Correction

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Jaundice is the commonest presentation of patients with liver and biliary disease. The cause can be established in most cases by simple non-invasive tests, but many patients will require referral to a specialist for management. Patients with high concentrations of bilirubin (> 100 µmol/l) or with evidence of sepsis or cholangitis are at high risk of developing complications and should be referred as an emergency because delays in treatment adversely affect prognosis.

Jaundice

Hyperbilirubinaemia is defined as a bilirubin concentration above the normal laboratory upper limit of 19 µmol/l. Jaundice occurs when bilirubin becomes visible within the sclera, skin, and mucous membranes, at a blood concentration of around 40 µmol/l. Jaundice can be categorised as prehepatic, hepatic, or posthepatic, and this provides a useful framework for identifying the underlying cause.

Around 3% of the UK population have hyperbilirubinaemia (up to 100 µmol/l) caused by excess unconjugated bilirubin, a condition known as Gilbert's syndrome. These patients have mild impairment of conjugation within the hepatocytes. The condition usually becomes apparent only during a transient rise in bilirubin concentration (precipitated by fasting or illness) that results in frank jaundice. Investigations show an isolated unconjugated hyperbilirubinaemia with normal liver enzyme activities and reticulocyte concentrations. The syndrome is often familial and does not require treatment.

Prehepatic jaundice

In prehepatic jaundice, excess unconjugated bilirubin is produced faster than the liver is able to conjugate it for excretion. The liver can excrete six times the normal daily load before bilirubin concentrations in the plasma rise. Unconjugated bilirubin is insoluble and is not excreted in the urine. It is most commonly due to increased haemolysis—for example, in spherocytosis, homozygous sickle cell disease, or thalassaemia major—and patients are often anaemic with splenomegaly. The cause can usually be determined by further haematological tests (red cell film for reticulocytes and abnormal red cell shapes, haemoglobin electrophoresis, red cell antibodies, and osmotic fragility).

Hepatic and posthepatic jaundice

Most patients with jaundice have hepatic (parenchymal) or posthepatic (obstructive) jaundice. Several clinical features may help distinguish these two important groups but cannot be relied on, and patients should have ultrasonography to look for evidence of biliary obstruction.

The most common intrahepatic causes are viral hepatitis, alcoholic cirrhosis, primary biliary cirrhosis, drug induced jaundice, and alcoholic hepatitis. Posthepatic jaundice is most often due to biliary obstruction by a stone in the common bile duct or by carcinoma of the pancreas. Pancreatic pseudocyst, chronic pancreatitis, sclerosing cholangitis, a bile duct stricture, or parasites in the bile duct are less common causes.

In obstructive jaundice (both intrahepatic cholestasis and extrahepatic obstruction) the serum bilirubin is principally
conjugated. Conjugated bilirubin is water soluble and is excreted in the urine, giving it a dark colour (bilirubinuria). At the same time, lack of bilirubin entering the gut results in pale, “putty” coloured stools and an absence of urobilinogen in the urine when measured by dipstick testing. Jaundice due to hepatic parenchymal disease is characterised by raised concentrations of both conjugated and unconjugated serum bilirubin, and typically stools and urine are of normal colour. However, although pale stools and dark urine are a feature of biliary obstruction, they can occur transiently in many acute hepatic illnesses and are therefore not a reliable clinical feature to distinguish obstruction from hepatic causes of jaundice.

**Liver function tests**

Liver function tests routinely combine markers of function (albumin and bilirubin) with markers of liver damage (alanine transaminase, alkaline phosphatase, and γ-glutamyl transferase). Abnormalities in liver enzyme activities give useful information about the nature of the liver insult: a predominant rise in alanine transaminase activity (normally contained within the hepatocytes) suggests a hepatic process. Serum transaminase activity is not usually raised in patients with obstructive jaundice, although in patients with common duct stones and cholangitis a mixed picture of raised biliary and hepatic enzyme activity is often seen.

Epithelial cells lining the bile canaliculi produce alkaline phosphatase, and its serum activity is raised in patients with intrahepatic cholestasis, cholangitis, or extrahepatic obstruction; increased activity may also occur in patients with focal hepatic lesions in the absence of jaundice. In cholangitis with incomplete extrahepatic obstruction, patients may have normal or slightly raised serum bilirubin concentrations and high serum alkaline phosphatase activity. Serum alkaline phosphatase is also produced in bone, and bone disease may complicate the interpretation of abnormal alkaline phosphatase activity. If increased activity is suspected to be from bone, serum concentrations of calcium and phosphorus should be measured together with 5′-nucleotidase or γ-glutamyl transferase activity; these two enzymes are also produced by bile ducts, and their activity is raised in cholestasis but remains unchanged in bone disease.

Occasionally, the enzyme abnormalities may not give a clear answer, showing both a biliary and hepatic component. This is usually because of cholangitis associated with stones in the common bile duct, where obstruction is accompanied by hepatocyte damage as a result of infection within the biliary tree.

**Plasma proteins and coagulation factors**

A low serum albumin concentration suggests chronic liver disease. Most patients with biliary obstruction or acute hepatitis will have normal serum albumin concentrations as the half life of albumin in plasma is around 20 days and it takes at least 10 days for the concentration to fall below the normal range despite impaired liver function.

Coagulation factors II, V, VII, and IX are synthesised in the liver. Abnormal clotting (measured as prolongation of the international normalised ratio) occurs in both biliary obstruction and parenchymal liver disease because of a combination of poor absorption of fat soluble vitamin K (due to absence of bile in the gut) and a reduced ability of damaged hepatocytes to produce clotting factors.

**Drugs that may cause liver damage**

**Analgesics**
- Paracetamol
- Aspirin
- Non-steroidal anti-inflammatory drugs

**Cardiac drugs**
- Methyldopa
- Amiodarone

**Psychotropic drugs**
- Monoamine oxidase inhibitors
- Phenothiazines (such as chlorpromazine)

**Others**
- Sodium valproate
- Oestrogens (oral contraceptives and hormone replacement therapy)

**The presence of a low serum albumin concentration in a jaundiced patient suggests a chronic disease process**
Serum globulin titres rise in chronic hepatitis and cirrhosis, mainly due to a rise in the IgA and IgG fractions. High titres of IgM are characteristic of primary biliary cirrhosis, and IgG is a hallmark of chronic active hepatitis. Ceruloplasmin activity (ferroxidase, a copper transporting globulin) is reduced in Wilson’s disease. Deficiency of α1 antitrypsin (an enzyme inhibitor) is a cause of cirrhosis as well as emphysema. High concentrations of the iron carrying protein ferritin are a marker of haemochromatosis.

Autoantibodies are a series of antibodies directed against subcellular fractions of various organs that are released into the circulation when cells are damaged. High titres of antimitochondrial antibodies are specific for primary biliary cirrhosis, and antismooth muscle and antinuclear antibodies are often seen in autoimmune chronic active hepatitis. Antibodies against hepatitis are discussed in detail in a future article on hepatitis.

### Imaging in liver and biliary disease

Plain radiography has a limited role in the investigation of hepatobiliary disease. Chest radiography may show small amounts of subphrenic gas, abnormalities of diaphragmatic contour, and related pulmonary disease, including metastases. Abdominal radiographs can be useful if a patient has calcified or gas containing lesions as these may be overlooked or misinterpreted on ultrasonography. Such lesions include calcified gall stones (10-15% of gall stones), chronic calcific pancreatitis, gas containing liver abscesses, portal venous gas, and emphysematous cholecystitis.

Ultrasonography is the first line imaging investigation in patients with jaundice, right upper quadrant pain, or hepatomegaly. It is non-invasive, inexpensive, and quick but requires experience in technique and interpretation. Ultrasonography is the best method for identifying gallbladder stones and for confirming extrahepatic biliary obstruction as dilated bile ducts are visible. It is good at identifying liver abnormalities such as cysts and tumours and pancreatic masses and fluid collections, but visualisation of the lower common bile duct and pancreas is often hindered by overlying bowel gas. Computed tomography is complementary to ultrasonography and provides information on liver texture, gallbladder disease, bile duct dilatation, and pancreatic disease. Computed tomography is particularly valuable for detecting small lesions in the liver and pancreas.

Cholangiography identifies the level of biliary obstruction and often the cause. Intravenous cholangiography is rarely used now as opacification of the bile ducts is poor, particularly in jaundiced patients, and anaphylaxis remains a problem. Endoscopic retrograde cholangiopancreatography is advisable when the lower end of the duct is obstructed (by gall stones or carcinoma of the pancreas). The cause of the obstruction (for example, stones or parasites) can sometimes be removed by endoscopic retrograde cholangiopancreatography to allow cytological or histological diagnosis.

 Percutaneous transhepatic cholangiography is preferred for hilar obstructions (biliary stricture, cholangiocarcinoma of the hepatic duct bifurcation) because better opacification of the ducts near the obstruction provides more information for planning subsequent management. Obstruction can be relieved by insertion of a plastic or metal tube (a stent) at either endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography.

Magnetic resonance cholangiopancreatography allows non-invasive visualisation of the bile and pancreatic ducts. It is

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<tr>
<th>Autoantibodies and immunoglobulin characteristics in liver disease</th>
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<tr>
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<td>Primary biliary cirrhosis</td>
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<td>Autoimmune chronic active hepatitis</td>
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<td>Primary sclerosing cholangitis</td>
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**Ultrasonography is the most useful initial investigation in patients with jaundice**

Computed tomogram of ampullary carcinoma (white arrow) causing obstruction of the bile duct (black arrow, bottom) and pancreatic ducts (white arrowhead)
superseding most diagnostic endoscopic cholangiopancreatography as faster magnetic resonance imaging scanners become more widely available.

Liver biopsy

Percutaneous liver biopsy is a day case procedure performed under local anaesthetic. Patients must have a normal clotting time and platelet count and ultrasonography to ensure that the bile ducts are not dilated. Complications include bile leaks and haemorrhage, and overall mortality is around 0.1%. A transjugular liver biopsy can be performed by passing a special needle, under radiological guidance, through the internal jugular vein, the right atrium, and inferior vena cava and into the liver though the hepatic veins. This has the advantage that clotting time does not need to be normal as bleeding from the liver is not a problem. Liver biopsy is essential to diagnose chronic hepatitis and establish the cause of cirrhosis.

Ultrasound guided liver biopsy can be used to diagnose liver masses. However, it may cause bleeding (especially with liver cell adenomas), anaphylactic shock (hydatid cysts), or tumour seeding (hepatocellular carcinoma or metastases). Many lesions can be confidently diagnosed by using a combination of imaging methods (ultrasonography, spiral computed tomography, magnetic resonance imaging, nuclear medicine, laparoscopy, and laparoscopic ultrasonography). When malignancy is suspected in solitary lesions or those confined to one half of the liver, resection is the best way to avoid compromising a potentially curative procedure.

S D Ryder is consultant hepatologist, Queen's Medical Centre, Nottingham NG7 2UH. The ABC of diseases of liver, pancreas, and biliary system is edited by I J Beckingham, consultant hepatobiliary and laparoscopic surgeon, department of surgery, Queen's Medical Centre, Nottingham (Ian.Beachingham@nottingham.ac.uk). The series will be published as a book later this year.

BMJ 2001;322:33-6

Summary points

- An isolated raised serum bilirubin concentration is usually due to Gilbert's syndrome, which is confirmed by normal liver enzyme activities and full blood count
- Jaundice with dark urine, pale stools, and raised alkaline phosphatase and 7-glutamyl transferase activity suggests an obstructive cause, which is confirmed by presence of dilated bile ducts on ultrasonography
- Jaundice in patients with low serum albumin concentration suggests chronic liver disease
- Patients with high concentrations of bilirubin (> 100 µmol/l) or signs of sepsis require emergency specialist referral
- Imaging of the bile ducts for obstructive jaundice is increasingly performed by magnetic resonance cholangiopancreatography, with endoscopy becoming reserved for therapeutic interventions

An experience that changed my practice

Breaking news

I had recently been appointed as senior registrar in respiratory medicine and was keen to impress. She was a young woman who had been referred to the chest clinic by her general practitioner. He was unhappy that her symptoms were recurring. The initial impression had been that she may have underlying asthma to explain her troublesome cough. However, investigations on these lines were negative, and even a methacholine challenge test proved inconclusive. Nevertheless, her cough seemed to have improved with lignocaine nebulisation.

She was intelligent and gave a good history. She denied any cough now, but was worried about noisy breathing at night. Her flustered husband often woke her up, she said, and told her to “stop whistling.” On examination she certainly had a few wheezes, but they were localised to the right side. The only investigation that had not been done during her previous visits was a bronchoscopy, and without wasting any time I proceeded to do just that despite a normal chest x-ray examination. A vascular, fleshy tumour was seen occluding a segment of the right lower lobe. There was a flurry of activity as multiple biopsies were taken along with photographs.

Despite being a little dopey the patient had sensed that something was amiss, and as I wheeled her out on the trolley she held my arm and emphatically asked me what I had found. I spent considerable time with her, gently explaining the possible diagnosis and allaying her anxiety as much as I could. She seemed to be reassured. I thought that it was a job well done and proceeded to the next case with considerable euphoria.

Suddenly there was a sickening thud followed by pandemonium. I rushed out to see a big man sprawled in the recovery room next to the woman I had just left. The nurses were pushing the crash trolley towards him, and she had sat up, frozen with fear. As I rushed towards the man I shouted to her, “What happened?” I still remember her frantic reply, “I just told him what you had found.”

For me this was an object lesson. Her husband had simply fainted and yet was seconds away from being possibly wrongly cardioverted. It made me realise that in communicating good or bad news a loving partner matters almost as much as the patient and is just as vulnerable. The capacity for fidelity, for belief, for suffering is mutual. These are things you do not find in books, but you become a little wiser and a little humbler from experience.

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Most of the outcome studies we examined used a rigorous methodology and rated highly for sample formation, adjusting for differences between the groups, and the objectivity of the outcomes being measured. However, they rarely considered the full implications of using the patient as the unit of analysis rather than randomising work units (such as practices). This may reflect the difficulties of researching a technology with which we are striving to keep up. Allocation by practice reduces the confounding effect of participating in research on those researched. However, computerisation in primary care is so widespread that finding practices which do not have the specific system feature to be evaluated as well as adequate controls is virtually impossible. Randomising practices to receive particular systems is also problematic. Not only is this expensive, but it often seems inconsequential; no sooner has the system been evaluated than it has been modified or updated and requires further evaluation.

The most fruitful areas of current research are preventive care, prescribing support, chronic disease monitoring, test ordering, and hospital referral. Few studies have dealt with nursing research in general practice, and little has been published on the impact of computers on other members of the primary care team.

Conclusions

It is over three decades since information technology was first introduced to primary care. In the 1960s its use centred on collating patient data; in the 70s the possibility of electronically linking primary and secondary care emerged; in the 80s computers were introduced to the consulting room; and in the 90s the internet provided the potential to obtain and review useful information during the consultation. After 30 years of analysing the “potential” benefits of computers, perhaps we should allow information technology in primary care to mature. In the 21st century we should accept that the computer is a useful tool. Rather than continually describing its capabilities, research must move forward to evaluate key outcomes for patients, practices, and the health service as a whole.12

The results of this systematic review are also available in a MS Access database, which can be obtained on disk from E Mitchell.

We thank everyone who provided us with information for this review. We thank the expert panel who participated in our Delphi study, which we know was time consuming. We also thank Dr Sue Ross for her advice and Michere Beaumont for secretarial support.

Contributors: EM conducted the Delphi study, designed the review protocol and search strategy, conducted the literature retrieval, reviewed all abstracts identified, read all potentially relevant articles, scored all articles included in the review, and wrote the initial draft of the paper. FS reviewed all abstracts identified, read all potentially relevant articles, scored all articles included in the review, and contributed to and edited the paper.

Funding: This study was funded by a grant from the Chief Scientist Office of the Scottish Executive Health Department (K-OPR/2/2D300).

Competing interests: None declared.

(Received 18 September 2000)

Corrections and clarifications

ABC of diseases of liver, pancreas, and biliary system: Investigation of liver and biliary disease

In this article by I J Beckingham and S D Ryder (6 January, pp 33-6) the flow diagram illustrating the investigation and referral of patients with jaundice in primary care unfortunately offered two management plans (instead of one) for patients with bilirubin concentrations > 100 μmol/L. The box below the first downward arrow should read “bilirubin ≥100 μmol/L.”

Randomised controlled trial of homoeopathy versus placebo in perennial allergic rhinitis with overview of four trial series

A keyboard slip resulted in an error in table 2 of this paper by Taylor and colleagues (19-26 August, pp 471-6). The mean difference between groups for evening nasal inspiratory peak flow should be 14.1 [not 12.1].

In-flight medical emergencies: an overview

In the section entitled “automatic external defibrillators” in this article by Tony Goodwin (25 November, pp 1338-41) it was wrongly stated that Virgin Atlantic Airways was the first airline to carry such equipment; in fact, British Caledonian was the first, in 1986.