Chapter 30
Jaundice

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Key Points
- Jaundice is not a diagnosis but a manifestation of pathology.
- Jaundice requires the evaluating doctor to examine comprehensively, investigate appropriately and commence management diligently.
- The causes of jaundice include life-threatening conditions that require resuscitation and stabilisation.

Introduction

Jaundice is a common clinical presentation to the emergency department that can be caused by a variety of disorders. It is not a diagnosis but a feature of elevated serum bilirubin and a marker of hepatobiliary or haematologic dysfunction. Patients with jaundice could present with symptoms such as abdominal pain, itching or fever. Jaundice means yellowish staining of the skin, sclera and mucous membranes by bilirubin [1]. The normal serum concentration of bilirubin is less than 1 mg/dL [17 μmol/L], and it is not clinically detectable until serum bilirubin reaches 2.5 mg/dL [1]. The total bilirubin can be divided into two fractions: conjugated [direct] bilirubin and unconjugated [indirect] bilirubin. Identification of the type can help to narrow down the cause of jaundice. The key questions to ask when seeing a patient with jaundice in the emergency department are as follows:

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- Type of jaundice and underlying process causing it
- Is it an acute process or acute on a background of chronic liver disease
- Is there liver failure

This chapter provides an overview of the diagnostic approach and early management of jaundice in adults.

Metabolism

Bilirubin is derived predominantly [80 %] from the breakdown of haemoglobin present in the red blood cells and the rest comes from haeme-containing proteins [1, 2]. The reticuloendothelial cells destroy the red blood cells, releasing water-insoluble unconjugated bilirubin into the circulation where it is bound to albumin and enters liver cells. In liver it undergoes glucuronidation by a family of enzymes called uridinediphospho-glucuronosyltransferases [conjugation] [2, 3]. The conjugated bilirubin is actively transported across the canalicular membranes into the biliary system. This is then stored as part of bile in the gallbladder and released into the duodenum [3, 4]. Most of the bile salts are de-conjugated in the terminal ileum and absorbed by the intestinal epithelial cells which then enters the portal circulation and returns to the liver [enterohepatic circulation]. The bile that is not absorbed enters the colon where the colonic bacteria break bilirubin to stercobilin or urobilinogen. The former is excreted in the stool, whilst the latter is reabsorbed into the bloodstream and excreted in the urine [4]. Conjugated bilirubin can also enter the circulation from diffusion out of the hepatocytes. Bilirubin is filtered by the glomerulus and then reabsorbed. Under normal circumstances, no conjugated bilirubin is excreted, but if the filtered load exceeds the absorptive capacity, conjugated bilirubin can be detected in the urine [4].

Clinical Presentation

The cause of jaundice is wide, and they have symptoms of these diseases. The duration of symptoms is also varied. Patients with jaundice may present with the following:

- No symptoms or extrahepatic manifestation of the liver disease
- Change of skin or eye colour or symptoms of acute illness
- Weight loss or pruritus if non-infectious aetiology
- Abdominal pain with bile duct stones and pancreatic or biliary tract cancers
- Can present with life threatening features in patients with massive haemolysis, acute cholangitis, fulminant liver failure and acute fatty liver of pregnancy [5]. These conditions should be treated as a medical emergency when resuscitation, stabilisation and treatment should be started in the emergency department with early involvement of the specialists.

Jaundiced patients with acute liver failure are very ill at presentation and require close monitoring whilst in the emergency department as the mortality approaches 80 % in this situation [5]. The two most common causes of acute liver failure worldwide are paracetamol poisoning and viral hepatitis [5, 6].

Causes of Jaundice

The bilirubin metabolism occurs in three phases: pre-hepatic, hepatic and post-hepatic and any problems at each of these phase deals to development of jaundice. Jaundice is thus classified as pre-hepatic, hepatic and post-hepatic jaundice which is shown in Table 30.1.

The cause of jaundice can also be divided by the type of bilirubin elevated [conjugated or unconjugated]. Some of the disease processes or conditions can cause both types of hyperbilirubinaemia. The causes of *unconjugated [indirect] hyperbilirubinaemia* are tabulated in Table 30.2. *Conjugated [direct] hyperbilirubinaemia* occurs uncommonly due to inherited causes [Dubin-Johnson and Rotor syndrome], but the most common causes are acquired. These are tabulated in Table 30.3.

Diagnostic Approach

Approach to a jaundiced patient begins by taking a detailed history, careful physical examination and initial laboratory results. A possible cause could be obtained in most cases from this, or it will help to direct the relevant investigations needed to identify the cause. The sensitivity of history and examination in identifying intrahepatic vs extra-hepatic disease as a cause for jaundice was 86 % in 220 subjects from a study in Scandinavia [7].

Table 30.1 Causes of jaundice

Pre-hepatic causes	Intrahepatic causes	Post-hepatic causes
Haemolysis	Hepatocellular disease	Gallstones, biliary strictures
Reabsorption of a large haematoma	Viral infections	Infections – [cytomegalovirus [CMV], Epstein-Barr virus [EBV] and HIV]
Drugs	Chronic alcohol use	Malignancy
Haemolytic anaemia	Autoimmune disorders	Pancreatitis
G6PD deficiency	Drugs, pregnancy	
Hereditary spherocytosis	Parenteral nutrition	
Sickle cell disease	Dubin-Johnson syndrome	
	Rotor's syndrome	

Table 30.2 Causes of unconjugated hyperbilirubinaemia

Overproduction of bilirubin	Impaired bilirubin uptake	Impairment of conjugation
Haemolysis, mechanical valves, paroxysmal nocturnal haemoglobinuria, disseminated intravascular coagulation and haemolytic uraemic syndrome	Heart failure, portosystemic shunts and drugs like probenecid and rifampicin	Gilberts, Crigler-Najjar syndrome, Wilson disease and advanced liver cirrhosis

Table 30.3 Causes of conjugated hyperbilirubinaemia

Hepatocellular injury	Cholestasis
Hepatocellular carcinoma, cholangiocarcinoma, metastatic disease, secondary biliary cirrhosis, cryptogenic cirrhosis	Intrahepatic Viral hepatitis, alcoholic hepatitis, non-alcoholic steatohepatitis, primary biliary cirrhosis, drugs and toxins, sepsis/ hypoperfusion, infiltrative diseases, total parenteral nutrition, pregnancy and cirrhosis
Hereditary [Wilson's disease, alpha-1-antitrypsin deficiency, haemochromatosis]	
Viral hepatitis [CMV, HSV], bacterial: [tuberculosis', leptospirosis, syphilis, brucellosis], fungal [candida, histoplasmosis, cryptococcus], parasitic[ascaris, clonorchis, schistosomiasis, echinococcus] protozoa [amoebiasis, plasmodia, babesiosis, toxoplasmosis, leishmaniasis]	Extrahepatic Bile duct stones, tumours, primary sclerosing cholangitis, AIDS cholangiopathy, acute or chronic pancreatitis, strictures and parasitic infections
Toxic medications [alcohol, chlorinated hydrocarbons, Amanita phalloides toxin, aflatoxin]	
Immunologic [autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis] and nonalcoholic steatohepatitis	

History

A detailed history should include the following:

- Duration of onset and associated symptoms, presence or absence of pain, fever, constitutional symptoms and weight [loss/gain].
- History of abdominal operations [gallbladder/liver/pancreatic surgery]
- Medication use [prescribed, over-the-counter drugs, herbal preparations, food supplements and recreational drugs]
- Hepatitis risk factors [travel, intravenous drug use, sexual contacts]
- History of inherited disorders [both liver diseases and haemolytic disorders]
- Alcohol consumption and toxic substance exposure

Clinical Examination

Check for tachycardia [fever, anaemia or distress from pain], tachypnoeic and/or hypoxic [effusions/ascites/sepsis/anaemia/pulmonary oedema] and hypotension [anaemia, sepsis, fluid shifts].

- Signs of chronic liver failure [ascites, splenomegaly, spider naevi, palmar erythema, gynecomastia] or acute liver failure.
- Disease-specific features such as Kayser-Fleischer rings in Wilson disease, xanthomas in primary biliary cirrhosis, hyperpigmentation of haemochromatosis or a Courvoisier sign [malignancy].
- Abdominal examination
  - Assess liver size [enlarged in hepatitis, tumours or shrunken in cirrhosis] and tenderness [cholestasis, heart failure or inflammation].
  - Ascites [chronic liver disease, rapid onset in portal vein thrombosis or tender in spontaneous bacterial peritonitis].
  - A Murphy's sign indicates acute cholecystitis.
  - Charcot's triad [fever, right upper quadrant pain and jaundice] indicates ascending cholangitis.
- Cardiorespiratory examination to look for signs of heart failure, effusions or pulmonary oedema [from heart failure, sepsis or end-stage liver disease].
- Neurological examination to assess the mental status [conscious level, orientation and cognitive function].

Interpretation of Laboratory Tests

The initial laboratory tests should include full liver function tests, full blood count, coagulation screen and albumin. The abnormalities in each of the liver tests help to identify the various causes of jaundice.

Normal alkaline phosphatase [*ALP] and aminotransferases [ATS]*

- Hepatic injury or biliary disease is not the cause of jaundice.
- Jaundice is due to haemolysis or inherited disorders of bilirubin metabolism.

Raised ALP predominantly: suggests biliary obstruction or intrahepatic cholestasis

- Elevated in non-liver causes such as bone diseases and pregnancy.
- Measure GGT if this raised confirms hepatic origin of ALP.

Predominant ATS elevation: suggests cause is by intrinsic hepatocellular disease

- Further tests should be performed to evaluate a cause: viral hepatitis; liver autoantibodies [autoimmune liver disease]; serum levels of iron, transferrin and ferritin for haemochromatosis; serum levels of copper and caeruloplasmin for Wilson disease; and alpha-1-antitrypsin activity for alpha-1-antitrypsin deficiency.

  Prothrombin time and albumin: measures synthetic function of the liver

- If PT does not correct with vitamin K it suggests moderate to severe hepatocellular disease but in cases of obstructive jaundice PT will correct with vitamin K administration.
- Albumin [low albumin] is affected predominantly in chronic disorders.

Radiological Tests

- Ultrasonogram is the first-line test recommended [8] due to its wide availability, low cost and no radiation exposure. This is the most sensitive imaging technique for detecting biliary stones and benign obstruction.
- Computed tomography is the recommended test if malignant process or pancreatic disease is suspected. Scanning can provide more information about liver and pancreatic parenchymal disease [9].
- If parenchymal involvement of the liver is suspected, then magnetic resonance imaging is the test of choice [8].
- Endoscopic retrograde cholangiopancreatography is primarily a therapeutic procedure [10] and is recommended for post-operative biliary leaks or strictures, palliation of malignant biliary obstruction, pancreatic duct stones or leaks and diagnosis of pancreatic malignancies [10–12].

Liver Biopsy

It provides information on liver architecture and is useful when blood/imaging results are not helpful but is rarely required in emergency situation [13–15].

Treatment

The cause of jaundice will direct the treatment i.e. when specific therapy must be initiated otherwise it is largely supportive if no specific cause is identified. Generally patients with fever, coagulopathy, altered mental status or intractable pain should be hospitalised and symptoms treated. Patients with massive haemolysis, acute cholangitis, fulminant liver failure and acute fatty liver of pregnancy [5] present with life-threatening features. These conditions should be treated as a medical emergency when resuscitation, stabilisation and treatment should be started in the emergency department with early involvement of the specialists.

Extrahepatic Obstruction

- Consider biliary drainage.
- Ascending cholangitis: start broad-spectrum antibiotics and obtain surgical review.
- Patients with sepsis – biliary drainage either by ERCP or cholecystostomy should be established [10, 16].
- For bile duct obstructions from gallstones or strictures [benign or malignant] patients will benefit from decompression by ERCP [10, 12, 17].

Hepatocellular Injury

- Exclude acute liver failure [evidence of coagulopathy or altered mental status].
- Hepatic encephalopathy can be treated with lactulose or phosphate enemas. Patients who present with severe encephalopathy [somnolence and coma] may need to be intubated to protect their airways and are at increased risk for developing cerebral oedema and herniation.
- Definitive treatment in some cases for fulminant liver failure is transplantation.

Paracetamol-Induced Liver Injury

- Treatment can prevent the development of acute liver failure and transplantation.
- Give activated charcoal if patients present within an hour of ingestion and if no contraindications [18–20].
- Treatment for paracetamol-induced liver toxicity is N-acetylcysteine [NAC] [19–21]. NAC is administered if serum paracetamol levels are above the treatment line on the Rumack-Matthew nomogram [18–22].
- The dose is 150 mg/kg IV over 60 min, then 50 mg/kg over 4 h and then 100 mg/kg over 16 h [18, 20].
- If given within 8 h of ingestion, NAC is 100 % protective from liver injury but shown to be beneficial if given after that time [18–20].

Other Causes of Hepatocellular Injury

- Corticosteroids for patients with autoimmune hepatitis [23–25].
- Drug-induced liver injury is managed conservatively. Stop the offending drug and wait for bilirubin to normalise [26, 27]. This can take few weeks to months. Trial of short course of steroids or ursodeoxycholic acid can be tried [26, 27].

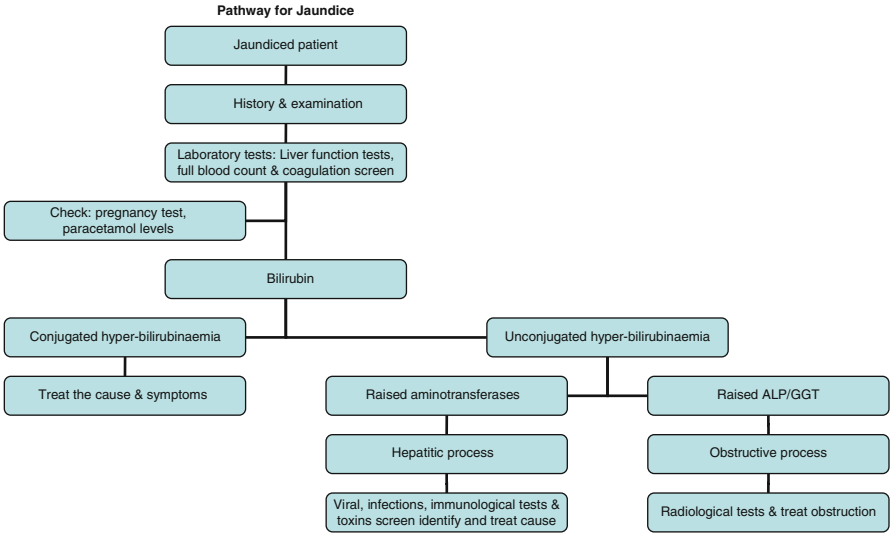
Pregnant Women

- *Hyperemesis gravidarum* generally occurs in the first trimester, characterised by nausea and vomiting. Jaundice is seen in half the women, the cause of which is unknown [28]. Jaundice disappears after resumption of oral intake, and treatment consists of hydration and anti-emetics [28].
- *Intrahepatic cholestasis of pregnancy* is an idiopathic cause of jaundice that occurs in the early third trimester presenting with pruritus followed by jaundice [29, 30]. These patients are at increased risk for preterm delivery and intrauterine foetal demise [29, 30].
- *Acute fatty liver of pregnancy* occurs in the third trimester, and sometimes it presents after delivery. Patients present with nausea, vomiting and right upper quadrant pain. Development of jaundice usually follows these symptoms. If untreated it can progress rapidly to fulminant hepatic failure and death. Prompt delivery is the treatment.

Haemolysis

- Massive haemolysis: Treatment depends on the cause of the haemolysis
- Drug-induced haemolytic anaemia should avoid the offending agent.
- Blood transfusion for those who are symptomatic.
- Discuss with haematologist in cases of disseminated intravascular coagulopathy.

Pathway for Jaundice



References

1. Trauner M, Fickert P, Zollner G. Genetic disorders and molecular mechanisms in cholestatic liver disease – a clinical approach. Semin Gastrointest Dis. 2001;12(2):66–88.
2. London IM, West R, Shemin D, Rittenberg D. On the origin of bile pigment in normal man. J Biol Chem. 1950;184(1):351–8.
3. Berk PD, Wolkoff AW, Berlin NI. Inborn errors of bilirubin metabolism. Med Clin North Am. 1975;59(4):803–16.
4. Schmid R. Bilirubin metabolism in man. N Engl J Med. 1972;287(14):703–9.
5. Lee WM. Acute liver failure. Am J Med. 1994;96(1A):3S–9.
6. Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137(12):947–54.
7. Pasanen PA, Pikkarainen P, Alhava E, Partanen K, Janatuinen E. Evaluation of a computer-based diagnostic score system in the diagnosis of jaundice and cholestasis. Scand J Gastroenterol. 1993;28(8):732–6.
8. Lalani T, Couto CA, Rosen MP, Baker ME, Blake MA, Cash BD, et al. ACR appropriateness criteria jaundice. J Am Coll Radiol. 2013;10(6):402–9.
9. Pasanen PA, Partanen KP, Pikkarainen PH, Alhava EM, Janatuinen EK, Pirinen AE. A comparison of ultrasound, computed tomography and endoscopic retrograde cholangiopancreatography in the differential diagnosis of benign and malignant jaundice and cholestasis. Eur J Surg. 1993;159(1):23–9.
10. Adler DG, Baron TH, Davila RE, Egan J, Hirota WK, Leighton JA, et al. ASGE guideline: the role of ERCP in diseases of the biliary tract and the pancreas. Gastrointest Endosc. 2005;62(1):1–8.
11. Baron TH. Endoscopy for bile duct stones. Minerva Gastroenterol Dietol. 2005;51(4): 289–301.
12. Baron TH. Palliation of malignant obstructive jaundice. Gastroenterol Clin North Am. 2006;35(1):101–12.
13. Poynard T, Benhamou Y, Thabut D, Ratziu V. Liver biopsy: the best standard…when everything else fails. J Hepatol. 2009;50(6):1267–8.
14. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology. 2009;49(3):1017–44.
15. McGill DB, Rakela J, Zinsmeister AR, Ott BJ. A 21-year experience with major hemorrhage after percutaneous liver biopsy. Gastroenterology. 1990;99(5):1396–400.
16. Wada K, Takada T, Kawarada Y, Nimura Y, Miura F, Yoshida M, et al. Diagnostic criteria and severity assessment of acute cholangitis: Tokyo guidelines. J Hepatobiliary Pancreat Surg. 2007;14(1):52–8.
17. de Groen PC, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM. Biliary tract cancers. N Engl J Med. 1999;341(18):1368–78.
18. Wolf SJ, Heard K, Sloan EP, Jagoda AS. Clinical policy: critical issues in the management of patients presenting to the emergency department with acetaminophen overdose. Ann Emerg Med. 2007;50(3):292–313.
19. Ferner RE, Dear JW, Bateman DN. Management of paracetamol poisoning. BMJ. 2011;342:d2218.
20. Pettie JM, Dow MA, Sandilands EA, Thanacoody HK, Bateman DN. An integrated care pathway improves the management of paracetamol poisoning. Emerg Med J. 2012;29(6):482–6.
21. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). N Engl J Med. 1988;319(24):1557–62.
22. Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics. 1975;55(6):871–6.
23. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and management of autoimmune hepatitis. Hepatology. 2010;51(6):2193–213.

24. Krawitt EL. Clinical features and management of autoimmune hepatitis. World J Gastroenterol. 2008;14(21):3301–5.
25. Gleeson D, Heneghan MA. British society of gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut. 2011;60(12):1611–29.
26. Hussaini SH, Farrington EA. Idiosyncratic drug-induced liver injury: an update on the 2007 overview. Expert Opin Drug Saf. 2007;13(1):67–81.
27. Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. Mayo Clin Proc. 2014;89(1): 95–106.
28. Larrey D, Rueff B, Feldmann G, Degott C, Danan G, Benhamou JP. Recurrent jaundice caused by recurrent hyperemesis gravidarum. Gut. 1984;25(12):1414–5.
29. Fisk NM, Bye WB, Storey GN. Maternal features of obstetric cholestasis: 20 years experience at King George V Hospital. Aust N Z J Obstet Gynaecol. 1988;28(3):172–6.
30. Fisk NM, Storey GN. Fetal outcome in obstetric cholestasis. Br J Obstet Gynaecol. 1988;95(11):1137–43.