Association between outcome and organ system dysfunction in dogs with sepsis: 114 cases (2003–2007)

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Objective—To determine whether multiple organ dysfunction syndrome (MODS) could be identified in dogs with sepsis secondary to gastrointestinal tract leakage, and whether the number of affected organ systems was significantly associated with mortality rate.

Design—Multicenter retrospective case series.

Animals—114 dogs.

Procedures—Medical records for dogs treated surgically because of sepsis secondary to gastrointestinal tract leakage between 2003 and 2007 were reviewed. Sepsis was diagnosed on the basis of results of bacterial culture of peritoneal fluid, gross evidence of gastrointestinal tract leakage at surgery, or both. Renal dysfunction was defined as a ≥ 0.5 mg/dL increase in serum creatinine concentration after surgery. Cardiovascular dysfunction was defined as hypotension requiring vasopressor treatment. Respiratory dysfunction was defined as a need for supplemental oxygen administration or mechanical ventilation. Hepatic dysfunction was defined as a serum bilirubin concentration > 0.5 mg/dL. Dysfunction of coagulation was defined as prolonged prothrombin time, prolonged partial thromboplastin time, or platelet count ≤ 100,000/μL.

Results—89 (78%) dogs had dysfunction of 1 or more organ systems, and 57 (50%) dogs had MODS. Mortality rate increased as the number of dysfunctional organ systems increased. Mortality rate was 70% (40/57) for dogs with MODS and 25% (14/57) for dogs without.

Conclusions and Clinical Relevance—Results indicated that MODS, defined as dysfunction of at least 2 organ systems, can be identified in dogs with sepsis and that organ system dysfunction increased the odds of death. (*J Am Vet Med Assoc* 2010;236:83–87)

Sepsis is defined as the systemic inflammatory response to identifiable infection, most often of bacterial origin. Systemic inflammation is manifested clinically as 2 or more of the following signs: hyper- or hypothermia, tachycardia, tachypnea, and an abnormal leukogram (ie, leukocytosis, leukopenia, or high-band neutrophil count).[1,2] Sepsis is well recognized in people and dogs and is associated with high mortality rates.[2,3] In dogs, for instance, reported mortality rates associated with septic peritonitis range from 21% to 68%.[4–6] The mortality rate associated with sepsis is thought to vary depending on multiple factors, including the presence of comorbid conditions (eg, advanced age and preexisting disease), type of bacterial organism (gram positive or gram negative), location of infection, systemic response, and development of organ dysfunction.[7,8]

Abbreviations

MODS	Multiple organ dysfunction syndrome
PT	Prothrombin time
PTT	Partial thromboplastin time
SOFA	Sepsis-related organ failure assessment
SPI	Survival prediction index

Multiple organ dysfunction syndrome has been defined as altered organ function in an acutely ill patient such that intervention is required to maintain homeostasis,[1] and the progression from sepsis to MODS has

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been well described and documented in people.[9] Organ systems that can be affected in patients with MODS include the renal, cardiovascular, respiratory, hepatic, hematologic, neurologic, gastrointestinal, endocrine, and immune systems.[10] Reported mortality rates for human patients with MODS range from 20% to 100%, but depend on the number, severity, duration, type, and combination of affected organ systems and the severity and duration of disease.[11–13] Not unexpectedly, mortality rates in people increase as the number of dysfunctional organ systems increases.[3,14]

Although the existence of MODS in dogs has been recognized clinically, there are few studies[15] documenting this syndrome in veterinary medicine. Additionally, to our knowledge, no studies have investigated the prevalence of MODS in canine patients with sepsis or examined whether organ dysfunction decreases the survival rate. Therefore, the objectives of the study reported here were to determine whether MODS could be identified in dogs with sepsis secondary to gastrointestinal tract leakage, and whether the number of affected organ systems was significantly associated with mortality rate. In accordance with a definition used in human medicine,[14] we defined MODS as dysfunction of ≥ 2 organ systems.

Materials and Methods

Criteria for selection of cases—Medical records of 7 veterinary teaching hospitals (ie, the Cummings School of Veterinary Medicine, Tufts University; Tufts Veterinary Emergency Treatment and Specialties; College of Veterinary Medicine, University of Pennsylvania; College of Veterinary Medicine, Michigan State University; Queen Mother Hospital for Animals, Royal Veterinary College; College of Veterinary Medicine, University of Georgia; and School of Veterinary Medicine, University of Montreal) were searched to identify dogs surgically treated between January 1, 2003, and December 31, 2007, because of sepsis secondary to gastrointestinal tract leakage of any cause.

Dogs were eligible for inclusion in the study if the diagnosis of sepsis had been confirmed on the basis of results of cytologic examination (ie, neutrophilia with intracellular bacteria), results of positive bacterial culture of peritoneal fluid, or gross evidence of gastrointestinal tract leakage that was documented during surgery. In addition, dogs were eligible for inclusion only if values for bilirubin concentration, creatinine concentration (minimum of 2 measurements), platelet count, and results of coagulation testing (PT, PTT, or both) were available and if equipment for monitoring cardiovascular status (eg, direct and indirect blood pressure measurement or central venous pressure measurement) and oxygenation status (eg, pulse oximetry and arterial blood gas analysis) had been available.

Dogs that died or were euthanized during surgery and dogs for which clinical or laboratory data were missing were excluded. One participating hospital submitted medical records only for those cases that met all inclusion criteria; the remaining 6 hospitals submitted records for all dogs with sepsis secondary to gastrointestinal tract leakage that were treated surgically.

Review of medical records—Information obtained from the medical records of dogs included in the study consisted of age, sex, hospitalization time, cause of gastrointestinal tract leakage, whether there was evidence or a history of organ dysfunction, whether there were any concurrent illnesses, and outcome. Organ systems that were evaluated included the renal, cardiovascular, respiratory, hepatic, and coagulation systems. Dogs were considered to have renal dysfunction if creatinine concentration increased ≥ 0.5 mg/dL from the preoperative value and there was no evidence of prerenal or postrenal azotemia. Prerenal azotemia was excluded if there was clinical evidence of adequate hydration or if central venous pressure was > 10 cm H_2O; postrenal azotemia was excluded if there was no evidence of urinary obstruction. Dogs were considered to have cardiovascular dysfunction if they had hypotension sufficiently severe to require vasopressor treatment after surgery. Dogs were considered to have respiratory dysfunction if supplemental oxygen administration or mechanical ventilation was required. The need for supplemental oxygen administration was determined on the basis of results of arterial blood gas analysis (ie, alveolar-arterial gradient in partial pressure of oxygen > 10 mm Hg) or results of pulse oximetry (Spo_2 < 95%) or if results of clinical assessment indicated a need for oxygen supplementation. Dogs were considered to have hepatic dysfunction if the highest measured value for bilirubin concentration was > 0.5 mg/dL. Dogs were considered to have coagulation dysfunction if PT or PTT was > 25% above the upper reference limit, if platelet count was ≤ 100,000/μL, or both.

The type of surgical treatment, (ie, celiotomy and lavage, celiotomy with primary closure of the source of leakage, closed abdominal lavage by use of a drain, and other) that had been performed at the discretion of the attending surgeon was recorded. Medical treatment was directed by the attending clinician. Details of these procedures and treatments were recorded.

Statistical analysis—Data were examined graphically to determine whether they were normally distributed. Continuous variables are summarized as median and range and were compared with a Mann-Whitney *U* test. Categorical variables are summarized as percentages of the total. Age was dichotomized (< 6 years vs ≥ 6 years). The number of organ dysfunctions was treated as categorical variables. The χ^2 test was used to determine whether categorical variables were significantly associated with outcome. Odds ratios and 95% confidence intervals were calculated for variables significantly associated with outcome in these univariate analyses. Multiple logistic regression analysis was used to identify variables independently associated with an increased risk of death. All variables with a value of $P < 0.10$ in bivariate analyses were included in the multivariate model. All analyses were performed with a commercially available software package.[a] Values of $P \leq 0.05$ were considered significant.

Results

One hundred fourteen dogs met the criteria for inclusion in the study. An additional 81 (42%) cases from

the 6 hospitals that submitted records for all dogs with sepsis of abdominal origin were excluded because of incomplete documentation of the variables necessary to identify organ dysfunction according to our study criteria. Median age of the 114 dogs included in the study was 6 years (range, 0.66 to 15 years). There were 68 males (50 neutered) and 46 females (42 spayed). Sixty-six (57.9%) dogs had developed sepsis as a result of primary nonneoplastic gastrointestinal tract leakage or perforation, 36 (31.6%) dogs as a result of dehiscence after gastrointestinal surgery, and 12 (10.5%) dogs as a result of neoplastic gastrointestinal tract perforation. Median hospitalization time was 5 days (range, 1 to 24 days). Sixty (52.6%) dogs survived to discharge from the hospital. Forty-two (36.8%) dogs were euthanatized, and 12 (10.5%) dogs died. Overall mortality rate was 47.4% (54/114).

Twenty-five (21.9%) dogs had no evidence of organ dysfunction, with 21 of the 25 (84%) dogs surviving to be discharged from the hospital. Thirty-two (28.1%) dogs had dysfunction of 1 organ system, with 22 of the 32 (69%) dogs surviving to be discharged; 26 (22.8%) dogs had dysfunction of 2 organ systems, with 12 of the 26 (46%) dogs surviving to be discharged; 17 (14.9%) dogs had dysfunction of 3 organ systems, with 4 of the 17 (24%) dogs surviving to be discharged; 11 (9.6%) dogs had dysfunction of 4 organ systems, with 1 of the 11 (9%) dogs surviving to be discharged; and 3 (2.6%) dogs had dysfunction of 5 organ systems, with none of the 3 dogs surviving to be discharged from the hospital. Median number of affected organ systems was 2 (range, 0 to 5), and 89 (78.1%) dogs had dysfunction of at least 1 organ system. Multiple organ dysfunction syndrome, defined as dysfunction of ≥ 2 organ systems, was diagnosed in 57 (50%) dogs. The mortality rate was 70% (40/57) for dogs with MODS, compared with 25% (14/57) for dogs with dysfunction of < 2 organ systems.

The odds ratio for the risk of death increased as the number of dysfunctional organ systems increased (**Table 1**). The odds of death was significantly ($P < 0.01$) higher for dogs with ≥ 1 dysfunctional organ system than the odds of death for dogs without organ system dysfunction.

Sixty-nine (60.5%) dogs met the criteria for coagulation dysfunction, with 28 of the 69 (41%) surviving to be discharged from the hospital. Fifty-six (49.1%) dogs met the criteria for hepatic dysfunction, with 21 of the 56 (38%) surviving to be discharged from the hospital. Thirty-six (31.6%) dogs met the criteria for respiratory dysfunction, with 10 of the 36 (28%) surviving to be discharged from the hospital. Twenty (17.5%) dogs met the criteria for cardiovascular dysfunction, with 2 of the 20 (10%) surviving to be discharged from the hospital. Fourteen (12.3%) dogs met the criteria for renal dysfunction, with 2 of the 14 (14%) surviving to be discharged from the hospital. One dog had preexisting chronic renal failure, and 1 had concurrent biliary rupture. For all 5 types of organ dysfunction, the presence or absence of organ dysfunction was significantly associated with outcome (**Table 2**). Multivariate analysis indicated that dysfunction of the respiratory, cardiovascular, renal, or coagulation system significantly increased the odds of death, independent of other factors. Age, sex, cause of gastrointestinal tract perforation, and the presence of hepatic dysfunction were not significantly associated with outcome in the multivariate analysis.

Table 1—Odds of death among dogs (n = 114) that underwent surgery because of sepsis secondary to gastrointestinal tract leakage, as a function of the number of dysfunctional organ systems.

No. of dysfunctional organ systems	Odds ratio	95% CI	*P* value
≥ 1	6.73	2.14–21.22	< 0.01
≥ 2	6.67	2.93–15.16	< 0.01
≥ 3	10.21	3.54–29.48	< 0.01
≥ 4	18.71	2.35–148.64	< 0.01

Odds ratio represents the odds of death in a dog with the indicated number of dysfunctional organ systems, compared with the odds of death in dogs with no affected organ systems.
CI = Confidence interval.

Discussion

Results of the present study indicated that MODS could be identified in dogs with sepsis of abdominal origin, and that organ system dysfunction increased the

Table 2—Results of bivariate (unadjusted) and multivariate (adjusted) analysis of factors potentially associated with outcome in dogs (n = 114) that underwent surgery because of sepsis secondary to gastrointestinal tract leakage.

	Unadjusted			Adjusted		
Factor	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age	1.41	0.72–2.14	0.832	1.13	0.065–3.12	0.93
Sex	1.1	0.02–1.45	0.242	0.80	0.42–2.51	0.42
Nonneoplastic leakage	1.162	0.74–2.60	0.420	2.73	0.87–4.2	0.33
Neoplastic leakage	0.97	0.62–1.96	0.760	1.01	0.72–1.37	0.042
Dehiscence of previous surgery	2.20	0.88–4.67	0.097	1.81	0.69–2.70	0.23
Cardiovascular dysfunction	2.35	1.75–3.16	< 0.001	3.39	2.71–6.1	0.004
Coagulation dysfunction	2.06	1.25–3.39	< 0.001	4.27	3.12–7.67	0.020
Renal dysfunction	2.04	1.29–2.79	< 0.001	2.22	1.41–3.01	0.034
Respiratory dysfunction	2.01	1.41–2.88	< 0.01	3.32	2.51–4.72	< 0.001
Hepatic dysfunction	1.91	1.25–2.90	< 0.01	1.11	0.88–2.21	0.09

Odds ratio represents the odds of death among dogs with the factor of interest, compared with the odds among dogs without the factor of interest; the odds of death in dogs ≥ 6 years old, compared with the odds among dogs < 6 years old; and the odds among males, compared with the odds among females.
CI = Confidence interval.

odds of death, with odds ratio increasing as the number of affected organ systems increased. The overall mortality rate for dogs in the present study was 47.4% (54/114), whereas mortality rate was 70% (40/57) for dogs with MODS, compared with a rate of 25% (14/57) for dogs with only 1 dysfunctional organ system. In addition, dysfunction of the respiratory, cardiovascular, renal, or coagulation system was independently associated with a significantly increased odds of death. Human studies[9,11,16] have similarly demonstrated that mortality rate increases in patients with sepsis as the number of dysfunctional organ systems increases. Interestingly, the presence of hepatic dysfunction was not an independent risk factor for death in the present study.

Criteria used to classify dogs in the present study as having organ dysfunction were adapted from criteria used in the multiple organ dysfunction score[17,18] and SOFA[19] scoring systems. Scoring systems have been used in human medicine to predict patient outcome on the basis of objective criteria for dysfunction of the renal, cardiovascular, respiratory, hepatic, hematologic, and neurologic systems. Neurologic dysfunction was not assessed in the study reported here because of inconsistent documentation of neurologic status in the medical records that were reviewed. In addition, organ dysfunction was not graded in severity, but was only classified as either present or absent.

In human medicine, renal dysfunction is most commonly identified on the basis of serum creatinine concentration or urine output. Many definitions for renal dysfunction exist in the human literature; however, in 2004, the first consensus definition for renal dysfunction was established.[20] Criteria used to define severity of renal dysfunction included serum creatinine concentration, glomerular filtration rate, and urine output.[20] In the present study, we used an increase in serum creatinine concentration of at least 0.5 mg/dL, compared with the preoperative value, to define renal dysfunction. This criterion has been demonstrated to be a sensitive indicator of acute renal dysfunction in people.[21,22]

Cardiovascular dysfunction was defined in the study reported here as hypotension severe enough to require vasopressor treatment, which is similarly assessed by application of the SOFA score in human patients. However, the severity of hypotension was not graded in our study. Additionally, we did not assess dogs for sepsis-induced myocardial depression, which is diagnosed on the basis of echocardiographically apparent biventricular dilation and reduced ejection fraction in human patients.[23] Myocardial depression can occur in patients with sepsis in the absence of hypotension and could thus be an earlier indicator of cardiovascular dysfunction.[24]

In humans, respiratory dysfunction can be identified by the ratio of arterial partial pressure of oxygen to inspired oxygen fraction or by the need for mechanical ventilation. Owing to inconsistent use of arterial blood gas analysis in dogs in the present study, respiratory dysfunction was considered to be present if there was a need for supplemental oxygen administration or mechanical ventilation. The clinical determination of the need for supplemental oxygen administration or mechanical ventilation may have differed among clinicians and institutions in the present study. Additionally, some dogs likely developed respiratory dysfunction secondary to aspiration pneumonia, whereas others may have developed acute lung injury or acute respiratory distress syndrome. The mortality rate may have varied depending on the underlying cause of respiratory dysfunction, although this was not investigated in our study.

Hyperbilirubinemia was used as a marker for hepatic dysfunction in our study and is similarly used in scoring systems applied to human patients. However, in our multivariate analysis, hepatic dysfunction was not independently associated with mortality rate. In some dogs, high bilirubin concentrations may have been a result of hemolysis associated with sample handling or RBC transfusions and were therefore not a true reflection of cholestasis associated with hepatic dysfunction.[25] We elected to use a serum bilirubin concentration > 0.5 mg/dL as our cutoff for a diagnosis of hepatic dysfunction. This value was chosen arbitrarily, as the contribution of cholestasis or hemolysis to hyperbilirubinemia was unknown. Additional serum biochemical analyses, including alkaline phosphatase and γ-glutamyltransferase activities, and RBC count determination, may have been helpful in differentiating cholestasis from hemolysis. However, the ability to consistently define hepatic dysfunction on the basis of a single criterion (ie, bilirubin concentration) in all dogs was considered preferable.

Coagulation dysfunction is assessed in human scoring systems on the basis of the presence or absence of thrombocytopenia. Studies involving dogs have reported variable results regarding thrombocytopenia in patients with sepsis. One study[2] demonstrated lower mean platelet counts in dogs with sepsis versus control dogs, whereas another study[26] found no difference in platelet counts, but significantly higher PT, PTT, and D-dimer concentrations and concentrations of fibrinogen degradation products as well as significantly lower protein C and antithrombin concentrations in dogs with sepsis, compared with healthy dogs. For dogs in the present study, PT, PTT, and platelet count were the coagulation variables most commonly measured and thus were used to assess coagulation dysfunction.

Several limitations existed for the study reported here. First, a large number of dogs with sepsis secondary to gastrointestinal tract leakage were excluded because of inadequate medical records. The exact number of dogs excluded for inadequate medical records is unknown since investigators were asked to submit only records with all data required for analysis. Therefore, the proportion of dogs with MODS in the present study is likely not an unbiased estimate of prevalence of this condition. For example, dogs with mild clinical signs that recovered rapidly may not have undergone the extensive laboratory testing required for dogs to be included in this study. Exclusion of these potentially less severely affected dogs from our study may have artificially increased the proportion of dogs with MODS and the overall mortality rate. In contrast, exclusion of dogs that did not survive surgery or that were euthanized without surgical treatment may have decreased the proportion of dogs with MODS and the overall mortality rate if these dogs were comparatively more critically ill.

Additionally, differences in the medical and surgical management of dogs may have affected the mortality rate or the likelihood of organ dysfunction. Assessment of these factors was not feasible owing to the retrospective nature of this multi-institutional study. Further, there were only 3 dogs with dysfunction of 5 organ systems, limiting our ability to perform statistical analyses. The small size of this group can be explained by the high mortality rate associated with multiple organ dysfunction. Finally, the decision by some clients to elect euthanasia may have affected the likelihood that organ dysfunction would develop. The impact of this on our data cannot be determined; however, because these owners had committed to treating their dogs surgically, we suggest that the decision to euthanatize would have been an indication of disease progression after surgery and a worsening prognosis.

Despite these limitations, the study reported here establishes that MODS can be identified in dogs with sepsis of abdominal origin. Dysfunction of any organ system should be considered a negative predictor of outcome in dogs with sepsis, as a significant association between the presence of organ dysfunction and death was identified. In addition, mortality rate increased as the number of affected organ systems increased.

a. SPSS, version 12.0, SPSS Inc, Chicago, Ill.

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