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Prevention of Spread of HCV

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Historically, the most reliable data on risk factors associated with acquiring hepatitis C virus (HCV) infection have been obtained from cohort (prospective) studies that determined the risk of developing acute infection after a specific exposure and case-control (retrospective) studies that determined if a history of exposure before onset of disease was associated with newly acquired (acute) hepatitis C. Risk factors identified by these studies in the United States included injecting drug use, blood transfusion and solid organ transplants from infected donors, occupational exposure to blood (primarily contaminated needle sticks), birth to an infected mother, sex with an infected partner, or multiple heterosexual partners.

The major limitation of such studies is that they are unlikely to identify associations with exposures that result only rarely in infections. For example, results of case-control studies have indicated no association between acquiring hepatitis C and exposures resulting from medical, surgical, or dental procedures. However, outbreaks of HCV infection have been associated with contaminated equipment in hemodialysis settings and unsafe injection practices in both inpatient and outpatient settings. Most of these outbreaks have involved patient-to-patient transmission. Only two instances of transmission have been reported from HCV-infected health care workers to patients in the United States. Neither of these was associated with the performance of exposure-prone invasive procedures, but rather with contamination of patients' narcotics used for self-injection.

The contribution of these various risk factors to the overall burden of HCV infections is influenced both by their efficiency in transmitting HCV and by the frequency of the exposure in the population. In the United States, the relative importance of the two most efficient exposures associated with transmission of HCV, blood transfusion and injecting drug use, has changed over time. Blood transfusion, which accounted for a substantial proportion of HCV infections acquired >15–20 years ago, rarely accounts for recently acquired infections. In contrast, injecting drug use consistently has accounted for a substantial proportion of HCV infections and currently accounts for 60 percent of HCV transmission. The relative importance of other exposures has changed little over time.

Unprotected sex with an infected partner or with multiple partners has accounted for an estimated 15 percent of HCV infections. Although the role of sexual activity in the transmission of HCV remains controversial, and the virus is inefficiently spread in this manner, the relatively substantial contribution of sexual exposures to the burden of disease can be explained by the fact that sexual activity with multiple partners is a common behavior in the population and that the large number of chronically infected persons provides multiple opportunities for exposure.

In contrast to sexual exposures, occupational and perinatal exposures contribute to a small proportion overall of infections, and together with nosocomial or iatrogenic exposures, they account for about 5 percent of HCV infections. HCV is not transmitted efficiently through occupational exposure. The prevalence of HCV infection among health care or public safety workers averages 1–3 percent and has not been affected by changes or improvements in barrier precautions. Transmission rates from HCV infected mothers to their infants average 5 percent or less, no associations have been demonstrated with mode of delivery or type of feeding, and infants who acquire HCV infection at birth may be less likely to develop chronic infection.

Thus, about 90 percent of HCV infections can be accounted for by known percutaneous or mucosal exposures to blood. In the remaining 10 percent, no recognized source for infection can be identified. Numerous studies have attempted to identify additional risk factors for HCV infection. While case-control studies of acute hepatitis C reported no association with tattooing, acupuncture, ear piercing, military service, or foreign travel, cross-sectional and prevalence studies of volunteer blood donors, disease-specific clinic patients, and veterans receiving care in VA hospitals have yielded conflicting results for some of these risk factors. The lack of consistency among studies of highly selected groups for which the temporal sequence of exposure relative to the disease was unknown is cause for concern about the generalizability of such results.

Strategies for reducing or eliminating the potential risk for transmission include: (1) screening and testing of donors; (2) virus inactivation of plasma-derived products; (3) risk reduction counseling and services; and (4) implementation and maintenance of infection-control practices. Strategies for reducing risks for chronic disease include: (1) identification, counseling, and testing of at-risk persons; and (2) medical evaluation and management of infected persons.

Health care professionals in all patient care settings routinely should obtain a history that inquires about blood transfusion, use of illegal drugs (injection and non-injection) and evidence of high-risk sexual practices, such as multiple sex partners or 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 of STDs such as HIV, HBV, syphilis, gonorrhea, and chlamydia.

Testing should be offered routinely to persons most likely to be infected with HCV, which include persons who ever injected illegal drugs; received plasma-derived products known to transmit HCV infection that were not treated to inactivate viruses; received transfusions or solid organ transplants before July 1992; and were long-term hemodialysis patients. Based on a recognized exposure, testing also is indicated for health-care workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood and for children born to HCV-positive women. Immune globulin and antiviral agents are not recommended for post-exposure

prophylaxis of hepatitis C.

HCV-positive persons with a long-term steady partner do not need to change their sexual practices; however, they should discuss with their partner the need for counseling and testing, and the couple should be informed of available data on risk for sexual transmission of HCV to assist them in making decisions about precautions, including the low, but not absent, risk for transmission. HCV-positive persons do not need to avoid pregnancy or breastfeeding, and determining the need for cesarean delivery vs. vaginal delivery should not be made on the basis of HCV infection status. There are no recommendations for routine restriction of professional activities for HCV-infected health-care workers, and persons should not be excluded from work, school, play, child-care or other settings on the basis of their HCV infection status.

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Sexual Activity as a Risk Factor for Hepatitis C Infection

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Percutaneous exposures are well-recognized risk factors for HCV, hepatitis B virus (HBV), and HIV. However, there are clear differences between these viruses with respect to their frequency of transmission through sexual contact. The accumulated epidemiological evidence indicates that HCV can be sexually transmitted but much less efficiently than HBV and HIV.

Epidemiological studies evaluating the magnitude of risk of HCV transmission by sexual activity have several methodological shortcomings that tend to overestimate the proportion of HCV infections associated with sexual contact. Early studies used first-generation anti-HCV assays, which have a higher false positive rate than second- and third-generation assays. Studies vary in the completeness of risk ascertainment and many fail to carefully exclude HCV acquisition from non-sexual sources. Non-disclosure of injection drug use (IDU) as a risk factor is particularly important since assessing the contribution of sexual activity to HCV transmission is difficult in the presence of IDU. Finally, only a limited number of studies perform virological analyses to confirm that sexual partners are infected with the same virus and to exclude acquisition from outside sources.

Reported rates of HCV infection in sexual partners differ by geographical region, with higher rates reported in countries with higher endemic rates of HCV infection. Rates of anti-HCV positivity also vary by risk group, with higher rates of HCV reported in persons with a history of sexually transmitted diseases (STDs) and lower rates in heterosexual partners in long-term relationships. This difference may reflect the frequency of exposure to different HCV-infected

sexual partners (higher in those with multiple partners than those in monogamous relationships). Alternatively, these risk groups may reflect differing rates of exposure to other non-sexual sources of HCV, such as IDU. The findings regarding sexual transmission in one group may not be generalizable to other groups or to the general population.

How Prevalent is the Risk Factor "Sexual Activity" in Persons with Acute Hepatitis C?

The Centers for Disease Control and Prevention collects detailed risk factor data on newly diagnosed cases of acute hepatitis C. In these surveillance studies, 15–20 percent of cases of acute community-acquired HCV occur in persons who report unprotected sexual contact with an anti-HCV positive person in the preceding 6-month period (two-thirds of cases) or multiple sexual partners (one-third of cases) as their only risk factor for HCV acquisition. Limited access to the sexual contacts prevents virological evaluation of the transmission events.

What is the Prevalence of HCV in Persons at Risk for Sexually Transmitted Diseases?

In U.S. seroprevalence studies conducted among sex workers, persons attending STD clinics, or persons participating in HIV surveillance studies, 1.6–25.5 percent of individuals are anti-HCV positive. In studies including persons with a history of IDU, anti-HCV positivity is more strongly associated with IDU than with factors related to sexual practices. In studies limited to individuals without a history of IDU, anti-HCV positivity is identified in 1.6–7 percent of STD clinic attendees, and risk factors associated with HCV are number of recent and lifetime partners, high-risk sexual contact (variably defined), and anti-HIV positivity. In homosexual and bisexual men, rates of anti-HCV positivity range from 2.9–12.7 percent with higher rates among those with HIV infection, but again IDU rather than sexual risk factors is most strongly associated with being HCV-positive.

What is the Prevalence of HCV in Monogamous Heterosexual Couples?

Among steady heterosexual partners of HCV-infected, HIV-negative persons, 0–24 percent are anti-HCV positive, with marked geographical variability. The median rate of anti-HCV positivity in sexual partners is 1.0 percent in North America and Northern Europe, 6 percent in Southern Europe, and 11 percent in Southeast Asia. Studies using genotyping or viral sequence analysis to assess anti-HCV concordant couples find lower rates of HCV transmission than studies using antibody testing alone. The duration of the sexual relationship is not predictive of HCV positivity in partners after adjusting for age. In studies comparing HCV positivity among sex partners vs. other family members, the rates of HCV positivity are higher in spouses than in other family members. However, after controlling for age and other parenteral exposures, anti-HCV positivity is no longer consistently associated with the type of relationship.

The majority of the published studies use genotyping rather than viral sequence analysis to evaluate anti-HCV concordant couples. Genotyping is suboptimal since HCV genotypes that are prevalent in the population may be present in partners even though they may have acquired the virus from different sources. For example, a study of 24 anti-HCV concordant couples found that 12 had concordant genotypes, 7 had discordant genotypes, and 5 were untypable. Seven of the 12 couples could be analyzed by sequence analysis, and only 3 were highly homologous and consistent with transmission. Thus, overestimation of HCV sexual transmission occurs if genotyping rather than sequence analyses is used to evaluate infected partners.

What is the Incidence of HCV Infection in "At Risk" Individuals?

In prospective studies (1–3.7 years follow-up) conducted in high-risk cohorts of non-IDU sex workers and patients in STD clinics, the incidence of HCV is 0.4–1.8/100 person-years (~1 percent). Small sample size precludes evaluation of specific sexual practices as risks for HCV acquisition. Undisclosed IDU may contribute the higher incidence of infection in this subgroup.

Based upon results from a prospective cohort of 499 Italian couples followed for a mean of 12.4 months, the incidence of new infection in sexual partners is 12 per 1,000 person-years. Sequence analysis of the HCV-positive couples reveals a high degree of sequence homology in only 50 percent of the couples, suggesting non-sexual sources of HCV acquisition and a true incidence of no more than 6 per 1,000 person-years. In retrospective cohorts of female partners of hemophiliacs, the incidence is 1 to 1.87 per 1,000 person-years; among male partners of women infected by contaminated anti-D immunoglobulin, the incidence is 0.28 per 1,000 person-years; and among liver clinic patients and their sexual partners, the incidence is 1 to 3.86 per 1,000 person-years.

Factors That May Affect the Risk of HCV Transmission by Sexual Contact

In studies involving persons at risk for STDs, HIV co-infection is an independent predictor of anti-HCV positivity in the majority of studies. In studies involving hemophiliacs with HIV and HCV, the rate of anti-HCV positivity is higher in female partners of dually-infected men compared to men with HCV infection only. Studies from STD clinic attendees also suggest that co-infection with other STDs or sexual practices which may traumatize the mucosa (anal receptive sex) may increase the risk of sexual transmission of HCV. Whether the risk of HCV transmission differs for males vs. females is unclear. In one study of heterosexual couples in STD clinics, females with HCV-positive partners were 3.7 times more likely to have HCV than females with HCV-negative partners; this pattern was not evident in males. The titer of HCV RNA and HCV genotype do not appear to influence the risk of HCV transmission, but high-quality studies to assess these virological factors are lacking.

Summary

The available data indicate that HCV can be sexually transmitted but the efficiency of transmission by the sexual route is low. The risk of sexual transmission of HCV is estimated to be 0.03 percent to 0.6 percent per year for those in monogamous relationships, and 1 percent per year for those with multiple sexual partners. Given these estimates of risk, the current recommendations are: 1) HCV-positive individuals in longer-term monogamous relationships need not change their sexual practices. If couples wish to reduce the already low risk of HCV transmission by sexual contact, barrier precautions may be used. Partners of HCV-positive persons should be considered for anti-HCV testing and 2) For HCV-infected individuals with multiple or short-term sexual partners, barrier methods or abstinence are recommended. Additional common-sense recommendations include the use of barrier precautions if other STDs are present, if having sex during menses, or if engaging in sexual practices that might traumatize the genital mucosa. Finally, couples should not share personal items that may be contaminated by blood such as razors, toothbrushes, and nail-grooming equipment.

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Maternal-Infant Transmission

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With the advent of effective screening methods for hepatitis C virus (HCV), new cases of transfusion-associated hepatitis C have become infrequent in children. Consequently, childhood acquisition of HCV infection through maternal-infant transmission has assumed new importance. Vertical, or more precisely, mother-to-infant, hepatitis C will likely be the major type of childhood chronic hepatitis C within 6–8 years. It has been difficult to determine the rate of mother-to-infant transmission, partly because reports of mother-to-infant transmission of HCV were based on small numbers of patients, with differing disease definitions and study design. These reports tended to be heterogeneous and conflicting. Moreover, factors which promote mother-to-infant transmission and the outcome of chronic HCV infection acquired by this route still require clarification.

The first problem encountered with mother-to-infant transmission of HCV infection relates to its scope. Available estimates as to the prevalence of detectable anti-HCV among pregnant women range from 0.6 percent to 4.5 percent (median of 11 reports: 1.2 percent), with considerable geographic variation. Women with chronic hepatitis C appear to tolerate pregnancy as well as other women with non-cirrhotic chronic liver disease. Trivial improvement in serum aminotransferases may occur. Maternal viral titers may rise toward the end of the third trimester.

A second important problem is how exactly to define mother-to-infant transmission of HCV infection. Many infants of mothers chronically infected with HCV are found to have detectable anti-HCV in their blood, acquired through passive transplacental transfer of the IgG-antibody. This passively-acquired antibody continues to be detectable in the infant for the first 12–15 months of life, occasionally as long as the first 18 months. Possible criteria for a more rigorous definition of mother-to-infant transmission of HCV infection include: detectable anti-HCV in an infant who is more than 18 months old, detection of HCV RNA in an infant who is 3–6 months old, detection of HCV RNA in the infant on at least two occasions, finding elevated serum aminotransferases in the child, or confirming identical genotype between mother and child. A reasonable diagnostic approach in the infant is positive serum HCV RNA on two occasions 3–4 months apart after the infant is 2 months old and/or anti-HCV detected after the infant is 18 months old.

Reports detailing mother-to-infant transmission of HCV have been reviewed from time to time. We carried out a critical review of the world literature published between 1992 and 2001. For inclusion, each study was required to have at least 10 mother-infant pairs; language restrictions were largely avoided. Criteria used for identifying mother-to-infant transmission of infection were (1) anti-HCV detected in an infant over 1 year old or (2) HCV RNA detected at least once in an infant 18 months old or less. Studies using first-generation ELISA or RIBA techniques without confirmatory PCR testing were excluded. A weighted rate of incidence was used to adjust for sample size and variance. Seventy-seven studies were included for review: almost all of these were prospective cohort studies. The number of mother-infant pairs in each study ranged from 10 to 1,338. Taken altogether, 383 cases of mother-to-infant hepatitis C were identified. If the mother was known only to be anti-HCV positive, the weighted rate of mother-to-infant transmission was 1.7 percent (compared to a crude rate of number positive/number at risk = 5.6 percent). If the mother was known to be viremic, that is, HCV RNA positive, the weighted rate of mother-to-infant transmission was 4.3 percent (crude rate = 8.1 percent).

Geographic variation was apparent from these studies. In Italian studies with viremic mothers, the mother-to-infant transmission rate (weighted) was 5.6 percent, in similar Japanese studies, 6.9 percent, and in studies with viremic mothers from elsewhere, 3.1 percent. As previously shown, co-infection with the human immunodeficiency virus (HIV) greatly increased mother-to-infant transmission of HCV: weighted rates from these studies were 19.4 percent for HIV-positive mothers compared to 3.5 percent for HIV-negative mothers. In six studies examining the importance of previous or ongoing intravenous drug abuse (IVDU), a subset of anti-HCV positive mothers (where maternal viremia was not reported) at higher risk for transmission of HCV was identified: the weighted rate of transmission was 8.6 percent in mothers who were anti-HCV positive and IVDU, compared to 3.4 percent in anti-HCV positive mothers without known IVDU.

Findings in the most recent prospective studies are similar. In a study from Ireland of 314 infants born to 296 anti-HCV-positive women, the rate of mother-to-infant transmission was 3.5 percent (minimum rate)–6.4 percent (based on observed cases). No significant differences were found with spontaneous rupture of membranes, duration of membrane rupture, vaginal delivery or cesarean section, or evident fetal distress. Infants tended to be small for gestational age, but this could not be attributed solely to maternal chronic hepatitis C. In a study of 2447 HIV-negative pregnant women from Italy, 78 women were identified as anti-HCV positive and these mother-child pairs were monitored for 2 years; 60 women were found to be HCV RNA positive. Eight infants were identified as infected with HCV: thus the mother-to-infant transmission rate was 13.3 percent. At 2 years of age, only two infants were still positive for HCV RNA, and therefore the overall mother-to-infant transmission rate was put at 3.3 percent. Mother-to-infant transmission correlated with high maternal viral load.

The maternal viral titer appears to be an important determinant of probability of mother-to-infant transmission of HCV infection. The critical level appears to be 10^5–10^6 copies per ml. Not all studies show a clear correlation between maternal viral titer and vertical transmission: the timing of when the titer determination was performed may be a confounder. In one study, high maternal titers of HCV correlated with virus detectable in colostrum. Data are inadequate to assess whether viral genotype makes a difference to the rate of mother-to-infant HCV transmission.

Mode of delivery has been examined as a possible determinant of mother-to-infant

transmission of HCV infection. In most studies suitable for evaluation the mode of delivery did not make an important difference to virus transmission. One study from Japan showed that vaginal delivery was associated with increased risk of mother-to-infant transmission of HCV compared to caesarean section when high viral load ($\geq 2.5 \times 10^6$ copies/mL) was present; however, maternal HIV status was not documented, and cesarean section operations were not classified as elective or emergency. Another study suggested that elective, but not emergency, cesarean section confers protection against mother-to-infant transmission. This study, however, was not stratified for HIV status. Anti-HCV positive mothers may be more likely to have cesarean section for reasons related to general obstetric management. Whether prolonged rupture of membranes prior to delivery enhances the mother-to-infant transmission rate remains uncertain. Use of fetal monitoring might be a risk factor for virus transmission but has not been investigated adequately.

Breastfeeding is generally not considered to be a risk factor for mother-to-infant transmission of HCV. In published studies the rate of transmission is nearly identical in breast- or bottle-fed infants. Whether these studies are adequate is open to question since duration and exclusivity of breastfeeding are not routinely described in detail. The safety of breastfeeding operates on the assumption that traumatized or cracked nipples are not present.

The outcome of mother-to-infant hepatitis C requires clarification. Subtleties of disease course are relevant to this discussion. Some infants may have transient viremia without real infection. Other infants may have acute, self-limited infection which is clinically inapparent (very early spontaneous resolution). Data relating to these early patterns of mother-to-infant HCV exposure/disease are scanty, mainly because of reluctance to take repeated blood samples from apparently healthy infants. Thus, outcome of mother-to-infant transmission of HCV is usually considered in terms of evolution to chronic hepatitis C, with later spontaneous clearance of HCV infection or progressive chronic liver disease. Whether children are more likely to clear chronic HCV infection than adults and whether transfusion-associated chronic hepatitis in children runs a different clinical course from chronic hepatitis C acquired by mother-to-infant transmission remain unanswered questions currently being investigated.

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Introduction to Therapy of Hepatitis C

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Since the 1997 NIH Consensus Development Conference: Management of Hepatitis C, several important advances have occurred which have significantly impacted therapy of hepatitis C, notably the availability of sensitive, specific, and standardized assays for identifying HCV RNA in the serum, (1) and the evaluation and FDA-approval of ribavirin and pegylated alpha interferon. The vast majority of treatment data has been collected in patients with chronic hepatitis C viral infection (HCV), clinically compensated liver disease due to HCV, elevated ALT or AST, no medical contraindication to treatment, and no other significant medical illness.

Therapeutic End Points

Sustained Virological Response

HCV RNA testing is conducted before, during, and at the end of treatment and 24 weeks later. It is now clear that *sustained virological response* (SVR), defined by the absence of detectable HCV RNA in the serum by RT-PCR at the end of treatment and 24 weeks after the end of treatment, is the optimal end point of therapy. Although a surrogate end point (2) (a biomarker intended to substitute for a clinical end point), SVR is associated with important clinical end points (characteristics that measure how a patient feels, functions, or survives). Marked improvements in health-related quality of life in patients with SVR has been demonstrated using standardized quality of life instruments (3). The effects of SVR on survival of patients with chronic HCV have not yet been precisely measured because of the necessity for long-term follow-up and the inclusion of large numbers of untreated patients or treated patients without SVR. Evaluation of other clinical end points which are likely to be associated with survival [liver histology, recurrence of detectable viremia, residual HCV in the liver, development of hepatocellular carcinoma (HCC)] has been conducted. In patients with SVR, followup liver biopsies (4–6) taken 1–11 years after treatment demonstrate clear improvement in 89–100 percent, and serial serum HCV RNA testing (4,5,7) revealed a recurrence of viremia *(late virologic relapse*) in only 0–4 percent. A low likelihood of late virologic relapse is supported by a recent large study in 400 patients with SVR (8) in whom HCV RNA was detectable in only 2 percent of liver biopsies taken 24 weeks after the end of treatment. These observations strongly suggest that the absence of detectable serum HCV RNA measured 24 weeks after the end of treatment will be associated with improvement in how patients feel and function, resolution of liver injury and reduction in hepatic fibrosis, and a very low likelihood of recurrent HCV infection, all of which are highly likely to improve patient survival. And, in two large recent studies from Japan, (9,10) treatment with interferon was associated with a reduction in development of hepatocellular carcinoma which was more pronounced in patients with SVR. These and other long-term follow-up studies in progress will be extremely important in defining the effect of SVR on survival in years to come. Since the Conference in 1997, large Phase III clinical trials in HCV patients naïve to treatment have demonstrated several major advancements in therapeutic agents. Lengthening the course of unmodified alpha interferon (α -IFN) monotherapy from 24 to 48 weeks, adding ribavirin to α interferon (α-IFN) for 24 or 48 weeks (11,12) and using pegylated alfa interferon (PEG IFN) compared to α interferon (α-IFN) for 48 weeks (13–15) increases the likelihood of SVR. And, in two recent large trials (16,17) in which ribavirin was given in combination with either PEG IFN or α –IFN, the overall rate of SVR was 54 percent and 56 percent with PEG IFN compared to 47 percent and 45 percent with α -IFN.

In these trials, multivariate analyses of baseline factors have identified several variables as being associated with the likelihood of SVR: HCV genotype other than 1, lower baseline viral load, lighter baseline weight or lower body surface area, younger age, absence of bridging fibrosis/cirrhosis, higher ALT quotient, and female sex. In several analyses, sex is no longer significant when weight is taken into account. Of these variables, viral genotype, HCV RNA level, and body weight are most strongly associated with SVR, but none of these factors singly or in combination are highly predictive of SVR. The patient's race, in particular, being an African-American, although not identified in multivariate analyses of these large trials, also appears to be potentially associated with response. (18) On-treatment factors have also been evaluated, and virologic response during the first 24 weeks of treatment has been identified as highly predictive of SVR. (17) In addition, the patient's ability to adhere to the regimen by taking 80 percent of the intended dose of the two therapeutic agents for at least 80 percent of the intended duration of treatment is also associated with higher SVR rates. (19) The optimal approach, therefore, is the initiation of a therapeutic trial and identification of the appropriate time for determination of virologic response (stopping rules). Further work is needed to understand and optimize adherence to therapy.

Virologic Response with Relapse

Virologic response with relapse is defined by the absence of detectable HCV RNA in the serum by RT-PCR at the end of treatment (virologic response) followed by subsequent detectability of HCV RNA in the 24 weeks after the end of treatment. In such patients, HCV is either present in the serum at levels too low for the assay to detect, or potentially sequestered in other compartments. The availability of more sensitive assays, such as TMA, (20) will be extremely useful in such patients. Future studies are needed to determine whether lengthening the course of treatment in patients with detectable serum HCV RNA using a more sensitive assay is associated with SVR.

Virologic Non-Response

Virologic non-response is defined as the presence of detectable HCV RNA at the end of treatment. In general, this category of patients treated with interferon-based therapy have been inadequately studied as regards the role of viral resistance, treatment adherence, and specific immunologic, environmental, genetic, or other factors which play a role.

Non-Virologic Therapeutic End Points

Biochemical response [the lowering of ALT to within the normal range at the end of treatment or at the end of treatment and for 24 weeks following treatment (sustained biochemical response)] continues to be evaluated in large trials, but there are few studies describing the long-term benefit of a sustained biochemical response in the absence of SVR. Although these studies suggest that long-term biochemical response is associated with a decreased frequency of hepatocellular carcinoma, (21–23) the groups are not controlled for baseline stage of fibrosis.

Histologic response or histologic improvement has been evaluated as a secondary end point in large, Phase III trials in which fixed-duration therapy was given. Comparing paired liver biopsies using standardized scoring systems, it is conventionally defined as at least a 2-point decrease from baseline biopsy in the inflammation score or in the total score or a 1-point decrease in the fibrosis score. (11–17)

The clinical value of a biochemical or histological response as a primary end point will be of great importance in ongoing and future treatment trials in patients for whom interferon-based therapy is contraindicated, those who cannot tolerate interferon treatment, or those whose infection does not virologically respond to interferon-based therapy. Long-term pegylated interferon therapy in virologic non-responders is being studied in several trials. Current and future studies using anti-inflammatory and anti-fibrotic agents will also assess these end points. And, in the future, these end points will be extremely important in studies using specific inhibitors of viral replication currently in development in order to determine the effects of *virologic suppression* as an end point of therapy.

Other Patient Populations

Large, definitive treatment trials have been conducted and reported in more than 10,000 adult patients with elevated aminotransferases, clinically compensated chronic liver disease due to HCV, and no other significant medical disorder. However, results from adequately designed and statistically powered studies of other patient populations (children, normal aminotransferases; decompensated liver disease; post-organ transplant; HIV co-infection; inherited blood disorders; renal disease; neuropsychiatric disorders; vascular disease; indigent, homeless, or substance-addicted) are not available. In order to determine the safety and effectiveness of HCV treatment in these populations, definitive trials need to be performed.

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Optimal Therapy of Hepatitis C

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Considerable progress has been made in therapy since the last Consensus Development Conference on Management of Hepatitis C in 1997. Using the sustained virologic response (SVR) rate as the standard definition of beneficial outcome of therapy, different treatments can be compared in various categories of patients. The combination of interferon alfa-2b and ribavirin resulted in SVR rates of 31–35 percent after a 24-week course and 38–43 percent

after a 48-week course of therapy. (1) The use of pegylated rather than standard interferon with ribavirin increased the response rate to 54–56 percent. (2,3)

The efficacy of two different formulations of peginterferon combined with ribavirin were assessed in two recent pivotal trials. The first of these compared two different doses of peginterferon alfa-2b plus ribavirin to standard interferon alfa-2b plus ribavirin for the initial treatment of chronic hepatitis C. (2) In the trial, 1,530 patients were randomized to receive either: (1) peginterferon alfa-2b (1.5 mcg weekly: higher dose) plus ribavirin (800 mg daily), (2) peginterferon alfa-2b (1.5 mcg weekly for 4 weeks followed by 0.5 mcg weekly: lower dose) plus ribavirin (1,000–1,200 mg daily), or (3) standard interferon alfa-2b (3 million units thrice weekly) plus ribavirin (1,000–1,200 mg daily). The treatment duration in all groups was 48 weeks. End-of-treatment virologic responses were achieved in 65 percent of patients treated with higher dose peginterferon, 56 percent treated with lower dose peginterferon, and 54 percent treated with standard interferon and ribavirin. Sustained virologic responses occurred in 54 percent of patients in the higher dose peginterferon group, 47 percent in the lower dose group, and 47 percent in the standard interferon group. Among patients treated with the higher dose of peginterferon, SVRs were significantly higher in patients infected with HCV genotype 2 or 3 (82 percent) than in those with genotype 1 (42 percent). The initial level of HCV RNA in serum also correlated with the SVR rates. Patients with high initial levels of HCV RNA, defined as greater than 2 million copies/ml, had significantly lower response rates than those with lower levels of virus (less than 2 million copies /ml) (42 percent vs. 78 percent). The degree of hepatic fibrosis had a lesser impact on the outcome of therapy: the SVR rate was 57 percent in those with no or minimal fibrosis compared to 44 percent among those with bridging hepatic fibrosis or cirrhosis.

A second recent large, randomized controlled trial compared peginterferon alfa-2a (180 mcg weekly) plus ribavirin 1,000 - 1,200mg daily) to the same dose of peginterferon alfa-2a alone, or standard interferon alfa-2b (3 million units thrice weekly) plus ribavirin (1,000–1,200 mg daily) in 1,121 patients. (3) End-of-treatment virologic responses occurred in 69 percent of patients treated with peginterferon alfa-2a plus ribavirin, 59 percent with peginterferon alone, and only 52 percent with standard interferon and ribavirin. Sustained virologic response rates were 56 percent, 30 percent, and 45 percent, respectively. As in virtually all studies of antiviral therapy, HCV genotype was a strong predictor of SVR, which occurred in 46 percent of those with genotype 1 compared to 76 percent with genotypes 2 or 3 in the peginterferon plus ribavirin group.

Thus, two large pivotal trials have shown that the combination of peginterferon and ribavirin given for 48 weeks yields the highest rate of sustained response. While this may be the most effective regimen overall, it may not be optimal for all patients and in all situations. At issue is the optimal dose of peginterferon, the optimal dose of ribavirin, and the optimal duration of therapy.

In the large trial of peginterferon alfa-2b, two doses of peginterferon were compared, both based upon body weight. (2) While the higher dose yielded a better overall response rate, SVR rates for patients with genotypes 2 and 3 were similar with the higher and the lower peginterferon doses (82 percent vs 80 percent). In the trial of peginterferon alfa-2a, a single dose not adjusted to body weight (180 mcg weekly) was tested, based upon previous studies which identified this to be the most effective dose when given alone without ribavirin. (4) Yet, in all of these studies, dose modifications because of side effects were common, and it is, therefore, possible that lower doses of peginterferon are just as effective and perhaps better

tolerated.

The optimal dose of ribavirin for use in combination with either form of peginterferon is also not clear. In the study of peginterferon alfa-2b, two doses were used: 800 mg of ribavirin per day with the higher dose of peginterferon alfa-2b was compared to the more standard dose of ribavirin of 1,000–1,200 mg daily (based on body weight) with the lower dose of peginterferon. Post-hoc analyses suggested that the 800 mg dose of ribavirin was suboptimal, in that response rates correlated with body weight, so that SVR rates increased as the ribavirin dose per kg body weight increased up to the highest rates, which were achieved at 13 mg/kg. Only the standard dose of ribavirin was used in the studies of peginterferon alfa-2a. (3) Clearly, the effects of these small differences in ribavirin doses need to be properly assessed in prospective controlled trials.

In both of the pivotal trials of peginterferon, therapy was given for 48 weeks. Thus, the relative efficacies of shorter or longer courses are not known. A full 48 weeks of therapy is clearly not needed to achieve SVR in all patients. Evidence from earlier studies of standard interferon with ribavirin suggested that 24 weeks of therapy was sufficient for patients with genotypes 2 or 3 and in patients with genotype 1 and low levels of HCV RNA. (1) Furthermore, sequential testing for HCV RNA levels suggests that patients who do not respond can be identified as early as 24 or even 12 weeks of therapy; (2,3) if so, their therapy could be curtailed early, thus minimizing side effects and cost. Future studies are needed to assess the optimal duration of therapy in different categories of patients as well as to assess the possible role of sequential measurements of HCV RNA levels as a means of determining the optimal duration of treatment.

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Retreatment of Patients With Chronic Hepatitis C

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A large number of patients with chronic hepatitis C have been treated with alpha interferon with or without ribavirin since the 1997 Consensus Development Conference. Unfortunately, a majority of these patients probably did not achieve a sustained virologic response (SVR). As new therapies are developed for hepatitis C, the issue of retreatment of these non-responders will continue to arise. Recommendations regarding retreatment should be based upon several factors: (1) the previous type of response, (2) the previous therapy and the difference in potency of the new therapy, (3) the severity of the underlying liver disease, (4) viral genotype and other predictive factors for response, and finally (5) tolerance of previous therapy and

compliance. (1)

Types of Non-Response

Patients who fail to achieve SVR can be categorized as either relapsers or non responders. In general, relapsers are more likely to achieve SVR during retreatment with a more potent regimen than are non-responders. Yet among patients referred to as non-responders, there is the subset who have a marked reduction without disappearance of HCV RNA (1–2 log units or more) during therapy. These partial responders may also be good candidates for retreatment, if a more potent regimen of therapy is being applied, such as the currently recommended combination of peginterferon and ribavirin. In at least one study of retreatment, only non-responders who had a decline in HCV RNA to an absolute titer <100,000 copies/ml during previous treatment with interferon alone achieved SVR when retreated with interferon and ribavirin. (2)

Retreatment of Non-Responders

The likelihood that non-responder patients will respond to retreatment depends in large part upon the previous therapy. Retreatment of non-responders with the same therapy will not result in viral clearance, whereas retreatment with a more potent regimen can result in SVR in a proportion of patients. Thus, preliminary results suggest that up to 30 percent of non-responders to the standard interferon/ribavirin combination became HCV RNA negative on retreatment using the peginterferon/ribavirin combination. (3,4) Higher rates occurred in patients with HCV genotypes 2 or 3 compared to genotype 1. Unfortunately, relapse was common once therapy was discontinued, so that the rate of SVR was only 15–20 percent overall.

Retreatment of Relapsers

Several studies have shown that patients with prior relapse have a high rate of SVR when retreated with more effective therapy. Thus, 50 percent of patients who relapsed following treatment with interferon alone achieved SVR when retreated with interferon/ribavirin combination. (5) The ability to achieve SVR following retreatment with peginterferon/ribavirin in patients who relapsed following interferon monotherapy or standard interferon/ribavirin therapy is currently being evaluated. The majority of relapsers become HCV RNA negative during retreatment, even when the regimen is the same. When the same regimen is used, however, virtually all patients relapse again after treatment is stopped. Extending the duration of retreatment without changing the dose or regimen may reduce relapse, but this has not been prospectively proven.

Severity of Liver Disease and Retreatment

Knowledge of the severity of the underlying liver disease is important in recommending retreatment of chronic hepatitis C. Patients with no or minimal fibrosis probably have an excellent long-term prognosis and low risk for developing cirrhosis or complications of chronic hepatitis C. These patients, therefore, could forgo retreatment and await further advances in therapy. On the other hand, patients with advanced fibrosis or cirrhosis are at increased risk for developing hepatic decompensation and should be considered for retreatment, especially if the previous treatment was interferon alone. For patients with intermediate degrees of fibrosis and disease activity, recommendations for retreatment should weigh the type of initial response, the improvement in treatment regimen, factors such viral genotype, initial titer of

HCV RNA, as well as tolerance of therapy.

Non-Responders to Combination Therapy with Peginterferon and Ribavirin

Patients who fail to respond even to the current optimal therapy with peginterferon/ ribavirin are a great challenge for management, particularly those with advanced fibrosis or cirrhosis. In several studies of standard interferon, up to 40 percent of non-responders developed evidence of a histological response despite persistence of HCV RNA. (6,7) These histological responses occurred largely among patients with a partial virological response as shown by a significant reduction in HCV RNA titer. In a prospective, randomized controlled trial, these histological improvements were shown to be maintained by continuation of interferon monotherapy. (8) The possible role of maintenance therapy with peginterferon alone in preventing further progression of cirrhosis, clinical decompensation, or development of hepatocellular carcinoma is currently the focus of a large-scale, multi-center U.S. trial, referred to as HALT-C. Until the results of that study or similar studies are available, the role of long-term, continuous therapy with peginterferon (or ribavirin or both) for non-responder patients must be considered experimental.

Tolerance and Compliance

An important reason for relapse and non-response to interferon therapy of hepatitis C is non-compliance. Non-compliance can be the result of severe side effects or lack of commitment by the patient, but also can be due to poor counseling regarding side effects and inadequate management. If the causes of non-compliance can be corrected or lessened, retreatment can be successful. In contrast, if side effects are intolerable despite adequate counseling and management, retreatment is unlikely to be successful and should not be encouraged.

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Treatment for Hepatitis C: A Systematic Review

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Introduction

Hepatitis C is a spherical enveloped RNA virus of the *Flaviviridae* family, which has been recognized as a major cause of chronic hepatitis and hepatic fibrosis that progresses in some patients to cirrhosis and hepatocellular carcinoma (HCC). In the United States, approximately 4 million people have been infected with hepatitis C (HCV) and 10,000 HCV-related deaths occur each year. Effective treatment strategies are needed to prevent hepatitis C-related morbidity and mortality.

Objective

We conducted a systematic review of the literature to determine: (1) the extent to which randomized controlled trials have shown the efficacy and safety of current treatment options for chronic hepatitis C in treatment-naive patients, including: pegylated interferon plus ribavirin; pegylated interferon alone; interferon plus ribavirin; and interferon plus amantadine; (2) the extent to which randomized controlled trials have shown the efficacy and safety of current interferon based treatment options (including interferon alone) for chronic hepatitis C in selected subgroups of patients, especially those defined by the following characteristics: age less than or equal to 18 years, race/ethnicity, HCV genotype, presence or absence of cirrhosis, minimal vs. decompensated liver disease, concurrent hepatitis B or HIV infection, non-response to initial interferon based therapy, and relapse after initial interferon based therapy; and (3) the long-term outcomes of current treatment options for chronic hepatitis C infection.

Methods

Literature Sources

Seven electronic databases were searched through DIALOG for the period from January 1996 to March 2002. Additional articles were identified by searching references in pertinent articles, hand searching relevant journals, and querying technical experts.

Eligibility Criteria

Exclusion criteria for review included: non-English language, articles limited to basic science or non-human data, previously reported data, and meeting abstracts. Inclusion criteria for review were: study designed to address our key question, information pertinent to management of hepatitis C, and 30 or more study subjects with hepatitis C. In addition, treatment articles reviewed were limited to randomized controlled trials. To explore modern treatment options, we limited eligible studies to those evaluating interferon alone or in combination with other treatment options, e.g., ribavirin, amantadine, etc., *and* where outcomes were assessed by virologic and/or histologic measures of outcomes. Studies of interferon alone were only included when the study participants were subgroups of interest, e.g., renal disease, HIV co-infection. Studies evaluating long-term followup could be either randomized controlled trials or cohorts but required at least 60 months of observation.

Assessment of Study Quality

Each eligible article was reviewed by a pair of reviewers, including at least one team member with relevant clinical training and/or one with training in epidemiology and research methods. Paired reviewers independently rated the quality of each study in terms of the following categories: representativeness of study subjects (5 items); bias and confounding (4 items); description of therapy (4 items); outcomes and follow-up (5 items); statistical quality and interpretation (4 items). Reviewers assigned each response level a score of 0 (criterion not met), 1 (criterion partially met), or 2 (criterion fully met) to each relevant item on the quality form. The score for each category of study quality was the percentage of the total points available in each category and therefore could range from 0–100 percent. The overall quality score was the average of the five categorical scores. We also documented source of funding.

Extraction of Data

The paired reviewers also abstracted data on type of study and geographical location; study groups; specific aims; inclusion and exclusion criteria, screening regimen; demographic, social and clinical characteristics of subjects, and results. Differences between the two reviewers in either quality or content abstraction were resolved by consensus.

Synthesis

Results of Literature Search

We identified 3,104 potentially relevant citations and 1,731 of these were deemed eligible for abstract review. Through the abstract review process, we identified 486 articles that could have been related to one of our key questions regarding treatment. After reviewing these 486 articles, we found 231 studies including 165 randomized controlled trials reporting on current treatment and 66 reporting on long-term outcomes. Data from these eligible studies will be presented in a series of evidence tables and figures highlighting their distinguishing characteristics, methodological strengths and limitations, and key findings.