The commonest causes of chronic or end-stage liver disease are alcohol and chronic viral hepatitis. In addition, there are a number of pathways to chronic liver disease, including auto-immune conditions (eg, auto-immune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis) and metabolic conditions (eg, genetic haemochromatosis and Wilson’s disease).

The severity of chronic liver disease is usually assessed by using the Childs-Pugh classification, which is based on five parameters: ascites, encephalopathy, nutritional status, serum albumin, and serum bilirubin. These parameters carry equal weighting towards the total score, with 15 being the highest attainable score (Table 1). The score is then converted into a designation of either Childs-Pugh A (5–6), B (7–9) or C (10–15) for practical purposes, with C representing the most advanced disease. Patients with Childs-Pugh A are often referred to as having compensated cirrhosis, while the presence of overt clinical complications defines the presence of decompensated disease. Renal function is often impaired in chronic liver disease and may be an important factor to consider in drug management.

The management strategy of any liver disease is a combination of treating the symptoms and complications that arise, as well as drug therapies relevant to the specific underlying diagnosis. Encephalopathy, ascites, spontaneous bacterial peritonitis, variceal bleeding and pruritus are the main complications at which drug therapy is directed. The treatment options for specific liver conditions are increasing, especially in the areas of auto-immune and viral disease. The increasing availability and success of liver transplantation has tended to change the emphasis of management, and it is often not appropriate to exhaust other options before referring the patient for a transplant.

The role of specific drugs in the overall management strategy will vary, depending on the specific condition and the stage of the disease.

**Table 1: Scoring for Childs-Pugh classification of liver insufficiency**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>2</td>
<td>Moderate or easily treated</td>
</tr>
<tr>
<td>Nutritional status</td>
<td>3</td>
<td>Severe or intractable</td>
</tr>
<tr>
<td>Serum bilirubin</td>
<td>4</td>
<td>Mild</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>5</td>
<td>Mild malnutrition</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>6</td>
<td>Severe malnutrition</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>7</td>
<td>&gt;50µmol/L</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>8</td>
<td>&gt;30–50µmol/L</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>9</td>
<td>&gt;30–35g/L</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>10</td>
<td>&gt;35g/L</td>
</tr>
</tbody>
</table>

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Dr Kennedy is specialist registrar and Dr O’Grady is consultant hepatologist at the Institute of Liver Studies, King’s College Hospital, London.
on physician preference and the relative strength of supporting services in individual institutions. An outline of the approach used at King’s College Hospital (KCH) for a number of complications is given in Table 2. Below is a discussion of the management of pruritus, ascites, spontaneous bacterial peritonitis, encephalopathy and variceal haemorrhage, as well as the various manifestations of chronic liver disease.

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**Pruritus**

Pruritus (itch) is a prominent symptom of cholestatic liver disease. The pathogenesis of pruritus in cholestatic liver disease remains a matter of debate, but therapies that deplete bile acids, as well as centrally acting agents are effective. Antihistamines are relatively ineffective, apart from their sedative effect, and should not be used as first-line therapy.

Colestyramine and colestipol are anion-exchange resins which are the usual first-line therapy. These agents act by binding bile acids and preventing their reabsorption. They are insoluble in water, non-absorbable, and are usually taken before meals to maximise the amount of bile acids sequestered. Colestyrlemine is usually started at a dose of 4g once or twice daily and colestipol as 5g once or twice daily. The dose is titrated to give adequate relief without causing diarrhoea, but palatability also restricts dosing. These drugs may reduce the absorption of drugs taken at the same time. To avoid this, drugs should be taken one hour before or four hours after colestyramine or colestipol. Drugs that are particularly susceptible to the absorption-reducing effect of the anion-exchange resins are thyroxetine, ursodeoxycholic acid (UDCA), digoxin, propranolol, hydrochlorothiazide, tetracycline and penicillins. Long-term therapy with anion-exchange resins can also cause depletion of the fat-soluble vitamins. Rifampicin induces hepatic microsomal enzymes and has now been shown to benefit some patients. The dose used should be 600mg per day and improvement begins between one and three weeks after commencement of therapy. Problems relate to hepatotoxicity and interaction with other drugs.

The opioid antagonists naloxone, naltrexone and nalmefene have also been shown to be effective. The disadvantage of naloxone therapy is that subcutaneous injection is required, in contrast to naltrexone and nalmefene, which are substantially more bioavailable after oral administration. The dose of naloxone is 0.4mg subcutaneously, and the dose of nalmefene ranges from 5mg twice daily to 40mg three times daily.

Ondansetron, a 5HT3-antagonist, has recently been shown in non-comparative studies to be beneficial, removing itch 30 minutes after an 8mg bolus intravenous injection, with improvement lasting for more than 24 hours. Although it has the advantage of being available as an oral preparation, improvement of pruritus has not yet been confirmed with this route of administration.

UDCA, at 10mg per kg per day in two divided doses, is frequently used in cholestatic liver disease, and long-term use has been shown to improve pruritus, although it has been observed that it can occasionally worsen it.

Plasmapheresis (replacement of the plasma fraction of blood), albumin dialysis (molecular absorbent recirculating system [MARS], see p133), and charcoal haemoperfusion (circulation of blood through a cartridge containing charcoal adsorbent) are effective, but are used only in desperate situations, as in cases of severe psychological problems associated with intractable pruritus, which can include suicidal tendencies. Intractable pruritus is often the factor determining the timing of transplantation for patients with primary biliary cirrhosis.

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**Ascites**

The precise mechanism by which ascites develops in chronic liver disease is unclear, but portal hypertension, reduced oncostatic pressure and activation of the renin-angiotensin–aldosterone axis as a consequence of vasodilation are contributory factors. Therapy should include reduction in sodium intake (ranging from salt-free diets to those containing only 22mmol Na+ per day), fluid restriction and diuretics.

Diuretic therapy is usually initiated with an aldosterone antagonist such as spironolactone, either alone or in combination with a loop diuretic. Typically, spironolactone is introduced at a dose of 100mg per day, but it could be several days before a therapeutic effect is observed. Therapy may be initiated with loop diuretics such as furosemide (40mg per day) if the ascites is severe and the patient is admitted to hospital. The doses of diuretics are gradually increased to achieve a maximum daily weight loss of 0.75kg per day. More aggressive body weight reduction in the absence of peripheral oedema is likely to lead to intravascular fluid depletion.

Dose escalation should be stopped if the serum Na+ level decreases to less than 130mmol per litre, or if the creatinine level rises to more than 130µmol per litre. Ascites is considered to be diuretic-resistant when daily doses of spironolactone 300–400mg or furosemide 120–160mg are reached. Diuretic-resistant ascites is associated with a one-year survival rate of 25–50 per cent, and the suitability of the patient for liver transplantation should be considered. The other therapeutic options available include serial therapeutic paracentesis with fluid replacement, peritoneovenous shunt or transjugular intrahepatic portosystemic shunting (TIPS).

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**Bacterial peritonitis**

The detection of spontaneous bacterial peritonitis (SBP) requires a high index of suspicion, as the conventional signs and symptoms of peritonitis are rarely present. Diagnostic paracentesis is mandatory in any patient with ascites who is showing signs of decomposition, pyrexia or abdominal pain. SBP is associated with a high mortality rate of up to 40 per cent. A polymorphonuclear leucocyte count greater than 250 cells per mm3 is indicative of infection. The causative organism is of enteric origin in approximately three-quarters of infections and of skin origin in the remaining one-quarter.

Cefotaxime 2g given eight-hourly has been shown to be effective in 85 per cent of patients with SBP, compared with the combination of tobramycin and ampicillin, which is effective in 56 per cent of patients. Other agents have also been shown to be of similar efficacy to cefotaxime, such as amoxicillin and clavulanic acid (250mg/125mg) three times daily, and ceftriaxone 2g per day. Prophylaxis against SBP is recom-

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**Table 2: Therapeutic options in the management of hepatic disorder complications**

<table>
<thead>
<tr>
<th>Pruritus</th>
<th>Bleeding varices</th>
<th>Encephalopathy</th>
<th>Ascites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colestyramine</td>
<td>Octreotide infusion</td>
<td>Lactulose</td>
<td>Paracentesis (drainage of ascites through a cannula placed in the peritoneal cavity)</td>
</tr>
<tr>
<td>Ursodeoxycholic acid</td>
<td>Varical banding/ sclerotherapy</td>
<td>Metronidazole</td>
<td>Sodium and fluid restriction</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Tamponade (limited duration)</td>
<td>Transplantation</td>
<td>Spironolactone Addition of furosemide</td>
</tr>
<tr>
<td>Naloxone</td>
<td>TIPS or surgical shunt (in transplant candidate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Transplantation (earlier in primary biliary cirrhosis patients)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TIPS = Transjugular intrahepatic portosystemic shunts

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**Sodium and fluid restriction**

- **Sodium and fluid restriction** is important in the management of ascites. A sodium intake of 22mmol Na+ per day is recommended, with a fluid intake restricted to 2L per day. Loop diuretics such as furosemide (40mg per day) are initially used, with titration to achieve a maximum daily weight loss of 0.75kg per day. However, more aggressive weight reduction should be avoided, as it may lead to intravascular fluid depletion.

**Immediate treatment of ascites**

- **Immediate treatment of ascites** is essential in the management of SBP. The immediate use of antibiotics is critical, with a combination of cefotaxime (2g given eight-hourly) and ampicillin (2g given every six-hourly) being recommended. Other agents such as ceftriaxone (2g per day) and imipenem (500mg every eight-hourly) can also be used.

**Long-term management of ascites**

- **Long-term management of ascites** involves the use of diuretics, with a combination of furosemide (20–40mg per day) and spironolactone (25–50mg per day) being recommended. Other agents such as torasemide (10–20mg per day) and amiloride (5mg per day) can also be used.

**Complications of ascites**

- **Complications of ascites** include peritonitis, respiratory failure, renal failure, and concurrent infections. The management of these complications involves the use of antibiotics and supportive care, with a focus on maintaining fluid balance and preventing electrolyte imbalances.

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11. Cefotaxime 2g given eight-hourly has been shown to be effective in 85 per cent of patients with SBP, compared with the combination of tobramycin and ampicillin, which is effective in 56 per cent of patients. Other agents have also been shown to be of similar efficacy to cefotaxime, such as amoxicillin and clavulanic acid (250mg/125mg) three times daily, and ceftriaxone 2g per day. Prophylaxis against SBP is recom-
mended in patients with a low protein level in their ascites (less than 10g per litre), and in patients with previous episodes of SBP or gastrointestinal haemorrhage, because they are particularly susceptible to SBP. Studies of long-term use have indicated that nor-floxacin 400mg per day reduced the chance of recurrence of SBP from 68 per cent in the control group to 20 per cent in the active treatment group.

### ENCEPHALOPATHY

Encephalopathy is a major neuro-psychiatric complication of cirrhosis. The earliest manifestation of this slowly progressive condition is altered sleep pattern, which eventually progresses to coma. Common precipitating factors include gastrointestinal bleeding, SBP, constipation, dehydration, hypokalaemia, sedative use, and a high oral protein load.

Previous biochemical studies all point towards increased brain ammonia levels as the main factor in the multifactorial aetiology of encephalopathy. Neomycin, which was the traditional treatment, has largely been abandoned because of the toxicity associated with chronic usage. Metronidazole is sometimes used as an alternative to neomycin. Restriction of dietary protein is standard practice but protein intake should not be less than 1g per kg per day.

Non-absorbable disaccharides such as lactulose or lactitol are routinely used to decrease ammonia production in the gut. They alter the handling of nitrogen within the intestine by decreasing transit time and increase nitrogen fixation by bacteria in the colon, thus increasing the soluble nitrogen output in the faeces. Lactulose is given in doses of 30–40ml per day, titrated to produce two or three bowel motions daily.

An alternative strategy for lowering blood ammonia is the stimulation of ammonia fixation. Randomised controlled clinical trials have shown L-ornithine–L-aspartate (OA) to be effective in lowering blood ammonia and producing an improvement in psychometric test scores in cirrhotic patients with hepatic encephalopathy. Sodium benzoate has also been found to reduce blood ammonia. Significant improvements in neuropsychiatric status have been reported with the benzodiazepine receptor antagonist, flumazenil, although the effect is with actively bleeding varices. It was associated with significant systemic vasocnstrictive adverse effects and was reported to be effective in approximately 50 per cent of patients. The combination of nitrates and vasopressin ameliorates some of the systemic side effects of vasopressin, notably coronary vasoconstriction. Randomised trials have questioned the efficacy of vasopressin because it has no effect on mortality rates.

The synthetic vasopressin analogue, terlipressin (glypressin), has been found to be highly effective in controlling bleeding and in reducing mortality. It has a longer biological activity and a more favourable side effect profile than vasopressin.

Somatostatin causes selective splanchnic vasoconstriction and decreases portal pressure without adverse effects on the systemic circulation. Octreotide is a somatostatin analogue which has been shown to reduce portal pressure in animals, but no improvement in survival or control of bleeding has been shown in a large randomised clinical trial comparing it with placebo. The results of clinical trials that assessed the efficacy of lanreotide, another somatostatin analogue that could potentially cause more aggressive lowering of portal pressure, are being awaited.

Endoscopic variceal sclerotherapy has largely been superseded by varical band ligation. Other measures include injection of cyanoacrylate or bucrylate, which are tissue adhesives that have reportedly controlled bleeding in about 90 per cent of cases. However, there were significant reports of rebleeding (similar to those of sclerotherapy) and other complications in the form of cerebrovascular accidents related to injection of tissue adhesives.

Balloon tamponade (compression) with a Sengstaken (oesophageal and gastric balloon) or Linton (gastric balloon) can control bleeding in up to 90 per cent of cases, although about 50 per cent rebled when the balloon is deflated. The role of tamponades is to secure haemostasis in severe cases for short periods until alternative approaches are available. However, they are associated with serious complications such as oesophageal rupture and ulceration, as well as respiratory complications such as aspiration pneumonia. Nevertheless, they have a life-saving role in cases of massive uncontrolled varical haemorrhage.

TIPS has been shown to be highly effective in the management of uncontrolled varical haemorrhage. It has been shown that TIPS can be performed successfully in this situation with rapid control of bleeding. The main problems are the limited availability of this procedure, shunt stenosis or occlusion in up to 25 per cent of cases and encephalopathy in up to 30 per cent of patients.

### FORMS OF LIVER DISEASE

Chronic liver disease includes conditions such as primary biliary cirrhosis, primary sclerosing cholangitis, auto-immune liver disease, viral hepatitis, alcoholic liver disease and Wilson’s disease.

Primary biliary cirrhosis Primary biliary cirrhosis (PBC) is a presumed auto-immune, chronic cholestatic disease of the liver. PBC is caused by granulomatous destruction of the interlobular bile ducts and it predominantly affects middle-aged women. Most cases (60 per cent) are diagnosed when asymptomatic, with abnormal liver biochemistry and/or the presence of antimitochondrial antibodies. The cholestatic associated with PBC is generally slowly progressive until cirrhosis and liver failure occur.

**Treatments** Treatments for PBC over the past 30 years have included anti-inflammatory, immunosuppressive, anticholestatic and anti fibrin drugs, but a specific effective treatment remains elusive. Liver transplantation is the treatment of choice for end-stage disease and the best results are obtained when it is performed before the serum bilirubin exceeds 150–170µmol per litre.
Serum values for vitamins A and E have been shown to be low in a minority of patients before they develop jaundice. They can be treated by supplementation with tocopherol (vitamin E). Parenteral vitamin K (10mg) can be administered parenterally to correct a coagulopathy secondary to vitamin K deficiency. It is important to bear in mind that fat-soluble vitamin replacement in patients with hyperbilirubinaemia is best given in the water-soluble form of the fat-soluble vitamins.

Osteoporosis is usually associated with PBC and appears to be aggravated by the use of corticosteroid therapy. It is unclear whether osteoporosis can be prevented or treated satisfactorily in patients with PBC. However, evidence suggests that women who use hormone replacement therapy have a lower risk of osteoporosis than those who do not. The transdermal administration of oestrogens may be more appropriate in post-menopausal women with chronic cholestasis. Therapy with a bisphosphonate has been shown to prevent steroid-induced osteoporosis in PBC.

The total serum cholesterol may be elevated in patients with PBC. It tends to decrease with disease progression and is significantly reduced by treatment with UDCA. Fractionation of the triglyceride fractions shows high-density lipoprotein levels to be greater than low-density lipoprotein levels, and treatment with UDCA further lowers low-density lipoprotein and increases high-density lipoprotein values. Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors have been shown to be beneficial in reducing levels of cholesterol, and even bile acids, in some studies.

UDCA can be used to delay disease progression. It increases the rate of transport of intracellular bile acids into the canaliculus in patients with both PBC and primary sclerosing cholangitis (PSC, see below). It is a safe drug, with diarrhoea being its most prominent side effect. The once-daily or divided doses of 10–15mg per kg per day, given after a meal, have shown some benefit on the biochemical markers of cholestasis. It has also been shown that once-daily or twice-daily dosing may be more effective than evening doses. UDCA is widely used at a dose of 10–15mg per kg per day. It has consistently improved liver tests in several controlled trials but unfortunately none of these studies showed an improvement in the natural history of the disease. The use of steroids or immunosuppressive agents has not been highly successful except in children.

Auto-immune liver disease

The International Auto-immune Hepatitis Group (IAIHG), the main group involved in the study of AIH, has described criteria to aid the physician in diagnosing patients with definite or probable auto-immune hepatitis (AIH). This diagnosis of AIH is based on liver histology, serum biochemistry, and the presence of certain immunoglobulins and autoantibodies. Seronegativity for hepatitis B and C are necessary, as well as the absence of other aetiological factors such as alcohol consumption and exposure to hepatotoxic drugs.

The disease predominantly affects females, and the distribution of age at onset is bimodal (in puberty and again between the fourth and sixth decades). The disease can present at any age in males. There are no features of AIH which are indicative of it, but the condition tends to respond to corticosteroid therapy. A minority of patients may present with a severe, acute, uncontrollable hepatitis for which the only treatment is liver transplantation.

Treatment

Treatment is aimed at inducing remission. Corticosteroids, with or without azathioprine, are the mainstay of treatment in this condition. The initial dose to achieve remission has been variable but in general, high doses are no more effective than prednisolone at a dose of 0.5mg per kg per day. Azathioprine is usually started at a dose of 1–2mg per kg per day for its steroid-sparing effect. Remission cannot be induced by azathioprine alone. The transaminases, such as aspartate transaminase, are monitored initially on a weekly basis to assess response to therapy, and full blood counts (FBCs) are carried out regularly to detect azathioprine-induced myelosuppression.

The main aim of treatment is to achieve complete remission as early as possible and then to prevent relapses, as each relapse and associated liver damage is believed to hasten the progression to cirrhosis or exacerbate existing cirrhosis. Once biochemical remission has been achieved, it is important to ensure that this is confirmed by liver biopsy, as less than half of cases in apparent remission on the basis of biochemical parameters are confirmed histologically. AIH is a naturally fluctuating condition and patients who appear to be stable or in remission can have periodic flare-ups at any time. Alternative agents have been used for immunosuppression in AIH and these are as diverse as tacrolimus, ciclosporin, cyclophosphamide, mycophenolate mofetil, budesonide, D-penicillamine and UDCA.

Hepatitis B infection

Hepatitis B virus (HBV) infection is one of the commonest infectious diseases in the world, and is estimated to affect more than two billion people. Patients with chronic HBV infection can remain asymptomatic for long periods. However, it is estimated that 2 per cent of patients with chronic HBV infection develop cirrhosis each year, and 15–25 per cent of patients with chronic HBV infection will die prematurely from cirrhosis or hepatocellular carcinoma (HCC).

The detection of HBV-DNA in patients means that viral replication is occurring. Furthermore, the presence of hepatitis B e antigen (HBeAg) in the serum indicates active replication of the virus in the liver, while anti-HBe implies that replication is occurring at a much lower level or that viral deoxyribonucleic acid (DNA) has become integrated into hepatocyte DNA. Treatment is therefore aimed at the conversion of patients from a high to a low replication phase as evidenced by HBsAg seroconversion to anti-HBe with loss of detectable serum HBV-DNA. This end-point is associated with lowered or normal alanine aminotransferase (ALT) levels and reduced hepatic inflammation. The long term objective of antiviral therapy is to delay or prevent histological progression to cirrhosis and/or HCC and thus increase survival.

Interferon alfa-2b

Interferon alfa-2b is currently recommended for patients with compensated chronic HBV with detectable hepatitis B surface antigen (HBsAg), HBeAg, and HBV-DNA in the serum. Inter-
Lamivudine Lamivudine is a nucleoside analogue that inhibits viral DNA synthesis. It is absorbed from the gastrointestinal tract and is prescribed as a once-daily preparation of 100mg to achieve maximal suppression of serum HBV-DNA. Lamivudine is a nucleoside analogue that inhibits viral DNA synthesis. It is an effective therapy in most patients and hepatic transplantation is curative in individuals presenting with irreversible liver failure. Lamivudine can be discontinued in some Childs-Pugh A patients may deterio-
rate during therapy, necessitating withdrawal of interferon. Patients are monitored every one to four weeks depending on their tolerance to ther-
apy and the severity of disease. Markers for HBV should be obtained at baseline, at the end of treatment and 12 months later to assess response to therapy. Some side effects of interferon are common but manageable (eg, influenza-like symptoms), but others necessitate dose reduction or discontinua-
tion of therapy (eg, thrombocytopenia and depression).

Lamivudine Lamivudine is a nucleoside ana-
logue that inhibits viral DNA synthesis. It is absorbed from the gastrointestinal tract and is prescribed as a once-daily preparation of 100mg to achieve maximal suppression of HBV-DNA. Lamivudine is renally excreted and caution must be exercised in patients with renal impairment, but no clinically sig-
ificant drug interactions have been reported. Lamivudine has demonstrated effi-
cacy in the treatment of HBeAg-positive chronic HBV. This efficacy is manifested as improved histology, HBeAg seroconversion, suppression of serum HBV-DNA and nor-
malisation of serum ALT levels.

Studies have demonstrated that most patients who achieved HBeAg seroconver-
sion also lost detectable HBV-DNA and a significant proportion of patients showed an improvement in liver histology.77 Serum HBV-DNA levels fell rapidly and remained at least 94 per cent below baseline values during the administration of lamivudine.77 Serum ALT levels also fell, and 50 per cent of patients achieved and maintained normal ALT levels two years after therapy. There was up to a 33 per cent rate of loss of HBeAg for patients receiving lamivudine for three years.77 Lamivudine can be discontinued in patients who achieve HBeAg seroconver-
sion. Patients in whom lamivudine has been discontinued before achieving loss of HBeAg or HBeAg seroconversion revert to serum ALT levels that are in the pretreat-
ment range or higher. Partial resistance to lamivudine occurs through the development of mutations in 7–10 per cent of patients per year of therapy. However, there appears to be some benefit from continuation of therapy in these patients.

One advantage that lamivudine has over interferon is that it does not precipitate hepatic decompensation. It is now the drug of choice in the treatment of chronic HBV infection with end-stage liver disease and can serve as a bridge to transplantation for decompensated cirrhotic patients.79,80 It is now also the first line agent in the treatment of recurrent HBV infection when passive immunisation with hepatitis B immunglobulin (HBlg) fails.79,80 It is not yet established whether lamivudine prophylaxis after transplantation can replace or reduce the need for the more expensive HBlg.80

Hepatitis C infection The primary aim of therapy for patients with hepatitis C virus (HCV) infection is viral eradication, defined as undetectable HCV-ribonucleic acid (RNA) six months after termination of anti-
viral therapy. Secondary goals of antiviral therapy include slowing of disease progres-
sion, improvement in liver histology, prevention of HCC and improvement in quality of life.

Patients with abnormal liver enzymes or detectable HCV-RNA should have a liver biopsy and the presence of significant fibro-
sis or necro-inflammatory activity identifies the candidates for antiviral treatment. Treat-
ment of HCV infection has improved significantly since the introduction of comb-
ined interferon-alfa and ribavirin therapy in 1998. Factors associated with an unfavourable response to therapy include HCV genotype 1, high viral load, and liver cirrhosis. Patients with these features contin-
ue to have sustained response rates of less than 30 per cent.

The standard combination therapy for HCV infection comprises interferon-alfa (3MU three times per week) and ribavirin (1,000–1,200mg per day) for 6–12 months. The development of polyethylene glycol (PEG) interferon has improved treatment outcomes even further. Clinical trials of once-weekly dosing with PEG interferon,82 when given alone or in combination with ribavirin,82 have produced sustained virolog-
ic response rates of greater than 50 per cent. PEG interferon has also given encouraging response rates for patients with liver cirrho-
sis.83 It is not yet clear if PEG interferon should be combined with ribavirin.84

Alcoholic Liver disease Apart from absti-
ence, there are few specific treatments for alcohol-related liver disease. Treatment with prednisolone 30–40mg per day for 28 days has shown to improve short-term sur-
vival in patients with severe biopsy-proven acute alcoholic hepatitis.85 A similar benefit has also been described with pentoxifylline, an inhibitor of tumour necrosis factor, at a dose of 400mg three times daily.86

Other therapies that have been used to a lesser degree include anabolic agents (oxan-
drolone), colchicine, and antioxidants (polyenylphosphatidylcholine [PPC], sily-
marin, alpha-tocopherol, selenium).

Wilson's disease Wilson's disease is an autosomal recessive disorder of copper metabolism. It can present as chronic hepati-
tis, asymptomatic cirrhosis, acute liver failure, as well as neuropsychiatric symptoms and cognitive impairment. Copper chelation is an effective therapy in most patients and hepatic transplantation is curative in individu-
als presenting with irreversible liver failure. Penicillamine is the agent of choice in sys-
temic chelation therapy. It promotes urinary copper excretion in affected patients and prevents copper accumulation in presym-
tomatic individuals.87,88 The initial treatment dose of 1.5–2g per day is given in divided doses. Most patients will be asymptomatic within four months, but neurological symp-
toms may worsen initially due to deposition of mobilised copper in the basal ganglia. Other potentially serious adverse effects include renal dysfunction, haematological abnormalities and disseminated lupus ery-
thematosus. As a result, regular full blood counts and electrolyte analyses are required, along with small doses of pyridoxine (25mg) to counteract the antipyridoxine effect of penicillamine. Triethylenetetramine dihydrochloride (trientine) is an alternative chelating agent. It is usually given at a dose of 1.2–2.4g daily in two to four divided doses before food. Although somewhat less effective than peni-
cillamine in removing copper, significant improvement has been reported in many patients.89,90 Zinc acetate is also useful, but works slowly and has been used primarily in maintenance therapy. It is relatively free from adverse effects and a dose of 75mg must be divided into at least two doses to be effec-
tive. In addition to chelation therapy, zinc salts can also be added to the therapeutic regimen to prevent copper absorption.

References


