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Outcome of Dogs with Diabetic Ketoacidosis: 127 Dogs (1993–2003)

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The aim of this study was to retrospectively describe the outcome of 127 dogs with naturally occurring diabetic ketoacidosis (DKA) and to examine the association between outcome of canine DKA and clinical and clinicopathologic findings. Eighty-two (65%) dogs were diagnosed with DKA at the time of initial diagnosis of diabetes mellitus (DM). Eighty-seven dogs (69%) had one or more concurrent disorders diagnosed at the time of hospitalization. Commonly identified concurrent conditions included acute pancreatitis (52, 41%), urinary tract infection (21, 20%), and hyperadrenocorticism (19, 15%). Dogs with coexisting hyperadrenocorticism were less likely to be discharged from the hospital ($P = .029$). Of 121 treated dogs, 89 dogs (70%) survived to be discharged from the hospital, with a median hospitalization of 6 days. Nonsurvivors had lower ionized calcium concentration ($P < .001$), lower hematocrit ($P = .036$), lower venous pH ($P = .0058$), and larger base deficit ($P = .0066$) than did survivors. Time from admission to initiation of subcutaneous insulin therapy was correlated with lower serum potassium concentration ($P = .0056$), lower serum phosphorus concentration ($P = .0043$), abnormally high white blood cell count ($P = .0060$), large base deficit ($P = .0015$), and low venous pH ($P < .001$). Multivariate analysis showed that base deficit was associated with outcome ($P = .021$). For each unit increase in the base deficit, there was a 9% greater likelihood of discharge from the hospital. In conclusion, the majority of dogs with DKA were not previously diagnosed with DM. Concurrent conditions and electrolyte abnormalities are common in DKA and are associated with length of hospitalization. Survival was correlated to degree of anemia, hypocalcemia, and acidosis.

Key words: Acidosis; Canine; Diabetes mellitus; Electrolytes; Insulin.

Diabetic ketoacidosis (DKA) is a severe, life-threatening complication of diabetes mellitus, characterized by the biochemical triad of hyperglycemia, acidosis, and ketosis.[1–7] Dogs with DKA usually are thought to have type I diabetes mellitus (DM), which occurs as a result of relative or absolute insulin deficiency.[8] Decreased insulin concentration coupled with increased counterregulatory hormone concentrations may (glucagon, cortisol, catecholamines, and growth hormone) contribute to the development of DKA.[1–7] The rise in counterregulatory hormone concentrations is believed to be due to presence of concurrent disease.[1–7] This hormonal imbalance of hypoinsulinemia and increased counterregulatory hormone concentrations may contribute to increased peripheral lipolysis and ultimately to the production of the ketone bodies acetoacetate, beta-hydroxybutyrate, and acetone.[2,6] Accumulation of ketoacids beyond a basal concentration leads to development of metabolic acidosis.

The purpose of this study was to describe the outcome of dogs with naturally occurring DKA and to examine the association between outcome of canine DKA and clinical and clinicopathologic findings.

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Materials and Methods

Criteria for Selection of Cases

A computer search of all dogs admitted to the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania (MJR-VHUP) between January 1993 and January 2003 with a coded medical diagnosis of DKA was performed. Two separate computerized databases were searched for the coded diagnosis of DKA. One of the databases was a computerized system of patient discharge orders created by clinicians and the other was a medical record database created by document management and information technology personnel. Medical records were reviewed in detail by one of the authors (DZH). Inclusion criteria consisted of clinical signs suggestive of diabetes mellitus (eg, polyuria, polydipsia, polyphagia, weight loss), persistent hyperglycemia with glucosuria, or persistent hyperglycemia despite insulin treatment. Additional inclusion criteria included the presence of ketonuria and acidosis, which was defined by a venous blood pH < 7.35. Animals were excluded if the complete medical record was not available or if urinalysis and venous blood gas analysis were not performed at initial examination.

Procedures

Past medical history, signalment, physical examination findings, clinicopathologic test results, urinalysis, aerobic urine culture, endocrine test results, histopathology, chest and abdominal radiographs, abdominal ultrasonographic imaging findings, treatment, outcome, and necropsy results were recorded. Findings are reported from the time of initial examination at MJR-VHUP, and all testing was performed at MJR-VHUP unless otherwise noted. Follow-up information regarding additional DKA episodes at MJR-VHUP was recorded when available.

Clinicopathologic Findings. Findings of clinicopathologic test results were recorded in the majority of dogs included in this study. Serum was subjectively evaluated for lipemia. Total serum phosphorus, potassium, and magnesium concentrations are reported from the time of initial examination and the lowest serum electrolyte concentration during hospitalization (P_{min}, K_{min}, Mg_{min}) was recorded for each dog. Venous pH, lactate concentra-

tion, ionized magnesium concentration, base deficit, and ionized calcium concentration were analyzed at the time of initial examination with a point-of-care analyzer.[a] Aerobic urine culture was performed on urine obtained by cystocentesis.

Endocrine Testing. Hyperadrenocorticism (HAC) and hypothyroidism were diagnosed based on history, clinical signs, and appropriate endocrine testing or histopathology as previously described.[9–11] Adrenal-axis testing performed at the time of a DKA episode was not considered sufficient for a diagnosis of HAC unless additional adrenal-axis testing was performed after adequate glycemic control was achieved.

Histopathology and Imaging. All biopsies, necropsies, and imaging were performed at MJR-VHUP and results were reviewed by a board-certified pathologist or radiologist at the time of hospitalization. Acute pancreatitis was suspected if ultrasonographic findings matched previously described diagnostic criteria.[12,13]

Outcome Variables. Length of time from admission to administration of SC insulin, length of hospitalization, and whether the animal was discharged from the hospital were evaluated.

Data Analysis. Continuous variables were assessed for normality by visual inspection and the Shapiro-Wilks test. Median, minimum, and maximum were used to describe nonparametric variables. Unpaired *t*-test or Wilcoxon rank sum test was used to compare continuous variables among groups, depending on whether data were normally or not normally distributed, respectively. Categorical variables were described with frequencies, proportions, or percentages (95% confidence interval [CI]). The Fisher's exact test or χ^2 test was used to compare categorical variables among groups. The Fisher's exact test was used when the expected value in a table cell was <5. The binomial exact method was used to calculate the 95% CI for the percentages. If the point estimate of the percentage was at the extreme end of possible values (eg, 0% or 100%), one-sided 97.5% CI was reported.

A multiple logistic regression model was used to investigate the independent association of selected clinicopathologic variables (ie, potassium, phosphorus, ionized magnesium, ionized calcium, base deficit, white blood cell count, hematocrit) with the discharge outcome variable. The model initially was developed by univariate logistic regression of each clinicopathologic variable and outcome. Likelihood ratio tests were done to determine the significance of all covariates. Covariates with *P*-values $\leq.20$ from the univariate analysis were used to create a multivariable model. The phosphorus variable was not linear in the logit form and therefore was dichotomized into low or not low and entered into the multivariate logistic regression model in this form. Backward stepwise logistic regression then was performed on this multivariable model. Covariates were sequentially removed based on the *P*-value of the likelihood ratio test (the covariate with the highest *P*-value was removed at each step) until the remaining covariates all had *P*-values of $\leq.05$ for testing the null hypothesis that the effect (slope) of the covariate was 0, resulting in an intermediate model. Covariates that had univariable regression *P*-values $>.20$ were sequentially added to the intermediate model to see if any were significant. The result was the main-effects model. The model was assessed for goodness of fit using the Pearson's χ^2 test.

Multiple linear regression models similarly were developed for the association of the same variables (potassium, phosphorus, ionized magnesium, ionized calcium, base deficit, white blood cell count, hematocrit) with the outcome variables length of time from admission to administration of SC insulin and length of hospitalization. Unfortunately, residual analysis of these models showed heteroscedasticity that could not be corrected with logarithmic transformation of the included variables. Therefore, associations of these variables with these outcomes were only assessed using the univariate linear regression analysis.

For all comparisons, a *P*-value of $<.05$ was considered significant. All statistical analyses were performed using a statistical software package.[b]

Results

The medical records of 297 dogs were evaluated and 127 dogs met the criteria for inclusion in the study. Dogs were excluded from the study if the complete medical record was not available or if urinalysis and venous blood gas analysis were not performed (64 dogs), if venous pH was $\geq$7.35 in dogs with ketonuria (53 dogs), if there was inaccurate medical diagnosis (29 dogs), if there was no evidence of ketonuria or acidosis at the time of initial examination (13 dogs), or if there was a lack of ketonuria in dogs with acidosis (11 dogs).

Signalment and History

The median age of dogs at the time DM was diagnosed was 8 years (range, 4 months to 16 years). The median age of dogs at the time DKA was diagnosed was 8 years (range, 8 months to 16 years). The median time interval between diagnosis of DM and DKA was 11.6 months (range, 0–72 months). Eighty-two (65%, CI 55–73%) of the dogs were diagnosed with DKA at the time of initial diagnosis of DM.

Fifty-two dogs (41%, CI 32–50%) were neutered male dogs, 44 (35%, CI 26–44%) were neutered female dogs, 12 (9%, CI 5–16%) were intact female dogs, and 15 (12%, CI 7–19%) were intact male dogs. Twenty-seven dogs (21%, CI 15–29%) were of mixed breeding, 10 (8%, CI 4–14%) were Miniature Poodles, 10 (8%, CI 4–14%) were Toy Poodles, 8 (6%, CI 3–12%) were Rottweilers, 7 (5%, CI 2–11%) were Yorkshire Terriers, and the rest were of various other less represented pure breeds.

Sixty-six dogs (52%, CI 43–61%) did not receive insulin before referral to the MJR-VHUP. Forty-five of 127 dogs (35%, CI 27–44%) had received insulin therapy for at least 7 days before initial evaluation at the MJR-VHUP. Thirty-eight of the 45 dogs (84%, CI 71–94%) had insulin type, insulin dose, and dosing interval available for review. Twenty-seven (71%, CI 54–85%) received Humulin-N[c] insulin, 7 (18%, CI 8–34%) received Humulin-L[d] insulin, and 4 (11%, CI 3–25%) received Humulin-U[e] insulin. Nineteen (50%, CI 33–67%) received insulin twice per day, 17 (45%, CI 29–62%) received insulin once per day, 1 dog (2.5%, CI 0–14%) received insulin 3 times per day, and 1 dog (2.5%, CI 0–14%) received insulin at longer intervals than every 24 hours. The median insulin dosage was 0.88 units/kg (range, 0.28–2.80 units/kg). Ten of the insulin-treated dogs (26%, CI 13–43%) received a dosage of insulin less than 0.5 units/kg, and 6 dogs (15%, CI 6–31%) received an insulin dosage that was greater than 1.5 units/kg. Sixteen newly diagnosed diabetic dogs had insulin therapy initiated immediately before

Table 1. CBC findings in dogs with diabetic ketoacidosis (DKA).

Variable	No. Tested	Median	Range	Above RR	Normal Value	Below RR	Reference Range (RR)
RBC (10^6/L)	116	6	2–9	3 (3%)	69 (59%)	44 (38%)	5.83–8.87
Hb (g/dL)	113	13	5–21	1 (1%)	52 (46%)	60 (53%)	13.30–20.5
Hct (%)	117	40	15–61	1 (1%)	55 (47%)	61 (52%)	40.3–60.3
MCV (fL)	117	69.0	57–82	8 (7%)	100 (85%)	9 (8%)	62.7–75.5
MCHC(g/dL)	112	33.0	22–50	7 (6%)	68 (61%)	37 (33%)	32.2–36.3
Platelets (10^6/L)	115	377,000	90,000–1,427,000	56 (49%)	58 (50%)	1 (1%)	177,000–398,000
WBC (cells/L)	118	21,350	4,500–64,000	67 (57%)	50 (42%)	1 (1%)	5,300–19,800
Neutrophils (cells/L)	117	18,000	1,700–54,000	77 (66%)	39 (33%)	1 (1%)	3,100–14,400
Band neutrophils (cells/L)	117	270	0–7,500	72 (62%)	45 (38%)	0 (0%)	0
Lymphocytes (cells/L)	117	950	0–5,800	1 (1%)	63 (54%)	53 (45%)	900–5,500
Monocytes (cells/L)	117	1,500	0–12,000	63 (54%)	49 (42%)	5 (4%)	100–1,400
Eosinophils (cells/L)	117	0	0–2,100	1 (1%)	116 (99%)	0 (0%)	0–1,600

referral to MJR-VHUP and were treated for a period of <7 days.

One hundred fourteen dogs (90%, CI 83–94%) had polyuria and polydipsia, 111 (87%, CI 80–93%) had lethargy, 110 (87%, CI 79–92%) had inappetence or anorexia, 106 (83%, CI 76–89%) had vomiting, 69 (54%, CI 45–63%) had weight loss, 27 (21%, CI 14–29%) had diarrhea, 5 (4%) had hematuria or pollakiuria, and 4 (3%) had weight gain.

Physical Examination Findings

Fifty-nine of 118 dogs (50%, CI 41–59%) had subjectively overweight body condition, 31 dogs (26%, CI 18–35%) had normal body condition, and 28 dogs (24%, CI 16–32%) were considered underweight. At the time of initial evaluation, most dogs were moderately dehydrated (61/122, 50%, CI 41–59%) or severely dehydrated (50/122, 41%, CI 32–50%), and a few 11 were well hydrated (9%, CI 4–16%). Sixty-five dogs (65/127, 51%, CI 42–60%) had cranial organomegaly, 46 dogs (36%, CI 28–45%) had abdominal pain, and 39 (30%, CI 23–40%) had cardiac murmurs. Thirty-six dogs (28%, CI 21–37%) had possible neurologic abnormalities, including mental dullness (26 dogs), weakness or conscious proprioceptive deficits (7 dogs), or seizures (3 dogs). Thirty-one dogs (24%, CI 17–33%) had dermatitis or otitis, 29 dogs (23%, CI 16–31%) had alopecia, 25 dogs (20%, CI 13–28%) had dyspnea, coughing, or abnormal lung sounds, and 26 (20%, CI 14–29%) had cataracts.

Clinicopathologic Findings

A CBC was available in the majority of the animals (Table 1). Quantitative platelet counts were performed in 102 dogs, and a platelet estimate was provided in an additional 13 dogs. Forty-five dogs (38%) had subjectively lipemic serum. Severely lipemic blood samples prohibited measuring some of the variables on the CBC[f] and serum biochemistry screen[g] in 6 dogs. Sixty-one (61/117, 52%, CI 43–61%) of the dogs were anemic at the time of evaluation. Most anemic dogs had normochromic-normocytic anemia. Serum phosphorus concentration was not correlated with anemia ($P = .86$). Sixty-seven dogs (67/118, 57%, CI 47–66%) had leukocytosis and 43/67 (64%, CI 52–76%) of these dogs also had an increase in band neutrophils. Leukocytosis was not significantly associated with pancreatitis ($P = .74$) or pneumonia ($P = .86$).

A complete serum biochemistry screen was available for review in 119 of 127 dogs (94%, Table 2). All but 2 dogs were hyperglycemic at the time of initial examination. Two dogs (2%) had normal blood glucose concentrations initially, but had documented persistent hyperglycemia, despite insulin treatment within the first 14 hours of admission.

Median serum phosphorus concentration in 120 dogs was 4.2 mg/dL (range, 0.9–28.5 mg/dL) at initial examination. Initial serum phosphorus concentration was below the reference range in 35/120 dogs (29%, CI 21–38%). Measurements of serum phosphorus concentration were repeated in 64 of the 85 dogs in which serum phosphorus concentration initially was normal or increased. Thirty-one dogs (31/64, 48%, CI 36–61%) had serum phosphorus concentration decrease below the reference range during hospitalization. Overall, 66 (55%, CI 46–64%) dogs (35 dogs initially and 31 additional dogs at a later time during hospitalization) had hypophosphatemia. Median phosphorus concentration in 66 dogs with hypophosphatemia was 2.0 mg/dL (range, 0.8–2.7 mg/dL).

Median serum potassium concentration in 120 dogs was 3.9 mmol/L (range, 2.1–7.0 mmol/L) at initial examination. Initial serum potassium concentration was below the reference range in 54/120 dogs (45%, CI 36–54%). Measurements of serum potassium concentration were repeated in 62 of the 66 dogs in which serum potassium concentration initially was normal or increased. Fifty-six dogs (56/66, 84%, CI 74–92%) had serum potassium concentration decrease below the reference range during hospitalization. Overall, 110 (92%, CI 85–96%) dogs (54 dogs initially and 56 additional dogs at a later time during hospitalization) had hypokalemia. Median potassium concentration in 110 dogs with hypokalemia was 3.1 mmol/L (range, 2.0–3.6 mmol/L).

Median total serum magnesium concentration in 67 dogs was 2.0 mg/dL (range, 0.6–3.9 mg/dL) at initial examination. Initial serum magnesium concentration was below the reference range in 19 dogs (28%, CI 18–

Table 2. Serum chemistry results in dogs with diabetic ketoacidosis (DKA).

Variable	N	Median	Range	Above RR	Normal Value	Below RR	Reference Range (RR)
Glucose (mg/dL)	120	413	71–1,070	118 (98%)	2 (2%)	0 (0%)	65–117
BUN (mg/dL)	119	28	2–231	55 (46%)	59 (50%)	5 (4%)	5–30
Creatinine (mg/dL)	119	1.1	0.3–7.6	22 (18%)	69 (58%)	28 (24%)	0.7–1.8
Phosphorus (mg/dL)	120	4.2	0.9–28.5	35 (29%)	50 (42%)	35 (29%)	2.8–6.1
Total calcium (mg/dL)[a]	119	8.7	4.0–11.4	0 (0%)	17 (14%)	102 (86%)	9.8–11.7
Sodium (mmol/L)	121	139	116–185	17 (14%)	39 (32%)	65 (54%)	140–150
Potassium (mmol/L)	120	4.0	2.1–7	17 (14%)	49 (41%)	54 (45%)	3.9–4.9
Chloride (mmol/L)	119	106	58–155	12 (10%)	37 (31%)	70 (59%)	109–120
Total CO_2 (mmol/L)	117	10	5–23	0 (0%)	19 (16%)	98 (84%)	17–28
Total protein (g/dL)	117	5.9	3.2–10	10 (9%)	74 (63%)	33 (28%)	5.4–7.1
Albumin (g/dL)	118	2.9	1.1–4.7	15 (13%)	73 (62%)	30 (25%)	2.5–3.7
Globulins (g/dL)	116	2.8	1.9–5.5	2 (2%)	94 (81%)	20 (17%)	2.4–4.0
ALT (U/L)	119	174	18–982	68 (57%)	51 (43%)	0 (0%)	16–91
AST (U/L)	100	87.5	18–726	65 (65%)	34 (34%)	1 (1%)	23–65
ALP (U/L)	118	818	86–6,160	114 (97%)	4 (3%)	0 (0%)	20–155
GGT (U/L)	97	20	9–1,704	40 (41%)	57 (59%)	0 (0%)	7–24
Total bilirubin (mg/dL)	119	0.6	0.1–4.6	24 (20%)	88 (74%)	7 (6%)	0.3–0.9
Cholesterol (mg/dL)	118	313	102–1,363	56 (47%)	59 (50%)	3 (3%)	128–317
Calculated osmolarity (mOsm/L)	118	295.9	258.9–379.3	62 (53%)	54 (46%)	2 (2%)	264–292
Anion gap (mmol/L)	111	27	9–62	85 (77%)	26 (23%)	0 (0%)	8–21
Total magnesium (mg/dL)[a]	67	2.0	0.6–3.9	11 (16%)	37 (55%)	19 (28%)	1.6–2.5
Amylase (U/L)	53	1,626	214–19,219	31 (58%)	21 (40%)	1 (2%)	339–1,536
Lipase (U/L)	54	1,396.5	242–6,556	28 (52%)	26 (48%)	0 (0%)	72–1,310

[a] Values for ionized calcium and ionized magnesium concentration are reported in Table 3.

41%). Measurements of serum magnesium concentration were repeated in 29 of 48 dogs in which serum magnesium concentration initially was normal or increased. Twenty-one dogs (21/29, 72%, CI 53–87%) had serum magnesium concentration decrease below the reference range during hospitalization. Overall, 40 (60%, CI 47–72%) dogs (19 dogs initially and 21 additional dogs at a later time during hospitalization) had hypomagnesemia. Median magnesium concentration in 40 dogs with hypomagnesemia was 1.4 mg/dL (range, 0.5–1.5 mg/dL). Initial ionized magnesium concentration was normal in 33/61 dogs (54%, CI 41–67%), abnormally high in 25/61 dogs (41%, CI 29–54%), and low in only 3/61 dogs (5%, CI 1–14%).

Venous blood gas analysis was performed in all dogs (Table 3). Plasma lactate concentration was not correlated with venous pH ($P = .77$).

Most dogs (101/117, 86%, CI 79–92%) had hypersthenuria, 16 (14%, CI 8–21%) had isosthenuria, and no dogs had hyposthenuria. Most dogs (118/122, 97%, CI 92–99%) had urine pH between 5 and 7.5, and 4 dogs (3%, CI 1–8%) had a urine pH >7.5. One hundred twenty-seven dogs (100%, CI 97–100%) had ketonuria, 123 dogs (97%, CI 92–99%) had glucosuria, 107 (107/123, 87%, CI 80–92%) had proteinuria, 100 (100/123, 81%, CI 73–88%) had hemoglobinuria, 54 (54/121, 45%, CI 36–54%) had bilirubinuria, and none of the dogs lacked urobilinogen in their urine. Most dogs (100/107, 93%, CI 91–99%) had ≤5 WBC/high power field (hpf) and 7 dogs (7%, CI 3–13%) had >5 WBC/hpf.

Aerobic urine culture was performed in 106 dogs (83%). Twenty-one dogs (20%, CI 13–29%) had aerobic bacterial growth and 85 dogs (80%, CI 71–87%) had no aerobic bacterial growth on urine culture. *Escherichia coli* was the most common bacteria cultured (8 dogs, 38%, CI 18–61%); it was isolated from 7 dogs as a single agent of infection and from 1 additional dog with a mixed bacterial infection.

Imaging Studies

Thoracic radiographs were performed in 102 dogs. Abnormal thoracic radiographic findings in 70 dogs

Table 3. Venous blood gas results in dogs with diabetic ketoacidosis (DKA).

Variable	No. Tested	Median	Range	Above RR	Normal	Below RR	Reference Range (RR)
Venous pH	127	7.3	6.926–7.346	0 (0 %)	0 (0 %)	127 (100%)	7.35–7.47
iCa^{2+} mmol/L	116	1.1	0.55–1.35	1 (1%)	55 (47%)	60 (52%)	1.13–1.33
iMg^{2+} mmol/L	61	0.4	0.22–0.82	25 (41%)	33 (54%)	3 (5%)	0.25–0.41
HCO_3 (mEq/ml)	127	12.6	3.7–24.7	1 (1%)	8 (6%)	118 (93%)	20–24
Base deficit	127	−14.5	−27.1–1.2	0 (0 %)	5 (4%)	122 (96%)	−4 to +4
Lactate (mmol/L)	107	2.0	0.1–14.3	35 (33%)	69 (64%)	3 (3%)	0.60–2.5

included hepatomegaly (45 dogs), pulmonary alveolar pattern (14 dogs), cardiomegaly (7 dogs), pulmonary interstitial pattern (4 dogs), peritoneal effusion (4 dogs), hypocirculation (4 dogs), pulmonary edema (1 dog), and a pulmonary nodule (1 dog).

Abdominal radiographs were performed in 55 dogs. Findings were similar to those previously reported in dogs with diabetes mellitus[14] and did not definitively identify any coexisting disease not noted with other imaging modalities. Abdominal ultrasonography was performed in 95 dogs. Abnormal ultrasonographic findings in 95 dogs included hyperechoic liver (87 dogs); enlarged, irregular, hypoechoic pancreas with hyperechoic mesentery consistent with a diagnosis of acute pancreatitis (48 dogs); hyperechoic renal cortices (32 dogs); abdominal nodule or mass (17 dogs); and cystic calculi (7 dogs).

Concurrent Conditions

Eighty-seven dogs (69%, CI 60–76%) had a concurrent disorder diagnosed at the time of evaluation for DKA. Thirty-four (27%, CI 19–35%) dogs had >1 concurrent condition at the time of diagnosis of DKA. Presence of concurrent disorders was not different when comparing dogs in which DM was diagnosed at least 1 week before examination for DKA to dogs recently diagnosed with DM.

Acute pancreatitis was diagnosed in 52 dogs (41 %, CI 32–50%) based on clinical signs suggestive of the disease and appropriate ultrasonographic or histopathologic findings. Fifty of 52 dogs with acute pancreatitis had vomiting, 50 dogs had lethargy, 49 had anorexia, and 13 had diarrhea. Ultrasonography was consistent with a diagnosis of acute pancreatitis in 48 dogs and histopathology was diagnostic of acute pancreatitis in 6 dogs. Two dogs had both ultrasonography and histopathology findings that were diagnostic of acute pancreatitis and 4 dogs with a histopathologic diagnosis of acute pancreatitis did not have abdominal ultrasound performed. Dogs with acute pancreatitis were significantly more likely to have abdominal pain ($P = .0026$), required significantly longer hospitalization (median, 7 days versus 6 days, $P = .0090$) and had longer time to SC insulin (median, 96 hours versus 60 hours, $P = .036$) compared with dogs without acute pancreatitis. Body condition, hematocrit, white blood cell count, venous pH, base deficit, anion gap, lipemia, and blood glucose, lactate, sodium, potassium, phosphorus, total magnesium, ionized magnesium, and ionized calcium concentrations were not significantly different between dogs with coexisting acute pancreatitis compared with dogs without acute pancreatitis. The incidence of acute pancreatitis was not different when comparing dogs that had DM for >1 week with dogs that had DM for <1 week ($P = .084$).

Forty-two of the dogs in this study were tested for hyperadrenocorticism. A diagnosis of hyperadrenocorticism was refuted in 23 dogs based on adrenocorticotropin hormone (ACTH) stimulation test results (12 dogs), low-dose dexamethasone suppression (LDDS) test results (5 dogs), or both (6 dogs).

A diagnosis of hyperadrenocorticism was confirmed in 19 (15%, CI 9–22%) dogs. Ten of the 19 dogs were diagnosed with hyperadrenocorticism within 4 months after the time of evaluation for DKA. Eight of these 10 dogs had adrenal-axis testing that was consistent with a diagnosis of hyperadrenocorticism, 4 had ACTH stimulation tests performed, 3 other dogs had both ACTH stimulation and LDDS tests performed, and 1 additional dog had a LDDS test performed. The dog diagnosed by an LDDS test only was tested 4 months after its DKA episode. Two additional dogs were euthanized at the time of the DKA episode and histopathologic evaluation confirmed bilateral adrenal hyperplasia and pituitary microadenoma. The median time to SC insulin was significantly shorter in dogs with HAC compared with animals without HAC (60 hours versus 96 hours, $P = .029$), but the median length of hospitalization was not significantly different between the 2 groups (6 days versus 7 days, $P = .22$).

Nine dogs were diagnosed with hyperadrenocorticism before evaluation for DKA. Five dogs had LDDS tests performed, 4 dogs had ACTH stimulation tests performed, and 2 dogs had both an ACTH stimulation test and an LDDS test performed. Eight dogs were being treated medically for hyperadrenocorticism at the time of their DKA episode. Seven of these dogs received mitotane and 1 dog was treated with selegiline. In the 9th dog, mitotane therapy had been discontinued and replaced with oral prednisone due to a hypoadrenocortical crisis.

Thirteen of 127 dogs (10%, CI 5–17%) were receiving oral corticosteroids at the time of evaluation for DKA or had received a corticosteroid injection within 2 weeks of evaluation for DKA. Dose range, type of corticosteroid, and indication for its use varied among these 13 dogs.

Bacterial pneumonia was suspected in 8 dogs (6%, CI 3–12%) in this study based on clinical findings and radiographic evidence of alveolar lung disease. Tracheal wash fluid cytology and aerobic culture was positive for growth in 7/8 dogs. One additional dog was treated for presumptive aspiration pneumonia based on radiographic findings and presence of an inflammatory leukogram.

Other concurrent disorders included uterine disease (5 dogs), severe dermatitis (4 dogs), histopathologically confirmed neoplasia (2 dogs), and *Trichuris vulpis* infestation (1 dog). None of the dogs included in the study had a confirmed diagnosis of hypothyroidism.

Postmortem Examination

Gross and histological postmortem examinations were performed in 8 of 38 dogs (21%) that died or were euthanized. Histopathology was consistent with acute pancreatitis (6 dogs), pituitary-dependent hyperadrenocorticism (2 dogs), perforating duodenal ulcer and focal peritonitis (1 dog), renal tubular necrosis (1 dog), and pyelonephritis (1 dog).

Treatment

One hundred twenty-one dogs (95%) received IV fluids as part of their medical treatment. Of the 6 dogs

Table 4. Outcome variables.

Variable	No. of Dogs	Discharge from Hospital: 89 Dogs Discharged (Median)	Discharge from Hospital: 38 Dogs Not Discharged (Median)	Discharge from Hospital: P^*	Time to SC Insulin: r^{**}	Time to SC Insulin: P^*	Length of Hospitalization: r^{**}	Length of Hospitalization: P^*
Glucose (mg/dL)	127	403	482	.050	.12	.27	.11	.32
Lactate (mmol/L)	107	1.8	2.0	.56	0.06	.59	.01	.93
Na (mmol/L)	121	139	135	.17	.10	.38	.01	.93
K (mmol/L)	120	3.9	3.9	.64	−.30	.0056	−.16	.14
K_{min} (mmol/L)	113	2.8	2.9	.60	−.34	.0017	−.14	.065
P (mmol/L)	120	4.1	4.4	.26	−.31	.0043	−.29	.0055
P_{min} (mmol/L)	95	2.0	2.0	.99	−.40	<.001	−.23	.057
tMg (mg/dL)	65	2	1.4	.070	−.07	.65	−.29	.038
iMg^{2+} (mmol/L)	61	0.39	0.41	.93	−.004	.97	.13	.38
iCa^{2+} (mmol/L)	116	1.14	1.04	<.001	.10	.40	−.06	.59
tCa (mg/dL)	118	8.95	8.1	<.001	−.25	.020	−.20	0.059
Base deficit	127	−14.1	−17.95	.0066	−.34	.0015	−.30	.0033
Venous pH	127	7.25	7.21	.0058	−.37	<.001	−.29	.0048
Hematocrit (%)	117	42	37.5	.036	.12	.30	.53	.52
WBC ($10^3/\mu L$)	118	21160	24900	.28	.30	.0060	.06	.55
Anion gap (mmol/L)	11	26.5	27	.29	.06	.60	−.07	.53

* P = P value ($P < .05$ considered significant).
** r = Spearman rank correlation coefficient.

that did not receive IV fluids, 3 were not admitted for hospitalization and were transferred to a local veterinarian for continued care, 2 were euthanized within 1 hour of admission, and 1 was adequately hydrated. Eighty-one of the 121 dogs (67%) given IV fluids therapy received Normosol-R[h], 17 (14%) each received 0.9% sodium chloride or Plasmalyte–R[i], and 6 (5%) received 0.45% sodium chloride. Ninety-six (79%) dogs received continuous IV potassium supplementation, 55 (45%) received continuous IV phosphorus supplementation, and 33 (27%) received continuous IV magnesium supplementation. Forty-one dogs (34%) received continuous IV sodium bicarbonate therapy. Dogs that received IV sodium bicarbonate supplementation had a significantly lower venous pH compared with dogs that did not receive IV sodium bicarbonate therapy ($P < .001$). Ninety-nine dogs (82%) were treated IV with antimicrobials. Eighteen dogs (15%) were given with total parenteral nutrition (TPN) for a median of 3 days (range 1–8 days).

Most of the dogs in the study (111/121, 92 %) received an IV constant-rate infusion (CRI) of regular (Humulin-R[j]) insulin for treatment of hyperglycemia. Median duration of insulin CRI was 54 hours (range, 1–252 hours). Twenty-two of 111 dogs (20%) treated with IV insulin CRI also received IM or SC regular insulin before switching to treatment with SC intermediate-acting insulin. Six additional dogs were treated with IM or SC regular insulin only before switching to treatment with SC intermediate-acting insulin. Eighty-three of 121 treated dogs (69%) survived to receive treatment with intermediate-acting SC insulin.

Outcome

Median time from initial evaluation to SC administration of intermediate-acting insulin was 79 hours (range, 0–432 hours). The time from initial evaluation to administration of SC intermediate-acting insulin was significantly inversely correlated with initial serum phosphorus concentration, P_{min}, initial serum potassium concentration, K_{min}, and venous pH, and directly correlated to base deficit and leukocytosis (Table 4). Time from initial evaluation to administration of SC intermediate-acting insulin also was increased in dogs that received IV supplementation of potassium ($P < .001$), phosphorus ($P < .001$), magnesium ($P = .0045$), or sodium bicarbonate ($P = .0099$).

Median length of hospitalization was 144 hours (range, 0–552 hours). Length of hospitalization was significantly inversely correlated with initial serum phosphorus concentration, total magnesium concentration, and venous pH, and directly correlated to the base deficit (Table 4). Length of hospitalization also was increased in dogs that received IV supplementation of potassium ($P = .018$), phosphorus ($P < .001$), magnesium ($P < .001$), or sodium bicarbonate ($P = .0015$).

Eighty-nine dogs (89/127, 70%) survived and were discharged from the hospital. Median duration of hospitalization was 6 days (range, 1–23 days). Thirty-two dogs (25%) were euthanized after a median hospitalization time of 19 hours (range, 1–156 hours). Six animals (5%) died during hospitalization, with a median hospitalization time of 96 hours (range, 24–252 hours). The median ionized calcium concentration, total calcium concentration, hematocrit, and venous pH were significantly higher and the median initial base deficit smaller in dogs that survived compared with dogs that did not survive (Table 4). Dogs that received IV sodium bicarbonate therapy also were significantly less likely to be discharged from the hospital ($P = .0070$). Survival was not associated with

supplementation of phosphorus ($P = .69$), magnesium ($P = .26$), or potassium ($P = .22$).

Outcome also was not different when comparing dogs in which DM was diagnosed at least 1 week before examination with dogs in which DM was diagnosed within a week of examination for DKA. Outcome was not correlated to sex, age, hydration status, or use of TPN. Outcome was not associated with presence of acute pancreatitis or urinary tract infection. However, dogs with HAC were significantly less likely to be discharged from the hospital ($P = .029$) and significantly more likely to be euthanized ($P = .029$) compared with dogs that were not diagnosed with HAC. Acute pancreatitis was not diagnosed more commonly in dogs that had HAC compared with dogs that did not have HAC. Venous pH also was not significantly different between dogs with HAC and dogs without HAC. After multivariate analysis was performed, base deficit was the only variable significantly associated with outcome ($P = .021$). For each unit increase in the base deficit, there was a 9% greater likelihood of discharge from the hospital (CI 1–19%).

Fifty-four dogs (60%) had follow-up information available for review. Median follow-up time was 3.5 months (range, 0.25–75 months). Nine animals had >1 DKA episode. One of these dogs presented 5 years after the initial DKA episode for evaluation of a jejunal mass and a second episode of DKA. Median time between first and second DKA episodes in the remaining 8 dogs with repeated DKA episodes was 5.5 days (range, 1–60 days). Four of the 8 dogs (50%) were euthanized at the time of the second DKA episode. Two dogs had 3 DKA episodes that occurred within 1 month of the initial DKA episode.

Discussion

Sixty-five percent of dogs with DKA were newly diagnosed diabetics. Children with newly diagnosed type I DM also are at increased risk for DKA.[15,16] Increased incidence of DKA in newly diagnosed diabetic children is linked to young age (<4 years of age), absence of an immediate relative who is diabetic, inadequate health insurance, and use of certain drugs such as glucocorticoids and some antipsychotics.[15–17] Some of these risks may apply to dogs, in that owners of newly diagnosed diabetic dogs fail to recognize clinical signs of poor diabetic regulation or may wish to delay veterinary care due to the associated expense.

Hypokalemia and hypophosphatemia were common in dogs with DKA. Potassium and phosphate shift from the intracellular space to the extracellular space as a result of hyperglycemia, acidosis, and hypoinsulinemia.[2] Osmotic diuresis or fluid therapy cause extracellular potassium and phosphate depletion, leading to whole-body depletion of these electrolytes.[2] Hypokalemia and hypophosphatemia may be exacerbated by anorexia and vomiting. Hypokalemia, hypophosphatemia, and IV supplementation with potassium or phosphorus were associated with increased time from initial evaluation to administration of SC insulin and with prolonged hospitalization. However, potassium and phosphorus depletion were not associated with survival. We conclude that, although hypokalemia and hypophosphatemia contribute to morbidity, they do not increase mortality, most likely because they are monitored carefully and treated as needed.

Although many dogs had decreased total magnesium concentration, ionized magnesium concentration was normal or high in most DKA dogs. Ionized magnesium concentration was not correlated to time from initial evaluation until administration of SC insulin, length of hospitalization, or survival. However, IV magnesium supplementation was associated with increased time from initial evaluation until administration of SC insulin. This finding may have been due to the fact that normal values for ionized magnesium concentration were not established until recently in our institution,[18] and IV magnesium supplementation may have relied on clinical rather than biochemical observations. Ionized magnesium depletion appears to be uncommon in dogs with DKA and is not associated with outcome.

Concurrent disorders were diagnosed in almost 70% of dogs with DKA, and approximately 33% of these dogs had >1 concurrent condition at the time of diagnosis of DKA. The most common concurrent disorder was acute pancreatitis. Although dogs with acute pancreatitis required significantly longer hospitalization and time to initiation of SC insulin therapy compared with dogs that did not have acute pancreatitis, presence of acute pancreatitis or other concurrent disease was not associated with survival. In humans, patients with coexisting pancreatitis have lower mean pH, higher anion gap, and higher serum-glucose concentration compared with patients without coexisting pancreatitis. Similar findings were not identified in the dogs in this study. Concurrent disease is a common precipitating factor for DKA in humans[2,16,19] and is associated with increased mortality of humans with DKA.[19]

Coexisting HAC was confirmed in 15% of the dogs in this study. Dogs in which adrenal-axis testing was performed during the DKA episode were not considered positive for HAC unless additional follow-up adrenal-axis testing was performed after adequate glycemic control was achieved. Dogs with coexisting HAC were significantly less likely to be discharged from the hospital and significantly more likely to be euthanized compared with other dogs. However, dogs with HAC did not have more acute pancreatitis or lower venous pH compared with other dogs. Insulin resistance, thromboembolic disease, and infections are all common in dogs with HAC and may have contributed to the poor outcome of dogs with HAC. It is also possible that diagnosis of 2 endocrinopathies requiring intense long-term treatment influenced the decision for euthanasia in dogs with HAC.

Bacterial urinary tract infection was confirmed in 20% of dogs and pneumonia was diagnosed in 6% of

dogs in this study. Infection is the most common concurrent disorder in humans with DKA.[19,20]

Several dogs received antimicrobials before examination and treatment may have altered results of bacterial cultures. Therefore, infection may be more common in dogs with DKA than is apparent from this study. Leukocytosis was associated with increased time to SC insulin administration but not with survival. Whereas leukocytosis typically is an indication of inflammation or infection, a study of children with DKA failed to find an association between bacterial infection and leukocytosis.[21] Furthermore, the presence of leukocytosis was significantly correlated to pH and bicarbonate concentration, leading to the conclusion that leukocytosis most likely reflects the severity of DKA rather than infection.[21]

Forty-five dogs received insulin for at least 7 days before examination for DKA. Many of these 45 dogs were treated with insulin inadequately either by administering the insulin only once a day (17 dogs) or by administering a dosage <0.5 U/kg (10 dogs). It is possible that inappropriate frequency of insulin administration or insulin dosage may have contributed to development of DKA in these dogs. Inadequate insulin therapy is associated with increased risk of DKA in humans with previously diagnosed DM.[15]

Dogs in this study were less likely to be discharged from the hospital if they were treated with IV sodium bicarbonate. Dogs treated with bicarbonate also had significantly lower venous pH compared with dogs that did not receive bicarbonate ($P < .001$). Profound acidosis likely prompted clinicians to administer sodium bicarbonate to dogs that had a poor prognosis before treatment. Prospective studies are needed to ascertain the value of alkali therapy in dogs with severe DKA.

Severity of acidosis was the only variable that was significantly correlated to all 3 outcome parameters, including time until SC insulin therapy, length of hospitalization, and survival. Additionally, multivariate analysis found that base deficit was the only variable significantly associated with outcome. For each unit increase in the base deficit, there was a 9% greater likelihood of discharge from the hospital. Low venous pH (<7.0) has been identified as an important predictor of mortality in humans with DKA.[19] Degree of acidosis is likely an important predictor of outcome because it reflects the severity of vital clinical parameters, such as hydration status and electrolyte abnormalities.

We analyzed variables associated with outcome using logistic regression with discharged or not discharged as the outcome variable. Survival analysis would have been a more rigorous evaluation of outcome that would incorporate time to discharge as well as discharged or not. We chose the less rigorous approach to answer the question, ''Will the animal be discharged or not?''

In conclusion, most dogs with DKA are newly diagnosed diabetics, and it appears that many of the dogs previously treated with insulin are treated inadequately. Hypokalemia and hypophosphatemia are common in dogs with DKA and contribute to increased morbidity but not to increased mortality when they are recognized and appropriately treated. Decreased ionized magnesium concentration is uncommon in dogs with DKA and is not associated with outcome. Severity of acidosis is associated with outcome. Concurrent disorders are observed often in dogs with DKA, and acute pancreatitis is noted most frequently. Although acute pancreatitis does prolong hospitalization, it is not associated with survival. Dogs with coexisting HAC were significantly less likely to be discharged from the hospital compared with dogs that were not diagnosed with HAC. Seventy percent of dogs with DKA survive and are discharged from the hospital after a median hospitalization time of 6 days.

Footnotes

[a] Stat Profile, NOVA Biomedical Corporation, Waltham, MA
[b] Intercooled Stata 8.0 for Windows, Stata Corporation, College Station, TX
[c] Humulin-N, Eli Lilly and Co, Indianapolis, IN
[d] Humulin-L, Eli Lilly and Co, Indianapolis, IN
[e] Humulin-U, Eli Lilly and Co, Indianapolis, IN
[f] Hematology analyzer, Celldyne 3500, Abbot Laboratories, Abbot Park, IL
[g] Chemistry analyzer, Kodak Ektachem 250, Eastman Kodak Co, Rochester, NY
[h] Normosol-R, Abbott Laboratories, Abbott Park, IL
[i] Plasmalyte-R, Baxter Healthcare Corporation, Deerfield, IL
[j] Humulin-R, Eli Lilly and Co, Indianapolis, IN

References

1. Bruyette DS. Diabetic ketoacidosis. Semin Vet Med Surg (Small Anim) 1997;12(4):239–247.

2. Chiasson JL, Aris-Jilwan N, Belanger R, et al. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Can Med Assoc J 2003;168(7):859–866.

3. Diehl KJ, Wheeler SL. Pathogenesis and management of diabetic ketoacidosis. In: Kirk RW, Bonagura JD, eds. Kirk's Current Veterinary Therapy XI, Small Animal Practice. Philadelphia: WB Saunders; 1992:359–363.

4. Feldman EC, Nelson RW. Diabetic ketoacidosis. In: Feldman EC, Nelson RW, eds. Canine and Feline Endocrinology and Reproduction, 2nd ed. Philadelphia: WB Saunders; 1996:392–421.

5. Kerl ME. Diabetic ketoacidosis: pathophysiology and clinical and laboratory presentation. Compend Contin Educ Pract Vet 2001;23(3):220–226.

6. Laffel L. Ketone bodies: A review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes Metab Res Rev 1999;15(6):412–426.

7. Nelson RW. Diabetes Mellitus. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine. 5th ed. Philadelphia: WB Saunders; 2000:1438–1460.

8. Parsons SE, Drobatz KJ, Lamb SV, et al. Endogenous serum insulin concentration in dogs with diabetic ketoacidosis. J Vet Emer Crit 2002;12(3):147–152.

9. Feldman EC. Hyperadrenocorticism. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine, 5th ed. Philadelphia: WB Saunders; 2000:1460–1488.

10. Scott-Moncrieff JC, Guptill-Yoran L. Hypothyroidism. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary

Internal Medicine, 5th ed. Philadelphia: WB Saunders; 2000:1419–1429.

11. Hess RS, Kass PH, Van Winkle TJ. Association between diabetes mellitus, hypothyroidism or hyperadrenocorticism, and atherosclerosis in dogs. J Vet Intern Med 2003;17(4):489–494.

12. Saunders HM. Ultrasonography of the pancreas. Probl Vet Med 1991;3:583–603.

13. Hess RS, Kass PH, Shofer F, et al. Evaluation of risk factors for fatal acute pancreatitis in dogs. J Am Vet Med Assoc 1999;214:46–51.

14. Hess RS, Saunders MH, Van Winkle TJ, et al. Concurrent disorders in dogs with diabetes mellitus: 221 cases (1993–98). J Am Vet Med Assoc 2000;217(8):1166–1173.

15. Dunger DB, Sperling MA, Acerini CL, et al. European Society of Paediatric Endocrinology consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child 2004;89(2):188–194.

16. Rewers A, Chase HP, Mackenzie T, et al. Predictors of acute complications in children with type 1 diabetes. J Am Med Assoc 2002;287(19):2511–2518.

17. Mallare JT, Cordice CC, Ryan BA, et al. Identifying risk factors for the development of diabetic ketoacidosis in new onset type 1 diabetes mellitus. Clin Pediatr (Phila) 2003;42(7):591–597.

18. Fincham SC, Drobatz KJ, Gillespie TN, et al. Evaluation of plasma-ionized magnesium concentration in 122 dogs with diabetes mellitus: a retrospective study. J Vet Intern Med 2004;18(5):612–617.

19. Efstathiou SP, Tsiakou AG, Tsioulos DI, et al. A mortality prediction model in diabetic ketoacidosis. Clin Endocrinol 2002; 57:595–601.

20. Lebovitz HE. Diabetic ketoacidosis. Lancet 1995;345:767–772.

21. Flood RG, Chiang VW. Rate and prediction of infection in children with diabetic ketoacidosis. Am J Emerg Med 2001;19(4): 270–273.