

# Diagnosing canine pancreatitis

*Pancreatitis diagnosis depends on factors ranging from history and clinical presentation to histopathology results.*



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**P**ancreatitis has historically been a difficult disease to definitively diagnose. The diagnosis usually depends on the analysis of history, clinical presentation, biochemical abnormalities, and imaging study and histopathology results. Part of the diagnostic difficulty is that the exact cause of pancreatitis is not well understood, and the presenting clinical signs differ between species and depend on the severity of the disease. Another major problem in diagnosis has been the lack of a sensitive and specific test that can be performed in the hospital. This article will examine some of the factors associated with pancreatitis as well as the diagnosis of this challenging disease.

## Pathophysiology

Pancreatitis, which can manifest in either acute or chronic forms, is an inflammatory disease. More specifically, the disease involves autodigestion and necrosis of the pancreas followed by inflammation.<sup>1</sup>

Even though the exact mechanisms of the disease are poorly defined, there is a common pathophysiology involved in the

disease process. The pancreas produces zymogens, which are inert and inactive precursors to pancreatic proteolytic enzymes. When trypsin activates zymogens within the pancreas itself, they break down the surrounding tissue and initiate autodigestion. This, in turn, releases a cascade of both systemic and local inflammatory mediators such as cytokines, which attract other inflammatory cells to the pancreas.<sup>2</sup>

The initial event that sets enzyme activation in motion is the conversion of trypsinogen to trypsin, which then saturates the pancreatic secretory trypsin inhibitors. It is thought that a disturbance in cellular metabolism or an increase in the permeability of the lipoprotein membrane results in the abnormal fusion of zymogens and protease-containing lysosomes, which in turn causes trypsinogen activation and conversion to trypsin. Once the trypsin is present in sufficient quantities, it can further activate other zymogens, causing a self-perpetuating cascade of autodigestion. In a healthy Pet, plasma protease inhibitors in the bloodstream, such as alphamacroglobulins, are critical in stopping the systemic effects of free proteases in the body.

**Table 1. Risk factors for pancreatitis**

- Breed (Terriers, Miniature Schnauzers)
- Advanced age
- Obesity
- Concurrent endocrine disease
- Hypercalcemia
- Gastrointestinal disease
- High-fat diets
- Trauma
- Sulfonamides
- Azathioprine
- Potassium bromide
- Infection

However, the overwhelming amount of activated trypsin and other protease enzymes present in the serum in severe acute pancreatitis causes the consumption of serum and tissue antiproteases. This process then results in the activation of the kinin, coagulation, fibrinolytic and complement cascades leading to systemic problems such as hemorrhage, shock, disseminated intravascular coagulation (DIC) and vascular collapse.<sup>1,3,4</sup>

The chronic form of the disease results from the fibrosis and parenchymal atrophy that follows the acute necrosis and inflammation. Repeated episodes of acute pancreatitis create more fibrosis and atrophy that can lead to permanent damage over time.

### Causes of pancreatic disease

A number of factors are thought to contribute to pancreatitis (*Table 1*). [See also *DataSavant*, page 17] In general, pancreatitis tends to occur in neutered, middle-aged, overweight dogs. A breed correlation can be found as well, most notably in Miniature

Schnauzers and Terriers.<sup>2</sup> Nutritional factors have also been identified. Obese dogs are at greater risk for pancreatitis, and recent consumption of a fatty meal is a common finding. Hypertriglyceridemia may induce pancreatitis through the toxic effects of fatty acids (generated by pancreatic lipase) on the pancreas. This may explain the development of pancreatitis after a fatty meal.<sup>5</sup>

Many drugs can potentially cause pancreatitis, but a few are more commonly associated with the disease. These drugs include seizure medications, such as potassium bromide; chemotherapy drugs, such as L-asparaginase and azathioprine; and antibiotics, such as tetracycline and the sulfonamides.

Trimethoprim-sulfamethoxazole has been thought to cause an immune-mediated pancreatitis in dogs.<sup>5</sup>

While steroids are a suspected cause of pancreatitis, no clinical evidence exists to support that claim. Steroids cause an elevation in serum lipase, but no associated pancreatic lesions are found on biopsy. It is thought that steroids induce a lipase isoenzyme that may be of hepatic origin.<sup>2</sup>

A variety of diseases and metabolic disorders have also been shown to cause pancreatitis. In dogs with hepatobiliary disease and inflammatory bowel disease, it is possible for the inflammatory process to extend into the pancreas. Any surrounding inflammation—as in the case of neoplasia, for example—can cause pancreatic duct obstruction.<sup>6</sup> Because of the close association of the biliary and pancreatic duct openings in the duodenum (*Figure 1*, page 27), increased intraduodenal pressures caused by vomiting can result in a reflux of digestive enzymes or gastrointestinal bacteria into the pancreas or liver. Blunt trauma to the

abdomen, and even surgery, are capable of producing pancreatic inflammation, most likely due to hypovolemia, ischemia or reperfusion injury.<sup>6</sup> Other metabolic diseases, such as hypercalcemia and immune-mediated disease, have also been implicated as causes of pancreatitis. Infectious etiologies have been described in cats; however, this is not a common cause of canine pancreatitis.

### Clinical signs of pancreatitis

The clinical signs of pancreatitis in a Pet depend greatly on the severity of the disease, which can range from subclinical to life-threatening. The more common clinical signs result from pancreatic inflammation or from the systemic effects of the pancreatic inflammation, resulting in the release of inflammatory mediators.<sup>7</sup> In general, clinical signs depend on whether the pancreatitis is acute or chronic.

Dogs and cats can have different clinical presentations. Although this article focuses on dogs, there are some important differences between the two presentations that practitioners need to note. Dogs are likely to present with vomiting, anorexia, dehydration, abdominal pain and fever. Dogs will often posture with their front paws and legs on the ground and their rear limbs extended in an upward position. This is a response to cranial abdominal pain and is referred to as the “praying position” or “position of relief” (*Figure 2*).<sup>3</sup> Cats usually show signs of anorexia, lethargy and weight loss. Vomiting, however, occurs in only approximately 33 percent of feline pancreatitis cases.<sup>1</sup>

In dogs with severe acute pancreatitis, clinical signs include fever from systemic inflammation and/or sepsis; cardiovascular shock from severe hypovolemia and/or

Figure 1

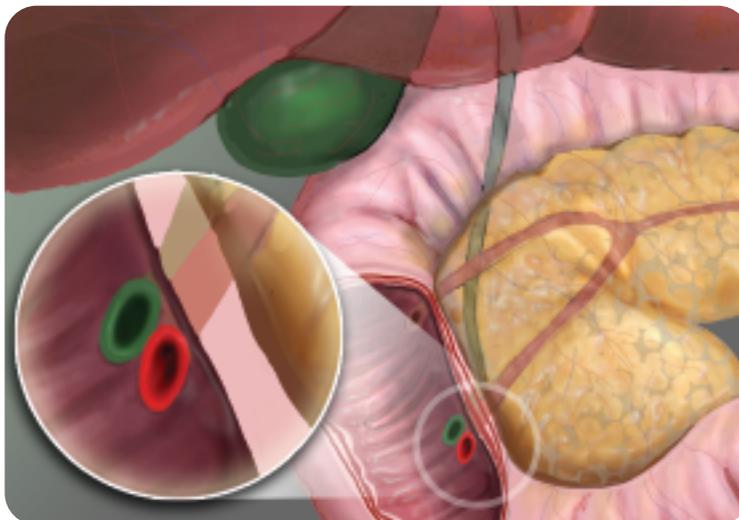


Figure 2

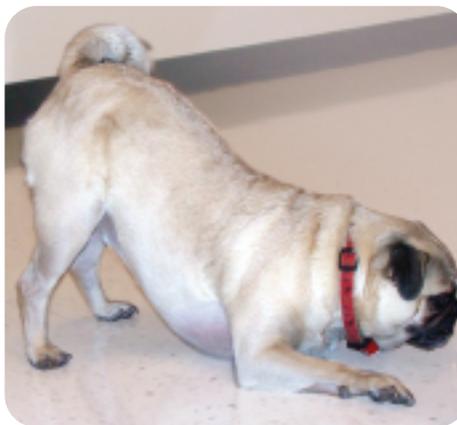


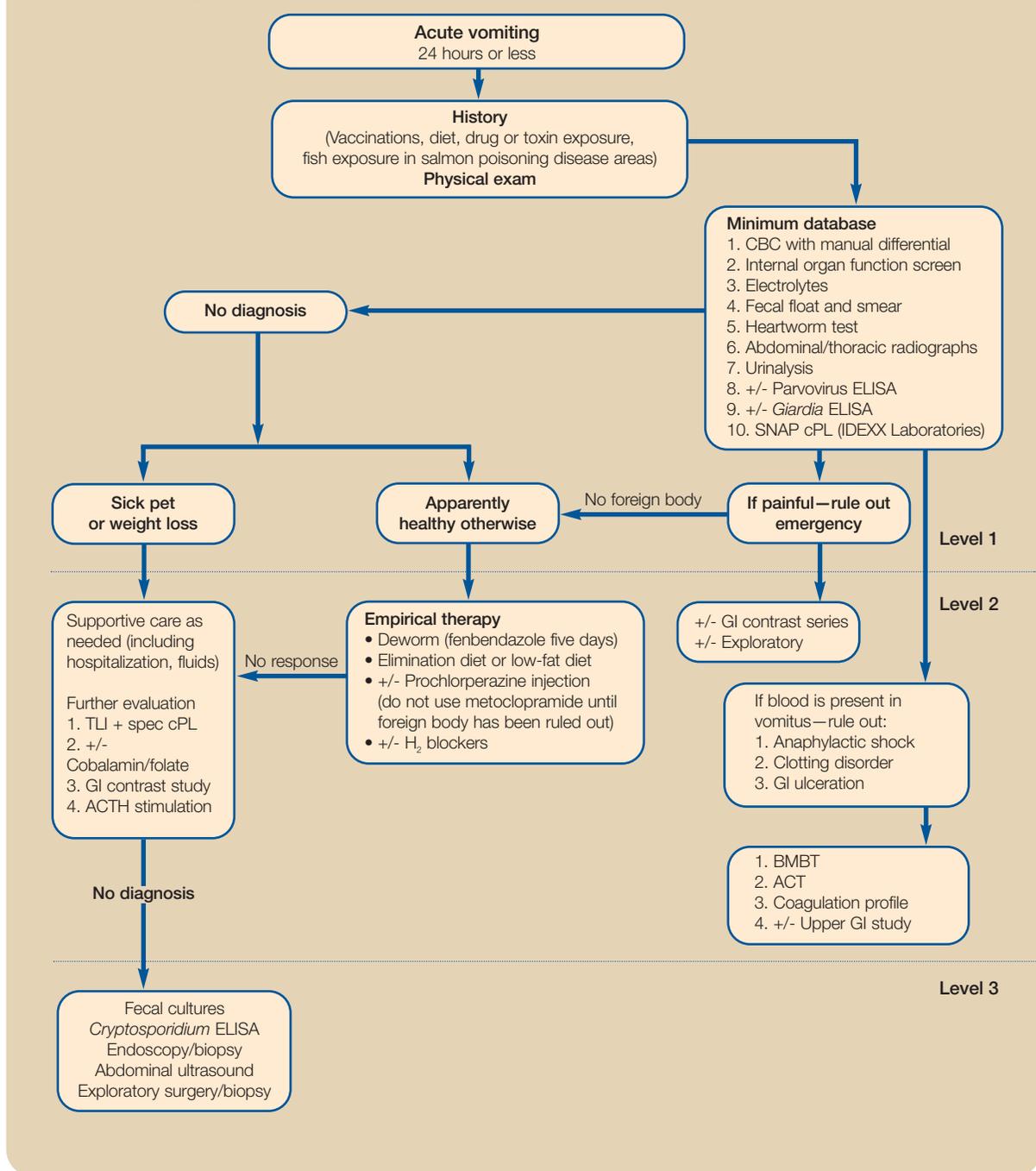
Figure 1: There is a close anatomical relationship between the bile duct (green) and the pancreatic duct (red) as they enter the duodenum. This close relationship can contribute to shared pathology in the liver and the pancreas.

Figure 2: Dog exhibiting signs of cranial abdominal pain by adopting the “praying” posture, with head down and paws outstretched.

hypotension; renal failure from tubular degeneration and respiratory compromise due to pulmonary edema and organ failure. Severe pancreatic inflammation induces systemic activation of the body’s immune system, as well as inflammatory modulators such as cytokines. This results in marked systemic inflammatory activation, causing injury and inflammation in additional organ systems, which can lead to multisystemic organ failure.<sup>8</sup>

### Diagnosis of pancreatitis

When examining the diagnosis, it is important to remember that none of the hematologic or serum chemistry changes will

**Figure 3: Diagnostic Algorithm for Acute Vomiting in the Dog**

specifically indicate pancreatitis. Because the clinical signs vary for this disease, a complete history, physical examination and diagnostic workup are needed to dis-

tinguish pancreatic disease from the myriad of other disorders that may result in the same clinical signs. (Figure 3 depicts a diagnostic algorithm for acute vomiting in

the dog.) The effectiveness of various tests for diagnosing pancreatitis will be discussed in this article.

### Blood tests

**Serologic markers.** Two serologic markers are available for pancreatic enzymes: trypsin-like immunoreactivity (TLI) and pancreatic lipase immunoreactivity (PLI). Both are exclusively pancreatic in origin. While not perfect, these markers are currently the most sensitive and specific available for pancreatitis. TLI testing detects serum trypsinogen and trypsin. Trypsin is

enzymes associated with severe renal insufficiency, which lower the test's specificity as well.<sup>9</sup> Despite its apparent shortcomings in the diagnosis of pancreatitis, however, TLI is still the most important test for the diagnosis of exocrine pancreatic insufficiency (EPI).

The PLI test is the most clinically applicable test currently available for dogs presenting with acute pancreatitis. It measures a structurally distinct lipase produced only by the pancreas. The rationale for measuring PLI is that pancreatic lipase is cleared more slowly from circulation than trypsin and trypsinogen, which increases the sensitivity of the test for acute pancreatitis. The reported sensitivity of PLI in diagnosing pancreatitis is greater than 80 percent. It also has been shown that renal disease and the administration of corticosteroids do not result in elevated PLI levels.<sup>6,10</sup> This makes the test more specific than elevated amylase and lipase, which are affected by both gastrointestinal and renal disease. There is currently an in-house semiquantitative pancreas-specific lipase test available for dogs (SNAP cPL–IDEXX Laboratories). There is a 94.0 percent to 97.4 percent agreement between the results obtained using the SNAP cPL test and the reference laboratory cPLI test (SNAP test package insert). The ability to rapidly analyze a sensitive and specific test in the hospital will be a valuable tool for the veterinary clinician.

**Amylase and lipase.** Hyperamylasemia and hyperlipasemia are both associated with pancreatitis, but in one study only 50 percent of dogs with elevated lipase and amylase were shown to have pancreatitis.<sup>10</sup> The reason for this is that the two enzymes are not pancreas-specific; they also are produced in the liver and

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found in the serum only when pancreatic inflammation has occurred.<sup>9</sup> Experimental studies have shown that trypsinogen and trypsin are markedly elevated in the early stages of pancreatitis but are rapidly cleared and return to normal in the first twenty-four hours.<sup>6</sup> Thus, samples for TLI analysis should be drawn as soon as possible after the onset of clinical signs.<sup>9</sup> Thirty percent to 40 percent of cats and dogs with pancreatitis will have increased serum TLI levels.

The specificity of TLI has been shown to reach 65 percent. TLI is not a sensitive test, with sensitivity values that run as low as 33 percent.<sup>10</sup> This is partly due to the rapid clearance of trypsinogen and trypsin. TLI elevations can also be caused by malnourishment in the dog or chronic pancreatitis, or decreased renal clearance of the

gastrointestinal tract. Additionally, these enzymes are excreted by the kidneys, so any decrease in glomerular filtration rate (GFR) or renal function will result in elevated amylase and lipase values, often as high as 2.5 to 3 times the normal values. It is important to understand that elevated amylase and lipase are not diagnostic for pancreatitis, and that normal values do not rule out pancreatitis. Elevated results should always be interpreted in light of concurrent dehydration or renal disease.

**Biochemical changes.** Several biochemical changes, in addition to amylase and lipase elevations, can occur in patients with pancreatitis. Liver enzyme activities can be increased because of hepatocellular damage, whether from local pancreatic inflammation, the transport of pancreatic enzymes in the lymphatics, concurrent multiple organ failure or decreased hepatic perfusion due to hypovolemia. Alkaline phosphatase (ALKP) may be two to 15 times normal and alanine aminotransferase (ALT) may be two to five times normal. The serum bilirubin concentration can be elevated as a result of bile duct inflammation and obstruction. Bile duct obstruction will also lead to ALKP and ALT elevations. Azotemia (elevated BUN and creatinine) and elevations in total protein and albumin concentrations often occur secondary to dehydration due to vomiting, decreased fluid intake and movement of fluid into the third space due to vascular injury. If there is enough systemic inflammation to cause protein leakage out of the vascular system, albumin concentrations may be low.<sup>10</sup>

**Glucose.** Hyperglycemia is a common finding in dogs with pancreatitis. This may be due to stress hyperglycemia or concurrent diabetes mellitus. Hyperglycemia is not

a diagnostic marker for pancreatitis, but may be suggestive. Hypoglycemia may also be seen in severe pancreatitis due to concurrent liver disease or sepsis.<sup>10</sup>

**Calcium.** Hypocalcemia occurs from low albumin, intracellular shifts of calcium and deposition of calcium in saponified peripancreatic fat.<sup>6,10</sup>

**Hematologic results.** The complete blood count results in pancreatitis are nonspecific and depend upon the severity of disease. One of the more common findings in dogs with severe pancreatitis is neutrophilia with a left shift, but a stress

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leukogram with only mild neutrophilia and no left shift may occur in mild cases. Sepsis and severe systemic inflammation can result in neutropenia with a degenerative left shift. If DIC is present, then platelets may be decreased. Dogs with dehydration will have elevated hematocrits and total red blood cell numbers.<sup>6</sup>

### Imaging studies

**Radiography.** Abdominal radiographs have limited use in diagnosing pancreatitis, but they are helpful in ruling out other causes of vomiting, such as gastrointestinal foreign bodies. However, a few radiographic changes may be suggestive of, but not diagnostic for, pancreatitis. These include decreased contrast with an increased soft-tissue density in the cranial abdomen, a gas-filled stomach, the pres-

ence of a gas-filled duodenum and a widening of the angle between the pylorus and duodenum.<sup>11</sup>

**Ultrasonography.** Ultrasonography is more sensitive than radiography in diagnosing pancreatitis. However, finding the pancreas and accurately evaluating it can be difficult and require an expert knowledge of anatomy and ultrasound imaging because of abnormalities caused by pancreatic inflammation, edema and necrosis. Some of the more common ultrasonographic findings are an enlarged pancreas, hypoechoic mass effect to the pancreas, hyperechoic peripancreatic fat and fluid accumulation around the pancreas.<sup>10,12</sup> Peritoneal effusion can also be identified. Extrahepatic biliary obstruction should be ruled out during an abdominal ultrasound.

**Biopsy/histopathology.** The last diagnostic test to consider is biopsy with histopathology. This remains the gold standard for the diagnosis of pancreatitis. Biopsy can be performed surgically, or a fine-needle aspirate can be taken with ultrasound guidance. Aspiration may help rule out the presence of pancreatic neoplasia. Surgical biopsy of the pancreas does not induce pancreatic inflammation or necrosis if the blood supply is not disrupted. However, Pets presenting for acute pancreatitis are often too unstable to undergo anesthesia for the biopsy; therefore, biopsy is not recommended for most cases of acute pancreatitis. It may be a valuable tool to consider in dogs that present with recurrent episodes.

## Discussion

In conclusion, even though pancreatitis has historically been a difficult disease to diagnose, new advances in blood testing

such as cPLI and the increasing usage of ultrasound in general practice are giving veterinarians a fighting chance at making a timely, accurate diagnosis. 

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