Severe sepsis in cats: 29 cases (1986–1998)

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Objective—To document the clinical, clinicopathologic, and pathologic findings in cats with severe sepsis, identify abnormalities unique to this species, and identify criteria that could be used antemortem to diagnose the systemic inflammatory response syndrome in cats.

Design—Retrospective study.

Animals—29 cats confirmed to have severe sepsis at necropsy.

Procedure—Pertinent history, physical examination findings, and results of hematologic and biochemical testing were extracted from medical records.

Results—Clinical diagnoses included pyothorax, septic peritonitis, bacteremia secondary to gastrointestinal tract disease, pneumonia, endocarditis, pyelonephritis, osteomyelitis, pyometra, and bite wounds. Physical examination findings included lethargy, pale mucous membranes, poor pulse quality, tachypnea, hypo- or hyperthermia, signs of diffuse pain on abdominal palpation, bradycardia, and icterus. Clinicopathologic abnormalities included anemia, thrombocytopenia, band neutrophilia, hypoalbuminemia, low serum alkaline phosphatase activity, and hyperbilirubinemia. Necropsy findings included multiorgan necrosis or inflammation with intralesional bacteria.

Conclusions and Clinical Relevance—Results suggest that severe sepsis in cats is characterized by lethargy, pale mucous membranes, signs of diffuse abdominal pain, tachypnea, bradycardia, weak pulses, anemia, hypoalbuminemia, hyperthermia, and icterus. Recognition of this combination of clinical findings should facilitate the diagnosis of severe sepsis in cats. (J Am Vet Med Assoc 2000;217:531–535)

Sepsis is a clinical syndrome resulting from disseminated bacterial infection and the associated inflammatory response, which is termed the systemic inflammatory response syndrome (SIRS). The definitions of sepsis and SIRS have been the subject of much controversy in the human clinical literature. In 1992, a group of human intensivists developed a consensus statement defining SIRS, sepsis, severe sepsis, and septic shock with the goal of facilitating communication among physicians. This statement defined “sepsis” as SIRS secondary to bacterial infection and defined the term “severe sepsis” as sepsis accompanied by a combination of organ dysfunction, hypoperfusion, or hypotension. “Septic shock” was defined as severe sepsis with hypotension that is refractory to intravascular fluid loading. Clinical criteria for the diagnosis of SIRS in humans include changes in body temperature (>38°C [100.4°F] or <36°C [96.8°F]), heart rate (>90 beats/min), respiratory rate (>20 breaths/min or PaCO2 <32 mm Hg), and leukogram (WBC count >12,000/µl or <4,000/µl or >10% band neutrophils) that together reflect the severity of systemic (or endothelial) disturbance. In the veterinary literature, it has been suggested that a clinical diagnosis of SIRS can be made on the basis of criteria extrapolated from the human literature.24 However, a previous attempt to objectively evaluate criteria for diagnosis of SIRS in dogs found that the criteria were a sensitive but nonspecific aid to the diagnosis of sepsis in dogs.3

Clinical and laboratory abnormalities associated with sepsis have been well-described in dogs and other species.1,8-10 Classic findings of sepsis include fever or hypothermia, tachycardia, hyperemic mucous membranes, bounding pulses, tachypnea, and leukocytosis or leukopenia. Severe sepsis is associated with pale mucous membranes, weak pulses, and prolonged capillary refill times. Although there are many reports of experimentally induced endotoxic shock in cats,8-10 abnormalities associated with naturally occurring severe sepsis in cats have not been well-described. Clinical experience suggests that the classic hemodynamic changes reported for other species may not be typical of cats with severe sepsis.

The purposes of the study reported here were to document the clinical, clinicopathologic, and pathologic findings in cats with severe sepsis and to identify abnormalities unique to this species. In addition, we sought to identify criteria that could be used antemortem to diagnose SIRS in cats.

Criteria for Selection of Cases

The database of the Department of Pathobiology at the University of Pennsylvania was searched to identify cats in which a diagnosis of sepsis or septicemia had been made between 1986 and 1998. Pathology reports and histopathology slides for cats identified with this initial search were then reviewed to determine whether the cats met the inclusion criteria. Cats were included in the study if there was histopathologic evidence of bacterial infection with multiorgan necrosis, inflammation with intralesional bacteria, or both. In all instances, bacteria were cultured antemortem or were identified histologically in necropsy specimens. Medical records of cats considered for inclusion in the study were reviewed.

Procedures

Pertinent history, physical examination findings, and results of hematologic and biochemical testing were extracted from medical records of cats included in the study. Because certain tests were repeated during...
the course of hospitalization in some cats, serial values for certain variables were not available for these cats. Therefore, to ensure that the described clinical findings corresponded temporally with the necropsy findings, only values that were recorded within 12 hours of death or euthanasia were selected for inclusion in the study. In addition, some hematologic and biochemical tests were not performed on all cats. Therefore, values were not available for all cats.

Data for cats included in the study were applied to clinical criteria previously suggested for diagnosis of SIRS in humans, and cutoffs for diagnosis of SIRS in cats were identified.

Results

Twenty-nine cats with severe sepsis met the criteria for inclusion in the study. Mean ± SD age was 3.5 ± 4.1 years (range, 8 weeks to 14 years). Age distribution appeared to be bimodal, with 12 (41%) cats < 1 year old and 8 (28%) cats > 3 years old. There were 14 males and 15 females. Twenty-two cats were domestic shorthairs, 3 were domestic longhairs, and 4 were purebreds. All cats > 6 months old were neutered.

According to the owners, 4 cats appeared ill for < 24 hours prior to examination at the veterinary teaching hospital, 15 cats were ill for 24 to 72 hours, and 10 cats were ill for > 3 days. Mean ± SD hospitalization time prior to death or euthanasia was 30 ± 4.1 hours (range, 4 hours to 7 days).

Clinical diagnoses included pyothorax (7 cats), septic peritonitis (5), bactereemia secondary to gastrointestinal tract disease such as salmonellosis (5), pneumonia (4), endocarditis (4), pyelonephritis (2), osteomyelitis (1), pyometra (1), and bite wounds (1). Antemortem diagnoses were consistent with the pathologic diagnoses. Multiorgan necrosis or inflammation was observed at necropsy in all cats. Septic peritonitis was confirmed in 7 cats, 4 of which had an identifiable lung abscess that had ruptured. In the remaining 22 cats, there was multiorgan necrosis or inflammation involving the lung (13 cats), kidney (12), liver (9), heart (9), peritoneum (8), small intestine (7), brain (6), lymph nodes (6), spleen (5), colon or rectum (2), and adrenal glands (2). Each of the following sites were involved in at least 1 cat: bone marrow, skin, subcutis, urinary bladder, uterus, thymus, middle ear, eye, pancreas, mandible, and nasal cavity. Bacteria were identified in all 29 cats and included gram-negative bacteria in 8 cats, gram-positive bacteria in 11, and mixed bacterial infection in 10. In 12 cats, antemortem bacterial culture yielded Escherichia coli (7 cats), Pseudomonas spp (2), and beta-hemolytic Streptococcus spp (3). Eighteen cats were tested for FeLV antigen by use of an in-house ELISA; results for all cats were negative.

Physical examination revealed marked lethargy and pale mucous membranes in all 29 cats. Twenty-three cats had poor pulses or pulses that were not palpable. Mean ± SD heart rate was 137 ± 45 beats/min (median, 129 beats/min; range, 72 to 230 beats/min). Heart rate was < 140 beats/min in 19 (66%) cats. Mean ± SD rectal temperature was 37.2 ± 2.5 C (99.0 ± 4.5 F; median, 36.9 C [98.5 F]; range, 32.6 to 41.7 C [90.7 to 107.1 F]). Seventeen (59%) cats had hypothermia (rectal temperature < 37.8 C [100 F]), and 10 (33%) had a fever (rectal temperature > 38.9 C [102 F]). Rectal temperature did not appear to be associated with heart rate; bradycardia (heart rate < 140 beats/min) was detected in 10 of the 17 (60%) cats that were hypothermic and in 5 of the 10 (50%) cats that had a fever. Systolic blood pressure was measured by means of Doppler sphygmomanometry in 9 cats; 7 were hypotensive (systolic blood pressure < 90 mm Hg). Severity of pain was subjectively assessed in 23 cats. Twenty-two cats were considered to have signs of diffuse pain on abdominal palpation, even though 11 of these cats did not have abdominal disease. Mean ± SD respiratory rate was 54 ± 20 breaths/min (median, 49 breaths/min; range, 11 to 88 breaths/min). Tachypnea (respiratory rate > 40 breaths/min) was detected in 21 cats; 4 of these cats did not have evidence of thoracic disease. Icterus was evident on physical examination in 21 cats. Other physical examination findings varied depending on the underlying cause of sepsis.

Thirteen of 27 (45%) cats had anemia (PCV < 27%; Table 1), and 2 (7%) had hemoconcentration (PCV > 45%). Five of 15 cats had leukocytosis (WBC count > 19,500/µl); none had leukopenia. Band neutrophils were detected in 9 of the 15 cats, and absolute number of band neutrophils exceeded the number of mature neutrophils in 3 cats. Twelve of 27 (44%) cats had hypoglycemia (glucose concentration < 75 mg/dl);

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. tested</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Range</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV (%)</td>
<td>27</td>
<td>27 (14.3)</td>
<td>24</td>
<td>7–65</td>
<td>27–45</td>
</tr>
<tr>
<td>Total solids (g/dl)</td>
<td>27</td>
<td>6.5 (1.5)</td>
<td>6.6</td>
<td>3.1–8.5</td>
<td>5.5–7.1</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>27</td>
<td>75.5 (46)</td>
<td>56</td>
<td>14–180</td>
<td>75–199</td>
</tr>
<tr>
<td>Urea nitrogen* (mg/dl)</td>
<td>21</td>
<td>30 (22)</td>
<td>30</td>
<td>5–90</td>
<td>&lt; 26</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>26</td>
<td>144 (8.1)</td>
<td>147</td>
<td>120–158</td>
<td>148–157</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>26</td>
<td>4.0 (1.3)</td>
<td>3.7</td>
<td>2.2–8.1</td>
<td>3.5–5.1</td>
</tr>
<tr>
<td>WBC (× 10³/µl)</td>
<td>25</td>
<td>20.5 (2)</td>
<td>15.6</td>
<td>8–50</td>
<td>5.5–19.5</td>
</tr>
<tr>
<td>Band neutrophils (× 10⁹/µl)</td>
<td>15</td>
<td>0.7 (2)</td>
<td>0.9</td>
<td>0–3.3</td>
<td>0</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>12</td>
<td>1.97 (0.42)</td>
<td>2.0</td>
<td>1.1–2.6</td>
<td>2.7–3.9</td>
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<tr>
<td>Total bilirubin (mg/dl)</td>
<td>16</td>
<td>2.9 (0.01)</td>
<td>3.0</td>
<td>0.5–8.7</td>
<td>0.1–0.5</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>14</td>
<td>13.7 (13)</td>
<td>17</td>
<td>0–84</td>
<td>23–107</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>11</td>
<td>86 (137)</td>
<td>45</td>
<td>15–343</td>
<td>20–107</td>
</tr>
</tbody>
</table>

*Estimated by use of a dipstick.

ALP = Alkaline phosphatase. ALT = Alanine transaminase.
none had hyperglycemia. Fourteen of 26 (54%) cats had hypokalemia (plasma potassium concentration < 3.5 mEq/L), and 6 (23%) had hypoglycemia (plasma concentration < 148 mEq/L), and 6 (23%) had hypokalemia (plasma potassium concentration < 3.5 mEq/L), but the hypokalemia appeared to be unrelated to bradycardia. All 12 cats in which serum albumin concentration was measured had hypoalbuminemia (serum albumin concentration < 2.7 g/dl).

Total bilirubin concentration was measured in 16 cats, and 10 (63%) had hyperbilirubinemia (total bilirubin concentration > 1.0 g/dl). Serum alkaline phosphatase (ALP) activity was within the reference range in the 14 cats in which it was measured. Serum alanine transaminase (ALT) activity was measured in 11 cats and was high in 2 cats with evidence of hepatic necrosis at necropsy. Serum hepatic enzyme activities were not available for the remaining 8 cats with evidence of hepatic necrosis, hepatic inflammation, and bile stasis at necropsy. Three additional cats had necropsy findings of bile stasis without associated inflammation but were not clinically icteric. These 3 cats had moderate anemia and serum total bilirubin concentration and ALP and ALT activities that were within reference ranges.

The following cutoffs for making a clinical diagnosis of SIRS were selected: rectal temperature > 39.7 C (103.5 F) or < 37.8 C (100 F), heart rate > 225 beats/min or < 140 beats/min, respiratory rate > 40 breaths/min, and WBC count > 19,500/µl or < 5,000/µl or band neutrophil fraction > 5%. Twenty-five of 29 cats fulfilled the rectal temperature criterion, 20 of 29 fulfilled the heart rate criterion, 21 of 29 fulfilled the respiratory rate criterion, and 14 of 15 fulfilled the WBC count criterion. All 29 cats fulfilled at least 2 of the 4 criteria; all 15 cats for which results of a CBC were available fulfilled at least 3 of the 4 criteria.

Discussion

Results of the present study suggest that common clinical abnormalities in cats with severe sepsis include lethargy, pale mucous membranes, signs of diffuse abdominal pain, tachypnea, bradycardia, weak pulses, anemia, hypoalbuminemia, hypothermia, and icterus.

Confirming a clinical diagnosis of sepsis or severe sepsis can be difficult. Results of bacterial culture of blood samples can be used to confirm bacteremia, and measurement of serum endotoxin concentrations can be used to confirm endotoxemia.16,17 However, these data were not available for cats included in the present study. Therefore, we used necropsy data to identify cats eligible for inclusion in the study. The inclusion criteria included necropsy confirmation of systemic bacterial infection with multiorgan involvement characterized by bacterial thrombi or multifocal necrosis with or without inflammation. The application of such strict inclusion criteria had the advantage of ensuring that all cats included in the study died as a result of severe sepsis. To ensure that clinical findings corresponded temporally with the necropsy findings, we only used data collected within 12 hours of euthanasia or death.

The disadvantage of using such strict inclusion criteria is the possibility that our findings reflect nonspecific end-stage changes in moribund animals, rather than specific abnormalities associated with severe sepsis. Mean duration of hospitalization in this study was 30 hours. A review of the medical records in which serial results of routine monitoring were available showed that with the exception of 1 cat, the clinical appearance throughout the period of hospitalization did not differ greatly from appearance within 12 hours prior to euthanasia or death (ie, findings used in the present study). In addition, although the clinical appearance of cats included in the present study may be common to numerous severe disorders, our clinical experience suggests that this appearance represents naturally occurring severe sepsis in cats.

Classic reports of sepsis in other species describe an initial hyperdynamic phase characterized by tachycardia, fever, and hyperemic mucous membranes secondary to peripheral vasodilation followed by, with development of severe sepsis, a hypodynamic phase characterized by vasoconstriction, tachycardia, pale mucous membranes with prolonged capillary refill time, and poor pulse quality. All cats in the present study appeared to be in the hypodynamic phase, which is consistent with severe sepsis. Seven cats in this study were hypotensive despite IV fluid administration and were considered to be in septic shock. The classic hyperdynamic phase associated with sepsis in other species was not evident in any of these cats. One cat that was hospitalized for 5 days initially had hyperthermia and tachycardia, but hyperemic mucous membranes and peripheral vasodilation were not recognized. This cat subsequently developed bradycardia and hypothermia 24 hours prior to euthanasia.

Certain abnormalities in cats in the present study appeared to be unique to this species. In other species, tachycardia usually persists during the hypodynamic phase of sepsis. In contrast, cats in the present study frequently had relative bradycardia, and none had a heart rate > 230 beats/min (the term relative bradycardia is used to denote an inappropriately low heart rate, given the hemodynamic status of the cat; healthy cats can have resting heart rates < 140 beats/min). The cause of relative bradycardia in these critically ill cats remains unclear. Mild bradycardia of unknown cause has been demonstrated in children with sepsis,14 and a case report in the human literature suggests an association between hypothermia secondary to sepsis and subsequent development of bradycardia.15 In the present study, however, we could not document a correlation between hypothermia and bradycardia.

Other possible mechanisms of bradycardia should be considered. It has been proposed that cats may not develop tachycardia in response to hypotension because of simultaneous baroreceptor stimulation of vagal and sympathetic fibers.16 Cats with experimentally induced endotoxemia have decreased left ventricular contractility17,18 and increased left ventricular end-diastolic pressure.19 Increased ventricular end-diastolic volume, resulting in stretch of left ventricular receptors, has been shown to elicit reflex bradycardia through vagal stimulation.20,21 Although the relationship between increased end-diastolic volume and increased end-diastolic pressure in cats with sepsis is not clear,
these factors may contribute to the seemingly inappropriate bradycardia seen with severe sepsis in cats.

Signs of pain were a consistent finding in cats in the present study and have been reported as being common in this species.22,31 Interestingly, signs of diffuse pain on abdominal palpation were the most common manifestation and were evident even in cats that had no evidence of abdominal disease. Diffuse pain of this type has also been reported for dogs with sepsis.17,18

Twenty-four cats in the present study had evidence of pulmonary or pleural disease (pyothorax, pneumonia, or pleuritis), and 17 of these cats had a high respiratory rate (> 40 breaths/min). In cats, the lungs appear to be uniquely susceptible to damage during shock or sepsis,8,24 and the lung is a major site of bacterial clearance in this species.8 Pulmonary pathologic changes in cats with experimentally induced endotoxemia include pulmonary hypertension, capillary protein leakage, pulmonary thrombi, type 2 cell hyperplasia, and hyaline membrane formation.15,16 In the present study, histopathologic evidence of pulmonary disease included pneumonia, edema, thromboemboli, and hemorrhage. In addition, type 2 cell hyperplasia and hyaline membrane formation were seen in 2 cats.

Hemococoncentration is common in dogs with sepsis but was uncommon in cats in the present study, and anemia was a much more common finding. Anemia is commonly associated with feline inflammatory diseases, and it is likely that its pathogenesis in cats with sepsis is complex and multifactorial. Weiss and colleagues27,28 demonstrated accelerated erythrocyte destruction after experimental induction of abscesses in cats. Their results suggested that neutrophil and macrophage activation increased erythrocyte surface IgG, which initiated premature erythrocyte clearance, resulting in a low-grade hemolytic anemia. Additionally, feline erythrocytes are exceptionally susceptible to oxidative damage because of 8 reactive sulfhydryl groups on the hemoglobin protein.26 The high prevalence of Heinz body anemia in cats with inflammatory conditions is associated with low activities of the intracellular antioxidant glutathione.29 Inflammatory disease is also associated with secondary failure of erythropoiesis in humans.30 Unfortunately, reticulocyte counts are not available for cats in the present study, but bone marrow hypopcellularity was evident in 4 cats, and hypercellularity was evident in 5. Seven cats had evidence of extramedullary hematopoiesis. Marrow erythropagocytosis in 2 cats may also have been suggestive of an immune-mediated cause of anemia.

Variable derangements in blood glucose concentration are well-documented in dogs with sepsis; the typical pattern is hyperglycemia followed by hypoglycemia.25 Euglycemia is more consistently reported in the few published studies of sepsis in cats.5,33 Hypoglycemia reportedly may develop in cats with experimentally induced endotoxemia26 and is associated with an increased mortality rate in dogs with naturally occurring sepsis.8 In the present study, 12 of 27 cats had hypoglycemia. All 7 cats < 6 months old had hypoglycemia at the time of admission. Pediatric patients have a reduced ability to compensate for metabolic stress, possibly because of decreased glycogen reserves, low body fat, and decreased gluconeogenic precursors.25

Hypoalbuminemia was a consistent finding in the present study and is common in animals with naturally occurring or experimentally induced sepsis.8,25 The decrease in serum albumin concentration has been attributed to increased vascular permeability with leakage of plasma proteins and a shift of hepatic synthetic pathways towards acute phase proteins.3 Decreased colloid oncotic pressure predisposes to formation of edema, particularly when crystalloid fluids are administered. Peripheral edema was evident in 4 of the 7 cats in the present study that had been hospitalized for longer than 3 days, and a third of the cats in this study had evidence of pulmonary edema on necropsy.

Icterus was common in cats in the present study and has been previously reported as common in septic cats.30 Sepsis-induced cholestasis in dogs has been well described, but the characteristic histopathologic findings of this syndrome were not seen in cats in the present study, and no evidence of posthepatic obstruction was found, although 3 cats had histopathologic evidence of bile stasis without hepatic necrosis or inflammation. In contrast to findings in other species,3,33 serum ALP activity was not high in cats in the present study. Three of the 11 cats in which serum ALT activity was measured had moderately high activities; however, these 3 cats had normal total bilirubin concentrations. The histopathologic findings and low ALP activity argue against cholestasis and primary hepatic dysfunction as major mechanisms for icterus in these cats. Because anemia was a prominent feature of cats in the present study, hemolysis remains a likely cause of the icterus.

Although we used necropsy findings to identify the cats for inclusion in this study, the diagnosis of sepsis or severe sepsis is usually made on the basis of clinical, rather than pathologic findings. A set of criteria for clinical diagnosis of sepsis or severe sepsis in human beings, based on initial identification of SIRS, has been well-documented. The physiologic derangements associated with these criteria in humans are nonspecific and can occur with nonpathologic states. However, recognition of SIRS in conjunction with clinical signs of sepsis or severe sepsis is useful for determining the extent of the systemic disturbance and facilitating clinical communication. Towards this goal, several sets of criteria for identifying SIRS in cats have been proposed in the veterinary literature.17 However, a consensus position has not been established, nor have these values been clinically evaluated. On the basis of findings in the present study, particularly the rarity of the hyperdynamic phase of sepsis, we suggest that a unique set of criteria that is more reflective of the increased incidence of inappropriately low heart rates and the higher respiratory rate needed for diagnosis of tachypnea is needed for identification of SIRS in cats. Therefore, we propose that a tentative clinical diagnosis of SIRS can be made in cats that fulfill at least 3 of the following 4 criteria: rectal temperature > 39.7 °C
(103.5 F) or < 37.8 C (100 F), heart rate > 225 beats/min or < 140 beats/min, respiratory rate > 40 breaths/min, and WBC count > 19,500/μl or < 5,0000/μl or band neutrophil fraction > 5%. Prospective studies are required to determine the sensitivity and specificity of these criteria.

References


