Abstract

Icterus in canine and feline patients frequently represents an underlying condition. A thorough history and physical examination can provide important clues as to the causes of icterus. Diagnostic testing and imaging can determine the appropriate therapeutic approach to resolving clinical signs.
The term “icterus” is used interchangeably with jaundice and refers to the yellow discoloration of tissues (e.g., blood, skin, mucous membranes) resulting from accumulation of bilirubin. Icterus is a clinical manifestation of an underlying disease and results from hyperbilirubinemia, which occurs when the rate of bilirubin production exceeds the rate of elimination. Reference values for bilirubin in dogs and cats vary between external laboratories; however, when serum levels are greater than 2 mg/dL, icterus will be seen in the patient and in collected specimens. Icterus is a highly specific indicator of hyperbilirubinemia associated with either increased bilirubin formation (e.g., hemolysis) or decreased bilirubin excretion (e.g., hepatobiliary disease). Despite excellent specificity, however, sensitivity is low; icterus and hyperbilirubinemia are found only in patients with moderate to severe hepatic insufficiency and in less than 50% of dogs and cats with hepatic disease. Therefore, increased bilirubin concentrations can result from nonhepatic causes.

**BILIRUBIN PHYSIOLOGY**

Bilirubin is mostly formed by the breakdown of the red oxygen-carrying pigment heme and the waste products of red blood cell (RBC) metabolism. RBCs contain hemoglobin molecules that are broken down to heme and globin. Heme is released from hemoglobin via the

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**Take-Home Points**

- Icterus results from hyperbilirubinemia, an excess amount of bilirubin in blood.
- Understanding bilirubin metabolism is essential for interpreting clinical pathology results.
- A complete history and physical examination can often suggest the underlying cause of icterus.
- Differentials for hyperbilirubinemia can be categorized as prehepatic, hepatic, and posthepatic icterus.
- Radiology and ultrasonography are the imaging modalities most often used to evaluate icteric patients.
- Hepatic biopsy is the most prognostic of all laboratory testing for the veterinarian to make a definitive diagnosis.
- Treatment, medical management, and prognosis are dependent on the underlying cause.
mononuclear phagocytic system (typically macrophages) found in the spleen, liver, lungs, lymph nodes, and bone marrow. Heme is converted by heme oxygenase to biliverdin, which is then converted by biliverdin reductase into unconjugated bilirubin. Unconjugated bilirubin is water insoluble and is released into the bloodstream, combined with albumin, and taken up by hepatocytes. In the liver, the unconjugated bilirubin is conjugated to glucuronic acid to form bilirubin glucuronide, or conjugated bilirubin, which is water soluble. The hepatocytes release the conjugated bilirubin into the bile by active transport before it is stored in the gallbladder until the animal eats, after which it enters the duodenum via the common bile duct and travels to the small intestine. Bacterial enzymes in the small intestine remove glucuronide from the conjugated bilirubin, and fecal bacteria reduce the bilirubin to urobilinogen.

At this point, urobilinogen has multiple pathways. In the small intestine, most urobilinogen is oxidized to urobilin and stercobilin, which are excreted in feces, giving them their characteristic brown color. The remaining urobilinogen in the small intestine is reabsorbed into the enterohepatic circulation, removed from the portal blood by the liver, reexcreted into bile, and ultimately reenters the enterohepatic circulation. Some urobilinogen in the hepatic portal vein will bypass the liver and enter the general circulation, traveling to the kidneys to be converted into urobilin and excreted in urine, giving urine its yellow color.

CAUSES OF ICTERUS
If any part of the bilirubin metabolism pathway is disrupted, the animal might become icteric and be classified as having prehepatic, hepatic, or posthepatic icterus (FIGURE 1). BOX 1 lists diseases and disorders known to cause hyperbilirubinemia in dogs and cats.
Prehepatic
Icterus is considered prehepatic when RBC breakdown exceeds the liver’s conjugation capacity, resulting in excess levels of unconjugated bilirubin. The liver has a tremendous ability to metabolize excessive bilirubin; prehepatic icterus results only when RBC destruction is moderate or severe (e.g., intravascular and extravascular hemolytic anemias), likely caused by immune-mediated hemolytic anemia (IMHA) in dogs, infectious diseases in cats (e.g., *Mycoplasma* species infection), and adverse drug reactions. Feline RBCs are particularly sensitive to oxidative damage, and hemolysis can follow another disease, such as hepatic lipidosis.

Hepatic
Hepatic icterus in dogs and cats is associated with hepatocellular dysfunction or intrahepatic cholestasis, resulting in accumulation of conjugated and unconjugated bilirubin. Cholestasis is the reduction or stoppage of flow of bile through the bile ducts, which causes a buildup of substances that would normally be excreted through the bile. Cholestasis can be caused by disorders of the liver, bile duct, or pancreas. Hepatic icterus can result from primary and secondary causes, such as toxins, immune-mediated or inflammatory conditions, infectious diseases, neoplasia, or genetic abnormalities of copper metabolism.

Posthepatic
Posthepatic icterus is caused by an obstruction, either partial or complete, of the biliary system and can result from abnormalities within the biliary canaliculi or secondary to diseases affecting organs surrounding the biliary tree. Trauma to the biliary system can result in leakage of bile into the abdomen, bile peritonitis, and resorption of the bilirubin into plasma, causing icterus. Excess conjugated bilirubin is regurgitated from hepatocytes that flow back into the sinusoids and into the systemic circulation, resulting in bile peritonitis and resorption of the bilirubin into plasma, causing icterus.

**Prehepatic**
- Immune-mediated hemolytic anemia (primary or secondary)
- Infectious (e.g., *Mycoplasma* species, *Babesia* species, *Cytauxzoon felis*, *Ehrlichia*)
- Heinz body hemolytic anemia
  - Toxins/drugs (e.g., acetaminophen, onions, garlic, zinc)
  - Metabolic diseases
- Hypophosphatemia
- Disseminated intravascular coagulation
- Blood transfusion reactions
- Envenomation
- Genetic disorders (e.g., frailty syndrome, phosphofructokinase deficiency, pyruvate kinase deficiency)

**Hepatic**
- Infectious
  - Viral (e.g., feline infectious peritonitis virus, feline leukemia virus, feline immunodeficiency virus, canine adenovirus type 1)
  - Bacterial (e.g., *Leptospira* species, *Salmonella* species, *Rickettsia*)
  - Protozoal (e.g., *Toxoplasma gondii*, *Neospora caninum*)
- Fungal (e.g., *Histoplasma*, *Coccidioides*)
- Parasitic (e.g., *Heterobilharzia americana*, visceral larval migrans)
- Inflammatory/immune-mediated disease
- Hepatic lipidosis
- Feline triaditis
- Cirrhosis
- Toxins (e.g., *Amanita* species, aflatoxin, Sago palm, cyanobacteria)
- Drugs (e.g., carprofen, acetaminophen, azathioprine, methimazole, oral benzodiazeptines)
- Copper-associated hepatopathy
- Lysosomal storage disease
- Neoplasia

**Posthepatic**
- Intraluminal bile duct obstruction (e.g., mucocele [rare in cats], cholelithiasis, cholecystitis, inflammation, stricture, infection [including parasite-induced], neoplasia)
- Extraluminal bile duct obstruction (e.g., pancreatic disorders, neoplasia [e.g., pancreas, duodenum], lymphadenopathy, intestinal disease, duodenal/intestinal foreign body)
- Bile duct or gallbladder rupture
Posthepatic icterus disorders that obstruct bile flow are more common in dogs than cats; diseases such as cholelithiasis, pancreatitis, infection, neoplasia, and infectious cholangitis causing partial obstruction are more common in cats.\textsuperscript{3} Bile retained in the liver is toxic and leads to hepatocellular degeneration; prolonged extrahepatic cholestasis can lead to hepatic disease and complicates the distinction between hepatic and posthepatic icterus.\textsuperscript{6}

**PATIENT EVALUATION**

Evaluation of the icteric patient should include a history, physical examination, and diagnostic testing that includes a complete blood count (CBC), serum chemistry profile, urinalysis, and abdominal imaging (preferably ultrasonography). This minimum database will help classify the icterus as prehepatic, hepatic, or posthepatic and can be used to determine the best course of treatment for the patient.

**Signalment and History**

Signalment and a complete detailed history are integral parts of the diagnostic workup. The signalment can provide clues to the cause of icterus as certain breeds are predisposed to genetic disorders (e.g., copper storage disease in Bedlington terriers, Labrador retrievers, and Dalmatians). Patient age is also relevant. For example, an unvaccinated puppy is more likely than an adult dog to have canine adenoviral hepatitis.\textsuperscript{3} Recent travel, vaccination status, and parasite prevention should be confirmed. Clients should be asked whether their pet might have had any possible known exposure to toxins, medication ingestion, environmental changes, and previous illness. Clients should be asked about the onset and chronicity of icterus. Acute cases of prehepatic icterus can include clinical signs such as anorexia, weakness, lethargy, tachypnea, and discoloration of the urine or feces. Hepatic and posthepatic icterus are more likely to be progressive over several weeks with various signs of vague inappetence, depression, weight loss, polyuria/polydipsia, bruising, and severe vomiting and diarrhea.\textsuperscript{6}

**Physical Examination**

Examination may reveal a yellow discoloration on the inside surfaces of the ears, caudoventral abdomen, sclera, conjunctiva, gingiva, soft palate, vulva, or penis (FIGURE 2).\textsuperscript{6,8} General signs of anemia and prehepatic icterus include tachycardia, weak pulse, pale mucous membranes, weakness, and lethargy. Animals with acute hepatitis caused by infectious agents or an inflammatory process may be febrile.\textsuperscript{7} An ophthalmologic examination is essential, especially in cats, to identify ocular lesions associated with multisystemic diseases (e.g., lymphoma, feline infectious peritonitis, feline retrovirus infection).\textsuperscript{8} Central neurologic signs, including ptalism (excessive salivation or drooling) in cats, might indicate hepatic encephalopathy (HE).\textsuperscript{8} During palpation, abdominal distension may be detected, caused by cranial abdominal pain, hepatomegaly, splenomegaly, or ascites, which are more frequent with hepatic obstructive disorders. Close inspection of the skin and mucous membranes may reveal petechiae and ecchymosis (bleeding abnormalities associated with IMHA) or disseminated intravascular coagulation (DIC). Rectal palpation can reveal melena or evidence of gastrointestinal (GI) bleeding secondary to drug exposure and/or liver failure.\textsuperscript{3}

**FIGURE 2.** Yellow discoloration of (A) the sclera in an icteric cat and (B) the gingiva in an icteric dog.
LABORATORY EVALUATION

CBC results will usually identify hemolytic prehepatic icterus. A serum chemistry profile will confirm hyperbilirubinemia and can be used to evaluate other values affected by hepatobiliary disorders. Urinalysis results can help identify multiorgan dysfunction. Additional diagnostic testing for specific infectious diseases, immune-mediated disorders, and inflammatory processes may be indicated.

Hematology

Initially, a hematocrit should be measured to determine if the animal has prehepatic icterus. Hemolysis must be severe enough to cause moderate to severe anemia. A packed cell volume less than 20% and normal total protein is suggestive of hemolytic anemia. If the hematocrit is normal and the anemia is mild, causes for hyperbilirubinemia are more likely to be hepatic and posthepatic. A blood smear will help identify RBC morphology and characterize anemia.

- Macrocytic, hypochromic regenerative anemia, with pronounced poikilocytosis, anisocytosis, large platelets, and regenerative leukocytosis may be caused by hemolysis.
- Microcytic, normochromic nonregenerative anemia may be caused by chronic liver disease.
- Microcytic, hypochromic amenia is caused by chronic blood loss that can result from severe flea infestation or GI bleeding.
- Numerous Heinz bodies indicate RBC injury from hepatic lipidosis in cats, oxidant drugs, or toxins.
- Autoagglutination and spherocytosis in conjunction with an inflammatory leukogram confirms immune-mediated destruction of RBCs, as in patients with IMHA. The presence of schistocytes should warrant coagulation testing for DIC.
- Thrombocytopenia can develop secondary to liver failure or severe inflammatory disorders, such as pancreatitis or bile peritonitis.

Serum Chemistry

The chemistry panel should include alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), cholesterol, blood urea nitrogen (BUN), albumin, glucose, and bilirubin. Increased ALT and AST enzymes indicate hepatocellular damage, and increased ALP and GGT levels indicate cholestasis. Increased ALP and normal GGT levels in obese, jaundiced cats are pathognomonic for hepatic lipidosis. However, high serum enzyme activity is nonspecific and may reflect changes in hepatocellular membrane permeability, enzyme induction in the liver, or changes in other organ systems. Decreased BUN, albumin, cholesterol, and glucose levels indicate significant hepatic impairment and/or infection. In patients with ascites, changes in serum electrolytes may represent third-spacing of fluids.

Urinalysis

Conjugated bilirubin can be excreted by the kidneys and qualitatively detected in urine by using reagent strips. Bilirubinuria represents residual conjugated bilirubin that has been filtered by the kidneys but not reabsorbed by renal tubules. Urine should be tested within 30 minutes of collection; when the sample is left at room temperature and exposed to air, bilirubin metabolizes to biliverdin, which cannot be detected on a reagent strip. Bilirubin is also light sensitive; therefore, urine should not be stored in clear containers. In dogs, the renal threshold for bilirubin is low; the canine kidney can convert hemoglobin into bilirubin, conjugate it, and excrete it into urine. Small amounts of bilirubin in concentrated urine samples, especially from male dogs, is normal and bilirubinuria may be detected before icterus can be discerned. Cats differ in that their renal threshold is considerably higher, and bilirubinuria does not occur in a normal sample and indicates disease in this species. Other markers in urine that may help with identifying the cause of icterus are proteinuria, glycosuria, and renal tubular casts.

Secondary Laboratory Evaluations

Further diagnostics are sometimes indicated to help
determine the extent of hyperbilirubinemia and disease, as well as the best course of treatment. Additional diagnostics can include retrovirus testing for feline infectious diseases, pancreatic-specific lipase immunoassay to evaluate for pancreatitis, bile acid testing to determine liver function, cobalamin and folate testing for small intestinal disease, and a Coombs test for IMHA. When hepatic lipidosis or neoplasia are suspected, hepatic aspirate analysis should be performed. Culture and cytology of bile can help differentiate between suppurative and lymphocytic forms of cholangitis. The single most prognostic test is hepatic biopsy, which is usually required for definitive diagnosis of diseases such as hepatitis, cirrhosis, cholangitis, hepatic lipidosis, and neoplasia.\(^4\)

Noninvasive biopsy methods include ultrasonography-guided fine-needle aspiration and percutaneous needle biopsy, or forceps biopsy via laparoscopy of the liver and gallbladder. Posthepatic disorders often need more invasive exploratory methods to obtain a biopsy sample or relieve an obstruction.\(^6\) Before performing a biopsy by any method, clotting profiles (activated partial thromboplastin time, prothrombin time, and protein-induced vitamin K absence) and a platelet count should be determined as coagulopathies can result from inadequate synthesis or activation of clotting factors and vitamin K deficiency because of cholestasis; hemorrhage can occur even with normal coagulation. Abdominal free fluid in patients with hepatic and posthepatic disorders should be sampled and submitted for culture and cytology. Abdominal fluid should be tested for bilirubin; although uncommon, biliary system rupture is diagnosed when the bilirubin level is higher than that in serum, and if identified, urgent surgery is required.\(^{10}\)

### Diagnostic Imaging

The imaging procedures most often used to evaluate icteric patients are abdominal radiography and ultrasonography. Survey abdominal radiographs can evaluate liver size, identify masses or effusions, and detect calcified choleliths in patients with extrahepatic biliary obstruction, foreign bodies, or metallic objects in the GI tract. Thoracic radiographs can be included to assess for metastatic disease, pneumonia, or other secondary conditions. Abdominal ultrasonography is more specific than radiography and is a useful tool for visualizing the biliary system, hepatic parenchyma, bile ducts, and gallbladder as well as identifying abdominal effusion.\(^4\) Ultrasonography has the additional benefits of detecting abnormalities with adjacent organs and structures (e.g., pancreas, duodenum, spleen, liver, kidneys, lymph nodes) and facilitating noninvasive sampling procedures for cytology, culture, and biopsy.\(^{5,11}\) Advanced imaging techniques that can be used to diagnose bile duct obstruction with posthepatic disorders are hepatobiliary nuclear scintigraphy and computed tomography.\(^5\)

### TREATMENT AND MANAGEMENT

#### Medical

The range of diseases and disorders causing icterus are numerous, and a diagnostic workup may be a
prolonged process. A more specific and long-term therapeutic plan depends on the diagnosis; if a definitive diagnosis cannot be made, supportive care can be initiated. Prehepatic and hepatic causes of icterus (e.g., hemolytic anemia, toxicity) can be treated medically, and some forms of posthepatic icterus (e.g., biliary rupture, extrahepatic biliary obstruction) require surgical intervention.4,10

Because icterus will resolve on its own, treatment is directed at the primary disease and not the hyperbilirubinemia itself. Crystalloid fluid therapy is based on the individual patient and is used to correct fluid deficits, maintain hydration, remedy electrolyte and metabolic derangements, and provide colloid fluid support for animals unable to maintain oncotic pressure (osmotic pressure induced by proteins, usually albumin) due to hypoalbuminemia.7,11 For patients with painful conditions (e.g., pancreatitis), analgesics should always be considered. Neurologic abnormalities, such as seizures and behavior changes, are common in animals with severe hepatic disease and occur secondary to hypoglycemia or HE.10 Intravenous dextrose supplementation helps stabilize hypoglycemia, and lactulose administered orally or rectally is given to treat HE.7 For patients with anemia, blood transfusions and vitamin K1 supplementation are indicated for coagulation support. To control nausea and vomiting and to inhibit gastric ulceration, antiemetics (e.g., maropitant [Cerenia; Zoetis, zoetisus.com]), prokinetics, and proton pump inhibitors (e.g., omeprazole) are used. Use of antimicrobial agents to treat infections should be based on culture and sensitivity results. Corticosteroids and other immunosuppressive drugs control the immune destruction of RBCs, as with IMHA.8 For patients with lymphoma or other types of neoplasia, chemotherapy is recommended. To reduce liver inflammation and minimize oxidative injury, secondary therapy with hepatoprotectants and antioxidants (e.g., milk thistle, ursodeoxycholic acid, s-adenosylmethionine) can be beneficial.10 Some commonly used drugs are metabolized in the liver. Diazepam has the potential to cause acute, fulminating hepatic failure in cats, with a high mortality rate.1 Multidrug protocols are commonly used and patients should be monitored closely for any adverse effects.

Nutritional
Nutritional therapy plays a supportive role in managing icterus but is a primary treatment for several disorders (e.g., hepatic lipidosis, HE, pancreatitis). Diets should be easily digestible, highly palatable, and calorically dense; provide adequate protein, fat, essential micronutrients, and macronutrients; and be easy for the client to prepare and feed in frequent small meals.13,14 Malnutrition can exacerbate disease processes and negatively affect treatment outcomes.14 Impaired dietary intake, malabsorption associated with severe cholestasis or portal hypertension, and catabolism all contribute to protein/calorie malnutrition, which results in loss of muscle mass and hypoalbuminemia.14 Negative protein and energy balance promotes HE, reduces immune response, and increases chance of death.14 Therapeutic diet plans may need to be modified according to the patient’s nutritional status and underlying disorder.12 BOX 2 lists goals for optimizing food digestion and assimilation and achieving voluntary food consumption.13

Whenever possible, nutritional support should be provided via the enteral route to provide energy and nutrients that support the function of the GI tract.12 A feeding tube may be required if the animal does not voluntarily eat on its own or consume at least 85% of its resting energy requirement.7 Patients that are anorexic for more than 3 to 5 days require a feeding tube, and cats with hepatic lipidosis usually need immediate tube feeding.14 Nasogastric tubes are inexpensive, easily placed without general anesthesia, and recommended as a short-term solution.13 Esophagostomy or gastrostomy tubes are preferred for longer-term dietary support. Force feeding of cats is not recommended due to learned food aversions, and use of appetite stimulants remains controversial as they may delay initiating regimented nutritional support.13,14
ROLE OF THE VETERINARY NURSE

Veterinary nurses are vital to the supportive and nursing care of the icteric patient and are the first to detect subtle changes in clinical signs. Alerting the veterinarian to suspected changes may help reverse or minimize complications. A few responsibilities of the veterinary nurse include assessing the patient’s response to treatments, advocating for patient comfort and providing analgesia when indicated, efficiently monitoring decompensated patients under anesthesia, understanding pharmacodynamics of drugs and their effects on body systems, and providing effective client communication and education for at-home care of the icteric pet.

CLIENT COMMUNICATION AND EDUCATION TIPS

● Provide verbal and printed information about the disease and its cause, the medical condition diagnosed by the veterinarian, procedures and/or tests performed, and treatments involved.
● Describe step-by-step instructions for medication administration, feeding or dietary requirements, and long-term management. Set aside an appropriate amount of time if a demonstration is indicated.
● Establish a recheck appointment, and follow up with frequent phone calls to monitor the patient’s progress and help prevent setbacks during recovery.

SUMMARY

Icterus in any patient indicates a significant underlying pathologic disorder and is a highly specific clinical sign of hyperbilirubinemia. A multitude of disease processes result in icterus, and knowledge of biliary metabolism and pathophysiology can help with developing a logical approach to classifying the underlying cause as prehepatic, hepatic, or posthepatic. A thorough history, physical examination, and diagnostic workup can be used to develop a therapeutic plan specific to the animal’s condition. Veterinary nurses are essential for providing expert patient care and educating clients to ensure successful outcomes.

References


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Lara began her second career as a licensed veterinary technician after earning her degree from LaGuardia Community College in 2011. Lara obtained her VTS certification in 2019 and has experience working in general practice for over 10 years. She currently works at the veterinary technology department at LaGuardia and assists with instructing veterinary nursing students. Lara has an affinity for passing on knowledge to others who aspire to work in the veterinary profession.
Icterus in Dogs and Cats

TOPIC OVERVIEW
The focus of this article is to provide an overview of icterus in dogs and cats, including pathophysiology, clinical evaluation, treatment, medical management, and nursing care. Readers will learn about bilirubin metabolism and pathophysiology as well as the value of identifying and recognizing clinical manifestations of hyperbilirubinemia.

LEARNING OBJECTIVES
Upon completion of the article, readers will have a better understanding of hyperbilirubinemia and will be able to classify icterus as prehepatic, hepatic, or posthepatic. Comprehension of clinical signs and diagnostic results can not only assist with medical management and developing optimal treatment options but will also be helpful in providing practical client communication and education for owners.

1. Icterus and hyperbilirubinemia are indicators of disease with high specificity and low sensitivity.
   a. True
   b. False

2. Unconjugated bilirubin is water insoluble and taken up by hepatocytes when combined with which protein?
   a. Hemoglobin
   b. Albumin
   c. Amino acids
   d. Transferrin

3. Hepatocytes release conjugated bilirubin into the bile by _____ before it is stored in the gallbladder until feeding.
   a. Passive transport
   b. Diffusion
   c. Active transport
   d. Osmosis

4. Prehepatic icterus occurs when moderate or severe red blood cell destruction is present and includes what type(s) of anemia?
   a. Intravascular
   b. Extravascular
   c. Hemolytic
   d. A and B

5. Hepatic icterus results in the accumulation of _____ bilirubin.
   a. Serum
   b. Conjugated
   c. Unconjugated
   d. B and C

6. Complete blood count results can usually identify which type of icterus?
   a. Posthepatic
   b. Hepatic
   c. Prehepatic
   d. Hyperbilirubinemia

7. A packed cell volume less than _____ and _____ total protein is suggestive of hemolytic anemia and prehepatic icterus.
   a. 30%, increased
   b. 35%, decreased
   c. 30%, normal
   d. 20%, normal

8. Urine samples should be kept at room temperature for more than 30 minutes when testing for bilirubinuria on a urine reagent test strip.
   a. True
   b. False

9. Which sampling method is the most prognostic test for the veterinarian to make a definitive diagnosis of the icteric patient?
   a. Fine-needle hepatic aspirate
   b. Bile acid test
   c. Hepatic biopsy
   d. Fluid analysis

10. Which medication should NOT be included in a therapeutic plan for an icteric cat?
    a. Antimicrobials
    b. Diazepam
    c. Lactulose
    d. Milk thistle