Current knowledge and future perspectives on acute hepatitis C

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Abstract

Acute hepatitis C virus (AHCV) infections are frequently seen worldwide in certain risk groups with an annual incidence rate varying between 0.08% and 66%. Although this incidence is substantial, a delayed diagnosis during chronic infection is most often made in the absence of clinical symptoms in the acute phase of the infection. Current used methods to diagnose AHCV are IgG antibody seroconversion and repeated HCV RNA measurements though no definite diagnostic test is currently available. Progress in the field of adaptive and innate immune responses has aided to both advancements in the field of HCV vaccine development and a more basic understanding of viral persistence. The rapid changes in the treatment of chronic HCV will affect therapeutic regimens in AHCV in the coming years leading to shorter treatment courses and pegylated interferon-free modalities. This review gives an overview of the current knowledge and uncertainties together with some future perspectives on acute HCV epidemiology, virology, immunology and treatment.
Introduction

Throughout the world, acute hepatitis C virus (AHCV) infections remain common within specific populations. With about 170 million chronic carriers, there is a continuous pool out of which new infections arise (1). Recent studies report ongoing transmission within the major risk group of injecting drug users (IDU). Moreover, in recent years a new epidemic of AHCV has emerged as a sexually transmitted infection in human immunodeficiency virus (HIV) infected men who have sex with men (MSM) outside the context of injecting drug use.

An AHCV infection is mostly asymptomatic, or at least stays undetected and leads to chronicity in 74% (95% CI 72% - 79%) of reported cases (2). Because of this silent infection, patients are mostly diagnosed in the chronic phase. This results in a paucity of studies evaluating viral and immunologic characteristics of AHCV. Furthermore, due to suboptimal study design (often retrospective cohorts) and small numbers of enrolled patients per study, many issues remain pending. This review gives an overview of the current knowledge and uncertainties together with some future perspectives on acute HCV epidemiology, virology, immunology and treatment.
Epidemiology

Three major populations at risk for AHCV can be identified, each with differing modes of transmission, occurring with different frequencies in different parts of the world: injecting drug users, patients at risk of nosocomial infection and HIV positive MSM(1).

Sharing of injecting equipment among drug users is a major risk factor for AHCV and IDU accounts for most AHCV infections worldwide. Currently, it is estimated that there are 0.75-1.0 million active IDU in Europe alone(3). AHCV incidence within this group varies between 2.7 and 66 per 100 person years of follow up (PYFU)(4). This results in an anti-HCV prevalence of above 50% in Europe and around 67% worldwide(5, 6). A remarkable example of the ongoing epidemic in IDU outside Europe is within young adult IDU in the United States with reported incidences as high as 27 per 100 PYFU(7, 8). During the last decade this epidemic has expanded to rural areas and has been associated with increased prescription opiate use(9). In the IDU population a variety of interventions have been implemented that resulted in a reduced AHCV incidence. Most implemented interventions are opiate substitution and needle exchange programs of which high coverage of combined programs is associated with a reduction in AHCV incidence(10, 11). However, HCV incidence within IDU does not seem to decline to the very low levels that have been observed for HIV(12). This difference might lie within the virologic characteristics of the virus as HCV is about 10 times more likely to be transmitted through a needle puncture than HIV(13). Furthermore, HCV transmission might also occur through sharing of drug use equipment other than needles or via tattooing (i.e snorting straws).

Within the European health care system HCV transmission still occurs. For example, according to the national surveillance system in France, these infections (mainly invasive procedures) account for up to 25% of all AHCV infections diagnosed(14). However, for hospitalized patients in Europe the risk of AHCV infection via blood transfusion or via medicinal use of contaminated needle injections is now nearly abolished. In contrast, high
rates of AHCV infections within health care systems occur in developing countries. There are several developing countries which do not screen blood donors for HCV because of limited health budget, leading to transmission of HCV. The most dramatic example is Egypt, in which the iatrogenic transmission of HCV during the era of parenteral anti-schistosomal therapy mass-treatment between 1960 and 1980 led to a nationwide epidemic. As a result, between 10-20% of the total Egyptian population is currently infected, most of them with genotype 4. Because of inadequate sterilization of healthcare equipment and the high prevalence in the general population, HCV continues to spread in Egypt(15). Therefore, its annual number of new AHCV infections is estimated around 150,000(16). Intra-familial transmission (3%) and heterosexual transmission (0.07%) seem to be of limited importance(15, 17).

In contrast to the low incidence of heterosexual HCV transmission stated above, HCV is considered a sexually transmitted disease among MSM. More specifically and for partially unknown reasons, this AHCV epidemic has been limited largely within HIV positive MSM(18). In Europe, during the past decade incidence was rising from 0.08/100 PYFU up to 1.75/100 PYFU(19-23). Currently, the epidemic appears to be leveling off in the Netherlands(24). Outside Europe (United States, Japan) this seems not the case, with recent reported incidences between 0.21/100 PYFU and 2.49/100 PFYU(25, 26). The AHCV reinfection rate is even higher with reported rates of 7.8 and 15.2 per 100 PYFU(27, 28). A supposed reason for this epidemic is the emergence of national and international networks of HIV positive men preferably having unprotected sex with HIV positive men (i.e. serosorting)(29). These could arise because of successful HIV treatment, widespread internet use and low-budget travel possibilities(20, 30). Determinants for HCV transmission are recreational drug use, sharing of snorting straws, receptive fisting, ulcerative sexually transmitted infections like syphilis, group sex and rectal trauma with bleeding(22, 31-33). There are also a number of potential mechanisms related to HIV that might result in enhanced infectivity and susceptibility to HCV,
including increase HCV loads in serum, semen and defects in the gastrointestinal immune system(34).

Despite adequate surveillance systems there is still a significant fraction (up to 45%) of AHCV infections for which the mode of transmission cannot be identified. Suggested explanations include denial of risk factors, transmission by acupuncture, tattooing, piercing or shaving at barbers(15, 35).
A heterogeneity in case definitions of AHCV infection is currently used. These differ widely between epidemiologic, immunologic and intervention studies. Also within these subgroups a wide range of criteria is used(36).

Diagnosing seroconversion remains the most important method for detection of AHCV infections(37). This approach, as is true also of demonstrating geno-conversion by genome amplification assays, relies on the availability of a recent pre-diagnostic sample. Although sample storage is common practice within the HIV co-infected patients in tertiary care centers in Europe, this is rarely done in other risk populations, who do not regularly visit the outpatients clinics. Therefore, most AHCV infections will remain undiagnosed. Alternatively, the combination of anti-HCV negativity and positive HCV RNA at a single time point is also highly suggestive of an acute phase of infection. However, in immunocompromised patients seroconversion takes time and remains absent in 2%-5% one year after infection(38, 39). If a patient is already anti-HCV and HCV RNA positive at the time of first sampling, IgG avidity testing can allow an estimation of infection duration(40). For diagnosing reinfection, HCV genome amplification is the gold standard. However HCV antigen, IgG avidity and IgG titer measurements are promising alternatives(39, 41).

Elevation of alanine transaminase (ALT) is still used in several definitions of AHCV. However, cut-off points differ widely across studies from any value above the upper limit of normal to 20 times the upper limit of normal(36). Interestingly, the presence of normal ALT values in the acute phase of infection has been reported, in association with fluctuating viremia(42). Thus, excluding a diagnosis of AHCV infection in a high-risk individual by relying on a normal ALT may not be appropriate.

**Predicting clearance**

The process leading to either clearance or chronicity is dependent on specific viral and host characteristics. These determinants are heavily debated because of small numbers of
patients enrolled in different AHCV cohorts: IDU, HIV co-infected, nosocomial infected or combined. In a recent multicenter study, patients with a genotype 1 infection had an adjusted hazards ratio (AHR) of 1.56 in favor of clearance(43). An additional important factor for spontaneous clearance is the diversity in quasispecies: increased quasispecies heterogeneity equates with longer estimated duration of infection and higher serum HCV RNA levels. The heterogeneity in quasispecies can be partially explained by the route of transmission (IDU versus sexual) (44) and the imperfect function of the viral RNA polymerase combined with a production of $10^{12}$ virions a day (45).

Important host protective factors which have been associated with spontaneous clearance are: nonblack race (Odds Ratio (OR) 5.15), female gender (AHR 2.16) (with a protective effect of oestrogen) and host interferon lambda gene 28B (IL28) C/C genotype (AHR 2.26) (43, 46, 47). Difference in host IL28 polymorphisms seems one of the few genetic predictors of viral clearance with CC as the most favorable genotype followed by CT and TT (48). The closely linked rs12979860 and rs8099917 subtypes are associated with clearance, treatment effect and progression to cirrhosis in chronic HCV. For example within a study among 190 women, spontaneous clearance was more common in patients with the C/C genotype (43/67; 64%) compared with C/T (22/90; 24%) or T/T (2/33; 6%) (P < .001) (49). The presence of hepatitis B antigens seems to be protective for chronicity (OR 2.91) (50). In contrary, infection with HIV is associated with progression to chronicity (OR 2.19) (46). However, when the immune status of a patient can be restored by combined antiretroviral therapy, the chance for spontaneous clearance seems to be increasing (51).

Several models have been developed to prevent unnecessary peginterferon-based treatment for patients who would have cleared HCV spontaneously (43, 52-55). These prediction algorithms rely on pathophysiological causative mechanisms but also on clinical or biochemical symptoms like jaundice, bilirubin or the IP-10 level, which may be a reflection of well-functioning immune system. These algorithms reliably predict spontaneous cure rates but have not been prospectively validated.
Immunoology

Cellular response

Mounting an effective T cell response is a key immunological element of spontaneous viral clearance (56). Specifically for AHCV mono-infections, several studies have demonstrated that a broad and vigorous HCV-specific CD4+ and CD8+ T cell response is associated with clearance of the infection (57-60). Similar observations linking T cell responses to spontaneous viral clearance have been made in HIV-infected patients with an AHCV infection. However, comparisons between AHCV mono-infected and HIV/AHCV co-infected patients reveal impaired responses in the latter group, which may account for the observed reduced clearance rates in this patient group (60, 61).

The innate immune response also plays a role in the acute stage of the disease though its exact contribution is unclear. HCV RNA is sensed through either the helicase RIG-I, forming a complex, or Toll-like receptors ultimately leading to production of Interferon alfa (IFN-alfa) and upregulation of interferon-stimulating genes (ISG) (62, 63). Differences in production of IFN-alfa, both in plasma and in the liver, have been attributed to the observed differences in spontaneous viral clearance rates between AHCV mono-infected and HIV/AHCV co-infected patients (64, 65). Several HCV proteins have been shown to interact with this intracellular signaling cascade, e.g., HCV protease, which cleaves the mitochondrial antiviral-signaling protein downstream of RIG-1 (63, 66).

Humoral response

The role antibodies play in spontaneous clearance of AHCV is less well understood (67). Early in vitro studies showed that highly specific neutralizing antibodies (NA) against HCV envelope proteins E1 and E2 were frequently present, with the hypervariable region 1 (HVR1) in the E2 as an important target for NA. However, there were technical limitations encountered e.g., use of pseudoparticle cell systems enabling only a limited number of viral genotypes together with the use of the general reference strain H77c. Despite the
development of JFH-1 cell culture system that accelerated neutralizing antibody research, how HCV evades neutralization still requires further definition. Partly, this can be explained by cell-to-cell spread via tight junctions(68), partly because of the high specificity of these antibodies for variants that can subsequently mutate under selection pressure. Despite evasion of the immune system, there is clinical evidence for a significant role of NA in protection against HCV. For example, from early hepatitis B immunoglobulin (HBIG) vaccination studies in liver transplant patients it became apparent that lower HCV recurrence rates were seen in those patients receiving HBIG(69). Furthermore, in AHCV patients, high NA titers corresponded with spontaneous viral clearance(70). Similar to the pattern of T cell responses, broadly neutralizing antibodies are again associated with resolving infections(70). Such NA may recognize conformational epitopes most often around the CD81 binding site, one of the co-receptors for HCV cell entry(71). Additionally, although a rare occurrence, NA binding to linear epitopes has been described(72) leading to the discovery of monoclonal antibodies such as AP33, with potent neutralization capacity(73).

**Vaccination**

One question in the era of direct acting antivirals (DAAs) is whether we still need a vaccine. It could be reasonably argued that since most people are unaware of their infection and its limited symptoms of disease, vaccination is the most effective way of HCV eradication. Moreover, adequate treatment gives no protection against re-infection(28). However, the correlates of immunity for HCV are still largely unknown hampering vaccine development(74). Based on the chimpanzee HCV model a limited number of vaccine candidates have advanced into human clinical testing with a varying degree of success(75). Different approaches have been tried; recombinant proteins, or peptides, DNA and viral vector based vaccines. Combining two e.g. a viral vector with a protein seems attractive, potentially providing both humoral and cellular immunity(76). For example, the combination of an adeno-viral vector with a recombinant HCV E1E2 protein was demonstrated to elicit a strong antibody and T cell response in mice and guinea pigs(77). A recent phase 1 human
study showed very high levels of CD4+ and CD8+ T cells can be induced using viral vectors based on rare adenovirus serotypes: currently, a phase 2 study using such vectors is underway to investigate the efficacy of such a prime-boost T cell vaccine approach in an injecting drug using community in Baltimore(78).
Treatment

Optimal timing of AHCV therapy

In clinical practice, the best moment to initiate therapy continues to be under debate. It is not easily predicted when chances of spontaneous clearance outweigh the effects of pegylated-interferon (pegIFN) based therapy. A model has been made to predict efficacy of treatment in comparison with the chances for spontaneous clearance and proposes to treat within the first two months or 4 months after transmission (53). However, this model assumes a reliable transmission date, which is often not the case. As a result, most physicians refrain from therapy during at least the first month after diagnosis to await spontaneous clearance. This is in line with the current European AIDS treatment network (NEAT) and European Aids Clinical Society (EACS) guidelines recommending a 4-week period to observe a potential HCV RNA decline of at least 2-log after which the chance of spontaneous clearance becomes substantially higher (37, 79). Without this 2-log decline, treatment can be initiated. However, observations within a large international study on 632 participants with AHCV mono-infection did not support this approach. Among patients with spontaneous clearance, 33% became HCV RNA negative later than 6 months after the estimated date of infection (43). This supports the tendency to wait for a longer period. As a result, current EASL and AASLD guidelines are inconclusive about the observation period (37, 80). This is also supported by a study in 130 mono-infected patients who were treated after a 12 week delay showing similar sustained viral response (SVR) rates when compared to data from studies using a 4 week observation period (81). In contrast, data from the German HepNET III study in AHCV mono-infection did not support a 12-week delay in treatment after diagnosis since this was associated with a lower SVR rate compared to immediate treatment (SVR 54% versus 67%) (82). However, because this difference in SVR rates was largely driven by the fact that more patients in the delayed treatment group got lost to follow up, the authors concluded that delayed treatment could be as effective when protocol and treatment adherence can be assured. Finally, in the light of pegIFN free therapies with cure rates
above 90% the debate will continue and delay of treatment will be expanded to wait for the
last patient to clear.

Rationale for treatment

AHCV is historically treated shorter and with higher SVR rates compared to chronic
infections. With new DAAs to come, the treatment of chronic HCV has become very effective
and early treatment may have no advantage with respect to SVR rates. As a result, current
AASLD guidelines advocate to wait until infection becomes chronic and select treatment
regimens without pegIFN(80). However, there are several reasons to still treat in the acute
phase, for example to reduce viral transmission or to treat symptomatic patients. In many
countries, the most important reason for treating with pegIFN based regimens during acute
infection is the lack of insurance coverage of new DAAs in patients without an urgent medical
need for HCV therapy. This is certainly not restricted to resource limited settings. In several
European countries (e.g. Belgium, the Netherlands, Spain, Italy, UK) DAAs can only be used
in patients with advanced fibrosis or cirrhosis. Even when DAAs can be used regardless of
fibrosis grade, DAAs are not EMA nor FDA registered for the treatment of acute HCV as
their efficacy in patients with acute HCV has not yet been studied. Therefore, despite its side
effects, pegIFN based acute HCV therapy will remain the only available option in many
countries for several years to come.

AHCV treatment regimen

Currently, pegIFN-alfa monotherapy, or in combination with ribavirin (in HIV co-infection) is
still the only treatment that has been adequately studied in patients with AHCV infection and
is approved for this indication. In AHCV mono-infected patients, cure rates between 71%
and 94% have been reported with pegIFN-alfa monotherapy(83, 84). As the therapeutic
mechanism for pegIFN-alfa and standard interferon-alfa is similar, starting the treatment with
high-dose standard interferon-alfa 2a or 2b is considerable in resource limited setting in
which pegIFN-alfa is not available or more costly.
The wide variety of cure rates within the HIV co-infected population makes it difficult to interpret the effect of different treatments. Small, mostly underpowered, cohort studies with a variable genotype distribution give an average cure rate of 61%(SD 17)(85). Although its role remains controversial, ribavirin is often added to pegIFN-alfa in HIV co-infection resulting in higher SVR in general. Most physicians start with pegIFN-alfa and ribavirin, with tapering or discontinuation ribavirin if adverse events occur(37, 85). However mono-therapy could be suitable in a subset of co-infected patients treated within the first weeks after AHCV diagnosis(86).

Duration of treatment

In most clinical studies and treatment guidelines, the duration of pegIFN-alfa therapy in HCV mono-infected patients has been 24 weeks. However, 12 weeks of therapy has also been used successfully in observational studies with cure rates of 72 and 74%(87, 88). In a recent large randomized controlled trial no difference in response rates between 24 weeks of pegIFN-alfa and 12 weeks of pegIFN-alfa (with or without ribavirin) was observed(81). As this study concluded that the only predictor of SVR was a rapid viral response at week 4, it is remarkable that this decision rule is not integrated in current EASL guidance(37).

For HIV co-infected patients, the NEAT AHCV guideline suggests to base treatment duration on the week 4 HCV RNA load. If HCV RNA is <600 IU/ml a treatment duration of 24 weeks is recommended with a duration of 48 weeks when HCV RNA is >600 IU/ml(85, 89).

DAAs in the treatment of AHCV

Several new classes of DAAs have shown cure rates above 90% in patients with chronic HCV in both HIV negative as well as positive patients. For the treatment of AHCV, only telaprevir, a first generation HCV protease inhibitor has been tested in a pilot study of AHCV infection in 19 co-infected patients. It was given for only 12 weeks in combination with pegIFN-alfa and ribavirin and a promising 84% SVR rate was seen(90). If these results can be confirmed by other ongoing study’s, the use of first generation protease inhibitors for the
treatment of AHCV could become an effective treatment strategy (91, 92). Currently, also
interferon free DAA containing studies are being set up (table 1) (93). However, so far, no
DAA containing regimen has been extensively studied in patients with AHCV. As such,
peginterferon based therapy is likely to remain part of the treatment armentarium for AHCV
during the next several years to come. DAAs will be added consecutively, with decreasing
treatment duration as a result (figure 1).
Conclusions and future directions

The AHCV field remains complex because of limited research into prevention, adequate diagnosis, treatment initiation and its regimens. Despite all efforts, there is still no conclusive evidence for a decline in spread of the virus within major risk populations. Even with high incidence rates, the identification and inclusion of substantial numbers of individuals with AHCV to allow trials to have sufficient power remains very challenging.

The availability of new DAAs will likely result in more cured patients. The high rate of adverse events and discontinuations in peginterferon-based therapy has led to a delay in treatment initiation in acute infections, with possible resultant onward transmission of infection. Due to projected significant costs and therefore limited worldwide availability of DAAs, it remains to be seen whether more advanced treatment approaches will have a substantial effect. The availability of a potent anti-HCV vaccine would be helpful, though the results from trials of candidates are still eagerly awaited.

Therefore, increased attention should be focused on screening and detection of AHCV cases. However, reducing the size of the infected population will probably not lead to the total extinction of HCV infections since acutely infected individuals might drive onward HCV transmission(94). The best way to eradicate a virus remains early identification for which better diagnostic tools are necessary in combination with low cost potent treatment.
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Conflict of Interest

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None
References

3. Annual report on the state of the drugs problem in Europe: European Monitoring Centre for Drugs and Drug Addiction; 2010.


Table 1: Current and future studies with DAAs in AHCV

<table>
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<tr>
<th>Study name</th>
<th>Coordinator</th>
<th>Therapy</th>
<th>HCV genotype</th>
<th>Duration (weeks)</th>
<th>HIV status</th>
<th>Number of patients</th>
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EMC: Erasmus Medical Center, the Netherlands; UKB: Universitätsklinikum Bonn, Germany; Kirby Institute, Australia; ACTG: Aids Clinical Trials Group, the United States of America; MHH: Medizinische Hochschule Hannover, Germany; BOC: boceprevir, PegIFN: pegylated interferon, RBV: ribavirin, SOF: sofosbuvir, LDV: ledipasvir; * estimated number
Figure 1: AHCV treatment and response prognosis