Retrospective Study

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Ionized calcium concentrations in cats with septic peritonitis: 55 cases (1990–2008)

Lindsay M. Kellett-Gregory, BSc (Hons), BVetMed (Hons); Elise Mittleman Boller, DVM, DACVECC; Dorothy C. Brown, DVM, MSCE, DACVS and Deborah C. Silverstein, DVM, DACVECC

Abstract

Objective – To report the prevalence of ionized hypocalcemia (iHCa) in cats with septic peritonitis, and to determine whether hypocalcemic cats had increased morbidity and mortality when compared with normocalcemic cats.

Design – Retrospective clinical study.

Setting – University teaching hospital.

Animals – Fifty-five client-owned cats with septic peritonitis.

Measurements – Medical records of 55 cats with confirmed septic peritonitis meeting the study inclusion criteria were reviewed. Information obtained included signalment, cause of peritonitis, length of hospitalization (LOH), length of ICU stay, and outcome. Results from serum biochemical analysis, blood gas analysis, and coagulation testing from the time of diagnosis, and all ionized calcium (iCa) measurements during hospitalization were recorded. Systolic blood pressure, the presence of arrhythmias and administration of vasopressor agents, blood products, and sodium bicarbonate were documented. iCa concentration at the time of diagnosis and lowest recorded value during hospitalization were compared with LOH and length of ICU stay, survival to hospital discharge, and clinical and clinicopathologic data.

Main Results – iHCa (iCa $<$ 1.20 mmol/L) was found in 89% of cats (49/55) at the time of diagnosis of septic peritonitis and 93% (51/55) at any time during hospitalization. There was no association between the presence or severity of iHCa at diagnosis and survival to hospital discharge. LOH ($P = 0.046$) and duration of ICU stay ($P = 0.026$) were significantly correlated with the lowest iCa recorded during hospitalization. Failure to normalize iCa during hospitalization was associated with a decreased survival rate to discharge ($P = 0.029$) in patients with iHCa. iHCa was not associated with an increased prevalence of hypotension, coagulopathy, arrhythmias, or evaluated therapies.

Conclusions – iHCa is more prevalent in cats with septic peritonitis than described previously. Failure of iCa to normalize during hospitalization may be a negative prognostic indicator. iHCa may be predictive of a longer LOH and ICU stay, but is not necessarily associated with a poorer prognosis.

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Introduction

Ionized hypocalcemia (iHCa) is a common electrolyte abnormality in critically ill people, occurring in up to 88% of ICU patients.[1] Numerous disease processes have been associated with the presence of iHCa including severe trauma, surgery, pancreatitis, and burn injuries.[2–7] iHCa has also been reported in 20–82% of septic human patients.[8–11] The pathogenesis of iHCa is not fully understood, but may be due to any of the following mechanisms: hypoparathyroidism secondary to parathyroid gland dysfunction[9,12] or cytokine-mediated suppression of parathyroid hormone release,[8,13] hypomagnesemia,[14–17] calcitriol deficiency or lack of activation,[9] alkalosis,[18] elevated procalcitonin concentrations,[19–23] accumulation of calcium within tissues, intracellular redistribution of calcium,[24–26] and chelation with lactate, bicarbonate or other anions.[13,27] In septic and critically ill people, the presence of iHCa has

From the Section of Critical Care (Kellett-Gregory, Mittleman Boller, Silverstein) and Section of Surgery (Brown), Department of Clinical Studies – Philadelphia, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104.

Address correspondence and reprint requests to
Dr. Lindsay Kellett-Gregory, BSc (Hons), BVetMed (Hons). Current address: Department of Veterinary Clinical Sciences, The Royal Veterinary College, University of London, North Mymms, Hertfordshire AL9 7TA, UK.
Email: lkellettgregory@gmail.com
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been associated with a greater severity of illness, increased length of hospitalization (LOH), and increased mortality rate.[1,2,8,9,11,20,28] Complications of iHCa include myocardial depression, hypotension, cardiac arrhythmias, muscle weakness, and coagulopathy.[29,30]

In veterinary medicine iHCa has been associated with increased morbidity and mortality in acute pancreatitis in cats, and in acute renal failure and diabetic ketoacidosis in dogs.[31–33] Holowaychuk and colleagues[31] recently found that iHCa was present in 16% of critically ill dogs, was more likely to occur in dogs with sepsis and was associated with longer LOH and ICU stays. In another study by Luschini et al,[a] iHCa was present in 25% of septic dogs where it was associated with an increase in mortality.

Septic peritonitis is a life-threatening condition with a mortality rate of 30–86% reported in cats.[34–38] Electrolyte derangements, hypotension, and coagulopathy are common with this condition. To our knowledge, there are no studies fully evaluating ionized calcium (iCa) concentrations in feline critically ill or septic patients, although iHCa was identified in 59% of cats with septic peritonitis in 1 study.[34]

The purpose of this study was to retrospectively evaluate iCa concentrations in a population of cats surgically treated for septic peritonitis, and to determine if hypocalcemic patients had an increased morbidity and mortality compared with normocalcemic cats. Additionally, attempts were made to determine if routinely measured biochemical or blood gas parameters (eg, phosphorus concentration or venous blood pH) had any influence on iCa concentration.

Our hypothesis was that iHCa would be common in cats with septic peritonitis, and that hypocalcemic cats would have an increased LOH, ICU stay, and increased morbidity and mortality as compared with normocalcemic cats.

Materials and Methods

Medical records of cats that presented to the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania were searched to identify all cats examined between January 1990 and December 2008 to determine eligibility into the study. The University of Pennsylvania Department of Pathobiology's database was also searched over this time period. Cats were included in the study if a diagnosis of septic peritonitis was confirmed by the presence of at least 1 of the following criteria: positive bacterial growth on culture of peritoneal fluid, intracellular bacteria seen on cytological examination of peritoneal fluid, or direct visualization of lesions compatible with septic peritonitis at surgery or necropsy. Cats were excluded from the study if the medical record was incomplete, the results of a venous blood gas analysis and serum chemistry analysis including measurement of iCa concentration at the time of diagnosis were unavailable, or they were found to have nonseptic peritonitis (eg, acute necrotizing pancreatitis). Cats were also excluded if appropriate therapy (ie, surgical exploration) was not attempted.

For cats meeting the study inclusion criteria, medical records were reviewed. Signalment, body weight, cause of septic peritonitis, LOH, length of ICU stay, and outcome were noted. All iCa measurements for each patient during hospitalization were recorded. In addition heart rate, systolic blood pressure, presence and character of arrhythmias, serum phosphorus concentration, blood lactate concentration, blood pH, venous carbon dioxide tension ($PvCO_2$), ionized and total blood magnesium concentration, prothrombin time (PT), and partial thromboplastin time (PTT) were recorded. When variables were measured at numerous time points during hospitalization data collected closest to the time of diagnosis of septic peritonitis and the time of lowest measured iCa measurement were recorded. In all instances data was collected within 4 hours of iCa measurement. The administration of blood products (packed RBC, fresh frozen plasma, and fresh whole blood transfusions), sodium bicarbonate solution and vasopressor agents were recorded. Additionally, any clinical signs and treatment of iHCa were recorded.

No intervention was performed as part of the study. iHCa was defined as any measurement obtained below the manufacturer's provided feline reference interval of 1.20–1.32 mmol/L for the point-of-care analyzer used for iCa measurement.[b] This analyzer measures iCa by ion-selective electrode potentiometry using either fresh whole blood or blood anticoagulated with lithium heparin. In this study, either fresh whole blood or blood collected into heparinized tubes was used for iCa measurement. Samples were analyzed within 5 minutes of collection according to standard hospital procedure.

Hypotension was defined as a systolic blood pressure of <90 mm Hg and coagulopathy as a $>20\%$ prolongation in the PT or PTT. Survivors were defined as those surviving to hospital discharge. Patients that were euthanized or died naturally were recorded as nonsurvivors.

Statistical analysis

Descriptive statistics were calculated. Continuous data were expressed as mean $\pm$ standard deviation (SD), unless not normally distributed in which case, median (range) were reported. Categorical data were expressed as frequencies.

Fisher's exact test was used to evaluate the association of the presence of iHCa at any time during hos-

pitalization with the following parameters: gender, breed, survival to hospital discharge, the presence of arrhythmias, hypotension, coagulopathy, or hyperphosphatemia and the administration of vasopressor agents, blood products, or sodium bicarbonate. Fisher's exact test was also used to evaluate the association between normalization of iHCa during hospitalization and survival to hospital discharge.

Student's *t*-test was used to evaluate the association of the presence of iHCa at any time during hospitalization with the following parameters: age, weight, length of ICU stay, LOH, heart rate, and systolic blood pressure. Univariate linear regression analysis was used to evaluate the association of iCa concentrations at any time during hospitalization with venous blood pH, $PvCO_2$, total calcium, phosphorus, albumin, ionized magnesium, total magnesium, and lactate concentrations.

iCa concentration at the time diagnosis of septic peritonitis and at the lowest recorded iCa measurement during hospitalization was tested for association with survival to hospital discharge by Student's *t*-test and for association with length of ICU stay and LOH by univariate linear regression analysis.

All analyses were performed using STATA 10 statistical software.[c] For all comparisons $P < 0.05$ was considered significant.

Results

The initial medical records search identified 633 patients, of which 578 were excluded due to: incomplete medical records (105), a final diagnosis of nonseptic peritonitis (447), or death or euthanasia before surgical exploration (26). Fifty-five cats were identified that met the inclusion criteria and were included in the study.

Median age was 6.0 years (0.15–17 y). There were 14 female cats (11 spayed and 3 sexually intact), and 41 males (39 castrated and 2 sexually intact). Median bodyweight was 4.7 kg (2.0–9.4 kg). There were 7 purebred, 44 domestic short-haired, and 4 domestic long-haired cats. The underlying causes of septic peritonitis are shown in Table 1.

Thirty-one of 55 cats (56%) survived to hospital discharge. Of the 24 nonsurvivors, 19 were euthanized (11 intraoperatively and 8 postoperatively) and 5 died (1 intraoperatively and 4 postoperatively).

Forty-nine of 55 cats (89%) had iHCa at the time of diagnosis of septic peritonitis with a mean iCa of 1.09 ± 0.11 mmol/L [reference interval 1.20–1.32 mmol/L] (Figure 1). Forty-seven cats had iCa measured on multiple occasions. During hospitalization, iCa decreased from initial levels in 34 cats. Overall 51 (93%) cats had iHCa at any point during their hospitalization with a mean lowest iCa of 1.00 ± 0.15 mmol/L [reference interval 1.20–1.32 mmol/L] (Figure 2).

Table 1: Underlying cause of septic peritonitis in 55 cats

Cause of sepsis	Number (%)
GI ruptured neoplasm	15 (27.3)
Trauma*	8 (14.5)
Iatrogenic†	7 (12.7)
Inflammatory GI disease	7 (12.7)
Septic uroabdomen	6 (10.9)
GI perforating foreign body	4 (7.3)
Not identified‡	4 (7.3)
Ruptured pyometra	3 (5.5)
Splenic abscess	1 (1.8)

*Traumatic injuries included dog bite wounds, gunshot wounds, vehicular trauma.

†Iatrogenic injuries included enterotomy dehiscence, peritoneal dialysis catheter associated infection, abdominal contamination during prior ovariectomy.

‡No cause for septic peritonitis identified at the time of surgical exploration or necropsy.

GI, gastrointestinal.

No significant differences were found in signalment, survival, LOH, or length of ICU stay between cats with or without iHCa at any time point during hospitalization (Table 2). iCa concentration at the time of diagnosis was not associated with duration of ICU stay ($P = 0.46$), LOH ($P = 0.18$), or survival to discharge ($P = 0.24$). The lowest recorded iCa concentration was, however, correlated with length of ICU stay ($P = 0.026$, $R^2 = 0.10$) and LOH ($P = 0.046$, $R^2 = 0.08$). Cats that were hypocalcemic but subsequently became normocalcemic were significantly more likely to survive to discharge compared with those in which iCa did not normalize ($P = 0.029$).

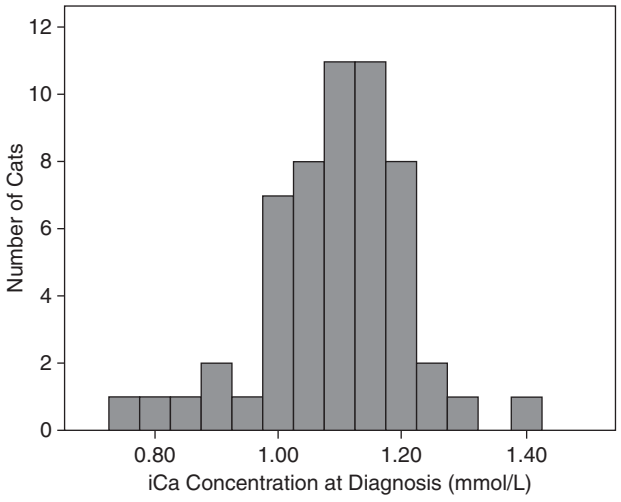

Figure 1: Distribution of ionized calcium (iCa) concentration at the time of diagnosis of septic peritonitis.

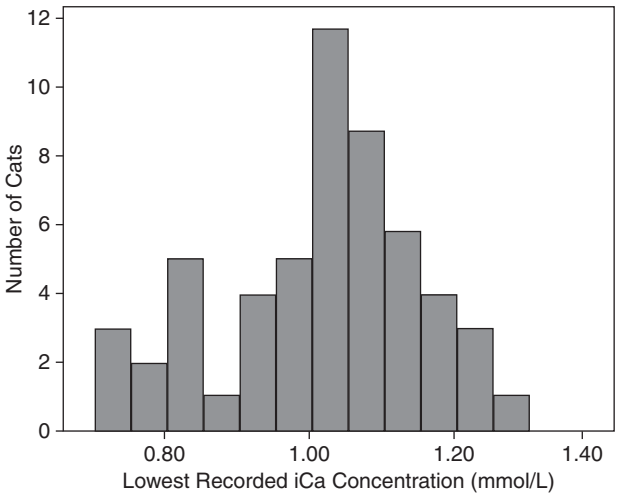

Figure 2: Distribution of ionized calcium (iCa) concentration at lowest point during hospitalization.

There was no significant difference in the cardiovascular, coagulation, and therapeutic parameters evaluated between these groups. All of the hypotensive cats had iHCa, although there was no significant difference in systolic blood pressure between cats with or without iHCa (Table 2). Of the 4 cats with arrhythmias detected, 3 were found to have intermittent ventricular premature complexes. One of the cats with iHCa had rapid ventricular tachycardia requiring antiarrhythmic therapy.

Of the evaluated biochemical parameters, iCa concentration was found to be significantly correlated with total serum calcium, venous blood pH, and serum phosphorus concentrations (Table 3). There was no significant difference between hypocalemic and normocalcemic cats and the presence of hyperphosphatemia (Table 2).

Clinical signs attributable to iHCa such as muscle fasciculations or hyperexcitability were not reported in any cat in this study. Intravenous calcium gluconate[d] therapy for the treatment of iHCa was administered to 10 cats, with a median iCa of 0.82 mmol/L (0.73–0.89 mmol/L) [reference interval 1.20–1.32 mmol/L]. Of these treated cats, 3 survived to hospital discharge. None of the treated cats were markedly hyperphosphatemic (mean 1.87 ± 0.87 nmol/L [5.8 ± 2.7 mg/dL], reference interval 0.97–2.13 nmol/L [3.0–6.6 mg/dL]). An intravenous bolus dose of calcium gluconate[d] of 50–100 mg/kg followed by a continuous rate infusion of 10 mg/kg/h was used in all cases. The indication for therapy was not recorded. No adverse effects of treatment were observed.

Discussion

Feline septic peritonitis is a relatively common disease process with a high mortality rate. In the current study, only 56% of patients survived to hospital discharge. This is consistent with the survival rate range of 14–70% found in other studies.[34–38]

Table 2: Selected variables associated with iHCa at any time point during hospitalization or normocalcemia in 55 cats with septic peritonitis

Variable	Hypocalcemic ($n = 51$)	Normocalcemic ($n = 4$)	*P* value
Mean initial iCa (mmol/L)	1.00 ± 0.12	1.33 ± 0.18	N/A
Age (years)	6.7 ± 4.5	7.0 ± 5.1	0.91
Gender, male	37	4	0.56
Breed, DSH	40	4	0.57
Weight (kg)	4.7 ± 1.8	4.8 ± 1.9	0.95
Died or euthanized	29	2	1.00
Length of ICU stay (days)	3.0 ± 2.3	2.0 ± 1.7	0.38
Length of hospital stay (days)	4.9 ± 4.0	2.5 ± 1.7	0.08
Heart rate (bpm)	190 ± 32	175 ± 23	0.33
Arrhythmia detected	3	1	0.27
Systolic blood pressure (mm Hg)	94 ± 31	125 ± 21	0.25
Hypotensive	12	0	0.57
Required vasopressor therapy	9	0	1.00
Coagulopathic	13	2	0.30
Received blood transfusion*	32	1	0.29
Received sodium bicarbonate	4	1	0.32
Phosphorus (nmol/L) [reference interval 0.97–2.13]	1.55 ± 0.55	1.78 ± 0.45	0.52
Phosphorus (mg/dL) [reference interval 3.0–6.6]	4.8 ± 1.7	5.5 ± 1.4	0.52
Hyperphosphatemic	7	1	0.48

Data represented as frequencies or mean ± standard deviation.
iCa, ionized calcium; N/A, not applicable; DSH, domestic short hair; bpm, beats per minute.

Table 3: Univariate linear regression analysis of iCa concentrations in relation to other biochemical parameters

Parameter	R^2	*P* value
Total calcium concentration	0.35	<0.001
Blood pH (venous)	0.07	0.001
Phosphorus concentration	0.06	0.002
Ionized magnesium concentration	0.02	0.40
Albumin concentration	0.01	0.42
P_vCO_2	0.01	0.44
Total magnesium concentration	0.007	0.72
Blood lactate concentration	0.0002	0.91

iHCa was found in 93% of cats at any time during their hospitalization. This is higher than previously described in veterinary studies where 16% of critically ill dogs and 25% of dogs with sepsis have been reported to have iHCa.[a,31] The results of this study are more consistent with the human literature, where iHCa has been found in 88% of critically ill patients and 82% of septic patients.[1,11] iHCa was found at the time of diagnosis of septic peritonitis in 59% of cats in a previous study.[34] In that study not all patients underwent surgical exploration and thus comparisons with the patient population in this study are difficult.

No association was found in this population between the presence of iHCa and survival to hospital discharge. This is similar to reports in critically in cats and dogs but in contrast to that in dogs with sepsis, cats with acute pancreatitis and many human patient populations where the presence of iHCa is a negative prognostic indicator.[a,6,28,32] In human trauma patients requiring fluid resuscitation, the post resuscitation iCa concentration is associated with outcome whereas earlier measurements are not.[7] In this study, measurements were taken at various, noncontrolled time points relative to the patient's diagnosis and fluid resuscitation; this may account for the lack of association found.

In this study, iHCa was defined as any measurement below the lower reference range limit for the analyzer used[b] (1.20 mmol/L) whereas other studies have utilized a lower reference range limit of 1.10 mmol/L. Clinical effects of iHCa are typically not present with concentrations >1.00 mmol/L, therefore this may be a more clinically relevant threshold for defining iHCa.[39] This study found no association between severity of iHCa and survival to hospital discharge but only a few cats had an iCa concentration <1.00 mmol/L at any time during hospitalization. Further studies investigating the effects of severe iHCa on outcome are warranted.

A recent canine study identified an association between the presence of iHCa at the time of ICU admission and a longer LOH.[31] In contrast, in the present study we found no such association at the time of diagnosis of septic peritonitis. The lowest iCa measurement recorded during hospitalization, however, was significantly correlated to duration of ICU stay and LOH. This study was conducted in a referral hospital with separate ICU and fluid therapy wards and thus the duration of ICU stay can be viewed as a surrogate marker of duration of unstable critical illness. Although the cats of this study were critically ill, the population was heterogenous with multiple underlying and concurrent diseases, as well as variable degrees of illness. Some cats presented to the hospital directly, whereas others were referred following variable fluid and medical therapy or anesthesia and surgery. This may have affected iCa concentration at the time of diagnosis and account for the lack of association found at this time point.[2,40]

Although the presence of iHCa was not associated with survival to discharge, cats that had iHCa with subsequent normalization had a significantly better survival to hospital discharge than those with a persistent iHCa. This association does not demonstrate causality however, and may simply indicate resolution of the underlying disease.

The current study did not demonstrate an association between the presence of iHCa and concurrent hypotension or vasopressor agent requirements in cats with septic peritonitis. Systemic hypotension may result from decreased effective circulating volume or systemic vascular resistance, and cardiac dysfunction. Maintenance of vascular resistance is dependent on vascular smooth muscle tone and the calcium-dependent process of phosphorylation of the myosin light chain. Calcium is also vital for the process of excitation-contraction coupling and normal myocardial function.[41] Myocardial depression associated with sepsis has been described in human and veterinary medicine.[42–44] In people concurrent sepsis and iHCa may result in significant decreases in cardiac contractility and myocardial failure.[45] iHCa has been associated with systemic hypotension and an increased requirement for vasopressor support in human ICU patients.[46] Hypotensive critically ill cats have been found to have an increased mortality rate compared with normotensive critically ill cats, although iCa concentration has not been found to differ between survivors and nonsurvivors.[47] To the authors' knowledge the effect of iHCa on blood pressure has not previously been investigated in veterinary patients.

iHCa has been associated with several electrocardiographic changes, including tachycardia and prolonged QT interval, deep wide T waves, or atrioventricular block.[39] A prolonged QT interval is considered to be a risk factor for the development of ventricular

arrhythmias, syncope, and death in people.[48] In this study, all the arrhythmias were ventricular in nature, however, iHCa was not associated with the presence of cardiac arrhythmias. As continuous ECG monitoring was not performed in all patients, the true prevalence and nature of arrhythmias, and any association with iHCa may not be represented with these data. The arrhythmias observed may not have been related to iHCa but other known risk factors common in septic patients (eg, decreased oxygen delivery, infarcts, or cytokine-mediated myocardial depression).

Calcium plays an essential role in coagulation, including platelet aggregation, fibrin polymerization, function of the inhibitory pathways, and expression of a procoagulant membrane.[49,50] As the iCa concentration necessary for these functions is thought to be far below physiologic levels, variations in calcium are unlikely to cause a clinically relevant impairment of coagulation.[30] Severe iHCa (iCa <0.6–0.7 mmol/L) has been associated with coagulation deficits,[30,51] and it is generally recommended that the iCa concentration be maintained ≥ 0.9 mmol/L.[49] The lack of association between iCa concentration and prolongation of PT or PTT in this study may be because the severity of iHCa was not sufficient to exert a clinically relevant effect on coagulation. There are also many other potential causes of coagulation derangements in septic cats, including cytokine-mediated endothelial dysfunction, platelet activation, and fibrinolytic system inhibition.[52]

Iatrogenic iHCa secondary to chelation by citrated blood products has been reported, with a linear relationship between the severity of iHCa and the amount transfused in human ICU patients.[7] Severe iHCa has also been reported following massive transfusion in dogs.[53] No association was found between administration of citrated blood products and iHCa in this study. This may have been influenced by the short-lived effect of citrate chelation and variable sampling timing relative to transfusion administration.

In addition to the ionized form, calcium exists in the blood bound to proteins and a variety of organic compounds, including phosphorus. Hyperphosphatemia is known to occur in cats for numerous reasons, including decreased glomerular filtration rate, which may occur frequently in cats in conjunction with, or independent of, a septic process. Phosphorus was found to be negatively correlated to iCa concentration in this study. Possible causes include chelation of iCa to phosphorus, and inhibitition of renal 1α-hydroxylase by increased phosphorus concentrations, decreasing calcitriol synthesis and hence intestinal calcium absorption.[54]

Other clinical signs of iHCa include muscle tremors or fasciculations, facial rubbing, stiff gait, restlessness or excitation, tetany, and hyperthermia. They are thought to occur with an iCa <1.0 mmol/L,[39] although the rapidity of onset is also important.[54] Although no such signs were reported in any cat in this study, the true prevalence may have been underestimated due to lack of notation in the medical record or masking of clinical abnormalities with drugs (eg, benzodiazepines).

Treatment of hypocalcemia in sepsis is controversial in both animal models and people. Although some studies found hemodynamic improvement with calcium therapy, others have actually found an association between calcium therapy and an increase in mortality.[24,45,55–58] Ten cats in this study received calcium supplementation but no treatment benefit could be demonstrated due to the nature of the study. Although no adverse effects of treatment were reported in any patient, it is possible there could have been subclinical deleterious effects such as precipitation of calcium in the soft tissues or excessive intracellular calcium accumulation leading to cell death. Therefore, routine treatment of iHCa in the septic patient cannot be recommended at this time.

A significant limitation of this study is the effect of potentially variable sample handling on iCa measurement. iCa results can be highly influenced by handling due to the dilutional and chelating effects of heparin and pH changes due to aerobic exposure of the sample.[59] All analyses were performed using a standard, recommended technique; errors due to sample handling are therefore likely to be minimal. Additional limitations include the inability to know if euthanasia was the result of medical or financial reasons, and to determine the underlying mechanism behind the high prevalence of iHCa. Also, therapies employed were variable and chosen at the discretion of the attending clinician.

In summary, iHCa was found to be more prevalent in cats with septic peritonitis than described previously. The severity of the iHCa was associated with a longer LOH and ICU stay, but no overall effect on survival to hospital discharge was identified in this study. The presence of iHCa was not associated with an increased prevalence of hypotension, coagulopathy, or arrhythmias and there was no statistical relationship with transfusion or sodium bicarbonate therapy requirements. Failure of iCa concentration to normalize during hospitalization may be a negative prognostic indicator, although treatment of iHCa remains controversial and of no proven benefit.

Footnotes

[a] Luschini MA, Fletcher DJ, Schoeffler GL. Ionized hypocalcemia among septic dogs and its association with morbidity and mortality. J Vet Emerg Crit Care 2008; 18(4): 413 (abstract).

[b] I-STAT Heska Corp, Loveland, CO.

[c] STATA 10, Statacorp LP, College Station, TX.
[d] 10% Calcium Gluconate Injection USP, APP Pharmaceuticals LLC, Schaumburg, IL.

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