American Journal of Gastroenterology
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Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2008.01825.x

CME

CLINICAL REVIEWS

Acute Hepatitis C: A Systematic Review

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INTRODUCTION: The annual incidence of acute hepatitis C virus (HCV) has fallen in recent years, primarily because of effective blood screening efforts and increased education on the dangers of needle sharing. However, hepatitis C infection is still relatively frequent in certain populations. Most patients infected with HCV are unaware of their exposure and remain asymptomatic during the initial stages of the infection, making early diagnosis during the acute phase (first 6 months after infection) unlikely. While some of those infections will have a spontaneous resolution, the majority will progress to chronic HCV. We scanned the literature for predictors of spontaneous resolution and treatment during the acute stage of HCV to identify factors that would assist in treatment decision making.

METHODS: A medical literature search through MEDLINE was conducted using the keyword "acute hepatitis C" with a variety of keywords focused on (a) epidemiology, (b) natural history and outcome, (c) diagnosis, (d) mode of transmission, and (e) treatment.

RESULTS: There are no reliable predictors for spontaneous resolution of HCV infection and a significant percentage of individuals exposed to HCV develop persistent infections that progress to chronic liver disease. An intriguing approach is to treat acute HCV and prevent the development of chronic hepatitis. Several clinical trials showed that treatment of hepatitis C infection during the acute phase is associated with high sustained virological response (SVR) rates ranging between 75% and 100%. Although there is a prevailing consensus that intervention during the acute phase is associated with improved viral eradication, relevant clinical questions have remained unanswered by clinical trials. Optimization of therapy for acute hepatitis C infection and identification of predictors of SVR represent a real challenge.

CONCLUSION: With more than 170 million chronic hepatitis C patients worldwide and an increase in the related morbidity and mortality projected for the next decade, an improvement in our ability to diagnose and treat patients with acute hepatitis C would have a significant impact on the prevalence of chronic hepatitis and its associated complications particularly in countries with a high endemic background of the infection.

(Am J Gastroenterol 2008;103:1283–1297)

INTRODUCTION

Although hepatitis C virus (HCV) only accounts for a minority of cases of clinical acute hepatitis, it is a major cause of chronic liver disease and liver transplantation in both developed and developing countries (1, 2). The global prevalence of HCV is 3% with 170 million persons infected worldwide (1–3). In the United States, nearly 2% of the population is infected (4, 5). In Western Europe, a low prevalence (>0.1%) is reported from the United Kingdom, Finland, and Germany and higher prevalence rates >1% are reported from Italy and France (1, 2, 6, 7). The prevalence of HCV infection is greater in Eastern Europe (median 2%, range 0.4–4.9%) (1, 3, 6). In Asia, the prevalence of HCV ranges between 2% and 5% (1, 2). Egypt has the highest prevalence of hepatitis C in the world, reaching 13% of the population, equating to an estimated 10 million anti-HCV-positive persons (8–10).

Acute HCV infection is typically defined as a new occurrence of viremia with conversion from an HCV-RNA negative to an HCV positive status. Acute HCV infection is asymptomatic in the majority of cases (11–13). HCV-RNA can be detected in the serum in almost all patients within 1–2 wk of exposure. Seroconversion is detected after 2–6 months (window period) or later in certain risk groups, making anti-HCV testing less reliable than HCV-RNA assessments for early diagnosis of acute HCV (11–16). The acute phase of infection is usually considered to be the first 6 months and this is the phase of infection in which spontaneous clearance is still possible (11). While 20–50% of patients with acute hepatitis achieve spontaneous resolution,

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between 50% and 80% of individuals develop chronic infection (11–13). Approximately 20% of chronic hepatitis C patients can be expected to develop cirrhosis; of these, 6% will decompensate to end-stage liver disease (ESLD) and an additional 4% will develop hepatocellular carcinoma (HCC) (11).

METHODS OF THE REVIEW

Literature Search and Identification of Relevant Studies

The author identified relevant English-language articles pertaining to acute HCV by searching the PubMed and EMBASE databases and Cochrane databases (1976–2007). The following search terms were used to identify primary articles: acute hepatitis and acute HCV with a variety of keywords focused on (a) epidemiology, (b) natural history and/or outcome, (c) transmission, (d) diagnosis, and (e) treatment of HCV during the acute phase. Eligible studies were peer-reviewed epidemiological and observational studies, prospective and retrospective case-control or cohort studies, controlled and uncontrolled randomized or nonrandomized trials, systematic reviews, and meta-analyses. Studies were assessed according to their methodological soundness, independently of the result. The bibliographies and references from the primary articles were then manually searched. When necessary, additional information from the original authors of some clinical trials was requested. Furthermore, experts in the field were contacted for their knowledge of other relevant published studies. Case reports and small case series reporting on fewer than five patients were not included in the review in an attempt to minimize potential reporting bias of uncharacteristic or nonrepresentative cases.

RESULTS

The initial search retrieved 2,002 articles at the title review level, of which 154 articles were considered by the author to contain relevant data on acute hepatitis C. Of these, 101 articles were eligible for full review, representing 20 clinical trials (83–89, 91–103) and 83 observational studies reporting on the epidemiology, diagnosis, natural history, and treatment of acute HCV.

Acute Hepatitis C Epidemiology and Geographic Variations

Because most acute HCV patients remain undiagnosed and the rates of spontaneous resolution of HCV infection are variable, little is known about the epidemiology of acute HCV. Robust epidemiological data are available only for those patients who progress to chronic infection, develop symptoms, and/or seek treatment. A precise estimation of the incidence of HCV infection is difficult to determine because most acute infections are asymptomatic and surveillance and reporting systems are inadequate in many countries (1, 17, 18). Because direct measurement of HCV incidence is difficult, estimation of incidence from available prevalence data is a more practical approach for estimating incidence on a global scale, although the results are sensitive to assumptions (1, 2). However, what we do know is that there are both geographic and temporal differences in the rates of acute HCV infection (17).

INCIDENCE OF HCV IN DIFFERENT GEOGRAPHIC REGIONS. The epidemiology of acute HCV has changed during the past decade, particularly in western countries. In the United States, the incidence of acute HCV has declined among the general population, different age groups, genders, and ethnic populations since 1989 (1–5, 18, 19). The incidence of HCV dropped in the United States from 130 per 100,000 in the 1980s to 0.2 per 100,000 in 2005 with 40,000 acute HCV cases reported per year (18, 19). In Italy, the surveillance system for acute viral hepatitis showed that the incidence (number of cases per 100,000 population) of hepatitis C decreased from 5 in 1985 to 1 in 1991 (7). The incidence of HCV infection is even lower in Northern Europe, Germany, the United Kingdom, and the Netherlands (1, 2, 6). HCV accounts for 10% and 8% of acute hepatitis cases in China and Japan, respectively (20, 21). In hyperendemic areas in Taiwan and Japan, the incidence rates of HCV infection were 110 per 10,000 and 28–36 per 10,000 persons, respectively (21, 22). The incidence is much higher in African countries and in Egypt in particular. In Egypt, the incidence rates of HCV were found to range from 0.8 per 1,000 person-years to 6.8 per 1,000 depending on the background prevalence (23–25). HCV accounts for 31% of acute viral hepatitis cases in Egypt (23).

AGE AND GENDER DISTRIBUTION. Specific data on the age, gender, racial, and ethnic distributions are scarce. However, the published data show some variations in different geographical areas. In the United States and Western Europe, most acute HCV infections occur in adults 30–49 yr old, and acute HCV seems extremely rare in children (4, 17, 18, 26). In the Far East, the mean age of individuals with acute HCV is 50 yr (21). In Egypt, high rates of infection are observed in all age groups including young individuals, indicating an ongoing high risk for acquiring HCV infection (23–25). More than 60% of acute HCV infections are in persons below the age of 25 yr. High incidence rates (14.1 per 1,000 person-years) have been detected in Egyptian children younger than 10 yr of age living in households with an anti-HCV-positive parent (23, 25). This high incidence in young persons could lead to future increases in chronic disease in these individuals and persistence of the high magnitude of the burden of HCV-related chronic disease in Egypt. The prevalence of acute HCV in both genders is controversial. While some studies showed higher HCV incidence among men (17–18, 21), other population-based surveys (7, 27) showed slightly higher rates in women than in men. However, additional epidemiological studies are needed to confirm that the risk of HCV transmission is greater in men.

Modes of Transmission: Changing Patterns in the West and East

Several modes of transmission of HCV are well documented and widely accepted; others are less well defined and require further study. HCV is most frequently transmitted through direct percutaneous exposure to infected blood. Risk factors for HCV transmission differ between developed and developing countries. Socioeconomic differences are likely to explain much of the geographic variability.

BLOOD TRANSFUSION. Percutaneous inoculation via transfusion is very efficient in transmitting HCV infection. Transfusion-associated cases occurred prior to routine donor screening in blood banks with second and third generation enzyme immunoassays, a procedure that resulted in a sharp decline in transfusion-associated HCV transmission (28). As of 2001, the risk of HCV infection from a unit of transfused blood is less than one per million transfused units. However, the risk of HCV transmission through blood has not been fully eliminated in some developing countries that lack the resources to implement adequate donor screening and continue to use commercial donors to supplement their blood supplies (29). In such countries, blood transfusion still accounts for some percentage of acute HCV cases.

INJECTING DRUG USERS. The number of cases of acute hepatitis C among injection drug users has recently declined in the United States and Europe due to the widespread implementation of harm reduction policies, syringe exchange programs, counseling of injecting drug users (IDUs) regarding protection from infection, and changing injecting behavior (30, 31). However, both incidence and prevalence of HCV infection remain high among new young drug injectors (19, 32, 33) since IDU is recognized as the risk factor in about 55% of the acute HCV cases reported in developed countries and in developing and transitional countries with high IDU prevalence such as Eastern Europe and Central and South Asia (34). Lower prevalence rates of IDU are reported from the Middle East and Africa (34) where IDU does not represent the major risk factor for acute HCV. Engagement in unsafe injection practices such as syringe sharing, sharing of injection equipment, engaging in sexual relationships with other IDUs increase the risk of HCV transmission (19, 28, 30, 31, 35, 36). IDU also accounts for a significant percentage of acute HCV cases.

SEXUAL TRANSMISSION. Sexual transmission of HCV has been controversial. Some case-control studies identified some well-documented instances of acute hepatitis C occurring after a defined sexual exposure (7, 18, 19, 35, 36). The rates of sexual transmission of HCV vary substantially between countries and geographic regions. Among patients with reported cases of acute hepatitis C in the United States, a history of sexual contact with a person infected with HCV can be elicited in approximately 15–20% of cases (18, 19). Studies showed that HCV sexual transmission increases with the number of lifetime sexual partners, high-risk sexual exposure, and unprotected sex (Fig. 1). It remains unclear whether the recent outbreaks of acute HCV in men who have sex with men (MSM), predominantly seen in HIV-positive individuals,

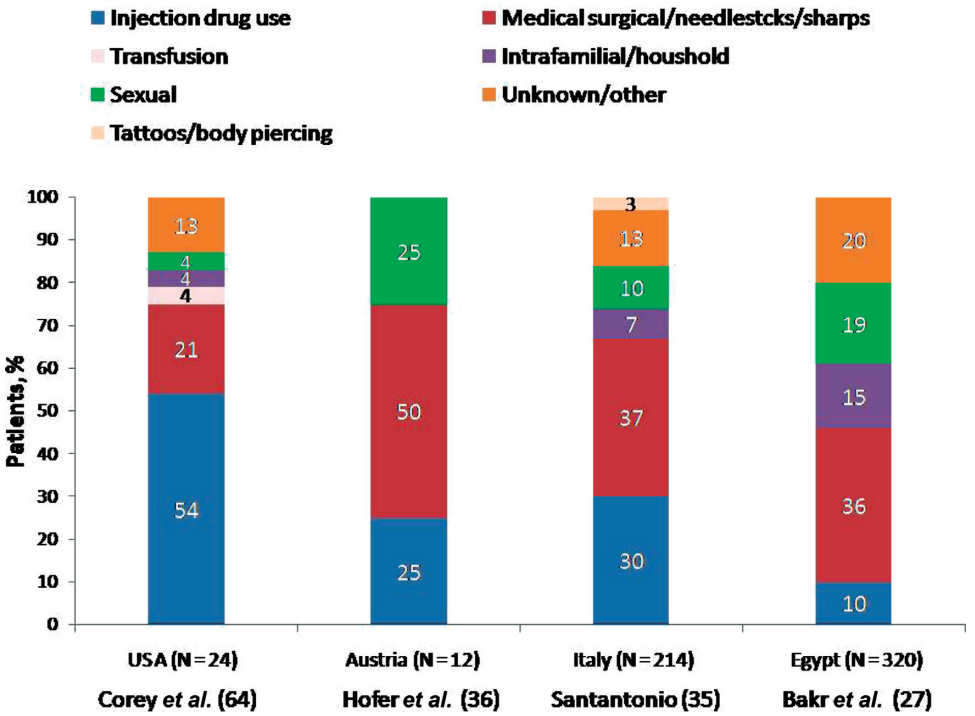

Figure 1. Sources of acute hepatitis C infection by geographic region.

reflects a predisposition to HCV secondary to HIV status *per se*, or whether this reflects differences in the behavior of HIV-positive *versus* HIV-negative MSM, or possibly increased screening in HIV-positive MSM (38–40). The interaction between these viruses is poorly understood. Additional studies are therefore needed to investigate the impact of HIV status on HCV transmission.

In Egypt, relatively higher rates of sexual transmission have been reported and reflect the higher background prevalence in this country. In rural Egypt, sexual transmission between monogamous spouses (41) ranged between 3 and 34% (95% CI 0–49%). Acute HCV is associated with a high temporal risk of transmission of HCV to sexual partners. Sexual transmission was confirmed by phylogenetic analysis in 15% of sexual partners of individuals with acute HCV (42).

Taken together, although some cases of acute HCV have been related to sexual transmission, the degree to which sexual transmission of HCV occurs is controversial because sexual transmission is difficult to confirm given that partners might have other risk factors for HCV transmission such as IDU. Phylogenetic analysis to identify genetic relatedness of HCV viral isolates in partners is required to confirm sexual transmission. All studies on the sexual transmission of hepatitis C are limited by the potential of the confounding variable of IDU or shared items such as razors and other items among sexual partners. Large studies directed at evaluating HCV-infected persons with multiple sexual partners are needed for accurate estimates of sexual transmission.

NOSOCOMIAL TRANSMISSION. Nosocomial transmission of HCV is becoming rare in the west but is considered a major risk factor that accounts for a significant percentage of the new cases of HCV in developing countries with high endemic backgrounds. Hemodialysis has been shown in several studies to be associated with the emergence of acute HCV (43–46). The high incidence and prevalence of HCV among dialysis patients can be attributed to several risk factors, including the number of blood transfusions, lack of adherence to infection control practices in dialysis units, transmission through dialysis machines, and ultrafiltrates (43, 45). Furthermore, hemodialysis patients require frequent hospitalizations and surgery, which increases their opportunities for exposure to nosocomial infections (18). The frequency of new HCV infections varies according to countries and hemodialysis centers. The prevalence of anti-HCV in chronic hemodialysis patients ranges between 10 and 20% in the west (43–46) and 40 and 85% in some developing countries (47, 48). The rate of seroconversion among hemodialysis patients with no other risk factors has been reported as 1.38–2.59% per year (49–51).

In developing countries, HCV infection has been associated with health-care-related procedures performed by traditional healers and folk medicine practices, acupuncture, tattooing, body piercing, and commercial barbering. Informal health-care providers and traditional healers perform services that may be associated with HCV transmission such as injections, dentistry, wound treatment, circumcision, excision, and scarification (52, 53). In rural Egypt, about 50% of deliveries are attended by traditional birth assistants (54). Lack of appropriate cleaning and disinfection of equipment used in these procedures contribute to HCV transmission and the emergence of new HCV cases.

OCCUPATIONAL EXPOSURES. Infection with HCV is an important occupational hazard for health-care workers. The risk of occupational HCV transmission increases with deep injuries and after procedures involving hollow-bore needles (55). In longitudinal studies, attempts have been made to assess the risk of infection associated with occupational exposures to HCV in the health-care setting. In these studies, transmission rates ranged from 0 to 10.3% (55–57). The substantial variation in transmission rates can be explained by differences in implementation of infection control policies and occupational infection surveillance systems in different countries. In the United States and Europe, acute HCV due to occupational exposure to HCV in the health-care setting is rare due to the strict implementation of universal precautions to prevent the spread of HCV in health facilities and the widespread adoption of needlestick-prevention devices in health-care settings (*i.e.*, safety-engineered needle devices, such as IV catheters and blood-drawing devices), together with other preventive measures and education (55–57). In developing countries, health-care workers are at increased risk for transmission following a needlestick or sharp injury from a source patient known to be infected with HCV (58, 59). In Egypt, the country with the highest prevalence of HCV worldwide, occupational transmission among health-care workers through needlesticks and sharp injuries contributes to new HCV cases given that needlestick-prevention devices are not yet adopted in most hospitals and health-care units in addition to inadequate compliance with universal, standard precautions in some health facilities (59).

INTRAFAMILIAL EXPOSURE. The role of intrafamilial HCV transmission is still controversial. However, several studies reported HCV spread in families with HCV-infected index cases. An Italian study (60) demonstrated an overall rate of HCV infection of 2.3% in offsprings of HCV positive individuals and the risk was significantly higher when the index case was female. In rural Egypt, intrafamilial HCV transmission is considered an important route of transmission where living in a house with an infected family member is a risk factor for HCV transmission. Analysis of data collected during surveys of Egyptian rural communities show that children whose parents had antibodies to HCV were at higher risk for contracting anti-HCV than children whose parents did not (23).

Taken together, IDU and to less extent sexual transmission represent the main risks for acute HCV in western countries. The picture is different in developing countries, in which

social and cultural differences combine to produce a very different set of risk factors for HCV. Nosocomial and iatrogenic transmission, occupational exposure, sexual and intrafamilial transmission in addition to IDU contribute to acute HCV cases in developing countries. Accurate risk factor assessment is essential for education targeted at risk reduction in culturally diverse populations.

Clinical Presentation and Diagnosis of Acute Hepatitis C: Cracking the Code of Early Detection

Unfortunately, there are no universally agreed-upon diagnostic criteria for acute HCV. A series of clinical features generally leads to a suspicion of acute HCV infection (13, 15). These "characteristics" include exposure to HCV during the previous 2–12 wk, development of symptoms, particularly jaundice, in a previously healthy individual, and an acute increase in alanine aminotransferase (ALT) levels to more than 10–20 times the upper limit of normal (with or without an increase in bilirubin) 2–8 wk after exposure coupled with detectable HCV-RNA 1–2 wk postexposure (11–16). Hepatitis C-specific antibodies (seroconversion) are detected 6–8 wk after infection, but sometimes seroconversion may be delayed (11, 15).

About 25–30% of patients with acute HCV develop symptoms (11, 13, 15). Acute HCV infection produces a wide range of clinical presentations from asymptomatic to icteric illnesses similar to other forms of acute viral hepatitis. Flu-like symptoms, fever, jaundice, dark urine, fatigue, nausea, vomiting, loss of appetite, and abdominal pain are commonly reported in symptomatic patients with acute HCV (11, 61). Acute HCV can be severe and prolonged, but is rarely fulminant (11, 13, 61). Symptoms, if they occur, develop 6–8 wk after exposure and may last for 3–12 wk in self-limited acute HCV and subside as ALT and HCV levels fall (10, 13, 61). However, the majority of individuals with acute HCV are asymptomatic and difficult to identify. Diagnosis of asymptomatic cases requires routine screening of those individuals who are in at-risk groups, have a history of exposure, or have abnormal liver function tests.

Natural History and Outcome of Acute Hepatitis C

HCV infection maybe self-limiting and can spontaneously resolve before proceeding beyond the acute phase, or may persist, leading to chronic infection. Estimates of spontaneous resolution range from 10 to 60%; conversely, 43 to 86% of cases are thought to progress to chronic infections (2, 11, 13, 61–64). Although these estimates vary widely, a general rule of thumb is that 20–40% of patients with acute HCV experience spontaneous resolution (11, 15, 61, 64–67). About 80% of patients with self-limiting hepatitis experience HCV-RNA clearance within 3 months of disease onset (11, 13, 15, 35, 36). Detectable HCV-RNA beyond 6 months after infection is usually associated with chronic evolution (11, 36, 60, 61). However, establishing just who may resolve before reaching the chronic phase has proved difficult because so few cases are actually detected. Predicting whether acute HCV infection will become chronic is important, because the acute phase of infection is the period when treatment is easier and is associated with higher response rates.

Can Spontaneous Resolution of Acute HCV Infection Be Predicted?

Although no reliable predictors for spontaneous resolution have been identified, several clinical features have been associated with spontaneous viral clearance in patients with acute HCV. Patients less than 40 yr of age are more likely to undergo spontaneous resolution (11, 63, 65–67). Interestingly, children with HCV infection have a 75–100% chance of spontaneous resolution (25, 26). Self-limiting disease is also significantly more common in women than men (40% *vs* 19%, $P < 0.01$) (13, 27, 63, 67). Several studies have identified symptomatic disease, particularly jaundice, as a predictor of spontaneous viral clearance, presumably reflecting a more effective host immune response that is capable of eradicating the virus by killing infected hepatocytes and that is responsible for clinical manifestations (11, 12, 61, 63–67). Individuals with coinfections such as those with concomitant HIV (38–40) or *Schistosoma mansoni* infection are far less likely to spontaneously clear HCV than those without (68, 69). Additionally, patients with weakened immune systems, such as organ transplant recipients, experience more frequent progression to chronic infection (70).

Several studies demonstrated that cellular immune responses play a crucial role in spontaneous resolution of acute HCV. Clearance of HCV is associated with the development of robust and multispecific $CD4^+$ and $CD8^+$ T-cell responses in blood and liver (65, 68–74) that, in some cases, can be maintained for years after recovery from acute disease (74). In contrast, individuals who progress to chronic infection fail to mount such a response or may have inadequate production of the cytokines essential to control viral replication (71, 72). Incomplete control of viral replication by CD8+ T cells in the absence of sufficient memory CD4+ T cells leads to viral persistence and emergence of cytotoxic T lymphocyte escape mutants (73, 75).

Some virological factors have been associated with spontaneous resolution. Farci *et al*. (76, 77) showed that acute resolving hepatitis was associated with homogeneity of the HCV quasispecies, whereas progressing hepatitis correlated with genetic diversity, presumably reflecting greater immune pressure during acute spontaneous clearance. Similarly, a reduction in genetic diversity leading to an increasingly homogeneous viral population was a consistent feature associated with viral clearance in sustained responders. No association between HCV-RNA levels and spontaneous resolution of HCV infection has been established. Similarly, no relationship between genotype and self-limited disease has been demonstrated outside of a single report (78) that has not been confirmed elsewhere.

Natural History and Clinical Presentation of Acute HCV Infection in Special Patient Populations

HEMODIALYSIS PATIENTS. Data on the natural history and clinical outcomes of acute HCV in end-stage renal disease (ESRD) are scarce due to the lack of longitudinal studies of adequate size and long follow-up. An understanding of the course of disease in such patients is crucial, however, to developing indications for therapy. The available data suggest that acute HCV infection among this patient group is usually asymptomatic and rarely recognized (43, 44, 50). Some hemodialysis patients may have delayed seroconversion and others may not develop hepatitis C antibodies despite the presence of viremia; thus, polymerase chain reaction (PCR) is necessary for diagnosis of these cases. The rates of spontaneous resolution in hemodialysis patients range between 20 and 34% and are thus similar to rates reported in nonuremic patients in analyses of community-acquired HCV (63, 64). Hemodialysis patients who newly acquire HCV infection and develop chronic HCV viremia may have significant liver disease and severe chronic hepatitis on liver biopsy despite normal liver enzymes (49, 51).

HIV-INFECTED PATIENTS. Little is known about the clinical presentation and course of acute HCV infection in HIV-infected patients. Coinfection with HCV is seen in 15–30% of the HIV-infected population of the United States (18, 79). Acute hepatitis C is mostly asymptomatic (11, 38). Diagnosis is made when investigating causes of unexplained liver enzyme elevation in an HIV-coinfected patient (40). Compared with HIV-uninfected patients, HIV-infected patients have higher HCV viral loads (80, 81), lower rates of spontaneous HCV clearance (40, 80), and sometimes accelerated liver disease in those who fail to clear the virus (80). HCV antibody may remain negative for up to 6 months and occasionally for longer periods. When serum HCV antibody is negative, serum HCV-RNA is a useful diagnostic tool that may aid in the prompt diagnosis of acute HCV infection (40, 80).

Treatment of Acute Hepatitis C

To date, the optimal treatment strategy in acute HCV infection is controversial given the variable rates of spontaneous resolution and the absence of symptoms in many patients. There are several factors that provide a rationale for treating patients with acute HCV such as the high rate of chronic evolution and the lack of reliable predictive factors for the outcome of acute infection. Compared with acute HCV, chronic HCV is associated with a worsening prognosis, the need for more intensive treatment with pegylated interferon (PEG-IFN) and ribavirin, longer treatment duration, and a decline in successful treatment outcomes. Conversely, intervention during the acute phase is associated with improved viral eradication using a monotherapy regimen that is better tolerated, less expensive, more convenient, and shorter than the currently approved combination therapies for chronic HCV (82). From the public health standpoint, early diagnosis and treatment in at-risk populations helps to reduce the risk of HCV transmission.

Evolution of Acute Hepatitis C Treatment

Several clinical trials addressed the optimal treatment regimen and showed significant improvement in the rate of sustained virologic response (SVR) rates with interferon (IFN)-based therapies compared with no treatment (82).

CLINICAL TRIALS USING CONVENTIONAL INTERFERON THERAPY. Most of the early studies of acute HCV were uncontrolled investigations in small patient groups, often employing biochemical endpoints. They were generally open-label studies using IFN α-2b at a dose of 3 MU three times weekly for variable durations. Overall, SVR rates ranged between 32 and 100% (83–89). However, the diverse enrollment criteria, small number of subjects, heterogeneity of the patients, lack of controls, different types and doses of IFNα, differences in the definition of response, and lack of sufficient follow-up periods to rule out late relapse render the results of such trials difficult to interpret given that 20–40% of patients with acute HCV may resolve spontaneously (11, 13, 65).

Adopting an early aggressive approach to therapy, patients with acute HCV were treated with IFN alfa-2b at a daily dose of 5 MU for 4 wk and then 5 MU three times weekly for a further 20 wk. The SVR rate was 98% with almost no dropouts or adverse events despite the high dose of daily interferon and the extended duration of treatment. Although Jaeckel *et al*. (84) achieved high efficacy rates using conventional IFN induction therapy, the necessity for daily injections with high doses of IFN during the first 4 wk of therapy represents significant inconvenience to patients with a high probability of adverse events and noncompliance particularly in IDUs.

CLINICAL TRIALS USING PEGYLATED INTERFERONS. Pegylation of the IFN alfa (PEG-IFNα) molecule was a major advance in the treatment of chronic HCV due to the higher SVR rates induced by PEG-IFNα. Furthermore, PEG-IFNα helped to reduce the number of outpatient visits and improved patient compliance due to the lower administration frequency (90). Subsequently, several randomized and nonrandomized clinical trials were conducted to assess the efficacy and safety of PEG-IFNα in acute HCV. The major modes of transmission of HCV in these trials were IV drug use, needle stick injuries, medical procedures, or sexual contact with known HCV positive partners. The SVR rates with treatment of 12–24 wk with PEG-IFN alfa-2b monotherapy ranged between 71 and 95% (91–98) (Table 1) depending on the populations treated, HCV genotypes, onset of therapy, and compliance to therapy. These SVR rates are broadly similar to the SVR rates reported using IFN induction therapy when it is initiated 8–12 wk after onset. A randomized

Table 1. Summary of Studies Evaluating Interferon-Based Therapy in Patients With Acute Hepatitis C Virus Infection

Study	Design	Patients (N)	Cohort	Mode of Transmission	HCV Genotypes Genotype (%)	Spontaneous Clearance N/n (%)	Treatment Regimen	Time to Initiation of Therapy	Duration of Therapy	SVR N (%)
Studies using conventional IFNα										
Vogel *et al*. (83)	Non-R	24	Whites Mostly symptomatic	IDU Medical procedure Unknown	1 (42) 2/3 (21) Mixed or NA (37)	NA	IFN alfa-2b 10 MU/day	NA	Until normalization of ALT 18–43 days	20/22 (91)
Jaeckel *et al*. (84)	Non-R	44	Whites Mostly symptomatic	Needle sticks/medical procedures(48%) IDU (20%) Sexual (23%) Unknown (9%)	1 (61) 2/3 (27) 4 (0) NA (12)	NA	Induction IFN alfa-2b 5 MU/day for 4 wk followed by IFN alfa-2b 5 MU tiw	Immediately (average of 89 days from infection to start of therapy)	20 wk	42/43 (98)
Nomura *et al*. (85)	R	30	Asians Mostly symptomatic (59%)	Needlesticks (30%) IDU (10%) Sexual (13%) Unknown (43%)	1 (87) 2/3 (13)	NA	Early intervention: IFN alfa (human lymphoblastoid IFN) 6 MU/day IM Late intervention: IFN alfa (human lymphoblastoid IFN) 6 MU/day IM	8 wk from onset of symptoms After 1-yr follow-up	4 wk	13/15 (87) 8/15 (53)
Pimstone *et al*. (87)	Non-R	10	Whites	Needlesticks (60%) IDU (1%) Others (39%)	1 (70) 2/3 (30)	3/10 (30)	Induction IFN alfa-2b 5 MU/day for 12 wk followed by IFN alfa-2b 3 MU tiw	14 wk‡	40 wk	7/7 (100)
Delwaide *et al*. (89)	Non-R	28	Whites 22/28 symptomatic		1 (12) 2/3 (5) 4 (1) NA (10)	19%	IFN alfa-2b 5 MU/day	Mean, 110 ± 44	8 wk	21/28 (75)
Studies using PEG-IFNα										
Rocca *et al*. (86)	Non-R	16	Whites Symptomatic (60%)	IDU (38%) Needle-sticks/medical procedure (25%) Piercing (6%) Sexual (19%) Unknown (2%)	1 (50) 2/3 (38) NA (12)	NA	Dosing regimens varied. PEG-IFN and/or IFN alfa-2b ± RBV	<70 days	Variable: 2.5–12 months	12/13 (92)
Gerlach *et al*. (65)	Non-R	60	Whites Symptomatic (85%)	IDU (25%) Medical procedure (33%) Sexual (10%) Needlstick injuries (9%)	1a (24) 1b (40) 2/3 (32) 4 (4)	24/54 (44)	IFN alfa 3–5 MU tiw IFN alfa 3–5 MU tiw + RBV PEG-IFN α-2a 80–100 μg/week PEG-IFN α-2a 80–100 μg/week + RBV	0–26 months from onset of symptoms	14–61 wk	7/10 (70) 9/10 (90) 1/2 (50) 4/4 (100)

Continued.

Table 1. Continued

Study	Design	Patients (N)	Cohort	Mode of Transmission	HCV Genotypes Genotype (%)	Spontaneous Clearance N/n (%)	Treatment Regimen	Time to Initiation of Therapy	Duration of Therapy	SVR N (%)
					Studies using PEG-IFNα					
Kamal *et al*. (92)	R	54	Whites Mostly asymptomatic	Mostly occupational exposure to needlesticks and sharp injuries or medical procedures	1 (37) 4a (90)	5/54 (9)	PEG-IFN α-2a 180 μg/week ± RBV 800 mg/day PEG-IFN α-2b 1.5 μg/kg/week ± RBV 10.6 mg/kg/day	12 wk from onset of symptoms or first detectable HCV-RNA	24 wk	17/20 (85)* 16/20 (80)†
Santantonio *et al*. (91)	Non-R	28	Whites Symptomatic (50%)	Medical procedures (37.5%) Sexual (19%) IDUs (12.5%) Unknown (31%)	1 (38) 2/3 (62)	11/28 (39)	PEG-IFN alfa-2b 1.5 μg/kg/week	12 wk from onset of symptoms	24 wk	15/16 (94)
Broers *et al*. (88)	Non-R	27	Whites Symptomatic (57%)	IDU (81%) Unknown (19%)	NA	5/27 (19)	PEG-IFN alfa-2b 1.5 μg/kg/week	100 ± 82 days from onset of symptoms or 63 ± 53 days from the first HCV detectable assay in patients without symptoms	24 wk	8/14 (57)
Wiegand *et al*. (93)	Non-R	89	Whites Symptomatic (60%) HIV coinfection (4%)	Medical procedures and needles sticks (30%) IDU (22%) Sexual (22%) Others (8%) Unknown (17%)	1 (66) 2/3 (22) 4 (1) not identified (11)	NA	PEG-IFNα-2b 1.5 μg/kg	76 days after infection	24 wk	63/89 (71)
Kamal *et al*. (94)	R	168	Whites Symptomatic and asymptomatic	Occupational exposure, medical procedures, IDUs	1b (40) 2/3 (8) 4 (58)	31/141 (22)§	PEG-IFNα-2b 1.5 μg/kg	8 wk from onset 12 wk from onset 20 wk from onset	12 wk	41/43 (95) 40/43 (93) 33/43 (77)
De Rosa *et al*. (96)	Non-R	19	Whites Mostly asymptomatic (74%)	IDU (74%) Sexual (16%) Needlesticks (10%)	1 (58) 2/3 (42)	NA	PEG-IFNα-2b 1.06–1.66 μg/kg/week	Mean 33.6 days, range 0–116 days	12 wk	14/19 (74)

Continued.

Table 1. Continued

Study	Design	Patients (N)	Cohort	Mode of Transmission	HCV Genotypes Genotype (%)	Spontaneous Clearance N/n (%)	Treatment Regimen	Time to Initiation of Therapy	Duration of Therapy	SVR N (%)
					Studies using PEG-IFNα					
Kamal *et al*. (95)	R	173	Whites Symptomatic and asymptomatic	Occupational exposure or medical procedures	Mostly 4a and 1b	29/131 (22)	PEG-IFNα-2b 1.5 μg/kg/week for PEG-IFN α-2b 1.5 μg/kg/week for PEG-IFN α-2b 1.5 μg/kg/week for	12 wk	8 wk 12 wk 24 wk	23/34 (68) 28/34 (82) 31/34 (91)
Corey *et al*. (66)	Non-R	24 and 15 were treated	Whites Symptomatic and non-symptomatic	IDU (60) Needlesticks (31) MSM (9)	1 (87) 2/3 (13)	29%	Variable regimen IFN-α-2b (9–42 MIU), or PEG-IFNα-2b 1.33 μg/kg per week or PEG-IFNα-2a (180 μg weekly) ± ribavirin 1,000–1,200 mg	21 days (range 14–183) after symptoms	30.7 ± 12 wk	18/24 (75)
Calleri *et al*. (97)	Non-R	46	Whites Symptomatic (23%)	IDUs (57%) Surgery (6%) Sexual (5%) Needle sticks (7%) Unknown (13%)		NA	PEG-IFNα-2b, 1.0–1.5 μg/kg weekly	1–90 days	12 wk	33/46 (72)
De Rosa *et al*. (98)			Whites Symptomatic and non-symptomatic	IDUs (100%)	1 (58) 2/3 (42)		PEG-IFNα-2b 1.33 μg/kg per week	12 wk	12 wk	17/23 (74)
					Studies in HIV patients with acute hepatitis C					
Vogel *et al*. (101)	Non-R	11	Whites HIV/HCV coinfection	IDU Sexual	1 (80) 2/3 (20)	NA	IFNα (2)[ω] PEG-IFNα (4)[ω] PEG-IFNα and ribavirin (5)[ω]	25 wk		10/11 (91)
Vogel *et al*. (102)	Non-R	47	Whites HIV/HCV coinfection	Sexual MSM (90%) IDU (10%)	1 (70) 2/3 (1) 4 (20)	NA	PEG-IFNα PEG-IFNα and ribavirin	24 wk 48 wk		22//36 (61)
Dominguez *et al*. (99)	Non-R	25	Whites HIV/HCV coinfection	Sexual IDU	1 (24) 2 (28) 4 (44) 1 + 4 (4)	1/25 (4)	PEG-IFNα-2a (180 μg/week) and ribavirin (800 mg/day)	3–24 wk	24 wk	10/14 (71)

Continued.

Table 1. Continued

Study	Design	Patients (N)	Cohort	Mode of Transmission	HCV Genotypes Genotype (%)	Spontaneous Clearance N/n (%)	Treatment Regimen	Time to Initiation of Therapy	Duration of Therapy	SVR N (%)
Studies in HIV patients with acute hepatitis C										
Serpaggi *et al.* (103)	Non-R	10	Whites HIV/HCV coinfection	Sexual MSM	4 (100)	NA	Dosing regimens varied. PEG-IFN and/or IFN alfa-2b ± RBV	NA	24 wk	0
Gilleece Y *et al.* (100)	Non-R	27	Whites HIV/HCV coinfection	Sexual MSM	1 (74) 4 (26)	24%	PEG-IFNα-2b 1.33 μg/kg per week	12 wk	24 wk	16 (59)
Studies on treatment of dialysis patients with acute hepatitis C										
Griveas I *et al.* (44)	N-R	6	Whites Chronic renal failure on hemodialysis	Nosocomial Iatrogenic??	1b (100)	NA	Peg-IFNα-2a 135 μg per week	NA	24 wk	4 (66)

HCV = hepatitis C virus; IFN = interferon; IM = intramuscular; NA = not available; Non-R = nonrandomized; PCR = polymerase chain reaction; MU = million units; PEG-IFN = pegylated interferon; R = randomized; RBV = ribavirin; RT = reverse transcription; SVR = sustained virologic response; LLOQ = lower limit of quantification; tiw = three times weekly; TMA = transcription-mediated amplification, MSM = men having sex with men.

*Patients receiving combination (PEG-IFN alfa-2a/2b and RBV) therapy.

†Patients receiving monotherapy (PEG-IFN 2a/2b) only.

‡Patient (N = 1) with nosocomial infection started treatment at week 20.

§Treatment arm only; N = 141 patients.

Treatment arm only; N = 131 patients.

#LLOQ not provided.

ωNumber of patients.

trial showed that adding ribavirin was not necessary for treatment of acute HCV monoinfection, as no significant difference was detected between the PEG-IFNα monotherapy and PEG-IFNα and ribavirin combination regimens for the overall cohort SVR rates (92). So far, no study has shown a benefit for combination therapy with interferon plus ribavirin. Most clinical trials showed that PEG-IFNα treatment of acute HCV was associated with fewer adverse events compared with chronic HCV. This might be explained by the use of a single agent and the shorter duration of treatment.

Taken together, recent data demonstrate that PEG-IFNα-2b monotherapy in acute hepatitis C induces high SVR rates and is well tolerated. PEG-IFNα monotherapy represents a viable alternative to aggressive induction therapy with conventional IFN and results in similar response rates without the associated complications.

Treatment of Acute HCV in Special Populations

TREATMENT OF ACUTE HEPATITIS C IN HIV-COINFECTED PATIENTS. Few studies evaluated PEG-IFN α-based therapy in HIV-coinfected patients with acute HCV infection (98–101). In a French study, a 71% SVR rate was achieved with combination therapy of PEG-IFN α (180 μg/week) and ribavirin (800 mg/day) for 24 wk (99). In another study from Germany, an overall SVR rate of 91% was achieved in coinfected patients treated with either IFNα, PEG-IFNα monotherapy, or PEG-IFNα and ribavirin therapy (100) (Table 1). Other studies (100–102) showed 59–61% overall SVR rates in HIV-positive patients with sexually transmitted acute HCV treated with PEG-IFNα or PEG-IFNα combined with ribavirin. Higher treatment response rates were observed in patients treated for over 48 wk compared with 24 wk (99). Patients infected with HCV genotype 4 showed lower SVR rates (103). Therapy for acute HCV may be associated with significant side effects including neutropenia, anemia, and depression. These data suggest that SVR rates in HIV-positive patients with acute HCV infection are lower than in HIV-negative subjects. HIV patients with acute HCV might require longer more aggressive therapy and the addition of ribavirin might be necessary. Further investigation is warranted to evaluate the efficacy and safety of acute HCV therapy in HIV-infected individuals and to elucidate the optimal components and duration of therapy.

TREATMENT OF ACUTE HCV IN PATIENTS RECEIVING HEMODIALYSIS. HCV is an increasingly recognized infection in patients on dialysis because it may increase morbidity and mortality after kidney transplantation. It is thus important to identify effective and safe antiviral agents for this group of patients. However, the literature on the efficacy and safety of IFN-based regimens in acute HCV in dialysis patients is limited to small nonrandomized studies. Published trials utilized conventional IFNα or PEG-IFNα given that ribavirin may be dangerous in dialysis patients, because it is

associated with hemolytic anemia and many dialysis patients are already anemic.

In one study (102), 23 hemodialysis patients with proven acute HCV were treated with either a low dose of IFNα (3 MU three times per week) for 12 months or a high dose (5 MU three times per week, preceded by a daily induction dose) for 6 months. The SVR rate was 38% in lower doses *versus* 57% in higher doses. In another study (43), six patients received PEG-IFNα2 in a dose of 135 μg, 3 months after the acute infection, for a 6-month period. Four patients responded to therapy. The optimal treatment of hepatitis C in dialysis patients remains to be established.

CHALLENGES IN TREATING ACUTE HEPATITIS C. Acute HCV infection is associated with variable spontaneous clearance rates, and IFN-based therapy is associated with both adverse events and significant cost. The optimization of acute HCV therapy is thus critical to ensure that SVR rates are maximized and chronic infection is prevented without exposing the patient to an unnecessarily long and costly treatment regimen with its associated adverse events. Given that most acute HCV cases are asymptomatic and that, as a clinical entity, acute HCV is not commonly seen in clinical practice, particularly in western countries, there is a paucity of large, multicenter, well-designed, randomized, controlled trials conducted with well-characterized cohorts for the treatment of this disease. Until recently, the onset and duration of therapy for acute HCV was not well defined; however, emerging data are helping to clarify the optimal timing and duration of therapy as well as determinants of SVR.

WHEN SHOULD ACUTE HCV PATIENTS BE TREATED? The appropriate timing of IFN-based therapy in acute hepatitis has not been accurately determined. This is because clinical trials enrolling well-characterized cohorts with known time of infection and conversion from HCV-negative to HCV-positive status are necessary to address this issue. The exact onset of infection could be determined in some incidents, such as needle-stick injuries, after unsafe medical procedures, or after unprotected sexual contact with an HCV positive partner. However, in many cases the actual time of HCV infection is difficult to determine. Thus, in most clinical trials, therapy was initiated at various time points ranging between 1 and 24 months from the appearance of symptoms, the first positive HCV-PCR, or at seroconversion. A randomized, controlled study showed that treatment of acute HCV infection within 8 wk of exposure yielded higher rates of SVR (87%) compared with the SVR rates (40%) achieved when therapy is delayed 112 months after exposure (84). In another study of acute HCV, patients were randomized to begin PEG-IFN 8, 12, or 20 wk after recognition of infection. A greater proportion of those who started treatment 8 or 12 wk after recognition achieved sustained viral suppression compared with those who started it 20 wk later (93). In studies in which treatment was initiated within 8–12 wk, the SVR rates ranged between 71 and 100% (83–85, 89, 90, 93, 95, 96) (Table 1**)**. Thus, there is a growing consensus that delaying treatment 3–4 months after the onset of infection is a reasonable strategy that gives every opportunity for patients to spontaneously clear the virus through HCV-specific T-cell activity, without jeopardizing treatment outcomes in those who will fail to spontaneously clear.

HOW LONG SHOULD ACUTE HEPATITIS C PATIENTS BE TREATED? The optimal duration of PEG-IFN treatment for acute HCV infections has not been adequately determined, as clinical trials have evaluated variable durations of conventional IFN treatment or PEG-IFN (ranging from 4 to 48 wk) with variable results, and most studies did not follow patients for sufficiently long enough periods to rule out late relapse (63, 81–87, 89–96). In patients in whom spontaneous resolution does not occur 3 months after infection, 12–24 wk of treatment has been shown to be effective and well tolerated in various clinical trials, and appears to provide the best SVR rates. Recently, four clinical trials showed that 12 wk of therapy may be sufficient for the treatment of acute HCV, particularly in nongenotype 1 patients (92, 93, 95, 96). PEG-IFN for 12 wk to treat hepatitis C has a compliance that is much higher, particularly in IDUs, than that reported with a 24-wk regimen. Adverse effects are minimal and follow-up of patients treated for 12 wk did not show an increase in relapse rates compared with those treated for 24 wk. Further studies are required to identify factors for individualizing the duration of therapy in acute HCV infection.

WHO IS LIKELY TO ACHIEVE SVR? To date, the predictors for SVR in acute HCV therapy have not been fully identified and further research is required. Recent data have shown some factors that might be considered when individualizing therapy for acute HCV infection. Several studies suggest that symptomatic patients, young individuals, and women respond better to treatment (81, 83, 91–96). Virological factors such as HCV nongenotype 1, low baseline viral load, and rapid virological response (undetectable serum HCV-RNA or a >2 $\log_{10}$ decrease at week 4) are probably associated with favorable treatment outcome (94, 97). HIV-coinfected patients may need combination therapy and require it for a longer duration. These data can be used as a platform for further research to optimize therapeutic options for patients with acute HCV, and to define optimal therapeutic outcomes in acute hepatitis. In addition, research to better describe patients who do or do not respond by evaluating the impact of factors such as gender, ethnicity, obesity, mode of transmission, HCV genotypes, and viral kinetics on response to therapy is needed. Another challenge is how to manage patients who relapse or who do not respond to therapy during the acute phase.

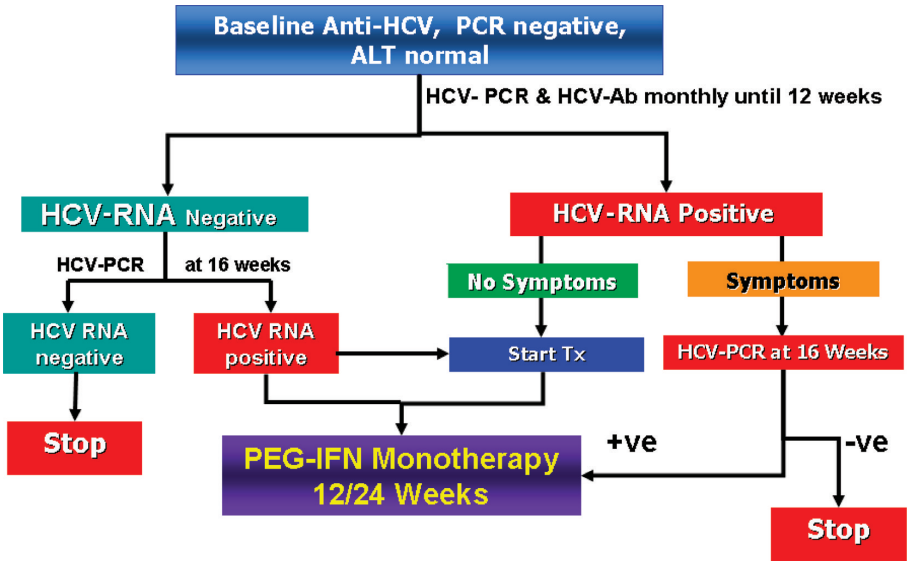

Figure 2. Proposed clinical algorithm for management of acute hepatitis C.

CAN ACUTE HCV THERAPY BE INDIVIDUALIZED? In an effort to improve rates of sustained response to interferon-based therapy for chronic hepatitis C, various strategies have been adopted for tailoring drug doses and treatment durations according to pretreatment parameters and on-treatment response to meet the needs of individual patients. A similar approach might be necessary to optimize acute hepatitis C treatment. Some studies showed that acute hepatitis patients infected with genotypes other than genotype 1 have higher rates of SVR (92–96). In one study (95), SVR was achieved in 60% and 88% of genotype 1 patients and in 93% and 100% of genotype 4 patients after 12 and 24 wk of treatment, respectively. Rapid virological response (undetectable HCV-RNA levels or >2 $\log_{10}$ decrease in HCV-RNA levels after 4 wk of therapy) was predictive of SVR (95, 98). Clearly, there is no "one size fits all" approach to treatment of patients with acute hepatitis C. If a patient appears likely not to have spontaneous resolution of infection, then a decision to treat needs to be individualized according to a variety of factors that could influence outcome such as baseline clinical condition, ethnic background, likelihood of adherence, genotype, and IDU history. However, more clinical trials are needed to clarify the impact of different pretreatment criteria and on-treatment viral kinetics on determining the onset and duration of an IFN-based regimen in the setting of acute hepatitis C.

CONCLUSIONS AND FUTURE PROSPECTS

Acute HCV is not a commonly encountered clinical entity due to its mostly asymptomatic nature and variable rates of spontaneous resolution. However, acute HCV represents an important window in the time course of this infection during which medical intervention is greeted with a high degree of success.

A proposed algorithm for the management of patients with acute HCV infection is shown in Figure 2. In the absence of contraindications to therapy, patients with acute HCV should be considered eligible for therapeutic intervention. The SVR rates in the acute setting far exceed those attained in patients with chronic HCV. For this reason, early intervention may be the best opportunity to attain viral eradication. An 8- to 12-wk window of "watchful waiting" between exposure to HCV and initiation of therapy is important to allow for the possibility of spontaneous resolution. Patients might be treated for 12 or 24 wk; however, further research is warranted to identify individuals eligible for the shorter regimen.

From a public health standpoint, health-care systems should adopt strategies to identify individuals at high risk for HCV infection and provide opportunities for education and behavior modification. In developing countries with a high endemic background of HCV infection, surveillance programs, and efforts to increase awareness, improve diagnosis, and facilitate treatment of acute HCV will have far-reaching implications for the management of chronic HCV, where current disease management and health outcome strategies are less effective.

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Received July 14, 2007; accepted December 12, 2007.

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CONFLICT OF INTEREST

The author declared no potential conflict of interest.

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