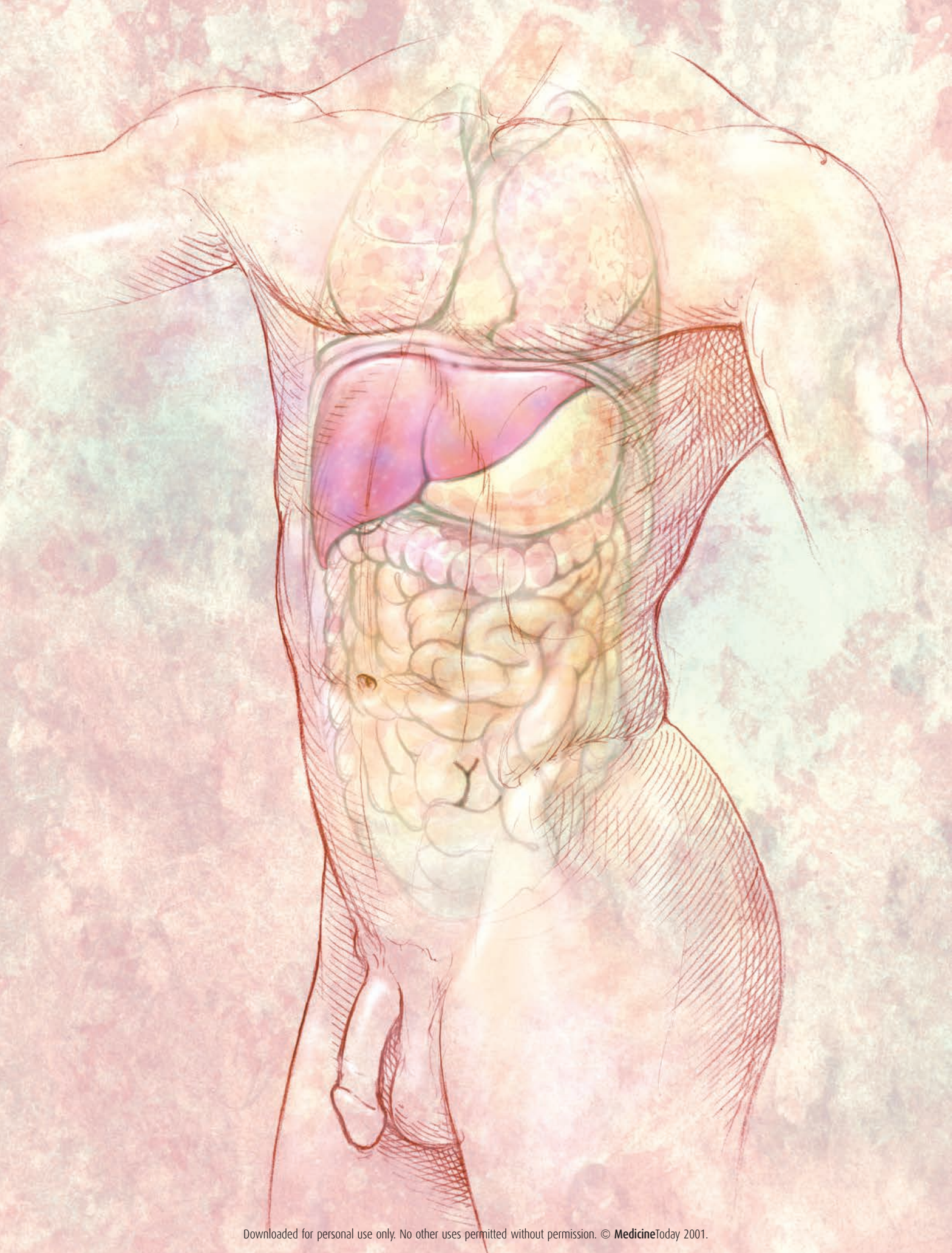

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Diagnosis and management of chronic liver disease

Many chronic liver diseases have specific therapies according to the underlying diagnosis. This article updates GPs on the diagnosis and management of these diseases, even though GPs may not be directly involved at the acute stage.

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Chronic liver disease is defined by the presence of either abnormal serum liver function tests (LFTs) or signs or symptoms of liver disease for longer than six months. Established cirrhosis may have similar presenting clinical signs and common issues in general management irrespective of the primary diagnosis.

This article discusses the diagnosis, clinical features and treatments of the major causes of chronic liver disease and outlines the latest management approaches.

Clinical presentation

History

Liver disease is usually suspected when abnormal liver function tests are found on routine investigation of asymptomatic patients, those with risk factors (see Table 1) or those being investigated for undiagnosed serious illness, and when patients present with suggestive symptoms or signs.

Patients with chronic liver disease may be asymptomatic. This includes 30 to 40% of cases of cirrhosis. The patient may complain of fatigue, weight loss, nausea, anorexia, jaundice, abdominal pain and change in the colour of the urine or stool. Loss of libido, swelling of the legs or abdomen, or gastrointestinal tract haemorrhage may be the presenting symptom of previously undiagnosed advanced liver disease. Table 1 lists the topics to be covered when taking the history.

Table 1. Suspected chronic liver disease: important topics in history taking

- Alcohol consumption (average grams/day)
- Regular medication (including herbal preparations)
- Recreational drug use (particularly intravenous)
- Sexual contacts and practices
- Tattooing/body piercing/acupuncture
- Family history of liver disease
- Overseas origin and residence, and travel
- Blood transfusion

Examination

Many patients with chronic liver disease may have a normal physical examination or only minimal features such as occasional spider naevi. However, the clinical signs of chronic liver disease may be

IN SUMMARY

- **The most common causes of chronic liver disease are fatty liver, alcohol, viral hepatitis and drug toxicity.**
- **A routine initial approach to investigation helps both diagnosis and treatment decisions.**
- **General management includes dietary and vaccination considerations.**
- **Specific treatment varies with the primary disorder and can significantly improve prognosis.**
- **Sudden weight loss in patients with fatty liver can precipitate worsening LFTs.**
- **Evidence of decompensation is associated with decreased survival.**
- **Liver transplantation provides good outcomes in selected patients.**

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Table 2. Chronic liver disease: clinical signs

- Muscle wasting
- White nails
- Pigmentation
- Palmar erythema
- Spider naevi
- Gynaecomastia
- Hepatosplenomegaly
- Testicular atrophy

specific, such as the Kayser–Fleischer pericorneal pigment rings of Wilson's disease. Table 2 lists clinical signs of significant chronic liver disease. Parotid enlargement and Dupuytren's contracture suggest an alcoholic aetiology.

Advanced cirrhosis leads to portal hypertension and hepatic failure, which may be manifested by jaundice, ascites, hepatic foetor and asterixis, hepatic encephalopathy and variceal bleeding.

Aetiology

The more important causes of chronic liver disease are listed in Table 3.

Table 3. Chronic liver disease: aetiology and investigations

Fatty liver (including non-alcoholic steatohepatitis)
Risk factors, imaging, biopsy

Alcohol
History, biopsy

Viral – hepatitis B, C and D
Viral serology

Metabolic disorders
Haemochromatosis
Iron studies, *HFE* gene test
Wilson's disease
Serum copper, caeruloplasmin
Alpha-1-antitrypsin deficiency
Serum alpha-1-antitrypsin

Chronic cholestasis
Primary biliary cirrhosis
Antimitochondrial antibody (AMA), biopsy
Primary sclerosing cholangitis
Endoscopic retrograde cholangiopancreatography

Autoimmune hepatitis
Antinuclear antibody (ANA), antismooth muscle antibody (SMA), immunoglobulins, biopsy

Venous obstruction, e.g. Budd–Chiari syndrome
Imaging

Drugs
History, biopsy

Cryptogenic

Investigation

Patients suspected of having chronic liver disease need investigation to assess their liver function and make a primary diagnosis. The flowchart on page 75 summarises the steps to investigation.

Haematology

A blood count and coagulation studies should be performed to exclude anaemia, thrombocytopenia or coagulopathy.

Liver function tests

LFTs may diagnose the type of chronic liver injury – hepatocellular or cholestatic – but not the underlying disorder.

Hepatocellular injury is characterised by elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and often also elevated gamma glutamyltransferase (GGT). Possible diagnoses include steatohepatitis, chronic viral hepatitis, alcoholic liver injury, metabolic liver disease, autoimmune hepatitis and drug toxicity.

Cholestasis is characterised by elevated serum alkaline phosphatase (ALP) and GGT, and primary diagnoses include biliary obstruction, primary biliary cirrhosis, primary sclerosing cholangitis, drug toxicity, primary and secondary neoplasms and infiltrative disorders such as amyloidosis, granulomas and lymphoproliferative disease. Isolated mild hyperbilirubinaemia may be due to Gilbert's syndrome, a congenital and benign disorder of bilirubin metabolism that is characterised by further elevation of unconjugated (indirect) serum bilirubin in the fasting state or with intercurrent infection.

Deteriorating liver function may be marked by an elevated serum bilirubin, low albumin and prolonged prothrombin time. A raised serum alpha fetoprotein may signify a complicating hepatocellular carcinoma.

Imaging

Imaging can detect abnormalities such as bile duct obstruction and primary and secondary neoplasms. Ultrasound is a convenient examination that is particularly useful for the detection of common bile duct dilatation and differentiation of cystic and solid lesions. Fatty liver may show increased echogenicity on ultrasound, but this finding is not diagnostic and other infiltrative disorders may give a similar appearance.

CT scans provide better resolution of the hepatic parenchyma than ultrasound, particularly in obese patients or when there is excessive bowel gas.

Specific tests

Although the clinical presentation or the pattern of LFT abnormalities or both should indicate how to proceed with management, specific tests are needed to exclude all aetiologies (see the flowchart on page 75). Of note, iron studies are performed to exclude haemochromatosis, for which an elevated transferrin saturation is the most useful initial marker. The diagnosis of haemochromatosis can be confirmed with a further blood test for the *HFE* gene.

Levels of serum copper and caeruloplasmin are usually reduced in Wilson's

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disease; urinary copper excretion and liver copper concentration (on biopsy) are performed for confirmation.

If ascites is present, a diagnostic tap should be routinely performed (in hospital) for a cell count, culture, protein concentration and cytology. A serum:ascitic albumin difference (that is, serum albumin minus ascitic albumin) of 11 g/L or more suggests that the fluid is a transudate associated with portal hypertension, and a difference of less than 11 g/L may indicate infection or malignancy (the latter is particularly likely in the presence of normal liver function).

Biopsy

Liver biopsy provides the ultimate examination of liver disease. It is mandatory in the assessment of autoimmune hepatitis and before treatment in chronic viral hepatitis. It may be required if a primary diagnosis is in doubt and histological information would be likely to influence treatment. It carries a small but significant risk of major bleeding (0.2%) and is now increasingly being performed under ultrasound guidance, routinely carried out as a day-stay admission.

General management issues

Diet

Patients with fatty liver often require correction of high fat intake, excess alcohol consumption and hyperlipidaemia. Weight reduction must be gradual as a precipitous fall can rarely induce liver failure.

Cirrhotic patients are often nutritionally deficient and have increased protein and total calorie requirements. A well-balanced diet providing a daily intake of 60 to 80 g of protein a day (about 1 g/kg) is advisable. As there is an impaired ability to store hepatic glycogen, carbohydrate-rich meals throughout the day may also be beneficial.

In decompensated cirrhosis, the classical teaching has been that the patient is protein intolerant despite often being protein deficient, and that excess protein in this case may precipitate hepatic encephalopathy. There is increasing evidence that only those patients with a large portosystemic shunt are susceptible to this problem and that protein restriction, even in the presence of encephalopathy, may be detrimental.

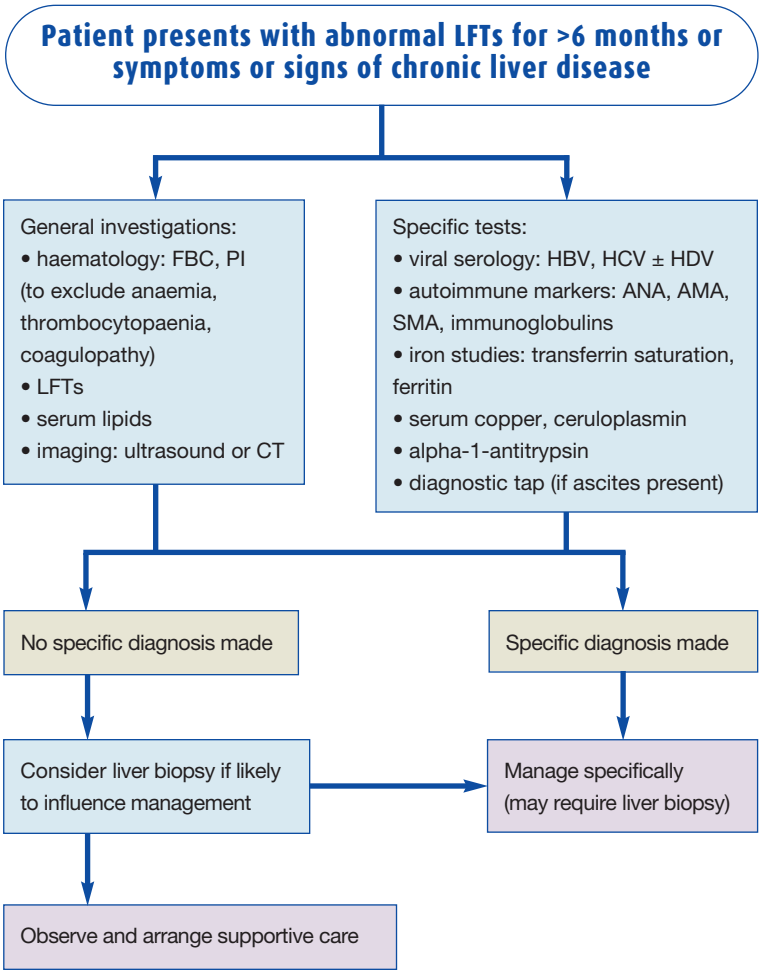
Branched chain amino acids have been used as an alternative nitrogen source in chronic liver disease patients as they have an anticatabolic effect.

Infectivity and sexual transmission

Patients who are positive for hepatitis B virus (HBV) surface antigen can transmit the virus to their partners, who should be vaccinated if they are surface antibody negative. Hepatitis C virus (HCV) appears to have a low risk of sexual transmission, but safe sex practices should be followed with casual contacts.

The blood of hepatitis B, C or D patients is infectious and patients should not share razors, toothbrushes, tweezers or the like.

Investigation of chronic liver disease



AMA = antimitochondrial antibody; ANA = antinuclear antibody; FBC = full blood count; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; LFTs = liver function tests; PI = prothrombin index; SMA = antismooth muscle antibody

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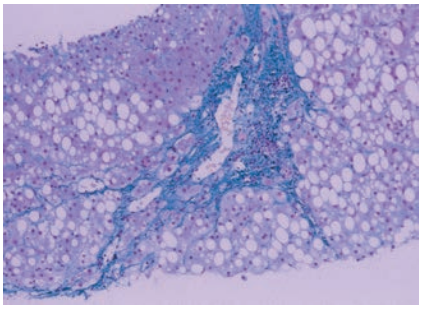

Figure 1. Fatty liver – large areas of fat deposition with Masson stain showing fibrosis.

Impotence and loss of libido are symptoms of cirrhosis, particularly in alcoholics. Abstinence from alcohol may improve these symptoms. Although hypogonadism is common in men, the administration of testosterone is not beneficial.

Oral contraceptive use and hormone replacement therapy should be closely monitored as both may cause cholestasis. The preferred administration of hormone replacement therapy in chronic liver disease is by cutaneous patches.

Vaccination

Acute hepatitis A or B in patients with pre-existing chronic liver disease may carry an increased risk of morbidity or mortality compared with that in patients without pre-existing chronic liver disease. This has particularly been observed if HAV infection is superimposed on chronic hepatitis B or C or other forms of chronic liver disease. Co-infection with more than one hepatitis virus is associated with more severe liver disease, and multiple co-infections may lead to fulminant hepatitis.

It is recommended that patients with chronic liver disease be vaccinated against hepatitis A and B. The available vaccines (Havrix 1400, VAQTA Hepatitis A Vaccine Inactivated, Twinrix, Engerix-B, H-B-Vax II) are safe and immunogenic in patients with mild to moderate chronic liver disease without decompensation. However, they have uncertain efficacy (hepatitis A vaccine) or poor immunogenicity (hepatitis B vaccine) in patients with advanced cirrhosis and in liver transplant patients.

Patients should have viral serology performed before vaccination as some may be carriers (hepatitis B) or already immune from previous exposure.

Management of underlying disorders

The latest approaches in management are outlined below.

Alcohol

Abstinence from alcohol remains the definitive approach. Dietary protein and vitamin supplementation is usually required. Withdrawal syndromes should be anticipated in heavy drinkers.

Fatty liver

Fatty liver (steatosis) is one of the most common causes of abnormal LFTs and is associated with alcohol consumption, obesity, diabetes and hyperlipidaemia (Figure 1). It usually has a benign non-progressive course.

Nonalcoholic steatohepatitis (NASH), however, may progress to fibrosis, and even cirrhosis and liver failure. It is being increasingly recognised, the differentiation from steatosis being made by histological features in the absence of alcohol. Controlled weight reduction, correction of hyperlipidaemia and diabetic control are the mainstays of therapy but may not prevent progression. The use of lipid lowering agents should be monitored closely as they can themselves induce LFT abnormalities (usually hepatitic).

Chronic hepatitis C

The objective in chronic viral hepatitis C treatment is to prevent progression to cirrhosis and its complications, including hepatocellular cancer and liver failure. Symptoms at presentation often include fatigue or right upper quadrant pain. Excessive alcohol (more than 50 g per day) will increase the rate of progression. Standard treatment has been monotherapy with interferon-alfa (Roferon-A, Intron A) for six to 12 months, but there is a high relapse rate in responders after treatment cessation and only 5 to 15% of patients achieve a sustained virological response (that is, remain HCV-RNA-negative).

Combination therapy with interferon-alfa-2b and the nucleoside analogue ribavirin (Rebetron Combination Therapy) is now the initial treatment of choice and is also used for those patients who relapse after interferon alone. Long term follow up data after combination therapy are not yet available, but results so far suggest a sustained response rate at least two to three times higher in treatment-naïve patients and up to 10 times higher in relapsers, compared to treatment with interferon alone. Factors associated with a poorer response to antiviral treatment include HCV genotype 1 (*v.* types 2 and 3) and a baseline viral load of two to three million copies per millilitre or more.

Chronic hepatitis B

Interferon-alfa used to be the standard treatment for chronic hepatitis B, with a response rate of 20 to 30% (that is, conversion of HBV e antigen to e antibody and loss of HBV-DNA). Newer oral nucleoside analogues include famciclovir (Famvir) and lamivudine (Zeffix). Lamivudine has shown efficacy at least equal to if not better than interferon, with the advantage of oral rather than subcutaneous administration. It induces seroconversion (e antigen to antibody) in about 20% of patients. However, lamivudine-resistant viruses are emerging, and future therapy is likely to be based on a combination of agents.

Autoimmune hepatitis

Features of autoimmune hepatitis range from acute hepatitis to established cirrhosis (Figure 2). Immunosuppression with either prednisone alone (Panafcort,

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Solone) or a combination of prednisone and azathioprine (Azahexal, Azamun, Imuran, Thioprine) leads to complete remission in about 65% of patients, and those with severe disease show improved survival. Azathioprine can be used as monotherapy once remission has been induced. Up to 80% of patients will relapse after treatment is stopped and maintenance therapy of low dose prednisone or azathioprine is usually required in the long term.

Primary biliary cirrhosis

About 90% of patients with primary biliary cirrhosis are female. Typical presentation includes pruritus, jaundice, elevated serum ALP and the presence of antimitochondrial antibody. Biopsy shows inflammatory destruction of small to medium-sized bile ducts (Figure 3). The only therapeutic option for end-stage primary biliary cirrhosis is liver transplantation and the terminal phase is defined by a serum bilirubin of greater than 100 μmol/L. Ursodeoxycholic acid (Ursofalk) may slow disease progression and improve transplant-free survival.

Primary sclerosing cholangitis

Characteristic symptoms of primary sclerosing cholangitis are fever and recurrent cholangitis associated with right upper quadrant pain and often jaundice. Diagnosis is by cholangiography. There is a strong association with ulcerative colitis, and cholangiocarcinoma occurs in 6 to 8% of patients. Liver transplantation is the only definitive therapy. The course of the disease is variable, with a mean survival of 12 years after diagnosis (without transplant). Aggressive endoscopic therapy with biliary stenting may give symptomatic improvement.

Haemochromatosis

Manifestations of haemochromatosis include fatigue, pigmentation, diabetes, arthropathy and hypogonadism. Weekly venesection remains the treatment of choice and 500 mL of blood removes about 250 mg of iron. Removal of increased iron stores before the development of cirrhosis allows normal life expectancy. Venesection continues until the transferrin saturation is less than 50%, serum ferritin is less than 50 μg/L and mild anaemia develops. Iron stores are then kept at the lower limit of normal (that is, serum ferritin in the range 5 to 100 μ/L) by maintenance venesection (usually required two to six times each year).

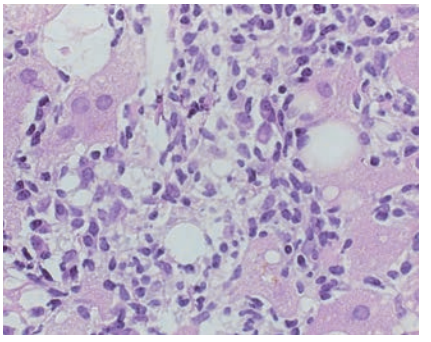
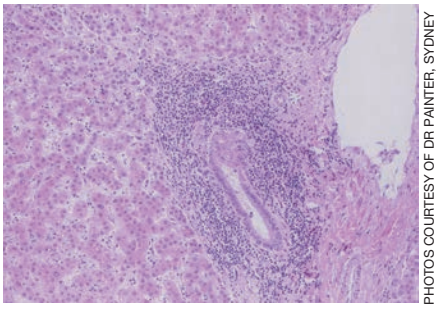


Figure 2. Autoimmune hepatitis – piecemeal necrosis (periseptal hepatitis).

The prolonged presymptomatic phase of haemochromatosis means that genetic screening should be performed in adult first-degree relatives of patients (see flowchart on page 80). The *HFE* gene contains two mutations, one of which (Cys282→Tyr, C282Y) is homozygous in over 85% of patients with hereditary haemochromatosis. The other mutation (His63→Asp, H63D) is not associated with the same degree of iron overload as the C282Y mutation. In Australia, about 1 in 200 people are homozygous for C282Y. Testing of neonates is not indicated at present and young children need only be screened if the parent without hereditary haemochromatosis has the C282Y or H63D mutation.

Venesection may be initiated without liver biopsy in patients homozygous for C282Y, less than 40 years of age and with normal LFTs as significant fibrosis is not found in patients under 40 years or with serum ferritin less than 1000 μg/L.



PHOTOS COURTESY OF DR PAINTER, SYDNEY

Figure 3. Primary biliary cirrhosis – inflammatory destruction of a small intrahepatic bile duct.

Wilson's disease

Acute hepatitis (particularly in children), cirrhosis and neuropsychiatric symptoms (such as tremor, dysarthria, dysphagia and behavioural abnormalities) may be presenting features of Wilson's disease. The condition most often presents in children or young adults but it also occurs in older patients.

Penicillamine (D-Penamine) promotes the urinary excretion of copper and is the drug of choice for acute treatment, although it may temporarily worsen neurological symptoms in some patients. Pyridoxine (vitamin B6) supplementation is recommended with penicillamine. Once a significant reduction in body copper has been achieved, oral zinc salts (which have a lower side effect profile than penicillamine) may be used to prevent intestinal absorption of copper.

Alpha-1-antitrypsin deficiency

Patients with alpha-1-antitrypsin deficiency will often present with cirrhosis. There is no specific treatment, but they should be encouraged to stop smoking, particularly in the presence of associated lung disease.

Drug-induced liver disease

Statins

HMG-CoA reductase inhibitors can induce transaminase elevation, which is mostly asymptomatic. This elevation usually occurs within the first 12 months

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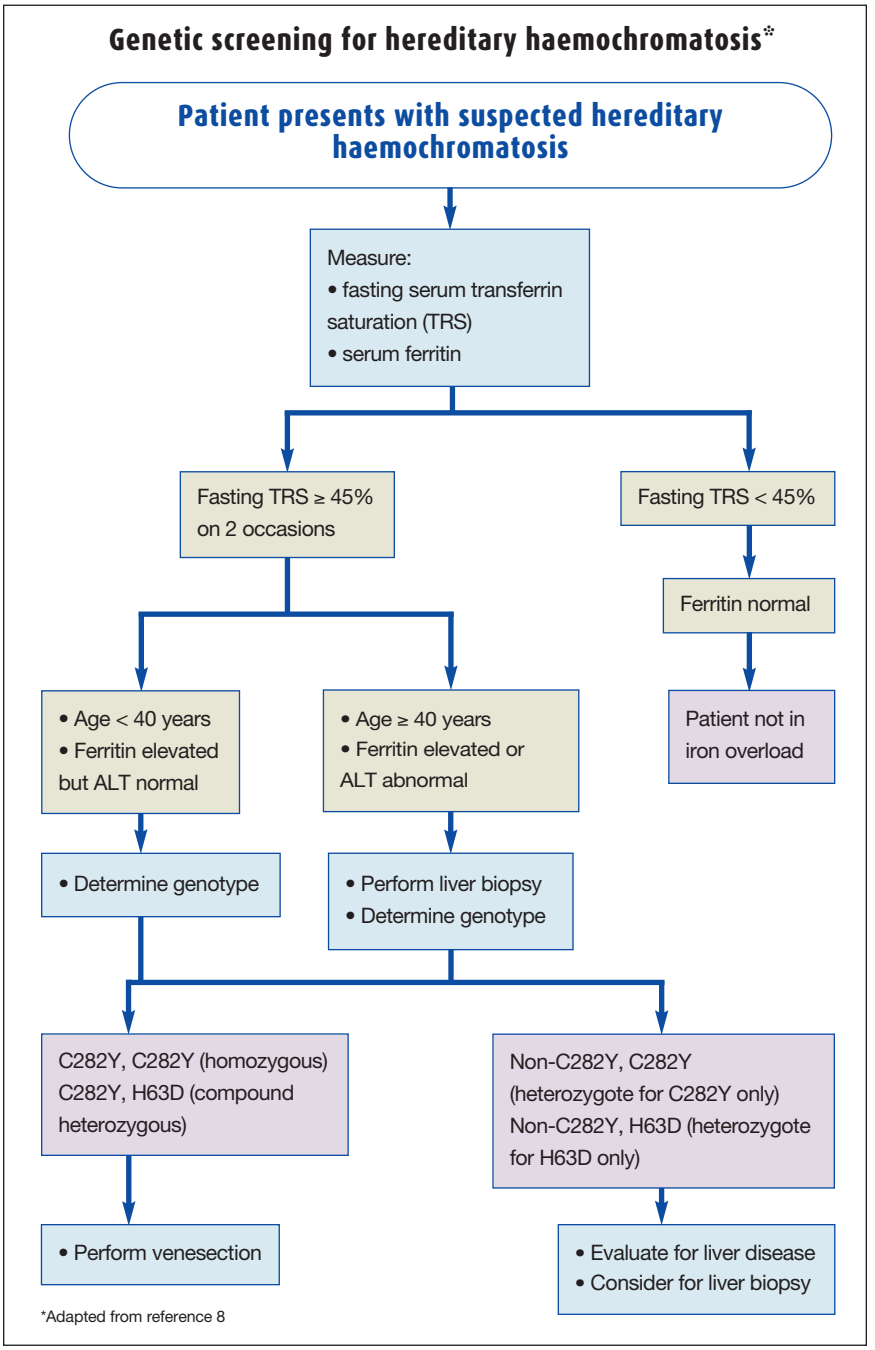

of treatment, is dose-dependent and subsides when the drug is stopped. Reports of overt hepatitis are rare. Abnormal liver biochemistry in fatty liver is not a contraindication to treatment (and may improve), although LFTs should be closely monitored.

Penicillins

Amoxicillin/clavulanic acid and flucloxacillin have been associated with protracted cholestatic hepatitis. This occurs most often in older patients and may present several weeks after the drug has been stopped. Nausea, fatigue, jaundice and pruritus are common, and markedly elevated transaminase and bilirubin levels may be observed. Complete recovery is usual but may take some months.

NSAIDs

NSAID-related hepatotoxicity usually manifests as asymptomatic transaminase elevation, although cholestasis and a mixed picture have also been observed. LFT abnormalities usually resolve with stopping of the drug. Severe hepatitis is very uncommon and fatal liver injury is rarely reported.

Antidepressants and anticonvulsants

Antidepressant medication (monoamine oxidase inhibitors, tricyclics and nontricyclics) and anticonvulsants can cause hepatocellular and cholestatic injury. LFT changes and symptoms (including those of hypersensitivity) usually resolve within eight weeks of stopping the drug, but may be prolonged.

Other drugs

Amiodarone is associated with both acute and chronic liver injury. Mild transaminase elevation is common, but prolonged abnormality or elevation two to three times the upper limit of normal requires either stopping of the drug or liver biopsy as insidious cirrhosis can occur.

Methyldopa and nitrofurantoin are two older drugs that have well documented liver toxicity. Both can induce asymptomatic and occasionally severe acute injury, and have also been associated with chronic hepatitis with autoimmune features.

Management of complications of decompensated cirrhosis

Variceal bleeding

Varices arising from portal hypertension are most often seen in the distal oesophagus and stomach but are occasionally found elsewhere – for example, the rectum, colon or colostomy sites (Figure 4a). Variceal bleeding is often massive and

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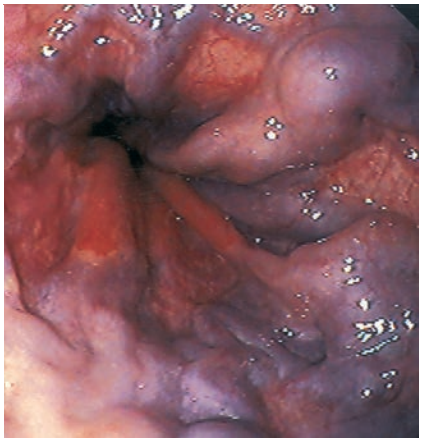

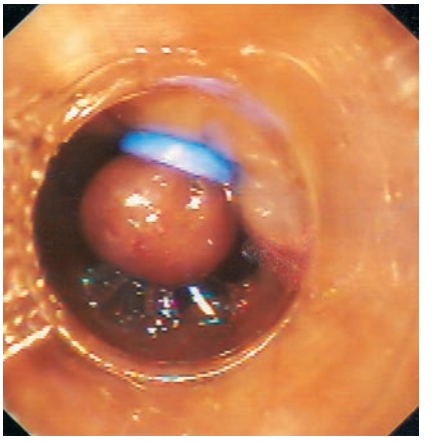

FIGURES 4A AND B COURTESY OF DR M. BOURKE, SYDNEY

Figures 4a and b. a (left). Large distal oesophageal varices. b (right). A banded oesophageal varix.

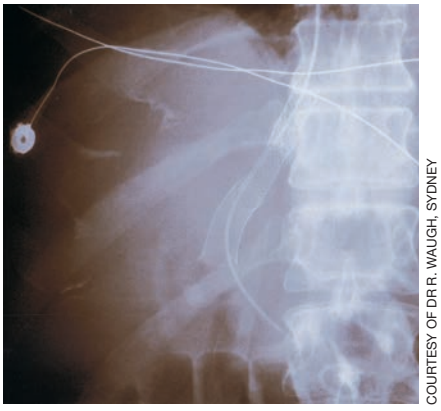

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Figure 5. Transjugular intrahepatic portosystemic shunt (TIPS). Plain x-ray showing the metallic TIPS stent *in situ*.

constitutes a medical emergency. Death may be due to shock or aspiration, or subsequent encephalopathy, infection or renal failure. Beta blockers, usually propanolol (Deralin, Inderal), are effective in primary prevention but may not affect survival.

Endoscopic banding ligation is now replacing endoscopic injection sclerotherapy because it is comparable or superior to the former procedure in arresting bleeding, and also has lower rates of rebleeding within one month and complications (Figure 4b). Other early treatments include balloon tamponade and intravenous splanchnic vasoconstrictors such as somatostatin. The use of tissue adhesives and thrombin to treat bleeding oesophageal or gastric varices requires further assessment.

Transjugular intrahepatic portosystemic shunt (TIPS) placement reduces portal pressure and is the procedure of choice in refractory variceal bleeding (Figure 5). It is performed by an interventional radiologist and can be undertaken in patients who are considered unfit for major surgery.

Ascites

The appearance of ascites in a cirrhotic patient carries a poor prognosis (about 20% five-year survival). The aim of medical treatment is the mobilisation of intra-abdominal fluid by creating a net negative sodium balance. The mainstays of therapy are dietary fluid and salt restriction, and oral diuretics. Caution is the rule as treatment can lead to intravascular fluid depletion, hyponatraemia, renal failure and encephalopathy. Fluid restriction (usually less than 1.5 L/day) is often required, and added salt should be avoided. Spironolactone (Aldactone, Spiractin), with or without frusemide, is used if diet alone is unhelpful or the volume of ascites demands more active treatment. The aim of diuretic therapy is to achieve a weight loss of 300 to 500 g/day. The patient should, therefore, weigh him/herself daily to help assess fluid loss.

Large volume paracentesis (in the order of 4 to 6 L/day) is often performed as a day-stay procedure, although it may not be appropriate for patients with severe liver failure. Peritoneovenous (LeVeen) shunts and TIPS have been used to treat refractory ascites but are associated with significant morbidity, particularly in patients with more advanced liver disease.

Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis is an infection of ascitic fluid due to bacterial translocation from the gut and reduced phagocytic and antimicrobial capacity. It is diagnosed on clinical suspicion (fever and significant abdominal pain or tenderness may be absent) and analysis of ascitic fluid, which will show a polymorph count above 250 cells/μl. The infection is mostly monomicrobial (usually coliforms or streptococci).

A third generation (intravenous) cephalosporin is the treatment of choice. Oral quinolones such as norfloxacin (Insensye, Norflohexal, Noroxin) are used in patients at high risk of developing spontaneous bacterial peritonitis, such as those hospitalised for gastrointestinal bleeding. Aminoglycosides are contraindicated. The long term prognosis is poor, with a one-year survival of 25 to 30%.

Hepatic encephalopathy

The level of hepatic encephalopathy ranges from mild confusion to coma, and typical signs include a flapping tremor (asterixis), slurred speech and constructional apraxia. The first sign may be a reversal of normal sleep patterns that can be worsened by sedative agents. There is almost always a precipitating factor. This must be looked for, and is often transient and reversible. Possible factors include gastrointestinal haemorrhage, dietary protein overload, infection (especially spontaneous bacterial peritonitis), constipation, dehydration and drug use (especially benzodiazepines).

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Treatment aims to reduce production and absorption of gut toxins such as ammonia using oral antibiotics – usually neomycin (Neosulf) – and a cathartic agent such as lactulose (Actilax, Duphalac, Genlac, Lac-Dol). Protein restriction is not essential unless there is a definite history of protein-induced symptoms.

Liver transplantation

Liver transplantation is well established as the ultimate treatment option for chronic liver disease that has progressed to poorly controlled liver failure. The leading single indication in adult patients is now chronic hepatitis C. Overall five-year survival approaches 80%, but individual survival outcomes vary.

Liver grafts may become reinfected in patients transplanted for chronic HCV infection. Recent advances in antiviral therapy have virtually abolished recurrent HBV infection post-transplant.

Autoimmune disease may also recur in the graft, but does not affect survival.

Summary

The diagnosis of chronic liver disease can be made in the asymptomatic patient by the observation of incidental abnormal liver biochemistry. Typical symptoms and signs may be present in various combinations. The most common causes are fatty liver, chronic viral hepatitis and alcohol.

The first step in management is to establish a primary diagnosis if possible, using appropriate blood tests, radiographic imaging and, perhaps, liver biopsy. Many liver diseases have specific therapies according to the underlying diagnosis. Signs of decompensation are associated with decreased survival. Liver transplantation is the final option in end stage disease, with good outcomes in appropriately selected patients. MT

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