Jaundice: applying lessons from physiology
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Abstract
Jaundice is a common symptom as well as a sign in medical and surgical gastroenterology practice. Understanding the pathway of bilirubin metabolism helps in a logical approach to the pre-hepatic, hepatocellular and cholestatic mechanisms of development of jaundice. Clinical evaluation and easily available blood tests in combination with non-invasive imaging should establish the diagnosis in most cases. Further management may require advanced and invasive techniques, the choice of which should be based on the benefit–risk ratio in a particular clinical scenario, access to these techniques and local expertise.

Keywords biliary imaging; bilirubin; jaundice; liver disease; metabolism

Jaundice is derived from the French word ‘jaune’ meaning yellow discoloration. It is the most common sign of liver disease. It is characterized by yellow discoloration of the skin and mucous membranes due to an abnormal increase in serum bilirubin concentration. Tissue deposition of bilirubin occurs only in the presence of hyperbilirubinaemia and is usually a sign of liver disease or, less commonly, haemolytic disorder. Clinical examination usually reveals the degree of hyperbilirubinaemia. The earliest place to manifest jaundice is the sclera owing to the high elastin level in the scleral tissue and the affinity of bilirubin for it. Scleral icterus indicates a serum bilirubin of at least 50 μmol. A greenish tinge to the icterus indicates long-standing jaundice and is due to oxidation of bilirubin to biliverdin.

Other causes of yellowing of the skin are carotoneoderma which is due to excess consumption of carotene-containing foods like carrots and leafy vegetables; here the sclera are spared and the yellow pigmentation is concentrated over the palms, soles, forehead and nasolabial creases. Drugs such as quinacrine and exposure to phenols also cause yellow discoloration. Another indicator of jaundice is dark urine or tea- or cola-coloured urine, which patients commonly describe.

There are various causes of jaundice and attempts to classify jaundice date back to Hippocrates. By the time of William Osler distinctions were made between obstructive and non-obstructive jaundice. From the latter part of the twentieth century, with better understanding of bilirubin metabolism, progress in imaging technology and sophisticated biochemical methods, it has been possible to elucidate the exact cause of jaundice. Hyperbilirubinaemia occurs when the balance between production and clearance is altered, and so logical evaluation of a jaundiced patient requires understanding of bilirubin production and metabolism.

Bilirubin metabolism
The metabolism and transport of bilirubin is summarized in Figure 1.

Sources of bilirubin
Bilirubin, a tetrarpyrole pigment moiety, is a breakdown product of haem (ferroprotoporphyrin IX). In a healthy person daily bilirubin production averages about 0.5 mmol (250–300 mg). About 80% of this bilirubin is derived from breakdown of haemoglobin from senescent RBCs in the reticuloendothelial system, 15% from ineffective erythropoiesis in the bone marrow, and 5% from turnover of haem proteins such as myoglobin, catalases and the cytochrome enzyme system elsewhere in the body.

Production of bilirubin
The production of bilirubin takes place in the reticuloendothelial system in a two-step process. The first step is oxidation of haem by haem oxygenase, which involves breaking open of the α-bridge, resulting in the formation of biliverdin. The second

Overview of bilirubin metabolism and transport
Haem oxygenase

Biliverdin reductase

OATP

UDP-GT

MRP2

PLASMA

HEPATOCELLAR

BILE

Haemoglobin and Haem proteins

Biliverdin

Bilirubin

Albumin–bilirubin complex

Bilirubin glucuronide

Bilirubin glucuronide

MRP, multidrug resistance protein; OATP, organic anion transporter; UDP-GT, uridine diphosphoglucuronyl transferase

Figure 1
step is reduction of this green pigment by biliverdin reductase to colourless bilirubin.

**Plasma transport**
The bilirubin formed in the reticuloendothelial cells is virtually insoluble in water and potentially toxic. To be transported in blood it binds reversibly and non-covalently with albumin.

**Hepatic uptake**
Unconjugated bilirubin tightly bound to albumin is transported to the liver where the bilirubin, but not the albumin, is taken up across the basolateral membrane of the hepatocytes by a carrier-mediated transport process, possibly via a member of the organic anion transporter family. Within the cytosol, two cytosolic binding proteins, ligandin Y and Z, transport the bilirubin to the smooth endoplasmic reticulum of the hepatocyte for conjugation with glucuronic acid and also to prevent efflux of bilirubin back into the plasma.

**Hepatic conjugation**
In the presence of the co-substrate uridine diphosphate, the enzyme uridine diphosphoglucuronyl transferase (UDP-GT) mediates conjugation of the hydrophobic bilirubin to hydrophilic bilirubin monoglucuronide and diglucuronide conjugates, which are suitable for excretion. UDP-GT activity is well maintained in both acute and chronic hepatocellular damage, and even increased in cholestasis.

**Biliary excretion**
Bilirubin monoglucuronide and diglucuronide then diffuse from the endoplasmic reticulum towards the apical cell membrane or the canalicular membrane to be excreted into the bile canaliculi by an ATP-dependent export pump belonging to the multidrug resistance protein (MRP) 2. This represents the rate-limiting step in synthesis in bilirubin metabolism. This step is affected in both acute and chronic hepatocellular injury, thus explaining the rise in predominately conjugated bilirubin in such cases. Small amounts of conjugated bilirubin are secreted across the sinusoidal membrane by MRP3 directly into the bloodstream and undergo renal excretion. Normally 80–85% of the bile is made of bilirubin diglucuronide and 15–19% of bilirubin monoglucuronide, with the remainder comprising traces of unconjugated bilirubin. The conjugated bilirubin excreted into bile drains into the duodenum and passes unchanged in the proximal small bowel until it reaches the distal small bowel and colon, where it is hydrolysed by intestinal bacterial β-glucuronidase to unconjugated bilirubin. This is then further reduced by the gut flora to colourless urobilinogen. 80–90% of this is excreted in the faeces either unchanged or oxidized to urobilin or stercobilin, which imparts the natural colour to the stools. The remaining 10–20% of the urobilinogen is absorbed passively and circulated in the enterohepatic circulation for reconjugation and excretion in the bile. A trace of this urobilinogen in the enterohepatic circulation escapes hepatic uptake and enters the systemic circulation to be filtered across the glomerulus and excreted in the urine.

**Measurement of bilirubin**
Serum bilirubin is measured using a variation of the original Van den Bergh colorimetric reaction. Indirect and direct refer to the total and conjugated bilirubin concentrations respectively. With the Van den Bergh method, the normal total serum bilirubin concentration is 17 μmol ( < 1 mg/dl). Up to 30%, that is 5.1 μmol (0.3 mg/dl) is in the conjugated form. Increased understanding of bilirubin metabolism and sophisticated methods of bilirubin measurement have led to the belief that the bilirubin monoglucuronide fraction is higher in jaundiced patients with hepatobiliary disease. Unconjugated bilirubin is bound to albumin and hence not filtered in the glomerulus, but conjugated bilirubin is; almost all of it is reabsorbed by the proximal tubules and very small traces are excreted in urine. Thus, the presence of bilirubinuria is a suggestion of liver disease. However, in prolonged cholestatic jaundice the conjugated bilirubin fraction in serum binds to albumin covalently; bilirubin levels decline more slowly than clinical recovery owing to the longer half-life of albumin.

**Disorders of bilirubin metabolism**
Hyperbilirubinaemias can result from any defects in the steps of bilirubin metabolism mentioned earlier. Thus overproduction, impaired uptake and conjugation lead to unconjugated/indirect hyperbilirubinaemia, and impaired excretion of bilirubin from damaged hepatocytes or bile ducts leads to direct/conjugated hyperbilirubinaemia.

**Overproduction of bilirubin**
Haemolytic disorders, either inherited or acquired, leading to excessive haem breakdown cause hyperbilirubinaemia. In these conditions, the serum bilirubin rarely exceeds 86 μmol/litre (5 mg/dl). Generally these groups of patients have elevated serum haptoglobin and reticulocyte counts, and there are no alterations in liver enzymes (Table 1). Accelerated haemolysis, especially in inherited conditions, is associated with formation of pigment gallstones, which may obstruct the biliary tree and lead to conjugated hyperbilirubinaemia with elevated liver enzymes.

**Impaired uptake and conjugation**
Certain drugs, such as rifampicin and probenecid, cause unconjugated hyperbilirubinaemia by reducing hepatic uptake. Rare inherited syndromes such as Crigler–Najjar syndromes I and II and Gilbert’s syndrome are caused by dysfunctional or absence of UDP-GT Genzyme activity. Crigler–Najjar syndrome type I is very rare and is characterized by a complete absence of UDP-GT activity leading to neonatal kernicterus and death. Crigler–Najjar syndrome type II is more common; there is reduced activity of the enzyme and patients live to adulthood. Gilbert’s syndrome is quite common and is due to reduced enzyme activity; it manifests clinically as very mild jaundice, especially in times of physiological stress.

**Impaired excretion**
Elevated conjugated hyperbilirubinaemias occur in two rare syndromes, namely Rotor’s syndrome, which is due to defective storage of bilirubin in the hepatocytes, and Dubin–Johnson syndrome, which is due to a defect in the MRP2 gene. Both these cause asymptomatic jaundice and run a benign course. When a clinician encounters a patient with jaundice, a basic liver function test can indicate the pattern of jaundice, whether hepatocellular or cholestatic. In hepatocellular conditions
(Table 2) there is a disproportionate rise in concentrations of cellular enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) compared with alkaline phosphatase (ALP). However, in cholestatic conditions (Table 3) there is a significant rise in the ALP rather than ALT. This is not a strict criterion, but can be used as a general guide to direct the

**Causes of isolated hyperbilirubinaemia**

<table>
<thead>
<tr>
<th>Hyperbilirubinaemia</th>
<th>Cause</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect</td>
<td>Inherited haemolytic disorders</td>
<td>Spherocytosis, elliptocytosis</td>
</tr>
<tr>
<td></td>
<td>Acquired haemolytic disorders</td>
<td>Glucose-6-phosphate dehydrogenase and pyruvate kinase deficiency, Sickle cell disorder</td>
</tr>
<tr>
<td></td>
<td>Ineffective erythropoiesis</td>
<td>Immune haemolytic anaemia, Paroxysmal nocturnal haemoglobinuria</td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
<td>Crigler–Najjar syndrome types I and II, Gilbert’s syndrome, Dubin–Johnson syndrome, Rotor syndrome</td>
</tr>
</tbody>
</table>

**Hepatocellular conditions causing jaundice**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis</td>
<td>Hepatitis A, B, C and E, Epstein–Barr virus, Cytomegalovirus, Herpes simplex</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Dose dependent, e.g. paracetamol overdose, Idiosyncratic, e.g. isoniazid</td>
</tr>
<tr>
<td>Autoimmune hepatitis/overlap syndromes</td>
<td>Wilson’s disease, Haemachromatosis, Non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>Medications/drugs</td>
<td>Non-steroidal anti-inflammatory drugs, Insulin, Oral contraceptive pill</td>
</tr>
<tr>
<td>Environmental toxins</td>
<td>Vinyl chloride, carbon tetrachloride, bush tea, kava kava, mushroom</td>
</tr>
<tr>
<td>Metabolic causes</td>
<td>Wilson’s disease, Haemachromatosis, Non-alcoholic fatty liver disease, α1-antitrypsin deficiency</td>
</tr>
<tr>
<td>Vascular causes</td>
<td>Budd-Chiari syndrome, Ischaemic hepatitis</td>
</tr>
</tbody>
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**Cholestatic conditions causing jaundice**

<table>
<thead>
<tr>
<th>Jaundice</th>
<th>Cause</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic hepatitis</td>
<td>Drugs</td>
<td>Pure cholestasis – anabolic steroids, oral contraceptive pill, Cholestatic hepatitis – co-amoxiclav, flucloxacillin, erythromycin estolate, Chronic cholestasis – chlorpromazine</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td></td>
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<tr>
<td>Primary sclerosing cholangitis</td>
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<tr>
<td>Vanishing bile duct syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inherited</td>
<td></td>
<td>Chronic rejection, Drugs – chlorpromazine, Progressive familial intrahepatic cholestasis</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td>Cholestasis of pregnancy, Sepsis, Total parenteral nutrition, Paraneoplastic syndrome, Graft vs. host disease, Benign postoperative cholestasis</td>
</tr>
<tr>
<td>Obstructive</td>
<td>Malignant</td>
<td>Cholangiocarcinoma, Pancreatic cancer, Gallbladder cancer, Periampullary cancer, Malignant involvement of the porta hepatis, lymph nodes</td>
</tr>
<tr>
<td>Benign</td>
<td></td>
<td>Choledocholithiasis, Primary sclerosing cholangitis, Chronic pancreatitis, AIDS cholangiopathy</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; EBV, Epstein–Barr virus.
investigations appropriately. Bilirubin is, however, raised in both conditions and cannot be used to differentiate between the pathological processes. Prolonged prothrombin time can occur with both hepatocellular and long-standing cholestatic jaundice. Correction of the prothrombin time after administration of vitamin K is suggestive of cholestasis, which would have resulted from malabsorption of vitamin K. Failure of correction of the prothrombin time indicates inability to synthesize clotting factors from vitamin K, indicating significant hepatocellular injury. Thus the pattern of liver enzymes, albumin and prothrombin time usually indicates whether a jaundiced patient has a hepatocellular or a cholestatic disease.

Hepatocellular conditions that cause jaundice most commonly include viral hepatitis, alcohol, drugs and cirrhosis from any cause. Wilson’s disease should be considered in patients who are young (< 40 years of age); it mimics acute viral hepatitis with disproportionate hyperbilirubinemia (due to Coombs’ negative haemolytic anaemia), a particularly low ALP level, and an ALP to bilirubin ratio of less than 4. Middle-aged women presenting with jaundice, malaise, arthralgias and fever should raise the suspicion of autoimmune hepatitis. Alcohol-related liver diseases are associated with a minimal or no elevation of ALT (usually less than 250 U) and an AST to ALT ratio of at least 2:1. However, in patients with acute viral hepatitis, toxoin- and drug-mediated or even ischaemic hepatitis, the ALT can reach very high values, typically greater than 500 U in the acute setting. Drug-induced jaundice is either dose related, as with paracetamol overdose, or idiosyncratic, occurring in a minority of patients taking a large number of drugs such as such as diclofenac, phenytoin, co-amoxiclav and antituberculous drugs. In patients with jaundice due to cirrhosis, there is a modest elevation of bilirubin and liver enzymes as it represents the end stage of chronic hepatocellular injury. Chronic viral hepatitis should always be a consideration, especially in patients with risk factors (previous infusion of blood products, surgical interventions and intravenous drug abuse). Clues to the diagnosis of haemochromatosis are the presence of diabetes, arthritis and greyish complexion of the skin, although patients are increasingly diagnosed at an early stage. Cirrhosis due to α1-antitrypsin deficiency may not coexist with lung disease and can be identified only by specific investigations.

When the pattern of liver injury is cholestatic, the next step is to investigate whether the cholestasis is due to biliary obstruction or not, using a variety of imaging modalities. In patients with apparently non-obstructive cholestatic jaundice the diagnosis is often made by serological testing and/or liver biopsy. A number of conditions that cause hepatocellular jaundice can also present a cholestatic picture such as acute alcoholic hepatitis, hepatitis B and C, ductopenic rejection after liver transplantation. A variety of drugs also cause cholestatic jaundice, including the esterolate salt of erythromycin, ampicillin, flucoxacinil, clavulnic acid, imipramine, chlorpromazine and oral contraceptive pills; in these cases the jaundice has a temporal relationship with drug usage. Drug-induced cholestatic jaundice usually resolves after withdrawal of the offending drug, but occasionally can lead to chronic cholestasis and progressive fibrosis. Primary biliary cirrhosis should be suspected in middle-aged women presenting with pruritus, jaundice and excessive fatigue. Primary sclerosing cholangitis is characterized by intrahepatic and extrahepatic stricturing, and 75% of these patients have inflammatory bowel disease. Cholestasis of pregnancy occurs in the third trimester of pregnancy and tends to recur in subsequent pregnancies. Other causes of non-obstructive intrahepatic cholestatic jaundice include sepsis, which leads to down-regulation of transporters such as MRP2 by proinflammatory cytokines, and total paren-teral nutrition.

Obstructive jaundice implies obstruction of the biliary system either within or outside of the liver. Generally jaundice only develops when the majority of the biliary drainage is impaired, so obstruction from truly intrahepatic cholangiocarcinoma may not cause clinical jaundice. Both benign (choledocholithiasis) and malignant (pancreatic, bile duct and gallbladder cancers) conditions present with jaundice. Chronic pancreatitis can cause distal bile duct stricturing where the duct traverses the head of the pancreas. AIDS cholangiopathy is due to opportunistic infection of the biliary epithelium, resulting in stricturing mimicking primary sclerosing cholangitis. Biliary strictures causing jaun-dice also can occur after hepatic arterial infusion of chemotherapeutic agents, or may result from surgical injury to the bile duct or the hepatic artery.

Diagnostic approach to the patient with jaundice

The key steps in the evaluation of a patient with jaundice are:

• history taking and clinical examination
• screening laboratory tests and formulation of a working differential diagnosis
• specialised tests to further narrow down the diagnosis.

History and clinical examination

A carefully elicited history and physical examination in the light of routine laboratory screening tests can correctly differentiate between hepatocellular and cholestatic jaundice in up to 75% of cases. Physical examination provides important clues in a patient with jaundice. Fever and abdominal tenderness, especially in the right upper quadrant, suggest cholangitis and biliary sepsis. A palpable gallbladder has been considered a sign suggestive of pancreatic neoplasm and against choledocholithiasis (Courvoisier’s law), but this finding is neither sensitive nor specific. Ascites, spider naevi and gynaecomastia are suggestive of chronic parenchymal liver disease. Xanthomas are suggestive of primary biliary cirrhosis, skin hyperpigmentation in haemachromatosis and Kayser-Fleischer rings in Wilson’s disease.

Initial laboratory evaluation

A battery of tests is helpful in the initial investigation of a jaun-diced patient. These include bilirubin, liver enzymes (ALT, AST and ALP) and prothrombin time. The activity of ALP rises significantly in the setting of biliary obstruction and intrahepatic cholestasis. However, an increase in ALP may reflect release of isoenzymes from extrahepatic tissues, especially from bones. Thus more specific markers of biliary canicular enzymes, such as γ-glutamyl transferase and 5’-nucleotidase, are estimated to confirm the hepatic origin of the elevated ALP level. Amino transferases AST (found in the cytosol and mitochondria of hepatocytes and other extrahepatic tissues such as cardiac and...
skeletal muscle) and ALT (predominantly seen in the cytosol of hepatocytes) are elevated in liver cell damage caused by viral infection, ischaemia, toxins and drugs. Predominant aminotransferase (ALT, AST) elevation compared with ALP suggests hepatocellular disease. However, chronic alcohol excess leads to a deficiency of pyridoxal 5-phosphate, a necessary co-substrate for aminotransferases. Deficiency of co-substrate results in a modest or no elevation of ALT (and a corresponding serum AST to ALT ratio of >2) that has been considered characteristic of alcoholic liver disease.18 Acute Wilson’s disease can also present with a similar biochemical picture. Measurement of markers of copper metabolism, such as caeruloplasmin and serum copper, in the setting of acute Wilson’s is of little use.4,19 Haemolysis leads to AST release from erythrocytes and causes excess elevation of AST, with an AST to ALT ratio above 2.2. A combination of high bilirubin (due to coexistent haemolysis) and low ALP is also a characteristic feature of acute liver failure due to Wilson’s disease. A combination of a ratio of ALP (U) to total bilirubin (mg/dl) of below 4 and an AST to ALT ratio above 2.2 has a very high sensitivity and specificity for the diagnosis of Wilson’s disease in subjects presenting with acute liver failure.

There are, however, exceptions to the rule as a rise in ALT to up to ten times the upper limit of normal can occur in choledocholithiasis with cholangitis.20 In addition, the levels of liver enzyme elevation do not reflect the severity of liver injury nor the prognosis of the patient.19

Prothrombin time is a measure of the activity of the clotting factors I, II, V, VII and X, which are synthesized in the liver. Prolongation of the prothrombin time reflects hepatocellular injury or a deficiency of vitamin K, which is involved in the synthesis of clotting factors II, VII, IX and X. Correction of prothrombin time after parenteral administration of vitamin K reflects cholestasis/biliary obstruction causing vitamin K malabsorption.

Thus, integrating the history, physical examination and initial laboratory tests helps to distinguish pre-hepatic from hepatocellular or cholestatic causes of jaundice. Further selection of appropriate special investigations, imaging in particular for biliary obstruction, is based on this initial information.

### Imaging studies

Imaging methods used for the evaluation of jaundice are summarized in Table 4.

#### Abdominal ultrasonography

Abdominal ultrasonography21–23 is the initial imaging of choice to obtain information about the hepatic parenchyma and the intrahepatic and extrahepatic biliary tree. It is non-invasive and reproducible. However, there is an element of interobserver variation in real-time ultrasonography. A major disadvantage is that interpretation can be difficult in obese patients, and periampullary lesions and distal common bile duct pathology cannot be easily made out because of obscuring bowel gas. The sensitivity and specificity of detecting biliary obstruction in jaundiced patients vary from 55 to 91%, and 82 to 95% respectively, depending on the site of obstruction and radiographer’s experience.

#### CT scan of the abdomen

Abdominal CT21,23–25 is an alternative means of obtaining information about the obstructed biliary tree; it gives a more accurate measurement of the calibre of the dilated biliary tree and the level of obstruction. It is also good for imaging of the pancreas and periampullary region. CT has the ability to detect subcentimetre lesions. Sensitivity is in the range of 63–96% with specificity of up to 100% for detecting the calibre of the dilated biliary tree and locating mass lesions.

### Comparison of performance characteristics of imaging modalities

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Morbidity (%)</th>
<th>Mortality (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal ultrasonography</td>
<td>55–91</td>
<td>82–95</td>
<td>–</td>
<td>–</td>
<td>Non-invasive, portable, operator dependent, difficult interpretation in obese patients and bowel gas may obscure distal biliary tree</td>
</tr>
<tr>
<td>Abdominal CT</td>
<td>63–96</td>
<td>93–100</td>
<td>–</td>
<td>–</td>
<td>Non-invasive, better resolution than ultrasound, radiation- and contrast-induced renal toxicity</td>
</tr>
<tr>
<td>MRCP</td>
<td>84–100</td>
<td>94–98</td>
<td>–</td>
<td>–</td>
<td>Non-invasive, superior to cross-sectional imaging for biliary tree visualization. Claustrophobia limits patient compliance, may miss small-calibre duct disease</td>
</tr>
<tr>
<td>ERCP</td>
<td>89–98</td>
<td>89–100</td>
<td>3</td>
<td>0.2</td>
<td>Direct imaging, permits sampling, therapeutic intervention, associated complications</td>
</tr>
<tr>
<td>PTC</td>
<td>98–100</td>
<td>89–100</td>
<td>3</td>
<td>0.2</td>
<td>Similar to ERCP but more useful for lesions proximal to the common hepatic duct, difficult if intrahepatic ducts not dilated</td>
</tr>
<tr>
<td>EUS</td>
<td>89–97</td>
<td>67–98</td>
<td>–</td>
<td>–</td>
<td>Superior to cross-sectional imaging, ability to obtain histology from pancreatic lesions</td>
</tr>
</tbody>
</table>

ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; MRCP magnetic resonance cholangiopancreatography; PTC, percutaneous transhepatic cholangiography.

Table 4
Magnetic resonance cholangiopancreatography
Magnetic resonance cholangiopancreatography (MRCP)\textsuperscript{26} allows clear-cut and rapid delineation of the biliary tree, and is superior to ultrasonography or CT. With increasing availability, it’s use is growing in clinical practice. It has a sensitivity of 84–100% and specificity of 94–98% in detecting lesions of the biliary tree. An advantage of this modality is that it does not require administration of contrast and has running costs comparable to those of diagnostic endoscopic retrograde cholangiopancreatography (ERCP).

Endoscopic retrograde cholangiopancreatography
ERCP has been considered the ‘gold standard’ for the investigation of biliary tree pathology in most cases. It involves passage of an endoscope into the duodenum, catheterization of the ampulla of Vater, and injection of contrast medium into the biliary tree and/or pancreatic duct for direct visualization of the pancreaticobiliary tree. It is invasive, involving the use of sedation, analgesia and contrast medium. It is highly accurate in diagnosing obstruction of the biliary tree, and permits acquisition of biopsy or brushings for cytology, and therapeutic procedures such as sphincterotomy, stone extraction, stricture dilatation and stent insertion. ERCP is highly accurate in the diagnosis of biliary tree pathology with a sensitivity of 89–98% and specificity of 89–100%\textsuperscript{21}. The overall technical success rate is above 90%. However, it is also associated with risks of pancreatitis (2% in low-risk individuals and an overall mean rate of around 5%). Other complications such as bleeding, perforation and respiratory complications (3%) are more common when interventional procedures are performed.\textsuperscript{27} The overall cost of ERCP is much higher than that of all other non-invasive imaging.

Percutaneous transhepatic cholangiography
Percutaneous transhepatic cholangiography (PTC) involves passage of a fine-needle catheter through the skin into the liver to cannulate a peripheral bile duct until bile is aspirated, and obtaining images of the biliary tree with injection of contrast medium. This procedure is used when ERCP has been unsuccessful or considered not feasible owing to altered anatomy (following surgery). In patients with known hilar strictures, PTC has been recommended by some as a preferred initial investigation because of the modest success rate when ERCP is used for decompression in such a clinical scenario. The procedure has a sensitivity and specificity of 98–100% and 89–100% respectively. The morbidity and mortality are similar to that of ERCP.\textsuperscript{28,29}

Endoscopic ultrasonography
Endoscopic ultrasonography (EUS) generates images of the biliary tree with a sensitivity and specificity comparable to that of MRCP.\textsuperscript{30,31} and has the advantage of permitting sampling of pancreatic lesions and more accurate staging of neoplasms comparable to that of CT. In selected cases of doubtful obstruction of the biliary tree, the choice of direct progression to therapeutic ERCP following EUS is an added advantage. The risk of the procedure is similar to that of any diagnostic upper gastrointestinal endoscopy, with mortality and morbidity rates of less than 0.1% when biopsy is involved.\textsuperscript{32} EUS is useful when the patient is thought to be a high-risk candidate for ERCP or PTC.

Nuclear imaging studies
Although a non-invasive test useful in investigating biliary disease, such as cholecystitis and biliary dyskinesias, nuclear imaging has limited value in the investigation of a jaundiced patient.\textsuperscript{22}

Diagnostic strategies for imaging
The choice and order of imaging modalities depend on the clinical probability of biliary obstruction causing jaundice (Figure 2). Based on a clinical decision analysis model of obstructive jaundice, several diagnostic imaging modalities have been compared.\textsuperscript{33,34} The implication of these studies is that, if the suspicion of biliary obstruction is high and initial ultrasound does not reveal a dilated biliary system, then further studies to visualize the biliary system should be pursued. Thus in a jaundiced patient the initial approach to investigation of the biliary tree would be either an ultrasound or CT scan. If the bile ducts are dilated the next step would be direct visualization with ERCP or PTC, with institution of appropriate treatment at the same sitting if possible. However, if the biliary tree is not dilated on the initial screening ultrasound or CT, then further investigations are based on the clinical likelihood
of biliary obstruction. If the likelihood of biliary obstruction is low, then investigations should be directed towards diagnosing intrinsic liver disease. In cases of intermediate suspicion of biliary obstruction, then MRCP or EUS is the investigation of choice before investigation of hepatic disorders. In patients in whom ERCP or PTC is the preferred investigation, the default choice would be ERCP as it offers a broader range of interventional options than PTC. Clinical strategies depend heavily on the local expertise and availability of a particular specialist procedure such as MRCP and EUS.

In a patient with biliary obstruction, therapy is directed at relieving the obstruction. The available options are interventional endoscopic and radiological modalities, including sphincterotomy, balloon dilatation of focal strictures, and placement of drains or stents. The choice of investigatory and therapeutic strategy will depend on the location of the obstruction and its likely cause. Focal intrahepatic strictures are generally amenable to a radiological approach to balloon dilatation. Lesions distal to the confluence of the hepatic ducts are generally amenable to ERCP.

Serology

When imaging studies do not reveal biliary obstruction, jaundiced patients with biochemical evidence of cholestasis and or hepatocellular dysfunction should be evaluated for evidence of underlying liver disease. In the light of clinical suspicion, based on the initial clinical history and presentation, various laboratory tests should be performed. These include hepatitis viral serology for hepatitis B and C in chronic cases, and hepatitis A and E, Epstein–Barr virus and cytomegalovirus for acute presentations; iron studies such as serum iron concentration, ferritin and transferrin saturation for haemochromatosis; serum copper and ceruloplasmin for Wilson’s disease; autoantibody profile (antinuclear antibodies, liver-kidney microsomal antibody and smooth muscle antibody) with serum immune electrophoresis or immunoglobulin estimation for autoimmune hepatitis; antimitochondrial and antibody for primary biliary cirrhosis; and α1-antitrypsin for α1-antitrypsin deficiency. If none of these serological investigations reveals the cause of jaundice, liver biopsy is suggested, which will which provide precise details of the hepatic lobular architecture; special histological stains can be used to elucidate the cause in most cases of undiagnosed persistent jaundice.

Summary

The key to the diagnosis and management of patients with jaundice is to distinguish initially whether the pattern of liver injury is hepatocellular or cholestatic. In cholestatic conditions, it is important to consider non-obstructive causes and to confirm biliary obstruction with less invasive imaging modalities, followed by appropriate techniques to establish the diagnosis as well as institute prompt treatment. The choice of test and technique in an individual patient depends on a combination of clinical decision making, availability and expertise in particular techniques.

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