

An overview of hepatitis: part 2

In part 2 of this overview of hepatitis, Gareth Nickless looks at viral hepatitis and its treatment

Viral hepatitis is a common cause of both acute and chronic liver disease. The viruses usually implicated are A, B, C, D and E. Viruses differ by their mode of transmission, the liver damage they cause and how they can affect health. Occasionally Epstein-Barr virus, herpes simplex and cytomegalovirus are involved. A hepatitis G virus has also been identified, but its role in liver disease is unclear. This article focuses on hepatitis infections A to E.

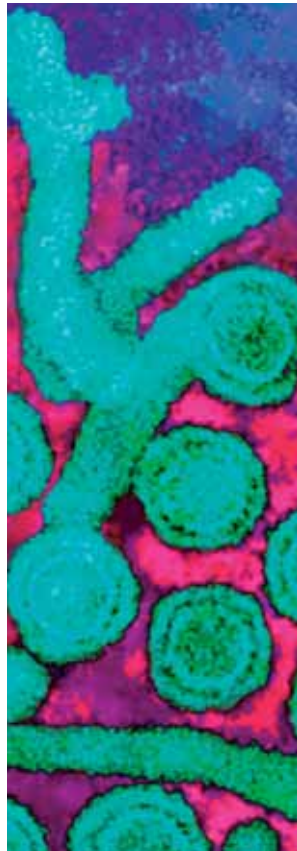
Hepatitis A

Hepatitis A is an RNA virus, which is mainly transmitted by the faeco-oral route — either directly between people or through contaminated food (typically fruit and vegetables or shellfish from waters contaminated with sewage) and drink. Hepatitis A infection is not common in the UK — around 1,000 infections are notified per year in England and Wales. The number of cases has decreased over the years but occasional outbreaks are seen in some communities. People who are at the highest risk of contracting the virus include:

- Those living in institutions
- Those working in microbiology laboratories or infectious diseases units
- Those travelling to areas where there is a high or intermediate prevalence (eg, Africa, the far east and the Indian subcontinent)
- Homosexual men
- Those with haemophilia (since viral inactivation procedures are ineffective against the virus)
- Intravenous drug misusers

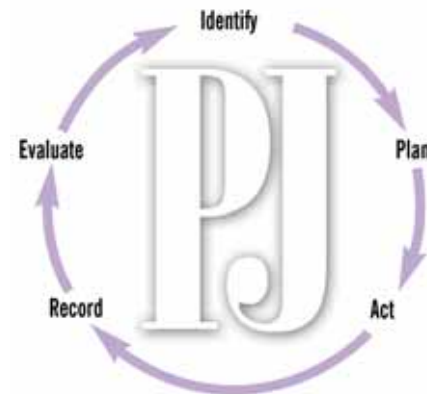
After an incubation period of two to six weeks, the patient will present with jaundice and possibly enlarged liver, spleen and lymph nodes (ie, hepatomegaly, splenomegaly and adenopathy, respectively). A prodrome consisting of anorexia, fever, nausea and joint pain can precede these symptoms. Diagnosis is aided by raised transaminase enzymes (see part 1 of this overview, *PJ*, 5 April, pp411–4) and IgM (which confirms recent infection). IgG will remain detectable for life following infection, explaining why patients tend to acquire life-long immunity following acute infection. Hepatitis A infection of patients with chronic liver disease is particularly dangerous because they usually develop a more severe acute illness.

Treatment The infection is usually self-limiting, with jaundice resolving after a few weeks, but the patient's transaminases may take a few months to normalise. Patients infected with the hepatitis A virus do not develop chronic liver disease (which may be



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Hepatitis B is spread via infected blood or body fluids



Identify knowledge gaps

1. Which viruses commonly cause acute hepatitis?
2. What are the implications for patients who become infected with hepatitis B or C?
3. What advice can pharmacists give on the prevention of hepatitis infection?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.uptodate.org.uk). This article relates to "common disease states" and "health education and promotion" (see appendix 4 of "Plan and record").

seen in those infected with the B and C viruses — see below) and the development of acute liver failure is rare. There are no effective antiviral agents against hepatitis A. Treatment is largely supportive and includes monitoring for and dealing with hypoglycaemia and symptoms, such as joint pain and itching.

Patients should be encouraged to rest, eat and drink well. They should abstain from alcohol until their liver function test (LFT) results return to normal.

Hepatitis B

Hepatitis B is a DNA virus that is usually spread via infected blood or body fluids. The most common modes of transmission are:

- Sexual intercourse
- Blood-to-blood (eg, intravenous drug misusers sharing contaminated needles, or contaminated tattoo needles)
- Mother to baby (transmission can occur during delivery or breastfeeding)

Rates of transmission via transfusions or blood products have declined due to screening and viral inactivation. There is also a risk of transmission to patients undergoing haemodialysis due to contaminated dialysis equipment, spillage of infected blood and the

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impaired immunity in these patients. However, rates have declined since the Rosenheim Report in 1972 which aimed to eradicate hepatitis B virus (HBV) from dialysis units.

Infection can be acute or chronic (defined by the British Liver Trust as infection for over six months). It is estimated 180,000 that people in the UK are chronically infected with HBV, with 7,700 new cases being identified each year.

The symptoms of acute illness are similar to those seen with acute hepatitis A infection, but the illness has a more insidious onset. Jaundice may be seen in 30–50 per cent of adults, but in those who do not develop the typical symptoms of hepatitis (it is estimated that about two-thirds of those infected are asymptomatic), diagnosis relies on abnormal LFTs and the presence of the following serological markers:

- HBV DNA (This can be present in both acute and chronic infection.)
- Hepatitis B surface antigen ([HBsAg] This can be detectable in both acute and chronic infection. Seroconversion [the development of detectable antibodies] occurs in a few patients and is most likely to occur during the first year.)
- IgM antibodies to hepatitis B core antigen (HBcAg)
- Hepatitis B e antigen ([HBeAg] This is an indicator of viral replication and is related to infectivity. However, some patients have mutant viruses that do not give rise to HBeAg so the absence of the antigen does not exclude active viral replication. Patients who are HBeAg-negative experience fluctuating symptoms and have a poorer prognosis than those who are HBeAg-positive and are thought to be more resistant to treatment. Seroconversion occurs following an exacerbation. Patients who develop viraemia and acute hepatitis following seroconversion do so because the virus has mutated into an HBeAg-negative strain.)

Acute hepatitis B infection may progress to fulminant hepatic necrosis, which can be fatal. Chronic carrier status (defined as the presence of HBsAg for at least six months) occurs in 5–10 per cent of patients infected. Up to 25 per cent of these patients will develop cirrhosis of the liver and are at risk of developing hepatocellular carcinoma.

Treatment As for acute hepatitis A infection, treatment of acute HBV infection is largely supportive because most patients are able to clear the virus. However, for those who develop chronic HBV infection, interferon or antiviral therapy should be considered. The products licensed for chronic HBV infection include peginterferon alfa-2a and lamivudine. Patients should have LFTs every three months and serological markers should be checked every six months to monitor treatment efficacy. The National Institute for

Panel 1: Guidance on hepatitis B treatments

According to the National Institute for Health and Clinical Excellence, treatment with peginterferon alfa-2a is an option for the initial treatment of chronic HBV but its use is limited by a 50 per cent failure rate and a high incidence of relapse.

Adefovir may be used when peginterferon alfa-2a is unsuccessful, poorly tolerated or contraindicated. Adefovir should not be used before lamivudine has been tried, but it may be used alone or in combination with lamivudine where resistance to lamivudine has developed or is likely to be achieved rapidly.

The Scottish Medicines Consortium has appraised individual drugs but has not, with the exception of adefovir (which is to be reserved for patients who demonstrate lamivudine resistance), indicated whether a drug should be first- or second-line.

In England, since treatments for chronic HBV infection are excluded from the payment by results scheme, it would seem reasonable to use NICE approved treatments first because funding for these must be made available by primary care trusts. Currently, therefore, entecavir and telbivudine are likely to be reserved for patients who are unable to tolerate or have failed on peginterferon alfa-2a, lamivudine and adefovir. Funding is likely to have to be secured on an individual patient basis so pharmacists may find themselves involved with the application for such bids and should be involved with the production of local guidelines on the use of these drugs.

Health and Clinical Excellence issued a technology appraisal on HBV treatments in 2006 (see Panel 1).

Peginterferon alfa-2a Peginterferon alfa-2a is a covalent conjugate of the interferon alfa-2a protein, which acts as an immunostimulating agent, plus bis-(monomethoxy polyethylene glycol). The pegylated component increases the half life of the drug, allowing weekly (as opposed to thrice weekly) injections. Only the Pegasys brand is licensed to treat chronic HBV infection, for which it is used at a dose of 180µg weekly, injected subcutaneously into the thigh or abdomen. Patients are usually given their first few doses at the clinic then shown how to self inject at home and advised to rotate injection sites.

Side effects are usually dose-related and consist of influenza-like symptoms, lethargy and nausea. Depression is also recognised and there have been reports of suicide in patients receiving interferon. According to studies, these side effects limit the duration of treatment to 48 weeks.

Lamivudine Lamivudine is a nucleoside analogue that is metabolised by both infected and uninfected cells to an active triphosphate derivative, which acts as a substrate for HBV viral polymerase. Used at a dose of 100mg *od*, the drug is suitable for both the initial treatment of chronic HBV infection and in patients with decompensated liver disease (see Definitions panel in part 1, *PJ*, 5 April, pp411–4). In patients with compensated disease, treatment should be continued until seroconversion is achieved but, in those with decompensated disease treatment can be life-long. Side effects include gastrointestinal disturbances, anorexia, pancreatitis and lactic acidosis.

Adefovir dipivoxil Adefovir dipivoxil is a pro-drug of adefovir, a nucleotide analogue of adenosine monophosphate. Following uptake into mammalian cells, host enzymes convert

For those who develop chronic hepatitis B infection interferon or antiviral therapy should be considered

the drug to adefovir diphosphate, which inhibits viral DNA polymerases needed for viral replication. Adefovir is licensed for use in chronic HBV infection with either compensated disease with evidence of viral replication and histologically documented active liver inflammation or in decompensated liver disease. The usual dose is 10mg *od*, but this should be reduced in patients with renal impairment.

Side effects include nausea, vomiting, diarrhoea and, in some cases, renal impairment.

Entecavir Entecavir is a guanosine nucleoside analogue that inhibits the functions of HBV viral polymerase. It is licensed for use in patients with chronic HBV infection with compensated liver disease, evidence of viral replication and histologically documented acute liver inflammation or fibrosis.

The dose depends on whether or not the patient has previously been treated with nucleoside analogues. Patients who have not should receive 500µg daily, whereas those with lamivudine-resistant chronic HBV should receive 1mg daily. Doses should be taken at least two hours before or two hours after food. Side effects are mostly gastrointestinal. Thrombocytopenia is recognised as a less common adverse effect.

Telbivudine Telbivudine is a synthetic thymidine nucleoside analogue that inhibits HBV DNA polymerase. After being converted to the active triphosphate form it is incorporated into viral DNA and causes chain termination. Telbivudine is licensed for use in adults with compensated disease and evidence of viral replication.

The usual dose is 600mg daily, with the dosage interval being increased in patients whose creatinine clearance is less than 50ml/min. Although the optimum duration of treatment is unknown, the manufacturer suggests that discontinuation of treatment should be considered if HBsAg seroconversion has been achieved or loss of efficacy is seen.

The most common side effects include dizziness, headache and gastrointestinal disturbances. Severe acute exacerbations of chronic hepatitis B are relatively frequent and are characterised by raised levels of alanine aminotransferase (ALT), thus it is advised that hepatic function should be monitored periodically during treatment. In some patients, serum values of ALT will rise and HBV DNA levels will fall.

Because the viral DNA integrates with host DNA, eradication of the virus is difficult. Therefore, it appears that treatment with antivirals should be life-long in all patients.

Conception, pregnancy and breastfeeding Women of child bearing age should use effective contraception while they are taking these antivirals.

There are inadequate data on the use of these drugs in pregnancy so treatment should only be used during pregnancy if the benefit

Panel 2: Prevention of hepatitis

- At risk individuals should receive appropriate vaccinations (see Panel 3).
- Travellers to areas where hepatitis A is endemic should be advised to avoid drinking local water (and ice cubes) and eating shellfish, uncooked vegetables, unpeeled fruit and ice cream, and to avoid cleaning teeth with tap water.
- People should be advised to practise good personal hygiene (eg, not to share toothbrushes or razors with others).
- People should be advised to practise safer sex.
- Intravenous drug abusers should be encouraged to use needle exchange schemes.

Panel 3: Hepatitis vaccinations

Vaccines are available to protect against hepatitis A and B viruses. Readers are advised to consult the latest edition of 'Immunisation against infectious disease — The Green Book' for information on vaccines and vaccination procedures, including the recommended individuals who should be vaccinated against hepatitis A and B. The vaccines are safe in pregnancy and there is no evidence of any risk in breastfeeding.

Hepatitis A The hepatitis A vaccine can be given alone or in combination with vaccines for hepatitis B or typhoid vaccine. When given alone or in combination with the typhoid vaccine, a single dose is given followed by a booster six to 12 months later in order to extend immunity to hepatitis A from 12 months to beyond 10 years. When given with the hepatitis B vaccine, three doses are needed (at zero, one and six months), followed by a booster after 12 months.

Those travelling to endemic areas should be advised to visit GP or travel clinic four to six weeks before travelling for vaccination with formaldehyde inactivated virus. Vaccination is also recommended for at risk groups, such as staff and residents of homes for those with severe learning difficulties and sewage workers.

Immunoglobulin antibodies is considered only of value to prevent infection in close contact with confirmed cases where there has been a delay in identifying cases or for people at high risk of severe disease.

Hepatitis B The UK is one of the few developed countries that does not routinely immunise children against hepatitis B. Instead, the vaccine is recommended that high risks groups, such as intravenous drug misusers and health care professionals who have direct contact with blood, are given inactivated HBsAg and immunisation requires three doses over six months. The duration of immunity is unknown. There have been calls for the hepatitis B vaccine to be added to the childhood immunisation programme.

outweighs the potential risk. Animal studies with lamivudine have demonstrated reproductive toxicity, but the risk to humans is unknown. In addition, since the drug readily crosses the placenta, the manufacturer advises that it should be avoided during the first trimester.

There is no information on the effect of these drugs on the vertical transmission of HBV and infants of infected mothers should receive a vaccine (a specific hepatitis B immunoglobulin rather than the inactivated virus surface antigen) as soon as possible after birth.

Mothers should also avoid breastfeeding while taking lamivudine because it is present in breast milk. The manufacturers of adefovir dipivoxil, entecavir and telbivudine advise women not to breast feed.

Hepatitis C

Identified in 1989, hepatitis C (HCV) is a single stranded RNA virus. There are six genotypes of this virus with different prevalences throughout the world. Genotypes 1, 2 and 3 are the most common in the UK. Genotypes 2 and 3 respond best to treatment, whereas genotype 1 is the most difficult to treat. The

virus is mainly transmitted via infected blood and blood products. Infection is highly prevalent in intravenous drug misusers where it reaches almost 70 per cent in the UK. The incidence of transmission via blood transfusions has declined in recent years due to donor screening programmes.

Most people infected with the virus are asymptomatic; those who develop acute hepatitis experience milder symptoms than those seen in patients infected with HBV. However, the risk of developing chronic infection is 50–80 per cent — significantly higher than with HBV infection. The liver stays inflamed and about 20 per cent of those chronically infected will develop cirrhosis of the liver — the likelihood increasing in patients over 40 years of age, men and those who consume more than six units of alcohol per day.

The risk of developing hepatocellular carcinoma increases with the duration of infection and chronic HCV infection accounts for a quarter of all liver cancer cases worldwide. It is not known why some people do not develop chronic infection.

Treatment Treatment of chronic HCV involves a combination of peginterferon and ribavirin. Peginterferon may be used as monotherapy if ribavirin is not tolerated or contraindicated. There are two manufacturers of each product. Roche produces Copegus (ribavirin) and Pegasys (peginterferon) and Schering-Plough produces Rebetol (ribavirin) and ViraferonPeg (peginterferon).

The Pegasys brand is also licensed for use in patients who have liver cirrhosis. The doses (and duration of treatment) of ribavirin and peginterferon depend on the brands used and the genotype affecting the patient. (Readers are referred to the products' summaries of product characteristics for more details.)

The marker of response to these treatments is the sustained virological response, which is characterised by the virus being undetectable six months after treatment has finished. NICE revised its recommendations in August 2006 to include patients with mild chronic HCV infection as being eligible for treatment. It also comments that treatment can be delayed until the disease has reached a moderate stage ("watchful waiting"). However, there is a risk that patients will develop liver cirrhosis if this strategy is used.

There is a risk of bone marrow suppression, and especially anaemia, with ribavirin therapy. Patients should have their full blood count measured weekly for the first four weeks of treatment, then monthly. Opinion differs on the action to take if haemoglobin values fall. Reducing the ribavirin dose is an option but carries the risk of reduced efficacy. The use of recombinant human erythropoietin has been shown to be effective, but remains unlicensed for this purpose.

Ribavirin is contraindicated during pregnancy and women of childbearing age, and their male partners must use contraception during treatment and for four months after it has finished. Infected men and their female

Resources

- Travel health information sheets on hepatitis are available from the National Travel Health Network and Centre (www.nathnac.org).
- National Institute for Health and Clinical Excellence guidance on adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B and peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C is available at www.nice.org.uk.

partners should each use effective contraception during treatment and for seven months after it has finished.

All patients chronically infected with HCV should abstain from alcohol. Many patients will experience loss of appetite and digestion problems and may develop intolerance to fatty foods. Patients should be advised to eat little and often and have their weight monitored closely.

Hepatitis B or C/HIV co-infection

Patients who are HIV-positive are commonly infected with either HBV or HCV by the same route of transmission and measures to prevent transmission of all these viruses are vital. The natural course of HBV and HCV is accelerated in HIV-positive patients and treatment is more difficult than in those who are not infected with HIV.

Hepatitis D

Also known as a delta virus, the hepatitis D virus consists of the HBsAg around a core of delta antigen (HDAg) and a small amount of single-stranded circular RNA. It is an incomplete RNA virus that can only replicate in the presence of HBV and is spread by the same routes.

Co-infection with the hepatitis D virus increases the risk of both acute liver failure and cirrhosis. Hepatitis D infection should be suspected when a patient with chronic HBV infection develops signs of acute hepatitis. Infection can be prevented by immunising against HBV.

Hepatitis E

Hepatitis E is an RNA virus similar to hepatitis A both in the mode of transmission and clinical presentation. Although it does not appear to increase the risk of chronic liver disease it may cause acute liver failure and mortality is significantly increased in pregnant women, in whom it reaches 20 per cent. Treatment of the acute illness is the same as for acute hepatitis A.

The pharmacist's role

Infection with viral hepatitis can cause anything from a minor illness to a life threatening episode of acute liver failure, cirrhosis of the liver and even hepatocellular carcinoma. Pharmacists can play a useful role giving information about hepatitis and advising on how to prevent it (see Panel 2, p479). They can also contribute to infection prevention by operating needle exchange schemes.

Those infected with hepatitis should be advised to avoid alcohol. Pharmacists should also be aware that patients who are chronically infected with either HBV or HCV may have difficulty with working full time and obtaining some types of insurance or a mortgage.

The management of chronic hepatitis B and C will become more complex in future with the introduction of new agents and pharmacists should make sure they keep up to date with this.

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Visit the National Travel Health Network and Centre website and find out about the resources available.
2. Run a campaign to promote safe alcohol consumption.
3. Find out about running a needle exchange scheme.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?