Diabetes ketoacidosis and diabetes ketosis in 54 dogs: a retrospective study

Diabetes ketoacidose en diabetes ketose bij 54 honden: een retrospectieve studie

V. De Causmaecker, S. Daminet, D. Paepe

Department of Small Animal Medicine and Clinical Biology
Faculty of Veterinary Medicine, Ghent University
Salisburylaan 133, B-9820 Merelbeke, Belgium

dominiquepaepe@ugent.be

ABSTRACT

Diabetes ketoacidosis (DKA) and diabetes ketosis (DK) are severe complications of diabetes mellitus (DM). A retrospective study on 54 dogs with diabetes keto(acido)sis (DK(A)) was performed. The patients were mostly middle-aged to old female intact dogs with a history of polyuria/ polydipsia, lethargy, anorexia, vomiting, weight loss, diarrhea, hematuria, pollakisuria or shock. In 57.4% of the dogs, a previous diagnosis of DM was not established. Diabetes keto(acido)sis was frequently associated with a concurrent disease such as pancreatitis (22.2%), hypercortisolism (7.4%), neoplasia (24%), infections (24%), renal failure (13%) or heart failure (7.4%). To evaluate the patient and to search for a concurrent disease, a complete blood count and serum biochemistry, blood gas analysis, urinalysis, urine culture, thoracic radiographs and/or abdominal ultrasound were performed. The treatment of the DK(A) depended on the concurrent disease, the blood values and the symptoms of the dog. The prognosis was poor, since 48% of the dogs died or were euthanized within 2 weeks after diagnosis. Relapse occurred in 5 dogs (9.3%), mostly within 6 months.

SAMENVATTING

Diabetes ketoacidose (DKA) en diabetes ketose (DK) zijn ernstige complicaties van diabetes mellitus (DM). Een retrospectieve studie van 54 honden met DK(A) werd uitgevoerd. De meeste honden waren vrouwelijke, intacte honden van middelbare tot hoge leeftijd met een anamnese van polyurie/polydipsie, lethargie, anorexie, braken, vermageren, diarree, hematurie, pollakisurie of shock. Bij 57,4% van de honden werd geen voorafgaande diagnose van DM gesteld. Diabetes keto(acido)sis was frequent geassocieerd met een bijkomende ziekte, zoals pancreatitis (22,2%), hypercortisolisme (7,4%), neoplasie (24%), infectie (24%), nier- (13%) of hartfalen (7,4%). Om de patiënt goed te evalueren en om op zoek te kunnen gaan naar een ermee gepaard gaande ziekte werden een volledig bloedonderzoek (hematologie en serumbiochemie), een bloedgasanalyse, een urineonderzoek, een urinecultuur en röntgenopnamen van de thorax en/of een echografie van het abdomen uitgevoerd. De behandeling van DK(A) was afhankelijk van de ermee gepaard gaande ziekte, de bloedwaarden en de symptomen van de hond. De prognose was gereserveerd aangezien 48% van de honden gestorven of geëuthanaseerd werd binnen de 2 weken na de diagnose. Vijf honden (9,3%) hervielen, meestal binnen de 6 maanden na de diagnose.

INTRODUCTION

Diabetes keto(acido)sis (DK(A)) is one of the most severe endocrine emergencies in companion animals. Diabetes ketoacidosis (DKA) is characterized by hyperglycemia, glucosuria, ketonuria and acidemia, and diabetes ketosis (DK) is characterized by hyperglycemia, glucosuria and ketonuria (Greco, 1997; Kerl, 2001a; Hume *et al.*, 2006). In DK(A), blood glucose concentration increases and intracellular glucose concentration decreases because of lower insulin activity. This can be due to an absolute or relative lack of insulin production in the pancreas, a decreased activity of insulin receptors on the cells, or a combination of both (Hume *et al.*, 2006). In physiologic circumstances, insulin also limits lipolysis. During lipolysis, free fatty acids are released into the circulation and are converted into triglycerides and a low concentration of ketones in the liver. Some of the ketones are used as an energy source and the rest of them are buffered in the blood and excreted by the urinary and respiratory systems. In DK(A), the inhibiting function of insulin on lipolysis ceases, and a surplus of ketones is produced. Because of this, the buffering capacity of the blood is exceeded and systemic acidemia develops in patients with DKA (Chastain, 1981; Greco, 1997; Kerl, 2001a). Furthermore, glucagon, which stimulates ketogenesis, the stress hormones (cortisol and epinephrine), as well as growth hormone which support lipolysis and insulin resistance, all play a role in the pathogenesis of DK(A).

Diabetes keto(acido)sis often occurs together with a concurrent disease such as acute pancreatitis, urinary

tract infection, hypercortisolism (HC) or, less frequently, in combination with pneumonia, pyometra, dermatitis, neoplasia, kidney failure or heart failure (Chastain, 1981; Macintire, 1995; Nicols and Crenshaw, 1995; Kerl, 2001a; Hume *et al.*, 2006).

Dogs presented with DK(A) usually show one or more of the following symptoms: polyuria/ polydipsia (pu/pd), lethargy, anorexia, vomiting, weight loss, diarrhea, hematuria, pollakisuria or shock (Chastain, 1981; Macintire 1993; Greco, 1997; Kerl, 2001a; Hume *et al.*, 2006). Although DK(A) is a complication of diabetes mellitus (DM), most dogs presented with DK(A) had not previously been diagnosed with DM (Hume *et al.*, 2006). Indeed, Hume *et al.* (2006) showed that 82 of 127 dogs with DK(A) (65%) had had no prior signs of DM at presentation.

To evaluate the general condition and to search for underlying causes, a complete blood count (CBC), serum biochemistry, blood gas analysis, urinalysis, urine culture, thoracic radiographs and abdominal ultrasound (US) are advised as initial diagnostic tests in patients with DK(A). Diagnostic testing for HC is best delayed until or repeated after resolution of the DK(A) crisis in order to minimize the influence of the disease on the screening tests for HC (Nicols and Crenshaw, 1995; Kerl, 2001a; Feldman and Nelson, 2004a; Feldman and Nelson, 2004b; Hume *et al.*, 2006).

The treatment of DK(A) includes IV infusion (preferably 0.9% NaCl), often supplemented with potassium (K) and sometimes phosphorus (P), antibiotics, short-acting insulin IV (constant rate infusion), IM or SC, and treatment of the concurrent disease (Chastain, 1981; Macintire, 1995; Nicols and Crenshaw, 1995; Greco, 1997; Kerl, 2001a; Hume *et al.*, 2006). The administration of bicarbonate for the treatment of acidosis is only necessary if the pH < 7.10, because acidosis is usually corrected by the administration of IV fluids and insulin (Chastain, 1981; Nicols and Crenshaw 1995; Greco, 1997; Kerl, 2001a).

The prognosis of DK(A) depends to a very great extent on the underlying cause. In any case, the prognosis is generally considered poor, with mortality rates of 29-30% being described in other studies (Macintire, 1993; Hume *et al.*, 2006). The death of the dogs is usually due to a severe underlying disease, to severe metabolic acidosis or to complications.

The aim of this retrospective study was to review the medical records and to describe the signalment, the symptoms, the physical and clinicopathological abnormalities, the therapy used and the outcome of the dogs presented with DK(A), and to compare these results with other retrospective studies on DK(A).

MATERIALS AND METHODS

Criteria for selection of cases

A computer search for all dogs admitted to the Department of Small Animal Medicine and Clinical Biology of the Ghent University Faculty of Veterinary Medicine between June 2001 and April 2008 was performed. The medical records were reviewed in detail by one of the authors. Patients were included if they had been diagnosed with DKA or DK. Diagnosis of DKA was made based upon the presence of: hyperglycemia, glucosuria, ketonuria and blood acidosis (pH < 7.35). For diabetes ketosis, the same criteria needed to be present, except for the acidosis. Patients were excluded if the medical record was incomplete.

Procedures

Medical records were reviewed for the following: signalment, clinical signs, medical history, previous administration of insulin, concurrent disease, CBC, electrolytes, serum biochemistry, coagulation profile, urinalysis with calculation of urinary protein to creatinine ratio (UPC), urine culture, medical imaging, endocrine testing (for hypothyroidism or HC), treatment and outcome.

The concurrent diseases were divided into 3 groups: diseases that were thought to be the underlying cause for DK(A), diseases that were a complication of DK(A) and diseases of which the relationship with DK(A) was not clear.

Diseases that could cause DK(A) included all diseases that cause either a deregulation of DM or an insulin resistance, such as infections or inflammations (pyometra, urinary tract infection, dermatitis, pneumonia, gingivitis, abscesses, pancreatitis, hepatitis, splenitis), endocrine disorders (HC, hypothyroidism, diestrus, cystic ovaria), administration of glucocorticoids, obesity, neoplasia, renal failure, heart failure and recent anesthesia.

Diseases or conditions that were suspected to be a complication of DK(A) included disseminated intravascular coagulation (DIC), pleural effusion, enlarged liver, cataract, paraparesis and polyneuropathy.

The outcomes were evaluated both on a short-term basis (within 2 weeks after admission) and on a long-term basis (after 2 weeks post-admission).

Statistical analysis

The data was interpreted by means of descriptive statistics. The results were expressed as mean ± SD with range. Because different laboratories with different reference ranges were used for the clinicopathologic tests, only the percentages of dogs having values above, within or beneath the reference range were provided.

RESULTS

Detection of DKA and DK cases

Fifty-four dogs were included in this study. Blood pH was measured in 31 of those 54 dogs, presence of ketones in the urine was measured in 49 dogs, and both

Table 1. Prevalence of dog breeds diagnosed with diabetes keto(acido)sis (DK(A)).

Breed	Total
Labrador Retriever, Mixed Breed	9
Yorkshire Terrier	5
Maltese Dog, Rottweiler	4
Tibetan Terrier, Bichon Frisé, Belgian Shepherd Malinois, English Cocker Spaniel, Pincher	2 each
West Highland White Terrier, Cavalier King Charles Spaniel, Clumber Spaniel, Chihuahua, Shetland Sheepdog, Alaskan Malamute, Doberman, Miniature Poodle, Samoyed, Belgian Sheepdog, Siberian Husky, Border Collie, Polski Owczarek Nizinny	1 each

were measured in 31 dogs. Dogs for which pH was not determined were included as DK. This resulted in a diagnosis of DKA in 21 dogs and of DK in 33 dogs.

Signalment

The mean age of the dogs at the time DK(A) was diagnosed was 9.2 ± 2.3 years (range, 5 to 15 years). Twelve dogs (22.2%) were male intact dogs, 7 (13%) were male neutered dogs, 23 (42.6%) were female intact dogs and 12 (22.2%) were female spayed dogs.

The breed distribution is shown in Table 1.

History and clinical signs

Thirty-one dogs (57.4%) had not previously been diagnosed with DM at the time of diagnosis of DK(A). Twenty-three dogs (42.6%) had previously been diagnosed with DM and 17 (73.9%) of them had already been treated with insulin (Caninsulin®; 9 dogs 1x/day, 7 dogs 2x/day, and in 1 dog the frequency of prior insulin administration was not noted in the file). Nine of the treated dogs had had problems with their regulation, for which reason the insulin dosage had often been changed in an effort to find the correct dosage. In two of the female dogs treated, insulin had recently been discontinued by the veterinarian after the dogs were spayed. Six dogs (26%) had not yet been treated, either for practical reasons (aggressive dog, owners could not give insulin at the same time every day) or because the veterinarian had not yet started treatment. The mean age of the dogs at the time DM was diagnosed was 8.3 ± 2.0 years (range, 4 to 12 years). The mean time interval between the diagnosis of DM and DK(A) was 11.8 ± 14.2 months (range, 1 week to 4 years).

Forty-three (79.6%) dogs had pu/pd, 39 (72.2%) had lethargy, 41 (75.9%) had anorexia, 36 (66.7%) were vomiting, 30 dogs (55.6%) showed weight loss and 15 dogs (27.8%) had diarrhea. Other less frequent owner complaints were the presence of a distended abdomen (n= 8; 14.8%), weakness (n= 5; 9.3%), melena (n= 3; 5.6%), fecaloid vomiting (n= 2; 3.7%) and nasal crusts (n= 3; 5.6%), as well as oliguria, coughing, swallowing problems, polyphagia, weight gain, constipation or hematuria, each in 1 dog (1.9%).

Physical examination findings

Fourteen dogs (26%) had an overweight body condition (body condition score > 3/5), 10 dogs (18.5%) showed shock symptoms (pale mucosae, tachycardia, weak pulse), 8 dogs (14.8%) had dyspnea, 4 (7.4%) had tachypnea, 4 (7.4%) had halitosis and 3 dogs (5.6%) showed ataxia. Blindness, fever, hard stools and a thin skin were each observed in 2 dogs (3.7%).

Clinicopathologic findings

Depending on the presentation of the dog and the suspicion of underlying causes, specific parameters in the CBC, biochemistry, coagulation and electrolytes were measured in a number of animals at the time of initial examination. The number of patients tested for each parameter and the results are described in Table 2. In some dogs, only the blood urea nitrogen (BUN) or the serum creatinine was elevated (Table 2), though in 30 of 54 dogs (55.6%), both BUN and creatinine were elevated.

Urinalysis was performed in most dogs, the results of which are presented in Table 3. Urine specific gravity (SG) was not evaluated because the SG depended on previous infusion therapy and was influenced by dilution due to glucosuria. In all dogs with proteinuria based on a urine dipstick, the UPC was measured and found to be increased in 27 of 31 dogs (87.1%). The mean UPC was 4.06 ± 4.1 (range, 1.01 – 21.3).

In 30 dogs (55.6%), a urine culture was performed. The culture was positive for *Escherichia coli (E. coli)* in 3 (10%) of these dogs, and negative in 26 (86.7%) dogs. One dog (3.3%) had a negative urine culture at presentation, but had a positive culture for *E.Coli* on a second sample after 1 week of hospitalization.

Medical imaging

An abdominal ultrasound was performed in 43 dogs (79.6%) and showed abnormalities in 28 dogs (51.9%). These abnormalities included hepatomegaly (n=19), signs of pancreatitis (a hypoechoic pancreas with hyperechoic fat surrounding it)

Table 2. Results of complete blood count, biochemistry, coagulation and electrolytes in dogs with DK(A) + the percentages of normal, elevated and decreased results.

	Number of dogs tested	Normal (% of the dogs tested)	Elevated (% of the dogs tested)	Decreased (% of the dogs tested)
pH	n= 31	10 (32.3%)	0	21 (67.7%)
HCT[a]	n= 54	23 (42.6%)	1 (1.9%)	30 (55.6%)
White blood cell count	n= 54	20 (37%)	30 (55.6%)	4 (7.4%)
Thrombocytes	n= 49	22 (44.9%)	25 (51%)	2 (4%)
Glucose	n= 54	0	54 (100%)	
Triglycerides	n= 13	2 (15.4%)	11 (84.6%)	
Cholesterol	n= 15	4 (26.6%)	11 (73.3%)	
Albumin	n= 40	28 (70%)	3 (7.5%)	9 (22.5%)
Proteins	n= 52	39 (75%)	5 (9.6%)	8 (15.4%)
Potassium	n= 51	32 (62.7%)	9 (17.6%)	10 (19.6%)
Phosphorus	n= 15	6 (40%)	7 (46.7%)	2 (13.3%)
Chloride	n= 42	31 (73.8%)	1 (2.4%)	10 (23.8%)
Sodium	n= 51	17 (33.3%)	1 (2%)	33 (64.8%)
Calcium	n= 24	21 (87.5%)	1 (4.2%)	2 (8.3%)
Magnesium	n= 1	1 (100%)	0	0
Elevated BUN[b] **with normal creatinine**	n= 52		2 (3.8%)	
Elevated creatinine with normal BUN	n= 53		4 (7.5%)	
Coagulation profile:				
PT[c]	n= 19	14 (73.7%)	2 (10.5%)	3 (15.8%)
APTT[d]	n= 19	13 (68.4%)	4 (21%)	2 (10.5%)
Fibrinogen	n= 18	10 (55.6%)	8 (44.4%)	0
D-dimers	n= 14	3 (21.4%)	11 (78.6%)	0
Liver values:				
AST[e]	n= 42	20 (47.6%)	mild[i]: 16 (38%) moderate: 6 (14.3%) severe: 0	
ALT[f]	n= 42	23 (54.8%)	mild: 18 (42.9%) moderate: 1 (2.4%) severe: 0	
δGT[g]	n= 42	22 (52.4%)	mild: 18 (42.9%) moderate: 2 (4.8%) severe: 0	
ALP[h]	n= 40	6 (15%)	mild: 16 (40%) moderate: 9 (22.5%) severe: 9 (22.5%)	
Bile acids	n= 17	8 (47%)	9 (53%)	
Bilirubine	n= 5	5 (100%)	0	
Amylase	n= 4	2 (50%)	1 (25%)	1 (25%)
Lipase	n= 4	2 (50%)	2 (50%)	0

[a] hematocrit
[b] blood urea nitrogen
[c] prothrombin time
[d] activated partial thromboplastin time
[e] aspartate aminotransferase
[f] alanine aminotransferase
[g] δ-glutamyl transpeptidase
[h] alkaline phosphatase
[i] elevated liver values are divided into mild (2 to 3 x elevated), moderate (5 to 10 x elevated) and severe (> 10 x elevated).

(n=11), signs of hepatitis (a hypoechoic liver, sometimes heterogeneous with nodules in it) (n=1), nodules in the spleen (n=5), adrenomegaly (unilateral in 2 dogs, bilateral in 2 dogs), cystic ovaria (n=3), cystitis (thickening of the bladder wall without loss of layering) (n=1), peritonitis (n=1), enlarged kidneys (n=2), nodules in the liver (n=2), foreign body in the stomach (n=1) and hypomotility of the gastrointestinal tract (GI tract) (n=1).

Thoracic radiographs were performed in 33 dogs (61.1%) and abnormalities were found in 6 (11.1%) of them. These abnormalities included a broncho-interstitial pattern of the lungs (n= 2), pleural effusion (n=1), signs of hypovolemia (heart and blood vessels in the lungs were smaller than normal) (n=2), collapse of the caudal lung lobes (n=1), hepatomegaly (n=1) and an osteoma in the pleura (n=1). In 13 dogs (24%), abdominal radiographs were taken and only 2 (3.7%) of them showed abnormalities: one dog had a mass in the abdomen, the origin of which could not be determined, and one dog had a liver mass.

Concurrent diseases

Of the 54 dogs diagnosed with DK(A), 48 (88.9%) of them had a concurrent disease.

Disorders considered to be possible causes for DK(A)

Acute pancreatitis was diagnosed in 12 dogs (22.2%), based upon compatible clinical signs and abdominal ultrasound. Two dogs (3.7%) had chronic pancreatitis (compatible ultrasound images and cytology of the pancreas).

Three dogs (5.6%) were diagnosed with spontaneous hypercortisolism, and 1 dog with iatrogenic hypercortisolism. Table 4 presents which diagnostic tests were used to confirm HC and the time of testing in relation to admission. In another 3 dogs, this diagnosis was suspected although not confirmed, due to euthanasia or natural death. In an additional 4 dogs, the screening tests for HC were negative. Two dogs with spontaneous HC were treated with trilostane (Vetoryl®). Treatment for spontaneous HC was declined by one owner. The iatrogenic HC was due to cortisone treatment for skin disease and the therapy was stopped after DK(A) diagnosis.

Three dogs (5.6%) had a concurrent urinary tract infection with E.Coli, diagnosed with a positive urine culture. In one other dog, the urine culture was initially negative, but a second culture, which was performed after 4 days of urinary catheterization, was positive for E.Coli.

Table 3. Numbers of dogs in which urine parameters were evaluated with a dipstick + the percentages of abnormal results.

	Measured	Abnormal
Glucosuria	n= 49	49 (100%)
Ketonuria	n= 49	46 (93.9%)
Proteinuria	n= 46	31 (67.4%)
Hemoglobinuria	n= 45	25 (55.6%)
Bilirubinuria	n= 45	6 (13.3%)

Three dogs (5.6%) were presented with suspected concurrent pyometra, which was confirmed with abdominal ultrasound.

Thirteen dogs (24%) were strongly suspected of neoplasia at the time of DK(A). Seven of them (13%) had a mammary gland tumor, and five others had a history of mammary gland tumor removal. Two dogs (3.7%) had an abdominal mass. This mass was palpated on abdominal palpation and observed on abdominal radiographs (n= 1) or abdominal ultrasound (n= 1). In 2 dogs a liver mass was detected during abdominal ultrasound. One dog had a tumor of the anal sacs and one dog had a tumor of the pancreas. In none of the patients was histology performed because the owners did not want further investigation (n=4), or the patients had been euthanized (n=6) or had died naturally (n=3).

Based on clinicopathologic abnormalities and abdominal ultrasound findings, acute renal failure (ARF) was diagnosed in 5 dogs (9.3%) and chronic renal failure (CRF) in 2 dogs (3.7%).

Four dogs (7.4%) were presented with a heart murmur on auscultation. In 3 of these dogs, degenerative mitral valve disease was diagnosed on echocardiogram, and in one dog no obvious cause for the heart murmur was found.

Obesity was diagnosed in 14 dogs (26%).

Less frequent concurrent diseases or conditions included dermatitis, pneumonia, presence of cutaneous abscesses and splenitis in 1 dog (1.9%), gingivitis and recent anesthesia in 2 dogs (3.7%), and hypothyroidism and cystic ovaria in 3 dogs (5.6%).

Table 4. Screening tests performed in 4 dogs to diagnose HC and time of testing relative to time of DK(A) diagnosis.

Dog	Tests performed	Time of testing relative to time of DK(A) diagnosis
1	ACTH[a] stimulation test	8 and 17 weeks after DK(A)[b] (iatrogenic hypercortisolism)
2	LDDST[c]	1 and 4 weeks after DK(A)
3	ACTH stimulation test	A few weeks before DK(A)
4	ACTH stimulation test	2, 4 and 8 weeks after DK(A)

[a] adrenocorticotropic hormone
[b] diabetes keto(acido)sis
[c] low-dose dexamethasone suppression test

Disorders suspected to be a complication of DK(A) instead of a cause

Disseminated intravascular coagulation was diagnosed in 3 dogs (5.6%) and pleural effusion, cataract, paraparesis and polyneuropathy were each diagnosed in 1 dog (1.9% each).

Diseases for which the relationship with DK(A) is not clear

This group of diseases consists of the presence of uroliths and nodules in the spleen in 2 dogs (3.7%) and pulmonary fibrosis, skin nodules, lameness, gallbladder mucocoele, epilepsy, gastritis, immune-mediated skin disease and foreign bodies in the gastrointestinal tract, each in 1 dog (1.9% each).

Treatment

The corner stone of treatment consisted of fluid therapy, insulin, nutritional support, electrolyte supplementation and symptomatic treatment such as anti-emetics, antibiotics, and analgesia. The treatment of 47 dogs is summarized in Table 5. Seven dogs did not receive any treatment because they were euthanized on the owners' request before treatment was initiated.

All the dogs received adapted nutritional support during their hospitalization, and all the dogs that went home received a diet adjusted for DM, except for 2 dogs that needed a special diet because of other medical problems.

Outcome

The mean duration of hospitalization for all the dogs (treated or non-treated) was 4.7 ± 4.1 days (range, 0 – 16 days). The mean duration of hospitalization for the dogs in which treatment was initiated was 5.5 ± 3.9 days (range, 0.5-16 days). Eight dogs (14.8%) were euthanized immediately after diagnosis of DK(A) because of financial restrictions or poor prognosis. Another 10 dogs (18.5%) were euthanized within 2 weeks after diagnosis because of financial concerns or because the condition of the dog had either not improved or had worsened. Another 8 dogs (14.8%) were euthanized after the first 2 weeks post-diagnosis, 6 of them because they had a second episode of DK(A) (all within 6 months after diagnosis of DK(A)) and 2 of them for reasons unrelated to DK(A) (1 dog with serious bite wounds after 1.5 years, and 1 dog with a bleeding tumor of the spleen after 2.5 years).

Eight dogs (14.8%) died naturally within 2 weeks after the diagnosis of DK(A). Another 9 dogs (16.7%) died naturally after the first 2 weeks post-diagnosis for

Table 5. Treatments used for diabetes keto(acido)sis + percentages of dogs treated.

Treatment		Total	Percentage of the treated dogs
Fluid therapy:	NaCl 0.9%	45	95.7 %
	Glucose 5%	18	38.3 %
	Haes Steril	6	12.8 %
	Hartmann	6	12.8 %
	Sterofundin	4	8.5 %
Plasma transfusion		9	19.1 %
Potassium supplementation	19	40.4 %	
Bicarbonate supplementation		4	8.5 %
Broad spectrum antibiotics	42	89.4 %	
Insulin:	Actrapid®	39	83 %
	Caninsulin®	28	59.6 %
	Monotard®	3	6.4 %
H2-antihistaminics:	Ranitidine (Zantac®)	31	66 %
	Cimetidine (Tagamet®)	7	14.9 %
Anti-emetics:	Metoclopramide (Primperan®)	19	40.4 %
	Maropitant (Cerenia®)	2	4.3 %
Sucralfaat (Ulcogant®)		2	4.3 %
Analgesia:	Buprenorfine (Temgesic®)	9	19.1 %
	Methadon	2	4.3 %
Diuretics:	Mannitol	1	2.1 %
	Furosemide	2	4.3 %
Nutritional support:	Naso-esophagal feeding tube	2	4.3 %
	Total Parenteral Nutrition	2	4.3 %
Others:	Levothyroxine (Forthyron®)	2	4.3 %
	Heparin	1	2.1 %
	Phenobarbital (Gardenal®)	1	2.1 %
	Prednisolone (Codipred®) (because of immune-mediated skin disease)	1	2.1 %

unknown reasons (n=6) (5 months, 6 months and 2, 3 or 4 years after diagnosis) and for reasons unrelated to DK(A) (n=3) (3 months and 2 years after diagnosis).

In summary, at the time of writing, only 10 (18.5%) of the 54 dogs were still alive, with a mean follow-up time of 13.4 ± 13.2 months (range, 0.5 – 42 months). Twenty-six (48%) of the dogs had died within 2 weeks post-admission, another 17 dogs (31.5%) had died after two weeks post-admission for DK(A). One dog was lost for follow-up.

A relapse of DK(A) occurred once in five dogs and twice in two dogs after they survived initial hospitalization. The mean duration between diagnosis of DK(A) and first relapse was 2.3 ± 1.8 months (range, 0.5 – 5 months). Of the 2 dogs that had a second relapse, one relapsed 6 months after the first relapse, and the other 2 months after the first relapse. Only one dog survived the relapse(s); all the other dogs were euthanized after their first or second relapse.

DISCUSSION

The signalment of the dogs presented with DK(A) was largely similar to that described in previous studies (Feldman and Nelson, 2004b; Hume *et al.*, 2006). The most common age to develop DK(A) is middle-aged to old (Feldman and Nelson, 2004b; Hume *et al.*, 2006). In our study, the mean age was 9.2 years, which is comparable to the mean age of 8 years in a recent large retrospective study (Hume *et al.*, 2006). Diabetes keto(acido)sis is most frequently seen in female dogs (Feldman and Nelson, 2004b), although in the study by Hume *et al.* (2006), 53% of the patients were male. In our study, the largest group of patients were female intact dogs (42.6%), which can be due to the insulin-antagonizing effect of progesterone (further explanation: see below). In our study, the most frequently presented breeds were the Labrador Retriever, Mixed Breed, Yorkshire Terrier, Maltese Dog and Rottweiler. These breeds are in part the same as in the study by Hume *et al.* (2006), in which the Mixed Breed, Poodle, Rottweiler and Yorkshire Terrier were the most commonly affected breeds. The difference in breed prevalence between studies can be due to differences in breed popularity in various countries.

Although DK(A) is considered a complication of DM, 57.4% of the dogs presented with DK(A) had not previously been diagnosed with DM. In the literature this percentage is even higher (65% in Hume *et al.*, 2006).

As in previous studies, the most frequent symptoms of DK(A) were pu/pd, anorexia, vomiting, lethargy, diarrhea and weight loss. Other, less frequent problems, such as the presence of abdominal distension or melena, often depend on the concurrent disease (Chastain, 1981; Macintire, 1993; Greco, 1997; Kerl, 2001a; Hume *et al.*, 2006). Physical examination findings such as shock, tachypnea and dyspnea, as well as the severity of clinical signs, often depend on the duration of the illness. Therefore the condition in which the dog is presented often depends on the quickness of the owner's response and the severity of the concurrent disease (Feldman and Nelson, 2004b; Hume *et al.*, 2006).

Diagnosis of DK(A) and concurrent diseases was made by evaluation of the clinical signs, blood examination, urinalysis and medical imaging. Monitoring of hematocrit, total plasma protein concentration, albumin, blood glucose, venous blood gasses, BUN, serum creatinine and serum electrolytes was regularly performed to guide proper fluid therapy. Venous blood gas analysis (pH and bicarbonate concentration) was only measured in 31 of 54 dogs. This can in part be explained by the absence of an available blood gas analyzer during the first years of this study. Of the 31 dogs in which blood gasses were measured, 21 had a pH below 7.35, and it was these dogs that were diagnosed as having DKA. One of these dogs showed a negative urine stick for ketones, but this result was probably false negative because urine sticks do not detect ß-hydroxybutyrate (an important ketone in the urine). This dog was included in our study based upon the presence of hyperglycemia, glucosuria, acidemia and compatible clinical signs. The other 10 dogs and the dogs for which pH was not determined were included as DK. A portion of these dogs possibly had DKA, but because of the unknown pH, this group of dogs was included as DK. This is different from some other studies that only retrospectively evaluated DKA patients (Macintire, 1993; Hume *et al.*, 2006).

At presentation, low levels of sodium, chloride and potassium were found in 64.8%, 23.8% and 19.6%, respectively, of the patients in which serum electrolytes were measured. One possible reason for the electrolyte abnormalities observed is the excessive urinary loss caused by the osmotic diuresis induced by glucosuria and ketonuria. In addition, diarrhea and vomiting can also contribute to these losses (Macintire, 1993; Nicols and Crenshaw, 1995; Kerl, 2001a; Feldman and Nelson, 2004b). Hyperkalemia (hyperK) was detected in 17.6% of the dogs evaluated. The serum potassium concentration depends on the duration of the illness, renal function and previous nutritional state of the dog, and can vary during hospitalization as a result of fluid and insulin administration (Feldman and Nelson, 2004b). In this study, 2 of the 5 dogs with ARF also showed hyperK, (though potassium was not measured in 1 of the 5 dogs). Hypomagnesemia is described in patients with DK(A). Serum magnesium was not measured in this study. Two recent studies found that ionized magnesium depletion is uncommon in dogs with DK(A), and therefore of minor importance (Fincham *et al.*, 2004; Hume *et al.*, 2006). In this study, 13.3% of the dogs in which phosphorus was measured showed hypophosphatemia, (which was mild). In the study by Hume *et al.* (2006), 5.5% of the dogs showed hypophosphatemia, and phosphorus depletion was

associated with slower stabilization of the patient's condition. Hypophosphatemia can contribute to hemolysis, skeletal muscle weakness, leukocyte dysfunction and poor tissue oxygenation (Macintire, 1997; 't Hooft *et al.*, 2005).

Azotemia was present in 55.6% of the dogs, a fact which could be explained by prerenal or renal causes, or a combination of the two. Liver enzymes were increased in about half of the dogs. This can be due to hepatocellular damage, severe acidosis, hypovolemia, hypoxia or extra hepatic biliary obstruction (Kerl, 2001a; Feldman and Nelson, 2004b).

Fifty-five percent of the dogs showed leukocytosis, which was a result of the release of stress hormones, concurrent severe inflammation (such as pancreatitis or pyometra) or the presence of infections (Kerl, 2001a; Feldman and Nelson, 2004b). In human medicine, it has been shown that leukocytosis more likely reflects the severity of the DK(A) rather than the presence of infection (Hume *et al.*, 2006). Despite the fact that dogs with DK(A) are often dehydrated, 55.6% of the dogs were anemic. In dogs with DK(A), the most obvious reasons for the anemia are blood loss, hemolysis, infection, inflammation, chronic renal failure and metabolic diseases such as hypothyroidism, hyperestrogenism or liver disease (Feldman, 2005; Giger, 2005). Fifty-one percent of the dogs showed a thrombocytosis, which is not clearly described in the literature. The thrombocytosis was considered reactive and can occur secondarily to systemic inflammatory disease (especially involving the intestines, kidneys or joints), acute infections, surgery, neoplasia, chronic blood loss and endocrine disorders (especially hypercortisolism) (Bass and Schultze, 1998).

Three dogs had a urinary tract infection (*E. coli)* on a urine culture at presentation, and 1 dog developed a urinary tract infection during hospitalization. A possible explanation for the infection of this patient could be the presence of a urinary catheter, which predisposes for lower urinary tract infection (Ogeer-Gyles *et al.*, 2006; Bubenik *et al.*, 2007).

Possible causes for the elevated UPC's in 87.1% of the dogs are glomerulonephritis secondary to infections or inflammations, neoplasia, glomerular damage related to DIC or glomerular microangiopathy associated with DM (Brunker, 2005; Lees *et al.*, 2005; Grauer, 2007).

In 88.9% of the dogs a concurrent disease was diagnosed, and in 77.8% of the dogs one or more of their concurrent diseases could have been a possible cause for DK(A). The absence of the diagnosis of a concurrent disease in the other dogs was due to immediate death in 2 dogs, owners that refused further investigation in 3 dogs, and no concurrent disease being found in 1 dog, despite adequate work-up. The most common concurrent disease was acute pancreatitis.Pancreatitis was a disease commonly seen with DK(A) in previous studies as well (Chastain, 1981; Nicols and Crenshaw, 1995; Kerl 2001a; Feldman and Nelson, 2004b; Hume *et al.*, 2006). According to Feldman and Nelson (2004b), necrotizing pancreatitis is the most common cause of euthanasia during the first days after diagnosis of DK(A). In Chastain (1981), 21% of the surviving dogs showed signs of acute pancreatitis, and 80% of the dead dogs had acute or chronic pancreatitis. On the other hand, in a study by Hume *et al.* (2006), dogs with acute pancreatitis were hospitalized longer, but the presence of acute or chronic pancreatitis had no influence on survival. But then again, in our study, 6 of the 12 dogs with acute pancreatitis and both dogs with chronic pancreatitis died or were euthanized during the first episode of DK(A), and 1 dog was euthanized in the second episode of DK(A) combined with acute pancreatitis.

Hypercortisolism is also a common concurrent disease and sometimes a cause of DK(A) (Chastain, 1981; Kerl, 2001a; Feldman and Nelson, 2004a; Feldman and Nelson, 2004b; Hume *et al.*, 2006). Dogs with HC produce large amounts of glucocorticoids, which stimulate lipolysis and promote protein catabolism and the conversion of amino acids into glucose by liver and kidney, which results in DK(A). Screening tests for HC are not reliable during illness and should be performed when the patient is clinically stable, starts eating and the electrolyte and metabolic abnormalities have been normalized. The administration of exogenous corticoids has the same effects and can result in DK(A) (Feldman and Nelson, 2004a; Feldman and Nelson, 2004b). In the study by Hume *et al.* (2006), the presence of HC led to a larger percentage of euthanasia. This is similar to our study, where 4 of the 7 dogs suspected of or diagnosed with HC were euthanized during the first episode of DK(A), and 1 dog was euthanized during the second episode combined with HC.

Bitches in diestrus also have a greater risk of developing DK(A). These dogs produce larger amounts of progesterone, which has an antagonizing effect on insulin and stimulates growth hormone, which in turn results in insulin resistance. This should be considered in each intact bitch and in dogs with cystic ovaries (Chastain, 1981; Feldman and Nelson, 2004b). In this study, 2 of the 3 dogs with cystic ovaries had no second concurrent disease, so dogs with cystic ovaries should be considered to be at risk for developing DK(A).

Hypothyroidism has also been identified as a cause of DK(A). The exact mechanism is not clear, but most authors propose that a post-receptor defect in insulin-mediated glucose transport and metabolism exists (Feldman and Nelson, 2004a). In this study, 3 dogs had concurrent hypothyroidism, which in each case had been diagnosed before the DK(A) episode. Two of them had then been treated successfully with Levothyroxine (Forthyron®), so the hypothyroidism in these two dogs was unlikely to be the cause of the DK(A). In the third dog, however, the owners had stopped treatment for hypothyroidism, which therefore could have contributed to the development of DK(A).

Furthermore, obese dogs often show insulin resistance because of down-regulation of the insulin receptors, a decrease of insulin receptor binding and intracellular defects in glucose metabolism (Feldman and Nelson, 2004a). Obesity was commonly seen in our study, though it was often not the only diagnosed disorder associated with DK(A).

Dogs with DM are more susceptible to developing concurrent infections because of the immunosuppressive effects of DM and the higher glucose levels in the blood. They are predisposed to bacterial infections such as pyometra, urinary tract infections, dermatitis, pneumonia, gingivitis, abscesses and splenitis (Chastain, 1981; Nicols and Crenshaw, 1995; Kerl, 2001a; Feldman and Nelson, 2004a; Feldman and Nelson, 2004b; Hume et al, 2006). Hepatitis is also regarded as a concurrent disease and possible cause of DK(A) in some textbooks (Feldman and Nelson, 2004b).

In this study, 5 dogs were diagnosed with acute and 2 dogs with chronic renal failure. Dogs with DM can develop glomerular microangiopathy, which possibly leads to glomerulosclerosis. This can cause proteinuria and renal failure. Renal failure results in decreased renal clearance of insulin, decreased renal production of glucose by gluconeogenesis and decreased sensitivity of the tissues to insulin (Chastain, 1981; Nicols and Crenshaw, 1995; Kerl, 2001a; Feldman and Nelson, 2004a; Feldman and Nelson, 2004b). On the other hand, acute renal failure can also be a complication of DK(A) rather than a cause, and as a complication it is secondary to dehydration, hypotension, the underlying disease (e.g. pyometra, pancreatitis) and the presence of DIC.

Endocrine neoplasias such as pheochromocytoma and glucagonoma have an obvious disrupting effect on insulin metabolism, but nonendocrine tumors, such as lymphoma, mast cell tumor and others, can also cause DK(A). The exact mechanism is not clear, but those tumors might have an effect on hormone production, liver function, fat metabolism and reaction of tissues to insulin (Feldman and Nelson, 2004a). In this study, 13 dogs (24%) were presented with neoplasia (mammary gland tumor, liver mass, anal sac tumor and pancreas tumor).

The treatment of the dogs depended largely on the general clinical condition, the clinicopathologic abnormalities and the concurrent disorders, and was comparable to that in the study by Hume *et al.* (2006), except that phosphate supplementation was not performed in our study. However, our protocol has recently been changed, so that the monitoring and supplementation of P is now part of the routine protocol. The most serious consequence of hypophosphatemia is hemolysis (Macintire 1997; 't Hooft *et al.*, 2005). However, the supplementation of P requires intensive monitoring, since oversupplementation can induce acute renal failure or hypotension. Phosphate can be given orally or intravenously and is available in the form of potassium phosphate or sodium phosphate ('t Hooft *et al.*, 2005).

At our clinic, the initial insulin therapy in dogs with DK(A) consisted of intermittent IM and SC administration of short-acting insulin (Actrapid®) in accordance with the scheme in Figure 1. Serum glucose concentration is monitored hourly during IM insulin administration and every 3 hours during SC administration. Once the dog is clinically stable and starts to eat, and once most of the electrolyte and acid-base abnormalities are corrected, the short-acting

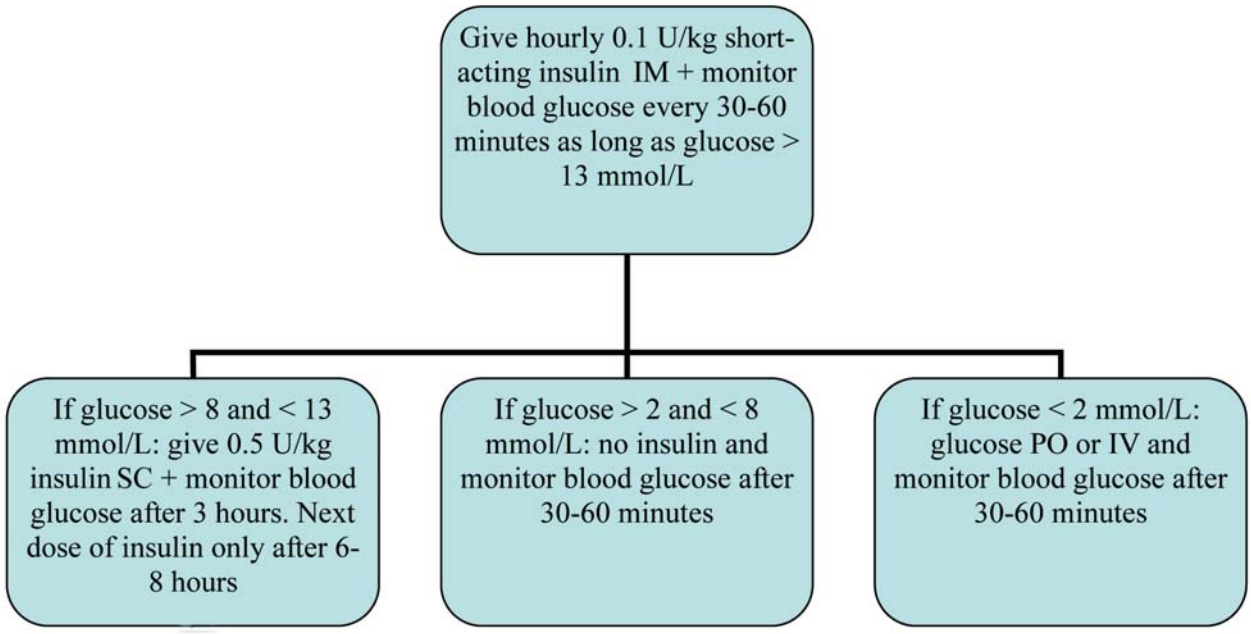

Figure 1. Protocol used in the clinic of the Department of Small Animal Medicine for the initial treatment with short-acting insulin of patients with diabetes keto(acido)sis. Glucose supplementation (maintenance Dextrose 5%) should also be administered if blood glucose < 13 mmol/L. Stop glucose 5% infusion if glucose is > 13 mmol/L.

insulin is replaced by an intermediate acting insulin (Caninsulin®). Further details of the treatment are beyond the scope of this article.

In this study, 48% of the dogs died or were euthanized within 2 weeks after diagnosis of DK(A). In other studies, 29% (Macintire, 1993) or 30% of the dogs (Hume *et al.*, 2006) died or were euthanized during initial therapy. The higher mortality rate in our study can be explained by the interpretation of the term "initial therapy duration". In our study, the outcome of the initial therapy was evaluated 2 weeks after the DK(A) diagnosis, and in all discharged cases, it included the entire period that the animal was hospitalized and the first days of treatment by the owner at home. . In other studies, the initial therapy duration was defined as the time until the most important blood values of the dog were normalized, while the dog was still in the hospital. This was usually a shorter period than 2 weeks. Another possible explanation of the higher mortality rate in our study is that our hospital also accepts primary non-referred cases, whereas other studies such as Hume *et al.* (2006) were performed in strictly secondary or tertiary care facilities. In these facilities the owners already knew about the diagnosis of DK(A) and they were motivated to start treatment. In our study, the owners were hearing the DK(A) diagnosis for the first time, so a portion of them were less motivated to start with intensive treatment and decided to euthanize the dog.

Possible reasons for the high mortality rate of DK(A) patients in this and other studies can include severe electrolyte and acid-base abnormalities, which can become life threatening, the presence of a severe concurrent disease such as pancreatitis, HC or pneumonia, the risk of complications (DIC, ARF), and the intense and prolonged hospitalization, which can become very expensive (Chastain, 1981; Macintire, 1993; Kerl, 2001b; Feldman and Nelson, 2004b; Hume *et al.*, 2006). To maximize the chances of survival, dogs with DK(A) are best referred to a clinic with an intensive care unit, blood (gas) analysis and continuous monitoring.

In this study, 5 of the surviving dogs (9.3%) showed 1 or more relapses. All dogs developed their relapse within 6 months after DK(A) diagnosis and all except 1 dog were euthanized at the time of their first or second relapse. In Hume *et al.* (2006), 9 of 54 surviving dogs had a relapse. The mean duration time between the first and the second episode in that study was 5.5 days. The shorter time interval was probably for the same reason as the lower mortality rate in the same study. Based on our study and the study by Hume *et al.* (2006), owners of dogs with DK(A) must be informed that a relapse is likely within the first 6 months after DK(A) diagnosis, but that it is less likely after this period.

In conclusion, most dogs with DK(A) were female intact dogs without a previous history of DM. In dogs that had previously been diagnosed with DM, the condition had not been well regulated. Diabetes keto(acido)sis was often associated with a concurrent disease. The most frequently observed concurrent diseases were pancreatitis, HC, neoplasia, infections, renal failure and heart failure. Treatment depended on the concurrent disease, the blood values and the symptoms of the dog. Addressing the often present concurrent disease is mandatory. The prognosis is poor since 48% of the dogs died within 2 weeks after diagnosis, though it depends on the severity of the signs and the concurrent disease. The most common complication after initial recovery is the recurrence of a DK(A) episode, which often results in euthanasia. Diabetes keto(acido)sis is a life threatening condition requiring aggressive therapy and ICU monitoring.

LITERATURE

Bubenik L.J., Hosgood G.L., Waldron D.R., Snow L.A. (2007). Frequency of urinary tract infection in catheterized dogs and comparison of bacterial culture and susceptibility testing results for catheterized and noncatheterized dogs with urinary tract infections. *Journal of the American Veterinary Medical Association 231 (6),* 893-899.

Bass M.C., Schultze A.E. (1998). Essential thrombocythemia in a dog: Case report and literature review. *Journal of the American Animal Hospital Association 34,* 197-203.

Brunker J. (2005). Protein-losing nephropathy. *Compendium of Continuing Education for the Practicing Veterinarian,* 686-695.

Chastain C.B. (1981). Intensive care of dogs and cats with diabetic ketoacidosis. *Journal of the American Veterinary Medical Association 179 (10),* 972-978.

Feldman B.F. (2005). Nonregenerative anemia. In: Ettinger S.J., Feldman E.C. (editors). *Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat.* 6th Ed., Elsevier Saunders, St. Louis, Missouri (USA), p. 1908-1929.

Feldman E.C., Nelson R.W. (2004a). Canine Diabetes Mellitus. In: Feldman E.C., Nelson R.W. (editors). *Canine and Feline Endocrinology and Reproduction.* 3rd Ed., Elsevier Saunders, St. Louis, Missouri (USA), p. 486-538.

Feldman E.C., Nelson R.W. (2004b). Diabetes Ketoacidosis. In: Feldman E.C., Nelson R.W. (editors). *Canine en Feline Endocrinology and Reproduction.* 3rd Ed., Elsevier Saunders, St. Louis, Missouri (USA), p. 580-615.

Fincham S.C., Drobatz K.J., Gillespie T.N., Hess R.S. (2004). Evaluation of plasma-ionized magnesium concentration in 122 dogs with diabetes mellitus: a retrospective study. *Journal of Veterinary Internal Medicine 18,* 612-617.

Giger U. (2005). Regenerative anemias caused by blood loss or hemolysis. In: Ettinger S.J., Feldman E.C. (editors). *Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat.* 6th Ed., Elsevier Saunders, St. Louis, Missouri (USA), p.1886-1907.

Grauer G.F. (2007). Measurement, interpretation and implications of proteinuria and albuminuria. *Veterinary Clinics of Small Animal Practice 37,* 283-295.

Greco D.S. (1997). Endocrine emergencies. Part 1. Endocrine pancreatic disorders. *Compendium of Continuing Education for the Practicing Veterinarian 19 (1),* 15-23.

't Hooft K.V., Drobatz K.J., Ward C.R. (2005). Hypophos-

phatemia. *Compendium of Continuing Education for the Practicing Veterinarian 27 (12),* 900-911.
Hume D.Z., Drobatz K.J., Hess R.S. (2006). Outcome of dogs with diabetic ketoacidosis: 127 dogs (1993–2003). *Journal of Veterinary Internal Medicine 20,* 547-555.
Kerl M.E. (2001a). Diabetic Ketoacidosis: Pathophysiology and clinical and laboratory presentation. *Compendium of Continuing Education for the Practicing Veterinarian 23,* 220-229.
Kerl M.E. (2001b). Diabetic Ketoacidosis: Treatment, recommendations. *Compendium of Continuing Education for the Practicing Veterinarian 23,* 330-340.
Lees G.E., Brown S.A., Elliot J., Grauer G.F., Vaden S.L. (2005). Assessment and management of proteinuria in dogs and cats: 2004 ACVIM Forum Consensus Statement (small animal). *Journal of Veterinary Internal Medicine 19,* 377-385.
Macintire D.K. (1993). Treatment of diabetic ketoacidosis in dogs by continuous low-dose intravenous infusion of insulin. *Journal of the American Veterinary Medical Association 202 (8),* 1266-1272.
Macintire D.K. (1995). Emergency therapy of diabetic crises: Insulin overdose, diabetic ketoacidosis, and hyperosmolar coma. *The Veterinary Clinics of North America. Small Animal Practice 25 (3),* 639-650.
Macintire D.K. (1997). Disorders of potassium, phosphorus, and magnesium in critical illness. *Compendium of Continuing Education for the Practicing Veterinarian 19 (1),* 41-49.
Nicols R., Crenshaw K.L. (1995). Complications and concurrent disease associated with diabetic ketoacidosis and other severe forms of diabetes mellitus. *The Veterinary Clinics of North America. Small Animal Practice 25 (3),* 617-624.
Ogeer-Gyles J, Mathews K, Weese J.S., Prescott J.F., Boerlin P. (2006). Evaluation of catheter-associated urinary tract infections and multi-drug-resistant Escherichia coli isolates from the urine of dogs with indwelling urinary catheters. *Journal of the American Veterinary Medical Association 229 (10),* 1584-1590.