

Comparison of clinical findings between dogs with suspected anaphylaxis and dogs with confirmed sepsis

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OBJECTIVE

To compare clinical signs, laboratory test results, and imaging findings between dogs with suspected anaphylaxis and dogs with sepsis.

DESIGN

Retrospective case-case study.

ANIMALS

10 dogs with suspected anaphylaxis and 22 dogs with confirmed sepsis that met the criteria for systemic inflammatory response syndrome.

PROCEDURES

Medical records for dogs in each group were reviewed and data extracted regarding signalment; reason for hospital admission; physical examination findings; results of CBC, serum biochemical analysis, coagulation testing, cytologic examination, and microbial culture; and imaging reports.

RESULTS

All dogs in the anaphylaxis group fulfilled the criteria for systemic inflammatory response syndrome. Dogs in both groups had gastrointestinal signs, lethargy, mentation change, and bleeding abnormalities. Dogs with suspected anaphylaxis had a significantly higher eosinophil count and serum alanine aminotransferase activity and lower blood pH than dogs with sepsis. Dogs with sepsis had a significantly higher band neutrophil count, serum globulins concentration, and serum alkaline phosphatase activity and lower serum glucose concentration. Dogs in both groups had intracavitary free fluid and ultrasonographic findings of thickened intestines, gas or fluid-filled intestines, and a thickened gallbladder wall.

CONCLUSIONS AND CLINICAL RELEVANCE

Clinical signs, laboratory values, and imaging findings may be similar in dogs with sepsis or anaphylaxis. Given the marked difference in prognosis and treatment, early differentiation is important. Anaphylaxis should be considered if a septic nidus cannot be identified, and supportive care should be considered for such patients. (*J Am Vet Med Assoc* 2017;251:681–688)

Anaphylaxis is a sudden, severe systemic allergic reaction that occurs after contact with an allergen.¹ The condition is characterized by initial immunologic sensitization to an antigen and production of IgE that binds to receptors on basophils and mast cells. Subsequent exposure results in cross-linking of the antigen between 2 IgE molecules, followed by a massive systemic response mediated by the release of vasoactive substances, including histamine, heparin, proteases, and proteoglycans.²

Moderate to severe anaphylactic reactions cause profound physiologic changes, but clinical signs are species specific and dependent on the organ containing the highest concentration of mast cells. In cats, horses, and humans, pulmonary pathological effects

predominate. These species typically have respiratory distress characterized by airway edema, bronchospasm, and low oxygen saturation.³ Additionally, cardiovascular, gastrointestinal, and cutaneous signs can occur.^{4,5} Because of a high concentration of mast cells in the liver, dogs have a unique manifestation of anaphylaxis. Profound splanchnic vasodilation commonly results in a severe decrease in cardiac output, decreased perfusion, and secondary portal hypertension.⁶ Cutaneous manifestations are less common and are typically mild and transient, with signs including angioedema of the face and ears, urticaria, erythema, wheals and hives, and pruritus.⁷ Respiratory abnormalities are not consistently identified in affected dogs.⁸

Systemic anaphylactic reactions in dogs can be challenging to diagnose owing to variability in severity and onset, lack of an obvious inciting cause, and nonspecific clinical signs.^{9,10} Reactions may occur immediately after contact with the stimulus, may be delayed, or may be biphasic. Biphasic reactions are those in which there is an initial reaction to a stimulus, followed by recovery and a second reaction within 72 hours after the initial one.² The clinical

ABBREVIATIONS

ALP	Alkaline phosphatase
ALT	Alanine transaminase
CI	Confidence interval
PT	Prothrombin time
SIRS	Systemic inflammatory response syndrome

signs can mimic those of other disease processes that cause a similar SIRS. Sepsis, for example, is characterized by the development of SIRS plus evidence of an infectious agent.¹¹

In veterinary patients, sepsis most commonly results from peritonitis, prostatitis, pyometra, pneumonia, or infected wounds¹² and may result in clinical signs similar to anaphylaxis. The lack of a specific test to diagnose anaphylaxis makes a definitive diagnosis impossible. Sepsis in dogs may be associated with an apparent lack of inciting nidus and nonspecific clinical signs in addition to SIRS. On arrival at the emergency room, dogs with either anaphylaxis or sepsis may have similar clinical signs, and markers that could differentiate the 2 would be helpful to clinicians. The objectives of the retrospective study reported here were to compare initial complaints, clinical signs, hematologic abnormalities, and diagnostic imaging results at hospital admission between dogs with suspected anaphylaxis and dogs with confirmed sepsis.

Materials and Methods

Animals

Medical records were reviewed to identify all dogs admitted by the Emergency and Critical Care Service of the University of Illinois Veterinary Teaching Hospital between January 2009 and August 2014 that fulfilled the criteria for either suspected anaphylaxis or confirmed sepsis. To be included in the anaphylaxis group, dogs were required to have a history of being healthy followed by a sudden onset of clinical signs (minutes to hours) and at least one of collapse (witnessed by the owner or lateral recumbency at admission), hypotension (systolic arterial blood pressure ≤ 90 mm Hg as measured by Doppler ultrasonic flow detector), gastrointestinal signs (vomiting, diarrhea, or signs of nausea), and cutaneous signs (erythema, angioedema, or urticaria) and have complete resolution of clinical signs within 72 hours after admission. Dogs were excluded from the anaphylaxis group when they had any preexisting health conditions (not pertaining to anaphylaxis) that could explain the onset of clinical signs.

To be included in the sepsis group, dogs were required to have SIRS plus evidence of intracellular bacteria on fluid cytologic examination, growth on bacterial culture medium, or physical evidence of gross contamination (eg, purulent fluid or fecal material) at surgery or necropsy. Dogs with a suspicion of sepsis without a confirmed diagnosis were excluded from the study. The definition of SIRS for this purpose was having 2 or more of rectal temperature $> 39.2^{\circ}\text{C}$ (102.6°F) or $< 37.8^{\circ}\text{C}$ (100°F), heart rate > 120 beats/min, respiratory rate > 20 breaths/min, WBC count $> 16,000$ or $< 6,000$ cells/mL, or $> 3\%$ band neutrophils identified on CBC.¹¹

Medical records review

Data were extracted from each dog's medical record regarding signalment, complaint at admission,

physical examination findings, hematologic test results (CBC, serum biochemical analysis, coagulation testing, and venous blood gas analysis), cytologic and bacterial culture results, imaging reports, progression of disease and resolution of clinical signs, medical or surgical treatments provided during hospitalization, duration of hospitalization, and survival (yes or no) to hospital discharge. If certain hematologic tests had been performed multiple times, only results from the initial tests were analyzed for study purposes. For dogs in the anaphylaxis group, records were also reviewed in an attempt to determine the causative allergen.

Statistical analysis

Physiologic, hematologic, and other continuous data were assessed for normality of distribution through examination of skewness, kurtosis, and normality plots and the Shapiro-Wilk test. Normally distributed continuous variables are reported as mean $\pm$ SD, and nonnormally distributed continuous variables and ordinal variables are reported as median (range). Categorical variables are reported as counts and percentages.

Continuous signalment data were compared between anaphylaxis and sepsis groups with the Mann-Whitney *U* test. The χ^2 or Fisher exact test was used to compare categorical and ordinal data between groups. Logistic regression was used to evaluate associations of historical findings and clinical signs with anaphylaxis or sepsis, and results are reported as ORs and 95% CIs. Continuous data regarding physical examination findings at hospital admission (rectal temperature, heart rate, respiratory rate, and blood pressure) and hematologic data were compared between groups by means of the Student *t* test or the Mann-Whitney *U* test, depending on the data distribution. Interval from hospital admission to improvement and duration of hospitalization were compared between groups by use of the Student *t* test and Mann-Whitney *U* test, respectively. Values of $P \leq 0.05$ were considered significant. All data analyses were performed with a statistical software program.^a

Results

Signalment

Ten dogs (4 spayed females, 1 sexually intact female, 4 neutered males, and 1 sexually intact male) were included in the suspected anaphylaxis group. Median age was 3.2 years (range, 1.0 to 11.0 years), and median body weight was 9.3 kg (20.5 lb; range, 4.5 to 44.2 kg [9.9 to 97.2 lb]). This group included mixed-breed dogs ($n = 2$), Yorkshire Terriers (2), and a Boxer, Dachshund, Cavalier King Charles Spaniel, Labrador Retriever, Rat Terrier, and Vizsla (1 each). Twenty-two dogs (7 spayed females, 2 sexually intact females, 9 neutered males, and 4 sexually intact males) were included in the sepsis group, which included mixed-breed dogs ($n = 8$), Labrador Retrievers (2), Boston Terriers (2), Border Collies (2), and a Bea-

gle, Bearded Collie, Cocker Spaniel, German Short-haired Pointer, Greyhound, Miniature Dachshund, Miniature Poodle, and Rottweiler (1 each). Median age was 7.4 years (range, 2.6 to 14.6 years), and median body weight was 20.7 kg (45.5 lb; range, 1.7 to 59.5 kg [3.7 to 130.9 lb]). Dogs in the anaphylaxis group were significantly ($P = 0.03$) younger than dogs in the sepsis group, but no other significant differences in signalment variables were identified between groups.

Reasons for hospital admission

All dogs in the anaphylaxis group were admitted to the Emergency and Critical Care Service within a median of 5 hours (range, 0.2 to 12 hours) after the onset of clinical signs, with 4 dogs admitted directly and 6 referred by their primary veterinarian. One of the dogs had been vaccinated 1 hour prior to the onset of clinical signs. For all other dogs in this group, the inciting cause of the anaphylaxis was not obvious. For dogs in the sepsis group, the median duration of clinical signs prior to hospital admission was 48 hours (range, 3 to 1,080 hours), with 12 dogs admitted directly and 10 referred by their primary veterinarian. Dogs in the sepsis group had a significantly ($P < 0.001$) longer interval from onset of clinical signs to hospital admission than did dogs in the anaphylaxis group. No significant ($P = 0.70$) difference was identified between groups with respect to the number of cases referred versus the number directly admitted to the hospital.

Table 1—Number of dogs with various clinical signs at hospital admission categorized by whether they had suspected anaphylaxis or confirmed sepsis.

Clinical sign	Anaphylaxis (n = 10)	Sepsis (n = 22)	P value
Inappetence	1	14	0.02
Abdominal pain	3	17	0.02
Vomiting	6	13	0.96
Diarrhea	2	4	0.90
Hypersalivation	1	0	0.31
Abdominal distention	1	8	0.15
Petechiae or ecchymoses	2	2	0.40
Evidence of gastrointestinal bleeding (eg, hematemesis or melena)	2	3	0.65
Lethargy	4	13	0.32
Altered mentation	7	12	0.41
Sudden collapse	7	2	0.002
Limping	0	2	1.00
Polydipsia	0	1	1.00
Weakness or shaking	0	4	0.28

For dogs with sepsis, causes included gastrointestinal rupture (n = 10), septic peritonitis (abdominal effusion) of unknown etiology (5), uterine rupture (4), foreign body (3), dehiscence of resection and anastomosis (3), hepatobiliary disease (3), neoplasia (2), pyometra (2), ruptured gallbladder (2), gastric dilatation-volvulus (1), unknown (1), neoplasia (1), artificial insemination (1), and ruptured hepatic mass (1). Sepsis was confirmed for all dogs in this group by cytologic examination of cavity effusion samples (n = 18), bacterial culture of effusion samples (2), and visible evidence of gastrointestinal wall rupture and gross contamination within the abdomen at surgery (2). Twelve dogs had no previous or concurrent health issues.

Clinical and laboratory findings

At hospital admission, all dogs in the anaphylaxis group fit the criteria for SIRS. No significant differences were identified between groups regarding proportions of dogs with various clinical signs at hospital admission, which included signs of gastrointestinal upset, lethargy, and altered mentation and manifestations of hemostatic abnormalities (eg, petechiation, ecchymoses, hematochezia, melena, or hematemesis; **Table 1**). Sudden collapse was 25 times as likely in dogs with suspected anaphylaxis as in dogs with confirmed sepsis (OR, 25.0; 95% CI, 3.2 to 100.0; $P = 0.002$). In addition, dogs in the sepsis group were approximately 8 times as likely to have signs of abdominal pain (OR, 7.9; 95% CI, 1.5 to 42.6; $P = 0.02$) and approximately 16 times as likely to have had signs of inappetence prior to hospital admission (OR, 15.8; 95% CI, 1.7 to 148.1; $P = 0.02$) as dogs in the anaphylaxis group. For dogs with a blood pressure recording at admission, hypotension was identified in 5 of 9 dogs in the anaphylaxis group and 7 of 18 dogs in the sepsis group, and these proportions did not differ significantly.

No significant differences in heart rate, respiratory rate, or blood pressure were identified between groups (**Table 2**). Rectal temperature was significantly ($P = 0.002$) lower in the anaphylaxis group. Several similarities were evident between groups in results of CBC, serum biochemical analysis, blood gas analysis, and coagulation testing (**Table 3**). Dogs in the anaphylaxis group had a significantly higher eosinophil count, serum sodium and chloride concentrations, and serum ALT activity and lower blood pH and fibrinogen concentration. Dogs with sepsis had

Table 2—Values of physiologic variables at hospital admission for the dogs in Table 1.

Variable	Anaphylaxis (n = 10)	Sepsis (n = 22)	P value
Heart rate (beats/min)	142 ± 31	161 ± 38	0.16
Respiratory rate (breaths/min)	40 ± 13	46 ± 16	0.48
Rectal temperature (°C)	37.3 (35.6–38.8)	39.2 (34.1–40.5)	0.002
Systolic arterial blood pressure (mm Hg)	92 ± 39	110 ± 56	0.40

Data represent mean ± SD for normally distributed variables and median (range) for nonnormally distributed variables.

Table 3—Values of hematologic variables at hospital admission for the dogs in Table 1.

Variable	Reference interval	Anaphylaxis (n = 10)	Sepsis (n = 22)	P value
Neutrophils (X 10 ³ cells/mL)	3.00–11.50	9.75 (2.99–20.60)	7.65 (0.31–48.30)	0.44
Band neutrophils (X 10 ³ cells/mL)	0.00–0.30	0.08 (0.00–2.42)	2.70 (0.01–10.10)	0.04
Lymphocytes (X 10 ³ cells/mL)	1.00–4.80	0.82 (0.15–2.41)	0.39 (0.05–1.68)	0.33
Monocytes (X 10 ³ cells/mL)	0.20–1.40	0.09 (0.03–1.44)	0.25 (0.02–2.35)	0.28
Eosinophils (X 10 ³ cells/mL)	0.10–1.00	0.12 (0.01–0.62)	0.00 (0.00–0.22)	< 0.001
Nucleated RBCs (cells/100 WBCs)		1.5 (0.0–4.0)	1.0 (1.0–11.0)	1.00
Platelets (X 10 ³ cells/mL)	200.00–900.00	136.13 ± 72.37	224.80 ± 139.56	0.07
PCV (%)	35.00–52.00	58.00 ± 11.50	54.56 ± 13.00	0.50
Total solids (mg/dL)	5.90–8.00	6.31 ± 0.75	6.99 ± 1.45	0.21
pH	7.39–7.49	7.30 (7.09–7.35)	7.37 (7.22–7.463)	< 0.001
Bicarbonate (mmol/L)	17.08–24.68	16.65 (13.10–18.70)	18.15 (6.40–51.00)	0.19
Lactate (mmol/L)	0.44–2.93	6.75 (0.60–11.90)	3.60 (0.90–20.20)	0.25
Sodium (mmol/L)	144.00–151.00	145.85 (141.40–153.10)	143.10 (128.20–149.60)	0.047
Potassium (mmol/L)	3.90–5.50	4.08 ± 0.44	4.17 ± 0.55	0.92
Chloride (mmol/L)	110.04–117.96	116.10 (110.40–127.70)	112.15 (88.90–117.50)	0.04
Ionized calcium (mmol/L)	1.17–1.37	1.14 ± 0.12	1.10 ± 0.12	0.48
Phosphorus (mg/dL)	2.70–5.20	4.44 ± 1.13	5.45 ± 2.57	0.52
Ionized magnesium (mmol/L)	0.47–0.62	0.52 ± 0.11	0.45 ± 0.09	0.10
Glucose (mg/dL)	77.96–129.84	151.50 (73.00–248.00)	86.50 (8.00–405.00)	0.002
BUN (mg/dL)	9.10–24.50	18.00 (14.00–36.00)	21.50 (5.00–99.00)	0.38
Creatinine (mg/dL)	0.73–1.19	1.20 (0.70–2.00)	1.10 (0.50–7.00)	1.00
Albumin (g/dL)	2.50–3.80	2.41 ± 0.53	2.44 ± 0.83	0.86
Globulins (g/dL)	2.60–3.20	2.09 ± 0.61	3.06 ± 0.69	< 0.001
ALT (U/L)	8.00–65.00	456.00 (211.00–5820.00)	71.00 (9.00–1599.00)	0.002
ALP (U/L)	7.00–92.00	71.50 (31.00–133.00)	173.00 (19.00–1692.00)	0.02
γ-Glutamyltransferase (U/L)	0.00–7.00	7.20 ± 9.20	2.00 ± 17.20	0.14
Total bilirubin (mg/dL)	0.10–0.30	0.30 (0.10–0.60)	0.30 (0.10–6.70)	0.62
PT (s)	6.00–10.00	10.8 (8.3–19.5)	8.5 (7.7–26.1)	0.19
aPTT (s)	9.00–15.00	18 (11.6–24.5)	13.3 (9.0–85.2)	0.45
Fibrinogen (mg/dL)	117.00–271.00	126.00 ± 71.79	321.11 ± 216.60	0.03

aPTT = Activated partial thromboplastin time.

See Table 2 for key.

a significantly higher band neutrophil count, serum globulins concentration, and serum ALP activity and lower serum glucose concentration. No other differences in hematologic test results were identified.

Six dogs in the anaphylaxis group had peritoneal effusion (2 of these also had pleural effusion). Abdominocentesis was performed for 5 dogs with anaphylaxis, and obtained fluid samples were cytologically classified as modified transudate (n = 3), transudate with blood contamination (1), and pure hemorrhage (1). All 22 dogs with sepsis had peritoneal effusion and pleural effusion. Abdominal fluid analysis revealed an exudate for all dogs with sepsis, with septic suppurative inflammation identified in 20 (91%) dogs and nonseptic suppurative inflammation identified in 2 (9%) dogs. The 2 dogs with nonseptic suppurative inflammation had leakage of gastrointestinal contents discovered at surgery. The pleural effusion was not analyzed in any dog from either group.

Abdominal ultrasonography was performed by residents under supervision of a board-certified radiologist for 6 dogs in the anaphylaxis group and 12 dogs in the sepsis group. Findings common to the 2 groups included gas or fluid-filled stomach or intestines (4 dogs in the anaphylaxis group and 5 in the sepsis group), thickened intestinal walls (2 in each group), and a thickened gallbladder wall (2 in each group). Other ultrasonographic findings in the ana-

phylaxis group included cystoliths (n = 1) and non-obstructive foreign body (1). Additional findings in the sepsis group included generalized hyperechoic mesentery consistent with peritonitis (n = 5), sublumbar lymphadenopathy (4), echogenic sediment in the gallbladder (4), hyperechoic mesentery surrounding the gallbladder (3), pancreatitis (2), intestinal mass (2), pyometra (2), suspected prostatic abscess (1), mineralized deposits in the kidneys (1), hydronephrosis and hydroureter (1), splenic thrombus (1), obstructive intestinal foreign body (1), and mottled appearance of the gallbladder wall (1).

Initial treatments given to dogs were defined as any treatments given in the emergency room prior to transfer to the intensive care unit for continued medical management (anaphylaxis) or to surgery for control of the underlying source of disease (sepsis). Treatments in the anaphylaxis group included isotonic crystalloid fluids (n = 10), diphenhydramine (7), antiemetics (7), synthetic colloid solutions (5), antimicrobials (5), fresh frozen plasma (3), opioid analgesics (2), corticosteroids (2), and antiarrhythmic drugs (1). In 1 dog, exploratory laparotomy was performed because of clinical suspicion of sepsis and the presence of peritoneal effusion. Initial treatment in the sepsis group included crystalloid fluids (n = 15), antimicrobials (7), opioid analgesics (6), synthetic colloid solutions (6), dextrose supplementation (5), dissociative analgesics

(1), calcium gluconate supplementation (1), antiarrhythmic drugs (1), and diuretics (1). Sixteen of the 22 dogs with sepsis underwent abdominal laparotomy to identify and correct the underlying cause of sepsis.

Outcomes

Mean $\pm$ SD interval from hospital admission to improvement (defined as resolution of clinical signs) was 62.29 ± 46.87 hours in the sepsis group ($n = 7$) and 15.25 ± 11.05 hours in the anaphylaxis group (10; $P = 0.01$). Mean duration of hospitalization was 3.9 ± 1.2 days in the sepsis group and 1.5 ± 1.6 days in the anaphylaxis group ($P = 0.007$). Given the inclusion criterion that required dogs in the anaphylaxis group to have clinical improvement within 72 hours after hospital admission, all (100%) dogs in that group survived to hospital discharge. The inclusion criteria prevented comparison of the 2 groups in terms of duration of hospitalization or survival. Only 7 (32%) dogs in the sepsis group survived to hospital discharge. All 7 dogs with sepsis that survived underwent exploratory laparotomy to treat the underlying cause of the sepsis. Of the remaining 15 nonsurviving dogs, 6 were euthanized immediately after a diagnosis of sepsis was confirmed by cytologic examination, 3 were euthanized during surgery, 1 died during surgery, 3 died after surgery, and 2 were euthanized after surgery owing to clinical decline. The reason for euthanasia was not specified in the medical records of the 11 euthanized dogs.

Discussion

In the present retrospective study, considerable overlap was identified between dogs with suspected anaphylaxis and dogs with confirmed sepsis in clinical signs; physical examination findings; presence of SIRS; hematologic, biochemical, and coagulation abnormalities; presence of intracavitary free fluid; and imaging findings. Gastrointestinal signs at hospital admission were common in both groups. During anaphylaxis, high concentrations of mast cells present in the liver and gastrointestinal tract undergo degranulation. Histamine is released, causing vasodilation and increased blood flow in the hepatic artery with concurrent constriction and increased resistance in the hepatic vein.^{7,13} The resulting hepatic congestion and secondary portal hypertension result clinically in nausea, vomiting, diarrhea, melena, hematochezia, and hematemesis in dogs with anaphylactic reactions.⁸ Septic patients frequently develop gastrointestinal signs from primary disease of the gastrointestinal tract and can also have vasoconstriction of splanchnic vessels in an attempt to maintain coronary and cerebral blood flow during distributive shock.¹⁴ This decrease in gastrointestinal perfusion leads to tissue hypoxia and disruption of intestinal mucosal integrity and manifests clinically as vomiting, diarrhea, or bleeding within the gastrointestinal tract.¹⁵⁻¹⁷

Dogs in both groups in the present study had evidence of altered hemostasis, including petechiation or ecchymoses, gastrointestinal bleeding, throm-

bocytopenia, and prolonged PT and activated partial thromboplastin time. Dogs with anaphylaxis^{13,18} and sepsis^{12,19} reportedly undergo upregulation of procoagulant processes and downregulation of anticoagulant and fibrinolytic processes, leading to a disseminated intravascular coagulation-like syndrome.

All dogs with suspected anaphylaxis in the study reported here fulfilled the criteria for SIRS. Hypotension was also a common finding at hospital admission. Both sepsis and anaphylaxis are associated with a state of distributive shock, resulting from release of proinflammatory mediators causing abnormal systemic and coronary vascular tone, vasodilation, increased vascular permeability, extravasation of up to 35% of the blood volume, systemic hypotension, myocardial depression, and severely compromised venous return.^{8,14,19-24} Dogs in both groups had hypotension in addition to fulfillment of the SIRS criteria. It has been suggested that the detection of SIRS at time of hospital admission should increase suspicion of sepsis¹¹; however, clinicians should bear in mind anaphylaxis may mimic sepsis and therefore anaphylaxis should be considered if a septic nidus cannot be detected.

Hyperlactatemia, low blood bicarbonate concentration, and acidemia were identified in dogs in both groups of the present study, likely as a result of hypoperfusion and distributive shock that occurs with both diseases. Alterations in multiple hematologic variables, including increases in PCV and serum phosphorus, BUN, and creatinine concentrations were likely a result of vasculitis leading to fluid extravasation, secondary hemoconcentration, and decreased glomerular filtration by the kidneys. Similarly, the hypoalbuminemia identified in dogs in both groups was likely secondary to increased vascular permeability and protein leakage into the extravascular space. Although dogs with anaphylaxis had significantly higher serum ALT activity and dogs with sepsis had significantly higher serum ALP activity, increases in liver enzymes (including serum ALT and ALP activities and total bilirubin concentration) were common in both groups.

Increases in hepatobiliary variables have been reported for both diseases secondary to abnormal blood flow, hepatocellular ischemia, and cholestasis.^{12,13,25} In dogs with anaphylaxis in particular, the histamine release that causes vasodilation of the hepatic artery and constriction of the hepatic venous sphincters leads to congestion of the liver and subsequent ischemic injury.⁸ This mechanism likely results in more clinically important hypoxic damage and release of hepatocellular enzymes (such as ALT) during anaphylaxis versus other disease states (such as sepsis). Ionized hypocalcemia is common in critically ill dogs²⁶ and may be a result of abnormal parathyroid gland function,^{27,28} hypovitaminosis D,²⁷ and shifting of calcium concentrations within the tissues.²⁹ The mechanisms are likely to be the same in dogs with anaphylaxis, although to the authors' knowledge, ionized hypocalcemia associated with anaphylaxis has not been described in the human or veterinary literature.

On abdominal ultrasonography, several dogs in each group in the present study had evidence of thickened or fluid-filled intestines. These changes likely resulted from splanchnic congestion in dogs with anaphylaxis and from primary gastrointestinal disease or secondary to ileus and intestinal wall edema in dogs with sepsis. Edema of the gallbladder wall was identified in 2 of the 6 dogs with anaphylaxis and 2 of the 12 dogs with sepsis for which abdominal ultrasonography had been performed. One dog in the sepsis group with such edema had a gallbladder rupture, and the other had an unrelated jejunal perforation.

Edema of the gallbladder wall is characterized by wall thickening that produces an apparent halo or double-rim effect and distinctive striations in the wall. In a previous report⁸ regarding anaphylaxis and allergic reactions in dogs, the halo sign was identified in 93% of dogs with anaphylaxis. This was a considerably higher proportion than was identified in the present study (2/5 in anaphylaxis group and 2/12 in sepsis group), which may have been attributable to the fact that not all dogs with suspected anaphylaxis received a complete abdominal ultrasonographic examination. Only 5 and 12 dogs in the anaphylaxis and sepsis groups, respectively, underwent a complete abdominal ultrasonographic examination. However, in the authors' experience, edema of the gallbladder wall can occur with other diseases that cause cholestasis or inflammation and vasculitis, such as primary liver disease, portal hypertension, decreased lymphatic drainage of the gallbladder, peritoneal sepsis (as in the present study), or pancreatitis. Prospective studies of the prevalence of such edema in dogs with anaphylaxis versus dogs with septic and nonseptic SIRS would be an interesting addition to the veterinary literature.

Intracavitary effusion was a common finding in both groups in the study reported here. In both anaphylaxis² and sepsis,¹² endothelial damage and an increase in vascular permeability caused by vasculitis can cause pleural or peritoneal effusion regardless of the origin of the inflammation. In sepsis, rupture of a visceral organ can also lead to intracavitary effusion. In the present study, the intracavitary fluid in dogs with anaphylaxis was classified as nonseptic transudate or modified transudate, whereas the dogs with sepsis had mostly septic suppurative effusions. Given the high prevalence of effusion in dogs with anaphylaxis and sepsis alike, the presence of intracavitary fluid alone should not be used to help differentiate between the 2 diseases, although the cytologic appearance of effusion samples may be helpful.

One of the young dogs with suspected anaphylaxis in the study reported here was believed to be septic at hospital admission given its clinical signs, hematologic abnormalities, and imaging findings. The dog had sudden collapse, was hypothermic, and had clear signs of abdominal pain on palpation and a large amount of abdominal petechiation. This dog had initially been brought to the primary veterinarian, who reported septic abdominal fluid on abdominocente-

sis. Abdominal ultrasonography revealed moderately fluid-filled small intestines and colon and a mineralized foreign body in the intestines, and repeated abdominocentesis revealed a nonseptic modified transudate. Given the intestinal dilation and concern regarding the foreign body and sepsis, exploratory laparotomy and intestinal biopsies were performed. Results of laparotomy and histologic examination of biopsy specimens were unremarkable. Supportive IV fluid administration and antihistamine and antimicrobial treatment was continued, and the clinical signs resolved within 12 hours after surgery. The authors believe that this case is a particularly good example of overlap between the 2 diseases and the potential for clinical confusion during diagnosis.

No definitive test exists for the diagnosis of anaphylaxis. Tests used in humans to support a diagnosis include serum tryptase activity, plasma urine histamine concentration, and urine N-methylhistamine concentration.³⁰ These analytes are nonspecific, commonly result in misdiagnosis, and, to the authors' knowledge, have not been validated in veterinary species.² In all but 1 dog with suspected anaphylaxis in the present study, the cause of the hypersensitivity reaction was unknown. Definitive diagnosis of sepsis requires the identification of an infectious agent, but in many situations this is difficult and may require bacterial culture, and bacterial culture may not yield reliable growth.³¹ Although many attempts have been made to identify reliable biomarkers of sepsis, including procalcitonin,³² C-reactive protein,³³ natriuretic peptides,³⁴ and vascular endothelial growth factor,³⁵ more clinically applicable studies are needed to validate the use of these biomarkers to differentiate sepsis from noninfectious causes of SIRS.

Although the clinical manifestations of anaphylaxis and sepsis in dogs overlapped in many ways in the study reported here, the prognoses were markedly different. Only 32% of dogs with sepsis survived to hospital discharge, whereas all dogs with anaphylaxis survived (with survival being a component of the inclusion criteria). Dogs with sepsis often continue to deteriorate despite aggressive medical interventions until the septic nidus is identified and eliminated. These dogs have a reported 20% to 68% mortality rate even with appropriate medical and surgical treatments.^{11,12,36,37} Although severe anaphylaxis can be life-threatening, appropriate and timely supportive care, including IV fluid and antihistamine administration, helps to dampen endogenous compensatory mechanisms that can worsen circulatory function.² Despite minimal supportive care, dogs in the anaphylaxis group had a comparatively fast resolution of clinical signs and brief hospitalization period. A combination of IV crystalloid fluid administration with or without colloid solutions and diphenhydramine resulted in 8 of 10 dogs in the anaphylaxis group having resolution of clinical signs within 16 hours after hospital admission. The other 2 dogs had resolution of clinical signs within 32 hours after hospital admission, which is consistent with human reports of ana-

phylaxis.^{38,39} One dog received dexamethasone and crystalloid fluid (IV) at the referring veterinarian's clinic, and the owner reported considerable clinical improvement by the time the dog was admitted to our hospital. None of the surviving dogs with sepsis had clinical improvement with medical treatment alone, and all required surgery to remove the septic nidus.

An interesting feature of the present study was that all dogs with suspected anaphylaxis improved with IV fluid and antihistamine administration (with or without corticosteroids). None of the dogs received epinephrine, which is reportedly the recommended treatment for severe hypersensitivity reactions. Epinephrine is a potent α - and β -adrenoceptor agonist and is used to restore blood pressure to within reference limits by increasing cardiac inotropy and causing vasoconstriction that maintains total peripheral resistance.⁴⁰

Despite the strong anecdotal evidence for the use of epinephrine, only a limited number of clinical trials have been reported regarding the use of drugs in acute anaphylactic reactions in veterinary or human medicine.² Epinephrine use for anaphylaxis in dogs with experimental ragweed hypersensitivity⁴¹ and humans with insect-sting hypersensitivity²⁰ failed to result in improvement in hypotension and reverse cardiovascular collapse. The study⁴¹ involving dogs showed that epinephrine at high doses had adverse effects on cardiac function. Indeed, epinephrine has been associated with severe adverse effects, including ventricular arrhythmias, myocardial infarction, severe hypertension, and pulmonary edema.⁴⁰

Although the anaphylactic reactions of the dogs in the present study may not have been severe enough to require epinephrine administration, another possibility is that epinephrine may not be necessary when appropriate supportive care is provided. Given the results of the present study and the potential associated adverse effects of epinephrine use, we recommend that epinephrine be used only for dogs with distributive shock that fail to respond to fluids, antihistamines, and corticosteroids.

The present study had several limitations, including the lack of a definitive test for the diagnosis of anaphylaxis. Diagnosis was based on suspicion, lack of identification of other diseases, and rapid response to minimal supportive care. In addition, the inclusion criteria (that dogs in the anaphylaxis group had resolution of clinical signs within 72 hours after admission) prevented meaningful comparison of hospitalization periods or mortality rates between the groups. Other limitations included the retrospective nature and small sample size.

Despite the aforementioned limitations, the overlap in the pathophysiologic features of anaphylaxis and sepsis in the dogs of the present study suggested that the 2 diseases may be difficult to differentiate at hospital admission. Many of the dogs in the anaphylaxis group were suspected to be septic at admission, and the exploratory laparotomy that was performed in 1 dog on the basis of these suspicions yielded no

remarkable findings. This dog was treated with supportive care after surgery and was clinically normal by the following morning. Given that anaphylaxis and sepsis have markedly different treatment protocols and prognoses, it may not be appropriate to assume the presence of sepsis on the basis of clinical signs without definitive demonstration of an inciting infectious organism. If no septic nidus is identified in a dog with SIRS and other causes of SIRS (eg, pancreatitis) have been ruled out, a brief trial of supportive care (6 to 8 hours) should be considered.

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Footnotes

- a. SPSS, version 24, SPSS Inc, Chicago, Ill.

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