

## ACUTE HEPATITIS C VIRUS INFECTION

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Around 25% of people infected with hepatitis C virus (HCV) are able to clear the infection spontaneously, while the majority become chronically infected, with a subsequent risk for the individual patient of progressive inflammatory liver disease, cirrhosis, hepatocellular carcinoma and liver-related death (Figure 1). Much is known about the epidemiology, pathogenesis, diagnosis and management of chronic HCV infection. In comparison, knowledge about acute HCV infection is patchy. In this article, we will highlight concerns relating to acute HCV infection and suggest that public health bodies responsible for managing the HCV epidemic should redirect at least some of their resources to dealing with these issues.

### Natural history of the disease

Most patients with newly-acquired HCV infection do not present with an acute hepatic illness – most estimates suggest only 10-15% of cases are acutely jaundiced. In the remainder, the infection is either asymptomatic, or may present with mild constitutional symptoms (nausea, loss of appetite, fatigue, vague abdominal pain), with an alanine aminotransferase (ALT) which peaks below 1,000 UI/ml. As a result, few such cases come to medical attention or are tested for evidence of HCV infection [1].

Given the largely asymptomatic nature of the acute infection, as well as the fact that most acute infections occur in injecting drug users (IDUs) who are hard to reach, and that a diagnosis of acute infection can be difficult to prove (see below), most studies of the natural history of acute HCV infection contain relatively few patients. A recent review [2] identified 675 individuals in 31 studies (mean 22 per study, range 4-67). Clearance of infection ranged from 0-80%, with a weighted mean of 26%. Females were more likely to clear infection than males (40% versus 22%), and patients identified because of clinical presentation with acute illness were more likely to clear infection than those identified as a result of screening protocols i.e. in post-transfusion or sero-incident (i.e. demonstration of infection by serial testing and revelation of seroconversion from negative to positive) studies (31% versus 18% and 18%).

### Epidemiology

Many countries have surveillance systems that record new diagnoses of HCV infection. In England and Wales, new diagnoses are reported to the Health Protection Agency, which produces annual reports showing trends in the identification of anti-HCV positive sera [3]. In the Netherlands virological laboratories report positive serology and positive HCV RNA to the National Institute for

Public Health and the Environment (RIVM). However, these data do not distinguish between acute and chronic infections, and it is highly likely that the vast majority of the reported cases are from patients with chronic infection.

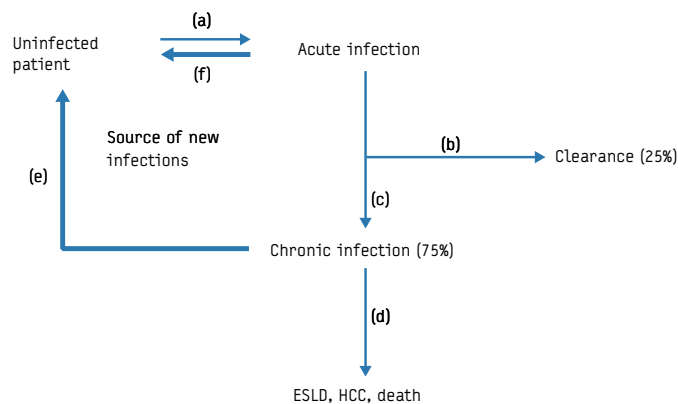
In the United States, there is a reporting scheme for acute viral hepatitis. Reporting is voluntary, and the US Centres for Disease Control and Prevention produce annual reports, the latest of which, published in March 2008, contains data pertaining to 2006 [4]. The case definition for acute HCV infection has both clinical and laboratory components – see Table. Note that this case definition will not discriminate between acute infection and an acute exacerbation of chronic infection. In 2006, 802 cases of acute HCV infection were reported, a population incidence of 0.3/100,000. 41% of these cases were hospitalised, and 66% jaundiced. Taking into account under-reporting, and the fact that the large majority of acute HCV infections do not present with jaundice, this equates to an estimated 19,000 new infections. Risk factors present in acute cases included injecting drug use (54%), surgery (16%), sex with known positive partner (10%) and occupational exposure (1.5%) (some patients had more than one risk factor). The data allow identification of trends, assessment of the impact of preventive strategies, and can highlight areas of concern should these arise. The data show an encouraging decline in the number of cases of acute HCV infection reported since 1992 (Figure 2).

In Europe, the European Centre for Disease Prevention and Control (ECDC) has produced its first Annual Epidemiological Report on Communicable Diseases in Europe [5]. The HCV data within the report demonstrate a steady increase in the "Incidence rate of hepatitis C cases in EU and EEA/EFTA countries by year reported 1995-2004" (fig 4.18.1, page 113), but this clearly does not relate to incident infection, but to an unspecified amalgam of chronic and acute infections, the bulk of which will be chronic. Indeed, the conclusions of the HCV section of the report contains the statements: "There are clear limitations with the HCV surveillance data...", "...the data are inadequate to describe the true HCV infection trend and disease burden." and "The real transmission pattern... should be more thoroughly investigated in the EU...".

Recent papers describing experience with acute HCV demonstrate that, while most patients are IDUs, transmissions are also occurring through other routes. Many reports cite high risk sexual behaviour as a significant risk factor for heterosexual transmission [4,6,7], while outbreaks of HCV infection amongst HIV-infected men who have

**FIGURE 1**

**The natural history of HCV infection**



New infections (arrow a) are either cleared spontaneously (arrow b, 25%) or give rise to chronic infection (arrow c, 75%). Chronically infected patients are then at risk of life-threatening complications of liver disease (arrow d). Uninfected individuals acquire infection either from chronically-infected individuals (arrow e), or from other recently infected individuals (arrow f). The relative contributions of these two distinct sources towards incident infection is currently unknown. Control strategies aimed at chronically-infected patients may reduce the likelihood of individuals progressing to chronic liver disease (arrow d), but have relatively little effect on acute transmissions (reducing arrow e but having no effect on arrow f). Focussing on acute infections may allow therapy and thereby prevent chronic infection (arrow c), and may also significantly reduce further onward transmission (arrow f).

\* ESLD = end stage liver disease  
 \*\* HCC = hepatocellular carcinoma

sex with men have recently been reported from the UK, France and the Netherlands [8,9,10]. Iatrogenic infection is also reported at alarmingly high rates, with even minor procedures such as receiving an injection while in hospital being significantly linked to acute infection [4,6,7,11,12].

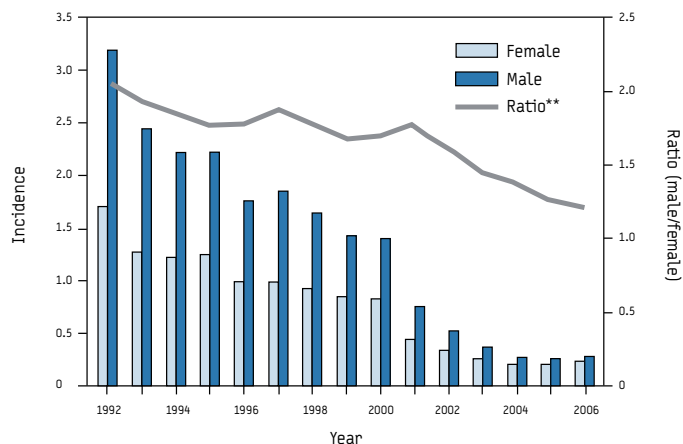
**Diagnosis**

Current algorithms for the diagnosis of HCV infection involve the detection of anti-HCV antibodies and/or HCV RNA in a serum sample. While such testing is able to distinguish between past, cleared HCV infection, and current infection, it does not allow determination of whether the infection is acute or chronic. The presence of IgM antibodies, the usual serological marker of acute infection, is unreliable in the context of HCV infection [13]. Clinical diagnosis, i.e. in a patient presenting with an acute jaundice and possibly even a history of recent exposure, has an extremely low sensitivity, as the vast majority of acute cases do not present in this way, and will also have a specificity of less than 100% through failure to distinguish acute infection from an acute exacerbation of chronic infection. Diagnosis of acute HCV infection is therefore difficult.

Demonstration of sero- or genoconversion in serial samples taken from the same patient would provide definitive proof of recent acquisition of infection in that individual. However, long-term serial sampling of high-risk populations is notoriously difficult to achieve, especially outside carefully conducted and well-funded research studies, and therefore adoption of such a strategy for monitoring incidence trends is likely to be expensive, subject to considerable sampling bias, and unlikely to generate robust data.

**FIGURE 2**

**Incidence (per 100,000 population) of acute hepatitis C, by sex and year – United States, 1992 – 2006\***



\* Until 1995, acute hepatitis C was reported as acute hepatitis non-A, non-B  
 \*\* The bars indicate the rate per 100,000 population (left y-axis) by sex; the line is the ratio (right y-axis) of the incidence among males compared to that among females.

Taken (with permission) from Wasley et al; Surveillance for acute viral hepatitis – United States, 2006, MMWR Surveillance Summaries 2008; 57(2): 1-24.

**TABLE**

**Case Definition for Acute Viral Hepatitis C, US Centers for Disease Control and Prevention National Notifiable Disease Surveillance System**

<b>Clinical case definition:</b>
acute illness with 1) discrete onset of symptoms (e.g. nausea, anorexia, fever, malaise, abdominal pain) AND 2) jaundice or raised serum alanine aminotransferase (ALT)
<b>Laboratory criteria:</b>
serum ALT higher than seven times the upper limit of normal, AND IgM anti-HAV negative, AND IgM anti-HBc negative, or if not performed, HBsAg negative, AND either anti-HCV or HCV RNA positive

Two approaches to diagnosis of acute infection that are showing some promise are window-period testing, and IgG avidity determination. The former is based on the principle that in an acute infection, there is a window period where HCV RNA will be detectable within the peripheral blood, but anti-HCV antibodies will not. Thus, RNA testing of antibody negative sera should identify acute infection. Knowledge of the length of the window period (best estimates give median duration of 58 days, 95%CI 45-75, ref 15) allows conversion of the percentage of antibody negative RNA positive sera derived from the population under study into an incidence rate. Studies using this approach have recently been published from both the United States and the United Kingdom [14,15], demonstrating widely differing rates according to the nature of the study population. The potential expense of RNA testing on a large-scale for surveillance purposes can be reduced to some extent by testing of pooled samples, albeit with some loss of sensitivity.

IgG avidity (or antigen-binding force) increases over time following antigen challenge. Thus, virus-specific IgG in the weeks following an acute infection will be of low avidity, while that associated with a chronic infection will have matured into high avidity. Assays can distinguish between low and high avidity antibody, based on the extent to which antigen-antibody binding is disrupted by the presence of a chaotropic agent. Results are usually expressed as an avidity index (AI), calculated as the optical density generated in the presence of the chaotropic agent divided by that produced in its absence. An AI <0.3 (or 30%) equates to low avidity, while anything >0.7 (or 70%) represents high avidity. Such assays perform very well when analysing seroconversion panels [16,17], providing clear cut-off AI values which distinguish samples taken within 20-100 days of infection from those derived from patients with chronic infection. Importantly, samples from chronically infected patients with acute exacerbations have high avidity (as would be expected), increasing the specificity of this approach [17]. However, there is no current standardised agreed methodology for these assays – reports differ in terms of which chaotropic agent is used (e.g. urea, guanidine), at what molarity, and at what stage in the assay it is used (e.g. addition to serum diluate, addition to wash buffer).

### Treatment

Interest in this area was stimulated by the seminal study which demonstrated a sustained virological response (SVR) in 43/44 (98%) patients with acute infection using standard interferon, conducted at a time when average SVR rates in patients with chronic infection treated with combination interferon and ribavirin therapy were below 50% [18]. A number of studies have replicated this encouraging finding viz. that early treatment is associated with significantly higher clearance rates, although as would be expected, response rates decline if patients do not adhere to their therapeutic regimens [19]. Some controversies remain. A multi-centre trial from Egypt, USA and Germany demonstrated high response rates using pegylated interferon alone for only 12 weeks, and also showed that, for genotype 2 or 3 infection, delaying onset of therapy until 12 weeks (and possibly longer) after diagnosis, thus allowing patients to achieve spontaneous clearance, did not impact on overall SVR rates, although this was not true for genotype 1-infected patients [20]. A separate study from the same group demonstrated better response rates for genotype-1 infected patients treated for 24 weeks as opposed to 12 weeks [21]. European experience suggests that pegylated interferon alone is sufficient, while American recommendations suggest that the use of ribavirin should also be considered on an individual basis [22]. It seems sensible to recommend combination therapy for HIV-infected patients who acquire acute HCV infection, as response rates are generally not as high in this patient group compared to monoinfected patients.

### Public health aspects

Although HCV is a transmissible disease, current management of HCV-infected patients for the most part does not reflect this fact. The vast majority of patients attending specialist clinics for assessment and management acquired their infection many years ago, and are likely to be no longer at significant risk of transmitting their infection to others, as their own risk behaviour (e.g. injecting drug use) will have ceased. Thus, there is little point in undertaking standard public health measures to deal with an infectious disease, such as contact tracing and identification of the infectious source, when dealing with a chronically infected patient. However, even for those patients who are still active IDUs, contact tracing, which may identify other infected individuals who may benefit from therapy, is often complicated and not routine practice.

Considerable effort is expended by governments and health departments on encouraging patients who might have chronic HCV infection to come forward for appropriate testing and therapy, which overall results in around 50% cure. While this is excellent news for the individuals concerned, as it reduces if not entirely prevents their individual risk of suffering progressive liver disease (arrow d in fig 1), the impact of such a strategy on incident infections is hard to gauge. Incident infections arise from one of two sources – individuals with acute infection (arrow f, Figure 1), and individuals with chronic infection (arrow e, Figure 1). The relative contribution of these two distinct sources towards incident infection is not known. The majority of patients with chronic infection undergoing therapy in specialist clinics are no longer IDUs, and therefore we argue that a strategy based on treatment of chronic infection alone will not have a major impact on incident infections.

An alternative approach to the HCV epidemic would be to concentrate efforts on the acutely infected patient. There are cogent reasons for this, although we acknowledge that identification and treatment of acutely infected patients presents considerable challenges:

- Treatment of acutely infected patients is far more effective than for those who are chronically infected. Thus, there is considerable benefit to the individual concerned in being diagnosed and offered therapy at this stage of their infection. Successful therapy also reduces the future numbers of patients with chronic infection (arrow c, Figure 1) and its downstream [?] life-threatening complications;
- Knowledge of who has been recently infected will allow the implementation of standard public health approaches to the control of an infectious disease. Contact tracing will identify other infected individuals, perhaps most likely with chronic infection, but possibly also some with acute infection who would benefit from therapy. It may be possible to pinpoint an infectious source, and thereby interrupt future transmissions (arrow f, Figure 1) e.g. by education/provision of clean injecting materials. The effectiveness and cost-effectiveness of any of these interventions has not yet been adequately studied.
- Mathematical modelling has demonstrated that unless there is a dramatic (e.g. >80%) reduction in the acquisition of new HCV infections, then the numbers of patients presenting with HCV-related cirrhosis, hepatocellular carcinoma, and liver-related death will continue to increase for at least the next 30 years [23]; and
- Accurate data on incident infections would allow appropriate monitoring of trends, recognition of changes in patterns of transmission, assessment of the efficacy of intervention strategies (e.g. public education campaigns) and long-term modelling of and planning for the HCV epidemic.

The implementation of such a strategy would require a reliable means of identifying individuals with acute HCV infection, most of whom would be asymptomatic. As discussed above, laboratory methodologies for this are being developed. Avidity testing of antibody positive sera from high-risk individuals using a standardised laboratory protocol, plus RNA testing of antibody negative sera, would fulfil this requirement. Secondly, patients with acute infection would need to enter appropriate care pathways. This will certainly present a challenge, but a number of centres have reported successful engagement with and treatment of active IDUs [24-27], so it is clearly not insurmountable. Proper assessment is required of the potential effectiveness and cost-effectiveness of reconfiguring services and resources to dealing with this particular challenge.

## Conclusions

It is our belief that an understanding and control of acute HCV infection is important, for the reasons outlined above, and currently not sufficiently studied. We do not wish to belittle the efforts and benefits of strategies aimed at identifying and treating patients with chronic infection, and agree that both approaches (i.e. diagnosing acute and chronic infections) should play an important role in controlling HCV. However, failure to address adequately acute transmission of HCV infection will undermine long-term attempts to reduce HCV-associated disease burden. Iatrogenic and nosocomial infections are still occurring, and are largely unrecognised. Meaningful surveillance of acute HCV infection, especially in Europe, is virtually non-existent and will require careful case definition and adoption of standardised diagnostic assays, such as window period and avidity testing. Treatment of acute infection is effective, but precise regimens are not universally agreed.

Our collective failure to identify patients with newly-acquired infection, combined with a lack of understanding of transmission patterns and dynamics, will ultimately undermine public health efforts aimed at reducing the disease burden arising from chronic HCV infection. In collaboration with the ECDC, the Viral Hepatitis Group of the European Society of Clinical Microbiology and Infectious Diseases is keen to establish European-wide systems of laboratory diagnosis and surveillance of acute HCV infection.

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