Investigation of jaundice

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Abstract

Jaundice is a clinical sign that reflects an accumulation of bilirubin in the blood. It can result from increased bilirubin production, inability of the liver to conjugate bilirubin or failure to excrete bilirubin into the biliary tree. Appropriate investigation of jaundice starts with a history of associated symptoms, and risk factors for liver disease. Clinical examination should look for stigmata of chronic liver disease and signs of specific liver diseases. Initial blood tests should assess liver injury and synthetic function. A combination of urinalysis and the pattern of abnormal liver function tests can indicate whether the jaundice is likely to be hepatitic or cholestatic, and can guide further investigations. This review describes bilirubin metabolism, the causes of jaundice and the appropriate investigation of jaundice.

Keywords Biliary obstruction; cirrhosis; haemolytic anaemia; hepatitis; hyperbilirubinaemia; jaundice; liver injury; MRCP

Key points

- History, examination, urinalysis and blood tests should determine whether jaundice is likely to reflect cholestasis, hepatic injury or isolated hyperbilirubinaemia.
- In the first instance:
  - Isolated bilirubinaemia should prompt a haemolysis screen
  - Cholestatic jaundice should prompt urgent liver ultrasonography
  - Hepatitic jaundice should prompt a liver aetiology screen
- A variety of imaging techniques can be used to investigate jaundice. Ultrasonography is the initial investigation. For suspected cholestatic jaundice, subsequent investigation typically involves magnetic resonance cholangiopancreatography, with endoscopic retrograde cholangiopancreatography reserved for treatment. For hepatic pathology, cross-sectional imaging can be more valuable
- Liver biopsy can be considered if the cause of jaundice remains unclear and this is going to affect treatment

Definition of jaundice

Jaundice describes yellow discoloration of the skin, mucous membranes and sclera. Normal serum bilirubin levels are <17 micromol/litre; jaundice becomes clinically apparent when bilirubin is >34 micromol/litre. Jaundice can signify underlying hepatobiliary or pancreatic disease that requires systematic investigation.

Pathology and pathogenesis

An understanding of bilirubin metabolism and clearance can aid effective management of jaundice (Figure 1). Most bilirubin (80%) is formed after the breakdown of red blood cells. The typical lifespan of a red blood cell is 120 days, after which it is destroyed in the reticuloendothelial system. Haem, from haemoglobin, is converted to biliverdin and then (unconjugated) bilirubin. Bilirubin circulates in blood bound to albumin until it is taken up by hepatocytes.

Within the hepatocyte, bilirubin is conjugated with glucuronic acid by UDP-glucuronosyltransferase, rendering it water-soluble. Conjugated bilirubin can be excreted into bile and pass into the gut. Only 2% of bilirubin in the gut is absorbed, the remainder being degraded by colonic bacterial enzymes to form urobilinogen. Some urobilinogen re-enters the liver, but about 90% is converted into stercobilinogen, which is excreted in the faeces.

Determining whether the hyperbilirubinaemia is conjugated or unconjugated can reveal where bilirubin metabolism/clearance is defective and therefore give clues to the underlying aetiology:

- **Unconjugated hyperbilirubinaemia** can result from overproduction of bilirubin, impaired hepatic uptake or abnormalities of bilirubin conjugation (Table 1).
- **Conjugated hyperbilirubinaemia** can be caused by hepatocellular injury, intrahepatic cholestasis or biliary obstruction (Table 2).

Diagnostic work-up in jaundice

The initial diagnostic work-up of jaundiced patients includes a thorough history and examination.

History

Enquire about:

- the onset and duration of jaundice
- associated symptoms (itch, loss of appetite, weight loss, pale stools, steatorrhoea, dark urine, fever, abdominal pain)
- history of obesity, metabolic syndrome and other systemic conditions such as cystic fibrosis and inflammatory bowel disease

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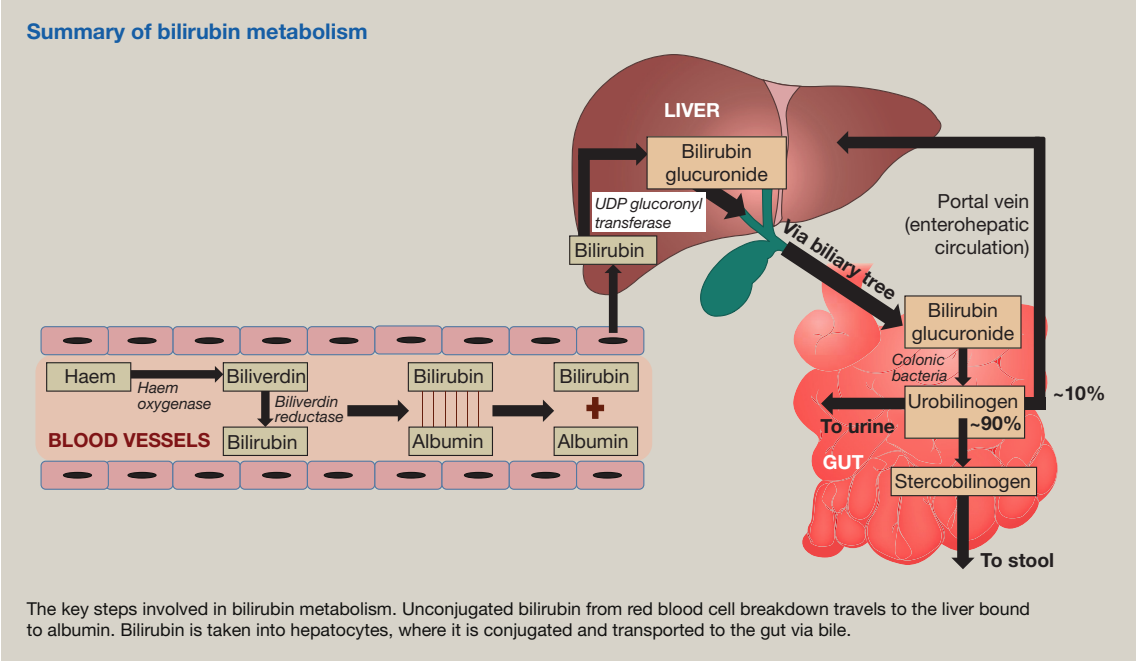

Figure 1

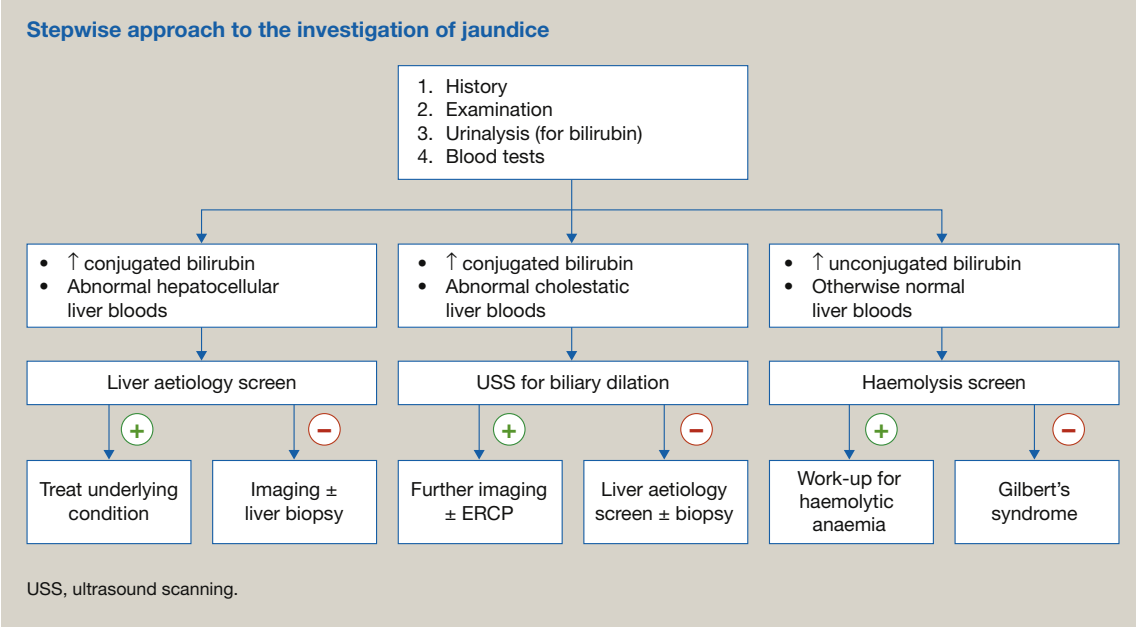

Figure 2

- drug history (including prescribed medications, over-the-counter medications and recreational drug use)
- family history (jaundice, liver disease, cancer, haemolytic anaemia)
- social history (alcohol consumption, occupation)
- risk factors for viral hepatitis and HIV (sexual contacts, blood transfusions, intravenous drugs, tattoos, country of birth, foreign travel).

Examination

Physical examination can reveal signs of chronic liver disease, such as:

- finger clubbing
- leuconychia
- palmar erythema
- Dupuytren's contracture
- bruising
- scratch marks
- spider naevi

Causes of unconjugated hyperbilirubinaemia

Increased bilirubin production	Impaired hepatic bilirubin uptake	Impaired bilirubin conjugation
Extra- or intravascular haemolysis caused by: • Red blood cell membrane disorders (e.g. hereditary spherocytosis) • Red blood cell enzyme disorders (e.g. glucose-6-phosphate dehydrogenase deficiency) • Haemoglobin disorders (e.g. sickle cell anaemia) • Autoimmune haemolytic anaemia	Hepatic failure Portosystemic shunts Medications (rifampicin, probenecid) Congestive cardiac failure	Gilbert's syndrome Crigler–Najjar syndrome Neonate Advanced cirrhosis Hyperthyroidism Medications (ethinylestradiol)

Table 1

Causes of conjugated hyperbilirubinaemia

Intrahepatic cholestasis	Hepatocellular injury	Extrahepatic cholestasis
Primary biliary cirrhosis Alcoholic hepatitis Non-alcoholic steatohepatitis Viral hepatitis Drugs (e.g. corticosteroids, antibiotics and neuroleptic medications) Herbs/toxins (e.g. Jamaican bush tea, arsenic) Infiltrative diseases (e.g. lymphomas, sarcoidosis) Pregnancy Hereditary conditions	Viral hepatitis Alcoholic hepatitis Non-alcoholic steatohepatitis Autoimmune liver disease Drugs (including idiosyncratic drug reactions) Neoplasia (e.g. hepatocellular carcinoma) Infiltrative diseases (e.g. lymphomas, sarcoidosis) Vascular (e.g. Budd–Chiari syndrome, severe heart failure) Metabolic/hereditary conditions	Choledocholithiasis (gallstone disease) Neoplasia (e.g. pancreatic cancer, cholangiocarcinoma) Primary sclerosing cholangitis Acute or chronic pancreatitis Benign strictures

Table 2

- gynaecomastia
- caput medusae
- hepatomegaly
- splenomegaly
- hepatic encephalopathy
- ascites.

There can also be signs to suggest specific diseases, such as:

- hyperpigmentation (haemochromatosis)
- Kayser–Fleischer rings (Wilson's disease)
- tendon xanthomas primary biliary cholangitis
- Courvoisier's sign, which is more suggestive of pancreatic or gallbladder malignancy ('a painless enlarged gallbladder with jaundice is unlikely to be gallstones').

Investigations (Figure 2)

Urinalysis: this can help to determine whether the hyperbilirubinaemia is conjugated or unconjugated. As unconjugated bilirubin is water-insoluble, it is not detectable in urine. However, if excess conjugated bilirubin is unable to enter the gut (e.g. obstructive jaundice), 50–90% is excreted in the urine, which is detectable on urinalysis. This gives the urine a dark colour, whereas the stools are pale (as there is no stercobilinogen in them).

Blood tests: these include a full blood count, quantification of conjugated (direct) and unconjugated (indirect) bilirubin in the blood, and liver blood tests. The basic liver panel should include measurement of total bilirubin, alkaline phosphatase, aminotransferases, γ-glutamyltransferase and albumin in serum, as well as prothrombin time. Serum albumin and prothrombin time are used to indicate the liver's synthetic function. A low albumin concentration and prolonged prothrombin time (from reduced vitamin K) suggest liver failure.

Patients with jaundice resulting from hepatocellular injury generally have a disproportionate elevation in serum aminotransferases compared with alkaline phosphatase and γ-glutamyltransferase; in a cholestatic process, the opposite occurs. The pattern of aminotransferases can also be important; alcoholic steatohepatitis is usually associated with higher values for aspartate aminotransferase (AST) than alanine aminotransferase (ALT), whereas in viral hepatitis ALT is typically higher than AST. However, there is often a mixed picture and this distinction is not always clear.

A raised unconjugated bilirubin concentration is sometimes the only derangement in liver blood tests, suggesting a normal liver and biliary tree. The cause of this hyperbilirubinaemia can be increased haemolysis or inherited disorders of bilirubin metabolism, such as Gilbert's syndrome. With haemolysis,

the degree of hyperbilirubinaemia is relatively mild (typically 68–102 micromol/litre). An isolated conjugated hyperbilirubinaemia can result from Rotor and Dubin–Johnson syndromes. In patients with unremarkable liver blood results, consider alternative causes of skin discoloration, such as Addison's disease, anorexia nervosa, ingestion of β-carotene-rich foods (carotenaemia) or use of spray-tanning products.

A synthesis of information from the history, examination, urinalysis and basic blood tests generally allows the next step to be determined:[1]

- **If the impression is of cholestatic jaundice**, the next step is abdominal ultrasonography to determine whether there is biliary dilatation, suggesting obstruction.
- **If the impression is of hepatocellular injury**, the next step is a liver aetiology screen. This includes serological testing for viral hepatitis (A, B, C and in certain patients also E), other viridae (cytomegalovirus, HIV, Epstein–Barr virus), antimitochondrial antibodies (for primary biliary cholangitis), serum immunoglobulins, antinuclear and anti-smooth muscle antibodies and liver–kidney microsomal antibodies (for autoimmune hepatitis), serum ferritin and transferrin saturation (for haemochromatosis), serum ceruloplasmin (for Wilson's disease), serum α_1-antitrypsin (for α_1-antitrypsin deficiency) and α-fetoprotein (for hepatic malignancy).
- **If there is isolated hyperbilirubinaemia**, additional blood tests, including serum lactate dehydrogenase, serum haptoglobin, Coomb's test and a blood film, help to diagnose haemolytic anaemia.

Imaging of the liver and biliary tree: ultrasound scanning is usually the initial imaging modality of choice in suspected cholestatic jaundice. It is non-invasive, inexpensive and widely available. It has a sensitivity of 55–91% for detecting dilated bile ducts and biliary obstruction.[2] It can also detect gallstones and periampullary masses, and provide information on the hepatic echostructure and features of portal hypertension.

If the cause of biliary dilatation remains unclear, or more detailed imaging is needed, magnetic resonance cholangiopancreatography (MRCP) is performed. This non-invasive technique provides high-resolution imaging without contrast. MRCP is commonly used to confirm choledocholithiasis before embarking on more invasive procedures such as endoscopic retrograde cholangiopancreatography (ERCP). Magnetic resonance imaging with different contrast and diffusion-weighted imaging can allow assessment of the liver parenchyma and characterize liver lesions.

Computed tomography (CT) can reliably detect ductal dilatation and is superior to ultrasonography in determining the underlying cause of jaundice, particularly for visualizing the pancreas. However, CT involves exposure to radiation and nephrotoxic contrast agents, and only 10% of gallstones are visualized on CT.

Endoscopic ultrasonography is an invasive technique in which an ultrasound probe is lowered into the duodenum during gastroscopy, providing detailed information about the biliary tree and pancreas. It allows for biopsies and fine needle aspiration, and is particularly useful for staging periampullary malignancies.

Intraductal ultrasound (IDUS) is a newer imaging modality that involves cannulation of the common bile duct or main pancreatic duct with a mini-probe to visualize the biliary and pancreatic ducts. Passage of the probe can be difficult in tortuous ducts, but IDUS is more accurate than ERCP for detecting small stones in dilated ducts, and in determining the nature of bile duct strictures.

More invasive procedures such as ERCP are generally reserved for therapeutic interventions, for example stone removal or stricture dilatation. ERCP can also be used to obtain tissue from biliary strictures to identify malignancy. There is an associated morbidity (3%) and mortality (0.2%), with bleeding, cholangitis and pancreatitis being the most common complications.[3] Particularly in cases where there is difficulty distinguishing between a benign and malignant biliary stricture, ERCP can be combined with cholangioscopy, which permits direct visualization of the biliary tree using a fibreoptic or video-endoscope.

Percutaneous transhepatic cholangiography (PTC) involves percutaneous access to a peripheral hepatic bile duct, with injection of contrast. Similarly to ERCP, biliary brushings can be obtained and stents inserted. PTC is particularly valuable if the ampulla is not readily accessible, and in patients with hilar/biliary strictures after hepatectomy. The choice of imaging technique is usually governed by availability, patient-related factors and clinical suspicion.

Liver biopsy: if patients have jaundice and deranged liver blood results, with a normal liver aetiology screen and imaging, liver biopsy can be considered. This decision is influenced by the likelihood of clinically significant liver disease and the potential therapeutic benefit. Liver biopsy is particularly useful for diagnosing autoimmune liver disease and certain biliary tract disorders (e.g. small duct primary sclerosing cholangitis). However, adverse effects include pain (20%), and severe complications (including haemoperitoneum, puncture of other organs, pneumothorax and biliary peritonitis) occur in 0.57% of patients.[4] Furthermore, sampling errors can occur and studies have shown discordance rates of up to 30% when the right and left lobes are sampled, even in homogenously distributed disease.[5] ◆

KEY REFERENCES

1 Newsome PN, Cramb R, Davison SM, et al. Guidelines on the management of abnormal liver blood tests. *Gut* 2018; **67:** 6–19.

2 Pedersen OM, Nordgard K, Kvinnsland S. Value of sonography in obstructive jaundice. Limitations of bile duct caliber as an index of obstruction. *Scand J Gastroenterol* 1987; **22:** 975–81.

3 Bilbao MK, Dotter CT, Lee TG, et al. Complications of endoscopic retrograde cholangiopancreatography (ERCP). A study of 10,000 cases. *Gastroenterol* 1976; **70:** 314–20.

4 Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiol of the French Association for the Study of the Liver (AFEF). *Hepatol* 2000; **32:** 477–81.

5 Regev A, Berho M, Jeffers LJ, et al. Sampling error and intra-observer variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol* 2002; **97:** 2614–8.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 24-year-old woman presented with symptoms of a cold and a fever.

On clinical examination, she was noted to have mild jaundice. Abdominal examination was unremarkable. She had noticed jaundice once before, following a period of sleep deprivation due to stress

Investigations

- Haemoglobin 123 g/litre (115–165)
- Mean cell volume 88 fl (80–96)
- White cell count 7.3 × 10^9/litre (4.0–11.0)
- Total bilirubin 68 micromol/litre (1–22)
- Conjugated bilirubin 7 micromol/litre (<3.4)
- Alanine aminotransferase 20 U/litre (5–35)
- Alkaline phosphatase 93 U/litre (45–105)

What is the most likely cause of this patient's jaundice?

A. Acute viral hepatitis
B. Gilbert's syndrome
C. Alcoholic hepatitis
D. Primary biliary cirrhosis
E. Haemolytic anaemia

Question 2

A 78-year-old man presented with jaundice. He had no pain, but there was a loss of appetite and a weight loss of 14 kg over the previous 3 months. He had recently been found to have diabetes mellitus. On clinical examination, he looked cachectic. His abdomen was soft and non-tender but there was a palpable mass in the right upper quadrant.

Investigations

- Haemoglobin 143 g/litre (130–180)
- Mean cell volume 85 fl (80–96)
- White cell count 6.3 × 10^9/litre (4.0–11.0)
- Total bilirubin 140 micromol/litre (1–22)
- Conjugated bilirubin 100 micromol/litre (<3.4)
- Alanine aminotransferase 10 U/litre (5–35)
- Aspartate aminotransferase 120 U/litre (1–31)
- Alkaline phosphatase 500 U/litre (45–105)

What is the most likely cause of this patients' jaundice?

A. Cholecystitis
B. Pancreatic cancer
C. Hepatocellular cancer
D. Viral hepatitis
E. Non-alcoholic fatty liver disease

Question 3

A 49-year-old woman presented with right upper quadrant abdominal pain, jaundice and fevers.

On clinical examination, her temperature was 38°C, heart rate 120 beats/minute, and blood pressure 90/65 mmHg.

Investigations

- Haemoglobin 132 g/litre (115–165)
- Mean cell volume 82 fl (80–96)
- White cell count 7.8 × 10^9/litre (4.0–11.0)
- Total bilirubin 140 micromol/litre (1–22)
- Conjugated bilirubin 10 micromol/litre (<3.4)
- Alanine aminotransferase 130 U/litre (5–35)
- Aspartate aminotransferase 120 U/litre ((1–31)
- Alkaline phosphatase 500 U/litre (45–105)

What is the first priority in the management of this patient?

A. Administering fluids and antibiotics intravenously
B. Arranging an urgent inpatient ultrasound scan
C. Arranging urgent inpatient endoscopic retrograde cholangiopancreatography
D. Performing a 'liver screen'
E. Arranging urgent magnetic resonance cholangio-pancreatography