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Харківський національний медичний університет

MODERN PRACTICE OF INTERNAL MEDICINE WITH EMERGENCY CONDITIONS

Management of patients with jaundice

Guidelines for students and interns

СУЧАСНА ПРАКТИКА ВНУТРІШНЬОЇ МЕДИЦИНИ З НЕВІДКЛАДНИМИ СТАНАМИ

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Management of patient with jaundice

General Outcome

The students should be able to describe main links of pathogenesis, clinical features, diagnostic and treatment of jaundice.

The aim of this topic is to provide the student with an opportunity to:

- Provide a basic overview of the pathophysiology, diagnosis, and classification of jaundice.
- Evaluate guideline-based management strategies for the treatment of jaundice.
- Develop an individualized pharmacotherapy and monitoring plan for the management of jaundice, when given specific patient information.

Specific Learning Outcomes:

Upon successful completion of this unit, the students should be able to:

1. Describe the jaundice classifications.
2. Describe the main mechanism of etiopathogenesis.
3. Describe the main clinical features of jaundice.
4. List and describe the group of drugs that are used in the treatment of jaundice and give specific examples of each.
5. Make a treatment plan the jaundiced patient.

Specification of the theoretical question for training of "Management of the jaundiced patient"

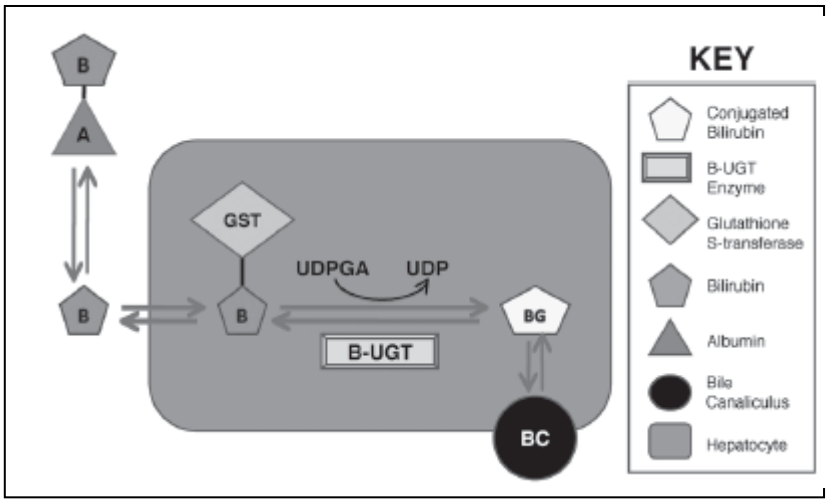
Student must know:

1. What is the definition of jaundice?
2. What are the main causes of jaundice?
3. What are the main pathogenetic links of jaundice?
4. What are the main types of jaundice?
5. What laboratory tests are used in the jaundiced patient?
6. What imaging studies are used in the jaundiced patient?
7. What treatment methods are used in the jaundiced patient?

Jaundice is not a diagnosis *per se* but rather a physical manifestation of elevated serum bilirubin. It is not a common chief complaint. Instead, the jaundiced patient often presents with a related symptom, (e.g., abdominal pain, pruritis, vomiting, or substance ingestion). Hyperbilirubinemia is only dangerous in and of itself in neonates, where it can cross the blood brain barrier and deposit in the brain tissue, causing encephalopathy (kernicterus). In adults, jaundice serves as a marker for potentially serious hematologic or hepatobiliary dysfunction such as massive hemolysis, fulminant hepatic failure, or ascending cholangitis. Indeed, these are the cases where the emergency physician must intervene aggressively in order to maximize good outcomes. Fortunately, the majority of jaundiced patients have a more indolent course and the emergency physician serves as a facilitator in the diagnostic work-up, initiating management and ensuring that an appropriate disposition is made. Whether jaundice is the presenting complaint or an incidental physical finding, it requires the physician to be an astute diagnostician. Because the differential is so broad, a thorough history and physical examination must be performed – a challenge in even a moderately busy department. The history and physical examination will help narrow the differential diagnoses, driving the work-up and disposition. The clinical pathway provided can be used as a quick reference to help facilitate caring for these patients.

Etiology and pathophysiology

Jaundice is the physical manifestation of elevated serum bilirubin. The normal serum concentration of bilirubin is less than 1 mg/dL (17 μmol/L). Typically, jaundice is not detectable clinically until serum bilirubin reaches 2.5 mg/dL. It is first seen in the conjunctiva or oral mucous membranes such as the hard palate or under the tongue. As the serum concentration of bilirubin rises, jaundice proceeds caudally. Encephalopathy becomes a concern at levels of 20–25 mg/dL. Comprehending normal bilirubin metabolism is crucial to understanding the pathologic conditions that cause jaundice. Bilirubin is derived from the breakdown of heme molecules; the majority (80 %) is from senescent red blood cells (RBCs). The remaining 20 % comes from other heme-containing proteins. The reticuloendothelial cells of the liver and spleen destroy the RBCs, releasing unconjugated bilirubin into the circulation. While in circulation, bilirubin is bound to albumin and enters hepatocytes passively, where it undergoes glucuronidation by a family of enzymes called uridinediphospho-glucuronosyltransferases (UGT). The conjugated bilirubin molecules are actively transported across the canalicular membranes into the biliary system. This is detailed in *figure*.



Bilirubin conjugation

Bilirubin is stored as part of bile in the gallbladder and emptied into the duodenum. In the colon, the majority is metabolized to stercobilin or urobilinogen by colonic bacteria. Stercobilin is excreted in the stool. Urobilinogen is reabsorbed into the bloodstream and excreted in the urine. The remainder of conjugated bilirubin in the gut is de-conjugated and taken up by intestinal epithelial cells. From there, it enters the portal circulation and returns to the liver (enterohepatic circulation). Conjugated bilirubin can also enter circulation from diffusion out of the hepatocytes. Once in circulation, it is filtered by the glomerulus and then reabsorbed so that no direct bilirubin is excreted under normal conditions. When the filtered load of direct bilirubin exceeds the tubular absorptive capacity, direct bilirubin appears in the urine. Thus glomerular filtration plays a role in determining serum levels of direct bilirubin, and patients who have both liver disease and renal insufficiency can have extraordinarily high bilirubin levels. In the laboratory, conjugated bilirubin is the fraction that reacts directly with the reagents. Thus it is reported as "direct" bilirubin. The unconjugated fraction requires the addition of an accelerator compound and is referred to as "indirect" bilirubin. There is an extensive differential diagnosis for hyperbilirubinemia that is initially narrowed by identifying the fraction of bilirubin that is elevated (direct versus indirect). For primarily direct hyperbilirubinemia, potential causes are further divided into cholestatic versus hepatocellular injury patterns based on the liver function tests.

Conditions causing indirect hyperbilirubinemia

There are three basic pathophysiologic mechanisms that lead to indirect hyperbilirubinemia: overproduction of bilirubin, impaired bilirubin uptake, and impaired conjugation. Causes of indirect hyperbilirubinemia are presented in *table 1*.

Table 1

Causes of indirect hyperbilirubinemia

Increased bilirubin production	Hemolysis (intravascular or extravascular) Impaired RBC synthesis (megaloblastic, sideroblastic, iron deficiency anemia, lead poisoning)
Impaired hepatic bilirubin uptake	Congestive heart failure Portosystemic shunts Drugs (rifampin, probenecid)
Impaired bilirubin conjugation	Crigler-Najjar syndrome Gilbert's syndrome Neonates Hyperthyroidism Ethinyl estradiol Liver diseases (chronic persistent hepatitis, advanced cirrhosis, Wilson's disease)

Overproduction of bilirubin

Overproduction of bilirubin is due to decreased synthesis or increased destruction (hemolysis) of RBCs. The differential diagnosis for hemolytic anemia is listed in *table 2*. Decreased RBC synthesis occurs in various anemias (iron deficiency, megaloblastic, and sideroblastic) and lead poisoning. In these conditions, the reticuloendothelial cells of the bone marrow degrade heme molecules that are not incorporated into RBCs.

Impaired bilirubin uptake

Conditions that cause decreased hepatic circulation, such as congestive heart failure or portosystemic shunts, can lead to decreased bilirubin uptake in the sinusoids. Cirrhosis, Gilbert’s syndrome, and drugs such as rifampin or probenecid can have the same effect.

Impaired conjugation

Impaired conjugation results from impaired or absent UGT in the hepatocytes. Inherited causes for this include Gilbert's syndrome and Crigler-Najjar syndrome. Acquired causes include hormonal modulation (hyperthyroidism and ethinyl estradiol), antibiotics (gentamycin, novobiocin), and liver disease (chronic hepatitis, cirrhosis, and Wilson's disease).

Conditions causing direct hyperbilirubinemia

There are multiple acquired and inherited causes for direct hyperbilirubinemia. The most familiar causes are the Dubin-Johnson and Rotor syndromes.

Table 2

Causes of hemolysis

Congenital	Hereditary spherocytosis Glucose-6-phosphate dehydrogenase deficiency (G6PD) Sickle cell disease
Acquired	Autoimmune Cold and warm agglutinins Drug-induced Microangiopathic hemolytic anemia (MAHA), disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) Paroxysmal nocturnal hemoglobinuria (PNH) Mechanical valve

The former affects the biliary excretion of organic anions while the latter is a disorder of hepatic storage of bilirubin. Both are benign syndromes that have fluctuating elevations of both conjugated and unconjugated hyperbilirubinemia. Additionally, there are other conditions, progressive familial intrahepatic cholestasis, and benign recurrent intrahepatic cholestasis that cause a conjugated hyperbilirubinemia as a result of reduced bile flow. Acquired conditions can be divided into biliary obstruction, intrahepatic cholestasis, and hepatocellular injury. Both inherited and acquired causes are summarized in *table 3.*

Table 3

Causes of direct hyperbilirubinemia

Extrahepatic cholestasis (biliary obstruction)	Choledocholithiasis Intrinsic and extrinsic tumors Primary sclerosing cholangitis AIDS cholangiopathy Acute or chronic pancreatitis Strictures Parasitic infections
Intrahepatic cholestasis	Viral hepatitis Alcoholic hepatitis Non-alcoholic steatohepatitis Primary biliary cirrhosis Drugs and toxins Sepsis/hypoperfusion Infiltrative diseases Total parenteral nutrition Pregnancy Cirrhosis
Hepatocellular injury	See *table 7*

Extrahepatic biliary obstruction

Extrahepatic biliary obstruction can lead to both a conjugated and unconjugated hyperbilirubinemia. As conjugated bilirubin increases in the hepatocytes, glucuronidation is reversed and some of the unconjugated bilirubin leaks into the plasma. Alkaline phosphatase (AP) and gamma-glutammyltransferase (GGT) are also elevated due to dilated biliary ducts. The differential diagnosis is provided in *table 4* and includes cholelithiasis, tumors, infectious causes, pancreatitis, primary sclerosing cholangitis, and strictures. Gallstones can directly or indirectly obstruct extrahepatic bile ducts; an example is the Mirizzi syndrome where an impacted cystic duct stone causes gallbladder distension and leads to hepatic duct compression. Both intrinsic and extrinsic tumors can lead to extrahepatic cholestasis. Common causes are pancreatic carcinoma, hepatocellular carcinoma (HCC), cholangiocarcinoma, and metastatic disease. Infectious causes can include ascending cholangitis, parasitic infections, and AIDS cholangiopathy. Parasites include *Ascaris lumbricoides* (which migrates into the bile ducts from the intestines) and liver flukes (such as *Clonorchis sinensis* which lay eggs in the smaller bile ducts). Cryptosporidium, cytomegalovirus, and HIV most commonly cause AIDS cholangiopathy.

Table 4

Causes of extrahepatic cholestasis

Tumors	Cholangiocarcinoma Pancreatic carcinoma Periampullary carcinoma Metastatic disease
Infection	AIDS cholangiopathy cytomegalovirus (CMV), *Cryptosporidium* spp, HIV Parasitic infection *Ascaris lumbricoides*
Cholangiopathy	Choledocholithiasis Biliary stricture Primary sclerosing cholangitis Sphincter of Oddi dysfunction
Pancreatitis	Acute or chronic

Intrahepatic cholestasis

There are a number of conditions that lead to intrahepatic cholestasis either primarily or as a result of hepatocellular injury. Please refer to *Table 5* for a complete list. These patients usually present in a similar fashion to extrahepatic obstruction but have patent bile ducts.

Table 5

Causes of intrahepatic cholestasis

Acute hepatocellular injury	Viral hepatitis Alcoholic fatty liver/hepatitis Non-alcoholic steatohepatitis
Chronic hepatocellular injury	Primary sclerosing cholangitis Primary biliary cirrhosis Drugs Hepatitis Cirrhosis
Multifactorial	Total parenteral nutrition Systemic infection Postoperative Sickle cell disease/crisis Organ transplantation (rejection, graft vs. host, venoocclusive disease
Miscellaneous	Hypotension/hypoxemia/congestive heart failure (CHF) Budd-Chiari syndrome Parasitic infection
Inherited/endocrine	Benign recurrent cholestasis Pregnancy Thyrotoxicosis
Infiltrative/granulomatous	Amyloidosis Lymphoma Sarcoidosis Tuberculosis

Hepatocellular injury

A list of conditions causing hepatocellular injury is provided in *Table 6*. There is considerable overlap between these conditions and those that cause intrahepatic cholestasis. This is due to the variable presentation and natural progression of many of these diseases. The primary mechanism can be distinguished based on the level of elevation of the various hepatic markers. Elevation of transaminases relative to bilirubin and alkaline phosphatase favors a hepatocellular injury pattern whereas elevation of bilirubin and alkaline phosphatase relative to transaminases favors a cholestatic picture. Toxic doses of APAP cause hepatic necrosis by overwhelming the usual metabolic pathways of glucuronidation and sulfation. When this happens, the primary route of metabolism becomes oxidation by cytochrome P450. This produces the reactive electrophilic molecule N-acetyl-p-benzoquinoneimine (NAPQI). Under normal conditions, the free radicals from this species are scavenged by glutathione. In massive overdoses, the glutathione reserves are depleted leading to oxidative damage to the hepatocytes.

Table 6

Differential diagnosis of hepatocellular jaundice

Neoplasms	Hepatocellular carcinoma Cholangiocarcinoma Metastatic disease (gastrointestinal, genitourinary, bronchogenic)
Hereditary	Wilson's disease Alpha-1-antitrypsin deficiency Hemochromatosis
Miscellaneous	Secondary biliary cirrhosis Cryptogenic cirrhosis
Infections - viral	Hepatitis viruses (A-E) Herpes viruses (CMV, HSV) Hemorrhagic viruses (Ebola, Marburg, Lassa, yellow fever) Adenovirus, enterovirus
Infections – bacterial	Tuberculosis (TB) Leptospirosis Syphilis Abscesses Brucellosis Rickettsia Whipple's disease
Infections – fungal	Candida Blastomyces Cocciodies Histoplasmosis Cryptococcus
Infections – parasitic	Helminths – ascaris, clonorchis, schistosomiasis, echinococcus Protozoa – amebiasis, plasmodia, babesiosis, toxoplasmosis, leishmaniasis
Toxic	Medications Alcohol Chlorinated hydrocarbons Amanita phalloides toxin Aflatoxin Vitamin A1 Arsenic Pyrrolizidine alkaloids
Immunologic	Autoimmune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis Nonalcoholic steatohepatitis

Differential diagnosis

The differential diagnosis of jaundice is broad, and a precise diagnosis is not always possible. For this reason, the EP has two primary responsibilities: to identify and stabilize patients with life-threatening causes of jaundice (*table 8*) and to provide an appropriate work-up for non-emergent cases. The critical and emergent causes of jaundice include massive hemolysis, acute cholangitis, fulminant liver failure, acute fatty liver of pregnancy, and neonatal hyperbilirubinemia. Clues to a potentially critical patient with jaundice include altered mental status, fever, abdominal pain, bleeding, or hypotension. A patient with the triad of jaundice, right upper quadrant (RUQ) pain, and fever has acute cholangitis until proven otherwise. This collection of signs and symptoms is known as Charcot's triad and occurs in 50–75 % of patients with acute cholangitis. Patients with acute suppurative cholangitis may be septic with altered mental status and hypotension (Reynold's pentad). It is associated with increased morbidity and mortality. Bacteria can enter the biliary system through several mechanisms such as retrograde ascent from the duodenum, invasion from the portal venous system, or mechanical disruption from endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous drainage. Stents and gallstones can also serve as a nidus of infection. *E. coli, Klebsiella* spp, *Enterobacter* spp, and *Enterococcus* spp are the most common bacteria. Anaerobes are fairly uncommon. A jaundiced patient with elevated transaminases, encephalopathy, and coagulopathy is considered to have acute liver failure (ALF). If encephalopathy develops within eight weeks of the onset of illness, the condition is referred to as fulminant hepatic failure, whereas patients who develop encephalopathy in 8–26 weeks are said to have sub-fulminant failure. These patients are typically very ill at presentation and require close monitoring while in the emergency department. The mortality approaches 80 %.

History

A careful history and physical examination are essential in narrowing the differential diagnosis. A prospective series of 220 patients with jaundice and/or cholestasis found history and physical examination to be 86 % sensitive in identifying intrahepatic versus extrahepatic disease. In addition to jaundice, patients may also complain of pruritis or constitutional symptoms such as malaise, nausea, and anorexia as a result of the elevated serum bilirubin. Other complaints may include recent weight loss or increased abdominal girth from ascites. Important historical questions include time of onset, presence or absence of pain (quality, location, and radiation), fever, history of abdominal surgeries, birth history for neonates, medication history (especially the amount and time acetaminophen was taken), herbal medications, social history (including alcohol consumption, HIV and hepatitis risk factors, drug use, exposure to toxic substances or mushrooms, travel history, work history, and recreational history), and family history (including history of inherited diseases of liver or hemolytic disorders) (*table 7*).

Table 7

Historical factors

History of present illness/review of symptoms	Abdominal pain Nausea Fever Pruritis Weight loss/gain Approximate time and amount of medications taken in overdose
Past medical history	HIV history Liver disease
Medications	Prescription medications (statins, oral contraceptives) PRN medications (especially APAP) Herbal remedies
Social history	Alcohol use Drug use (mushrooms) Travel history Occupation (chemical exposures)
Family history	Liver disease Neoplasms

A thorough history can point to specific clinical syndromes. Jaundice with abdominal pain is suggestive of an obstructive cause or significant hepatic inflammation. Fever or chills associated with right upper quadrant pain is suggestive of acute cholangitis (Charcot's triad). Painless jaundice is classic for common duct obstruction due to a pancreatic head mass (*table 8*).

Table 8

Clinical syndromes suggested by history

Historical features	Suspected diagnosis
Fever, jaundice, right upper quadrant pain	Ascending cholangitis
Painless jaundice +/- weight loss	Biliary obstruction from pancreatic head malignancy
Jaundice with abdominal pain	Hepatic inflammation or biliary obstruction

Physical examination

The evaluation of any patient begins with careful consideration of the presenting vital signs. While they may not always help narrow the differential diagnosis in a patient presenting with jaundice, they will aid in determining urgency of interventions and disposition. Fever can indicate global infection from sepsis and bacteremia, or more focal infection such as hepatitis, ascending cholangitis, and cholecystitis. Tachycardia, although non-

specific, can indicate distress due to pain, fever, or anemia. Patients can be tachypneic and/or hypoxic as a result of pleural effusions in the case of end-stage liver disease or pulmonary edema in sepsis-associated acute lung injury. Hypotension could also be a marker of sepsis, anemia due to hemolysis, or fluid shifts in end-stage liver disease and pancreatitis. A global assessment of the patient will also aid in the differential diagnosis and disposition. Note if the patient appears to be in distress due to dyspnea, hypoperfusion, or pain. Alterations in mental status are important to note as acute or chronic liver failure can present with hepatic encephalopathy. The skin examination is often used to estimate the level of serum bilirubin. However, jaundice is optimally seen in natural light, a rare commodity in most EDs, so it may be difficult to detect. Classic teaching is that jaundice first appears in the sclerae, conjunctiva, and hypoglossal regions and generally spreads cephalocaudally. Additionally, there are other factors that can affect the correlation between clinical jaundice and total body bilirubin content. Drugs such as salicylates or sulfonamides and free fatty acids can displace bilirubin from albumin, causing it to deposit in the tissues; this makes the clinical appreciation of jaundice appear to be out of proportion from the laboratory measurement of bilirubin. Also, volume contraction may lead to increased serum albumin concentration, which will shift bilirubin from the tissues into the circulation, producing the opposite effect. With that said, assess for jaundice in any patient in whom there is a suspicion for liver disease. In addition, examine the skin for other sequelae of liver disease such as telangiectasias, gynecomastia, or *caput medusa*. The abdominal examination is also helpful in evaluating the patient with jaundice. Ascites is often present with acute or chronic liver disease. Rapid onset of ascites and hepatomegaly is concerning for portal vein thrombosis (Budd-Chiari syndrome) whereas ascites with abdominal tenderness is suspicious for spontaneous bacterial peritonitis. A tender liver margin can be indicative of hepatic congestion from cholestasis or congestive heart failure or can be indicative of inflammation from hepatocellular injury. The liver can either be enlarged (as in the case of hepatitis) or non-palpable (as in the case of cirrhosis). A Murphy's sign on examination can indicate acute cholecystitis. Auscultation of the lungs can reveal pleural effusion or pulmonary edema secondary to CHF, sepsis-associated acute lung injury, or end-stage liver disease. Perform a careful cardiovascular examination, looking for signs of right heart failure such as jugular venous distension, hepato-jugular reflux, and lower extremity edema. Hepato-jugular reflux occurs when gentle pressure over the patient’s right upper quadrant produces elevation in the jugular venous pressure. Right heart failure is caused by left heart failure or pulmonary hypertension. The right heart experiences elevated filling pressures leading to volume overload in the right-sided circulation including hepatic congestion. Perform a neurological exami-

nation to assess the patient's mental status including level of consciousness, orientation, and cognitive function. In addition, assess the patient for the presence of asterixis, a handflapping tremor. It is induced by having patients extend their arms and dorsiflex their wrists. If Wilson's disease is a consideration, a slit lamp examination can be performed to evaluate for a Kayser-Fleischer ring: a green to red pigment on the outer aspect of the cornea.

Laboratory diagnostic studies

The diagnostic tests ordered in the ED will vary greatly depending on how ill the patient appears as well as the likely causes of the jaundice. A wellappearing neonate may only require a total serum bilirubin measurement whereas a septic patient thought to be in fulminant liver failure will need comprehensive metabolic testing and imaging.

Liver function panel

At a minimum, any patient presenting to the ED with jaundice should have a serum bilirubin with quantification of the conjugated (direct) and unconjugated (indirect) fractions. The value in fractionating the bilirubin is to determine whether the jaundice is being caused by hepatic dysfunction. The total bilirubin concentration is not a sensitive indicator of hepatic dysfunction due to the liver's reserve capacity for metabolizing bilirubin. Elevated indirect bilirubin comes from conditions that cause either an overproduction of bilirubin or impaired hepatic uptake and conjugation. An elevated direct bilirubin fraction suggests a defect in hepatic excretion and is a more sensitive indicator of hepatic disease. In general, the normal values for indirect and direct bilirubin are less than 1.2 mg/dL and less than 0.3 mg/dL, respectively. Fractionated bilirubin is not useful in differentiating hepatocellular injury from cholestasis. The remainder of the hepatic panel is needed for this. If there is high clinical suspicion for liver disease, the aminotransferases, alkaline phosphatase (AP), albumin time, and prothrombin time should be evaluated. If these values are all normal, consider hemolysis or inherited disorders as the cause for jaundice. Gilbert's syndrome or Crigler-Najjar syndrome cause isolated unconjugated hyperbilirubinemia, and the Dubin-Johnson and Rotor syndromes cause isolated conjugated hyperbilirubinemia. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are two liver enzymes commonly used as markers of hepatocellular injury. A small fraction of asymptomatic patients can also have slight elevations. The absolute number of the elevation is not specific for a particular cause of injury; however, there is some clinical utility of the ratio of the two enzymes. An AST/ALT ratio of 2:1 suggests alcoholic liver disease. Elevations of alkaline phosphatase and bilirubin relative to the aminotransferases suggest intrahepatic or extrahepatic cholestasis. Alkaline phosphatase is also derived from bone, kidney, or placenta in the first trimester and can be elevated in diseases affecting those tissues as well. Correlation of elevated AP with elevations in either serum gamma-

glutamyl transpeptidase (GGT) or 5'-nucleotidase points to a hepatic source of AP. Both enzymes are secreted by bile canaliculi and elevations are sensitive for hepatobiliary disease. A normal 5'-nucleotidase does not rule this out, however.

Chemistry panel

The basic chemistry panel, including electrolytes and renal function, will not help narrow the differential diagnosis of jaundice. It will, however, aid in disposition because it will give further insight into the degree of illness. Jaundiced patients can have a depressed renal function from dehydration or sepsis. In severe liver disease, anuric renal failure can develop – also termed the hepatorenal syndrome. Patients with fulminant liver failure or sepsis can have disorders in acid/base homeostasis. This will be seen as a decreased bicarbonate concentration or an increased anion gap.

Complete blood count

A complete blood count (CBC) will not necessarily help to determine the etiology of jaundice but can aid in disposition. Patients with a white blood cell count (WBC) higher than 12,000 or below 4 000 or greater than 10 % bands may have sepsis. Low hemoglobin and hematocrit can signify anemia from chronic disease, hemolysis, or hemorrhage. A reticulocyte count and RBC indices will help in differentiation. A reticulocyte index of less than 2 % favors underproduction states such as anemia of chronic disease or iron, B_{12}, or folate deficiencies. Values greater than 2 % favor RBC loss or destruction, as in hemorrhage or hemolysis. Thrombocytopenia may be present due to chronic disease, infection, or medications.

Coagulation studies

The liver produces all factors in the clotting cascade with the exception of factor VIII and von Willebrand factor (vWF), which are produced by the vascular endothelium. As the liver begins to fail and the serum concentration of these proteins falls, the prothrombin time (PT) and the international normalization ratio (INR) will rise. This is a particularly serious finding as it indicates significant hepatic dysfunction. An elevated PT and partial thromboplastin time (PTT) can also be indicative of disseminated intravascular coagulation (DIC).

Other tests

Lactic acid levels can aid in the evaluation of tissue perfusion in the setting of shock. In the setting of liver failure from acetaminophen overdose, arterial lactate may have efficacy in helping to identify patients who will require liver transplantation. More specific tests can be sent based on the differential diagnosis generated by the history, physical examination, and liver panel. If hemolysis is suggested, consider sending a peripheral smear, Coomb's test, lactate dehydrogenase (LDH), and haptoglobin. An elevated LDH and de-

creased haptoglobin can help quantify the hemolysis. The peripheral smear can show the cause of the hemolysis such as spherocytes or sickle cells. A summary of peripheral smear findings can be found in *table 9*. If hepatocellular injury is suspected, other tests include acetaminophen (APAP) level and viral hepatitis serologies.

Table 10

Peripheral smear findings

	Diagnosis
Spherocytes	Hereditary spherocytosis, drug-induced hemolysis, autoimmune
Bite cells/Heinz bodies	G-6PD
Sickle cells	Sickle cell disease
Schistocytes	Microangiopathic hemolytic anemia

Determine an APAP level for any patient in whom there is any suspicion for ingestion or for whom the hepatocellular injury is undifferentiated. Treatment with Nacetylcysteine (NAC) is indicated for any value above the treatment line on the nomogram. Acute hepatitis can be caused by hepatitis A (HAV), hepatitis B (HBV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), Varicella-Zoster virus (VZV), and herpes simplex virus (HSV). Hepatitis B and C can also cause chronic hepatitis leading to hepatic fibrosis, cirrhosis, or hepatocellular carcinoma. Appropriate serologies are summarized in *table 10*.

Table 10

Hepatitis serologies

Hepatitis A	Anti-HAV IgM
Hepatitis B	Anti-HBc antibodies: (+) IgM for acute infection, (+) IgG for previous or ongoing infection HBsAg Anti-HBs: resolution or immunity HBeAg: increased viral replication Anti-HBe: waning viral replication
Hepatitis C	Anti-HCV HCV RNA
Hepatitis D	Anti-HDV
Hepatitis E	IgM anti-HEV
Other viruses	CMV, VZV, EBV, HSV

There are additional tests for less frequent causes of hepatic dysfunction such as autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson's disease, and alpha-1-antitrypsin deficiency. Detection of these conditions is often outside the scope of emergency medicine; however, the work-up

can be initiated in the ED in consultation with the patient's primary physician or the admitting hospitalist. These tests are summarized in *table 11.*

Table 11

Miscellaneous tests

Autoimmune hepatitis	Anti-smooth muscle antibodies (ASMA) Antinuclear antibody (ANA) Anti-liver/kidney microsome type 1 (anti-LKM1) Anti-soluble liver antigen (anti-SLA)
Hemochromatosis	Iron saturation, ferritin
Wilson's disease	Urinary copper, ceruloplasmin
Alpha-1 antitrypsin deficiency	Serum protein electrophoresis
Primary biliary cirrhosis	Anti-mitochondrial antibodies
Primary sclerosing cholangitis	p-ANCA

Radiology diagnostic studies

Imaging is indicated to differentiate between intraand extrahepatic etiologies of obstructive jaundice. For patients in whom there is concern for obstructive jaundice, the most commonly employed tests in the ED are ultrasound (US), computed tomography (CT), and hepatobiliary 99mTc-iminodiacetic acid (HIDA) scans. Other imaging modalities require more time, sedation, or specialist training. They include magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), and percutaneous transhepatic cholangiography (PTC). These are outside the scope of usual EM practice, but can be discussed with the appropriate consultants.

Ultrasound

The chief advantages are that it is the least expensive and invasive imaging technique available. In addition, it allows for the evaluation of adjacent structures such as the kidney and aorta. It can detect calculi in the gallbladder with 98 % sensitivity and 93.5–97.7 % specificity. It can detect the presence of obstruction with a sensitivity and specificity as high as 91 and 95 %, respectively. A dilated common bile duct (CBD) (greater than 5 mm) is diagnostic of extrahepatic obstruction. The only caveat is post cholecystectomy and liver transplant patients, who may have a slightly dilated common duct without obstruction. Sensitivity is lower (75 %) for detecting choledocholithiasis, partly due to overlying duodenal gas. Serial hepatic Doppler ultrasounds of patients with acute liver failure have shown that hepatic artery resistive index (HARI) is significantly higher for patients who fulfill transplant criteria, suggesting that this can be used as a diagnostic tool in patients who are transplant candidates. HARI has been previously evaluated in patients with liver transplants and cirrhosis.

Computed tomography (CT)

Contrasted CT of the abdomen has been shown to have similar sensitivity to 75 % in finding common bile duct stones. A small stone may be missed by thick cuts, and non-calcified stones may not be visualized at all. The chief advantage of CT over US is that other organs can be evaluated via CT. In the setting of acute liver failure, liver volume less than 1 000 mL on CT or hepatic necrosis greater than 50 % is associated with poor prognosis. Other advantages include that CT is often available at all hours in most hospitals. Other disadvantages include cost and the need to administer iodinated radiocontrast dye, which is contraindicated in patients with dye allergies or renal insufficiency.

Hepatobiliary iminodiacetic acid (HIDA)

HIDA is a valuable tool in the detection of biliary obstruction. Its utility lies primarily in the detection of cholelithiasis or cholecystitis. HIDA may be useful in the case of equivocal US. Disadvantages are that it is of limited value in patients with nonfunctioning gallbladders due to prolonged fasting or severe hepatic dysfunction. Also, it may not be available at all hours.

Endoscopic retrograde cholangiopancreatography (ERCP)

ERCP is an invasive procedure that allows for the direct visualization of the biliary tree and pancreatic ducts. For this reason, it is superior to CT or US for detection of site and cause of extrahepatic obstructions. Its main advantage is that there are many therapeutic and diagnostic options available. Common duct stones can be removed and stents placed if necessary. Tissue diagnosis can be obtained through brush biopsy or fine needle aspiration. In addition, endoscopic drainage can be performed for patients with malignant causes of obstruction. ERCP also allows for the use of endoscopic ultrasound (EUS). EUS is more invasive than transabdominal US or CT but allows for greater sensitivity in detecting pancreatic tumors and small common duct stones. The primary disadvantages of EUS are that it does not allow for the removal of the stones and it is not available in many institutions.

Magnetic resonance cholangiopancreatography (MRCP)

MRCP is the most sensitive of the non-invasive methods for detecting ductal calculi. In the presence of dilated ducts, sensitivity and specificity have been reported to be 90–100 %. Stones greater than 4 mm are readily seen as filling defects but cannot be differentiated from other filling defects such as blood clots, tumor, sludge, or parasites. It is a useful technique in the setting of failed ERCP or as an alternative to ECRP in the evaluation of choledocholithiasis hilar obstruction from ductal tumor or periductal compression.

Percutaneous transhepatic cholangiography (PTC)

PTC is an invasive procedure in which a needle is passed through the skin into the hepatic parenchyma and advanced into a peripheral bile duct. Contrast media is used to provide an image of the biliary tree. The sensitivity and specificity are nearly 100 % for diagnosing biliary tract obstruction. Major complications are 3–5 % and it is more expensive than CT or US.

Choice of imaging procedure

Of the aforementioned imaging modalities, CT and US are the two that are usually available. The diagnostic approach depends on the pre-test probability that the cause is obstructive rather than non obstructive as well as the pre-test probability that the obstruction is malignant versus benign. In cases in which clinical suspicion for malignant obstruction is high, CT is probably the best screening study. Not only can CT identify the site of the obstruction, but it is also 70 % accurate in staging and determining resectable versus unresectable disease. If the patient has a contraindication to IV dye such as a dye allergy or renal insufficiency, an ultrasound can be done to confirm the obstruction; the patient can then undergo MRI and/or MRCP for staging at a later date. If ultrasound is not available or there is clinical concern about other abdominal organs, a non-contrast abdominal CT may provide some information but will not be as sensitive as a contrast study. Patients with a high likelihood for benign obstruction, such as those with gallstones, usually present with acute onset of jaundice and abdominal pain. They may have a previous history of gallstones or biliary surgery. These patients are best screened with US because it is accurate, inexpensive, and noninvasive. The risk is that some common duct stones may not be visualized. If a common duct stone is identified or highly suspected based on the ultrasound, ERCP is indicated for removal. If the ultrasound is equivocal, consider HIDA scan, contrast CT, or consulting gastroenterology or general surgery for ERCP. Patients with prior biliary surgeries or suspected sclerosing cholangitis in whom biliary stricture is a diagnostic consideration should undergo MRCP to avoid the possibility of ERCP – associated ascending cholangitis. In patients with a low clinical likelihood for mechanical obstruction, the recommendations for initial imaging modalities are mixed. The American College of Radiology's (ACR's) appropriateness criteria for the jaundiced patient recommends starting with US32 whereas other sources recommend contrasted CT. The advantage of CT in this case is that it allows for the evaluation of the other abdominal structures, specifically the liver parenchyma, portal vein, inferior vena cava (IVC), and intrahepatic bile canicular system. If the imaging is negative for extrahepatic obstruction, further work-up will need to be done to assess for causes of intrahepatic cholestasis. Similarly, in patients with intermediate pre-test probability for obstruction, the initial choice of imaging depends on the dominant

clinical symptom. US is recommended if the sole question is whether or not obstructions exists. CT may be better if there is a need to assess other abdominal organs. Some patients may require both tests as, in many ways, the tests are complementary in providing diagnostic information that is of major importance in the initial work up of patients presenting with acute jaundice. Patients with inconclusive imaging can be referred for EUS, ERCP, or MRCP.

Treatment

Treatment will depend largely on the likely clinical entity causing the jaundice. Treatment is largely supportive; however, there are a few instances in which specific therapy must be initiated.

Hemolysis

In patients with massive hemolysis, treatment also depends on the cause of the hemolysis. Consider transfusion for patients with low hemoglobin/hematocrit or for those who continue to be symptomatic despite other therapeutic measures. Refer patients with hereditary spherocytosis for splenectomy. Those with glucose-6-phosphatase dehydrogenase deficiency or drug-induced hemolytic anemia should avoid the offending agent. Treat warm and cold agglutinins with corticosteroids. Patients with sickle cell crises should receive hydroxyurea, hydration, supplemental oxygen, and analgesia. Patients with thrombotic thrombocytopenic purpura/hemolytic uremic syndrome require plasma exchange and glucocorticoids. Patients with disseminated intravascular coagulopathy (DIC) are very ill and require massive amounts of blood products (packed red blood cells [PRBCs], fresh frozen plasma [FFP], platelets, and cryoprecipitate) in order to replete the missing elements of the coagulation cascade.

Extrahepatic obstruction

If the labs and imaging point to an obstructive picture, ascending cholangitis must be ruled out. Patients with ascending cholangitis must be managed expeditiously as they can develop septic shock at any time. Start all patients with this diagnosis on empiric antibiotics to cover gramnegatives and Enterococcus**.** Obtain surgical consultation early in patients presenting with sepsis and evidence of organ dysfunction, as they should have drainage established emergently via ERCP or cholecystostomy if they are unstable. Patients who are not septic at presentation can have a course of antibiotics and have drainage performed at a later time. Acute drainage is indicated for any patient who has persistent abdominal pain or develops sepsis. Patients should also be given IV hydration and adequate analgesia. Patients with extrahepatic obstructive jaundice without cholangitis require drainage. For benign obstructions such as gallstones or strictures, ERCP is indicated for stone removal. Patients with obstructive jaundice due to malignancy also benefit

from biliary decompression whether operative, endoscopic, or palliative. Once jaundice develops, the malignancies are associated with more advanced disease and increased morbidity and mortality. Patients with biliary obstruction are also at increased risk of infection due to poor neutrophil function. Obstructive jaundice is associated with altered fluid and electrolyte homeostasis that can result in dehydration and renal dysfunction. Biliary drainage has been shown to improve cardiac function and, not insignificantly, food intake. Preoperative drainage has not been shown to be beneficial in patients with obstructive jaundice secondary to malignancy who are undergoing surgery. Palliative biliary drainage is recommended for patients who are not surgical candidates. Endoscopic drainage with biliary stenting has been found to have fewer complications, though there is a higher rate of recurrent obstruction. For this reason, a surgical consultation should be obtained on all patients presenting to the ED with extrahepatic obstructive jaundice.

Hepatocellular injury

Patients with jaundice and transaminases out of proportion to elevation of AP have a hepatocellular injury pattern. It is essential that acute liver failure be ruled out in these patients. The diagnosis can be made if there is evidence of coagulopathy or altered mental status. The early signs of hepatic encephalopathy can be difficult to detect. It may be necessary to contact family members or the patient's nursing home and ask about sleep disturbances, agitation, and disorientation. Hepatic encephalopathy in acute liver failure initially presents as agitation, delusions, and hyperkinesias and can precede the development of jaundice. Unlike encephalopathy associated with chronic liver disease, it is relatively common but it progresses rapidly to deeper levels of ostentation and coma. As mentioned previously, coagulopathy can develop as the serum concentrations of factors II, V, VII, IX, and X fall. Fresh-frozen plasma (FFP) is recommended for any patient with active bleeding or prior to invasive procedures such as central lines or ICP monitors. It has not been shown to be beneficial in the absence of active bleeding. Patients with acute liver failure also have abnormal platelet function and thrombocytopenia. Platelet transfusion may be necessary for patients with counts below 20,000 per cubic millimeter. Patients with acute liver failure can also present with or develop circulatory collapse resembling septic shock. Hypotension develops as a result of hypovolemia, greatly decreased systemic vascular resistance, and increased interstitial edema. Approximately half of all patients with advanced hepatic failure will develop oliguric renal failure. Tissue hypoperfusion leads to diminished tissue oxygen extraction, anaerobic metabolism, and lactic acidosis. Patients should be supported with intravenous crystalloids to keep MAP >65 and urine output >0.5 mL/kg/hr. Patients who are still hypotensive (MAP <65) despite volume resuscitation should receive

inotropic support with dopamine or norepinephrine. Patients with acute liver failure are prone to hypoglycemia due to increased metabolic activity. Blood glucose should be closely monitored while in the ED, and abnormalities should be treated with intravenous glucose or insulin. Lastly, these patients are at increased risk of infection due to reduced immune response, multiple indwelling foreign bodies, and systemic steroids or H2 blockers. Broad-spectrum antibiotics can be initiated in the ED if the patient is febrile, has elevated WBCs, a bandemia, or a documented source of infection; outside of this, prophylactic antibiotics are not recommended and may select for resistant organisms. The definitive treatment for many patients with fulminant liver failure is transplantation. All patients presenting with acute liver failure should be considered for transfer to the closest facility with transplantation capabilities. Patients are candidates for transplant if they have normal function in other organs (e.g., brain and kidney) and if the disease is not likely to recur in the graft. The decision to transfer the patient to a transplant center should be made in conjunction with the transplant surgeon and should be considered as soon as the diagnosis of ALF is made.

Acetaminophen-induced liver injury

Acetaminophen-induced liver injury is one of the few scenarios in which the EP can intervene positively and potentially prevent the development of acute liver failure and the need for liver transplant. Treatment for acetaminophen-induced liver toxicity is N-acetylcysteine (NAC). The dose of NAC is a 140 mg/kg loading dose, then 70 mg/kg every 4 hours for 17 additional doses. 92 If given within eight hours of ingestion, NAC is 100 % protective from liver injury. It has also been shown to be beneficial if given after that time. Unfortunately, clinical signs of hepatotoxicity do not usually develop until the second or third day post-ingestion, when NAC is of questionable benefit. The American College of Emergency Physicians (ACEP) recommends administering NAC to patients with suspected acetaminophen overdose who are unable to be risk stratified by the Rumack-Matthew nomogram. Intravenous NAC is FDA-approved for acetaminophen overdose if given within eight hours of ingestion. The dose is 150 mg/kg IV over 60 minutes, then 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours. Advantages to this approach are shorter duration of therapy and no reduction in bioavailability of oral NAC due to charcoal administration or vomiting. It has been shown to be as safe and effective as oral NAC. Activated charcoal should be considered for acute ingestions if there are no contraindications. Further therapies should be coordinated with the local poison control center. Consider ICU admission or transfer to the nearest transplant center for wellappearing patients with moderately elevated INR or transaminases as they will require close monitoring.

Other causes of hepatocellular injury

Once acute liver failure and acetaminophen toxicity have been ruled out, treatment of patients with hepatocellular injury generally involves treatment of symptoms such as pain and nausea. Patients ith autoimmune hepatitis benefit from early administration of prednisone. Although there is no specific level of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that has been shown in the literature to mandate admission, patients with fever, coagulopathy, altered mental status, or intractable pain should be hospitalized.

Key points for jaundice

• All patients require a thorough history (including medications, drug and alcohol use, family history, and travel history) and a careful physical examination for the manifestations of liver disease.

• Check at least a total and direct bilirubin level on all patients. Most patients will also need a chemistry panel with liver function tests, a CBC with differential, and a PT/INR.

• Patients with jaundice and anemia due to massive hemolysis or dyserythropoiesis require admission.

• Patients with elevated alkaline phosphatase and gamma-glutamyltransferase likely have a biliary tract obstruction. They should get an imaging procedure in the ED (CT or US) and have a surgical or gastrointestinal consult, depending on the findings.

• Patients with primarily elevated aminotransferases (AST and ALT) have hepatocellular injury. They should be admitted if there is evidence of coagulopathy, sepsis, mental status changes, intractable pain, or nausea.

• Patients with the triad of hepatocellular injury, coagulopathy, and mental status changes have acute liver failure. They should be admitted to an ICU or transferred to the nearest liver transplant center.

• Any pregnant patient with jaundice should be managed in conjunction with the obstetrician. Patients who present with jaundice in the third trimester may require delivery and may need to be transferred to a center with high-risk obstetric and neonatal facilities.

• Well-appearing neonates with a serum bilirubin below 15 mg/dL can be discharged home with close follow-up.

• NAC is 100 % hepatoprotective if given within eight hours of acute acetaminophen ingestion; it may also be of benefit in late or chronic ingestions, and poison center consultation is recommended.

Summary

Jaundice is an infrequent complaint to the ED, but its presence on physical examination can indicate significant hepatic or hematologic pathology. The broad differential diagnosis spans the breadth of emergency medicine

from medical to surgical causes with special consideration to the pediatric and adult patients. All of this requires the EP to be an astute diagnostician by obtaining a detailed history and performing a thorough physical examination. In addition, some patients will require resuscitation and stabilization while in the ED for sepsis or acute liver failure. In cases such as acetaminophen overdose, prompt treatment can potentially save the patient's life. Finally, appropriate use of consultants and consideration of transfer can aid in the diagnosis and treatment of your patients.

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Навчальне видання

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Ведення хворих з жовтяницею

Методичні вказівки для студентів та лікарів-інтернів

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MODERN PRACTICE OF INTERNAL MEDICINE WITH EMERGENCY CONDITIONS

Management of patients with jaundice

Guidelines for students and interns