15.22.1 Investigation and management of jaundice 3

15.22.1 Investigation and management of jaundice 3049

CONTENTS 15.22.1 Investigation and management of jaundice 3049 Jane Collier 15.22.2 Cirrhosis and ascites 3058 Javier Fernández and Vicente Arroyo 15.22.3 Portal hypertension and variceal bleeding 3068 Marcus Robertson and Peter Hayes 15.22.4 Hepatic encephalopathy 3080 Paul K. Middleton and Debbie L. Shawcross 15.22.5 Liver failure 3089 Jane Macnaughtan and Rajiv Jalan 15.22.6 Liver transplantation 3100 John G. O'Grady 15.22.1 Investigation and management of jaundice Jane Collier ESSENTIALS Physiology of bilirubin Haem molecules are degraded in macrophages to biliverdin and then to bilirubin, which is selectively removed by hepatocytes from sinusoidal blood and conjugated, chiefly with two glucuronic acid moieties. Conjugated bilirubin is excreted into the bile, but in many liver diseases it refluxes back into blood from which some is filtered into and darkens the urine (choluria). In the distal intestine, conju- gated bilirubin is deconjugated and reduced to a series of uro- and stercobilinogens that give the normal colour to faeces. Clinical approach Jaundice is the clinical sign of hyperbilirubinaemia and usually in- dicates disease of the liver or biliary tree. Dark urine and pale stools indicate cholestasis. Stigmata of chronic liver disease do not define the cause of jaundice. Unconjugated hyperbilirubinaemia—presents with raised serum bili- rubin levels and normal other liver-related blood tests. Causes include haemolysis and benign inherited unconjugated hyperbilirubinaemia (i.e. Gilbert's syndrome). Conjugated hyperbilirubinaemia—routine liver-related blood tests cannot alone differentiate between intra- and extrahepatic causes of jaundice although high levels of transferases suggests hepa- titis (e.g. viral, autoimmune) or hepatic necrosis (e.g. paracetamol). Alcohol and drug histories are needed in those with both elevated alkaline phosphatase and transferases. Extrahepatic cholestasis should be sought by abdominal ultrasonography to detect a di- lated intra- and/or extrahepatic biliary tree (and often also to reveal its cause, e.g. gallstones, tumour). Further investigation depends on the clinical context: (1) likely large bile duct disease—endo- scopic retrograde cholangiopancreatography,

magnetic reson- ance cholangiography, and endoscopic ultrasonography; (2) likely intrahepatic cholestasis—autoantibodies, immunoglobulins, and liver biopsy. Introduction The commonest cause of jaundice varies geographically. Biliary ob- struction due to common bile duct stones or malignancy followed by liver injury due to alcohol are the commonest reasons for jaun- dice presenting in adults in the United Kingdom in both primary and secondary care. The five key components to identifying the cause of jaundice are the history, presence or absence of hepatosplenomegaly, pattern of liver function tests, chronic liver disease screen, and ultrasound examination. 15.22 Presentations and management
of liver disease

section 15 Gastroenterological disorders 3050 Physiology of bilirubin All haem molecules in haemoglobin or cytochrome enzymes are degraded in macrophages, especially in the spleen and liver, via bili- verdin to bilirubin. Haem oxygenase breaks open the asymmetric tetrapyrrole haem molecule specifically at the α-methene bridge, releasing carbon monoxide and iron, and forming biliverdin (Fig. 15.22.1.1). The excretion of carbon monoxide in breath can be used quantitatively to determine the breakdown of haem to bili- rubin, of which 200 to 350 mg (340–600 µmol) is produced daily. Biliverdin is green and is directly excreted in bile by birds, am- phibians, and reptiles, but not by mammals in which biliverdin is reduced by the macrophage cytosolic enzyme biliverdin reductase, chiefly to the yellow bilirubin IXα, which has then to be excreted. Bilirubin is surprisingly lipid soluble due to internal hydrogen bonding in the molecule so that it forms a tight, nonpolar, nonlinear structure. After release from macrophages, it is firmly bound to plasma albumin, so that none enters the urine. At high concen- trations in the blood, it slowly diffuses into tissues, where it can be toxic, particularly in the neonatal brain (kernicterus) or the kidney. Jaundice is less obvious in unconjugated than in conju- gated hyperbilirubinaemia since its diffusion into the tissues is more limited. Bilirubin is readily oxidized back to biliverdin, hence the green vomit of intestinal obstruction. The normal circulating pool of bilirubin in the plasma (approxi- mately 100 µmol) is almost all unconjugated. The normal range of plasma bilirubin is wide (approximately 5–19 µmol/litre), reflecting wide variations in the rate of conjugation in the liver. The distribu- tion of values is Gaussian, so that the true upper limit of normal is arbitrary (see ‘Hereditary hyperbilirubinaemia’). Hepatic enzyme- inducing drugs, such as barbiturates, reduce the plasma level by increasing the rate of conjugation in hepatocytes and hence the plasma clearance of bilirubin. Bilirubin is selectively removed by hepatocytes from sinusoidal blood, where its uptake is facilitated by the direct contact of plasma with hepatocytes in the interstitial space of Disse through fenestra- tions in the endothelium of hepatic blood capillaries. Although up- take and excretion predominate, dynamic studies show that there is also considerable reflux of bilirubin out of the cell back into the plasma. Within the hepatocyte, bilirubin is principally conjugated by one of the two specific isoforms of the microsomal enzyme uridine 5'- diphosphate-glucuronosyltransferase (UGT1A1), chiefly with two glucuronic acid moieties. Minor quantities of bilirubin are conju- gated with one glucuronic acid molecule (monoglucuronide) or with combinations of related sugars (xylose, glucose); a small amount of unconjugated bilirubin also appears in bile. The physical and chemical properties of the conjugated molecules are quite different from those of unconjugated bilirubin, for they lose the internal hydrogen bonding of bilirubin and become more linear, fully water-soluble molecules that are efficiently excreted in bile. In many liver diseases, conjugated bilirubin readily refluxes back into blood and, since it is water soluble and less firmly bound to albumin than unconjugated bilirubin, about 1% is filtered across the glomerular membrane and darkens the urine (choluria). Hepatocytes have at least six specific

active transporters at their apex for the excretion into the canaliculi of the major components of bile. Conjugated bilirubin is excreted out of the endoplasmic reticulum and then across the apical microvillous intercellular canalicular membrane into bile by the anionic conjugate transporter protein MRP2 (multidrug resistance-associated protein 2). MRP2 also transports other multivalent anionic drugs into bile, and is also present in the renal tubule and proximal small intestine. MRP3, and probably MRP1, transport conjugated bilirubin, bile acids, and drugs back out across the basolateral sinusoidal hepatocyte mem- brane into blood, and are upregulated by increased intracellular con- centrations of bilirubin. Hence, in cholestasis, conjugated bilirubin and drugs are safely excreted into urine. The urinary excretion of conjugated bilirubin is increased by the bile acids that also accumulate in cholestasis. If renal function is normal, this renal excretion of bilirubin eventually matches its normal rate of production when conjugated bilirubin levels in the plasma reach about 600 μmol/litre. With renal failure, or haemolysis, plasma levels rise higher little bilirubin, even if conjugated, diffuses through renal dialysis membranes. Deconjugated bilirubin can undergo a substantial enterohepatic circulation; it is absorbed from the colon, particularly when there is bile acid malabsorption and hence the concentration of bile acids in the colon is increased, for example, as a result of disease or resection of the ileum. This reabsorption then increases the concentration of bilirubin re-excreted in bile, and may in part explain the increased incidence of pigment gallstones in patients with ileal disease. Oral ursodeoxycholic acid also increases the enterohepatic recycling of bilirubin, perhaps by solubilizing bilirubin in the intestinal lumen, or by impairing the reabsorption of other bile acids in the ileum. This may explain the rim of calcification in an outer pigment layer of cholesterol gallstones during their treatment with ursodeoxycholic acid, and thus their frequent resistance to such dissolution therapy. Similarly, fasting increases unconjugated bilirubin levels in the plasma by increasing the reabsorption of bilirubin because it reduces intestinal motility and improves absorption. HAEM Haemoglobin and other haem proteins e.g. cytochromes, myoglobin (haem oxygenase) Iron, carbon monoxide Biliverdin Bilirubin Bilirubin conjugates (glucuronyl transferase) (biliverdin reductase) Protoporphyrin IX Protoporphyrinogen IX Coporphyrinogen Ill Uroporphyrinogen Ill Porphobilinogen (PBG) δ-Aminolaevulinic acid (ALA) Glycine+ succinyl CoA Fig. 15.22.1.1 The porphyrin–bilirubin pathway.

15.22.1 Investigation and management of jaundice 3051 In the distal intestine, conjugated bilirubin is deconjugated and reduced to a series of uro- and stercobilinogens that give the normal colour to faeces. Some colourless urobilinogen is nor- mally absorbed from the colon and undergoes an enterohepatic circulation, with a small amount being excreted in urine. If this biliary excretion is impaired in liver disease, or increased in haemolysis, then excess urobilinogen is excreted in urine, where it can oxidize on standing to dark brown urobilins. Urobilinogen is easily detected by routine clinical ‘stix’. Ehrlich’s aldehyde re- agent was at one time used; urine containing excess urobilinogen turns red with this reagent and the urobilinogen pigment can then be extracted into an organic solvent, such as chloroform. This is unlike the similar pigment formed from the more polar porphobilinogen adduct in acute porphyria, which remains in the upper aqueous phase. Aetiology A useful approach to investigation and managing jaundice is to think of the cause as either prehepatic, hepatic, or posthepatic (Table 15.22.1.1). Prehepatic jaundice The hallmark of prehepatic jaundice is that alanine aminotrans ferase (ALT) or aspartate aminotransferase (AST) and alka- line phosphatase (ALP) levels will all be normal. Unconjugated hyperbilirubinaemia is commonest, caused by haemolysis or Gilbert’s syndrome, which is the commonest of the hereditary hyperbilirubinaemia syndromes. Haemolysis Haemolysis due to haemolytic anaemias can be differentiated from Gilbert’s syndrome by the presence of anaemia, splenomegaly, and an

elevated reticulocyte count. Patients with haemolytic anaemias can also develop pigmented gallstones. Worsening of jaundice in a patient with known haemo- lytic anaemia associated with an elevated ALP level or serum trans- aminases and pain should prompt investigations to exclude bile duct stones. Other causes of haemolysis causing an unconjugated hyperbilirubinaemia include causes of a rapid breakdown in red blood cells releasing haemoglobin and saturation of bilirubin conju- gation in the liver, for example, massive blood transfusion and inef- fective erythropoiesis due to vitamin B12 deficiency. Hereditary hyperbilirubinaemia Causes of hereditary hyperbilirubinaemia are shown in Table 15.22.1.2. Gilbert's syndrome is recessively inherited and due to reduced bilirubin conjugation by UGT in hepatocytes. Low enzyme levels are due to a variant in the TATAA box in the UGT1A1 gene promotor which is found in 8% of the population. Genetic tests are available, although the diagnosis can usually be made confidently in the presence of an isolated unconjugated bili- rubin level in the absence of haemolysis. Bilirubin levels rarely exceed 70 μmol/litre and often increase following periods of starva- tion or with intercurrent illnesses. Crigler–Najjar syndrome is a rarer condition, presenting with jaundice in the neonate where there is either complete absence of the UGT enzyme (type 1) or less than 10% present (type 2). The former is often fatal due to kernicterus (bilirubin encephalopathy). Dubin–Johnson syndrome is a rarer, recessively inherited hyperbilirubinaemia where the bilirubin, unlike Gilbert's syndrome, is predominately conjugated. It is due to a mutation in the MRP2 gene (ABCC2) encoding a canalicular transport protein for con- jugated bilirubin. Bilirubin levels can be higher than in Gilbert's syndrome and it leads to a 'black' liver due to deposition of melanin- like pigment seen on liver histology. Some conjugated bilirubin is also transported back across the sinusoidal membrane into blood and then reabsorbed into the hepatocyte, where it is stored be- fore being secreted into the canaliculus. The inability to reabsorb this conjugated bilirubin, possibly due to mutations in the organic anion transport proteins (OATP), can also lead to a conjugated hyperbilirubinaemia. This condition is rarer than Dubin–Johnson syndrome and is known as Rotor's syndrome. Hepatic jaundice Causes include acute liver injury, chronic liver disease, and hep- atic infiltration. Acute liver injury such as viral hepatitis can lead (if severe) to acute liver failure with hepatic encephalopathy and coagulopathy. Pre-existing chronic liver injury such as cirrhosis can also present with jaundice, either due to progression of the underlying condition such as chronic hepatitis C, or due to an add- itional liver injury as seen with superimposed alcoholic hepatitis on a background of alcoholic cirrhosis. This explains why jaundice is a common presentation of previously undiagnosed alcoholic liver disease. Chronic biliary disease such as primary biliary cholangitis (pre- viously known as primary biliary cirrhosis) and primary sclerosing Table 15.22.1.1 Approach to diagnosing the cause of jaundice Type of jaundice Diagnoses to consider Prehepatic Unconjugated hyperbilirubinaemia Hereditary: Gilbert's syndrome Increased production: haemolysis Decreased uptake by hepatocytes: drugs Conjugated hyperbilirubinaemia Hereditary: Dubin–Johnson syndrome Hepatic Acute Chronic Infiltration Drugs Viral hepatitis, i.e. A to E, CMV, EBV Autoimmune hepatitis Alcoholic hepatitisa Ischaemic hepatitis Alcohol Viral hepatitis B, C, and delta (D) Biliary disease; PBC and PSC NAFLDb Hereditary; haemochromatosisb, Wilson's disease, α1-antitrypsin deficiencyb Metastases; lymphoma; amyloid Posthepatic Bile duct stones Chronic pancreatitis Obstruction from malignancy IgG4 disease a Although present acutely with hepatic inflammation, 80% cases will have cirrhosis. b Jaundice uncommon until end-stage liver disease. CMV, cytomegalovirus; EBV, Epstein–Barr virus; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis (previously known as primary biliary cirrhosis); PSC, primary sclerosing cholangitis.

section 15 Gastroenterological disorders 3052 cholangitis may present with jaundice before the development of other complications of cirrhosis such as ascites or hepatic encephal- opathy. This is due to relatively preserved hepatocyte function, con- trasting with disease directed at hepatocytes such as hepatitis C. In contrast, jaundice is a very late symptom of end-stage liver disease in chronic liver disease due to haemochromatosis, α1-antitrypsin defi- ciency, and nonalcoholic fatty liver disease. Jaundice from acute-on-chronic liver injury can also be caused by hepatocellular carcinoma or hepatotoxic drugs. In Wilson's disease, haemolysis may contribute to hyperbilirubinaemia in the presence of cirrhosis and lead to the clinical presentation. Posthepatic jaundice This leads to biliary obstruction and classically is associated with high ALP levels. The commonest causes are bile duct stones and malignant obstruction anywhere within the bile duct. Malignant obstruction includes cancer of the ampulla of Vater or pancreas, cholangiocarcinomas of the common bile duct or biliary hilum, ma- lignant lymph nodes at the hepatic hilum, and (rarely) intrahepatic metastases. Stones in the cystic duct can also cause external com- pression of the common bile duct, known as a Mirizzi's syndrome. Benign causes of biliary obstruction include chronic pancrea- titis, IgG4 disease, primary sclerosing cholangitis, and (rarely) surgical injury to the bile duct as a result of laparoscopic chole- cystectomy. Biliary obstruction in primary sclerosing cholan- gitis can be due to dominant biliary structures, development of a cholangiocarcinoma, or small biliary stones, but jaundice can also occur due to progression in intrahepatic biliary disease. Other Systemic infections can be complicated by jaundice, including mal- aria and leptospirosis. Low platelets, fever, and recent travel history to an endemic area are key to the former, whereas exposure to rat- infested water, conjunctival erythema, and early renal dysfunction can be key to the latter. Severe systemic bacterial infections can lead to the syndrome of intrahepatic cholestasis of sepsis in which endotoxin, tumour necrosis factor, and other factors affect biliary transport pro- teins on the sinusoidal and canalicular membrane of hepatocytes, leading to jaundice associated with high ALP levels. Other sys- temic illnesses that have been associated with jaundice include untreated severe thyrotoxicosis, polymyalgia rheumatica, and sys- temic vasculitis. Clinical features History Key features from the history in determining the cause of jaundice are summarized in Table 15.22.1.3. Dark urine and pale stools are usually present in posthepatic ob- structive jaundice but can also occur in severe liver injury. The pres- ence of epigastric or right upper quadrant pain as opposed to mild abdominal discomfort is highly suggestive of common bile duct stones and is one of the most important symptoms in differentiating the cause of jaundice. Fever suggests cholangitis due to common bile duct stones, par- ticularly in the presence of rigors. A high temperature can also be seen in hepatic infiltration from lymphoma but is usually low grade in acute viral A to E hepatitis. A sore throat with systemic viral symptoms suggests Epstein–Barr virus infection. Primary cyto- megalovirus infection can be seen in both immunosuppressed and nonimmunosuppressed adults and may be associated with diar- rhoea, high fever, and contact with young children. Weight loss is seen both in obstructive jaundice due to malig- nancy or chronic pancreatitis as a result of malabsorption, and in the catabolic state of chronic liver disease. Itching that precedes jaundice is very suggestive of chronic injury to small intrahepatic bile ducts such as occurs in primary biliary cholangitis or primary sclerosing cholangitis. Table 15.22.1.2 Causes of hereditary hyperbilirubinaemias Gilbert's syndrome Dubin–Johnson syndrome Rotor's syndrome Genetic basis UGT1A1 Chromosome 2 ABCC2 Chromosome 2 SLCO1B1 and -B3 Chromosome 2 Mechanism Low levels of hepatocyte UGT Unable to conjugate bilirubin Deficiency in the canalicular transport of nonbile acid organic anions Defective hepatic storage of conjugated bilirubin Bilirubin Fluctuating Unconjugated Usually <100 µmol/litre Fluctuating Conjugated 50–100 µmol/litre but can be much higher Fluctuating Conjugated Liver histology Normal No injury Black pigment No

injury Precipitants Fasting Pregnancy Oral contraceptive Oral contraceptive Diagnosis Unconjugated bilirubin in absence of haemolysis or genetic testing Urine coproporphyrins: high level of coproporphyrin type 1 Increased urine total coproporphyrins Prognosis No itching Good No itching Good No itching Good Crigler–Najjar syndrome type 1, unlike Gilbert's syndrome, is often fatal and is the complete inability to conjugate bilirubin by glucuronidation. ABCC2 gene encoding the canalicular export pump MRP2 (multidrug resistance-associated protein 2); SCL01B1 and -B3, genes encoding the sinusoidal organic acid transport proteins OATPB1 and OATPB3; UGT, uridine-diphosphate-5-gluconysyltransferase.

15.22.1 Investigation and management of jaundice 3053 Drugs A detailed drug history is very important, including over-the- counter medications such as nonprescribed herbal remedies and anabolic steroids which can be bought over the Internet and can cause acute liver injury. Although many drugs can cause idiosyn- cratic liver injury, common culprits include antibiotics such as co-amoxiclav, rifampicin/isoniazid, nonsteroidal anti-inflammatory drugs, antivirals such as efavirenz, immunosuppressants such as azathioprine, and high-dose statins. Oestrogens/progesterone at the lower doses now typically used in the oral contraceptive pill rarely cause cholestatic liver injury. The exception are individuals who carry mutations in the canalicular bil- iary transporter proteins, bile salt export pump (BSEP) or MRP3, where there is often a history of itching during pregnancy. The former is also known as benign recurrent cholestasis. Co-amoxiclav drug-induced jaundice differs from other drug- induced injury in that it can occur 4 to 6 weeks after stopping the drug. There are a few drugs where drug-induced liver injury can occur after many months after a drug has started (e.g. tetracyclines and nitrofurantoin). These drugs cause liver injury that mimics autoimmune liver disease. Paracetamol is an example of a drug which can cause acute liver failure. Jaundice is a relatively late symptom, preceded by a marked coagulopathy and encephalopathy. The pattern of liver injury with drugs varies from cholestatic liver function tests (high ALP concentrations) to hepatitic liver function tests (high ALT concentrations) or a mixed picture, em- phasizing the importance of a drug history when investigating jaundice. Drugs can also exacerbate pre-existing undiagnosed liver disease. Drug history should also include recent use of immunosuppressive agents. Immunosuppression with drugs such as cyclophosphamide and rituximab in the presence of chronic hepatitis B infection leads to a rise in hepatitis B virus DNA, and when immunosuppression stops and immune function improves, liver failure and jaundice can occur. Prednisolone can also lead to a flare in inflammation in chronic hepatitis B, resulting in acute-on-chronic liver failure. Alcohol Alcoholic liver disease is unlikely to be the only cause for jaundice in men who drink less than 50 units/week and women who drink less than 35 units/week for less than 5 years. However, other cofac- tors such as hepatitis C, hepatitis B, and nonalcoholic fatty liver dis- ease may pre-exist, contributing to chronic liver disease at a lower threshold. The average alcohol intake of those presenting with alco- holic hepatitis is greater than 100 units/week. Sexual history Unprotected sexual activity can lead to acute hepatitis B and in men who have sex with men hepatitis C can also be transmitted sexu- ally and present acutely. Travel history and history of vaccinations is important in identifying hepatitis A and E and other infections such as malaria. Intravenous drug use is a risk factor for hepatitis B, delta, and C. Other Table 15.22.1.4 lists some of the other rare causes of liver disease leading to jaundice in specific patient groups, including pregnancy and following bone marrow transplantation. Examination Clinical hepatomegaly suggests cirrhosis, hepatic infiltration, or hepatic venous outflow obstruction. The causes of hepatic infiltra- tion include hepatic metastases, primary liver cancer, lymphoma, and amyloid. The liver may be small or enlarged in cirrhosis. Stigmata of chronic liver disease such as

spider naevi are often present in cirrhosis, particularly in alcoholic liver disease, but club- bing is rare. Splenomegaly may indicate portal hypertension from chronic liver disease but will also be present in haemolytic anaemia and in rarer infiltrative liver diseases such as amyloid or lymphoma. In chronic liver disease, splenomegaly is often easier to identify by ultrasonography than by palpation. Ascites may be due to malignancy or a block to venous out- flow from the liver resulting in portal hypertension. The common Table 15.22.1.3 Hints from the history and examination in the diagnosis of jaundice History Abnormal liver
function test Possible diagnosis Inflammatory bowel disease Diarrhoea ALP PSC Ethnicity/country of birth ALT/AST Hepatitis B/C IV drug use/unscreened blood transfusions ALT/AST Hepatitis B/C Alcohol ALT/mixed Alcoholic disease Recent new drugs ALP or ALT Drug induced Recent immunosuppression ALT ALT/mixed Hepatitis E CMV Travel history ALT Hepatitis A, E Sexual history ALT Hepatitis B Other autoimmune disease ALT Autoimmune hepatitis Family history ± knee/metacarpophalangeal joint pain ± emphysema ± difficulty writing/ concentration Haemochromatosis α1-Antitrypsin Wilson's disease Table 15.22.1.4 Jaundice in specific clinical contexts Clinical context Diagnoses to consider Bone marrow transplantation Hepatic veno-occlusive disease Reactivation of hepatitis B Graft-versus-host disease Pregnancy (third trimester) Intrahepatic cholestasis of pregnancy Acute fatty liver disease of pregnancy HELLP/pre-eclampsia Bile duct stones Intensive care Intrahepatic cholestasis of sepsis Ischaemic cholangiopathy Ischaemic hepatitis Total parenteral nutrition HIV Immune reconstitution Indinavir/ritonavir Efavirenz HELLP, haemolysis, elevated liver enzymes, and a low platelet count.

section 15 Gastroenterological disorders 3054 causes of malignant ascites associated with jaundice are gastrointes- tinal malignancies such as pancreatic cancer and gastric cancer, ei- ther through peritoneal deposits or large-volume liver metastases which can cause portal hypertension. Ascites will be exudative in the former and transudative in the latter. Associated jaundice will be due to either biliary obstruction from the primary tumour or ma- lignant lymph nodes at the porta hepatis, or liver metastases with or without biliary obstruction. Hepatic venous outflow obstruction can be due to right heart failure or obliteration of the hepatic veins. Sinusoidal obstructive syndrome is the name given to obliteration of the hepatic veins and includes occlusion of the large hepatic veins, usually with clots (Budd–Chiari syndrome), and obliteration of the small hepatic veins (known as veno-occlusive disease). The latter is a complica- tion of bone marrow transplantation and other chemotherapeutic drugs. Budd–Chiari syndrome classically presents with sudden onset of ascites and hepatomegaly and mild to moderate elevations in bilirubin. Investigation Blood tests Liver functions tests It is helpful to differentiate hepatitic liver function tests where the transaminases are differentially elevated from cholestatic liver function tests where the ALP is the main abnormal liver blood test. Hepatitic liver function tests Table 15.22.1.5 summarizes the differential diagnosis of jaundice with hepatitic liver function tests. The most important differential is between acute viral hepatitis, drug-induced liver injury, and auto- immune liver disease. Very high ALT concentrations (often >10 000 IU/litre) sug- gest either paracetamol overdose or ischaemic hepatitis. In para-cetamol poisoning which presents with jaundice, paracetamol has usually been taken longer than 48 h before and is undetectable in serum, and the development of liver failure is indicated by a rising prothrombin time. Ischaemic hepatitis is seen with hypo- tension in the setting of right heart failure. In both conditions, the ALT falls with time after the initial injury and is paralleled by worsening jaundice. High ALT concentrations (usually >1000 IU/litre) suggest auto- immune liver disease, acute viral hepatitis, or drug injury. Hepatitis E is now recognized as a cause of endemic acute viral hepatitis in Northern Europe and the United States of America in the absence of a travel

history. In the presence of chronic hepatitis B, superinfection with hepatitis D should be excluded. In autoimmune liver disease, as well as positive antinuclear anti- bodies and/or smooth muscle antibodies, the IgG levels are often greater than 30 g/litre. A liver biopsy showing plasma cells is re- quired to confirm the diagnosis. In alcoholic liver disease, there is often an elevated ALP, with AST and ALT levels rarely above 250 IU/litre, even in the pres- ence of alcoholic hepatitis. This inflammatory response to al- cohol commonly causes jaundice but requires a liver biopsy to differentiate it from end-stage alcoholic cirrhosis. Higher levels of ALT suggest co-existent liver injury such as inadvertent para- cetamol toxicity. Persistently minor elevations in ALT levels (i.e. <100 IU/litre) are common in chronic hepatitis C and B, haemochromatosis, and nonalcoholic fatty liver disease. Although jaundice in these causes of chronic liver diseases is a late symptom of cirrhosis, they can coexist with alcoholic-induced liver disease and so should be considered in a patient with jaundice who may have cirrhosis. Haemochromatosis should be excluded by both a ferritin and a transferrin saturation, which is usually greater than 55%. The caveat is that transferrin is produced by the liver so in cirrhosis, transferrin saturation can be artificially elevated without signifi- cant iron overload. Alcohol can also increase the serum ferritin level, which falls on abstinence. The diagnosis of haemochroma- tosis is confirmed by genetic testing for the common HFE gene mutations. It is important to recognize, however, that ferritin is an acute-phase protein and the level will be very high in patients with acute liver failure, hence it rarely helps diagnosis if the ALT con- centration is greater than 1000 IU/litre. Nonalcoholic fatty liver disease is the commonest cause of ab- normal liver function tests in the presence of a negative chronic liver disease screen (Table 15.22.1.5), and in the absence of jaun- dice the key is to differentiate simple fatty liver disease (steatosis or nonalcoholic fatty liver disease), which is nonprogressive, from nonalcoholic steatohepatitis, which can progress to cirrhosis: an AST level greater than the ALT level in the presence of diabetes and hypertension suggests nonalcoholic fatty liver disease. An AST/ ALT ratio is consequently incorporated into several serological Table 15.22.1.5 Hepatitic liver function tests and the chronic liver disease screen ALT >10 000 IU/litre Consider: Ischaemic hepatitis Paracetamol overdose ALT >500 IU/litre Consider acute viral hepatitis: Hepatitis A IgM Hepatitis B surface antigen Monospot for Epstein–Barr virus infection Cytomegalovirus IgM Hepatitis E IgM Consider autoimmune hepatitis: Liver autoantibodies (antinuclear antibody, smooth muscle antibody, soluble liver antigen) IgG Consider: Drug-induced liver injury ALT< 500 IU/litre Chronic liver disease screena Hepatitis B surface antigen Hepatitis C antibody Ferritin + transferrin saturation Liver autoantibodies (antinuclear antibody and smooth muscle antibody) Immunoglobulins α1-antitrypsin Copper/caeruloplasmin (if age <40)b AMAa ALT< 250 IU/litre Chronic liver disease as above Also consider alcohol a If ALP level is elevated. b Wilson’s disease; often ALP low or normal and also haemolysis.

 noninvasive methods of assessing liver fibrosis, which are useful in assessing liver fibrosis when investigating cause of abnormal liver blood tests in the absence of jaundice. Cholestatic liver function tests (high ALP) Liver-related causes of elevated ALP and their investigation are shown in Table 15.22.1.6. Large duct biliary obstruction is the commonest cause of cholestatic liver function tests, followed by intrahepatic biliary in- jury affecting the small intrahepatic bile ducts. Hepatic infiltration due to compression of the sinusoids also causes high ALP levels. In contrast to high ALT levels, high ALP levels are also frequently seen in extrahepatic systemic conditions such as rheumatoid arthritis and polymyalgia rheumatic, but accompanying jaundice is unusual. Bile duct stones are usually associated with pain, but they can occur without symptoms, particularly if the bile duct is very dilated. Cholangitis

is a frequent associated complication which can mani- fest just as confusion in the elderly. Rigors are common as Gram- negative organisms usually cause sepsis. In the absence of extrahepatic biliary obstruction an anti mitochondrial antibody (AMA) test should be performed to ex- clude primary biliary cholangitis. This is positive in 90% of cases of primary biliary cholangitis, who are usually female. In AMA- negative individuals, magnetic resonance cholangiopancreatography (MRCP) should be done to exclude intrahepatic biliary disease such as primary sclerosing cholangitis, followed by a liver biopsy if the diagnosis remains unclear. Other autoantibodies such as gp210 and sp100 can be positive in the 10% of patients with primary biliary cholangitis who are AMA negative. IgG4 systemic disease is a recently recognized condition which can cause a sclerosing cholangitis picture on MRCP and occasionally mimic a hilar cholangiocarcinoma or inflammation of the pancreas (autoimmune pancreatitis) leading to a distal bile duct stricture. The diagnosis is made by the finding of IgG4 plasma cells on histology and/or elevated IgG4 in serum. Intrahepatic cholestasis of sepsis and ischaemic cholangiopathy should also be considered in patients with jaundice and high ALP levels in the intensive care setting. Intrahepatic cholestasis of sepsis is probably mediated through the effect of endotoxin on the biliary transported proteins on the canalicular and sinusoidal hepato- cyte membrane. Ischaemic cholangiopathy is rarer, but sometimes arises because the biliary system is dependent on blood flow from the hepatic artery, and prolonged hypotension can lead to necrosis of bile duct epithelium which sloughs off into the lumen causing biliary obstruction. This condition should be considered particu- larly in jaundiced patients who have had a high inotropic require- ment in cardiac intensive care units. Total parenteral nutrition is also associated with cholestatic liver function tests, which are com- moner following prolonged nutrition and where the lipid compo- nent is high. γ-Glutamyl transferase adds little to the investigation of jaun- dice, except in oestrogen or pregnancy-associated intrahepatic cholestasis. γ-Glutamyl transferase may differentiate between mu- tations in the ABCB11 gene encoding BSEP from mutations in ABCB4 encoding MDR3, both canalicular transport proteins, as it is normal in the former. Chronic liver disease screen Components of the chronic liver disease screen are shown in Table 15.22.1.5. Synthetic liver function tests A key to acute liver injury is a normal albumin. In posthepatic biliary obstruction, due to malabsorption of vitamin K from a lack of bile salts in the gut lumen, the prolonged prothrombin time will correct with intravenous vitamin K. The degree of elevation of prothrombin time in acute and chronic liver injury does not predict increased bleeding but is an important prognostic marker (Table 15.22.1.7). The triad of low platelets (due to reduced production as a result of low hepatic thrombopoietin production and increased consump- tion due to splenomegaly), prolonged prothrombin time, and low albumin suggests cirrhosis. Jaundiced patients with cirrhosis may have only mildly elevated ALP and ALT levels, and occasionally these can be normal, but the presence of a low albumin, platelets, and high prothrombin time will then differentiate cirrhosis from prehepatic jaundice. Ascitic tap A 10 to 20-ml sample of ascites should be sent for cytology, ascitic white cell count, bacterial culture, protein, and albumin (Table 15.22.1.8). The last of these will help distinguish exuda- tive from transudative ascites. A serum–ascitic albumin gradient (SAAG) of greater than 11 indicates a transudate. An ascitic pro- tein level is also helpful as in hepatic venous outflow obstruction, including right heart failure, although the ascites is a transudate it will have a high protein, helping to differentiate it from cirrhosis. Radiology Figure 15.22.1.2 summarizes the pivotal role of ultrasonography and biliary imaging in identifying causes of jaundice. Ultrasound examination This is the key investigation in excluding posthepatic jaundice. Dilated intrahepatic ducts indicate obstruction at the liver hilum, either due to cholangiocarcinoma or lymph node metastases. Gallbladder stones in a patient with biliary pain, even in the absence Table 15.22.1.6 Liver-related

causes of elevated ALP and their investigation Condition Investigation Bile duct obstruction Ultrasonography ± IgG4 ± blood culture Intrahepatic biliary disease Primary biliary cholangitis Primary sclerosing cholangitis Drugs Intrahepatic cholestasis of sepsis Total parenteral nutrition AMA/sp100/gp210 antibody MRCP History History History Hepatic infiltration: Lymphoma Acute leukaemia Metastatic cancer Hepatocellular carcinoma Liver biopsy Blood film Liver biopsy/CT scan α-Fetoprotein/CT scan/liver biopsy Note: high ALP (usually < 1000 IU/litre) can be seen in alcoholic liver disease (cirrhosis and alcoholic hepatitis).

section 15 Gastroenterological disorders 3056 of a dilated biliary system, suggest common bile duct stones, only 30% of which will be seen on ultrasonography. In acute liver injury, the ultrasound examination will be normal. The presence of splenomegaly and/or abnormal liver texture sug- gests underlying chronic liver disease. Classical nodular liver is not always seen on ultrasonography in the presence of cirrhosis. The hepatic veins can also be seen using Doppler ultrasonog- raphy, and in the presence of ascites this is important to exclude both hepatic venous outflow obstruction and portal vein occlusion, which can complicate cirrhosis or be caused by a complicating tu- mour. Hepatic infiltration from a tumour such as lymphoma or diffuse liver metastases can be difficult to see on ultrasonography. A CT scan is needed and should be considered when there is hepato- megaly and high ALP levels. Biliary imaging MRCP remains the diagnostic investigation of choice for identifying the cause of biliary obstruction. It may identify bile duct and cystic duct stones not seen on ultrasonography, although it can miss small gallbladder stones which are best seen by ultrasonography. It is also useful in mapping the extent of biliary obstruction in bile duct cancers, particularly hilar cholangiocarcinomas, to help in deciding if stenting will improve jaundice and decide between endoscopic and percutaneous approach. MRCP will also identify chronic pancreatitis and swollen pancreas typical of IgG4 disease. Endoscopic retrograde cholangiopancreatography (ERCP) is also used to confirm diagnosis and for therapy. Pancreatic CT is needed before endoscopic stenting to stage/assess operability of ampullary, pancreatic, or bile duct cancers because further assessment of oper- ability is impossible if post-ERCP pancreatitis occurs (1 in 20 risk). Liver biopsy Liver histology is often needed once posthepatic biliary obstruction and acute viral hepatitis have been excluded, to stage the degree of liver injury, to differentiate acute from chronic liver damage, and to aid diagnosis. It is a major component of the diagnostic criteria for autoimmune liver disease and is often needed to make a diagnosis in the presence of a hepatitic liver function test once acute viral hepa- titis has been excluded serologically. Percutaneous liver biopsy has a 0.5% risk of bleeding and a small risk of pneumothorax. Other rare complications include intrahepatic arteriovenous fistulae and haemobilia. Transjugular liver biopsy is indicated in the presence of ascites, a platelet count less than 50 × 109/litre, and a prolonged prothrombin time. Noninvasive markers of liver fibrosis such as FibroScan are less useful in the presence of jaundice as inflammation can increase FibroScan scores, incorrectly suggesting cirrhosis. Ascites also re- duces the sensitivity and specificity of FibroScan. Other tests In a patient with cirrhosis less than 40 years of age and with haem- olysis, particularly in the presence of a normal or low ALP, Wilson’s disease should be considered and examination for Kayser–Fleischer rings with a slit lamp should be performed. Table 15.22.1.8 Investigation of ascites Parameter Comment Serum–ascitic albumin gradient (SAAG)
<11 = exudate

11 = transudate Protein High in hepatic venous outflow obstruction despite SAAG >11 suggesting transudate Neutrophil count 250 cells/mm3 in spontaneous bacterial peritonitis Cytology High yield in ovarian cancer Amylase Pancreatic duct leak in chronic pancreatitis from pancreatic injury Rarely associated with jaundice from biliary obstruction Table 15.22.1.7 Scoring systems for liver disease severity Score components Bilirubin PT Creatinine Sodium Complications Other Acute liver failure Kings criteria: paracetamol Yes Yes Encephalopathy Kings criteria: nonparacetamol Yes Yes Age Cause Time to jaundice Chronic liver failure Child–Pugh Yes Yes Ascites Encephalopathy MELD Yes Yes Yes MELD-Na Yes Yes Yes Yes UKELD Yes Yes Yes Yes Maddreya Yes Yes a Used for alcoholic hepatitis. MELD, Model for End-Stage Liver Disease; Na, sodium; PT, prothrombin time; UKELD, United Kingdom model for end-stage liver disease.

15.22.1 Investigation and management of jaundice 3057 Management All potentially hepatotoxic drugs, including recently started medi- cation, should be stopped. Vitamin K will reverse abnormal coagu- lation in patients with posthepatic obstructive jaundice, allowing biliary intervention at ERCP, including sphincterotomy. Drugs that may adversely affect renal function, which is already compromised in cirrhosis and acute liver failure, should be avoided. High levels of bilirubin are also toxic to renal tubules. Itching due to large duct biliary obstruction can be difficult to palliate if the cause cannot be treated, but may respond to antihistamines and aqueous cream with 1% menthol. Treatments effective for itching due to intrahepatic biliary disease such as primary sclerosing cholangitis in- clude colestyramine, rifampicin, or naltrexone. Itching in patients with intrahepatic cholestasis of pregnancy responds to ursodeoxycholic acid. Although treating cholangitis associated with biliary obstruction may lead to improvements in both jaundice and liver function tests, investigation of the underlying cause should still be undertaken. In drug-induced jaundice, after stopping the causative drug, cholestatic liver function tests can take months to return to normal, whereas following hepatitic drug injury, liver function tests will often normalize within weeks. Further management is dependent on the cause identified fol- lowing blood tests and imaging (Fig. 15.22.1.2). Practice management guidelines are available through the websites of the European Associa tion for the Study of the Liver (http://www.easl.eu) and American Association for the Study of the Liver (http://www.aasld.org). FURTHER READING Buchman AI, Iyer K, Fryer J (2006). Parenteral nutrition-associated liver disease and role for intestinal and intestinal/liver transplant- ation. Hepatology, 43, 9–19. Bunchorntavakal C, Reddy KR (2013). Review article; herbal and dietary supplement hepatotoxicity. Aliment Pharmacol Ther, 37, 3–17. Chalasani N, et al. (2008). Causes, clinical features and outcome from a prospective study of drug-induced liver injury in the United States. Gastroenterology, 135, 1924–34. Chand N, Sanyal AJ (2007). Sepsis induced cholestasis. Hepatology, 45, 230–41. Erlinger S, Arias IM, Dhumeaux D (2014). Inherited disorders of bilirubin transport and conjugation: new insights into molecular mechanisms and consequences. Gastroenterology, 146, 1625–38. Halilbasic E, Claudel T, Trauner M (2013). Bile acid transporters and regulatory nuclear receptors in the liver and beyond. J Hepatol, 56, 156–68. Hennes EM, et al. (2008). Simplified criteria for the diagnosis of auto- immune hepatitis. Hepatology, 48, 169–76. Lok AS, et al. (2012). Reactivation of hepatitis B during immunosup- pressive therapy: potentially fatal yet preventable. Ann Intern Med, 156, 743–5. Martinez SM, et al. (2011). Non-invasive assessment of liver fibrosis. Hepatology, 53, 325–35. Purcell RH, Emerson SU

(2008). Hepatitis E: an emerging awareness of an old disease. J Hepatol, 48, 494–503. Rockey DC, et al. (2009). Liver biopsy. Hepatology, 49, 1017–44. JAUNDICE Normal ALT/ALP Normal albumin/platelets* Abnormal ALP/ALT Ultrasound scan Dilated CBD Undilated CBD**/* High ALT High ALP MRCP/ERCP **If pain and gallbladder stones and elevated ALP or ALT <1000 needs MRCP to exclude bile duct stones

• Suggestion of cirrhosis; splenomegaly/low platelets No evidence of haemolysis Unconjugated bilirubin Gilbert’s syndrome See Table 15.22.1.5 No cause identified Liver biopsy (diagnosis/staging) Exclude drugs AMA MRCP to exclude PSC Fig. 15.22.1.2 Summary of the investigation of jaundice. AMA, antimitochondrial antibody; CBD, common bile duct; PSC, primary sclerosing cholangitis.

Revision #1
Created 2026-01-22 16:38:41 UTC by Omar Ayman
Updated 2026-01-22 16:38:41 UTC by Omar Ayman