Clinical review

Preventing and treating hepatitis B infection

Rakesh Aggarwal, Piyush Ranjan

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Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226 014, India

Rakesh Aggarwal *additional professor*

Piyush Ranjan *senior research associate*

Correspondence to: R Aggarwal rakesh@sgpgi.ac.in

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Hepatitis B virus infection is a global public health problem, with approximately 400 million people chronically infected.[1 2] Each year it causes more than 500 000 deaths worldwide. Outcome of acute hepatitis B virus infection ranges from asymptomatic subclinical infection (70%) and symptomatic acute hepatitis (30%) to fulminant hepatic failure (0.1-0.5%).[3] A proportion of people infected with hepatitis B virus (5%-10% among adults) progress to chronicity, defined as persistence of infection for more than six months.[4] The rate of chronicity is much higher among neonates and children. The spectrum of chronic hepatitis B virus infection ranges from the asymptomatic carrier state to chronic hepatitis B, liver cirrhosis, and hepatocellular carcinoma. The clinical course of hepatitis B virus infection is complex and is influenced by several factors (box 1). Overall, chronic hepatitis progresses to end stage liver disease in 15-40% of patients.[5] The pathophysiology of chronic hepatitis B virus infection has been reviewed elsewhere.[6]

The magnitude and clinical consequences of chronic hepatitis B make a strong case for its prevention and treatment. This review, based on a Medline search and the authors' knowledge arising from their interest in the subject, summarises current knowledge about these aspects of hepatitis B virus infection.

Prevention of hepatitis B virus infection

Several strategies have been shown to prevent hepatitis B virus infection (box 2). Vaccination is the mainstay of prevention. Specific hepatitis B immunoglobulin (HBIg) and lamivudine are useful in specific settings.

Box 1: Factors influencing outcome of chronic hepatitis B virus infection

Viral factors:
- Level of hepatitis B virus replication
- Hepatitis B virus genotype
- Mutations in viral genome

Host factors:
- Age at acquisition of infection
- Immune status
- Concurrent infection with other hepatotropic viruses
- Alcohol intake

Box 2: Prevention strategies for hepatitis B

Hepatitis B vaccination:
- High risk groups
- All newborn infants

Screening of blood and blood products
Using universal precautions in healthcare settings
Avoiding needle sharing among injecting drug users
Promoting safe sex practices

Prevention in special settings:
- Preventing vertical transmission (giving hepatitis B vaccine and hepatitis B immunoglobulin to newborns of HBsAg and HBeAg positive mothers)
- Post-exposure prophylaxis (hepatitis B immunoglobulin)
- Preventing transmission in patients with liver transplants (lamivudine, adefovir, hepatitis B immunoglobulin)

General measures

General measures like practising universal precautions (using disposable needles and syringes and barrier contraception) have an important role. Routine screening of transfused blood and blood products (for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B core antigen (anti-HBc) has greatly reduced the risk of post-transfusion hepatitis B virus infection.

Hepatitis B vaccine

Hepatitis B vaccines are of two types, plasma derived and recombinant. Recombinant vaccines are produced by cloning the gene encoding HBsAg into yeast cells and are increasingly replacing plasma derived vaccines.

Vaccines are given in three doses (at 0, 1, and 6 months) of 10-30 µg (usually 20 µg for adults and 10 µg for children). The vaccines are extremely safe and induce antibodies that will neutralise HBsAg (anti-HBs) in most (>95%) recipients; antibody levels in excess of 10 mIU/ml are considered protective. Certain groups—people aged over 40, obese people, those with chronic renal failure, haemodialysis recipients, immunosuppressed individuals, organ transplant recipients—have poorer response rates. The protection lasts for at least 15 years,[7] and because of strong immunological memory it continues after anti-HBs has become undetectable.[8] Immunity is thus believed to be lifelong, and boosters are not recommended routinely; however, these may have a

P+ *A comparison of lamivudine and interferon for initial treatment is on bmj.com*

Classification of patients with chronic hepatitis B virus infection

Characteristic	Chronic hepatitis B*	Inactive HBsAg carrier
HBsAg	Positive for >6 months	Positive for >6 months
Alanine aminotransferase	Intermittently or persistently raised (>2 times upper limit of normal)	Normal
Serum hepatitis B virus DNA level	$>10^5$ copies/ml†	$<10^5$ copies/ml
Liver biopsy (histological activity index)	≥4‡	≤3

*No clinical or histological evidence of cirrhosis; this group is further subdivided into HBeAg positive chronic hepatitis B (HBeAg positive and anti-HBe negative) and HBeAg negative chronic hepatitis B (HBeAg negative and anti-HBe positive) forms.
†Hepatitis B virus DNA levels measured using a quantitative method (for example, quantitative polymerase chain reaction assay) or testing positive with a method other than polymerase chain reaction (for example, hybridisation assay) with sensitivity in the range of 10^5 copies/ml.
‡Necro-inflammatory score.[14]

role in immunosuppressed individuals and those at a particularly high risk of exposure. Non-responders to three doses may benefit from additional doses of the vaccine.[8]

The availability of effective and safe vaccines makes primary prevention of hepatitis B an attractive strategy.[7] Universal neonatal vaccination is effective and has been shown to favourably alter the clinical course of hepatitis B virus infection in regions where the disease is endemic.[9] This strategy is cost effective even in low income countries with intermediate hepatitis B virus endemicity rates.[10] Even in low endemicity regions like Europe, neonatal vaccination is preferable, although immunisation in late childhood or adulthood may be a reasonable alternative. Adults at high risk of hepatitis B (healthcare workers, public safety workers, homosexual men, injecting drug users, patients likely to receive multiple transfusions, haemodialysis patients) must be vaccinated.

The United Kingdom is one of the few developed countries that have not implemented universal neonatal hepatitis B immunisation. Because the burden of hepatitis B was low and individual rights were considered paramount, a policy of selective immunisation of newborns of carrier mothers and in high risk groups has been followed. This approach fails to identify a large proportion of those at risk and thus has had a limited impact. It is time that this policy is reviewed in the light of experience with selective immunisation, data on efficacy of universal immunisation from other countries, and the proved safety of recombinant vaccines.

Viral mutants that are not neutralised by antibodies induced by the available vaccines have been detected. Though currently a minor problem, these have led to a renewed interest in developing vaccines targeted at multiple viral antigens.

Prevention of hepatitis B virus transmission in special settings

Maternal-fetal transmission—All pregnant women should be screened for HBsAg. Among infants born to HBsAg positive mothers, the risk of vertical transmission is particularly high if the mother is positive for hepatitis B e antigen (HBeAg), has a high viral load, or is infected with HIV. Such infants should receive both vaccine and HBIg (0.5 ml) within 12 hours of birth. They should be tested for HBsAg, anti-HBs, and anti-HBc at 12 months of age; presence of anti-HBs indicates vaccine induced immunity and detection of both anti-HBs and anti-HBc indicates infection modified by immunoprophylaxis, whereas presence of HBsAg indicates failure of prophylaxis.

Accidental exposure to hepatitis B virus—People who have not been immunised and are exposed to hepatitis B (through needlestick injury, splashing, or sexual exposure to partners infected with hepatitis B virus) should receive HBIg (0.04-0.07 ml/kg) as soon after exposure as possible. Vaccination should be started simultaneously, with the first dose given at a site different from that for HBIg; an accelerated four dose immunisation schedule (0, 1, 2, and 12 months) is preferred in this setting.

Liver transplantation—Among patients who receive transplants because of hepatitis B virus related liver disease, infection of grafted liver is nearly universal. Lifelong HBIg after transplantation reduces the graft infection rate; however, this approach is costly and is associated with 20% infection by two years and emergence of HBIg-resistant hepatitis B surface protein mutants. Lamivudine, alone or in combination with HBIg, prevents recurrence of hepatitis B virus after transplantation.[11] In preliminary studies, adefovir has shown promise.

Treatment of chronic hepatitis B virus infection

Who needs treatment?

Patients with acute hepatitis B do not need treatment; those with fulminant hepatic failure should be considered for liver transplantation.

Patients with chronic hepatitis B virus infection should undergo a detailed evaluation to assess baseline liver function and the need for further treatment and follow up (box 3). Chronic hepatitis B virus infection is a heterogeneous condition and can be divided into many subsets based on clinical status and status of viral replication (table).

Inactive carriers of hepatitis B are healthy; have a low concentration of serum hepatitis B virus DNA (a measure of rate of viral replication; $<10^5$ copies/ml), or none; lack detectable HBeAg; have normal levels of alanine aminotransferase; and show little progression of liver disease. Though the exact relation between hepatitis B virus DNA levels and potential for liver damage is not known, it is generally believed that levels below 10^5 copies/ml are not associated with progression of liver injury.

Patients with chronic hepatitis B have viral replication, high hepatitis B virus DNA concentrations, and biochemical evidence of hepatitis. Chronic hepatitis B is either HBeAg positive (patients test positive for HBeAg) or HBeAg negative. The HBeAg negative patients lack detectable HBeAg despite a high rate of viral replication and high hepatitis B virus DNA levels; this paradox arises from a mutation (pre-core mutation) which permits viral replication but prevents production of HBeAg. HBeAg negative chronic

Box 3: Initial evaluation of a patient with chronic hepatitis B virus infection

- History and physical examination—Specifically look for symptoms and signs of portal hypertension (abdominal wall collaterals, splenomegaly, hypersplenism, ascites) and liver failure (jaundice, haematemesis, ascites, encephalopathy, etc)
- Laboratory tests—Liver function tests (aminotransferases, serum albumin, prothrombin time); complete blood counts, renal function tests
- Screen for oesophageal varices (upper gastrointestinal endoscopy)
- Screen for hepatocellular carcinoma (ultrasonography and α-fetoprotein levels)
- Tests for viral replication status (HBeAg, anti-HBe, hepatitis B virus DNA)
- Screen for coinfection with other parenterally transmitted viruses (anti-hepatitis C virus antibodies, HIV serology)
- Liver biopsy (optional)

hepatitis B has a poorer prognosis and treatment response than does HBeAg positive chronic hepatitis B.

Liver biopsy is the gold standard for determining disease activity (necro-inflammation) and stage (fibrosis),[12] but it is often contraindicated in patients with decompensated liver disease. Even in patients with compensated disease, though biopsy may provide information for therapeutic and prognostic decision making, it is frequently not done.[13]

The goal of treatment of chronic hepatitis B is to prevent progression to cirrhosis and hepatocellular carcinoma by preventing viral replication and suppressing necro-inflammatory activity. The unpredictable clinical course of hepatitis B virus infection, and poor response to treatment and doubts about its cost effectiveness, render therapeutic decisions difficult. In patients with decompensated cirrhosis, antiviral treatment has not been clearly shown to provide benefit, so liver transplantation is the only option. Histological cirrhosis is a poor prognostic marker among patients with compensated disease.

Patients in inactive carrier stage do not need treatment, since their liver disease progresses very slowly, if at all. The risk of developing hepatocellular carcinoma in these patients, though higher than in people without infection, is much lower than in HBeAg positive patients. Their alanine aminotransferase levels should be determined every 6-12 months,[13] and every two years they should be screened for hepatocellular carcinoma with ultrasonography and α-fetoprotein levels.[14] Though the evidence in favour of this approach is limited,[15] raised alanine aminotransferase in such patients may indicate HBeAg negative chronic hepatitis B and should prompt assessment for hepatitis B virus replication (hepatitis B virus DNA testing) and for other unrelated causes of liver injury (other hepatotropic viruses, alcohol, drugs, etc).

Only those patients who have chronic hepatitis B (active hepatitis B virus replication with a high viral load and ongoing necro-inflammation) qualify for treatment. Patients with chronic hepatitis B virus infection (HBsAg positive for >6 months), alanine aminotransferase persistently exceeding 1.5-fold to twofold higher than normal, hepatitis B virus DNA $>10^5$ copies/ml, and histological activity index >4 are the most suitable candidates for treatment (box 4); in a large meta-analysis, 32% of such patients showed HBeAg to anti-HBe seroconversion, as compared with 11% of untreated patients.[16] However, it is advisable to wait till transaminase has been raised for one to three months, in order to allow time for the spontaneous viral clearance that occurs in a sizeable proportion of such patients.[13 14 17] In patients with ongoing viral replication and normal transaminase concentrations, response rate is quite poor; in such patients alanine aminotransferase should be measured every three months, and they should be treated if raised concentrations persist.[18]

Some categories of patients with chronic hepatitis B (those with hepatitis C virus or HIV coinfection) do not respond as well to treatment.

Treatment end points

Response to treatment is expressed as a combination of the specific aspects of response studied (biochemical or alanine aminotransferase levels, virological or viral DNA levels, or histological activity), and the time of assessment in relation to treatment (box 5).

Alanine aminotransferase concentrations are a surrogate marker of ongoing necro-inflammatory activity and serve as an inexpensive and simple tool for monitoring response to treatment. Seroconversion (loss of HBeAg and appearance of anti-HBe), whether naturally acquired or treatment induced, is an important and a widely used treatment endpoint, since it is associated with a reduced rate of progression to cirrhosis of the liver and reduced likelihood of decompensation.[19 20] Although hepatitis B virus is not

Box 4: Treating chronic hepatitis B virus infection

Inactive HBsAg carriers
- Alanine aminotransferase every 6-12 months
  Screening for hepatocellular carcinoma

Chronic hepatitis B (active viral replication)
- Normal alanine aminotransferase:
  Treatment not recommended
  Alanine aminotransferase every 3-6 months
  Screening for hepatocellular carcinoma
- Raised alanine aminotransferase:
  Treatment indicated (interferon or lamivudine)

Cirrhosis
- Compensated:
  Treatment indicated (interferon or lamivudine)
  Poor response to treatment
- Decompensated:
  Lamivudine, liver transplantation

Difficult to treat patients
- Hepatitis C virus or hepatitis D virus coinfection
- Renal failure
- Immunocompromised (human immunodeficiency virus infection, chemotherapy)
- Decompensated cirrhosis

Box 5: End points of treatment for chronic hepatitis B virus infection

Treatment responses
Biochemical response—Return of alanine aminotransferase to within normal range
Virological response—Decline in hepatitis B virus DNA to $<10^5$ copies/ml
Serological response—HBeAg loss and appearance of anti-HBe
Histological response—Decrease in necro-inflammatory score by ≥ 2 points

Time frame for assessment of response
On-treatment response—Response assessed while receiving treatment
End of treatment response—Response assessed at the end of treatment duration
Sustained response—Response after a period off drugs (6 months or 12 months)

directly cytopathic, maintaining hepatitis B virus DNA concentration below a specified level is another useful treatment endpoint. Hepatitis B virus DNA level below 10^5 copies/ml is the most frequently used cut off for virological response; this can be assessed during treatment, at the end of treatment, or after treatment (sustained response). Since the main aim of treating chronic hepatitis B is to prevent progression of fibrosis and development of cirrhosis, liver biopsy may represent an ideal method of assessing response; however, its invasive nature and the risk of complications preclude its routine use. In patients with decompensated disease, Child-Pugh score may be a useful assessment tool.

Treatment options
Three drugs—interferon alfa, lamivudine, and adefovir—are approved in several countries for use in chronic hepatitis B. Of these, interferon has both antiviral and immunomodulatory activity; lamivudine and adefovir are primarily antiviral. Use of drugs with only immunomodulatory activity (thymosin α-1) is not well established. Emtricitabine, entecavir, telbuvidine, and clevudine are currently under investigation.

General advice
Avoiding alcohol, safe sexual practices, immunisation of household contacts, vaccination against hepatitis A (in low prevalence areas), and weight reduction should be advised. People who might spread hepatitis at work should either undergo treatment or change their profession. Immunosuppressive drugs should be used with caution in order to avoid activating hepatitis B virus infection.

Interferon
Interferon alfa, a host cytokine produced in response to any viral invasion, has immunomodulatory, antiviral, and anti-fibrotic properties. It was first used in the 1980s and was the first drug to be found useful in the treatment of chronic hepatitis B. The dose is 5 million units a day or 10 MU thrice weekly (30-35 MU/week), given subcutaneously, usually for 16 weeks.

Interferon can have several adverse effects. An influenza-like illness (fever, chills, headache, malaise, myalgias) occurs in 25-30% of patients but rarely needs discontinuation of treatment. More serious adverse events (myelosuppression (leucocytes $<1000/\mu l$ and platelets $<60\,000/\mu l$), emotional lability and depression, development of autoantibodies, and thyroid dysfunction) may lead to discontinuation of interferon; thus, pretreatment screening for psychiatric illness, low leucocyte and platelets counts, autoantibodies, and thyroid function is mandatory. Administration of corticosteroids before interferon treatment is not useful.

Interferon has been used in both types of chronic hepatitis B. In HBeAg positive patients, about a third show virological and histological response.[16] The factors that determine response to interferon are listed in box 6. Interferon induced seroconversion in HBeAg positive patients lasts for at least eight years,[19 20] but interferon induced responses are less durable in HBeAg negative chronic hepatitis B.[21] Though prolonging treatment for one to two years may improve the sustained response rates, the benefit in these patients remains less than that in HBeAg positive chronic hepatitis B.

Use of interferon in decompensated cirrhosis is associated with an increased risk of infections and exacerbation of liver injury. Response rate is also poor in patients with compensated cirrhosis, and there is a risk of precipitating liver decompensation.

Pegylated interferon, a longer acting interferon preparation, may be better than conventional interferon.[22] Data on its use in chronic hepatitis B are limited, precluding a recommendation for routine use.

Lamivudine
Lamivudine, a synthetic nucleoside (cytosine) analogue available since 1998, undergoes intracellular phosphorylation to its active metabolite lamivudine triphosphate and inhibits viral reverse transcriptase, causing premature chain termination during viral DNA synthesis.

In initial studies in patients with HBeAg positive chronic hepatitis B, treatment with lamivudine for 52 weeks fared better than placebo in inducing biochemical response, HBeAg to anti-HBe seroconversion, and histological response, and induced a reduction in hepatitis B virus DNA levels throughout the treatment period.[23 24] However, the response rate depends on duration of treatment: prolonged treatment is associated with higher seroconversion rates (21% at one year,

Box 6: Predictors of non-response to interferon in chronic hepatitis B

Viral factors:
- High serum hepatitis B virus DNA levels
- Mutant virus (for example, pre-core mutant with negative HBeAg)
- Co-infection with hepatitis C virus or hepatitis delta virus

Host factors:
- Normal transaminase activity
- Infection acquired in early childhood
- Male sex
- Asian ethnic origin
- Immunosuppression (including drugs, HIV infection)
- Decompensated liver disease

Additional educational resources

Information for patients

Hepatitis B Foundation (www.hepb.org)—Provides information for patients and families, and for healthcare professionals (in English and several other languages)

British Columbia Centre for Disease Control. Hepatitis (www.bccdc.org/topic.php?item=59)—Educational material on hepatitis B for patients

National Center for Infectious Diseases, Centers for Disease Control and Prevention. Viral hepatitis B (www.cdc.gov/ncidod/diseases/hepatitis/b/index.htm)—Educational material for patients and healthcare professionals on prevention guidelines for hepatitis B

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. Hepatitis publications (http://digestive.niddk.nih.gov/ddiseases/pubs/hepatitis/index.htm)—Information for patients on treatment and prevention of various forms of hepatitis. (Some documents are also available in Spanish)

About.com. Hepatitis (www.hepatitis.about.com/cs/hepatitisb)—Comprehensive information about hepatitis B treatment, with web links

Singapore Ministry of Health. Clinical Practice Guidelines. Chronic hepatitis B infection. April 2003. (www.guideline.gov/summary/summary.aspx?view_id=1&doc_id=3749)—Evidence based information about hepatitis B treatment and prevention

Everson GT, Weinberg H. *Living with hepatitis B: a survivor's guide*. Long Island City, NY: Hatherleigh Press. 2002. —Explains hepatitis B virus, disease associated with this infection, and its prevention and treatment

Green WF, Conjeevaram H. *The first year—hepatitis B: an essential guide for the newly diagnosed*. Emeryville, CA: Marlowe, 2002—Provides current and empathetic information for those wishing to take an active role in their hepatitis B treatment

Major reviews and guidelines on treatment of hepatitis B

Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000—summary of a workshop. *Gastroenterology* 2001;120:1828-53.

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Liaw YF, Leung N, Guan R, Lau GK, Merican I, Asian-Pacific Consensus Working Parties on Hepatitis B. Asian-Pacific consensus statement on the management of chronic hepatitis B: an update. *J Gastroenterol Hepatol* 2003;18:239-45.

Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, et al. A treatment algorithm for the management of chronic hepatitis B virus in the United States. *Clin Gastroenterol Hepatol* 2004;2:87-106.

29% at two years, 40% at three years).[25] However, with increasing duration of treatment, an increasing proportion of patients develop a mutation in the tyrosine-methionine-aspartate-aspartate (YMDD) motif in the catalytic domain of viral DNA polymerase, which confers lamivudine resistance (14% at one year to 69% at five years), which affects the disease course adversely. Higher pretreatment alanine aminotransferase levels predict a higher response rate; hepatitis B virus DNA levels do not influence response to lamivudine.

Lamivudine treatment in HBeAg negative chronic hepatitis B is associated with less durable responses and a higher rate of emergence of YMDD mutants (60% at four years).[26]

Lamivudine treatment in patients with decompensated cirrhosis related to hepatitis B and active viral replication is associated with higher Child-Pugh score and better transplant-free and overall survival than in historical controls.[11]

The benefit takes months to appear and increases with time; however, beyond a certain time point, the administration of this drug may be counterproductive because the risk of appearance of mutant strains increases with longer treatment. Lamivudine has an excellent safety profile, even in patients with decompensated liver disease.

In treatment-naive patients with chronic hepatitis B, interferon and lamivudine give similar response rates. Each drug has certain relative advantages and disadvantages (see bmj.com). Given the poor response rate with both drugs, patient's choice and cost may be important considerations. Failure to respond to interferon does not adversely influence response rates with lamivudine, but in patients with decompensated disease, lamivudine is the only viable treatment option.

Adefovir

Adefovir dipivoxil, a nucleotide analogue of deoxyadenosine monophosphate, inhibits viral reverse transcriptase activity in both wild-type and YMDD mutant hepatitis B virus.[27] Thus, it is the drug of choice for patients treated with lamivudine who have developed YMDD mutation. It has also been used in patients with HBeAg positive chronic hepatitis B [28] and HBeAg negative chronic hepatitis B,[29] with efficacy rates at one year similar to those with lamivudine, albeit with no drug resistant mutations. Adefovir may thus be a useful alternative to lamivudine in all types of patients, though further data are needed. Adefovir resistant mutants of hepatitis B virus have recently been described; their clinical importance needs further study.

Combination treatment

Available data show no benefit of the lamivudine-interferon combination over individual drugs.[13 14] Combinations of nucleoside analogues have not been adequately studied.

Liver transplantation in hepatitis B virus related liver disease

Hepatitis B virus related liver disease was once considered a relative contraindication for liver transplantation, but this is no longer the case, particularly in Asian countries. Preventing the graft becoming infected with hepatitis B virus has already been discussed. Treatment with lamivudine before the transplantation reduces the risk of recurrence through reducing the viral DNA load; adefovir may prove to be better because it is not associated with development of YMDD mutants. Antiviral drugs fare better than interferon in treating hepatitis B after liver transplantation.

Patients in special categories

HIV-hepatitis B virus coinfection—Patients with chronic hepatitis B and HIV infection have higher levels of hepatitis B virus DNA, worse outcome, and poor response to treatment. The need for highly active antiretroviral treatment (HAART) and anti-hepatitis B virus treatment should be assessed independently, using standard guidelines. The choice of drugs for hepatitis B virus infection depends on the need for concomitant antiretroviral treatment, level of immune suppression, and details of past drug treatment.[30 31] Tenofovir disoproxil has activity against both hepatitis B virus and HIV (wild-type as well as YMDD mutants) and may be particularly useful in such patients.

Summary points

- Hepatitis B is major global health problem; chronic infection causes major complications like cirrhosis and hepatocellular carcinoma
- Vaccination is the most effective method of preventing hepatitis B virus infection
- Acute hepatitis B does not need treatment
- The clinical course of hepatitis B is complex and not all patients progress to cirrhosis
- Among patients with chronic hepatitis B, only a subset (identified by presence of hepatitis B virus DNA) need treatment
- Drug treatment has limited efficacy, may have adverse effects, and is costly, so the need for treatment should be assessed cautiously
- Recommended drugs include α-interferon, lamivudine, and adefovir

The response of chronic hepatitis B to interferon treatment is reduced in patients with HIV coinfection; this drug should be used only in patients with a CD4 cell count >500/ml. Lamivudine monotherapy is associated with an inordinately high frequency of development of resistant mutants of both HIV and hepatitis B virus, and should not be used. If the patient needs HAART, lamivudine (150 mg twice daily) along with adefovir or tenofovir should be used in combination with a potent antiretroviral regimen. Even in patients in whom HAART is not indicated, lamivudine monotherapy should be avoided since drug resistant HIV mutants often develop and may prejudice future treatment.

Hepatitis C virus-hepatitis B virus coinfection—Outcomes for hepatitis B virus-hepatitis C virus coinfection are poorer than those of infection with hepatitis B virus alone, despite a lower hepatitis B virus replication rate in such patients. Patients with hepatitis B virus DNA level exceeding 10^3 copies/ml and undetectable hepatitis C virus RNA should be treated as for hepatitis B virus infection alone. Those with lower hepatitis B virus DNA levels and detectable hepatitis C virus RNA should initially receive interferon and ribavirin, and hepatitis B virus DNA should be measured at three months; if the levels have increased, lamivudine or adefovir may be added.

Patients receiving chemotherapy and immunosuppressants—To prevent reactivation of the hepatitis B virus, patients with evidence of hepatitis B virus infection who are to receive chemotherapy should receive lamivudine until three to six months after they finish. The use of interferon in this setting remains unclear and that of adefovir has not been studied.

Children—Because of immune tolerance, children with hepatitis B virus infection manifest liver disease only infrequently. If treatment is indicated, interferon or lamivudine may be used, as in adults. Adefovir has not been used in children.

Pregnant women—Potential benefits of use of lamivudine and adefovir during pregnancy must be weighed against risks. Lamivudine in the third trimester may prevent transmission of hepatitis B virus to the fetus.

Summary

Hepatitis B virus infection is a global public health problem. Hepatitis B vaccines are highly effective, long acting, and safe, making prevention and even eventual eradication possible. However, treatment options for patients who are already infected are limited. The currently available drugs are effective only in selected subsets of patients and have low efficacy rates, and their long term impact on occurrence of complications remains unknown.

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Understanding risk

I spent the afternoon before the Rugby Union world cup with a patient liaison group, fine tuning our anaesthetic literature for distribution to preoperative patients. An essential part of this sort of information is a risk-benefit explanation. Patients increasingly seem to expect that low risk is equivalent to no risk and that if something goes wrong it is a consequence of "fault" and lack of care. The only time people turn this perception of risk-benefit on its head is with the lottery: people regularly buy into the 1 in 14 million chance of winning the jackpot, but none would expect to be hit by lightning or die under anaesthesia—both of which are more likely.

I was healthy—a low risk for occlusive vascular events. I was 51 years old, a non-smoker for 20 years, body mass index 24.5, blood pressure a reasonable 135/85 mm Hg, blood cholesterol 5.6 mmol/l. I am not diabetic, and I exercised more than most (on the Thursday before my event I spent 90 minutes in the gym with my heart rate up to 150 beats/min without any problem), ate healthily, took multivitamins and minerals, and took aspirin 75 mg most days on the basis of the "big pill for the over 50s." (I hadn't got round to the ACE inhibitor, statin, and β blocker.)

It was then with some disbelief that, after walking back from our local shop (150 metres round trip), I felt a little "funny" and realised rapidly that I could not articulate. My left side became weak, and I could not stand up. By two days later, I had had a third occlusive vascular event that left me bewildered, exhausted, and bed bound.

Only two years previously, I had undergone an emergency appendicectomy. I chose my anaesthetist with care, and it was uneventful. However, I believe that if I had had my occlusive vascular event during the anaesthetic, there would have been an implication that my anaesthetist had done "something wrong." And yet he did not, but how else could one explain a fit man undergoing uncomplicated anaesthetic and surgery who had an occlusive vascular event?

After 25 or more years in anaesthetics, I think I had a reasonable understanding of the risks of my anaesthesia and surgery. I have accepted that my occlusive vascular event was independent of the anaesthesia—but how to explain that to the lay public if the interval between anaesthesia and adverse event had been two minutes rather than two years? I suspect that most would not believe it. I can imagine the soul searching of the anaesthetist and the hospital complaints procedure. And yet the adverse event was completely unpredictable; an act of God.

So it is a wonderful thing to share with a patient the risks of the procedure proposed. But how realistic is the understanding that goes with it?

A week after my occlusive vascular event, I underwent transoesophageal echocardiography, after being told the risk of oesophageal perforation was 1:1000 or so. Despite my experience of long odds less than a week previously, I underwent the procedure more worried about the effects of midazolam on my injured and confused brain. I went into the "1:1000 is not very high, it will be alright" mode.

And so hundreds of thousands of others, some far fitter than me, many less so, undergo anaesthesia and surgery having had the risks "explained" and having "understood" them. And none of them would seriously expect an adverse outcome to accompany the end of surgery. The most common adverse event related to anaesthesia is dental damage. People are most relieved to wake up to find their crowns intact, rather than appreciating that their intact brain is more important and less easily correctable.

David R Derbyshire *consultant in anaesthesia, Warwick Hospital (dr.derbyshire@ntlworld.com)*

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. Please submit the article on http://submit.bmj.com Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.