Hepatitis C

Acute hepatitis C virus infection: a neglected disease?

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A better understanding of the epidemiology and natural history of acute hepatitis C virus infection is vital for effective assessment of the impact of policies designed to reduce transmission

In the 16 years that have elapsed since the first report of identification of the hepatitis C virus (HCV), much has been learnt about the epidemiology, natural history, and consequences of chronic infection with this virus. Global estimates of 170 million infected individuals are widely quoted, with infection leading to cirrhosis, hepatocellular carcinoma, and consequent life threatening complications in 20–30% of infected individuals over a lifetime. Cofactors for disease progression, such as increased age at infection, male sex, and alcohol intake, have been described in multiple large scale studies. However, in marked contrast, there are major gaps in our understanding of the process of acute HCV infection, an event which must necessarily precede the development of chronic disease. There are no reliable or validated data on the incidence of acute infections, either at the national or global level. Precise behavioural and other risk factors for acquisition of acute infection are not well defined, even among injecting drug misusers, the largest “at risk” group of individuals, reflecting ignorance about possible routes and modes of transmission, and there are uncertainties about the percentage of acute infections which are spontaneously cleared, and the viral and host factors responsible for these fundamental differences in outcome.

Acute HCV infection is usually defined as the new occurrence of viraemia, at which stage serum from the patient is HCV RNA positive, anti-HCV negative. Seroconversion to anti-HCV positivity occurs after a variable period of time, known as the window period, which may last for six months or even longer, although most patients become antibody positive within three months of infection. A proportion of patients, variously estimated at approximately 20–40%, subsequently clear the virus spontaneously, while the majority go on to become chronic carriers, with all the attendant risks of long term development of life threatening liver disease. The cellular immune response

in individuals who spontaneously eliminate the virus is demonstrably of greater magnitude and breadth in comparison with those who fail to eliminate virus.¹ Antibodies may be lost over time in such individuals while cellular immune responses are maintained.² In contrast, long term loss of antibody in chronically infected individuals must be an extremely unusual occurrence, if it ever happens.

One approach in identifying factors related to viral clearance at the acute stage of infection is to compare the characteristics of anti-HCV positive HCV RNA negative patients (who have not received therapy) with those who have chronic infection (that is, HCV RNA positive), in the absence of any information about the nature and timing of the original acute infection. One such study, reporting data from a rural community in Egypt,³ is published in this issue of *Gut* (see page 1183). Bakr *et al* recruited 4720 adults from the village of Zawyat Razin, representing a sizeable proportion of the total population of the village. HCV antibody prevalence was 19.3%, consistent with several other reports of high seropositivity rates in Egypt. Interestingly, anti-HCV positivity was associated with having an antibody positive spouse, and with the duration of marriage, hinting at sexual or household transmission of HCV infection, both of which are contentious issues in the literature. Bakr *et al* found that 38.5% of the antibody positive individuals were HCV RNA negative, indicative of cleared infection, but the clearance rate was significantly higher in females (44.6%) compared with males (33.7%, adjusted odds ratio 1.77). This study was conducted in an environment where effective therapy for HCV has not been available, injecting drug use is not practiced, human immunodeficiency virus (HIV) infection is rare, alcohol use is extremely limited, and virtually all individuals are infected with the same genotype (4), all of which are positive design features, removing several possible confounding factors

from the data analysis. However, one major difference between the male and female populations of Zawyat Razin was the age distribution of anti-HCV positivity. While peak infection in males occurred in the 40–49 year age group and subsequently declined, the prevalence in women climbed steadily with age. This presumably reflects a difference in route of acquisition of infection, and indeed significantly more males (15.4%) than females (3.1%) gave a history of parenteral injections for schistosomiasis eradication. Thus there remains a possibility that the sex difference in clearance is secondary to differences in age at, and route of, acquisition of infection, although as the authors point out, there are no convincing published data that either of these parameters do influence clearance rates.

Conceptually, the most informative studies on the epidemiology and natural history of acute HCV infection are likely to be prospective in nature, following newly infected individuals through the disease process. However, there are very few studies of this type reported in the literature, and those that there are contain relatively few patients. It is easy to understand why. Acutely infected patients are usually asymptomatic, and therefore have no reason to present themselves for medical care or study. In industrialised countries, where the HCV epidemic is driven by injecting drug misuse, individuals acquiring acute infection will mostly belong to marginalised sections of society that do not readily access medical care, even if symptomatic. Furthermore, laboratory diagnosis of acute HCV infection is by no means straightforward. Seroconversion over a period of time must indicate infection occurring within the sampling period but that period may be too long to allow precise categorisation of an antibody positive individual as having acute infection or as already having progressed to the chronic phase. Window period diagnosis, evident as the presence of HCV RNA (or antigen) in a serum lacking anti-HCV, is also strongly suggestive of recent infection,⁴ but even here, there are doubts, with reports of some individuals maintaining this reactivity profile for months or even years before seroconverting.⁵ Even symptomatic patients with acute hepatitis present a diagnostic dilemma. If such an individual is already anti-HCV positive (and the majority are,⁶ the presence of HCV RNA does not necessarily mean acute infection—there may be other reasons for acute jaundice in a chronically infected individual—while conversely, the absence of HCV RNA does not rule out acute infection, as RNA may be cleared very quickly (and prior to

normalisation of alanine aminotransferase (ALT)) in some individuals.⁷

A recent systematic review of longitudinal studies of acute HCV infection⁸ bears out many of the above points. Micallef and colleagues⁸ identified 31 studies, which between them comprised 675 acutely infected patients. The mean number of patients per study was 22 (range 4–67), reflecting the difficulty in patient recruitment. Case definitions were not uniform. Twenty one studies included elevated ALT levels within their acute HCV infection definition, although the degree of elevation varied from two- to 20-fold. The time allowed for viral clearance varied from six to 48 months. Study settings could be classified into one of three categories: acute clinical (19 studies), post-transfusion (nine studies), and sero-incident (three studies) infection. Despite the potential biases consequent on comparing such diverse studies, and the paucity of patient recruitment, a number of interesting conclusions could be drawn. The overall clearance rate varied from 0% to 80%, with a mean (weighted for the numbers of patients in each study) of 26% (95% confidence interval (CI) 22–29%). This may in fact be a minimum figure as exclusion of patients who are RNA negative at the time of anti-HCV seroconversion creates a potential recruitment bias in the sero-incident studies. Also, extension of the time limit allowed for spontaneous clearance to beyond six months, as has been reported in some studies,⁹ may also elevate the rate of clearance. Clearance was less common among males than females (20% *v* 42%; relative risk 0.43 (95% CI 36–53)), supporting the conclusions of Bakr and colleagues³ discussed above, although none of the studies identifying this feature of acute infection were able to provide any insight as to the mechanisms underlying this observation. Clearance was not related to age at infection or genotype (1 *v* non-1). Higher clearance rates were reported among the studies of acute clinical infection (31%) compared with the post-transfusion (18%) and sero-incident (18%) studies. Factors not addressed in this review, but which have been reported elsewhere as predictors of clearance, include ethnicity,¹⁰ short incubation period,¹¹ specific HLA class II alleles,¹² and the strength and pattern of HCV specific CD4 cell responses.¹³ The increased clearance rates identified following acute icteric hepatitis are at least consistent with the latter, as hepatitis may be the result of a more vigorous immune response during the acute infection.

All of the above studies on acute HCV infection make the implicit assumption

that such infection is defined by the presence of HCV viraemia and/or anti-HCV responses. However, even this seemingly innocuous statement may be a simplification. Interesting data support the concept that individuals exposed to HCV may develop potent HCV specific CD4+ and CD8+ T cell responses, in the absence of any detectable viraemia or antibody response. Kamal *et al* demonstrated precisely this pattern of response in six of eight sexual contacts of patients with acute HCV infection.¹ Al-Sherbiny *et al* similarly demonstrated cell mediated immune responses in 13 of 71 (18%) seronegative and non-viraemic individuals with high risk exposure to HCV residing in a rural Egyptian community, compared with only one of 35 (3%) individuals with low risk exposure.¹⁴ These observations, similar to those made in the context of HIV infection, challenge our understanding and definitions of acute infection. Reliance on demonstration of viraemia and/or an antibody response may therefore significantly underestimate the true prevalence of acute infection with HCV.

A better understanding of the epidemiology and natural history of acute HCV infection is vital for a number of reasons. Absence of accurate data on incident infections precludes effective assessment of the impact of policies (for example, needle exchange schemes) designed to reduce transmission. Treatment of acute HCV infection results in clearance in over 95% of cases,¹⁵ and therefore it is to the advantage of the individual to know that they have suffered a recent infection. From a public health point of view, identification of acutely infected patients allows for introduction of standard measures to control the spread of an infectious disease, such as contact tracing and education, which in turn may identify more acutely and chronically infected individuals, but which is currently not practiced in any systematic way. Mathematical modelling data suggest that unless the incidence of acute infection is dramatically reduced (for example, by 80%), then the future burden of cirrhosis and other complications of end stage liver disease will not plateau until well after 2030, regardless of the impact of current policies on identification and treatment of chronically infected patients.¹⁶ While Micallef and colleagues⁸ systematic review of acute infection reports some interesting conclusions, it also serves to highlight the difficulties inherent in addressing this issue, and cross sectional retrospective surveys such as that of Bakr and colleagues³ cannot of themselves alleviate those difficulties. More attention

must be given to develop strategies for the diagnosis of acute HCV infection, both in individuals who access medical care for whatever reason and by establishing screening programmes among difficult to reach high risk populations who do not. Explanations of the intriguing data concerning apparently exclusive cellular immune responses to acute infection resulting in viral clearance in contacts of acutely infected patients are also needed, and would doubtless have a major impact on future vaccine design and strategies. Control of the health burden imposed by the current HCV epidemic will only be tenable when our knowledge and understanding of the transmission dynamics of, and immune responses to, acute HCV infection begins to approach that of the natural history of chronic infection. It is in this sense that acute HCV infection is indeed a neglected disease.

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EDITOR'S QUIZ: GI SNAPSHOT

Answer

From question on page 1064

Oesophagogastroduodenoscopy revealed a perforating plastic husk in the upper duodenum which could not be removed interventionally. The foreign body's free distal end caused a non-bleeding duodenal ulcer by mechanical irritation (fig 2). The proximal end was fixed and ingrown into the intestinal wall. At laparotomy the foreign body was found to be a ballpoint pen (fig 3) which the patient had swallowed six years ago as a bet. At that time she did not tell the

incidence to her mother and she herself forgot it since she had no symptoms for years. After surgery, the "ballpen-anaemia" resolved completely (haemoglobin 14.7 g/dl). Iron deficiency anaemia is the most common form of anaemia encountered in clinical practice and is an extremely common manifestation of chronic occult gastrointestinal bleeding. Standard care therefore includes evaluation of the gastrointestinal tract to rule out possible bleeding sites.

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Figure 2 Duodenal ulcer.

Figure 3 The "swallowed ballpoint pen" removed by laparotomy.