REVIEW ARTICLE

Acute Hepatitis C Infection

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Introduction

Hepatitis C is the main cause of chronic liver disease in many of countries, but since its discovery about 15 years ago through implantation of blood product screening there has been a constant decrease in the number of new cases of post transfusion acute hepatitis C (acute HCV). [1, 2, 3] This unfortunately did not translate to lower number of the end stage liver diseases caused by this virus and still in many countries it would be the most common indication of liver transplantation up to 2 more decades. [5, 6, 7] Despite blood screening, post transfusion acute HCV still occurs worldwide although it is becoming very rare. Other sources of HCV acquisition are rising and acute HCV is now a well established occupational hazard as well as nosocomial infection. [8, 9, 10] Although the total number of acute HCV infection has decreased in many communities; there is now a growing number acute HCV especially among intravenous drug abusers (IVDs) and those who had occupational or nosocomial infection.[11] There are some data indicating a good response of this group of acute HCV even to Interferon monotherapy, which is considered a suboptimal treatment in the cases of chronic HCV infection.[12] In this article the current data on acute HCV infection and its management would be reviewed. It is especially important to have a guideline on the management of acute HCV in each institution especially considering those who get this infection nosocomially. We hope this review would help in developing such guidelines.

Epidemiology of HCV infection

Hepatitis C virus (HCV) infection is endemic worldwide, with an estimated global prevalence of 3 percent.[9-11] Although the annual incidence of acute HCV infection has decreased, the sequelae of chronic HCV infection make HCV the leading indication for liver transplantation in many countries.[7, 13] The current mortality figures due to this infection are projected to increase 2- to 3-fold over the next 1 to 2 decades as patients with HCV infection develop cirrhosis and end-stage liver disease.[7] Using the past incidence of HCV infection, it has been projected that the number of persons infected for more than 20 years could increase substantially before peaking in 2015.[13, 14] Worldwide some 175 million of people are infected with this virus.[10, 11] The reported prevalence rates for HCV infection shows a wide range of variation in different countries. The lowest prevalence is reported from the United Kingdom and Scandinavia (0.01–0.1%).[11] Marginally higher values in the Americas, Western Europe, Australia, and South Africa (0.2– 0.5%); and intermediate prevalence in Brazil, Eastern Europe, the Mediterranean, the Mideast, and the Indian

subcontinent (1–5%) are reported.[11]

In Iran the prevalence also shows variation among provinces but overall prevalence among healthy blood donors is about 0.1% which is probably a 400% underestimation of prevalence in whole population.[15] In a recent review intravenous drug abuse was found to be the most common cause of this infection occurring in 68% of new cases followed by sexual and occupational exposures in 16 and 4 percent of cases respectively.[16] Post transfusion HCV was very rare. In Iran all blood products have been screened for HCV since 1996.There are no clear data on routes of acquisition of acute HCV in Iran. The only published case control study on risk factors of HCV infection in general population is a study on healthy Iranian blood donors.[15] The study indicates that transfusion, undergoing endoscopy, extramarital sexual activities, non-intravenous drug abuse, IVDs, and receiving wounds at war were found to be independent risk factors of being HCV-positive (Odds ratio: 17, 4, 42.2, 34.4, 52.8 and 5.2, respectively). No apparent risk factors could be demonstrated in 24.5% of the positive cases. The findings corroborate a recent case controlled study from Italy that found invasive procedures including endoscopy represent an important mode of HCV transmission.[17]

The situation probably has changed regarding post transfusion hepatitis since the screening of blood products and it is postulated that currently the most common cause of acute HCV in Iran would be IVDs in more than 75% of new cases. Occupational and nosocomial infections have also probably risen in number in the recent years as more HCV infected patients are being hospitalized and/or undergo invasive procedures including dental and other surgeries, angiography ,endoscopy and other procedures. Tattooing and having a hair cut under unhealthy conditions are also important neglected factors in Iranian community. The same situation has been reported from other countries.[18, 19, 20]

Diagnosis of acute HCV

Acute hepatitis C has become relatively uncommon in recent years mainly due to reduction of post transfusion cases. In those who become acutely infected, the disease is often mild or completely asymptomatic, and is rarely recognized outside prospective surveillance after exposure to known risk factors.[21] There are still no specific diagnostic tests to identify acute infection with HCV and to distinguish it from an acute exacerbation of chronic hepatitis C. For all these reasons acute hepatitis C is largely underdiagnosed. Acute hepatitis with jaundice is seen in no more than 20–25% of cases, and severe liver function impairment or failure are extremely rare events in the absence of hepatotoxic co-factors.[5,6] A more severe course of acute hepatitis C can be seen in patients with excess alcohol intake, or co-infection with HBV or HIV.[1,5,6] Thus currently the diagnosis of acute HCV infection is either through active surveillance after known exposure or speculative by highly raised transaminases (> x20) which is rare in chronic infection except in those with superimposed insults. So in the latter cases it is very important to exclude all other possible causes of acute hepatic damage including other viruses, toxins and drugs. Thus the asymptomatic presenter may be subdivided into those detected by surveillance within days of viral conversion, and those diagnosed fortuitously with biochemical hepatitis and anti HCV seroconversion.

In active surveillance for acute HCV use of qualitative HCV RNA on baseline and on weeks 2, 4, 8 has been suggested to diagnose the infection as early as possible .[22] Because the early diagnosis is not decision making in most instances, this approach may increase the cost without any benefit to the patient.[22] A more practical approach may be checking anti HCV antibody at baseline and at 2 and 4 months.[23] Alanine aminotransferase should be checked also at baseline and every 2 weeks for 3-4 months.[1,8,24] If at any time raised enzymes and / or seroconversion was detected then one may proceed to testing HCV RNA quantitatively. The situation in immunocompromised patients is quite different. In these patients acute HCV may develop without seroconversion. So in this special group HCV RNA testing may be justifiable from beginning.[24]

Natural History of acute HCV

One of major contradictive areas in the field of hepatology since the past decade has been the rate of chronicity after primary infection with HCV. Earlier studies mainly in patients with post-transfusion hepatitis C indicated that most patients became chronic carriers of the virus with chronicity rates above 85–90%.[6, 25] More recently, many new studies have clearly indicated that the risk of chronicity might be quite lower in other patient categories.[26] There are a number of co-factors and variables which affect such a risk. Studies in those who had repeated exposure to HCV including family members of chronic HCV carriers demonstrated that many of such individuals develop cellular immunity to HCV in the absence of overt infection without anti-HCV seroconversion. [27] These observations indicate a more frequent clearance of HCV than what was thought in the past.

Compared to HBV, rate of chronicity is high in every instance of acute HCV and in all patient categories. However, it can vary from as low as 40–50% to as high as 90–100%.[26-28] Several factors have been associated with lower risk of chronicity.[23] These include patient's age and sex, with younger and female patients having a lower rate of chronicity, the source of infection and size of inoculum. The highest risk for chronicity is associated with a large inoculum as with posttransfusion hepatitis compared to for instance needle stick with much lower inoculum size. Risk of chronicity also depends on the presence of other infections including HBV and HIV infections, alcohol abuse and the immune status of the host. Acute hepatitis C in patients with concurrent chronic HBV infection is associated with a substantial risk of fulminant hepatitis. [29] Acute HCV superinfection in patients with chronic HBV infection is clinically severe during its acute phase.[30] The long-term prognosis following acute HCV superinfection is much worse than that following HDV superinfection or active hepatitis B in terms of continuing hepatitis activity after HBsAg loss and the development of cirrhosis or hepatocellular carcinoma.[30] The presence of active HBV replication can inhibit the persistence of HCV infection and antibody responses to HCV. Acute HCV infection in HBsAg carriers with active HBV replication usually presents with transient HCV viremia with poor

antibody responses to HCV. Rate of chronicity is extremely high in patients with agammaglobulinemia.[31]

Effect of the age of acquisition on chronicity has been recently well shown. In the NHANES study from the United States, hepatitis C became chronic in 30% of infected subjects below the age of 20 years and 76% of those older that 20 years.[2] Race is also important and higher rates of chronicity have been found in black compared to Caucasians and Hispanic whites in the United States .[2] Interestingly blacks also respond poorly to current antiviral treatment with combined pegylated interferon and ribavirin.[2,21,24] These findings highlights the role of immunogenetic factors in both disease acquisition and progress.[21]

Antiviral antibodies are present in almost all patients with chronic hepatitis C except those who are immunosuppressed. These antibodies do not seem to be virus neutralizing. This is probably due to viral factors such as the high mutational rate of viral envelope proteins.[21,32,33] Studies on the antiviral T cell response have revealed the presence of virus-specific CD4+ helper and CD8+ cytotoxic T cells in a substantial proportion of patients with chronic hepatitis C.[21.32] Recent studies describe an association between strong CD4+ T helper cell activity to certain hepatitis C virus antigens and a self-limited course of acute hepatitis C and possibly also a sustained response to treatment with interferon.[21] Aside from younger age and female sex, certain HLA alleles are associated with spontaneous clearance of viremia.[34.35] HCV's high rate of chronicity may be related to the virus's high likelihood of mutation and the lack of, or failure to maintain, a vigorous T-lymphocyte response to infection.[21] The ALT profile during acute phase may also predict the outcome. It has been shown that the higher the ALT peak during acute disease, the lower the probability of virus persistence.[21] A monophasic pattern of ALT profile has also been shown to predict recovery while polyphasic ALT are often followed by chronic infection.[21,38,37] It should remembered that serum ALT levels may be extremely variable in acute hepatitis C and that ALT normalization after acute phase is not a reliable marker of recovery as there are patients who remain viremic despite complete and persistent normalization of ALT. [36,37]

Considering that approximately half of the patients with acute HCV recover spontaneously while the other half develop chronic infection, parameters able to predict the outcome would be extremely useful in the clinical management of these cases. Unfortunately no such parameter has been recognized yet. A single HCV RNA negative sample and/or normal ALT during the late phase of acute hepatitis C do not prove resolution of infection and prolonged follow-up with repeated testing for at least 12 months after diagnosis is necessary to prove that the infection has resolved.[36,37] Recent studies in patients with community acquired hepatitis C unrelated to blood transfusion indicate that most patients who eventually clear the virus do so within 3–4 months from clinical onset.[21-23,25-27] The elimination of the posttransfusion cohort that was described in earlier series, usually older ill patients with age-related and potential transfusion induced immunomodulation may explain the higher proportion of symptomatic acute presenters now being reported.[23] The shift to an otherwise healthy, younger group of patients may also explain the better overall outcome of acute infection even without treatment.

Recent series also make clear that acute sexually acquired hepatitis C is a real phenomenon.[11] Most of these patients were women, and most of the women usually became ill after having started a new sexual partnership with a chronically infected man.[23, 26]

Immunosuppressed patients such as transplant and chronic renal failure patients when infected are more likely to develop chronic infection although the acute infection is usually asymptomatic.[21-27] Whereas the healthy hospital personnel have more chance to develop florid acute attacks, they rarely progress to chronicity.[21-27]

In summary in posttransfusion acute HCV, the rate of spontaneous recovery is around 10-25%, whereas in non-post transfusion cases, it varies from 11–14% to 30–50%.[23] Patients with jaundice or marked elevation of transaminases seem more prone to recover spontaneously than asymptomatic ones with percentages of spontaneous recovery up to 50%. [21-27] Women, white patients, and young patients seem more likely to recover spontaneously.[21-27]

Should acute hepatitis C be treated?

The high propensity of acute HCV to become chronic provides a strong rationale for antiviral therapy.[23] Published studies on the treatment of acute HCV with interferon alfa monotherapy indicate that therapy significantly reduces (at least by 30–40%) evolution to chronic hepatitis.[38-43] Unfortunately, most of these studies have been small in size, uncontrolled, and highly heterogeneous as to patient features, dose and duration of treatment.

Another point of controversy is the time which one should wait before starting therapy in these acute cases. In a leading research considering this question Gerlach and his colleagues from Germany showed that out of 54 patients with acute HCV for whom the natural course was observed, 37 patients initially cleared the virus spontaneously within a mean of 8 weeks (range, 1–26 weeks).[26] Among these patients, HCV RNA remained definitively negative in 24 patients (65%), and relapsed in 13 after a median of 18 weeks (range, 8–86 weeks). This means 24 (44%) of these patients had a self limited disease with persistent clearance of the virus. These patients with self-limited disease were far more likely to have symptomatic onset of disease (especially flu-like symptoms), whereas no patient who presented asymptomatically lost HCV RNA without treatment (P=0.007). Antiviral therapy was commenced after 3 to 6 months following onset of symptoms and in 21 of 26 (81%) a sustained response was achieved. The Gerlach study therefore supports the contention that up o 44% of patients with acute hepatitis C may lose virus spontaneously and not require current expensive and potentially toxic therapy. One major question is whether one can predict the course from beginning and not to wait for spontaneous recovery in all cases.[23] As mentioned before current data do not show that any test could predict the course. The possible exception to this rule is measurement of the viral load during the very first weeks of presentation.[44] Patients who cleared definitively the virus showed a fast and continuous decline of viral load during the first 35 days .[44] However repeat viral load determinations, with its inherent cost and long turnaround times is probably not practical in most clinical settings .

At the same time delaying therapy by up to four months after the onset of symptoms does not seem to reduce the efficacy of treatment.[23]

What is the best treatment of acute HCV?

Treatment in these acute cases was tried even before discovery of HCV.[45] One of the initial reports was a Japanese trial comparing different dosages of IFN alfa in the treatment of non-A, non-B post transfusion acute HCV. [43] In this study a daily regimen of 6 MU for 2 months (cumulative dosage of 336 MU) gave a high rate (83%) of sustained virologic response (SVR).

One of the most publicized studies in this field was the study of Jaeckle and his colleagues from Germany which was published in the New England Journal of Medicine in 2001.[39] This study which was an open label trial of a 24 week course of interferon alfa monotherapy to treat acute HCV raised attention because of its dramatic finding of 98% SVR. Their therapeutic regimen consisted of daily high induction dose of IFN (5 MU daily for 4 weeks), and then 5 MU three times a week for another 20 weeks (cumulative dose 440 MU) with 98% of SVR. The mean period from exposure to therapy was 89 days (Range 30-112 days). Therefore, immediate treatment did not seem to be required to achieve this extremely high response rate. This study used IFN alfa-2 b monotherapy, whereas the best current therapy for chronic HCV infection is the combination of peginterferon (PEG IFN) and ribavirin (RBV).[24] It is difficult to imagine improving on a response rate of 98% through the use of the PEG IFN or addition of RBV. However, case series design of this study may have overestimated the response rate and therefore there may be a role for other treatments. The same authors have reported recently monotherapy with peginterferon alfa-2b for 6 months once a week was equally effective in the therapy of acute HCV infection as their initial protocol.[46] The optimal duration of treatment is not known yet. In a Japanese trial involving 30 patients short term IFN 6 months starting 8 weeks after symptoms resulted in SVR of 85% compared to SVR of 40% if treatment was started after one year.[43] In one of the most recent trials of short term treatments a SVR of 75% was attained in non posttransfusion related acute HCV compared to 19% in historical controls using a two month course of IFN 5 MU daily .[42] As the authors mentioned, prolonged therapy could have increased SVR. This trial, however, may not represent the usual cases of acute HCV as 78% of treatment group had jaundice. The average time from exposure until the start of therapy was 110 ± 44 days, and from presentation until the start of therapy was 55 ± 41 days.

In summary the optimal treatment schedule for acute HCV is still a matter of controversy. The effectiveness of IFN as treatment of acute HCV was recently assessed by a meta-analysis.[12] Considering the data in this metaanalysis one can draw the following conclusions:

1. Standard IFN monotherapy significantly improves sustained virologic response in comparison with no treatment.
2. A daily induction dose of standard IFN during the first month of therapy appears to provide better results than a low weekly dose.
3. Safety of therapy is good in acute HCV even in jaundiced patients.
4. There is no need and no data to support the inclusion of ribavirin in the treatment of acute HCV infection.
5. Shorter treatment duration may have some place in the treatment, but the results are still not good as standard therapy for 6 months.

Conclusions and Recommendations

Acute type C hepatitis represents nearly 15% of all acute hepatitis cases in the United States. The situation in Iran is not known, but the figure for the general population is probably lower while in special settings such as healthcare workers and IV drug abuser, the rate may be higher. The problem in healthcare workers is growing as there is an increasing prevalence of this virus in admits and in hospitals, especially in urban emergency departments with increased potential risk for needle-stick transmission. The problem of nosocomial transmission is also real with more use of invasive procedures and less adherence to disinfecting guidelines. Notably in a recent series of acute HCV 20%–50% of cases occurred in a nosocomial setting.

Current reports indicate more than 80% of IV drug abusers become infected with HCV after one year. This may be higher and faster if they are jailed. These two groups are now the major cases of newly diagnosed acute HCV while many other cases are not diagnosed because of indolent ature of this infection especially at its onset.

Up to 50% of non transfusion related cases of acute HCV may recover spontaneously. Among patients who cleared virus spontaneously, most do so within the first 12 weeks after the onset of symptoms, and no spontaneous viral clearance was observed after 16 weeks. Available evidence, therefore, suggests that the transition from acute, and potentially self-limited hepatitis C, to chronic disease occurs somewhere between 3 and 4 months after symptomatic onset. At this time whether one is now treating early chronic infection versus acute hepatitis may be a matter of semantics, but it raises the possibility of more favourable response in those with shorter duration of chronic hepatitis. In contrast with the case of acute hepatitis B, for which the definition of chronic hepatitis has generally been set, arbitrarily, at 6 months after disease onset, the number for hepatitis C now appears to be 4 months. For the acutely ill or jaundiced patient, realizing the subjectivity of the word “symptomatic introduction of potent antiviral therapy is no longer to be deemed urgent: watchful waiting, possibly with serial viral load determinations and antiviral therapy 4 months later is both practical and safe. If at this time HCV RNA is still positive qualitatively, the patient should be considered for treatment.

The appropriate treatment now seems to be a 6 month course of IFN alfa therapy with a dose of at least 5 MU three times weekly. There is no confirmed evidence whether treatment with PEG IFN or adding RBV may increase efficacy although this needs to be sought in large controlled trials. Induction therapy with daily doses of 5-10 MU IFN in the first 1-2 months of treatment may increase the efficacy. Short term therapy for two months may have effect but the results are generally not as good as 6 month treatment.

Those who are symptomatic have both a higher chance of spontaneous clearance and a better response to therapy. After needle-stick injury and in posttransfusion acute HCV infection, most cases are asymptomatic and the rate of spontaneous recovery is lower. Whether one should wait the four month period in these groups or start therapy earlier is not known.

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