

# An overview of hepatitis: part 1

The UK is the only major developed country showing an increase in the number of deaths from all forms of liver disease, including hepatitis. In part 1, Gareth Nickless focuses on non-viral hepatitis and drug use in liver dysfunction



The liver performs numerous essential functions

The liver is the largest internal organ of the human body and has a dual blood supply. The hepatic portal vein delivers blood from the intestine to be processed before being returned to the general circulation while the hepatic artery, which branches from the aorta, supplies the liver with oxygen. The individual functional units of the liver are called lobules. These are hexagonal arrangements of tissue formed around a central vein. A branch of the hepatic artery, a branch of the hepatic portal vein and a bile duct are situated at each edge of these lobules. Blood from each lobule flows into large capillary spaces (sinusoids), which are connected to the central vein.

The liver performs numerous essential functions of metabolism, synthesis and storage, including:

- Detoxifying waste products (eg, nitrogenous waste), hormones, drugs and other xenobiotics
- Producing plasma proteins (eg, albumin) and clotting factors
- Storing glycogen, fats, iron and vitamins

However, despite these numerous functions, there is little cellular specialisation — hepatocytes perform a wide variety of metabolic and secretory roles, and phagocytic activities are carried out by Kupffer cells.

When the liver comes into contact with toxins or viruses, it undergoes inflammatory (hepatitis) or fatty (steatosis) changes, or both (steatohepatitis). These changes are usually reversible — the liver can regenerate — but if the cause of the initial insult is not addressed

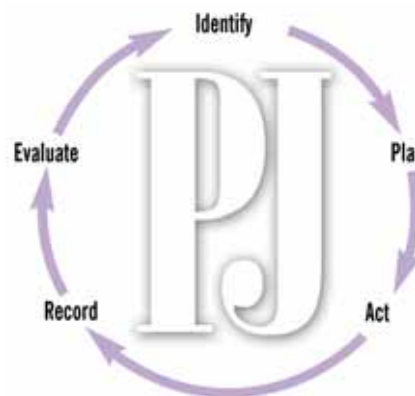
## Definitions

**Cholestasis** Impaired bile flow. This can be intra- or extra-hepatic (eg, gallstones blocking the bile duct) and may or may not be associated with hepatitis.

**Cirrhosis of the liver** A progressive disease of the liver (as a result of diffuse damage to hepatic parenchymal cells) associated with fibrosis, nodular formation and altered architecture. There is associated failure of hepatocyte function and resistance to hepatic blood flow.

**Compensated liver disease** Where a patient has known chronic liver damage but is asymptomatic, either because of prescribed medicines or because there is enough healthy liver tissue to carry out our normal functions

**Decompensated liver disease** Where a patient with compensated liver disease suddenly develops symptoms



## Identify knowledge gaps

1. Can you interpret liver function tests?
2. Can you list three non-viral causes of hepatitis and how they are treated?
3. How is drug handling altered in patients with liver dysfunction?

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

damage can progress to fibrosis (scarring and thickening of the smooth liver tissue) and cirrhosis of the liver (see Definitions panel), which result in complications, such as ascites (fluid in the abdomen), portal hypertension and oesophageal varices. Varices form when blood from the intestine cannot flow through the hardened liver and can result in internal bleeding (indicated by vomiting blood or tarry stools) if they burst.

Cirrhosis of the liver also increases the chances of a patient developing hepatocellular carcinoma, a condition with a life expectancy of no more than six months.

Use of the term "hepatitis" needs to be qualified because numerous factors can trigger inflammation, including:

- Alcohol
- Viruses (A-E)
- Drugs (including herbal remedies)
- Auto-antibodies
- Insulin resistance

## Diagnostic tests

A number of blood tests are used to assess liver function, but tests cannot be used to quantify this in the way that serum creatinine is used to assess renal function. The term "liver function tests" (LFTs) may be viewed as a

misnomer because some of the markers reflect liver damage rather than the ability of the liver to perform its usual functions. Further tests that may be requested during the investigation of liver dysfunction include ultrasound and biopsy.

**Blood tests** The tests that are commonly referred to as LFTs include measuring bilirubin, alkaline phosphatase (ALP) and albumin (see Panel 1). These help paint a picture of the type and cause of liver damage.

A “full liver screen” is also performed to help find the cause of liver disease. This will include looking for viruses, auto-antibodies (indicative of autoimmune hepatitis) and alpha feta protein (a tumour marker).

**Biopsy** Liver biopsy may be used to diagnose the cause of liver disease and assess the damage (eg, to differentiate between hepatitis and cirrhosis). The procedure is usually performed as a day case, under local anaesthetic. The most common complications are bile leaks and bleeding.

**Ultrasound** A liver ultrasound scan will identify extrahepatic duct dilation and can identify abnormalities, such as cysts and tumours. It can also help describe the appearance of the liver — for example, if a patient has a fatty liver, the echo is bright — and will establish whether a patient presenting with abdominal swelling has ascites.

### Acute hepatitis

The manner in which a patient presents with acute hepatitis depends on the cause. In addition, some patients with acute hepatitis may be asymptomatic. However, in all cases the potential exists for a patient to develop acute liver failure, which can result in:

- Jaundice
- Hypoglycaemia
- Hepatic encephalopathy (characterised by disturbance of consciousness that may progress to coma, psychiatric changes, flapping tremor and breath odour, and caused by the accumulation of waste products that the liver would normally remove)
- Haemorrhage

Acute liver failure can be life-threatening and a liver transplant may be required. This article looks at some of the non-viral causes of acute hepatitis, however, it is beyond the scope of this article to discuss the management of chronic liver disease.

**Alcoholic hepatitis** Excessive alcohol consumption — an increasing problem in the UK — can lead to a spectrum of histopathological changes, ranging from steatosis and steatohepatitis to fibrosis and cirrhosis of the liver.

Between 20 and 40 per cent of heavy drinkers will develop serious liver disease. Some of them will present with acute alco-

## Panel 1: Liver function tests

**Bilirubin** Bilirubin is a by-product of haem metabolism that is conjugated by the hepatocytes and transported to the bile ducts to form bile salts. When the liver is damaged, however, this function is impaired and bilirubin levels rise, leading to jaundice. Although a raised bilirubin indicates that something is wrong, it is not always a sign of liver disease. For example, in auto-immune haemolytic anaemia haemolysis will result in a larger quantity of bilirubin for the liver to process and, in patients with gallstones biliary obstruction can prevent conjugated bilirubin from reaching the gall bladder.

**Alkaline phosphatase** Alkaline phosphatase (ALP) is found in the epithelial cells that line branches of the bile duct. Raised levels are commonly seen in intra- and extra-hepatic cholestasis. ALP is also produced in the bone so conditions such as Paget’s disease can complicate the interpretation of ALP results.

**Transaminase enzymes** Transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) are the enzymes that are most specific to the liver. Levels are most likely to be raised during acute hepatocellular damage (ie, in acute hepatitis) but are usually normal in patients with cholestasis. In patients with gallstones in the common bile duct a mixed picture of both cholestasis and hepatitis (ie, raised hepatic and biliary enzymes) may be seen. However, in patients with cirrhosis of the liver ALT and AST levels may be normal, or only marginally raised, because there is little remaining healthy liver tissue left to damage.

**Gamma glutaryltransferase** Gamma glutaryltransferase (GGT) is found in high concentrations in the bile ducts and raised levels may be seen in patients presenting with cholestasis or cirrhosis. Unlike ALP, GGT is not present in bone so can be used to ascertain whether or not a high ALP result is due to bone disease. Patients prescribed drugs with enzyme-inducing properties (eg, phenytoin) can also have a raised GGT level, as will patients who have consumed a large amount of alcohol close to the blood test.

**Albumin** Albumin levels are useful in assessing the synthetic function of the liver. However, because plasma half-life is approximately 20 days, it takes at least a week for levels to fall below the reference range in a patient with liver damage. This result is, therefore, more useful for looking for chronic liver damage. It should also be remembered that other processes can cause a more rapid reduction in albumin levels (eg, the catabolic effects of infection).

**Prothrombin time** Prothrombin time (and thus international normalised ratio) may be increased in a patient with hepatobiliary disease for two reasons. First, vitamin K absorption may be impaired due to absence of bile in the gut and, secondly, the damaged hepatocytes will be unable to synthesise adequate clotting factors.

## Panel 2: The Glasgow alcoholic hepatitis score

	Score given		
	1	2	3
Age (years)	< 50	≥ 50	-
White cell count (10 <sup>9</sup> /L)	< 15	≥ 15	-
Urea (mmol/L)	< 5	≥ 5	-
Prothrombin time ratio	< 1.5	1.5–2	> 2
Bilirubin (µmol/L)	< 125	125–250	> 250

holic hepatitis, characterised by fever, tender enlarged liver and leukocytosis in association with other clinical and laboratory features of liver failure. Serum transaminases, gamma glutaryltransferase, ALP, bilirubin and prothrombin time can all be raised in patients with alcoholic hepatitis. In others, the first sign of a problem will be symptoms of either liver cirrhosis or hepatocellular carcinoma because, up until presentation, the patient has had compensated liver disease.

Alcoholic hepatitis is thought to involve a complex interaction between ethanol metabolism, and inflammatory and immune

processes. Ethanol oxidation generates free radicals, resulting in oxidative stress. Tumour necrosis factor- $\alpha$  levels have been reported to be raised in these patients and the biological activities of this cytokine are altered in alcoholic liver disease, favouring inflammation and apoptosis rather than hepatocyte proliferation.

Hyperbilirubinaemia and prolongation of prothrombin time (PT) have a prognostic value in alcoholic hepatitis. The following formula (Maddrey's discriminant function; DF) has been used to assess the severity of the condition and has been validated in several studies:<sup>1</sup>

$$DF = \frac{4.6 [PT_{\text{patient}} - PT_{\text{control(s)}}] + \text{Serum bilirubin}}{17.1}$$

A value greater than 32 effectively predicts a one-month mortality of 50 per cent.

However, more recently, another tool, the Glasgow alcoholic hepatitis score (GAHS), has been developed to identify patients at greatest risk of death during hospital admission and is described in Panel 2. Patients with a score less than 9 on day 1 were shown to have a 28-day survival of 87 per cent, whereas if GAHS is greater than or equal to 9, survival was reduced to 46 per cent.<sup>2</sup>

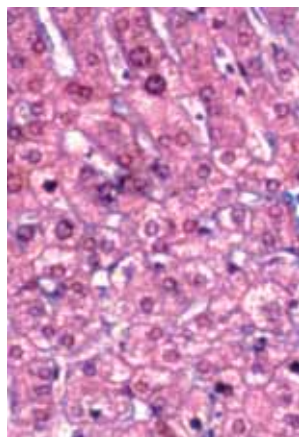
The mainstay of treatment is abstinence from alcohol and supportive care. However, in patients with jaundice or a DF greater than 32, or both, or in those with a GAHS greater than or equal to 9, intensive clinical management should start from admission to hospital. Specific treatments include nutritional therapy and corticosteroids.

**Nutritional therapy** Malnutrition in patients with alcoholic hepatitis has been shown to correlate closely with mortality. Nutritional support by mouth or by nasogastric tube (at least 25kcal/kg/day) should be started as soon as possible to support the metabolic functioning of the liver.

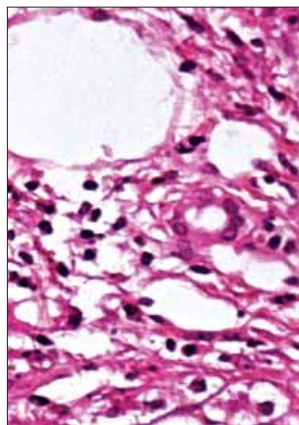
**Corticosteroids** Corticosteroids are used for their anti-inflammatory and immunosuppressant properties. However, studies have produced conflicting results — three meta-analyses have shown a beneficial role in alcoholic hepatitis, whereas one has questioned their efficacy.<sup>3,4</sup>

It should be noted, however, that some of the initial trials, which showed no benefit, may have included patients without alcoholic hepatitis and all the trials preceded the validation of the GAHS. Two trials containing patients with the worst prognosis (a DF > 32 or encephalopathy, or both) showed a survival benefit in steroid-treated patients.<sup>5,6</sup> It should also be noted, when looking at studies, that patients with alcoholic hepatitis form a heterogeneous population and it can be difficult to differentiate between severe acute alcoholic hepatitis and decompensated liver disease on a background of cirrhosis.

For patients with severe alcoholic hepatitis (DF > 32), the American College of Gastroenterology recommends prednisolone



**Hepatocytes perform a wide variety of metabolic and secretory roles**



**In alcoholic hepatitis, the liver's regular cellular structure can be disrupted by large vacuoles of fat (white).**

40mg daily for four weeks, followed by a gradual reduction to zero.

Patients with concomitant pancreatitis, gastrointestinal bleeding, renal failure or active infection were excluded from the trials and steroids should be avoided in these patients.

**Pentoxifylline** Pentoxifylline is a TNF- $\alpha$  inhibitor. In one study, 101 patients with severe alcoholic hepatitis were randomised to receive either pentoxifylline 400mg *tds* or placebo for four weeks. Pentoxifylline was associated with improved short-term survival. The benefit appeared to be related to the reduced risk of developing hepatorenal syndrome (a condition where renal failure develops secondary to liver disease).<sup>7</sup>

**Autoimmune hepatitis** Mainly affecting young females, autoimmune hepatitis is a relatively uncommon condition where patients present with fatigue, right upper quadrant pain, polymyalgia or arthralgia and abnormal LFT results. Approximately 20 per cent of patients will have another form of autoimmune disease, such as rheumatoid arthritis. Detection of antinuclear antibodies, anti-smooth muscle antibodies and high titres of immunoglobulins aids diagnosis. If the condition remains untreated, patients may develop cirrhosis of the liver.

Initial treatment involves prednisolone 50mg daily, which is reduced to a maintenance dose. This is followed by the introduction of azathioprine (1.5–2mg/kg/day), used for its steroid-sparing effects — it allows the dose of the steroid and, therefore, associated side effects to be reduced. Patients may also require ciclosporin.

Because many patients require long-term corticosteroid therapy, bone scans and measures to prevent osteoporosis should be implemented.

**Drug-induced hepatitis** Various drugs, (eg, carbamazepine, statins and ibuprofen), can cause hepatitis. Patients who develop drug-induced hepatitis often experience symptoms similar to those seen in acute viral hepatitis (see Part 2 [to be published on 19 April]) but incidence is rare. Patients can have abnormal LFT results with no clinically significant adverse effects when prescribed drugs such as isoniazid and anticonvulsants.

Although adverse drug reactions are a relatively uncommon cause of hepatitis, they should always be considered as a possibility until tests reveal another cause. Enzyme inducers, such as alcohol and rifampin, increase the risk of hepatotoxicity with other drugs. For example, alcohol depletes glutathione stores, so that if paracetamol is taken N-acetyl-*p*-benzoquinoneimine (a product of paracetamol metabolism that causes hepatocellular necrosis) accumulates.

Penicillins, especially flucloxacillin, can cause a mixed cholestatic hepatitis and this adverse drug reaction may not be seen until a few weeks after the course of antibiotic has been completed.

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Pharmacists should also be aware of hepatitis induced by herbal products. For example, in 2002, kava was banned after reports of hepatotoxicity.

The treatment of patients who present with drug-induced hepatitis requires withdrawal of the drug and supportive therapy. Specific antidotes are only available for paracetamol and iron. Once the patient has recovered, the condition that the offending drug was being used to treat usually needs to be re-addressed. However, there is potential for cross-sensitivity between drugs with similar chemical structures so, for example, patients who develop jaundice due to chlorpromazine should avoid all phenothiazines.

**Non-alcoholic fatty liver disease and steatohepatitis** Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver diseases where patients have steatosis that occurs in the absence of excessive alcohol consumption. It is now considered to be the most common liver problem in the western world, where it is estimated to affect up to 30 per cent of the population.

NAFLD includes non-alcoholic steatohepatitis (NASH), in which the accumulation of excess fat in the liver cells is associated with inflammation. A liver biopsy is required to make a definitive diagnosis and to distinguish between NAFLD and NASH.

Insulin resistance has been observed in up to 98 per cent of patients who have NAFLD. People with metabolic syndrome (characterised by obesity, type 2 diabetes, hypertension and hypertriglyceridaemia) are at risk of developing a fatty liver, which may progress to steatohepatitis and, ultimately, cirrhosis.

A diagnosis is usually made after other common causes (eg, viruses, autoimmune disease and alcoholism) are excluded. Many patients are asymptomatic and the disease is only discovered when abnormal LFTs are detected during routine tests. Some are not diagnosed until they present with the complications of hepatic cirrhosis, such as ascites or variceal bleeding.

There is no established pharmacological therapy for NAFLD or NASH. Insulin sensitising therapy (in the form of metformin and thiazolidinediones) has been investigated in several phase II and III studies. In one study,<sup>8</sup> metformin resulted in normalisation of LFT results, but the effect on liver histology was not assessed.

A large phase III study of metformin for NASH is currently in progress. A number of small studies have shown that thiazolidinediones improve histological data in patients with NAFLD. However, in two of these studies there was at least one case of hepatotoxicity necessitating the discontinuation of the drug.

### The pharmacist's role

Numerous factors may result in liver dysfunction, which ranges from acute hepatitis to cirrhosis of the liver. Pharmacists are suitably placed to advise on drug use in such patients

## Panel 3: Drug use in liver dysfunction

Some drugs should be avoided in patients with liver disease because they are either hepatotoxic or they exacerbate symptoms. For example, to avoid further inflammation paracetamol should be not be used in acute hepatitis. It may be used in chronic liver disease but at half the normal dose. Sedatives should be avoided if the patient is encephalopathic. Non-steroidal anti-inflammatory drugs should also be avoided because they can cause peptic ulceration, fluid retention (which will worsen ascites) and renal impairment (which can develop secondary to liver dysfunction).

The removal of hepatically cleared drugs from the body depends on two factors — enzyme functionality and the blood supply to the liver. The metabolic activity of the liver is reduced in both acute and severe chronic liver damage so the doses of many drugs must be reduced. In addition, the clearance of some drugs (eg, propranolol) is reliant on the rate at which they are presented to the liver. In hepatic cirrhosis the blood flow through the liver is reduced and portal hypertension may divert the blood away from the liver, increasing the bioavailability of some orally administered drugs. The degree to which a drug is bound to plasma proteins must also be considered. In chronic liver disease, for example, serum albumin levels are likely to be reduced, resulting in higher “free” concentrations of highly protein bound drugs, such as phenytoin and warfarin.

Drugs that undergo extensive hepatic metabolism will usually require a dose reduction. In acute hepatitis the general advice is to start with lower doses of hepatically cleared drugs and to titrate carefully. The summary of product characteristics should be consulted for each drug in question and, if possible, it is advisable to monitor plasma concentrations.

Pharmacists should also be aware of cases of hepatotoxicity when patients ask for advice on herbal medicines. For example, Shou Wu Wan, a Chinese herbal medicine used to treat alopecia, contains, among other ingredients, Radix Polygoni Multiflori. Seven of the 16 suspected reactions reported to the Committee on Safety of Medicines for Radix Polygoni Multiflori have described hepatobiliary disorders.

(see Panel 2). They should ensure that an accurate medication history is obtained when patients present with acute liver disease.

The second part of this article, to be published on 19 April, will look at viral hepatitis.

**To avoid further inflammation paracetamol should be not be used in acute hepatitis. It may be used in chronic liver disease but at half the normal dose**

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