Liver fibrosis and its end-stage cirrhosis is an enormous worldwide healthcare problem, causing more than 6000 deaths a year in the UK alone. Liver fibrosis represents the final pathological pathway in the development of many chronic liver diseases regardless of aetiology (box 1) and cirrhosis has previously been considered to be the stage at which fibrotic liver disease becomes irreversible. Cirrhosis can be defined histologically as ‘a diffuse process characterised by fibrosis and a conversion of normal architecture into structurally abnormal nodules’. The histological classification of cirrhosis depends on the size of these nodules, with micronodular cirrhosis being defined as having uniform nodules of less than 3 mm in diameter, whereas macronodular cirrhosis the majority of nodules are greater than 3 mm in diameter; a mixed nodularity may often exist. Cirrhosis may also be classified by aetiology; the two classifications are not mutually exclusive.

If the above histological definition of cirrhosis is reconsidered, two important concepts become apparent. Firstly, removal or control of the primary disease process may stabilise the cirrhosis, but the presence of architectural distortion leads to consequences that may not be directly related to the primary disease aetiology (eg, portal hypertension and oesophageal varices). Secondly, and perhaps more importantly, is the concept that fibrosis and cirrhosis represent a continuous pathological spectrum, characterised not only by an increase in total collagen and other matrix proteins compared with normal, but also qualitative changes in their nature and distribution within the liver. This concept is important because there is evidence that even comparatively advanced fibrosis can be reversed if the inciting stimulus is removed.

Pathogenesis of hepatic fibrosis/cirrhosis

Increasing evidence suggests that, regardless of the nature of the initial insult, the cellular mechanisms underlying hepatic fibrosis and cirrhosis are common, although the site of injury within the liver lobule may vary. For example, viral hepatitis initially causes periportal inflammation, whereas early injury in alcoholic liver disease is largely pericentral. Continued injury may, however, eventually lead to panlobular cirrhosis.

The hepatic stellate cell (also known as the lipocyte, Ito cell, perisinusoidal cell, or fat storing cell) has been clearly identified as the major cell type involved in matrix synthesis and metabolism, and therefore, as being pivotal in the pathogenesis of liver fibrosis/cirrhosis. In the normal liver, hepatic stellate cells (HSC) are situated in the subendothelial space of Disse and are primarily involved in retinoid storage. In areas of liver injury HSC proliferate, lose their retinoid droplets and are activated to a myofibroblast-like phenotype, the so-called ‘activated’ HSC. Studies in human liver disease and in various animal and cell culture models, have demonstrated that in this activated phenotype HSC are the major source of collagen and non-collagenous matrix proteins in fibrosis. Indeed mRNA transcripts for type I and type III collagen (which constitute the majority of the excess matrix protein that accumulates in fibrosis) are virtually confined to HSC, with little or no matrix mRNA being expressed by parenchymal cells. HSC have also been demonstrated to express a repertoire of enzymes from the metalloproteinase family which degrade excess collagen. Metalloproteinase activity has been shown to decrease in experimental fibrosis and specific tissue metalloproteinase inhibitors have been demonstrated to increase during fibrosis, suggesting that the control of matrix degradation, as well as synthesis, is fundamental to the development of cirrhosis.

The mechanisms controlling HSC activation and the factors regulating the synthesis and degradation of matrix proteins have thus become a principal area of research in liver fibrosis. The early events in HSC activation are potentially important targets for therapeutic intervention, but have only been partially elucidated. Hepatic macrophages (Kupffer cells) are probably key to HSC activation during injury. Kupffer cell products have been demonstrated to
Aetiology of cirrhosis

- drugs and toxins: alcohol, methotrexate, isoniazid, methyldopa
- infections: hepatitis B & C, Schistosoma japonicum
- autoimmune/immune-mediated: primary biliary cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis
- metabolic: Wilson's disease, haemochromatosis, α1-antitrypsin deficiency, porphyria (rarely glycogen storage diseases, galactosaemia, abetalipoproteinaemia, etc)
- biliary obstruction (secondary biliary cirrhosis): cystic fibrosis, atresia, strictures, gallstones
- vascular: chronic right heart failure, Budd-Chiari syndrome, veno-occlusive disease
- miscellaneous: sarcoidosis, intestinal bypass operations for obesity
- cryptogenic: unknown

Box 1

Laboratory investigations of relevance in the aetiology of liver cirrhosis

- viral hepatitis: hepatitis B / C serology
- primary biliary cirrhosis: antimitochondrial antibody (specifically M2 variant); serum IgM often increased
- autoimmune hepatitis: anti-liver/kidney microsomal (anti-LKM-1) antibody; smooth muscle antibody; serum IgG often increased
- α1-antitrypsin deficiency: α1-antitrypsin level and phenotype
- Wilson's disease: reduced serum copper; reduced serum ceruloplasmin; increased 24-h urinary copper
- haemochromatosis: increased serum ferritin; saturated plasma ferritin; determination of M2H mutation
- hepatocellular carcinoma: α-fetoprotein

Box 2

accelerate HSC activation in culture. The mechanisms underlying this stimulatory effect are not known, but growth factors, particularly transforming growth factor beta 1 (TGF-β1) have been implicated. Parenchymal cell necrosis may itself be important, possibly via the production of lipid peroxidases from injured cell membranes or by release of insulin-like growth factor from apoptotic cells. Once activated, HSC express numerous cytokines and their receptors, including platelet-derived growth factor, a potent proliferative cytokine for HSC, and TGF-β1 (a potent fibrogenic mediator) which may sustain activation, proliferation and fibrogenesis. The matrix synthesis as a result of HSC activation and proliferation (particularly collagen types I and III), is initially laid down in the space of Disse causing endothelial cells to lose their fenestrae (so-called 'capillarisation'). With progressive disease fibrous septae form which distort the liver parenchyma and ultimately the vascular structures become linked, leading to the grossly distorted architecture of cirrhosis. Once advanced fibrosis/cirrhosis is present, parenchymal dysfunction occurs and portal hypertension develops. The situation may be worsened by nodules of regenerating parenchymal cells expanding against a capsule of fibrotic bands. More recent evidence indicates that hepatocyte dysfunction occurs, in part, as a result of altered cell–matrix interactions which result from the replacement of the normal basement membrane-like matrix with fibrotic matrix.

The increasing insight into the cellular mechanisms underlying liver fibrosis and cirrhosis may lead to development of novel therapeutic approaches aimed at specifically blocking the fibrogenic cascade. These may include controlling HSC activation, neutralising the proliferative or fibrogenic mediators, by either receptor blockade or direct ligand blocking (fibrosis has been reversed in experimental models by the blockade of TGF-β1 activity, inhibiting matrix synthesis and enhancement of matrix degradation). Although these experimental approaches are theoretically attractive, they have the disadvantage that patients often present with relatively advanced disease. Thus, therapies based on reversing HSC activation and enhancing matrix degradation may hold the most promise for clinical application. To date, no antifibrotic treatment (including corticosteroids, prostaglandins and colchicine) has been shown to improve survival in patients with cirrhosis. The application of basic science to the design of new therapeutic strategies offers real hope that the treatment of liver fibrosis may become a therapeutic reality in the foreseeable future.

Clinical presentation

Patients with liver cirrhosis may present in a variety of ways. The diagnosis may be discovered incidentally; by the findings of a routine clinical examination, through laboratory results or by screening programmes (eg, hepatitis C in blood donors). Patients may present with non-specific symptoms, which commonly include lethargy, malaise and abdominal pain, or with symptoms more specific to liver disease, eg, pruritus, pigmentation, ascites, or jaundice. Signs of chronic liver disease that may be present include spider naevi, palmar erythema, gynaecomastia, splenomegaly, a flapping tremor, xanthelasma (in primary biliary cirrhosis) and Kayser-Fleischer rings (in Wilson's disease). The relative occurrence of the various symptoms and signs of chronic liver disease are difficult to quantify. They vary depending on aetiology, the stage of disease at the time of presentation and whether hepatocellular failure or portal hypertension predominates, for example, spider naevi can occur in between 10 and 70% of patients. For a more detailed comparison of the frequency of these clinical features see reference.) Unfortunately, patients often do not present until they have developed complications of cirrhosis (see below). The aim of subsequent investigations is to ascertain both the severity of the cirrhosis and the underlying aetiology. 'Routine' liver function tests should always be performed. Whilst these can theoretically remain within normal limits in cirrhosis, they serve as a useful baseline and may provide a pointer towards aetiology. Some of the more discriminating laboratory investigations in defining aetiology are listed in box 2, whilst the Child-Pugh classification (table) is a useful indicator of the clinical severity of cirrhosis. Ultimately, however, the majority of patients will require liver biopsy for an accurate diagnosis.

Diagnosis

IMAGING

As already emphasised, cirrhosis is ultimately a histological diagnosis. However, technical advances together with increased expertise have revolutionised non-invasive imaging of the liver parenchyma, which may demonstrate features suggestive of cirrhosis. Ultrasound, particularly with colour Doppler imaging to
Liver cirrhosis

measure changes in blood flow in the presence of portal hypertension, can, in experienced hands, provide a cheap, noninvasive and safe method of investigation. Importantly, ultrasound also provides a practical and widely available means of excluding biliary obstruction in patients who present with jaundice. Computed tomography (CT) scanning complements ultrasound imaging. In addition there may be classical appearances in some diseases, eg, haemochromatosis where the excess iron deposition causes a dramatic increase in hepatic density. Magnetic resonance imaging (MRI) is showing promise and is particularly valuable in determining the nature of focal lesions such as hepatic metastases or nodular regeneration which can be difficult to differentiate from cirrhosis by ultrasound. However, at present, ultrasound remains the first-line investigation of choice.

Many other radiological techniques are invaluable in specific situations, eg, endoscopic retrograde cholangiopancreatography in the diagnosis of sclerosing cholangitis. Similarly, an experienced radiologist is essential for the insertion and continuing functional assessment of transjugular intrahepatic portosystemic shunts (TIPSS) (see below).

LIVER BIOPSY

Despite the aforementioned advances in imaging and laboratory investigations, percutaneous liver biopsy remains the cornerstone of diagnosis. With cooperation and good communication of clinical details, an experienced histopathologist can often surmise a great deal from the liver biopsy. The procedure is quick and simple to perform in a cooperative patient with a normal INR and platelet count. Its risks, primarily haemorrhage, but also biliary peritonitis, haematoma and perforation of other viscera, are rare in experienced hands (several large series have reported mortality rates of between 0.01% and 0.1%). Percutaneous biopsy of focal lesions can be performed in conjunction with either ultrasound or CT imaging.

Several alternative methods are now available in specialist centres, which allow biopsy of individuals with deranged clotting and/or thrombocytopenia. Plugged liver biopsy is similar to the standard percutaneous technique, except that metal coils or gelatin sponges are injected down the tract immediately following biopsy. It requires considerable patient cooperation but can be used with a moderate coagulopathy. Transjugular liver biopsy is an extremely useful technique in patients with more severe clotting disorders, in which the risk of intraperitoneal bleeding is greatly reduced. Its disadvantages are that the biopsies are small and are taken "blindly". However, multiple biopsies may be taken and the patient may be sedated. Laparoscopic liver biopsy is yet another alternative, although not widely used in the UK. It too can be performed on a sedated patient with moderate coagulopathy and has the advantage of allowing direct visualisation of the liver.

The complications of cirrhosis and their management

OESOPHAGEAL VARICES

As a result of the rise in portal pressure, which accompanies cirrhosis, portosystemic anastomoses form at several anatomical sites, the most important of which is in the lower oesophagus. Large prospective studies have shown that 25–40% of cirrhotic patients with oesophageal varices eventually experience an episode of bleeding with the potential for serious complications and a reported mortality of 5–50% for a first bleed, depending on the severity of their underlying liver disease. Several new treatment modalities have been developed which are largely complementary.

Management of acute variceal haemorrhage

Initial management centres around effective resuscitation as the first priority. Once stable, endoscopy should be performed to confirm the site of bleeding, with prior orotracheal intubation, if necessitated by the patient's condition. This

<table>
<thead>
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<th>Score</th>
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<th>2</th>
<th>3</th>
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<tr>
<td>Serum bilirubin (μmol/l)</td>
<td>&lt; 35</td>
<td>35–51</td>
<td>&gt; 51</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>&gt; 35</td>
<td>30–35</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Asciites</td>
<td>None</td>
<td>Easily controlled</td>
<td>Poorly controlled</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
<td>Minimal</td>
<td>Advanced</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Excellent</td>
<td>Mild malnutrition</td>
<td>Poor, 'wasting'</td>
</tr>
</tbody>
</table>

Grade A = 5–7 points, Grade B = 8–12 points, Grade C = 13–15 points.
Factors precipitating acute on chronic encephalopathy

- increased dietary protein
- constipation
- gastrointestinal bleeding: occult or overt
- infection: often occult and commonly due to spontaneous bacterial peritonitis
- drugs: sedatives, opiate analgesics
- fluid or electrolyte disturbance: over-diuresis, hypokalaemia, paracentesis without suitable plasma expanders, diarrhoea and vomiting, metabolic alkalosis
- worsening liver disease

Box 3

will also provide an accurate diagnosis in the 30% of cirrhotic patients whose bleeding is not variceal in origin. Emergency sclerotherapy is widely considered the treatment of first choice and is now often used in combination with octreotide (see below). Sclerotherapy has been shown to be effective at controlling haemorrhage in 70–90% of patients, but has a significant complication rate of 10–20%, with mucosal ulceration occurring in up to 50% of patients. Endoscopic band ligation is gaining popularity as a first-line treatment, although the need to re-pass the endoscope through an overtube after loading each band has been, until very recently, a major disadvantage in the acute situation.

A Sengstaken-Blakemore tube can be used to control bleeding for short periods in difficult situations, until alternative treatments are available. Effective tamponade can be achieved in 90% of cases in experienced hands, but with the risk of a relatively high complication rate in unskilled hands. The commonest severe complications result from pressure necrosis of the oesophagus or airways obstruction by the oesophageal balloon or accumulated secretions.

Drug therapy is an important consideration in the control of acute haemorrhage. Vasopressin infusions have been used to control acute variceal bleeding for many years, with approximately a 50% success rate. Vasopressin is a systemic vasoconstrictor and can thus cause serious complications such as myocardial, limb and cerebrovascular ischaemia and infarcts.

Octreotide, a synthetic analogue of somatostatin which selectively vasoconstricts the splanchnic bed, has been widely used over the past few years with few side-effects. Randomised clinical trials have shown it to be more effective than vasopressin and, in some trials, as effective as controlling bleeding. Furthermore, when octreotide plus sclerotherapy was compared with emergency sclerotherapy alone, the former group had a lower rebleeding rate and lower transfusion requirements.

Patients with intractable bleeding may need to be considered for emergency surgery, either oesophageal transection or surgical shunting. More recently the development of TIPSS, which are placed radiologically, has reduced the role of surgery in acute variceal bleeding (see below).

Prevention of recurrent variceal bleeding and primary prophylaxis

Following an episode of acute variceal bleeding, the risk of rebleeding is approximately 60–80% over a two-year period, with a mortality of approximately 20% per episode. Prevention of further such episodes is thus a prime consideration, with the treatment of choice until recently, being accepted as repeated endoscopic sclerotherapy until ablation of the varices is achieved. Numerous clinical trials have shown lower rebleeding rates with courses of sclerotherapy and meta-analyses have demonstrated a survival advantage. However, over the last five years several randomised controlled trials have found endoscopic band ligation to be as effective as sclerotherapy with fewer complications, notably ulceration and strictures. Additionally, band ligation may be associated with a lower rebleeding rate and fewer treatments being needed to achieve variceal obliteration.

Non-selective beta-blockers, such as propranolol, have been shown in many clinical trials to be effective secondary prophylaxis against recurrent variceal bleeding, with a trend towards improved survival also being evident in some trials. Despite this evidence of their efficacy they are not widely used in the UK.

In addition, non-selective beta-blockers have been shown to be effective in primary prevention in patients with portal hypertension and oesophageal varices, in whom bleeding from portal gastropathy is also reduced. A recent randomised controlled trial compared a non-selective β-blocker (nadolol) alone to nadolol plus isosorbide mononitrate in the prevention of a first variceal bleed. The latter was observed to confer a significant benefit with, in addition, a trend towards a survival advantage. This is in stark contrast to injection sclerotherapy, which has not been shown consistently to reduce either the risk of bleeding or mortality when used as primary prophylaxis, with some studies showing an increase in both of these parameters. Similarly shunting, be it surgical or a TIPSS, has not been shown to be of any benefit as primary prophylaxis.

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is a common severe complication of liver failure. Its many precipitants are well documented (box 3) and early identification of any precipitant to an acute episode is fundamental to its successful management. The pathogenesis of hepatic encephalopathy remains unclear; several hypotheses have been proposed, and it is possible that the underlying mechanism is multifactorial. Most treatments, both established and experimental, are based on the following theories, which are outlined more fully elsewhere.
The ammonia hypothesis
This postulates that intestinal neurotoxins, primarily ammonia, but also mercaptans and short chain fatty acids, along with other products not adequately detoxified in the blood (due to a combination of portosystemic shunting and hepatocellular failure), cross the blood–brain barrier causing impaired central nervous system function and thus hepatic encephalopathy. Therapeutic measures are based on reducing production or decreasing absorption of intestinal ‘toxins’. They include restricted protein intake, enemas, and nonabsorbable disaccharides such as lactulose or lactitol, which both prevent constipation and alter nitrogen handling within the bowel. Nonabsorbable antibiotics, eg, neomycin, can also be used.

More recently there has been renewed interest in the ammonia hypothesis, with the focus on the excitatory neurotransmitter glutamate. Ammonia taken up by the brain is incorporated into glutamine and it is hypothesised that this may deplete cerebral glutamate leading to disturbances in glutamatergic transmission, which could account for the neuroinhibition of hepatic encephalopathy. This hypothesis is supported by the observation that cerebral levels of glutamate are decreased in various clinical and experimental models of hepatic encephalopathy. Although unproven, disturbances in glutamate transmission are theoretically attractive as they could explain the often significant role of the gastrointestinal tract in the development of hepatic encephalopathy.

The false neurotransmitter hypothesis
An imbalance between aromatic amino acids and branched chain amino acids is seen in patients with advanced liver disease. It has been suggested that hepatic encephalopathy may be precipitated by an increase in cerebral aromatic amino acids which are precursors to false neurotransmitters. An increase in the latter may in turn cause a reduction in neural excitement and an increase in neural inhibition. In an attempt to address this imbalance branched chain amino acids have been used in the treatment of hepatic encephalopathy, however the results of randomised controlled trials are somewhat heterogeneous. Branched chain amino acids may have a role in the nutritional support of cirrhotic patients (see below).

The ‘GABA-ergic’ hypothesis
Gamma-aminobutyric acid (GABA) is an important inhibitory neurotransmitter with a cognate receptor closely related to the benzodiazepine receptor. GABA levels have been shown to be elevated in the peripheral blood of both animal models and patients with hepatic encephalopathy. It has been hypothesised that increased cerebral GABA levels may lead to the development of hepatic encephalopathy. Several case reports and controlled trials have been published in which the benzodiazepine antagonist flumazenil has been used to treat hepatic encephalopathy. Again the results are variable and the treatment can at best be described as experimental. Thus, the current established management, although reasonably effective and theoretically rational, is essentially supportive with dietary measures to ensure an adequate but not excessive protein intake and lactulose or an alternative to avoid constipation. If hepatic encephalopathy proves intractable then this may itself be an indication for liver transplantation.

ASCITES
The presence of ascites is the first sign of decompensation in many cirrhotic patients and thus a poor prognostic sign. The precise mechanism by which ascites forms in cirrhosis is not fully understood and may well be multifactorial. Several theories have been proposed including the peripheral arterial vasodilator hypothesis, which postulates that splanchnic arteriolar vasodilatation secondary to portal hypertension is the primary event. This leads to ‘underfilling’ of the vascular compartment and activation of the renin–angiotensin–aldosterone system, increased sympathetic nervous system tone and an increased production of antidiuretic hormone. There is also evidence of sinusoidal hypertension with changes in hepatic lymph flow and altered hydrostatic forces favouring net loss of fluid from mesenteric capillary venules. Any reduction in hormonal clearance by the liver will result in an increase in their half-life, in the case of aldosterone, promoting sodium and water retention. Reduced oncotic pressure secondary to hypoalbuminaemia, will increase any tendency for ascites to form.

The aim of the medical treatment of ascites is the mobilisation of intra-abdominal fluid through the creation of a negative sodium balance. This can be achieved most simply by bedrest, fluid restriction and a low sodium diet. The aldosterone antagonist spironolactone is usually the first-line diuretic of choice, but if the ascites is severe, a loop diuretic such as frusemide may be used judiciously. Diuretic dosage is increased to achieve a target weight loss of
approximately 0.5–0.75 kg/day, with careful monitoring of electrolytes and renal function (5–10% of cirrhotics admitted to hospital for the treatment of ascites will not respond to diuretics, regardless of dosage).

Paracentesis was used in the treatment of ascites for many years, but was abandoned after the introduction of diuretics as it was considered to have an unacceptably high complication rate. However, over the last few years, several randomised controlled trials have shown large volume paracentesis to be safe provided intravenous infusion of 20% human albumin solution is undertaken concurrently.27 Several subsequent studies have looked at the necessity of using intravenous albumin in comparison with no albumin and other less expensive plasma expanders. The results are somewhat heterogenous, but the consensus is probably that albumin infusion (6–8 g/l ascites drained) prevents haemodynamic, vasoactive and neurohumoral disturbances and is thus probably the treatment of choice.27 28 Following paracentesis, measures should be undertaken to prevent the re-accumulation of ascitic fluid. Many would now advocate paracentesis as the treatment of choice for ‘tense ascites’, as it has been shown to be both more effective and to have a lower complication rate than diuretic treatment.

Peritoneovenous shunting can be useful in the occasional patient with refractory ascites who is not suitable for liver transplantation. It is, however, associated with a significant complication rate including disseminated intravascular coagulation, vascular thrombosis and stent occlusion.26 27 TIPSS shunts may have a role in the management of refractory ascites but this remains undetermined (see below).

HEPATORENAL SYNDROME

Hepatorenal syndrome is a functional renal failure which occurs spontaneously or as a result of fluid shifts in patients with severe liver disease, with the diagnosis being based on the exclusion of clinical, laboratory or anatomical evidence of other causes of renal failure.29 The haemodynamic changes are thought to be similar to those postulated in ascitic formation, but there is a paradoxical increase in renal vascular resistance and a marked decrease in renal cortical blood flow, with reduction in the glomerular filtration rate and a low urinary sodium, making hepatorenal syndrome in some ways analogous to acute pre-renal failure.30 31 Sustained volume expansion may bring no therapeutic benefit, but the maintenance of an optimal intravascular volume is a cornerstone of management if the patient's prognosis is to be maximised. The pathogenesis remains unclear despite numerous experimental and clinical studies which have postulated roles for various mediators, including nitric oxide, prostaglandins, and endothelin, and endothelial abnormalities in the development of the syndrome.26 30

As yet there is no unifying theory or effective treatment other than treatment of the underlying liver disease. Various treatment modalities, including shunting procedures and low dose dopamine infusions, have been reported to confer some benefit, but once established, mortality in the absence of transplantation is high.32 Normal renal function returns following successful transplantation.

SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous bacterial peritonitis, the spontaneous infection of ascitic fluid without any apparent intra-abdominal cause), is a frequent complication of cirrhosis with an associated mortality of approximately 30%.33 Bacteraemia is common in cirrhotics for a variety of reasons, including; impaired intestinal mucosal integrity, complement deficiency and dysfunction of the reticuloendothelial system. Patients with an ascitic protein concentration of less than 10 g/l have been shown to have an increased risk of spontaneous bacterial peritonitis.34 35 Most cases are caused by the Gram-negative aerobic bacilli which normally colonise the gut. Spontaneous bacterial peritonitis classically presents with abdominal pain and fever, but is frequently asymptomatic or an occult precipitant of hepatic encephalopathy. Diagnostic paracentesis should therefore be performed in any patient with ascites whose condition is worsening. To diagnose spontaneous bacterial peritonitis, ascitic fluid should be sent for a white cell count (in a Coulter counter) and cultured in blood culture bottles. Although cases may not fulfil the classical diagnostic criteria of an ascitic fluid polymorphonuclear count greater than 250 cells/mm³ and a positive culture, treatment often has to be started on the basis of clinical suspicion before culture results are available.36 An intravenous third generation cephalosporin (eg, cefotaxime) is generally considered the antibiotic of choice, with 80% resolution of infections being reported.33 Spontaneous bacterial peritonitis may recur, older texts quote a figure of up to two-thirds of patients having a further episode within a year, although current clinical experience suggests that this is an overestimate.
HEPATOCELLULAR CARCINOMA

Between 60% and 90% of patients with primary hepatocellular carcinoma (HCC) have underlying cirrhosis, (the fibrolamellar variant, a histological subtype, is commonly found in non-cirrhotic livers and tends to be associated with a better prognosis). HCC can complicate cirrhosis of any aetiology, but in the UK it is most commonly seen in association with alcoholic liver disease in addition to hepatitis B and C. It classically presents with anorexia, abdominal pain and weight loss, but is frequently asymptomatic, hence the importance of regular surveillance of cirrhotic patients with ultrasound and α-fetoprotein estimations. α-Fetoprotein levels are increased in 80% of patients with HCC, but can also be moderately elevated in cirrhosis in the presence of regenerative activity. A good ultrasound together with a contrast-enhanced CT can be highly suggestive, and hepatic arteriography (which can produce classical pictures, as the vascular supply of HCC is usually arterial) is extremely useful in atypical cases and for the planning of further treatment. The diagnosis should be confirmed, if possible, by a liver biopsy or a fine needle aspirate for cytology.

Treatment

HCC is associated with an extremely poor prognosis with a mean survival of less than a year.

‘Curative’—resection/transplantation Small solitary tumours (<4 cm) can be resected if the underlying liver function is well preserved. A five-year survival of around 50% has been reported in several series of selected patients, with prognosis related to the severity of the underlying liver disease. Liver transplantation is an alternative to surgical resection. Early series showed disappointing results, with high peri-operative mortality and recurrence rates, but with careful patient selection (those with small solitary tumours, particularly of the fibrolamellar variant, and no evidence of extrahepatic spread) the outcome can be improved.

Palliation A variety of modalities have been tried. Numerous series have been published, but few interventions have been shown to significantly alter survival and many carry an appreciable risk in patients with poor underlying liver function. Neither systemic chemotherapy or intra-arterial chemotherapy have been shown to improve survival rates. There have been some encouraging reports using tamoxifen, which is well tolerated. Hepatic artery embolization using gelatin foam or metal coils may result in substantial tumour necrosis. Embolization combined with chemotherapy (e.g., mitomycin C spheres in lipiodol), has also been used but no controlled trials have really shown either to improve survival. Direct injection of percutaneous ethanol under ultrasound guidance is probably the most effective palliation with a possible survival advantage for patients with small tumours who are not suitable for other treatments. However, further prospective controlled trials are needed to evaluate critically the most effective treatments.

NUTRITION

Although it has been recognised for years that many patients with chronic liver disease are malnourished, this aspect of their treatment has often been overlooked. This has, in part, been due to dietary protein restriction for the prevention of hepatic encephalopathy. However, studies have shown that poor nutritional state and poor clinical outcome following, for example, abdominal surgery or liver transplantation are correlated. Furthermore, controlled trials have shown that dietary supplementation can lead to improvements in, for example, liver function tests, various clinical parameters and survival.

Impaired dietary intake, as a consequence of anorexia, nausea, protein restriction and often an unpalatable low-sodium diet is almost certainly the principal cause of malnutrition in cirrhotics. There is, however, also evidence that cirrhosis itself leads to metabolic abnormalities and nutritional deficiencies. Several studies have documented poor calorie and protein intake in cirrhotics. Iron deficiency anaemia, often secondary to occult gastrointestinal blood loss, and multiple vitamin deficiencies as a result of poor intake, decreased absorption and abnormal metabolism, are also common.

It is indisputable that increasing oral protein intake leads to the development of encephalopathy in some patients with cirrhosis. But for many individuals with cirrhosis, dietary protein can be given with nutritional benefit and without the development of encephalopathy. Amino acid supplementation does not appear to carry the same risk and branched chain amino acids may actually improve the mental state of some patients with cirrhosis.

Factors predicting a favourable response to treatment of chronic viral hepatitis with α-interferon

<table>
<thead>
<tr>
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<th>Hepatitis C</th>
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<tr>
<td>• high serum transaminases</td>
<td>• low HCV RNA levels</td>
</tr>
<tr>
<td>• low HBV DNA levels</td>
<td>• genotypes II and III</td>
</tr>
<tr>
<td>• piecemeal necrosis on biopsy</td>
<td>• absence of cirrhosis</td>
</tr>
<tr>
<td>• female sex</td>
<td>• shorter duration of illness</td>
</tr>
<tr>
<td>• shorter duration of illness (ie, non-vertical transmission)</td>
<td>• higher age</td>
</tr>
</tbody>
</table>

Box 4
Other new developments in the treatment of liver cirrhosis

HEPATITIS B

Chronic hepatitis B occurs in 2–10% of those infected as adults and most of those infected as infants. There is a wide range in the histological severity of associated liver disease from very mild inflammation to cirrhosis. Any assessment must also include full consideration of the individual’s serological status. Antiviral chemotherapy is indicated in patients with advanced liver disease (usually taken as histological evidence of chronic active hepatitis), with decompensated cirrhosis being a contraindication. The best results are seen in patients who are HBeAg positive and have low concentration of hepatitis B viral (HBV) DNA in their serum and a serum alanine transaminase greater than 100 IU/l (box 4).40-42

Alpha-interferon remains the treatment of choice, (usually 5–10 mU subcutaneously, three times weekly, for four months).42 Patients with an alanine transaminase of less than 100 IU/l may respond more effectively after steroid pre-treatment.43 Nucleoside analogues, particularly lamivudine, show promise, especially when used with interferon in combination therapies.44 Early results using lamivudine to prevent hepatitis B recurrence following liver transplantation are also encouraging.45 Even with careful patient selection only about 40% of patients overall respond to the standard interferon regimens.46

Liver transplantation remains the only therapeutic option for patients with decompensated cirrhosis, but in the absence of specific measures the virus persists in about 80% of recipients, sometimes with the rapid development of recurrent liver disease. The one-year survival for such patients is only 50–60%.36 If there is no active viral replication, long-term treatment with high dose anti-HBs immunoglobulin reduces the risk of recurrent infection to 30%.

HEPATITIS C

There has been a vast increase in knowledge about this blood-borne virus since it was successfully cloned in 1989. The screening of blood donors, instituted in the UK in 1991, has dramatically reduced the incidence of post-transfusion hepatitis and led to the detection of many previously undiagnosed cases of hepatitis C, 60% of whom, without treatment, may develop chronic hepatitis with the risk of cirrhosis and hepatocellular carcinoma. The diagnosis is usually made by the detection of hepatitis C virus (HCV) antibodies, which must be confirmed by radio-immunoblot assay, followed by polymerase chain reaction amplification of viral RNA. Liver biopsy is essential in hepatitis C positive patients to stage the disease.

Antiviral chemotherapy is generally considered appropriate in patients with histological evidence of chronic active hepatitis (histological scoring systems have been devised to assess accurately the various parameters of inflammation), with decompensated cirrhosis being a contraindication to treatment. Interferon-α is the usual treatment (commonly 3 million units, three times a week, for six to 12 months) with most series reporting approximately a 50% response rate, with 50% of the responders subsequently relapsing.40-43 The factors thought to predict a good response to interferon-α are shown in box 4.42 Trials have suggested that higher doses or longer courses of treatment may be of benefit.40-42 Combination therapy, particularly interferon-α and the nucleoside analogue ribavirin, may also improve response rates.45

Liver transplantation in hepatitis C (as with hepatitis B) remains a difficult issue. HCV persists in over 75% of patients following transplantation, with chronic hepatitis recurring in approximately half of these.36 The recurrences do, however, seem less serious than in HBV, with two-year survival rates of 80–90% being reported, although the long-term prognosis remains unclear.36

TIPSS

TIPSS are intrahepatic shunts, connecting the hepatic and portal veins, that are inserted radiologically. A right jugular approach is used and once the hepatic vein is cannulated, a needle is advanced, under fluoroscopy or ultrasound guidance, through the liver parenchyma into an intrahepatic portal vein branch. The portal pressure is measured and the tract dilated until the desired reduction in pressure is achieved, a metallic stent can then be placed to maintain patency. This elegant procedure was first described in the late 1980s and has subsequently been extensively employed for a variety of indications in specialist centres.46

TIPSS have proved very successful in controlling acute, intractable variceal haemorrhage and for treating patients with recurrent haemorrhage, despite standard medical and endoscopic treatments. Furthermore, varices can be directly embolized with alcohol or metallic coils at the time of the procedure. Following their initial success, TIPSS became widely used for indications including refractory ascites, primary treatment for variceal haemorrhage, and
Indications / contraindications for liver transplantation

- all patients with chronic liver diseases should be considered as transplant candidates
- chronic liver diseases in which transplantation is clearly indicated: primary/secondary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, cryptogenic cirrhosis, biliary atresia, inborn errors of metabolism (α,α'-antitrypsin deficiency, haemochromatosis, paediatric conditions)
- 'absolute' contraindications to liver transplantation: extrahepatic sepsis, patients with AIDS, other conditions with a fatal prognosis, metastatic hepatobiliary malignancy
- conditions in which transplantation may be appropriate on an individual basis: hepatitis B and C, alcoholic liver disease, primary hepatocellular carcinoma, HIV-positive patients (who have not developed AIDS)

Box 5

Liver cirrhosis

even prophylaxis against variceal bleeding. However, initial enthusiasm for the procedure has now been tempered, as the longer term problems have become apparent. Hepatic encephalopathy is common, with prospective studies quoting incidences of between 15 and 30%, particularly when it has been present in the past. Most of these patients can be successfully managed medically, but some require revision of their shunt in an attempt to improve their encephalopathy.

Shunt stenosis with recurrent portal hypertension is common, occurring in one- to two-thirds within six to 12 months of placement. However dilatation or placement of a second stent is possible and can usually be performed as a day case procedure. For this reason a programme of surveillance of TIPSS recipients with Doppler scanning and angiography is essential.

LIVER TRANSPLANTATION

Liver transplantation has transformed the clinical outcome of patients with decompensated cirrhosis, with many centres now reporting excellent results. With careful patient selection, five-year survival for chronic liver disease of all aetiologies usually exceeds 80%, with patients enjoying a good quality of life.

In many cases there are clear indications or contraindications to transplantation (box 5). It is important to remember that the timing of transplantation is critical. For certain diseases, there are established models to predict the stage at which transplantation should be considered, before complications arise that may adversely effect survival. In other situations, the decision as to whether transplantation is a suitable treatment option can be more difficult. For example, liver transplantation in alcoholic liver disease is controversial. Most centres insist on a period of abstinence of at least six months and carefully assess an individual's psychosocial situation, before considering transplantation. Because alcoholic hepatitis is often coexistent with cirrhosis, abstinence may result in an improvement in liver function, possibly obviating the requirement for transplantation. Concerns regarding drug compliance and other coexistent alcohol-related pathologies are often cited, however, results of liver transplantation in carefully selected alcoholic patients are at least as good as in patients with liver disease of other aetiologies. Age itself is not a contraindication, although obviously the patient's overall condition must be considered.

The actual procedure, both the donor operation and the orthotopic transplantation, are well established. Newer developments include reducing techniques and segmental transplantation from living donors, in response to the shortage of size-matched donors for children. Auxiliary liver transplantation, in which a segment of donor liver is implanted in addition to the recipient's own (when there is a strong possibility that native liver function may recover) is another new development. To date this technique has predominately been used in acute liver failure, and although its role may increase it is unlikely to be of benefit in cirrhotics.

Although animal studies have suggested that the liver is less susceptible to rejection than other organs, acute and chronic rejection remain important causes of morbidity and mortality, with the need to balance the risk of rejection against the risk of opportunistic infections (eg, cytomegalovirus) being an ongoing clinical problem. The introduction of cyclosporin A in the 1980s led to a dramatic improvement in long-term graft survival. In 1994 a new immunosuppressant, tacrolimus was introduced. Two multicentre trials have shown tacrolimus to be superior to cyclosporin A, in terms of both acute and refractory rejection, but to be associated with a higher rate of side-effects. At present, it is thus probably indicated in those patients with recurrent or refractory episodes of rejection. Recently, there has been interest at the prospect of reducing or stopping immunosuppressants in long-term transplant patients. A small study has suggested that this may be possible in a significant number of patients, although the concept remains experimental at present.

Conclusions

There have been numerous advances in the management of chronic liver disease, with the emergence of specific therapies for several conditions, notably viral hepatitis, and advances in the techniques used to manage the complications of cirrhosis. The advent of successful liver transplantation offers effective treatment for patients with even end-stage liver disease. It is therefore imperative that individuals with established liver fibrosis, or conditions that may lead to it are identified and referred to a hepatologist for assessment.

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Liver cirrhosis.

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