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REVIEW

Controversies in and challenges to our understanding of hepatitis C

Robert G Batey

Robert G Batey, Area Director, Drug and Alcohol Clinical Services, Hunter New England Area Health Services. Newcastle, New South Wales, Australia
Correspondence to: Professor Robert Batey, Professor of Medicine, University of New South Wales, Bankstown Hospital, Eldridge Road, Bankstown. 2200, New South Wales, Australia. rbate@doh.health.nsw.gov.au
Telephone: +61-2-97229292 Fax: +61-2-97228570
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Abstract

Discovered in 1989, the hepatitis C virus (HCV) continues to cause significant morbidity and mortality world-wide despite a huge research commitment to defining and understanding the virus and the disease it causes. This paper discusses a number of areas where progress in the management of the HCV have not kept pace with the scientific understanding of the HCV. It is suggested that in the fields of HCV prevention and providing access to treatment, practice falls short of what could be achieved. The role of alcohol in the pathogenesis of HCV liver injury is discussed. Discrimination against those with HCV infection and particularly those in prison settings fails to match good clinical practice. The complicated processes of sharing information between specialty groups is also discussed in an attempt to optimise knowledge dissemination in this field.

Key words: Hepatitis C; Alcohol; Injecting drug use; Prisons; Genetic variation; Cirrhosis; Liver cell cancer

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INTRODUCTION

The hepatitis C virus was discovered in 1989 and in the 18 years since the ground-breaking report by Choo and colleagues[1] an enormous amount has been learned about the virus, the disease is causes and about ways and means of preventing transmission and treating those who have become infected. It is estimated that between 130 and 170 million individuals are infected with the hepatitis C virus (HCV) worldwide and transmission in high risk populations continues to add to this number at an unacceptable rate[2,3].

Treatments for this infection now offer up to a 90% success rate in clearing some genotypes of the virus from serum and liver with long-term follow-up now reaching to 16 years and demonstrating the sustainability of the viral control or eradication[4]. Virologists and molecular virologists have provided great insights into the complexity of this viral family which has 6 major genotypes and many subgenotypes[5,6]. A cursory review of the current literature however would leave many non-virologists unclear as to whether there are 6, 9 or 12 major genotypes. Current testing methodologies are not capable of giving absolutely clear definition of the infection in a proportion of patients, particularly those with more than one genotype infection and those co-infected with hepatitis B virus (HBV)[7-9]. Recent reports that the virus is now able to be cultured and studied as a virus rather than an RNA genome have excited the hepatitis C research field appropriately[10,11]. It has been remarkable how much progress has been made in expanding our understanding of this virus without the benefit of the live virus to work with. It is to be expected that much greater progress will be made now that the virus can be cultured and its responses to anti-virals tested *in vitro* as well as *in vivo*.

A number of contentious areas have developed in the field of hepatitis C medicine and virology and some of these areas will be addressed in this review. The positive developments in the HCV arena far outweigh the negatives that a review of contentious issues might address. Nevertheless it is relevant to address areas of contention as they teach us much about this disease and our response to it. Lessons can be learned about the virus and the disease it produces but also, and more challengingly, about our attitudes to patient groups, our unwillingness to learn from others' experiences and the problems of working across specialty areas in our community to advance preventative medicine strategies.

Controversial issues in HCV include: (1) societal attitudes to those most at risk of acquiring HCV; (2) attitudes to addressing the issue of HCV in prison populations; (3) the role of alcohol in the pathogenesis of liver damage experienced by those infected with the virus; (4) providing equitable and justifiable access to anti-viral therapies.

A number of challenges are posed by the HCV epidemic. One of these relates to the reported changing

genotype profiles in a number of countries[12-15]. This confronts clinicians and virologists with the reality that we are dealing with a very adaptive infectious agent and false steps taken in haste may leave the medical field carrying the consequences of poorly thought through strategies for a long time to come.

Further challenges include: the need to reduce the number of new infections as a matter of urgency; and the need to address the factors that prevent specialists in one discipline from learning from another specialty field despite evidence that this would be productive and beneficial to clinicians and patients alike.

In this review, each of these issues will be addressed in an endeavour to broaden thinking about, and thus responses to, this viral epidemic affecting millions worldwide.

CONTROVERSIES CAUSING DEBATE AND IMPEDING PROGRESS IN OUR UNDERSTANDING OF HEPATITIS C INFECTION AND THE PATHOGENESIS OF LIVER DISEASE

Societal attitudes to those most at risk of acquiring HCV

The majority of those who are now infected with the HCV in Western countries are individuals who inject drugs. The majority of these inject illicit drugs[16-29]. In some societies it is still possible to contract HCV infection from the health care system as precautions to guarantee the safety of the blood supply and to ensure adequate sterilisation of re-used medical equipment are not and often cannot be implemented fully. Efforts are being made in these countries to minimise the risk but it is clear that it will be some time before risks are reduced to zero, globally[30-32] (Table 1).

HCV infected populations believe that their situation is not recognised adequately by Governments, other funding agencies and by the population in general[33-39]. While the Australian Government launched the first National Hepatitis C Strategy in the world[40] populations in this country believe that much more should be done to decrease the number of new infections per annum and to increase availability of treatment for those infected. Given the national visibility of this disease one must ask why the apparent lack of support for those who are at risk and those who are infected. It may reside in the fact that the at-risk population is a population who by definition are functioning, at least some of the time, outside the law. It is a fact that at many levels, communities and Governments are slow to support the injecting drug using population.

In most countries, active injection use has until recently or still does exclude individuals from consideration for active anti-viral therapy[41-45]. More recently in some countries (Australia included), this restriction has been lifted. This change in policy allows individuals to access treatment if they are on a methadone or buprenorphine program[46-49] or if they are still actively using opioids and express a desire to undergo treatment for their HCV infection.

Table 1 Factors impeding our understanding of HCV issues world-wide

Societal attitudes to the infected community
Injecting drug use is seen as a moral weakness and thus not needing to be addressed
Infection is the fault of the infected individual
Why should society expend money on those who undertake illicit activities?
Societal attitudes to prisoners
Prisoners are imprisoned to be punished
Prison sentences are usually relatively brief so the prisoner can wait for assessment and treatment
Drugs are not available in prison so there is no need for prevention measures against HCV
Societal attitudes affect Health care worker attitudes
More discrimination against HCV infected individuals occurs in health care settings than in the general community
Patients unwilling to disclose (their condition?) for fear of discrimination leading to poor care

All these issues decrease open disclosure and impair a full understanding of HCV transmission.

The early restrictions on access to treatment for methadone patients or for active injecting users was seen as discriminatory behaviour imposed unjustly on IDU's by uncaring health bureaucracies. In reality there were major concerns about drug side effects and tolerability of the treatment program that lead to the decisions to focus treatment on those who were perceived to be more capable of completing the course of treatment required for reasonable success[50-52]. Recent publications now provide evidence for the efficacy and tolerability of treatment for those on methadone programs but very few active users are currently being offered treatment[52-56]. Why the apparent discrimination against those who continue to use illicit drugs? Those who work with regular heavy IDU's, stress the complexity of life for these individuals. When the demands of the treatment program and, in Australia, the fact that the Government funds only one course of treatment per individual are made known, most active users defer the uptake of treatment until the other aspects of their life are in order. This in fact is not discrimination but informed decision making in action. In reality, society is willing to support treatment when it is likely to be successfully delivered and when risk of reinfection after a course of treatment is minimised by active therapy for drug dependence. It is true that many would not want treatment to be wasted on those who are unable to adhere to the rigorous schedule of interferon/ribavirin therapy or on those who put themselves at risk of re-infection on completion. Is this discrimination, pragmatism or rational decision making in the face of escalating health care costs and limited health budgets? I suggest for most who argue for a reasoned allocation of this resource, it is the latter.

Should society care more about the population of injection drug users who are at risk of HCV (9700 new infections per annum in Australia, 88% of which will be in IDU's) or who are already infected with the HCV[57]. The answer here is yes but that concern may need to be expressed in ways different from those currently employed.

Society may need to spend much more energy and

resources reducing those burdens that drive young people to experimental drug use in the first place rather than providing the majority of funding to treat the consequences of unsafe injecting practices. Care should then be directed to those who are contemplating drug use to ensure they are well informed on the risks of injecting drug behaviours. Wherever possible, attempts must be made to ensure that early injecting drug behaviour is undertaken as safely as possible, with clean equipment. By the time the majority of young people present at a Drug and Alcohol Service in this country, they have already become infected. Health care staff, are unlikely to be able to attend injecting areas due to their own workloads but support and advocacy groups could do a lot more good at the coalface preventing infections than they do by attending committee meetings and conferences. Admittedly this will not assist those already infected but it is this latter group, which is best helped by the Health care system which does have treatments to offer.

The HCV epidemic will continue to grow as long as drug use is not accepted as a reality, and an attractive reality for many. Acceptance carries with it a need to then act rationally to minimise the damage it does while seeking to expand treatment services to meet the needs of those who are dependent or erratic users. Methadone and buprenorphine programs do reduce infection rates in dependent drug users. Prescribed amphetamines may achieve a similar effect. Resources need to be directed to these programs which, in many countries, are under resourced[58-62].

Attitudes to addressing the issue of HCV in prison populations

For many, prison is a place of punishment and that is all there is to it. The fact that prisons are an incubator for an infectious disease like HCV has no meaning for them. The reality is that in Western countries, a high percentage of prisoners are incarcerated for drug related crimes[63,64]. A high percentage of these inmates are HCV positive, the majority infected rather than immune. Drug use occurs in prisons despite significant effort being directed to keeping drugs out of prisons[65-67]. Individuals entering an Australian prison, HCV negative have a 10% per annum chance of becoming infected with the virus. Attempts to modify the prison experience in a way that would reduce risk of infection with blood-borne viruses and optimise the testing for and management of the HCV and HBV problems in prison do not meet support in any consistent way. These problems are experienced in Australia and around the globe[68-78]. It is encouraging that progress is being made in different ways in different countries. Drug free prisons are the least cost-effective and saleable solutions to this problem of a rampant epidemic in a subset of our community. The provision of testing facilities for HCV and HBV, support and advice for those who test positive and treatment of those who warrant it for their HCV are steps that should be taken in all prison settings. This is not the case in many jurisdictions. Reducing the risk of transmission within the prison population is not easy but treatment of infected individuals is one positive step in the correct direction. Offering clean razors, toothbrushes, possibly tattooing equipment will reduce risk of transmission from contaminated shared equipment in this setting. Offering access to methadone programs in prison will reduce the need to use illicit opioids and this has a major impact on risk of disease acquisition[74]. The need for and value of needle/syringe exchange programs in prison settings are debated energetically in most countries and only a few have implemented these. Where these programs exist they are declared to be safe and that they do not increase risk of harm to corrections officers[79-81]. Providing needles and syringes but not a pure drug to inject does appear difficult to justify to the community at large and it would be a brave soul who would recommend providing heroin in gaol to individuals whose heroin related crime has landed them in gaol in the first place. It is clear that optimal management of the anxiety, depression and dependence that characterises life for those behind bars should minimise the need for needle exchange programs in prison. Society will support rational endeavours based on facts that demonstrate the reasonableness of these endeavours. Prisoners do need more evidence to support preventive health measures if those measures appear irrational to the community. Progress will be made if those advocating for the prison population are prepared to mount factual arguments. Facts at present would justify testing, supportive care, anti-viral therapy and clean equipment for all activities which may be associated with transmission of blood-borne viruses in prison settings.

Despite obstacles, considerable work has been done in prison settings in relation to HCV. Research is being undertaken and treatment offered to some selected prisoners in some countries. This is encouraging but more needs to be done.

The role of alcohol in the pathogenesis of liver damage experienced by those infected with the virus

There are some who believe that liver disease in HCV infected individuals is all caused by excessive alcohol intake. This approach is seen in many who work in the Drug and Alcohol field and it is these Health care workers who are least likely to deal with the HCV epidemic in their clinic settings. This is a preventive health disaster. How can such beliefs be held in the face of such a body of knowledge in relation to HCV and hepatitis C liver disease?

(1) Many HCV infected individuals do drink above safe drinking levels. (2) Data suggest that drinking above 40 gm/d does worsen the degree of liver injury in HCV infected individuals[82-87]. (3) HCV histology has for years been recognised to differ from HBV histology and in HCV steatosis has been a feature reported from the early days of the study of this disease. (4) Reducing alcohol intake from any level tends to improve liver tests in patients with HCV infection, at least for a short period. (5) Women, who tend to consume less alcohol than men, tend to have milder HCV related liver disease.

In response to this argument many facts can be mounted which make a strong case that HCV related

liver disease, while worsened by heavy alcohol intake, is a specific entity requiring appropriate management by those informed about the condition.

(1) HCV infected abstaining individuals do develop liver injury with histological features typical of the pattern seen in others with HCV disease. (2) Studies of populations of HCV infected individuals who do consume alcohol show that consistent worsening of liver disease cannot be demonstrated until daily intake exceeds 40 g/d. (3) Reducing alcohol intake in infected individuals with abnormal liver tests may improve the liver tests in the short term but the improvement is not always sustained. (4) HCV effects on the hepatocyte have been shown to predispose to lipid accumulation and the steatosis and inflammation that accompanies the steatosis[88-90]. (5) Patients who continue to consume alcohol despite advice to reduce or cease intake can still achieve viral clearance on anti-viral therapy and this does improve hepatic histology.

The impact of alcohol on HCV viral replication remains controversial with some studies reporting that replication is increased in the presence of alcohol and other studies declaring that there is no effect[91,92].

In dealing with alcohol and HCV the available evidence should encourage every clinician dealing with HCV infected patients to become expert in the area of obtaining an alcohol intake history and to always be aware of the alcohol intake of patients being assessed for and undergoing treatment for HCV infection. Patients are well advised to reduce alcohol intake if they do have active HCV liver diseases and if they are undergoing treatment. Hepatologists do need to form strong links with local Drug and Alcohol Services to enable referrals for alcohol counselling to be made for relevant patients in a timely fashion. There is no doubting the fact that many patients with active HCV have problem alcohol consumption. Conversely, Drug and Alcohol services need to be more proactive in raising HCV in discussion with patients who may now have an alcohol dependence problem but who may, in the past, have had an injecting drug problem, placing them at risk of acquiring HCV. Drug and Alcohol Services should have an active policy of raising the issue of blood borne virus infection risk with all patients, offering and encouraging testing in all patients.

To drive more appropriate clinical management it is clear that more accurate data in relation to the interaction between alcohol and the HCV at clinical, pathophysiological and virological levels are required as a matter of urgency[93-96].

Providing equitable and justifiable access to anti-viral therapies

Treatment for HCV is successful in achieving a sustained viral response in an increasing number of patients as drugs and the protocols for using them improve[97-102]. Newer agents are being developed that will, in time, increase response rates in those with interferon resistant strains of infection[103-111]. Treatment is cost effective[112-116]. Given these realities it is surprising that only a minority of patients are receiving treatment for HCV infection. In Australia approximately 1% of infected patients are receiving treatment each year. The aim is to increase this to 5%-7% per annum as this is seen to be a rate at which some impact on the long-term complications of HCV will be demonstrable at a population level[57]. Treatment availability raises a number of important questions in relation to therapy and HCV infection.

(1) What limits treatment uptake in a country committed to addressing the HCV epidemic? (2) What level of treatment uptake will impact on the spread of the disease in specific populations e.g. prisons, injecting user groups, a general community with low prevalence of HCV infection? (3) Should all patients who request treatment receive it? (4) Should individuals be given access to more than one course of therapy? (5) How aggressive should clinics be at this stage in testing to allow early decisions to be made on treatment efficacy?

Research provides some guidance to assist the resolution of some of these dilemmas. Uptake of treatment has been slow in those countries that have made it relatively readily available and in part this has reflected patient resistance to a treatment that initially offered a low sustained response rate accompanied by significant side effects. Initially clinicians were cautious about use of the standard interferon but as experience with its use increased, so did willingness to encourage patients about its relative safety and acceptability. As sustained viral response rates increased with combination therapy more patients have come forward for treatment. Despite significant side effects of combination therapy, completion rates for treatment courses are in the range of 90%-95% in specialist liver clinics. Barriers to accessing treatment have been another factor causing patients to hold back from therapy. Liver biopsy was an absolute requirement for accessing Government funded treatment in Australia until April 2006. Patients often quoted the biopsy as a reason for not wishing to consider therapy and a significant number of those that had a biopsy were excluded from treatment by histological findings that were not of a severity to allow treatment to be funded. The latter outcome influences other patients to avoid biopsy. In December 2005 Australia removed the need for abnormal liver tests and in April 2006 the need for liver biopsy from requirements for accessing treatment with pegylated interferon and ribavirin and since April the number of patients being treated has increased from an average 2000 per annum to a projected 3500 for the coming 12 mo. Another problem affecting treatment numbers in many countries will be limited resources available in Liver clinic settings. Increasing patient numbers will exceed the capacity of clinics to safely treat these patients. Considerable effort has been made in many countries to increase the workforce capable of dealing with HCV management. In Australia two pathways being examined are: (1) encouraging shared care programs with general practitioners and (2) examining the role of nurse practitioners and clinical nurse consultants in prescribing anti-virals and managing cases in their own right.

General practitioners are being asked to take on the management of more and more diseases previously regarded as the property of specialist medical clinics in teaching hospitals. Very few are seeking to take up the challenge to treat HCV infected patients. Nurse practitioners represent the most likely group to enhance

services in Australia as they will be registered to prescribe specific drugs and linked to liver clinic teams they could greatly increase prescribing and management capacity.

Given increasing acceptability of treatment and a lowering of barriers to access it becomes relevant to ask - what level of treatment represents an appropriate level to impact on long-term sequelae and on transmission rates?

Law and colleagues (Projections committee) suggest that 7%-10% of the infected population should be treated per annum if cirrhosis, liver failure and hepatocellular carcinoma (HCC) are to be reduced in the decade ahead in Australia. Similar figures would be expected to apply for other Western countries. There are no published data identifying the treatment rates required to reduce transmission in a community of low or high prevalence. The question of who should be treated when resources are limited is also a difficult one. Australia dealt with this by limiting Government funded treatment to those with moderate fibrosis or mild fibrosis with significant inflammation until recently. Recent papers reporting greater viral clearance in those treated in the acute phase of their illness raise the concern that treatment should not be delayed if optimal outcomes are to be achieved[117-120]. Patients requesting treatment should be advised of expected outcomes and risks and if they continue to request treatment should e offered it in the absence of contraindications. The question of re treatment for either failed treatment or for re infection is receiving increasing attention as new studies show efficacy of moderate rates for re treatment[121,122]. Treatment of new infections should achieve expected results for that genotype. New algorithms for testing during treatment must be designed to allow optimising of treatment duration and viral sup pression[102,123,124]. Given limited resources it is imperative that clinicians stop treatment as soon as it is apparent that treatment is failing to achieve viral suppression or that it will be effective in 12 or 20 wk rather than have all patients treated for 24 or 48 wk. It may also be necessary to treat some patients longer to achieve a sustained viral response. Rational use of the current drugs demands more and earlier HCV RNA testing.

CHALLENGES FACING THE HCV FIELD

Reducing the number of new infections in all countries

This demands a range of responses, all of them difficult to achieve quickly. Where blood products cannot yet be guaranteed to be safe from blood-borne viruses, testing needs to be implemented as a matter of urgency. Sterilisation of reused medical equipment must be carried out at a level that ensures risks of acquisition are minimised. The greatest challenge globally is to reduce transmission in the injecting drug user population. In an ideal world injecting drug use would not be an issue or if it were a practice deemed acceptable it would be carried out using clean injecting equipment and pure medications. This is not likely to be the case in the foreseeable future. Until this does happen, Governments and non-Government organisations (NGO's) have to work to: (1) Increase the awareness of new recruits to injecting drug use of the risks of this practice, including the high rate of HCV acquisition. (2) Increase the availability of clean injecting equipment especially to those newly involved in injecting practices. (3) Decrease the attractiveness of illicit injecting drug use. (4) Increase the availability of opioid and other drug treatment programs so that the demand for injection drug use is reduced. (5) Increase testing of injecting drug users for all blood-borne viruses and increase the availability of appropriately timed treatment for HCV in this group.

Table 2 Reducing the number of new HCV infections

Actions that are required to achieve a reduction in new infections:
Acknowledging the existence of the epidemic
Overcoming denial of the pathogenicity of the HCV
Accepting that this disease is more prevalent than HIV
Defining the natural history more accurately
Increasing understanding of the biology of the HCV
Requires a greater funding base for research
Greater collaborative effort between clinical and research centres
Defining transmission risks accurately
Working with injecting user groups an essential requirement
Studies with the virus will allow a great expansion of knowledge
Responding to these risks adequately
Governments must commit to addressing the epidemic
Increasing access to treatment
Define clinical pathways
Optimise access to treatment for those with more severe disease
Advertise treatment efficacy more clearly
Improving treatment efficacy

The tragedy of our current situation is that young recruits to this destructive behaviour become infected 5-10 years before they are ready to present to a health care system for advice and treatment. The critical role of NGO's in reaching these young people before they become infected and providing them with information, support and clean injecting equipment cannot be underestimated. Current efforts need to be increased now. We do not need to wait for detailed sociological research studies to direct this effort (Table 2).

The need to address the factors that underlie a tendency of hepatologists to a slowness to learn from Infectious Disease and especially HIV clinicians about the optimal ways for dealing with viral infections

I venture into this area with trepidation and yet it is important to learn from our colleagues and to avoid making the same mistakes that others have if there are data to guide progress in this field. HIV clinicians learned early in the fight against this virus that several things were important in managing the infection: (1) single anti-viral therapies quickly lead to viral resistance. (2) management of viral diseases can be assisted greatly by monitoring viral kinetics and using the data to modify treatment protocols. (3) viral suppression may be the best that can be offered in some diseases. (4) viral suppression can improve prognosis to a significant degree. (5) viruses are highly developed organisms capable of modifying their behaviour in response to the efforts of man to eradicate them.

Hepatologists in many parts of the world have not all been willing to understand these lessons. It has taken some years for the data on viral kinetics and clearance rates to be

used in papers defining optimal treatment algorithms. We still have a long way to go to get these right. It is reassuring that standard therapy for HCV does incorporate two anti-viral agents. The need for better protocols remains a challenge especially for those infected with genotype 1 and 4 strains. One recent paper reporting the addition of amantadine to combination therapy for those failing standard treatment is a challenge for researchers seeking to increase overall cure rates in this disease[125]. Hepatitis C is being addressed more systematically than HBV has been over the past 15 years. The HBV field has a much greater challenge facing it as drug resistance to monotherapies used over the past several years becomes a major issue[126-128].

Infectious diseases physicians have been willing to address HCV in their practices for some time and it is imperative that this group of interested and highly capable physicians are not prevented from treating these patients simply because they are not hepatologists. As argued in this review, the workforce need in this field is great and all resources available to address patient needs should be harnessed in the struggle to control the HCV epidemic.

While end-stage HCV management is the province of the hepatology clinic, most patients with this disease will not reach that endpoint. With improving treatment options on the way and with early interventions which now include early treatment of HCV infection it is to be hoped that advanced HCV disease should become a problem of the past. Treatment of the viral infection in its early stages should be able to be undertaken by a range of clinicians with skills in monitoring viral presence and response to therapy. Virologists and infectious disease specialists are ideally trained to assist in this process. There are more than enough other liver diseases to keep hepatologists busy if even 80% of HCV infected patients were treated by other specialists and I include in this group, GP's trained to evaluate and manage HCV infection.

Specialty medicine has advanced the understanding of medicine greatly but it has done so at the cost of impairing communication between disciplines and Clinicians. That has been a costly negative aspect to current views of progress.

The HCV epidemic remains a major public health issue globally. The efforts directed to addressing this specific problem have been outstanding and much progress has been made in a range of areas relating to the virus and the disease associated with it. It is to be hoped that the next decade will see the introduction of new agents to control the virus, vaccines to protect and to enhance viral clearance mechanisms and more pressingly, new ways to protect young people from contracting the virus.

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