

# Icterus in Dogs and Cats: A Practical Diagnostic Approach

Michael Leib, DVM, MS, DACVIM  
Virginia-Maryland College of Veterinary Medicine  
Blacksburg, VA

Icterus, or jaundice, is defined as yellowish discoloration of the serum, skin, and mucous membranes. It is caused by excessive amounts of bilirubin, which occurs when the rate of production exceeds the rate of elimination. Bilirubin is a waste product of red blood cell metabolism without benefit to the body, but has major diagnostic implications in disease. Serum bilirubin must be approximately 2.5-3.0 mg/dl or greater to produce clinically detectable icterus.

## Pathophysiology

Bilirubin is a waste product of red blood cell metabolism that has important diagnostic implications in animals with hepatobiliary diseases. Most bilirubin is derived from the normal breakdown process of hemoglobin from senescent RBCs. Hemoglobin is phagocytosed by the reticuloendothelial system and converted into bilirubin. It is bound to albumin and transported to the liver, where it is taken up by the hepatocyte, conjugated with glucuronic acid, and secreted into bile canaliculi by active transport, which is the rate limiting step. Bile is stored within the gallbladder until feeding, when it enters the duodenum. Bacterial metabolism occurs in the small intestine producing several urobilins. One of these, urobilinogen, is reabsorbed within the small intestine, but most of it is removed from the portal blood by the liver and excreted back into bile. Urobilinogen which remains in circulation is removed by the kidney. In dogs, the renal tubules can convert hemoglobin to bilirubin, conjugate it, and excrete it into the urine. Urobilinogen remaining within the bowel may be passed in the feces or metabolized to stercobilins which impart color to the feces. Cats differ from dogs in that their renal threshold is considerably higher, and bilirubinuria does not occur in normal cats.

Elevated serum bilirubin is commonly found in hemolytic diseases, intrahepatic or extrahepatic cholestasis, or less commonly due to rupture of the biliary system, which is usually associated with trauma. The liver has a tremendous ability to metabolize excessive bilirubin, thus prehepatic, or hemolytic icterus, only results when moderate or severe red blood cell destruction is present. In general, higher levels are found in cases with extrahepatic cholestasis vs. intrahepatic cholestasis. However, it is possible to have normal serum bilirubin in a variety of hepatobiliary disorders. In cholestatic disorders, elevated serum AP occurs prior to any changes in bilirubin metabolism in both dogs and cats. As the cholestatic process progresses, bilirubinuria precedes hyperbilirubinemia in dogs, but hyperbilirubinemia precedes bilirubinuria in cats due to their higher renal threshold. Icteric plasma can usually be detected when bilirubin reaches 1.5-2.0 mg/dl. Serum bilirubin level must be >2.5-3.0 mg/dl to detect clinical icterus. Although it is possible to measure conjugated levels (as thus determine unconjugated levels) with the Van den Bergh test, the author has found little clinical significance for utilizing this test.

Obstruction of bile flow within the liver or during its extrahepatic transport, results in regurgitation of conjugated bilirubin from hepatocytes back into the sinusoids and into systemic circulation. Hepatocellular swelling, inflammation, necrosis, or fibrosis, especially in the periportal area, can obstruct bile flow. Hepatocyte dysfunction may interfere with the uptake, conjugation, or excretion of bilirubin and cause icterus. Thus, most hepatic disorders can cause intrahepatic icterus.

Several surveys of icteric cats have shown that the most common causes of icterus include: lipidosis, cholangitis, feline infectious peritonitis, toxic hepatopathy, hepatic neoplasia, sepsis, and hemolytic anemia. Post-hepatic disorders that obstruct bile flow occur more commonly in dogs than cats; examples include: gallbladder mucocoele, cholecystitis, cholelithiasis, pancreatitis, biliary carcinoma, pancreatic adenocarcinoma, and duodenal neoplasia. Trauma to the biliary system (gallbladder, common bile duct, cystic duct, or intrahepatic bile ducts) can result in leakage of bile into the abdomen, bile peritonitis, resorption of the bilirubin into plasma, and icterus.

Bile retained within the liver is toxic and leads to hepatocellular degeneration. Thus, prolonged extrahepatic cholestasis can lead to hepatic disease and complicate the distinction between hepatic and post-hepatic icterus.

## Clinical signs

Owners may notice icterus or it may be identified during physical examination. It is easiest to detect icterus in the sclera, conjunctiva, gingiva, hard palate, vulva or penis. It is more difficult to detect discoloration of the skin, but it can be noticed on the inside surfaces of the ears or on the caudoventral abdomen. The history may reveal exposure to potentially hepatotoxic drugs or chemicals. Abdominal trauma, often 5-10 days previously, may have occurred and resulted in leakage of bile.

Other clinical signs are dependent on the cause of icterus. Prehepatic, or hemolytic cases, are often weak, lethargic, and tachypneic, and may have dark discolored urine, a systolic heart murmur, not previously detected, or hepatosplenomegaly. Animals with hepatic or post-hepatic disorders may have some of the following signs: anorexia, weight loss, pyrexia, vomiting, diarrhea,

abdominal distention, encephalopathy, polyuria / polydipsia, or bruising or bleeding tendencies. Abdominal distention due to hepatomegaly or ascites or cranial abdominal pain may be detected during physical examination.

### **Diagnostic plan**

The most important initial diagnostic step with the icteric patient is to evaluate the hematocrit to determine if prehepatic, or hemolytic icterus, is present. Moderate or severe anemia with a normal total protein suggests hemolysis. The presence of hemolysis is also supported by hemoglobinuria or autoagglutination, although neither must be present. Further evaluation of hemolysis should include a review of red blood cell morphology for spherocytosis, hemoprotozoa, determination of the reticulocyte count, a Coombs test, and a FeLV ELISA test in cats.

If the hematocrit is normal or if mild anemia is present, the icterus is due to either hepatic or post-hepatic causes. The distinction between hepatic and post-hepatic disease is very important because hepatic disease can be diagnosed with a minimally invasive liver biopsy (often with the assistance of ultrasonography), while post-hepatic disorders often need more invasive exploratory surgery to diagnose and potentially relieve the obstruction. To obtain a liver biopsy via exploratory celiotomy, when less invasive methods are available, is not in the animal's best interests. The best method to distinguish hepatic from post-hepatic disorders is abdominal ultrasonography. Post hepatic disorders are associated with a distended gall bladder, and enlarged and tortuous cystic, bile, or intrahepatic bile ducts. A potentially neoplastic mass of the biliary system or pancreas, signs of pancreatitis (an enlarged hypoechoic pancreas with a hyperechoic rim and potentially plication of the duodenum), gallbladder mucocoele (immobile bile with fine striations) an echogenic cholelith, or a thickened gallbladder wall may be found. With intrahepatic disorders the liver may be enlarged and diffusely hyper or hypoechoic or contain focal or multifocal abnormalities.

Without ultrasonographic assistance the distinction between hepatic and post-hepatic disorders is much more difficult. If the animal is relatively bright and alert, post-hepatic disease is more likely present. Elevated resting or post-tolerance serum ammonia levels support hepatic disease. A serum AP increased 3 or more times more than an elevated serum ALT suggests post-hepatic cholestasis. Finally, very high serum bilirubin levels (>10-15 mg/dl) are most often associated with post-hepatic disorders. Finally, hypoalbuminemia and a low BUN support hepatic icterus. None of these criteria are absolutely reliable, but they do provide some assistance in making the decision to perform closed liver biopsy vs. exploratory surgery.

The complete diagnostic evaluation of a case of hepatic icterus should include a CBC, biochemical profile, urinalysis, FeLV / FIV ELISA in cats, abdominocentesis and fluid analysis (if ascites is suspected), coagulation profile, hepatic ultrasound, and a liver biopsy utilizing the least invasive method available. If examination of the ascitic fluid suggests bile peritonitis, diagnosis and treatment requires exploratory celiotomy. The pivotal step in evaluation of a suspected case of post-hepatic disease is ultrasonography. A laboratory minimum data base should be collected to evaluate concurrent disease as well as the metabolic effects of the primary disorder. Additional diagnostic tests depend on sonographic findings but may include thoracic radiographs to look for metastasis, and exploratory celiotomy for definitive diagnosis and relief of the obstructing process.

## **Icterus case 1**

### **Signalment**

Welsh corgi, MN, 8 year old

### **History**

- Icterus
  - Acute hemorrhagic diarrhea RX with metronidazole 500 mg BIDx7
  - Diarrhea returned and RX again
  - Anorexia on day 8, icterus day 11
  - RX IV fluids and enrofloxacin
  - Previous HX – acute pancreatitis 3 months ago, increased water consumption since then 2x
  - Vaccinations current, monthly milbemycin

### **Physical examination**

Icterus

### **Trifurcate icterus**

- Prehepatic – hemolytic
- Hepatic
- Posthepatic

### **Initial diagnostic plan**

- PCV – rule out hemolysis
- CBC, biochemical profile, UA
- Abdominal ultrasound

### Diagnostic results

	Presentation
PCV	42
BUN (6-28)	4
Bilirubin	7.3
ALT	2831
AP	1700
Cholesterol	562
USG	1.030
Urine bilirubin	4+

Abdominal ultrasound – liver slightly small, normal hepatic parenchyma, normal gall bladder and biliary system

### Differential diagnosis – hepatic icterus

- Drug-induced hepatotoxicity
- Chronic hepatitis
- Cholangitis
- Toxic hepatopathy
- Hepatic neoplasia - lymphoma
- Cirrhosis

### Diagnosotic plan

- Coagulogram – PT and PTT
- Parenteral vitamin K
- Liver biopsy

### Diagnostic results

- PT 7.3, PTT 9.3
- Laparoscopy – yellow liver, swollen rounded edges, lobular surface pattern
- Hepatic culture – negative aerobic / anaerobic
- Histopathology – suppurative hepatitis, lymphoplasmacellular cholangiohepatitis, hepatocyte vacuolation
- Hepatic copper 258 ppm (120-400)

### Therapy

- Hills K/d
- Cefadroxil – 4 weeks
- Ursodeoxycholic acid 15 mg/kg/day
- SAMe, milk thistle, vitamin E

### Case follow-up

	Presentation	2 weeks	4 weeks	10 weeks	20 weeks
Bilirubin	7.3	4.1	1.6	0.9	1.1
ALT	2831	1252	1604	995	81
AP	1700	3581	2875	5795	252
Cholesterol	562				

- 2 weeks – eating chicken, rice, cottage cheese, more active
- 4 weeks – eating well most days, active, vomits q 2-3 days
  - Prednisone 2 mg/kg/day
- 10 weeks – eating well, active, gaining weight
- 20 weeks – eating well active, gained 3 kg, intermittent diarrhea – resolved following withdrawal of prednisone, continuing ursodeoxycholic acid, SAMe, vitamin E
- 2 years – clinically normal, normal biochemical profile, ursodeoxycholic acid, SAMe, vitamin E discontinued after 7 months

### References

- Anderson JG, Washabau RJ. Icterus. Comp Cont Educ Pract Vet 14: 1045-1059, 1992.
- Meyer DJ. The liver part 1. Biochemical tests for the evaluation of the hepatobiliary system. Comp Cont Educ Pract Vet 4: 663-674, 1982.
- Engelking LR. Disorders of bilirubin metabolism in small animal species. Comp Cont Educ Pract Vet 10: 712 - 722, 1988.
- Meyer DJ, Chiapella AM. Cholestasis. Vet Clin North Am: Sm Anim Pract 15: 215-227, 1985.
- Hall RL. Laboratory evaluation of liver disease. Vet Clin North Am: Sm Anim Pract 15: 3-19, 1985.
- Rogers KS, Cornelius LM. Feline icterus. Comp Cont Educ Pract Vet 7: 391 - 402, 1985.
- Osborne CA, Stevens JB, Lees GE, et al. Clinical significance of bilirubinuria. Comp Cont Educ Pract Vet 1: 897-903, 1980.

Center SA, Baldwin BH, King JM, et al. Hematologic and biochemical abnormalities associated with induced extrahepatic bile duct obstruction in the cat. *Am J Vet Res* 44: 1822-1829, 1983.

Cornelius LM, DeNovo RC. Icterus in cats. In: Kirk RW (ed.). *Current Veterinary Therapy VIII*. Philadelphia, W B Saunders, 1983; 822-829.

Fahie MA, Martin RA. Extrahepatic biliary tract obstruction: A retrospective study of 45 cases (1983-1993). *J Am Anim Hosp Assoc* 31: 478-482, 1995.

Martin RA, MacCoy DM, Harvey HJ. Surgical management of extrahepatic biliary tract disease: A report of eleven cases. *J Am Anim Hosp Assoc* 22: 301-307, 1986.

Boothe HW, Boothe DM, Komkov A, et al. Use of hepatobiliary scintigraphy in the diagnosis of extrahepatic biliary obstruction in dogs and cats: 25 cases (1982-1989). *J Am Vet Med Assoc* 201: 134-141, 1992.

Neer TM. A review of disorders of the gallbladder and extrahepatic biliary tract in the dog and Cat. *J Vet Int Med* 6: 186 - 192, 1992.

Reed AL. Ultrasonographic findings of diseases of the gallbladder and biliary tract. *Vet Med* 90: 950-958, 1995.

Biller DS, Kantrowitz B, Miyabayashi T. Ultrasonography of diffuse liver disease. *J Vet Int Med* 6: 71 - 76, 1992.

Lamb CR. Abdominal ultrasonography in small animals: Examination of the liver, spleen and pancreas. *J Sm Anim Pract* 31: 6-15, 1990.

Yeager AE, Mohammed H. Accuracy of ultrasonography in the detection of severe hepatic lipidosis in cats. *Am J Vet Res* 53: 597-599, 1992.

Voros K, Vrabely T, Papp L, et al. Correlation of ultrasonographic and pathomorphological findings in canine hepatic diseases. *J Sm Anim Pract* 32: 627-634, 1991.

Nyland RG. Ultrasound patterns of canine hepatic lymphosarcoma. *Vet Radiol* 25: 167-172, 1984.

Crews LJ, Feeney DA, Jessen CR, et al. Clinical, ultrasonographic, and laboratory findings associated with gallbladder disease and rupture in dogs: 45 cases (1997-2007). *J Am Vet Med Assoc* 2009;234:359-366.

Cornejo L, Webster C. Canine gallbladder mucocoeles. *Compend Contin Educ Pract Vet* 2005;27:912-928.

Besso JG, Wrigley RH, Gliatto JM, et al. Ultrasonographic appearance and clinical findings in 14 dogs with gallbladder mucocoele. *Vet Radiol Ultrasound* 2000;41:261-271.

Center SA. Diseases of the gallbladder and biliary tree. *Vet Clin Nor Am* 2009;39:543-598.