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Screening and shouting about HCV

In this month's *Gut,* Ward and colleagues[1] report their study of the prevalence of hepatitis C virus (HCV) in women attending an inner London obstetric department (see page 277). The study was well designed and carefully executed. The methodology is valid and the findings are important. The authors make three key observations: that the prevalence of HCV in this population is high (0.8%); that uptake and acceptability of screening for HCV is good; and that many of the cases could not be identified by clinical criteria alone. Each of these findings is important in its own right. Together they reaffirm the importance of hepatitis C as a healthcare problem. They support the case for further investigation of screening strategies for HCV and suggest that antenatal screening should be considered carefully.

Accurate knowledge of the prevalence of a disease is particularly important when it is serious and treatable. In the 1970s the disease later recognised as hepatitis C was thought to be an inconsequential transaminitis that followed blood transfusion. Since the cloning of HCV in 1989, increasing knowledge of the natural history of hepatitis C has revealed a more serious outcome, at least for the minority of individuals who develop progressive fibrosis leading to cirrhosis, liver failure, and liver cancer.[2] In the past year, effective treatment has been licensed[3] and even more effective therapies may follow. Now that more is known of the natural history of hepatitis C and the clinical and cost effectiveness of treatment, accurate knowledge of the true prevalence of HCV infection is very important for those planning, funding, and delivering care to HCV infected individuals.

Early studies found that the prevalence of HCV infection was as low as 0.04% in populations that could be readily accessed, such as blood donors.[4] However, there are many reasons why this group may not be representative of the wider population, not least of all because they are carefully selected for being in good health. Following recognition of intravenous drug use as a major route of transmission of HCV, studies were conducted to measure the prevalence among injecting drug users; approximately 67% of subjects tested were infected.[5] Such widely diverse measurements in specific groups demonstrate the importance of selecting a representative sample to determine the prevalence in the general population. Screening studies in the general population are problematic, particularly when identification of infected individuals carries serious consequences for the patient, the carer, and the healthcare system. Pilot studies in discrete, representative, and informative populations are preferred.

Ward *et al* report the prevalence of HCV infection in antenatal clinic attendees in inner London. Antenatal clinic attendees are a particularly interesting sample population with specific demographic characteristics that introduce biases, some of which are desirable and others which are not. The women are generally of an age when they are likely to have been exposed to HCV if at risk. If infected they are likely to be early enough in the course of their disease to benefit from treatment. As a group, clinic attendees are likely to be accepting of a medical intervention that may benefit themselves and their children and of a screening test that can be incorporated within their routine antenatal care. Pregnancy is well distributed through social classes (although rates may differ). The disadvantage of selecting the antenatal population for screening is that HCV infection is known to be less common in women than in men. Also, by selecting only those women who can conceive, the study will exclude women rendered infertile as a result of liver disease. Thus the prevalence of HCV infection measured in this study is likely to be an underestimate of the true prevalence in the general population. The investigators work in inner London and care for an ethnically diverse population. However, this diversity is probably little different from that in most UK cities. Furthermore, Caucasian women were represented at the same frequency in the HCV positive group as in the whole sample, suggesting that ethnicity was not a major determinant of infection.

Ward *et al* found evidence of HCV infection in 0.8% of their sample of which 0.6% were viraemic. The ratio of viraemic to non-viraemic, antibody positive individuals is in keeping with knowledge of the natural history of HCV infection. These relatively high levels of prevalence are in keeping with other reports of antenatal screening[6] and anonymous testing of antenatal attendees.[7] If prevalence in the male population is correspondingly higher, the true population wide prevalence of HCV is likely to be more than 1% and similar to that reported in the USA.[8] Such a high level of infection establishes hepatitis C as a major healthcare problem for the 21st century and one that cannot and will not be ignored. These findings have serious consequences for the National Health Service and Department of Health in the UK.

The present study examined more than just prevalence and formed a pilot screening study. The National Screening Committee set stringent criteria (based on those of Wilson and Junger, adapted by Gray)[9] which must be met before a screening programme can be introduced. These criteria include demonstration of the importance of the health problem, an accepted treatment, an accurate, reproducible and acceptable test, and an adequate window of opportunity when patients with positive tests can be identified and treated. While aspects of testing are widely accepted, some of the other criteria remain controversial. Effective treatment is available but clinicians and those funding healthcare are at odds over the provision of treatment. The judgement of NICE is awaited. The investigators have added to the evidence that HCV is an important health problem but the wider public may yet require further convincing. The authors have measured the uptake and acceptability of screening in the antenatal clinic and found both to be high. In some ways this is unsurprising for the reasons stated above. A group of women who have already chosen to attend clinic, about to give birth to children in whom the majority will recognise considerable investment, might be assumed to be motivated. Women, unlike men, are already provided with national screening programmes for cervical and breast cancers and so might be more compliant with further screening programmes than men. However, without the evidence contained in this report, larger screening pilots and even national programmes could not be developed. The time has come for a good quality randomised controlled trial of screening for HCV.

One of the most interesting findings of Ward *et al*'s study is that clinical criteria failed to identify those women who had been infected with HCV; both those who remain viraemic as well as those who are merely HCV antibody positive. Early investigations found that infection could not be attributed to a specific risk factor in

up to 40% of infected individuals.[10] Most hepatologists, and particularly nurses who work with them, will have been aware that close questioning in private reveals the majority of unattributable exposures to be related in some way to intravenous drug use. In common with most previous studies, the authors found that exposure to illicit drugs, or a partner with a history of intravenous drug use or HCV infection, was over represented in the infected population. Unless contextually relevant, few patients are likely to admit to these risk factors when first interviewed. Anyone working in the field of viral hepatitis will be well aware that intravenous drug users come in all shapes and sizes. The stereotypic view of the opiate addict as a pale and spotty waif with pinpoint pupils has many exceptions and is in marked contrast with many occasional users of illicit stimulants such as amphetamine and cocaine who make up the majority of intravenous drug users in the UK. While the former population may be at greater individual risk the latter are more numerous and are likely to be at significant risk of HCV. In the absence of any reliable clinical discriminant test for HCV, a low threshold for the widespread use of a diagnostic test for the virus is indicated. Tattooing and piercing was also over represented among the HCV infected individuals, confirming the importance of these independent risks.

The report by Ward *et al* carries important messages about HCV. Patients, clinicians, and those planning healthcare alike should heed them. Further research into screening for HCV is required.

W ROSENBERG

Liver Group, Division of Cell and Molecular Medicine, University of Southampton, Mailpoint 811 Level D South Block, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK
Email: wmr@soton.ac.uk

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Improving prognosis in hepatorenal syndrome

Hepatorenal syndrome is a serious life threatening complication in end stage liver disease. A recent consensus conference has agreed definitions for hepatorenal syndrome and divided the syndrome into types I and II.[1] Type I is characterised by rapidly progressive renal failure with a doubling of serum creatinine to a level greater than 2.5 mg/dl or a halving of creatinine clearance to less than 20 ml/min in less than two weeks. In type II, serum creatinine must be greater than 1.5 mg/dl or creatinine clearance <40 ml/min but is more slowly progressive with a correspondingly better prognosis. Most patients pass through a sequence of ascites, followed by refractory ascites, and then hepatorenal syndrome. A large prospective study including patients with ascites demonstrated that hepatorenal syndrome developed in 18% at one year and in 39% at five years.[2] Prognosis was poor with median survival of 1.7 weeks and 90% mortality at 10 weeks. The pathogenesis of hepatorenal syndrome is believed to involve splanchnic vascular dilatation with resultant vasoconstriction in other vascular beds particularly affecting the kidney.[1] Therapies such as head out water immersion or liver transplantation can reverse this process but are not practical or rapidly available for many patients.[3 4]

Recent studies suggest that transjugular intrahepatic portosystemic stent-shunt (TIPS) or pharmacological therapy may be useful in this syndrome. The study by Brensing *et al* in this issue of *Gut*[5] describes the long term outcome in cirrhotics with hepatorenal syndrome treated with TIPS (see page 288). They divided their patients into those with hepatorenal syndrome types I and II. Three quarters responded to TIPS with improvement in renal function. One year survival in the treated group was 48%. On an intention to treat basis, one year survival was 39%. The survival of type II patients after TIPS was significantly better than that of type I patients (one year survival approximately 70% *v* 20%). These results are very encouraging. However, it is important to remember that this was not a controlled trial. In addition, we are told little about the selection criteria for this cohort of patients. It is difficult to judge whether this group is directly comparable with the cohort identified prospectively by Gines *et al*, which most comprehensively defined the natural history of this syndrome.[2] It is likely that the group with type I hepatorenal syndrome most closely resemble classical hepatorenal syndrome. Extrapolating from the graphs supplied, survival at 10 weeks in the type I hepatorenal syndrome group, by intention to treat, was 53% compared with 10% described by Gines *et al*.

These results are very encouraging but controlled trials are required to confirm improvement in prognosis. The results of a small controlled trial of TIPS compared with large volume paracentesis in 25 patients with refractory ascites would cause some concern in this regard. It is probably directly relevant as refractory ascites is frequently a forerunner of hepatorenal syndrome. While ascites improved in many treated patients, overall survival was significantly lower in the TIPS group (29% *v* 56%) at two years.[6] Four patients in each group had Pugh grade C liver disease. In the current study patients with serum bilirubin >15 mg/dl, a Pugh score >12, or spontaneous severe encephalopathy were excluded, which probably selected out some of the highest risk patients and may have improved the results.

Another choice for treating hepatorenal syndrome is long term vasoconstrictor therapy. A number of studies have shown that long term vasoconstrictor therapy improves renal function in patients with hepatorenal syndrome. These studies used the vasopressin analogues