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# Acute Hepatitis C: Diagnosis and Management



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## INTRODUCTION

**H**epatitis C virus (HCV) infection is associated with a high likelihood of progression to chronic infection, which in turn may lead to chronic liver disease, cirrhosis, and death. It is estimated that acute infection may lead to persistent infection in up to 85% of cases. Unfortunately, a majority of cases of acute hepatitis C (AHC) infection are asymptomatic and detection of the virus may go unnoticed for years until complications develop. Early detection of AHC, although clinically challenging, is ideal as response to therapy is maximized (1). The best approach to AHC patients continues to be controversial in most cases.

AHC typically follows a mild clinical course, or is usually completely asymptomatic. The minority will present with typical clinical symptoms of hepatitis, including jaundice. Fulminant hepatic failure is a rare event. In Italy, the 1995–2000 case fatality rate for AHC was 0.1%, which is higher than hepatitis A (0.01%), but

lower than acute hepatitis B (0.4%) (2). Coinfection with other hepatitis viruses may have contributed to the cases of severe acute hepatitis C infections (3).

Risk factors for acquiring AHC include blood transfusion, injection drug use (IDU), medical procedures, nosocomial exposure, vertical transmission from mother to fetus, and possibly sexual transmission. Acquiring HCV through blood transfusion is now highly unlikely with the introduction of serological screening assays in 1991 (4). Sexual transmission is a controversial mode of transmission as there is still no convincing evidence of the presence of HCV RNA in biological fluids (5). It is speculated that risky behaviors and sharing sharp utensils between couples may account for suspected cases of sexual transmission(6).

## DIAGNOSIS

There are no serologic markers diagnostic of AHC infection, thus, the diagnosis of AHC can be very difficult to establish. It is important for the physician to identify patients at risk. However, unless symptomatic,

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few patients will present to the physician for evaluation. One exception is medical personnel, as they are usually required to report needlestick injuries and other exposures to body fluids (7).

Diagnosis of AHC relies on the exclusion of other causes of acute hepatitis such as drug-induced, autoimmune, hepatitis A,B,E or other viruses. Published biochemical criteria for AHC include elevation of alanine aminotransferase (ALT) levels to 10 to 20 times the upper limit of normal with documented normal values within the previous year (7–9). Specific serological assays for HCV are divided into direct and indirect tests. Direct tests identify the virus and include qualitative or quantitative determination of HCV RNA or antigen. Indirect tests identify antibodies to viral proteins (1,10). The most reliable means of diagnosis is the demonstration of seroconversion to anti-HCV antibodies combined with the identification of HCV RNA in serum (7). If the previous antibody status is unknown or non-reactive, clinical and/or biochemical criteria along with a positive HCV RNA confirms the diagnosis (7). It is important to be aware that it takes up to six weeks for anti-HCV antibody seroconversion to occur in up to 80% of patients after exposure while PCR test results for HCV RNA typically become positive within two weeks of exposure (1,7,11). A positive PCR test is usually followed by an increase in ALT level days to weeks later. Therefore, a patient with a known contact or exposure to HCV may present to the physician before seroconversion, elevation of ALT level, and before PCR test results become positive (7).

#### **DIFFERENTIATING ACUTE HCV FROM REACTIVATION OF CHRONIC DISEASE**

In patients that present with acute hepatitis, a positive anti-HCV antibody test, and an unknown past antibody status, it is difficult to determine whether the infection is acute or a symptomatic reactivation of a chronic infection. Sagnelli, et al (12) investigated whether measuring serial titers of anti-HCV IgM antibody could identify AHC and discriminate between acute symptomatic HCV and reactivation of chronic HCV. Thirty-five consecutive patients with acute HCV identified by seroconversion and thirty-one consecutive

patients who had been anti-HCV positive for at least six months at the time of reactivation were evaluated and followed. The study found that in acute infection, high and variable titers of anti-HCV IgM were present, the highest titers of HCV IgM were reached five-to-fifteen days from the onset of symptoms. A decrease in titers with virtual undetectability was noted at two-to-six months. They concluded that these titers can distinguish these patients from patients with reactivation of chronic HCV, who generally have steady and lower antibody titers. Unfortunately, anti-HCV IgM antibody assays are currently not commercially available in the United States.

The challenge of AHC diagnosis lays in the fact that so many of the cases are mild or asymptomatic. A thorough clinical history is important to identify those patients at risk and knowledge of the serological tests available for diagnosis is crucial to detect AHC before progression to chronic infection. This allows for early treatment intervention and ultimately a better opportunity to clear the hepatitis C virus.

#### **MANAGEMENT**

There are several controversial issues regarding the management of AHC (Table 1). These include:

1. Who should be treated?
2. How should AHC be treated?
3. When should treatment begin?
4. How long should treatment continue?
5. How should patients be monitored after treatment?

#### **Who Should Be Treated?**

Because some patients with AHC may spontaneously clear virus, universal treatment of all confirmed AHC may not be the best strategy. Identifying those patients likely to clear spontaneously will avoid potentially toxic therapy. Micallef, et al (13) performed a systematic review of 31 longitudinal studies with a total of 675 AHC patients. The primary outcome of the review was a measure of spontaneous clearance of HCV infection. The study found that spontaneous viral clearance occurs in approximately one out of four patients with AHC, higher than previous estimates of

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**Table 1**  
**Controversies in the Management of Acute Hepatitis C Infection**

| <i>Controversy</i>                           | <i>Consensus Opinion</i>   |
|--|--|
| How is AHC diagnosed?                        | Documented seroconversion and ALT elevation to 1-20 times the ULN                                    |
| How many patients clear virus spontaneously? | Up to 25%, more common among those who have symptomatic acute infection                              |
| Who should be treated?                       | Those who fail to clear virus within 12 weeks of the onset of symptoms                               |
| When should treatment start?                 | Between 12 to 24 weeks after onset of symptoms. The earlier, the better the response                 |
| What medication(s) should be used?           | Pegylated interferon monotherapy once weekly using the same standard dose as for chronic hepatitis C |
| How long should treatment last?              | 24 weeks   |
| How is sustained response determined?        | A negative HCV-RNA test 6 months after completion of therapy   |

AHC = acute hepatitis C; ULN = upper limits of normal; ALT = alanine aminotransferase

10%–15% in other reviews of HCV natural history. Viral clearance was associated with gender, with around 40% of female subjects undergoing clearance compared with 19% of male subjects. The mechanism for this association is uncertain, but has also been reported in various other studies. They also found viral clearance to be more common among those with symptomatic acute HCV infection, which may be a marker of a vigorous immune response during early HCV infection. Oldach (14) mentions that immunologic studies of AHC indicate that robust and polyclonal CD4 proliferative responses to HCV antigens are a prerequisite to viral clearance. Unfortunately, not all patients generating such responses achieve a spontaneous cure, and over time these responses wane. It appears that an individual has the highest probability of achieving viral clearance in the early stages of infection, before host “accommodation” (waning of host immune responses) and virus adaptation (escape mutations or quasispecies) become established. Patients that fail to clear the virus after a certain time frame deserve consideration for treatment. While the optimal time frame has not yet been established, most

experts consider 12 weeks as a reasonable time to allow for spontaneous viral clearance.

One controversial topic involves how to approach injecting drug users (IDUs). In fact, IDU is now the most common risk factor for acquiring HCV infection, accounting for more than 60% of cases in the USA (15). Factors that limit treatment options include the potential risk of reinfection with HCV in active IDUs, the prevalence of social and psychological issues, potentially poorer compliance with therapy, and treatment side effects (16). Any attempts at treating this group of patients with antiviral agents should be accompanied by effective rehabilitation programs.

### How Should AHC Be Treated?

Most studies to date have evaluated non-pegylated interferon (IFN) monotherapy for treatment of AHC. In a meta-analysis of controlled trials on the treatment of AHC with IFN monotherapy, Licata, et al (17) analyzed studies comprising 640 patients; 320 treated with IFN and 320 untreated. Out of sixteen studies, eight were randomized clinical trials and eight non-randomized

clinical trials. Interferon monotherapy significantly improved the sustained virologic response (SVR) compared to no treatment. The benefit of HCV RNA clearance was significant and supported the decision to treat all patients with AHC. This study also supported the use of a high daily induction dose of non-pegylated IFN, which has also been found to be effective in previous studies (9). Other studies such as the one by Kamal, et al (18) have found equal benefit with once weekly dosing of pegylated IFN monotherapy.

The role of ribavirin in treating acute hepatitis C infection remains controversial. Ribavirin has been used extensively for chronic HCV and has been found to enhance the efficacy of interferon in chronic hepatitis C infection, primarily by decreasing risk of relapse. The efficacy of interferon monotherapy in acute disease is so high, that it would be difficult to improve by adding ribavirin. Accordingly, data from a small study by Rocca (19) comparing IFN with and without RBV does not suggest any improvement in efficacy. The only randomized trial to date comparing IFN monotherapy versus combination therapy also did not show benefit (20). It has been suggested that since the rate of SVR to IFN monotherapy is high in compliant patients, the addition of RBV will not likely improve the SVR, and may increase toxicity. Whether the addition of ribavirin may be helpful in difficult to treat HCV genotypes or with HIV coinfection (21), deserves to be studied and may require large randomized studies to detect a small but significant advantage to the addition of ribavirin.

### When Should Treatment Begin?

As many as one quarter of patients spontaneously clear AHC. The timing between onset of symptoms and viral clearance in these patients is not clear. Jaeckel, et al (9) identified forty-four patients with AHC. Patients were treated with IFN a-2b with an average time from infection to start of therapy of 89 days. They were treated with IFN a-2b five million u SQ daily for four weeks, then three-times-a-week for 20 weeks. At the end of therapy (EOT) and end of follow-up (24 weeks after EOT), 42 of 43 or 98% had undetectable HCV RNA and normal ALT. They concluded that all patients diagnosed with AHC be treated. Others

believe that patients with AHC should be monitored for a finite period of time to determine if spontaneous viral clearance will occur.

Gerlach, et al (8) studied sixty patients with AHC, 54 of which did not receive treatment. Of the 54 monitored, HCV infection cleared spontaneously within four months of acquisition in 24 (44%), 20 of the 24 cleared the infection within three months. Of the nine asymptomatic patients, the infection did not clear spontaneously in any. They recommend that in symptomatic patients, treatment be delayed by three-to-four months based on the fact that a significant proportion of these patients will have spontaneous clearance of HCV. In those that do not clear virus, initiating treatment at three-to-four months was still highly successful (80% SVR).

The timing between onset of symptoms and initiation of antiviral therapy affects SVR in those who fail to spontaneously clear virus, thus prolonged waiting is not recommended. In a study looking at the impact of onset of therapy with PEG-IFN a-2b on SVR, Kamal, et al (18) found that patients treated at eight, 12, and 20 weeks after failing to clear HCV spontaneously at eight weeks had SVR rates of 95%, 92%, and 76%, respectively. Therefore, it appears that earlier treatment within two-to-three months is superior to waiting longer after failing to clear virus. Of note, SVR rates were better for patients with genotypes 2, 3, and 4 than genotype 1. The genotype 1 patients that began treatment at week eight had a better response than those that started treatment later, but the number of patients studied was too low to arrive at any firm recommendations.

### How Long Should Treatment Continue?

Several studies have evaluated the response to different treatment durations. Santantonio, et al (22) assessed both the efficacy of a 24-week course of PEG-IFN a-2b monotherapy in AHC patients and whether waiting for 12 weeks after clinical presentation prior to initiating treatment still achieved a high response rate. Sixteen patients with AHC still viremic after 12 weeks were treated with PEG-IFN a-2b (1.5 ucg/kg once weekly) for 24 weeks and followed for at least 12 months. They found that a 24-week course of treatment induced resolution of AHC in 94% of patients. The

results provide support for waiting up to 12 weeks to evaluate for spontaneous clearance of the virus in patients presenting with symptomatic acute hepatitis C infection.

Calleri, et al (23) evaluated 31 patients who completed three months of PEG-IFN a-2b (1.5 µg/kg once weekly) monotherapy. The main goal of the study was to evaluate if a shorter course of treatment was equally effective to six months of treatment, with improvement in compliance and cost. They found that 71% (22 of 31) of patients remained HCV RNA negative at a median follow-up of seven months after treatment. They also found that complete responses to treatment were less likely in patients with HCV genotype 1 and 4 (62%) compared to genotype 2 and 3 (79%). An important finding in the study was that rapid virologic response (RVR) measured at week four of treatment predicted sustained viral response and could allow for shorter than 24 week therapy in those patients becoming HCV-RNA negative after four weeks of therapy.

Nomura, et al (24) performed a randomized, controlled trial looking at short-term therapy with IFN-a (six million u) every day for four weeks. Thirty patients were randomized to early intervention (eight weeks after onset of AHC) and late intervention (one year after onset of AHC). The SVR was significantly higher in the early intervention group (87%, 13 of 15) versus the late intervention group (40%, 6 of 15). Their conclusion was that short-term treatment in patients with AHC is associated with satisfactory results if initiated early in the disease course.

#### How Should Patients Be Monitored After Treatment?

Appropriate follow-up of patients with AHC is important as it is not uncommon for patients to develop chronic HCV infection despite a period of time where HCV RNA is not detectable (25). In the study by Gerlach, et al (8), 13 of 30 patients in whom chronic HCV infection developed had transient clearance of HCV viremia during observation.

Weigand, et al (26) assessed the clinical, virologic, and immunologic long-term outcome of 31 successfully treated patients with AHC who were negative by HCV-PCR at 24 weeks after treatment and then followed for a median of 135 weeks after finishing treat-

ment. They found that none of the patients had evidence of late virologic relapse. All patients remained HCV RNA negative by PCR and there was no evidence of low levels of persisting virus by a more sensitive TMA assay. A biochemical response was maintained with normal ALT levels in all but one patient.

Greisman (7) recommends a minimum follow-up of six months after completion of therapy to ensure an SVR in treated patients, the same follow-up period that is considered standard for chronically infected patients (27). Monitoring of untreated patients should be maintained for at least one year with serial testing for HCV RNA to evaluate for delayed clearance or for possible recurrence and eventual development of chronicity in patients that have cleared virus transiently.

#### CONCLUSIONS

Hepatitis C virus infection often leads to chronic hepatitis and early detection of the infection is of the utmost importance. Although occasionally symptomatic, a majority of infections are mild or without symptoms. The identification of patients at risk and appropriate serological testing is key to discovering the infection in its early stage. In this early stage, the infection can be monitored for clearance and treated appropriately if it persists. The studies evaluating treatment regimen, initiation, and duration demonstrate that the earlier treatment is initiated with IFN therapy the better, although symptomatic patients have a higher likelihood of spontaneously clearing virus and should be observed for at least 12 weeks to allow for spontaneous clearance of viremia.

Pegylated interferon monotherapy appears to be highly effective in achieving a sustained response, the addition of ribavirin does not seem to add much to efficacy in most cases. The duration of treatment, although no clear recommendations are established, appears to be 12–24 weeks of once weekly treatment. Longer duration of therapy should be favored for difficult to treat genotypes such as genotype 1 or 4, and for those who fail to clear virus after the initial 4 weeks of therapy. In patients that respond to treatment, it is important to provide appropriate follow-up to detect

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relapse. Although most studies show sustained SVR, there are select patients that develop chronic HCV infection despite transient clearance of virus. ■

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