Virus hepatitis update

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ABSTRACT Currently seven viruses, A, B, C, D, E, G and transfusion transmitted virus (TTV), are recognised in the hepatitis virus alphabet. Hepatitis G virus1 and TTV2 probably do not cause liver disease in humans. Hepatitis A and E usually cause a self-limiting hepatitis followed by complete recovery but occasionally cause fulminant hepatic failure. Hepatitis B and C are major public health problems worldwide due to their sequelae of chronic hepatitis, cirrhosis and primary liver cancer. Chronic hepatitis C is a particular health issue for Western Europe already, accounting for 40% of end-stage cirrhosis and 30% of liver transplants. The contribution of hepatitis C to chronic liver disease is predicted to rise in the future. Vaccines can prevent hepatitis A and B. Interferon alpha is effective treatment in 25–30% of patients with chronic hepatitis B or C. The prospects for treating chronic hepatitis B have been improved by the introduction of reverse transcriptase inhibitors. Lamivudine is the first drug of this class to be licensed. The optimal use of these new drugs is currently being studied. The success rate for treating chronic hepatitis C can be raised to around 40% with combination therapy of interferon alpha and ribavirin. A large research effort to discover new antiviral agents against hepatitis C is already giving the prospect of more effective therapies in the next few years.  

Hepatitis A virus

Hepatitis A virus (HAV) is a 27 nm single-stranded RNA virus of the picornaviridae family which is spread by faecal-oral contamination – a reflection of poor hygiene. Most infections in the UK are acquired from foreign travel. An effective vaccine for hepatitis A is available, and should be given to travellers to developing countries. An effective combination vaccine protecting against both hepatitis A and hepatitis B is also available3. To prevent spread of infection, household contacts of patients with hepatitis A should receive hepatitis A vaccination as well as immune globulin.

Hepatitis D virus (Delta virus)

Hepatitis D virus (HDV) is a 36 nm single-stranded RNA virus similar to a plant satellite virus. HDV is an incomplete virus that requires the presence of hepatitis B virus (HBV) in order to infect an individual. It is an important cause of fulminant hepatitis and aggressive chronic hepatitis in HBV carriers. Hepatitis D superinfection is common in Central Africa and in the Amazon Basin where it is known as Labrea hepatitis. Hepatitis D infected individuals respond poorly to interferon alpha (IFNα) therapy, but they are good transplant candidates – particularly those who are HDV antibody positive and HBV DNA negative4.

Hepatitis E virus

Hepatitis E virus (HEV) is a 27–34 nm single-stranded RNA virus of the calciviridae family. Like hepatitis A, hepatitis E is spread by faecal-oral contamination and is common in areas of poor hygiene. HEV is carried by cattle, and outbreaks are thought to arise from contamination of the water supply by cattle faeces. Also like hepatitis A, hepatitis E tends to cause a self-limiting acute hepatitis. However, for unknown reasons, in pregnant women hepatitis E infection carries a high mortality (20%) from fulminant hepatitis5. Furthermore, hepatitis E infection is the commonest cause of fulminant hepatitis in India6. A diagnostic blood test for hepatitis E antibodies is available, and a promising peptide vaccine is in development.

Hepatitis B virus

HBV is a 42 nm double-stranded DNA virus of the hepadnaviridae family. HBV can cause an acute hepatitis, but its public health significance arises because a proportion of infected patients become chronic carriers: there are estimated to be about 400 million carriers worldwide. Chronic carriage is indicated by the presence in blood of hepatitis B surface antigen (HBsAg) and of viraemia by HBe antigen (HBeAg). Past infection is indicated by the presence of hepatitis B surface antibody (HbsAb).

Seroconversion is the term used to describe the disappearance of HBeAg and the appearance of HBeAb. A better determinant of seroconversion is the disappearance of HBV DNA from the blood. In acute hepatitis B, only immunoglobulin (Ig) M anticore antibody (HbcAb) may be present. Following HBV infection, 5–10% of patients will develop chronic hepatitis. Seroconversion or the disappearance of HBV DNA from blood is the usual measure of treatment success.

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Management of patients with hepatitis B may be complicated by the appearance of several HBV variants (for a review see Ref 7). Mutations in the HBeAg open reading frame may lead to HBeAg negative mutants. In these patients, HBV DNA persists in the blood despite apparent seroconversion. These variants are associated with fulminant hepatitis. HBsAg escape mutants arise by mutations in the immunodominant region of the HBsAg gene. These mutations result in failure of hepatitis B vaccine and hepatitis B immune globulin (HBIG) treatment. Polymerase YMDD mutants arise from mutations in the active site of the virus polymerase. They are a consequence of the use of nucleoside analogue drugs such as lamivudine (see below). There are also reports of mutations in the core promoter and enhancer II region, which appear to be associated with fulminant hepatitis.

_Treatment of chronic hepatitis B_

**Interferon alpha.** Until recently, the mainstay of treatment of chronic hepatitis B has been IFNα at a dose of 9–12 MU three times a week for three months. A response rate of 25–30% in selected Caucasian patients may be expected, as judged by seroconversion or the disappearance of serum HBV DNA. This response is maintained in about 85% of patients89. A sudden rise (flare) in transaminases, which occurs in about 65% of patients either during or after IFN therapy, is believed to be due to the immune clearance of the infected liver cells. The loss of HBsAg and appearance of HBsAb may follow this, sometimes after years. However, not all patients with chronic hepatitis B are suitable for IFNα treatment. To achieve seroconversion rates of about 30%, patients must have low pretreatment HBV DNA levels (<200 pg/ml) and high serum transaminases (>100 iu/l). Treating patients who do not meet these criteria results in very low seroconversion rates (ca 5%).

**Antiviral drugs.** The prospects for treating chronic hepatitis B have been improved by the recent introduction of new antiviral drugs, reverse transcriptase inhibitors, that inhibit HBV polymerase. They are more potent than IFNα and can be given orally. Currently, lamivudine is licensed for clinical use, but other drugs such as famciclovir and adefovir dipivoxil will soon be available. Lamivudine therapy for 12 months causes the transaminases to normalise, seroconversion to take place, and HBV DNA to become undetectable. On stopping lamivudine, HBV DNA reappears in about 80% of patients; nevertheless, this treatment seems to result in improved histology and retarded fibrosis compared with control groups. A further advantage of lamivudine is that it is effective in patients with high HBV DNA levels and pre-core mutants. A drawback of lamivudine is the development of resistance due to mutations in the YMDD motif of the active site of the viral polymerase. This appears about nine months after starting therapy, the incidence increasing with the duration of treatment. Clinically, resistance is heralded by the reappearance of HBV DNA in the blood and may be associated with a rise in transaminases or a significant flare of hepatitis. Even in the presence of YMDD mutants, continued lamivudine therapy may lead to seroconversion. It is too early to know the optimal duration of lamivudine treatment.

**Hepatitis B recurrence after liver transplantation.** Hepatitis B will recur in the new graft after orthotopic liver transplantation. This can be prevented using either HBIG or lamivudine. Lamivudine may be used to suppress viral replication prior to transplantation so that the patient is HBV DNA negative when the transplant is performed. Preliminary studies indicate that this approach improves the outcome of transplantation. Lamivudine may also have a role suppressing viral replication after transplantation. Both lamivudine and HBIG therapies may fail, which appears to be related to high pre-transplant HBV DNA levels. Failure of HBIG therapy is due to the development of mutations in the immunodominant domain of HBsAg, while lamivudine failure is due to the development of mutations in the YMDD motif of the viral polymerase.

**Future possible therapies.** The future of hepatitis B treatment probably lies in combination therapy. Early data indicate that the combination of IFN and lamivudine may be superior to interferon alone. Lamivudine may also benefit patients with decompensated cirrhosis due to hepatitis B. Other future directions may include T cell vaccines and anti-sense molecular therapies.

**Co-infection**

Co-infection with HBV and HCV is seen in intravenous (IV) drug users and in areas of high HBV prevalence. It seems that these patients have more severe liver disease and are probably at increased risk of liver cancer. Acute HCV infection in patients with chronic HBV carries a substantial risk of fulminant hepatitis.

**Hepatitis C virus**

HCV is a 30–60 nm single-stranded RNA virus of the flaviviridae family. It is a major public health problem: there
are 170 million HCV carriers worldwide, of whom about four million are in the USA and five million in Western Europe. HCV exists as several distinct genotypes, classified as HCV-1 to -6. Isolates from a patient usually also contain many closely related genomes called quasispecies. The presence of quasispecies in HCV is thought to be the mechanism whereby the virus escapes host immune surveillance, and is probably the reason for the high rates of chronic infection, the difficulty in vaccine development and the variable response to therapy. Consensus statements on hepatitis C from the US and Europe provide excellent summaries of the field.

Hepatitis C is responsible for 20% of acute hepatitis, 70% of chronic hepatitis and 40% of end-stage cirrhosis in Europe. Furthermore, 60% of primary liver cancer and 30% of liver transplants are attributable to HCV infection. IV drug use or blood products usually transmit HCV. Sexual transmission is uncommon, even in highly promiscuous groups. Vertical transmission from mother to infant is also unusual (less than 6%), but it appears to be higher in women co-infected with HIV. Following infection with HCV, about 80% of patients will develop chronic HCV infection, of whom about 60% develop chronic hepatitis and 20% progressive liver disease with hepatitis, fibrosis and cirrhosis over 10–20 years. The factors associated with the development of cirrhosis in hepatitis C are older age when infected, male sex, co-existent alcoholism, HIV co-infection and HBV co-infection. Between 1% and 4% of HCV cirrhotic patients per year will develop primary liver cell cancer. It remains to be determined whether regular monitoring with ultrasound and alpha-fetoprotein estimations is of value. The standard test for the diagnosis of HCV infection is an enzyme-linked immunosorbent assay (ELISA). In the 10% of patients who have normal transaminase levels a qualitative test for HCV RNA is needed to confirm chronic hepatitis C infection. This test is also of value in the diagnosis of acute non-A non-B hepatitis.

**Treatment of hepatitis C**

Before commencing treatment, the HCV should be genotyped and a quantitative HCV RNA estimation performed. Like HBV, not all patients with HCV infection are suitable for treatment. The current consensus about which patients are appropriate for treatment includes patients with:

- abnormal liver function tests who are HCV RNA positive
- moderate to severe inflammation or fibrosis on liver biopsy
- acute hepatitis C infection.

It is also appropriate to treat patients who have HCV associated conditions, including cryoglobulinaemia, glomerulonephritis and vasculitis. Patients who do not appear to benefit from treatment include:

- active alcoholics
- active IV drug abusers

- decompensated cirrhotics
- patients with normal liver function tests and a negative HCV RNA test.

The role of liver biopsy in the routine clinical management of HCV infection is controversial. While a liver biopsy will rule out non-viral disease, it adds to the expense and complications of treatment. On the other hand, HCV RNA and liver function tests alone are sufficient to make the diagnosis and monitor treatment.

The first treatment shown to be effective in the treatment of HCV infection was IFNa, but only 25% of patients so treated show a sustained response (defined biochemically as normalisation of the serum transaminases, and virologically as loss of serum HCV RNA six months after the end of treatment). Recently, ribavirin has been licensed for use in combination with IFNa for HCV treatment. Both drugs have side effects: IFNa causes flu-like symptoms and depression, while ribavirin is associated with haemolytic anaemia and is both a teratogen and a mutagen.

**Combination therapy.** The HCV genotype and the viral load (VL) influence the response to IFNa/ribavirin combination therapy. Patients with genotypes HCV-2 and HCV-3 and low VL respond well to combination therapy, but patients with HCV-1B and HCV-4 and high VL are poor responders. Nevertheless, the results of combination therapy are almost twice as good as those with IFNa alone. Groups of good responders treated for 24 weeks with IFNa/ribavirin can expect a sustained response rate of about 46%23. About 29% even of the poorly responding HCV-1 group will respond. Patients of African origin appear to respond less well to treatment24.

The current recommendations for treatment are:

- IFNa/ribavirin for six months in patients with genotype HCV-2 and HCV-3, and also in patients with genotype HCV-1 and low VL.
- Combination therapy for 12 months in patients with HCV-1 and high VL.

Responses to IFNa/ribavirin combination therapy seem to be sustained into the long term. If responders have no detectable HCV RNA six months after treatment, 90% will remain HCV RNA negative with normal transaminases and improved histology 5–10 years later25,26. Even in the non-responders, therapy may protect against the development of primary liver cancer and reduce the degree of liver fibrosis. Consensus IFN and pegylated IFN are two modified IFNs which may be superior to IFNa. Retreatment with consensus IFN of patients who had relapsed from a course of IFNa gave sustained response rates similar to those obtained with IFN/ribavirin27. Pegylation of IFN leads to sustained high serum levels and higher response rates than with IFNa28.

**Hepatitis C recurrence after liver transplantation**

Recurrent hepatitis C after liver transplantation is almost universal29,30, but more benign than hepatitis B. Almost every patient has persistent viraemia, often with very high
HCV RNA levels. In most patients, the disease is mild and survival is good, but 5% develop rapidly progressive hepatitis and cirrhosis. There may be a place for IFN/ribavirin therapy in the rapidly progressive group. Overall survival appears to be similar to other chronic liver diseases after liver transplantation.

**Virus hepatitis – the future**

For hepatitis A and B, the aim should be prevention. Effective vaccines exist for both viruses. Universal antenatal screening will be introduced into the UK in 2000. By identifying affected mothers, this strategy should break perinatal transmission to infants. Prospects are good for improved antiviral drugs for hepatitis B and C treatment. Further progress will probably also come from optimizing combination therapy strategies. An enormous amount of effort in the pharmaceutical industry is currently devoted to developing new antiviral agents against HCV. Studies of the HCV sequence have identified at least three potential antiviral targets against which novel compounds are being developed to inhibit viral replication. These include:

- The 5' non-coding region where there is an internal ribosomal entry site which directs ribosome binding to the translation initiation codon.
- The non-structural protein 3 which encodes an unusual serine protease. The atomic structure of this serine protease has been determined to allow the application of rational design to drug development.
- The non-structural protein 5B which encodes the HCV RNA polymerase is also attracting attention.

Studies of potential antiviral agents in HCV have been hampered by the inability to propagate the virus in culture and the lack of an animal model. Progress has been made both in *in vitro* culture using HCV subgenomic replicons and in creating a small animal model by infecting tamarins with GBV/B virus which is closely related to HCV. This enormous scientific effort should yield effective new antiviral agents within the next five years.

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HIV/AIDS: A COMMONWEALTH CRISIS
The Challenge to Medical Education

Friday 13 October 2000
Royal College of Physicians, London

In 1999 the Commonwealth Heads of Government meeting declared HIV/AIDS a global disaster. Globally, 50 million individuals have been infected with HIV of whom 33 million are still alive. While the effects of this epidemic are felt most keenly in Africa and other developing countries, the rising cost of treatment is threatening the effectiveness of HIV programmes in the developed world.

The global scale of this crisis requires governments and medical professionals to examine the effects of the epidemic on medical care. The Royal College of Physicians of London, the Commonwealth Secretariat, the Commonwealth Medical Association and the Association of Commonwealth Universities are organising this one-day conference to provide an opportunity for the medical community and policy makers to focus on a number of vital issues such as:

- Will medical education as it is currently constituted be able to provide physicians with the skills necessary to meet the challenges they will face?
- How will medical services cope with the increasing demands placed on them by the epidemic?
- How can services be maintained in the face of increasing levels of infection amongst healthcare professionals?

If you would like to receive further information about this event please contact:
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