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# Acute Hepatitis C Virus Infection and Directly Acting Anti-Hepatitis C Virus Drugs

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**Abstract**

The best of care of Acute hepatitis C (AHC) infections in the evolving era of all oral directly acting antiviral drugs (DDAs) needs revision. The inevitable chronic liver disease in 80% of AHC infections justifies the advent of DDAs that expectedly will guarantee high cure rates. Unlike interferons, the short and ultra-short all oral DDAs regimens had revolutionized treatment strategies with better adherence and fewer complications. However, the costly price of DAAs added to the average expertise is still contrarily active. Up-to-date, studies concerning DAAs treatment for AHC mono-infection are sparse; indeed this represents an unmet need in modern AHC management.

**Keywords:** Acute hepatitis C; Antiviral drugs; Liver diseases

## Introduction

Extensive efforts of many scientists had been undertaken for a decade till discovery and isolation of HCV [1,2]. Acute HCV infection is rarely fulminant and mostly asymptomatically progresses to chronic liver disease, cirrhosis and the significant burden of associated morbidities [3].

Acute hepatitis C virus infection is a global infection with a varying incidence between countries and populations. In the United States, reporting new AHC cases has shown dramatic jump from 0.3 new infections per 100 individuals in 2010 reaching 0.7 new infections per 100 individuals by 2014 [4].

This blow is attributed to a rise in injection drug use among young adults [5]. In addition, a surge of acute hepatitis C has been found in human immunodeficiency virus (HIV)-infected men who have sex with other men (MSM) [6].

In developing countries, acute hepatitis C infections are mainly due to unsafe health care procedures; Egyptian mass antischistosomal treatment using inadequately sterilized syringes in the 1960s and 1970s is distinctive in this regard, while injection drug use takes the second position [7]. In Egypt, definite deterministic data concerning prevalence or incidence of AHC are lacking. Recent estimates of AHC have widely ranged from 3.4% to 78.7% of acute viral hepatitis cases, demographically predilecting the rural areas [8,9]. Either symptomatic or asymptomatic; AHC cohorts represent an open source of ongoing HCV infection.

The generally asymptomatic nature of AHC and lacking specific laboratory diagnosis are contributing the sparsely estimates relevant to AHC. Mass screening for AHC among symptomatic acute viral hepatitis cases definitely is an underestimate.

The occupational risk of acquiring AHC is still disappointingly high all over the world. In a recent meta-analysis, the reported AHC estimates among health care workers (HCW) from 1989 to 2014 had exceeded 200% higher prevalence than the public [10]. Furthermost, the situation is more critical in developing countries e.g. Egypt, and Nigeria, which are cursed by the triad of poverty, illiteracy, and of course disease [10]. Needle stick injuries are verified as the most deleterious risk accidents among HCW with an average rate of HCV infection of 0.5% [10]. Unfortunately, the lack of adequate reporting and surveillance data are pivotally responsible for the erroneous AHC estimates.

## The Problem of Acute HCV Infection

The first six months immediately following the primary acquisition of HCV refers to acute infection, even in absence of clinical features of hepatitis [11]. The gold standard for diagnosis of acute hepatitis C requires a positive test for HCV RNA; in some patients, the viraemia fluctuates and may drop to small values. Secondly, a documented antibodies seroconversion; together with serum alanine aminotransferase above 400 IU/l, mandates high grades of suspicion when an early case is encountered [12].

In immunecompetent persons; detection of seroconversion is difficult and positive HCV RNA and negative anti-HCV antibodies at the same time point are the prerequisites for diagnosing AHC [13]. The situation is different for the HIV patients who are under regular screen and storage of pre-diagnostic blood samples. Nevertheless, we should consider that some HIV patients unable to show such antibody response [14].

Actually speaking, exact identification of early HCV infections is like digging in the snow; only one-third of cases are symptomatic and even not all symptomatic patients show jaundice [15]. Also, documentation of AHC in asymptomatic and barely symptomatic patients harbors difficult discrimination from chronic infection. Indeed, in both acute and chronic infections, HCV RNA, HCV

antibodies and elevated transaminases can be jointly recognizable [16]. Additionally, the diagnosis can be overlooked by physicians and the patient with mild symptoms may not call for a medical consultation.

Official reporting of cases with documented AHC is another issue; ideally, the viral hepatitis case report form should be a beforehand paper in the all relevant clinics. All physicians, particularly, those in outreach clinics and hot areas, should participate in specific educational programs. Of note, monitoring for new cases and tuning up with the dominant pattern of viral transmission will assist to locate areas of potential epidemics and identify and follow groups at risk.

## Surveillance for AHC

Contrasting to HBV, HCV has no effective pre or post-exposure prophylaxis. Hence, surveillance for the acute infection in populations critically exposed to the infection, namely; men having sex with men, intravenous drug users and health personnel should seriously engage in HCV endemic areas [17].

Surveillance for AHC is considered one of the most deterministic reliable measures needed for augmenting national disease control strategies. In spite of the absence of the reliable affordable marker of AHC diagnosis, prompt uncovering of these cases is considered an advantageous step in cutting the virus infectious cycle. Proper surveillance of AHC might help in updating the viral epidemiological profile regarding incidence, transmission patterns, and outbreaks prediction. Recognition of the culprit infectious agent is substantially is advantageous for both the infected personnel and the whole community [18].

The populations at greatest risk of AHC, namely, HIV-positive and HIV-negative homosexual men as well as intravenous drug users are the ideal populations for regular surveillance and non-hesitant treatment for positive AHC cases. Notably, the likelihood of symptomatic acute hepatitis is significantly less in HIV-positive patients besides delayed seroconversion to anti-HCV positive [19].

## Acute HCV Infection in the Era of DDAs

In the era of interferon-based therapy, the conventional then the pegylated interferon with and without ribavirin had shown satisfactory cure rates compared to figures of treating chronic infections. However, the better response rate to interferon-based therapy in AHC, besides the shorter treatment duration, hadn't over-weighed the side effects and intolerability to interferon [20,21].

Starting from 2000, a light had shed on outbreaks of AHC in HIV-positive homosexual men. The HIV patients have other comorbidities that could represent contraindications to interferon therapy. The unaffordable cost of interferon treatment as well as the antiretroviral medications definitely impacted caring of this population. Most of HIV patients on antiretroviral were diagnosed to have AHC incidentally during routine checkups of liver function tests [22].

Following the advent of the new DAAs, AHC had barely been considered with few clinical trials. Most of these trials are dealing with AHC in HIV-positive patients. Evolution of the new protease inhibitors was inspiring for this special population. Three studies were evaluating protease inhibitors in AHC/HIV-co-infected genotype 1 men.

Telaprevir added to peginterferon and ribavirin were examined in two studies, with sustained response rate (SVR) achievement in only 84% and 56% respectively [23,24]. In the third study, boceprevir was added to peginterferon and ribavirin with 78% SVR rate [25]. The intolerability of the three combined drugs, the discouraging results, along with the high relapse rates determined on follow-up, was disappointing.

Coming to the era of polymerase inhibitors, sofosbuvir with ribavirin regimen was firstly tested in the NYC II on genotypes 1 HIV/HCV co-infected patients for 12 weeks mounting SVR achievement in 92% [26]. The same regimen was retested in SWIFT-C study on genotype 1 and 4 co-infected patients for the same duration, with only 59% of patients achieved SVR [27]. Minimizing the duration to only six weeks on genotypes 1 and 3 had downed the SVR achievements to 32% (DARE C II study) [28]. The reported low response rates of the sofosbuvir-ribavirin regimen in acute as well as chronic HCV infection, had justified the usage of more potent DAAs.

The tip of the chain was the comparative pilot SLAM-C study equating sofosbuvir added to either ledipasvir for four weeks or to simeprevir for eight weeks in AHC mono-infected patients. Paralleled superiority for both regimens (more than 90% in both arms) was determined and larger scale studies were recommended [29].

Early data of the German HepNet Acute HCV IV study had been presented in EASL ILC, 2016. The 20 AHC mono-infected genotype 1 patients included in this study had received a six-week course of ledipasvir-sofosbuvir. They are all sustained responders with excellent safety and tolerability profiles [30]. The last two mentioned studies are the premieres, submitting isolated AHC in non-HIV patients with evidently favorable results.

The American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD and IDSA), and the European Association for the Study of the Liver (EASL) had recommended treating AHC with the same but short (eight weeks) or ultra-short (six weeks) regimens like chronic hepatitis C for short (eight weeks). They advised longer durations for those with HIV or baseline HCV RNA higher than 1000, 000 IU/ml [31].

## When to Treat AHC

The ill compliance to interferon therapy for AHC had favored the wait for spontaneous clearance of the virus, particularly in those having an asymptomatic disease and other known predictors of a spontaneous cure [32]. Also, in those accidentally diagnosed with AHC whereas the chances for chronic disease are high, the wait strategy for variable durations was preferable. Contradicting this view is the research data showing better outcome with earlier therapeutic interference [33]. Therefore, the new age of interferon-free therapies with short-term treatment and high safety and tolerability figures, it seemed advantageous to cut the cycle off, treating all detected cases. In spite of the limited number of cases of DAAs treated AHC, the spectacular cure rates in mono-infected patients are supportive to the opinion of treating all documented cases. In a cost-benefit scale, the relatively high prices of DAAs should not interrupt the global efforts in HCV eradication.

## Conclusion

A significant proportion of newly acquired HCV infections can go unrecognized, thus re-enriching the HCV pool and wasting the continuous efforts in HCV containment. Preventive strategies aligned with effective viral hepatitis reporting system and intensified education

for both health-care providers and population should be expanded and frontline the battle against HCV. The fruitful outcomes of early DAAs studies on AHC might be significantly challenged by many obstacles. The undetermined natural history of AHC, the problematic diagnosis, the emergence of resistance-associated variants (RAVs), and the utmost viremia in HIV-positive patients are all potential barriers in this prospect. However, the decision of treating AHC cases should be instantly commenced.

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