood products (59,64,65) was frequent. The introduction of routine screening of blood and blood products has substantially reduced the risk of transmission following blood transfusion with screened blood (66). The residual risk for HCV transmission is estimated at 0.004% to 0.0004% per unit transfused in the United States (67). The reduction and elimination of HCV transmission through the global introduction of blood and blood product screening remain a priority.

Prevention activities: HCV screening of blood donors should be introduced as a comprehensive plan to improve the safety of the blood supply, using technology and infrastructure already in place for HIV and other blood-borne pathogens. Where no such infrastructure exists, public health authorities should establish one. Unfortunately, in many countries with developing or transitional economies, un-screened blood or blood products that have not undergone viral inactivation are still being used. Anti-HCV-positive individuals should not donate blood or blood components, organs, tissue or semen.

Injections used for immunizations, treatment and invasive medical procedures: Previous data have indicated that a history of injections correlates with infection with blood-borne

pathogens. Nosocomial transmission of HCV through the reuse of contaminated and/or inadequately sterilized syringes and needles used in medical and dental procedures and other medical practices, remains a major source of HCV infection in many developing countries and puts the general public in these areas at high risk of infection (68-72). It is estimated that 8 to 12 billion injections are given each year, many in developing countries, and that approximately 50% of these injections are unsafe (73). Clearly, there seems to be a massive overuse of injections that may not be medically indicated. Most countries lack programs to reduce the risk of infection from these sources. Furthermore, there is a lack of education of health care providers and of the public regarding the importance of this HCV transmission mode.

Follow-up studies of needlesticks from anti-HCV positive patients to health care workers sources indicate a 10% to 10% seroconversion rate in recipients (average 2% to 5%) (74-80). In contrast, transmission from infected health care workers to patients appears to be rare (81-83). Thus, there is no need to screen health care workers and remove anti-HCV positive individuals from performing blind procedures. Finally, transmission from patient to patient is uncommon in developed countries, except in dialysis settings or following the use of contaminated biologicals or multidose vials.

Traditional practices include rituals (eg, circumcision or scarification), traditional medicine (eg, blood-letting) and other activities that break the skin (eg, tattooing, ear or body piercing, and acupuncture). All are potential sources of infection with HCV and other blood-borne pathogens when contaminated instruments are used (63,71,84,85). Although an association between HCV infection and such types of risk has only been reported for body piercing in the United States (86,87), because most of these practices are not monitored, their potential for disease transmission is unknown in most parts of the world.

Prevention activities: Countries should prevent the use of blood-contaminated instruments, equipment and supplies, and should ensure adequate infection control practices involving medical, traditional and nontraditional medical procedures, folk medicine, tattooing, body piercing, acupuncture, scarification and circumcision. The extent to which these practices may contribute to infection with HCV and other blood-borne pathogens should be determined.

Health care professionals and the public should be educated regarding the risk of HCV transmission by contaminated injection and other equipment. Technological improvements, eg, autodestruct syringes, are to be encouraged to prevent the reuse of contaminated injection equipment. Screening of health care workers who sustain a percutaneous or mucosal exposure to anti-HCV-positive blood is recommended in order to detect acute disease, which is amenable to antiviral treatment (88,89). It has to be emphasized that due to the low transmission rate, there are no occupational restrictions for persons with HCV infection.

Injection drug abuse: In many developed countries, injection drug use is the major source of HCV infection (2,59,60).

The term 'injection drug users' includes not only persons who inject drugs regularly, but also persons who inject drugs sporadically and those who used drugs in the past.

Prevention activities: Programs that prevent initiation of illegal drug use should be established. Injection drug users should be well-taught to stop using drugs, to seek treatment or be advised not to share any drug injection or preparation equipment, and to achieve harm-reduction behaviours. Hepatitis A and B vaccinations should be offered to susceptible individuals.

Sexual transmission: There is a considerable amount of evidence against sexual HCV transmission from a number of studies (90-93). It is also noteworthy that, in most studies on the prevalence of HCV, infection in homosexual men is similar to that of the general population (66,94-96). On the other hand, evidence of sexual transmission among persons with multiple partners during unprotected sex or associated with sexually transmitted diseases is supported by case reports, case-control studies and population-based surveillance data (86,87). However, more research is needed to determine whether this represents sexual transmission or failure to detect percutaneous exposures.

The risk of sexual transmission among persons with a steady partner appears to be very low. In general, there is a considerable amount of evidence from a number of studies to conclude that the efficiency of transmission of HCV between sexual partners is limited.

Prevention activities: Harm-reduction counselling should be provided to persons with high risk sexual behaviours, and persons who participate in high risk sexual practices should engage in safe sex practices. Subjects should be advised that the risk of HCV transmission by sexual activity between stable partners is low, but not absent. Because of this low risk, no change in sexual practice is advocated for those in a stable sexual relationship. Some couples may choose to reduce this low risk by using latex condoms. Consideration may be given to testing the partner for HCV infection.

Horizontal and vertical transmission: Mother-to-infant transmission of HCV has been observed, but the risk is probably less than 5% unless the mother is co-infected with HIV (97). There is no association between transmission and the type of delivery (caesarian section versus vaginal delivery) and no association with maternal breast-feeding (98-103). Infected infants progress to chronic disease with a benign course, at least initially. The long term outlook is not known.

Within families, HCV can be percutaneously transmitted through potential sources that include shared use of razors or other objects that might inapparently transmit blood (eg, washcloths). From a public health perspective, there is no known method for preventing HCV transmission from infected mothers to infants. More research is needed to determine the risks, outcome and prevention of perinatal transmission.

Prevention activities: Personal articles that might have blood on them, such as toothbrushes or razors, and any item that pierces the skin, should not be shared. There are no rec-

ommendations against pregnancy, breast feeding or types of delivery.

SECONDARY PREVENTION

In general, there are two major objectives of screening for HCV infection:

- to prevent progression of chronic hepatitis C by identifying infected individuals for evaluation, counselling and treatment (if appropriate); and
- to prevent transmission to persons at risk.

For countries with more developed economic, medical and public health infrastructures, their HCV prevention strategy also should include the secondary prevention of HCV-related chronic liver disease through identification, testing and counselling of HCV-infected persons who would benefit from antiviral treatment to prevent progression of their chronic liver disease (2).

Therapy: Therapy for HCV infection is recommended to reduce inflammation, fibrosis, cirrhosis and HCC in chronically infected patients (4,104). At present, all effective licensed therapies for the treatment of hepatitis C are based on interferon-alpha (IFN α) or a combination of IFN α and ribavirin. Combination therapy with IFN α and ribavirin, a nucleoside analogue, has significantly enhanced sustained response rates (105). For acute viral hepatitis, treatment with IFN α results in a 50% to 70% sustained response rate (88). This rate declines to about 30% in patients with minimal or mild chronic hepatitis, and to about 10% among those with cirrhosis (106-109). The combination of IFN α and ribavirin is the first line of treatment for previously untreated (naive) patients without contraindications to ribavirin (4).

Treatment should be employed when there is a significant risk of disease, a reasonable chance of response and an acceptable cost. HCV genotypes 1 and 4 are more resistant to therapy, whereas genotypes 2 and 3 are relatively sensitive (106,107). Because the clinical disease and natural history do not appear to be influenced by geographic or demographic factors, the criteria for patient selection for therapy should be similar in all regions. However, the presence of resistant subtypes and a delayed presentation for therapy when cirrhosis already is present, affects disease management and response rates.

As part of management, alcohol intake should be reduced or preferably stopped. Similarly, unavailability or unreliable sources of antiviral agents and poor compliance of patients complicate treatment. Finally, cost limits therapy in most developing countries except for the very wealthy.

Two approaches to therapy have been proposed:

The **virological approach** seeks to identify, on the basis of viral load and genotype, patients with a high probability of response without concern for the severity of their liver disease. This approach is expensive and

requires specialized virological expertise and is, therefore, not applicable in all settings.

The **disease approach** involves focusing treatment on patients with acute disease or on those with moderate to severe chronic hepatitis who are at a higher risk of progressing to cirrhosis over a relatively short time. This is the preferred approach for settings with limited resources. In general, early treatment produces better results, and patients should be treated before their disease reaches an irreversible stage, eg, cirrhosis, especially if resources are limited.

Minimal requirements for treatment of chronic hepatitis C are anti-HCV positivity or the detection of HCV RNA, abnormal transaminase levels (alanine aminotransferase [ALT]) over at least six months, and histological finding of moderate or severe hepatitis with fibrosis (2,4,104). Thus, a liver biopsy is desirable unless clinically contraindicated.

Patients with minimal hepatitis often are not treated, depending on age and available resources. This approach will be modified as more effective and cost effective antiviral agents become available. Patients with compensated cirrhosis exhibit reduced responsiveness to antiviral agents and experience significant side effects. Depending on factors such as age and available resources, these patients should receive the lowest priority for treatment. Patients excluded from treatment include those with decompensated cirrhosis and carriers with persistently normal ALT levels.

Treatment: For now, patients with acute hepatitis should receive 3 to 6 MU IFN α three times per week (TIW) for at least six months until more effective regimens emerge. The most effective therapy for chronic HCV infection is a combination of IFN α and ribavirin. Ribavirin monotherapy is not recommended. Alternative forms of IFN (PEGylated IFN or consensus IFN) are under evaluation, and their use may lead to further improvements. The standard treatment for previously untreated (naive) patients with chronic hepatitis C is 3 to 6 MU IFN α TIW and 1000 to 1200 mg/day ribavirin for 12 months. However, recent data indicate that a regimen of IFN α and ribavirin for six months may be sufficient when treating patients infected with HCV genotype 2 or 3.

Adverse side effects to IFN and ribavirin are tolerable, but a fatal outcome (suicide, liver failure or sepsis) has been observed, primarily in patients with cirrhosis. Less severe side effects occur in less than 2% of treated patients, and include autoimmune disease (thyroid), fatigue, myalgia, bone marrow suppression requiring dose reduction and neuropsychiatric effects such as depression. All patients must be carefully monitored for side effects using appropriate biochemical, hematological and immunological tests by regular visits to the prescribing doctor. Appropriate medical records should be maintained.

Monitoring: Early response should be assessed by evaluating the patient's ALT or HCV RNA response at six months when a combination of IFN and ribavirin is used, and at three months if, according to available resources, IFN alone is used. The end-of-treatment response is assessed when

therapy is completed by ALT or HCV RNA assessment. Finally, a sustained response should be assessed by ALT or HCV RNA estimation six to 12 months after completion of treatment.

Types of response and management of treatment failures –

Sustained response: Sustained response is demarcated by clearance of HCV RNA from the blood and persistent normalization of serum ALT levels observed six to 12 months after therapy has ended (virological and biochemical response). This type of response leads to clinical amelioration of the patient's condition and to significant improvements of the liver histological inflammatory status. In many instances this response can be considered as an elimination of HCV and a cure for the patient.

Transient (relapsing) response: Transient (relapsing) response is denoted by complete virological and biochemical response at the end of treatment, followed by the re-emergence of virus and/or elevation of the ALT level during follow-up. Transient (relapsing) responders who were treated initially for six or 12 months with IFN alone can be considered for re-treatment with a combination treatment (IFN and ribavirin) for 12 months. Available data suggest that treatment with IFN and ribavirin produces a significant improvement in sustained result rates in this group.

Breakthrough response: Breakthrough response indicates temporary virological and biochemical response occurring during therapy followed by reappearance of HCV RNA and/or an abnormal ALT level before the end of treatment. When a breakthrough response occurs, treatment should be discontinued. There are no valuable options available, and patients should be considered for inclusion in trials of alternative treatment regimens.

Nonresponse: Nonresponse means that the HCV RNA re-

mains detectable and/or ALT fails to normalize throughout the treatment phase. When a discordant virological and biochemical response occurs, the virological response should take precedence when interpreting the response to therapy. Patients who fail to achieve a virological and/or a biochemical response following six to 12 months of therapy are unlikely to respond to additional treatment regimens.

CONCLUSIONS

The successful reduction of new HCV infections will rely on national public health programs aimed at preventing these infections. Secondary prevention of HCV-related chronic liver disease will depend on the existence of a public health effort that will provide the necessary infrastructure to the community. More research is needed to determine the epidemiology and the natural history of the disease to enable countries to prioritize their preventive measures and to make the most appropriate use of available resources. However, it should be stressed that prevention does not depend on these studies.

The development of more effective – and particularly more cost effective – treatments is of paramount importance for the majority of those with a persistent HCV infection. The same strategy that has been applied by the World Health Organization to reduce vaccine cost at the global level might be applied to reduce the costs of drugs used in the treatment of chronic hepatitis C.

Another important goal for the future is the development of an HCV vaccine, a task that will be met with many difficulties.

ACKNOWLEDGEMENTS: The authors thank Ms Sophia Desillas for editorial comments.

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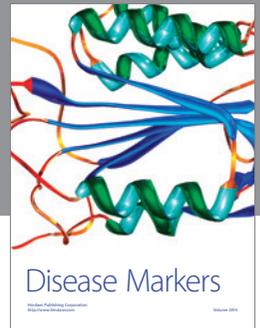
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