There is no mystery when it comes to a “yellow” cat. Icterus and jaundice—both of which describe a yellowish pigmentation of the skin—indicate hyperbilirubinemia, a 5- to 10-fold elevation in serum bilirubin concentration.

However, this is where the certainty ends and the diagnostic challenge begins. The icteric cat presentation is not a sensitive or specific marker of disease, despite the visually obvious and impressive clinical sign (Figure 1). The objective of this article is to briefly review differentials for hyperbilirubinemia in the cat, and present a diagnostic and therapeutic strategy that will help practitioners approach this problem in an efficient and effective manner.

**HYPERBILIRUBINEMIA: ORGANIZATION BY LOCATION**

The differentials for hyperbilirubinemia should be organized by location: prehepatic, hepatic, and posthepatic. While, in cats, it is common to find concurrent disease processes, starting from this foundation is the first step toward an effective and efficient diagnostic workup of icteric cats.

**Prehepatic Disease**

Hemolysis releases hemoglobin, which is then metabolized through biliverdin to bilirubin in the liver. Hepatocytes in the healthy feline liver have a large capacity for uptake, conjugation, and excretion of bilirubin.

Prehepatic icterus is most likely due to the combination of a large increase in bilirubin from hemolysis and a degree of intrahepatic cholestasis secondary to hypoxia. In dogs, the most common cause of prehepatic hyperbilirubinemia is immune-mediated hemolytic anemia (IMHA), but that condition appears to be quite rare in cats. The list of prehepatic causes of hyperbilirubinemia in cats is extensive (Table 1, page 40).

**Hepatic Disease**

A significant decrease, or loss, of hepatocellular function affects bilirubin metabolism, and frequently results in intrahepatic cholestasis (Table 1, page 40). Unconjugated bilirubin from damaged hepatocytes is present, although the majority of bilirubin that appears in the cat’s circulation is conjugated, having completed the metabolic step prior to encountering the cholestatic overflow into the vasculature.

**Posthepatic Disease**

Extrahepatic biliary disease interferes with the normal flow of bile and the final steps in bilirubin excretion, resulting in extrahepatic cholestasis (Table 1, page 40). As with intrahepatic disease, both unconjugated and conjugated bilirubin appear in the serum, rendering the biochemical distinction between conjugated and unconjugated serum bilirubin of minimal diagnostic importance.
COMMON CAUSES OF PREHEPATIC HYPERBILIRUBINEMIA

Infectious Disease
Infectious disease is a relatively common cause of prehepatic hemolysis in cats.

*Mycoplasma species*, particularly *Mycoplasma haemofelis*, can cause significant erythrocyte destruction, anemia, hyperbilirubinemia, and clinical disease. Outdoor, male, and/or shelter cats appear to be at increased risk, and coinfection with feline immunodeficiency virus (FIV) is common.3-5

Concurrent diseases, immunosuppression, and stress appear to impact the course and severity of disease and outcome of treatment. An eventual recurrence of disease is seen with some frequency in those cats that show a clinical response to treatment.

Feline leukemia virus (FeLV) infection can trigger a host immune response that results in immune-mediated prehepatic erythrocyte destruction. This may be the result of a virus-induced expression of antigens on the red blood cell (RBC) surface. Immune-mediated thrombocytopenia may accompany IMHA in cats with underlying FeLV infection.6

*Cytauxzoon felis* is transmitted by ticks (*Amblyomma americanum*) and appears to be increasing in prevalence and geographical distribution in the United States, expanding from the southeastern portion of the country. Risk for infection increases with increased exposure to the tick vector, and the progression of clinical disease is rapid and often fatal. Babesia felis can cause severe prehepatic hemolysis and anemia in cats, but appears to be rare outside of costal South Africa.7

Immune-Mediated Hemolytic Anemia
Primary IMHA appears to be quite rare in cats. It is difficult to characterize feline IMHA or determine risk factors because of the paucity of cases in the literature, but younger male cats may be overrepresented. The prognosis is guarded, with a mortality rate of 25%.8

Inherited Erythrocyte Disorders
Erythrocyte pyruvate kinase (PK) deficiency is a very rare inherited disorder transmitted as an autosomal recessive trait, causing prehepatic hemolysis.

Cats usually present as young adults, and the severity of the anemia and clinical signs is variable and may change over time, ranging from asymptomatic to hemolytic crisis.

The disease is most frequently described in Abyssinian and Somali breeds but may also be present in a variety of other purebred and domestic shorthair cats.9 Interestingly, Abyssinian and Somali breeds have also been shown to suffer from another inherited cause of prehepatic hemolysis: increased erythrocyte osmotic fragility. Genetic testing has been developed for screening cats for PK deficiency and is commercially available (vgl.ucdavis.edu/services/pkdeficiency.php)

Other Causes of Hemolysis
Hemolysis secondary to hypophosphatemia has become rare due to heightened awareness, diligent monitoring, and proactive intervention during the treatment of diabetic ketoacidosis.

Disseminated intravascular coagulation is also a rare occurrence, seen predominantly in the critical care setting, but serving as a reminder that prehepatic hemolysis can occur as a secondary consequence in a variety of diseases.

Feline erythrocytes are susceptible to oxidative stress, and a large variety of toxins and drugs (including acetaminophen, benzocaine, methylene blue, phenazopyridine, onions/onion powder, propylene glycol, and propylthiouracil) can cause Heinz body anemia or hemolytic destruction of RBC membranes.

COMMON CAUSES OF HEPATIC HYPERBILIRUBINEMIA

Feline Hepatic Lipidosis
Hepatic lipidosis appears to be a unique feline phenomenon, highlighting that hepatic metabolism in the cat is different from many other species.10 Although feline hepatic lipidosis may be an idiopathic (Figure 2) and, therefore, primary problem, it quite frequently occurs secondary to another disease that caused the cat to stop eating.

![FIGURE 2. The liver (seen laparoscopically) of a cat with idiopathic hepatic lipidosis.](image-url)
### Table 1.

**Hyperbilirubinemia in Cats: Differential Diagnoses & Clinical Signs**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Anorexia</th>
<th>Lethargy</th>
<th>Fever</th>
<th>Lymphadenopathy</th>
<th>Vomiting/Diarrhea</th>
<th>Weight Loss</th>
<th>Anemia</th>
<th>Abdominal Pain</th>
<th>Other Clinical Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prehepatic Hyperbilirubinemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mycoplasma species</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| x x x | | | | | | | | | | Hypothermia
|       | | | | | | | | | Physiologic murmur
|       | | | | | | | | | Increased heart rate/respiratory effort secondary to anemia
| *Cytauxzoon felis* |
| x x x | | | | | | | | | Dehydration
|       | | | | | | | | | Evidence of shock
|       | | | | | | | | | Progression to moribund dyspnea and hypothermia
| *Feline infectious peritonitis* |
| x x x | | | | | | | | | Effusive/wet FIP: Ascites, pleural effusion
|       | | | | | | | | | Dry FIP: Ocular and neurologic signs
| *Babesia species* |
| x x x | | | | | | | | | |
| *Feline leukemia virus* |
| x | | | | | | | | | Immune suppression
|       | | | | | | | | | Secondary infection
| *Feline immunodeficiency virus* |
| x x x | | | | | | | | | Oral inflammation
|       | | | | | | | | | Secondary infection and lymphoma
| *Immune-mediated hemolytic anemia* | x x x | | | | | | | | Signs of primary IMHA, excluding identifiable causes
|       | | | | | | | | | Pica
| *Erythrocyte PK deficiency* |
| x x x x | | | | | | | | | |
| *Increased erythrocyte osmotic fragility* |
| x x x x | | | | | | | | | |
| *Neonatal isooerythrolysis* |
| x | | | | | | | | | |
| *Transfusion reaction* | x | | | | | | | | |
| *Hypophosphatemia* | x x x | | | | | | | | |
| *Microangiopathic hemolytic anemia* | x x x | | | | | | | | |
| *Drugs, toxins, envenomation, oxidative stress* | | | | | | | | | |

**COMMON CAUSES OF POSTHEPATIC HYPERBILIRUBINEMIA**

**Extrahepatic Bile Duct Obstruction**

Cholelithiasis may be obstructive and is, thus, approached as a cause of extrahepatic bile duct obstruction (EHBO). Other causes of EHBO include tumors, nonneoplastic masses, cholecystitis, inspissated bile, cholangitis, and pancreatitis. The prognosis, even following successful surgery, is guarded.

**Cholangitis**

In contrast to dogs—in which hepatic disease is usually located in the liver parenchyma—feline liver disease typically targets the biliary system, and is most commonly seen as cholangitis. The World Small Animal Veterinary Association Liver Standardization Group clarified the terminology, defining feline cholangitis as *neutrophilic* (acute or chronic), *lymphocytic*, or secondary to liver flukes.11
### TABLE 1. (continued)

**Hyperbilirubinemia in Cats: Differential Diagnoses & Clinical Signs**

<table>
<thead>
<tr>
<th>Anorexia</th>
<th>Lethargy</th>
<th>Fever</th>
<th>Lymphadenopathy</th>
<th>Vomiting/diarrhea</th>
<th>Weight loss</th>
<th>Anemia</th>
<th>Abdominal pain</th>
<th>OTHER CLINICAL SIGNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic lipidosis(^{33,34})</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Idiopathic or secondary hepatic lipidosis</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Clinical signs vary with underlying etiology</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hiding, decreased interaction</td>
</tr>
<tr>
<td>Cholangitis(^{35,36})</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bacterial, acute or chronic neutrophilic, lymphocytic</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Dehydration</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Feline infectious peritonitis(^{37})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>See clinical signs of FIP (previous page)</td>
</tr>
<tr>
<td>Virulent systemic feline calicivirus</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral ulceration</td>
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<td></td>
<td></td>
<td>Upper respiratory signs</td>
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<td></td>
<td></td>
<td></td>
<td>Edema</td>
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<td></td>
<td></td>
<td></td>
<td>Ulcerative dermatitis</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Francisella tularensis(^{38})</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tachypnea and tachycardia</td>
</tr>
<tr>
<td>Drugs, toxins(^{39,40,d})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonspecific signs of intoxication</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Acute hepatic failure</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td>Amyloidosis(^{41})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Familial, Siamese, and other types of amyloidosis</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Sudden death</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute abdominal bleeding</td>
</tr>
<tr>
<td>Sepsis</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clinical signs associated with specific underlying etiology</td>
</tr>
<tr>
<td>Systemic inflammatory response syndrome(^{42,e})</td>
<td></td>
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<td></td>
<td></td>
<td>Collapse</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Bradycardia and hypotension</td>
</tr>
<tr>
<td>POSTHEPATIC HYPERBILIRUBINEMIA</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>See clinical signs associated with EHBO (below)</td>
</tr>
<tr>
<td>Cholelithiasis(^{43,44})</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>Coagulopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypotension and shock</td>
</tr>
<tr>
<td>Extrahepatic biliary obstruction(^{45})</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clinical signs may progress in cases of EHBO</td>
</tr>
<tr>
<td>Triaditis(^{46})</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Liver flukes(^{47})</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Platyonosomum concinnum)</td>
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</tr>
</tbody>
</table>

*EHBO = extrahepatic bile duct obstruction; FIP = feline infectious peritonitis; IMHA = immune-mediated hemolytic anemia*

---

**Feline Triaditis Syndrome**

*Feline triaditis* describes the concurrent conditions of cholangitis, pancreatitis, and inflammatory bowel disease in cats.

There is a common outflow track for the feline pancreas and bile duct as they approach the major duodenal papilla. This anatomic association makes it likely that inflammatory disease or infection in one of these tissues impacts the health and function of the associated tissues.

At this time it is unclear if the underlying etiology of triaditis is immune-mediated process, infectious, or multifactorial, making treatment decisions difficult. Significant local inflammation may create a functional EHBO that is not amenable to surgical removal, but must be addressed medically.

**Liver Fluke**

Feline liver fluke infection is geographical and
found in tropical environments, such as Florida, the Caribbean, and Hawaii, where land snails, lizards, and toads are the hosts. Infection is usually subclinical, although cats may present with nonspecific signs (Table 1).

**DIAGNOSTIC APPROACH TO AN ICTERIC CAT**
As with any diagnostic approach, the clinical evaluation of an icteric cat begins with signalment, history, and physical examination.

**Table 2.**

<table>
<thead>
<tr>
<th>DIFFERENTIAL DIAGNOSES</th>
<th>DIAGNOSTICS</th>
<th>TREATMENT OPTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prehepatic Hyperbilirubinemia</td>
<td>Complete blood count (CBC)</td>
<td>Doxycycline, 5 mg/kg PO Q 12 H for 14 d</td>
</tr>
<tr>
<td>Mycoplasma species23</td>
<td>Blood smear</td>
<td>Pradofloxacin, 5 mg/kg PO Q 24 H for 14 d</td>
</tr>
<tr>
<td></td>
<td>Serum biochemical profile</td>
<td>Enrofloxacin, 5 mg/kg PO Q 24 H for 14 d</td>
</tr>
<tr>
<td></td>
<td>Polymerase chain reaction (PCR)</td>
<td></td>
</tr>
<tr>
<td>Cytoszoon felis24</td>
<td>CBC</td>
<td>Atovaquone, 15 mg/kg PO Q 8 H</td>
</tr>
<tr>
<td></td>
<td>Blood smear</td>
<td>Azithromycin, 10 mg/kg PO Q 24 H</td>
</tr>
<tr>
<td></td>
<td>PCR</td>
<td></td>
</tr>
<tr>
<td>Feline Infectious Peritonitis Babesia species</td>
<td>CBC</td>
<td>FIP: Supportive care</td>
</tr>
<tr>
<td></td>
<td>Blood smear</td>
<td>Polyprenyl Immunostimulant (sassandsass.com)</td>
</tr>
<tr>
<td></td>
<td>PCR</td>
<td>Pentoxifylline, 10 mg/kg PO Q 12 H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prednisolone, 2-4 mg/kg PO Q 24 H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Babesiosis:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imidocarb dipropionate, 2.5 mg/kg IM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doxycycline, 10 mg/kg/day PO for 21 d</td>
</tr>
<tr>
<td>Feline Leukemia virus Feline Immunodeficiency Virus</td>
<td>FeLV: p27 antigen test</td>
<td>Blood transfusion</td>
</tr>
<tr>
<td></td>
<td>FIV: Antibody test</td>
<td>Supportive care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antiviral treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical therapy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prednisolone, 2.2 mg/kg Q 12 H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cyclosporine, 5 mg/kg Q 24 H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Chlorambucil, 2 mg/cat Q 3 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mycophenolate mofetil, 10 mg/kg Q 12 H</td>
</tr>
<tr>
<td>Immune-mediated Hemolytic Anemia8,25 (primary, excluding identifiable causes)</td>
<td>Saline agglutination</td>
<td>Prednisolone, 2.2 mg/kg PO Q 12 H</td>
</tr>
<tr>
<td></td>
<td>Coombs’ test</td>
<td>Mycophenolate mofetil, 10 mg/kg Q 12 H</td>
</tr>
<tr>
<td></td>
<td>In one report: Anemia was severe, with median packed cell volume of 12%</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte PK Deficiency26</td>
<td>Genetic testing</td>
<td>Breeding practices</td>
</tr>
<tr>
<td>Increased Erythrocyte Osmotic Frailty27</td>
<td></td>
<td>Supportive care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ursodeoxycholic acid, 5–15 mg/kg Q 24 H</td>
</tr>
<tr>
<td>Neonatal Isoerythrolysis28</td>
<td>Appropriate blood typing prior to breeding</td>
<td>Supportive care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiovascular support</td>
</tr>
<tr>
<td>Transfusion Reaction29</td>
<td>Pretesting donors</td>
<td>Supportive care</td>
</tr>
<tr>
<td></td>
<td>Blood-typing</td>
<td>Cardiovascular support</td>
</tr>
<tr>
<td></td>
<td>Crossmatching</td>
<td></td>
</tr>
<tr>
<td>Hypophosphatemia30,31</td>
<td>Electrolyte monitoring</td>
<td>Supportive care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment of underlying conditions</td>
</tr>
<tr>
<td>Microangiopathic Hemolytic Anemia32</td>
<td>CBC with platelets</td>
<td>Intensive monitoring</td>
</tr>
<tr>
<td></td>
<td>Clotting times</td>
<td>Cardiovascular support</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment of underlying conditions</td>
</tr>
<tr>
<td>Drugs, Toxins, Envenomation, Oxidative Stress</td>
<td>Various toxin assays</td>
<td>Remove exposure</td>
</tr>
<tr>
<td></td>
<td>Blood smear</td>
<td>Reduce remaining burden (eg, emesis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Support of target organs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasmapheresis</td>
</tr>
</tbody>
</table>

Signalment
The list of differentials for hyperbilirubinemia (Table 1) include breed-specific entries (eg, Abyssinian) and diseases that occur in certain age groups (eg, feline infectious peritonitis [FIP]). For many differentials the patient history is similar.

History & Clinical Signs
Anorexia is a key component in the presentation of cats with hepatic lipidosis and appears to be an early clinical manifestation of anemia in cats. Lethargy
can be difficult to appreciate in sedentary cats, and sick cats often hide, further delaying the owner’s observation of more obvious clinical signs.

Dog owners may notice changes in the color of urine or feces, but it is much less likely for cat owners to report pigmenturia or acholic feces in this fastidious species. It is also relatively unusual for cats to have dietary indiscretion of toxins, household products, medications, or human food, but certainly the potential for exposure should be investigated during the anamnesis.

The prevalence of multi-cat households also confounds the owner’s ability to appreciate changes in appetite, water consumption, or elimination habits.

**Physical Examination**

A complete physical examination, including body temperature, pulse, respiratory rate, fundic examination, cardiovascular auscultation, and abdominal palpation, is essential. Physical findings may indicate potential underlying etiologies, such as:

<table>
<thead>
<tr>
<th>DIFFERENTIAL DIAGNOSES</th>
<th>DIAGNOSTICS</th>
<th>TREATMENT OPTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEPATIC HYPERBILIRUBINEMIA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic lipidosis35,34 (idiopathic or secondary)</td>
<td>CBC, Serum biochemical profile, Urinalysis, FeLV/FIV testing, Bile acids, fPLI blood test, Ultrasound-guided liver FNA</td>
<td>Vitamin K1, 1 mg SC Q 12 H, Nutrition via E-tube</td>
</tr>
<tr>
<td>Cholangitis35,36 (bacterial, acute or chronic neutrophilic, lymphocytic)</td>
<td>Ultrasound-guided or laparoscopy-assisted cholecystocentesis and liver FNA, Cytology, Culture and sensitivity</td>
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**POSTHEPATIC HYPERBILIRUBINEMIA**

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EHBO = extrahepatic biliary obstruction; FeLV = feline leukemia virus; FIP = feline infectious peritonitis; FIV = feline immunodeficiency virus; FNA = fine needle aspiration; fPLI = feline pancreatic lipase immunoreactivity; PCR = polymerase chain reaction
as hepatomegaly with hepatic lipidosis, cranial abdominal discomfort with pancreatitis, and tachycardia with anemia.

The physical examination is often dominated by the color of the cat. Icterus is best appreciated as a discoloration of the mucous membranes, the sclera (Figure 3), and/or the inner aspect of the pinnae (Figure 4). The intensity and actual color may be influenced by the normal tissue color, degree of anemia, and perfusion.

The clinical condition and color of the cat are influenced by both the degree of anemia—mild to severe—and the time course of RBC destruction—acute or chronic.

Laboratory Analysis
Changes on the serum biochemical profile are nonspecific. The degree of elevation in total bilirubin is cited as a nonspecific but generally guides to the most likely location or etiology of the problem:

- **3 to 6 mg/dL** is associated with prehepatic hemolysis, FIP, pancreatitis, and sepsis
- **Greater than 12 mg/dL** is associated with hepatic lipidosis and EHBO.

**PREHEPATIC HYPERBILIRUBINEMIA DIAGNOSTICS**

**Blood Analysis**
The laboratory diagnostic workup for the vast majority of icteric cats starts with determining whether prehepatic hemolysis is present.

**Complete Blood Count**
Hemolysis can often be an extravascular antibody-mediated process in which the serum turns icteric. A simple hematocrit tube can be expected to identify a significant degree of anemia and a relatively normal serum total protein. Less frequently, the hemolysis occurs within the vasculature itself, in which case the serum may appear pink, while both the plasma (hemoglobinemia) and urine (hemoglobinuria) appear red.

A complete blood count (CBC) more accurately and completely characterizes the anemia as regenerative or nonregenerative; however, the regenerative process may take up to 5 days to manifest as an appropriate increase in the absolute reticulocyte count (> 40,000–60,000/μL, depending on the laboratory). A CBC also identifies other potentially important erythrocyte characteristics.

The degree of anemia is cited as a nonspecific but general indicator of the likelihood that feline icterus is the result of prehepatic hemolysis. As a rule of thumb, prehepatic hemolysis usually results in a packed cell volume (PCV) of less than 13% to 20%; however, the cat’s baseline or normal PCV, hydration status, and the time frame over which the hemolysis occurred may all impact the clinical signs, measured PCV, and elevation in total bilirubin.

**Blood Smear**
Careful examination of the blood smear is a critical step in any attempt to identify infectious organisms or indicators of immune-mediated agglutination.

**Infectious Disease**
Infectious disease testing is commonly used for prehepatic hyperbilirubinemia (Table 2, page 42).

**Mycoplasmosis**
In addition to hyperbilirubinemia, cats with mycoplasmosis are frequently hyperglobulinemic as a
result of chronic immune stimulation, and they may have mild to moderate elevations in liver enzyme activity as a result of anemic—hypoxia-induced hepatocyte necrosis.

**Feline Leukemia Virus**
There are a variety of technologies available to easily test for the FeLV p27 antigen, which is present in the majority of infected cats.

**Cytauxzoonosis**
Biochemical changes with *Cytauxzoon felis* are nonspecific, while anemia, pancytopenia, and thrombocytopenia may be seen on the CBC.

**Immune-Mediated Disease**
Diagnosing IMHA using persistent RBC agglutination, a positive Coombs’ test, RBC characteristics, and reticulocytosis can be challenging in cats; other potential causes of prehepatic hemolysis must be carefully considered.

Agglutination can be difficult to distinguish from normal rouleaux formation in the cat, but true RBC autoagglutination can be identified by mixing one drop of potassium ethylenediaminetetraacetic acid (K-EDTA) whole blood with 1 to 4 drops of 0.9% sodium chloride on a microscope slide. Macroscopic slide erythrocyte agglutination is seen in all IMHA cats, although it rarely persists following RBC washing.

Biochemical abnormalities are varied and inconsistent, although the majority of cats have a positive direct Coombs’ test, further supporting the diagnosis of IMHA. However, Coombs’ testing should be interpreted with caution and related to other clinical and hematologic findings.12

**Inherited Erythrocyte Disorders**
Biochemical and CBC parameters of cats with erythrocyte PK deficiency are nonspecific and inconsistent among patients, although hyperglobulinemia was frequently seen. Genetic testing and responsible breeding are clearly important considerations.

**HEPATIC HYPERBILIRUBINEMIA DIAGNOSTICS**

**Laboratory Analysis**
Hepatic hyperbilirubinemia is caused by significant primary hepatic disease. A minimum diagnostic database includes a CBC, serum biochemical profile, urinalysis, and FeLV/FIV status.

Once the cat is icteric, and prehepatic causes have been ruled out, the serum bilirubin is elevated to the point where a bile acids test for liver function is redundant; the results will be abnormal. With mild hyperbilirubinemia (< 2 mg/dL), a bile acids test may be warranted to assess liver function.

**Imaging**
Ultrasoundographic imaging of the entire abdomen by a board-certified specialist is an essential step in the assessment of the feline hepatobiliary system. Ultrasound is a powerful tool for assessing the liver parenchyma, visualizing the biliary system, and searching for EHBO.

**Fine Needle Aspiration**
Ultrasound-guided fine needle aspiration (FNA) is also a minimally invasive technique for acquiring samples of certain tissue, such as the liver, pancreas, and lymph nodes, and masses for cytology and culture. Coagulation parameters and clotting times should be determined prior to FNA.

**Hepatic Lipidosis**
In cats that present with hepatic lipidosis, it is critical to put diagnostic effort into identifying the disease that led to the cat’s anorexia in the first place, whether that is as simple as dental disease or as complex as feline pancreatitis. Failure to identify and address the concurrent condition is very likely to result in the cat being presented to the hospital again with the same complaint.

**Cholangitis**
The diagnostic effort of feline cholangitis is directed toward identification of the predominant inflammatory cell type present in the cat’s hepatobiliary system: acute neutrophilic, chronic neutrophilic, or lymphocytic.

FNA of the liver is a relatively simple procedure that may produce a cytologic sample suggestive of cholangitis, but this technique has significant limitations. It may be of low yield, resulting in a nondiagnostic sample, the nonspecific report of hepatocellular vacuolization, or an interpretation that would be different than that obtained by histopathology.13

Technically more challenging techniques, best performed by board-certified specialists with ample experience, are ultrasound-guided cholecystocentesis and laparoscopy-assisted gallbladder aspiration. For both procedures, samples are collected for cytology
and culture, since bile has been shown to be the sample most likely to yield an informative bacterial culture result.\textsuperscript{14,15}

Liver biopsy is required for a definitive diagnosis of hepatic disease.\textsuperscript{16}

The most common infectious organisms found in patients with neutrophilic cholangitis are enteric bacteria (e.g., \textit{E. coli}, \textit{Enterobacter}, \textit{Clostridia}) and antibiotics for treatment should be selected based on sensitivity.

**POSTHEPATIC HYPERBILIRUBINEMIA DIAGNOSTICS**

**Extrahepatic Bile Duct Obstruction**

Abdominal ultrasound of cats with EHBO frequently identifies distension of the gallbladder, common bile duct, and intrahepatic ducts (Figure 5).

**Triaditis**

Diagnosis of triaditis is based on identification of disease in each of the 3 tissues involved; the gold standard for diagnosis is histopathology. Less invasive diagnostics include the feline pancreatic lipase immunoreactivity (fPLI) blood test, abdominal ultrasound, liver FNA, cholecystocentesis, cytology, culture and sensitivity, and small intestinal endoscopic biopsy; however, these patients may have increased anesthetic risks.

Although not widely available in private practice, feline abdominal laparoscopy can be performed with equipment sized for pediatrics and allows the collection of tissue for histopathology (liver and pancreas) as well as direct aspiration of the gallbladder (Figure 6). \textbf{Liver Fluke}

Liver fluke eggs can sometimes be found in the feces or by bile cytology. A recent study assessing the use of percutaneous ultrasound-guided cholecystocentesis in cats known to be infected with \textit{Platynosomum} species flukes found the technique to be technically feasible and safe in cats with cholangitis.\textsuperscript{17}

**THERAPEUTIC APPROACH**

Detailed treatment protocols for specific differentials are beyond the scope of this article. However, some selected therapies are described.

Hydration status, pain (buprenorphine, 0.01 mg/kg sublingual Q 8 H), and vomiting (maropitant, 1 mg/kg SC Q 24 H) can all be addressed in a relatively effective manner and can significantly impact the clinical outcome.

Ursodeoxycholic acid (5−15 mg/kg Q 24 H) is an adjunct therapy that has been used in the successful treatment of bilirubin cholelithiasis, EHBO, and a Somali cat with PK deficiency, but it should not be used in place of antibiotics or prednisolone for lymphocytic cholangitis and neutrophilic cholangitis, respectively.\textsuperscript{18}

Adjunct therapy may include S-adenosylmethionine (90 mg/cat Q 24 H), silimarlin (2−5 mg/kg Q 24 H), and/or vitamin E (50 IU Q 24 H); however, there may be a limit to the number of medications an owner can administer to a cat.

**Selected Prehepatic Hyperbilirubinemia Treatment Options**

**Immune-Mediated Hemolytic Anemia**

In addition to supportive care, including blood products, cats with IMHA appeared to respond
to prednisolone therapy, although additional immunosuppressive drugs have also been used.

Anecdotal and case reports discuss the addition of cyclosporine (5 mg/kg Q 24 H), chlorambucil (2 mg/cat every 3 days), and mycophenolate mofetil (10 mg/kg Q 12 H) to treatment protocols, especially if prednisolone fails to improve the cat’s anemia.19,20

Feline Leukemia Virus
Although immunosuppression in FeLV positive cats is best avoided, in those patients with clear evidence of IMHA secondary to FeLV infection, blood transfusions are indicated and, if those fail, prednisolone (2.2 mg/kg Q 12 H) may be used as with primary IMHA patients.8,21

Erythrocyte PK Deficiency
Therapy for erythrocyte PK deficiency is supportive and nonspecific, and outcome depends, in large part, on the severity of presentation and use of transfusions to stabilize critical patients.

Selected Hepatic Hyperbilirubinemia Treatment Options
Treatment of hepatic causes of hyperbilirubinemia is best guided by histopathology, when possible, or cytology and culture.

Hepatic Lipidosis
The foundation of treatment for hepatic lipidosis is relatively simple: provide nutrition to the cat. The logistics may be challenging but the advent of esophagostomy tubes (E-tube) makes both nutrition and medication administration easier (Figure 7).

Nutrition is critical; therefore, placement of an E-tube should be encouraged early in the disease process if the cat is anorectic.

Vitamin K1 (1 mg SC Q 12 H) should be administered prior to E-tube placement if evidence of a coagulopathy is present.

Cholangitis
Degenerative neutrophils with pleomorphic bacteria from the bile of an acutely ill cat is consistent with acute neutrophilic cholangitis (Figure 8), and treatment is initiated with 2 months of antibiotics aimed at enteric bacteria: cephalosporins, amoxicillin and clavulanic acid (62.5 mg/cat Q 12 H), enrofloxacin (5 mg/kg Q 24 H), and metronidazole (7.5 mg/kg Q 12 H).

A mixed population of inflammatory cells or cytology dominated by lymphocytes in a cat presenting with a more chronic history of illness, or failure of initial antibiotic therapy, is consistent with chronic neutrophilic cholangitis or lymphocytic cholangitis, and prednisolone (2 mg/kg Q 24 H initially; taper to 0.5−1 mg/kg Q 48 H) is the foundation of treatment.22

Lymphocytic cholangitis is believed to be immune-mediated, and treatment includes prednisolone with or without a period of concurrent antibiotics, although other immunosuppressive medications, such as cyclosporine, have been used in these patients.

Selected Posthepatic Hyperbilirubinemia Treatment Options
Extrahepatic Biliary Obstruction
Posthepatic causes, such as EHBO, often require surgical intervention—laparotomy may be the only viable therapeutic option—and carry a poor
prognosis. Nonsurgical causes, such as pancreatitis and cholangitis, are medically managed and the prognosis is impacted by the severity of disease, response to treatment, and owner commitment.

**Triaditis**
The effective treatment of triaditis is complicated, but is initiated with supportive care targeting hydration, perfusion, electrolyte and acid–base balance, pain, and vomiting; then targets the aspect of the disease constellation that appears to have the greatest impact on the patient.

Antibiotics are administered in patients in which there is the potential for sepsis, gastrointestinal translocation, positive bacterial cultures, or a left shift with band neutrophils on the CBC.

Corticosteroids are usually avoided in the face of a positively identified bacterial component, although a single anti-inflammatory dose of glucocorticoid may be used to counter the inflammatory mediators. Without strong evidence of a bacterial infection, corticosteroids are often used to treat each separate component of feline triaditis: inflammatory bowel disease, pancreatitis, and lymphocytic-plasmacytic cholangitis.

Nutritional support in the form of E-tube placement is often implemented.

**Liver Fluke**
Medical treatment for liver fluke infection may be attempted with praziquantel (20–30 mg/kg Q 24 H for 3 days), but rare, severe cases may require surgery to remove a posthepatic biliary obstruction as identified with abdominal ultrasound.

**IN SUMMARY**
A thoughtful approach to hyperbilirubinemia, starting with localization of the disease and including the calculated consideration of differentials unique to that location, greatly enhances the efficient and effective diagnosis and treatment of the “yellow cat.” Organizing the effort in terms of pre-hepatic, hepatic, and post-hepatic conditions is a logical and time-tested approach that has been successfully applied to many icteric cats.

**CBC** = complete blood count; **EBHO** = extrahepatic biliary obstruction; **E-tube** = esophagostomy tube; *FeLV* = feline leukemia virus; *FIP* = feline infectious peritonitis; *FIV* = feline immunodeficiency virus; *IMHA* = immune-mediated hemolytic anemia; *PCV* = packed cell volume; *PK* = pyruvate kinase; *RBC* = red blood cell

**References**
47. Haney DR, Christiansen JS, Toll J. Severe cholestatic liver disease secondary to liver fluke (Platynosomum concinnum) infection in three cats. JAHA 2006; 42(3):234-237.
Learning Objectives
After reading this article clinicians should be able to differentiate the disease processes in cats with hyperbilirubinemia, formulate an efficient diagnostic path, and prepare an effective treatment protocol for these patients.

Overview
This article provides an overview of the differentials for feline hyperbilirubinemia, a diagnostic plan for identifying the underlying etiology of the condition, and a number of therapeutic options for these patients.

1. True/False: Icterus is a sensitive marker of the cause of hyperbilirubinemia in cats.
   a. True
   b. False

2. Locating the source of hyperbilirubinemia is an important diagnostic step. Which of the following is not normally a component of this localizing step?
   a. Prehepatic
   b. Hepatic
   c. Intrahepatic
   d. Posthepatic

3. Which of the following is the first and most cost-effective step toward the diagnosis of prehepatic hemolysis?
   a. Hematocrit tube (PCV/TP)
   b. Complete blood count
   c. Serum biochemical profile
   d. Coombs’ test

4. Which of the following is not considered a cause of hemolytic anemia in cats?
   a. FeLV
   b. Cytauxzoon felis
   c. Toxoplasmosis
   d. Mycoplasma hemofelis

5. Which of the following is the single most important component of the treatment plan for idiopathic hepatic lipidosis?
   a. Antibiotics
   b. Nutrition
   c. Glucocorticoids
   d. Vitamin E

6. Which of the following is not one of the WSAVA classifications of feline cholangitis?
   a. Acute neutrophilic
   b. Chronic neutrophilic
   c. Lymphocytic
   d. Acute eosinophilic

7. Cytology can be used to guide treatment in cases of feline cholangitis. If ultrasound-guided FNA of the liver revealed degenerative neutrophils with intracellular bacteria, the foundation of treatment would be which of the following?
   a. Interferon
   b. Amoxicillin and clavulanic acid
   c. Prednisolone
   d. Ursodeoxycholic acid

8. Which of the following is not considered a component of feline triaditis?
   a. Kidney
   b. Liver
   c. Pancreas
   d. Intestines

9. Which of the following is the treatment of choice in a cat in which biliary choleliths are causing an extrahepatic biliary obstruction?
   a. Ursodeoxycholic acid
   b. Prednisolone
   c. Surgery
   d. Antibiotics

10. Placement of an esophagostomy feeding tube allows the owner to administer which of the following to an icteric cat at home?
    a. Fluids
    b. Nutrition
    c. Medications
    d. All of the above