

Standard Article

J Vet Intern Med 2017;31:1414–1419**Evaluation of Gastric pH and Serum Gastrin Concentrations in Cats with Chronic Kidney Disease**M.K. Tolbert , S. Olin, S. MacLane, E. Gould, J.M. Steiner, S. Vaden, and J. Price

Background: Chronic kidney disease (CKD) is a highly prevalent condition in cats. Advanced CKD is associated with hyporexia and vomiting, which typically are attributed to uremic toxins and gastric hyperacidity. However, gastric pH studies have not been performed in cats with CKD.

Hypothesis/Objectives: To determine if cats with CKD have decreased gastric pH compared to age-matched, healthy cats. Based on previous work demonstrating an association of hypergastrinemia and CKD, we hypothesized that cats with CKD would have decreased gastric pH compared to healthy, age-matched control cats.

Animals: 10 CKD cats; 9 healthy control cats.

Methods: All cats with concurrent disease were excluded on the basis of history, physical examination, CBC, plasma biochemistry profile, urinalysis, urine culture, serum total thyroxine concentration, and serum symmetric dimethylarginine concentration (controls only) obtained within 24 hours of pH monitoring and assessment of serum gastrin concentrations. Serum for gastrin determination was collected, and 12-hour continuous gastric pH monitoring was performed in all cats. Serum gastrin concentration, mean pH, and percentage time that gastric pH was strongly acidic (pH <1 and <2) were compared between groups.

Results: No significant differences in serum gastrin concentrations were observed between groups (medians [range]: CKD, 18.7 ng/dL [<10 –659.0]; healthy, 54.6 ng/dL [<10 –98.0]; P -value = 0.713) or of any pH parameters including mean \pm SD gastric pH (CKD, 1.8 ± 0.5 ; healthy, 1.6 ± 0.3 ; P -value = 0.23).

Conclusions and Clinical Importance: These findings suggest that cats with CKD may not have gastric hyperacidity compared to healthy cats and, therefore, may not need acid suppression. Thus, further studies to determine if there is a benefit to acid suppression in cats with CKD are warranted.

Key words: Acid suppression; Famotidine; Feline; Omeprazole; Renal.

Chronic kidney disease (CKD) is a common condition with an overall prevalence rate as high as 50% in older cats.¹ The cause of CKD in cats is often unknown and therefore it is difficult to prevent. Thus, clinicians must focus their attention on pharmacologic and dietary management of CKD, which is aimed at slowing disease progression and improving quality of life. Advanced CKD in cats is commonly associated with hyporexia or anorexia, nausea, vomiting, or some combination of these.² Gastric erosion and ulceration, typically attributed to direct injury to the gastric mucosa as a result of circulating uremic toxins and gastric hyperacidity, are complications of end-stage renal

Abbreviations:

CKD	chronic kidney disease
H2RA	histamine-2 receptor antagonist
PPI	proton pump inhibitor

disease in humans. Thus, acid suppression is often recommended for humans with advanced renal disease and gastrointestinal (GI) bleeding.^{3,4} In contrast to humans, there are limited guidelines for the use of acid suppressants in cats with CKD. Gastric mineralization, gastric gland atrophy, and hypergastrinemia, but not ulcerative or erosive gastropathy, are most commonly observed in cats with CKD.⁵ Gastric pH studies have not been performed in cats with CKD. Therefore, the contribution of hypergastrinemia and, if present, gastric hyperacidity, to the development of gastric mineralization and clinical signs of GI upset, has not been determined. There is no direct evidence to support the use of acid suppressants in cats with CKD. Despite this, acid suppressants such as famotidine and omeprazole are commonly prescribed for cats with CKD. In a recent cross-sectional survey of 1,089 cats with CKD, famotidine was one of the medications most commonly administered (27% of cats).² In our hospital, it is common for cats with advanced CKD to receive >4 medications daily including antihypertensive drugs, antiproteinuric drugs, phosphorous-binding drugs, anti-emetics, appetite stimulants, and acid suppressants. This daily “pill burden” likely leads to poor owner compliance, compromised human-animal bond, and decreased quality of life for the cat.

Moreover, prolonged administration of acid suppressants to cats with CKD may not be safe. Chronic

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administration of acid suppressants has been associated with calcium and PTH derangements, osteoporosis, and pathologic fractures in at-risk human populations.^{6–8} In a pilot study of 6 healthy cats, decreased bone mineral content and rebound serum hypergastrinemia were observed. The development of these adverse effects as a result of chronic acid suppressant treatment would be particularly concerning in cats with CKD.^{10–12} Studies have not been performed to determine if acid suppressant administration is warranted in cats with CKD. Accordingly, the principal objective of our study was to determine if cats with CKD have decreased gastric pH compared to age-matched, healthy control cats. Based on previously published work demonstrating hypergastrinemia in cats with CKD,^{5,13} we hypothesized that cats with CKD would have decreased gastric pH and increased serum gastrin concentrations compared to age-matched, healthy control cats.

Materials and Methods

Study Animals

The Institutional Animal Care and Use Committee (IACUC) at the University of Tennessee approved the protocol for this study (Approval# 2331-0315). Client-owned healthy adult cats and cats with stable CKD were prospectively enrolled into the study from September 2015 to November 2016 from 2 veterinary hospitals (UTK Veterinary Medical Center, UTK VMC, and Appalachian Animal Hospital, AAH). All owners completed a consent form before study enrollment. Inclusion criteria for cats with CKD included body weight >3.0 kg, and CKD, defined in accordance with International Renal Interest Society (IRIS) stages II–IV CKD, including history and physical examination findings suggestive of CKD, a stable serum or plasma creatinine concentration >1.6 mg/dL, and urine specific gravity <1.035 on 2 separate occasions during a clinically stable period with adequate hydration. Inclusion criteria for healthy control cats included lack of azotemia, urine specific gravity (USG) >1.035, normal symmetric dimethylarginine (SDMA) concentration,^a good body condition, and no recent (<2 months) history of medication administration other than routine heartworm and flea preventatives. Exclusion criteria in either group included clinical or biochemical evidence of other systemic diseases such as uncontrolled hyperthyroidism, primary gastrointestinal (GI) or hepatobiliary disease, use of acid suppressants, phosphorous-binding drugs, or any other drug that could alter gastric pH including nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and antibiotics within the past 7 days before or during gastric pH monitoring. Because the majority of cats with CKD were eating a prescription diet formulated specifically for cats with CKD (“therapeutic renal diet”; n = 7 of 10 cats with CKD),^b healthy cats also were fed a therapeutic renal diet during pH monitoring to minimize the effect of diet as a confounding variable. A CBC, plasma biochemistry profile, urinalysis, urine culture, serum total thyroxine concentration, serum gastrin concentration, and blood pressure measurement were performed within 72 hours of pH monitoring. All blood tests, with the exception of serum gastrin and SDMA concentrations, were performed by the UTK clinical pathology service. For measurement of serum gastrin concentrations, serum was collected from blood tubes after centrifugation at 250 × g and stored in cryovials at –80°C. After study completion, serum was shipped on dry ice to the Gastrointestinal Laboratory at Texas A&M University. Serum gastrin concentrations were measured by an automated chemiluminescence, enzyme-labeled immunometric assay^c as previously described.⁹

Gastric pH Monitoring

A pH monitoring capsule^d was detached from its delivery device and was administered PO with a syringe-style pet piller^e as previously described¹⁴ and followed by PO administration of 3–5 mL of water. Before use, all pH capsules and receivers were calibrated as previously described according to the manufacturer’s instructions.¹⁶ Gastric pH recordings were obtained telemetrically at 6-second sampling intervals for 12 hours after pH capsule administration. Owners were instructed to keep the receiver within 6 feet of the cat during the 12-hour monitoring period. When passage of the pH capsule out of the stomach occurred before collection of 12 hours of data, as defined by a rapid and persistent increase in pH >4 (Fig 1), a new pH capsule was administered PO to obtain the remaining data. If the subsequently administered pH capsule remained in the stomach for 12 hours, those data were used and the first recorded data were not included. The pH data were uploaded to the computer by proprietary software^f after the monitoring period. Data from the esophageal and duodenal recording periods were discarded (Fig 1). Only data from the first 12 hours of recording were included in the analysis. Mean pH and mean percentage of time (MPT) that gastric pH was in 1 of 8 categories (ie, 0–1, 1–2...7–8) were calculated by the proprietary software supplied by the device manufacturer.

Statistical Analysis

The selected number of cats (n = 10 in each group) was based on power calculations derived from 2 sample *t*-tests. A significance level of alpha = 0.05 was used for sample size estimates as was power of 80%. The SAS Power and Sample Size application^g was used for all calculations. To detect a difference in means of 0.84 in gastric pH of cats with CKD compared to healthy cats assuming a common standard deviation (SD) of 0.5 (numbers based on preliminary data of pH distribution in healthy colony cats¹⁶ compared to cats with CKD), 7 cats per group would be required to determine that the 2 means are significantly different. To account for potential subject drop out, our goal was to recruit 9–10 cats per group. A 2 independent sample Welch’s *t*-test was used to evaluate for a significant difference in age between groups because variances were unequal. Mean gastric pH and the percentage of time gastric pH was <2 were compared between cats with CKD and healthy cats by a 2 independent sample pooled *t*-test. A pooled *t*-test was also used to evaluate for differences in mean pH between cats with early CKD (IRIS stage II) and cats with moderate-to-severe CKD (IRIS stage III and IV). Serum gastrin concentration, plasma creatinine concentration, and percentage time gastric pH was <1 were compared between groups by a Mann-Whitney *U*-test. Spearman’s rank correlation was performed to evaluate for a correlation among plasma creatinine concentration, serum gastrin concentration, and mean gastric pH. All data were analyzed by commercially available statistical software (SAS 9.4^g and IBM SPSS 24^h).

Results

Cats

Thirteen cats with CKD and 10 healthy cats were evaluated during the study period. Ten cats with CKD and 9 healthy cats met the inclusion criteria and completed the pH monitoring. Two cats with CKD were excluded for medically uncontrolled hyperthyroidism. One cat with CKD underwent pH monitoring but the capsule passed after 1 hour and a second capsule was not administered. One healthy cat had a USG <1.035.



Fig. 1. Example of gastric pH monitoring data in a healthy cat. The pH capsule transmits data from the esophagus (A), stomach (B), and duodenum (C). A rapid drop in pH below 2 and a rapid and persistent rise in pH above 4 characterize aboral transit into and out of the stomach, respectively. The horizontal red line denotes the 12 hours of pH data used for comparative analyses.

In total, 5 cats with IRIS stage II CKD, 4 cats with stage III CKD, and 1 cat with stage IV CKD were enrolled. There was a significant difference in the median plasma creatinine concentration between groups ($P = 0.001$). There was no significant difference in age between groups with a mean (\pm SD) age of 14.1 (\pm 5.4) years in CKD cats compared to a mean (\pm SD) age of 12.3 (\pm 1.7) years in the healthy control cats ($P = 0.35$). There were 5 castrated males and 5 spayed females in the CKD group and 2 castrated males and 7 spayed females in the healthy control group. The median body condition score of cats with CKD was 4 (range, 2–8). The median body condition score of healthy cats was 6 (range, 5–9). Muscle condition score would have helped insure that the degree of azotemia was not underestimated by muscle loss but regrettably was not collected. Cats with CKD were receiving the following medications or treatments for signs related to CKD: antihypertensive drugs (amlodipine, $n = 3$ or benazepril, $n = 1$), as needed or daily mirtazapine ($n = 4$), intermittent or daily SC fluids ($n = 4$), maropitant ($n = 1$), darbepoetin ($n = 1$), and polyethylene glycol 3350 OTC ($n = 1$). Two cats with CKD were receiving famotidine before study enrollment. Based on a study in dogs demonstrating normalization of serum gastrin concentration after withdrawal of famotidine for 7 days, the drug was discontinued in both cats for a minimum of 8 days before and during pH monitoring.¹⁵ Seven cats with CKD were eating a therapeutic renal diet at the time of pH monitoring. Six of the 10 cats with CKD were meal fed. None of the cats with CKD had a change in appetite during the pH monitoring period. Six of the 10 cats with CKD were reported to have a decreased appetite before and during the pH monitoring period. One cat with stage IV CKD did not eat immediately before and during the pH monitoring period. All 9 healthy cats had a good

appetite before pH monitoring. Seven of the 9 healthy cats were meal fed. Two of the 9 healthy cats had a decreased appetite during the pH monitoring period. All control cats had SDMA concentrations within normal limits (median: 12 μ g/dL; range, 8–14). Results of SDMA concentrations also were available in 7 of 10 cats with CKD. All were above the upper limit of the reference range (≥ 14 μ g/dL; median, 19; range, 17–36).

pH capsules

pH capsules administered on the first attempt were successfully retained in the stomach for the entire 12-hour period in 3 cats with CKD and 4 healthy control cats. The remaining cats had a second pH capsule administered to obtain the remaining data. One healthy control cat had to have a third pH capsule placed because the second pH capsule also exited the stomach early. The third pH capsule stayed in the stomach for the full length of the 12-hour monitoring period. Therefore, this data were used and data from the other 2 monitoring periods were discarded. The median duration of time the pH capsule stayed in the stomach on the first attempt was 6 hours (range, 46 minutes–48 hours). Oral administration of the pH capsule was occasionally challenging because of the length of the pH capsule, and required several attempts to achieve capsule ingestion, but no complications were observed as a result of PO administration of pH capsules.

Serum Gastrin Concentration and pH Monitoring

Serum gastrin concentration, mean gastric pH, and the percentage of time that gastric pH was strongly acidic (pH <1 and <2) in a 12-hour period were used for comparative analyses and are presented in Table 1

Table 1. Gastric pH values and serum gastrin concentrations in healthy cats and cat with chronic kidney disease (CKD).

Parameter	Control	CKD	<i>P</i> value
Mean \pm SD minimum pH (median, range)	0.3 \pm 0.3 (0.28, 0.06–0.73)	0.5 \pm 0.5 (0.5, 0.02–0.69)	
Mean \pm SD gastric pH (median, range)	1.6 \pm 0.3 (1.67, 0.96–2.06)	1.8 \pm 0.5 (1.87, 1.2–2.71)	0.23
Median percentage time (range) pH < 1	22.3 (0.3–66.9)	13.3 (0.3–50.4)	0.564
Mean percentage time \pm SD pH < 2 (median, range)	79.0 \pm 12.7 (82.6, 63.4–99.8)	70.9 \pm 12.2 (69.4, 57.2–88.0)	0.17
Median (range) serum gastrin concentration (ng/dL)	54.6 (< 10–98.0)	18.7 (< 10–659.0)	0.713

SD, Standard deviation.

and Figures 2–4. There was no significant difference in serum gastrin concentrations (Fig 4) between cats with CKD (median [range], 18.7 ng/dL [<10 –659.0]) and healthy control cats (median [range], 54.6 ng/dL [<10 –98.0]; $P = 0.713$). Serum gastrin concentration was not available for 1 healthy cat because this sample had been misplaced during storage. No significant differences were observed in any pH category between cats with CKD and healthy cats. The average minimum pH observed in either group also was similar. No differences in mean gastric pH were observed when comparing cats with early CKD (IRIS stage II) to cats with moderate-to-severe CKD (IRIS stages III and IV; $P = 0.56$). The mean gastric pH of the 2 cats receiving famotidine before study enrollment was 1.84 and 1.94, respectively. No correlation was identified between serum gastrin concentration or plasma creatinine concentration (Fig 3) and mean gastric pH ($P = 0.92$ and 0.29, respectively).

Discussion

We compared gastric pH and serum gastrin concentrations in cats with CKD to healthy control cats of

comparable age. No significant differences were observed with regard to their 12-hour mean gastric pH or percentage time the gastric pH was strongly acidic (pH <1 and <2). Moreover, the minimum pH was also similar between the 2 groups. The International Renal Interest Society (IRIS) recommends the use of a proton pump inhibitor in combination with anti-emetic drugs for the treatment of CKD-related GI signs such as hyporexia and vomiting. However, our sample of cats with CKD did not have gastric hyperacidity compared to age-matched, healthy control cats. Indeed, the majority of cats with IRIS stage III and IV CKD, including 2 cats that had been receiving acid suppressants 8 days before the start of the study, had a mean pH that was similar to or higher than the mean pH of healthy cats. Based on comparison of pH alone, these preliminary results suggest that acid suppression may not be needed in cats with CKD and, specifically, may not have been needed in the 2 cats that had received famotidine before being enrolled in the study. Moreover, there was no relationship between plasma creatinine concentration and mean gastric pH. These findings, in combination with histopathologic studies showing an absence of erosive and ulcerative disease in cats with CKD, suggest

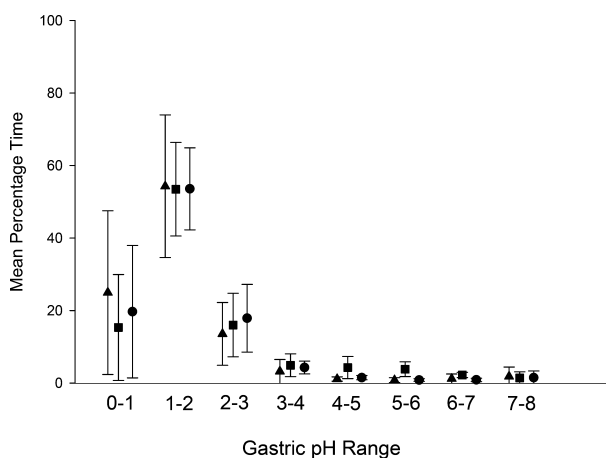


Fig. 2. Comparison of 12-hour gastric pH distribution in healthy cats and cats with CKD. Mean percentage time \pm SD pH is in one of eight pH categories in healthy cats (▲) and cats with stage II and stage III (■), and stage IV CKD (●).

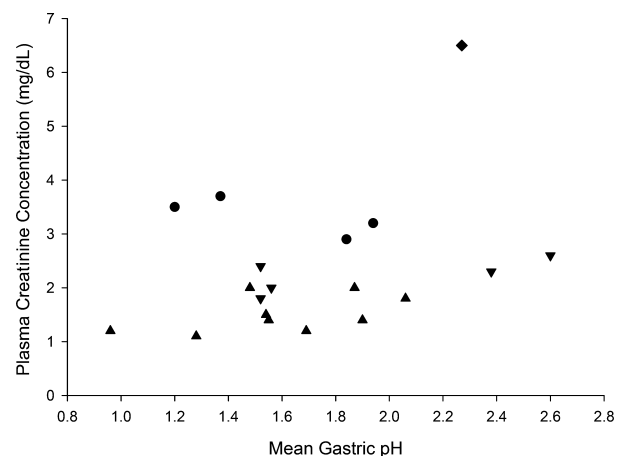


Fig. 3. Scatterplot of mean gastric pH and plasma creatinine in healthy cats and cats with chronic kidney disease (CKD). No relationship is observed between plasma creatinine and 12-hour mean gastric pH in healthy cats (▲) and cats with stage II (▼), stage III (●), and stage IV CKD (black diamond).

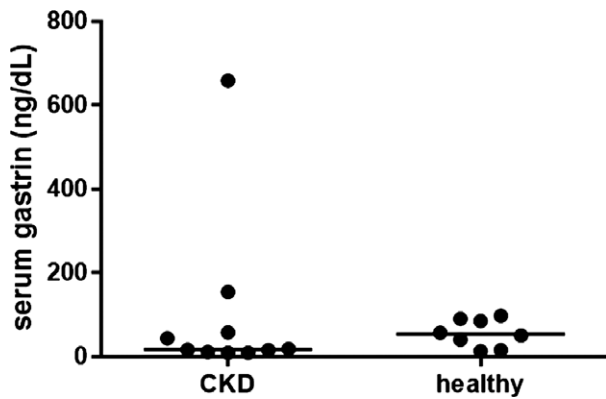


Fig. 4. Serum gastrin concentrations in cats with CKD and healthy control cats. Median serum gastrin concentration is represented by the horizontal bar.

that further studies to determine if there is any real benefit of acid suppression in cats with CKD are warranted.⁵

Serum gastrin concentrations were not significantly different between cats with CKD (median, 18.7 ng/dL) and healthy control cats (median, 54.6 ng/dL; $P = 0.713$). This finding is in contrast to previous studies using a larger cohort of cats (≥ 30 cats with CKD) that demonstrated significantly higher serum gastrin concentrations in cats with CKD compared to healthy control cats.^{5,13} At the same time, our findings are in agreement with another study that failed to demonstrate an association of serum gastrin concentrations and stage of kidney disease.⁵ In all studies, including our study, serum gastrin concentrations were highly variable in cats with CKD. Moreover, serum gastrin concentration did not correlate with plasma creatinine concentration in our study. Indeed, the 1 cat with stage IV CKD had only a mild increase in serum gastrin concentration (44.10 ng/dL).

We previously have shown that there is no buffering effect of food on gastric pH when pH capsules are adhered to the gastric mucosa of cats.¹⁶ However, pH capsules were administered PO in our present study, thus the presence of a meal could have had a bigger impact on our measurements of gastric pH. More cats with CKD had a decreased appetite before and during pH monitoring as compared to healthy control cats. Thus, we might have expected for healthy cats to have higher gastric pH as a result of the influence of food but this effect was not observed. Therefore, the buffering effect of food on gastric pH is unlikely to have played a role in failing to detect gastric hyperacidity in cats with CKD.

We also describe here a novel method for noninvasively assessing gastrointestinal pH without necessitating sedation or general anesthesia to secure the pH capsule to the GI mucosa. Although the pH capsule could be used to assess gastric emptying time as well as pH along the GI tract, PO administration of the pH capsules to assess continuous 12-hour gastric pH is not advised. This method proved to be time-consuming and cost

prohibitive because the majority of cats in this study necessitated the administration of 2 pH capsules to capture the entire 12-hour monitoring period. We have recently demonstrated that pH capsules can be placed in the gastric fundus by radiographic guidance.¹⁷ However, we chose to pursue PO administration of the capsules because none of the cats underwent medical procedures that necessitated sedation and unnecessary sedation of a cat with CKD was considered to be unethical because of its potential detrimental effect on residual renal function.

Our study included a small group of cats. Endoscopic evaluation of the stomach and acquisition of gastric tissue samples for histopathologic examination were not performed. However, evaluation of history, physical examination, and laboratory results did not identify any abnormalities suggestive of GI disease. Inclusion of cats with late-stage CKD for this type of study proved difficult. For this reason, 50% of the enrolled cats with CKD had IRIS stage II CKD. The IRIS group recommends consideration of acid suppressant treatment in cats with IRIS stage III and IV CKD. Thus, it is possible that inclusion of more cats with stage III or IV CKD might have resulted in a significant difference in serum gastrin concentration and gastric pH between groups. However, examination of gastric pH in cats with earlier stages of CKD has clinical relevance. The use of acid suppressants in cats with IRIS stage II CKD is common. In a retrospective of 89 cats with CKD, more cats with stage II CKD were receiving acid suppressants compared to those that were not.¹ In our study, there was no association between severity of renal disease and gastric hyperacidity. There also was no difference in mean gastric pH between cats with IRIS stage II CKD and cats with stage III or IV CKD. The single cat with stage IV CKD had one of the highest gastric pH values of either group. Although no significant differences were identified between groups, we observed that all gastric pH parameters including mean and minimum gastric pH were higher in cats with CKD compared to healthy, age-matched control cats. Although further study is needed, we hypothesize that gastric fibrosis and gastric gland atrophy observed in cats with CKD may lead to loss of parietal cell mass and a subsequent increase in gastric pH compared to healthy cats. In our study, 6 of the 10 cats with CKD had a decreased appetite and likely represent cats that veterinarians would consider good candidates for administration of acid suppressants. Thus, further study is needed to determine if there is any benefit to the use of acid suppressants for amelioration of GI signs in cats with CKD.

In conclusion, our results suggest that, in contrast to conventional assumptions, cats with CKD might not have gastric hyperacidity or hypergastrinemia when compared to age-matched healthy control cats. Thus, additional studies are warranted both to evaluate gastric pH in cats with later stages of CKD as well as to determine if there is an actual benefit of acid suppression in cats with CKD.

Footnotes

- ^a IDEXX Laboratories, Inc., Westbrook, ME
- ^b Royal Canin Veterinary Diet Renal cat food (all controls and n = 5 cats with CKD); Hill's Prescription Diet K/D feline (n = 2 cats with CKD)
- ^c Immulite 2000, Siemens Healthcare Diagnostics, Malvern, PA
- ^d Bravo pH capsule with delivery system, Given Imaging, Duluth, GA
- ^e JorVet Bullseye pet piller, Jorgensen Labs
- ^f Polygram Net Software, Given Imaging, Yokneam, Israel
- ^g SAS Institute Inc, Cary, NC USA
- ^h IBM Corporation, Armonk, New York
- ⁱ Gould E et al. J Feline Med Surg. Epub ahead of print. 2017 <http://journals.sagepub.com/doi/abs/10.1177/1098612X17718132?journalCode=jfma>
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Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

1. Marino CL, Lascelles BD, Vaden SL, et al. Prevalence and classification of chronic kidney disease in cats randomly selected from four age groups and in cats recruited for degenerative joint disease studies. *J Feline Med Surg* 2014;16:465–472.
2. Markovich JE, Freeman LM, Labato MA, et al. Survey of dietary and medication practices of owners of cats with chronic kidney disease. *J Feline Med Surg* 2014;17:979–983.
3. Bunchorntavakul C, Atsawarungrangkit A. Prevalence of asymptomatic gastroduodenal lesions and *Helicobacter pylori* infection in kidney transplant candidates. *J Med Assoc Thai* 2014;97(Suppl 11):S62–S68.
4. Sotoudehmanesh R, Ali Asgari A, Ansari R, et al. Endoscopic findings in end-stage renal disease. *Endoscopy* 2003;35:502–505.
5. McLeland SM, Lunn KF, Duncan CG, et al. Relationship among serum creatinine, serum gastrin, calcium-phosphorus product, and uremic gastropathy in cats with chronic kidney disease. *J Vet Intern Med* 2014;28:827–837.
6. Mizunashi K, Furukawa Y, Katano K, et al. Effect of omeprazole, an inhibitor of H⁺, K(+)–ATPase, on bone resorption in humans. *Calcif Tissue Int* 1993;53:21–25.
7. Moberg LM, Nilsson PM, Samsioe G, et al. Use of proton pump inhibitors (PPI) and history of earlier fracture are independent risk factors for fracture in postmenopausal women. *The WHILA study. Maturitas* 2014;78:310–315.
8. Wilhelm SM, Rjater RG, Kale-Pradhan PB. Perils and pitfalls of long-term effects of proton pump inhibitors. *Expert Rev Clin Pharmacol* 2013;6:443–451.
9. Gould E, Clements C, Reed A, et al. A prospective, placebo-controlled pilot evaluation of the effect of omeprazole on serum calcium, magnesium, cobalamin, gastrin concentrations, and bone in cats. *J Vet Intern Med* 2016;30:779–786.
10. Barber PJ, Elliott J. Feline chronic renal failure: Calcium homeostasis in 80 cases diagnosed between 1992 and 1995. *J Small Anim Pract* 1998;39:108–116.
11. Finch NC, Syme HM, Elliott J. Parathyroid hormone concentration in geriatric cats with various degrees of renal function. *J Am Vet Med Assoc* 2012;241:1326–1335.
12. Shipov A, Segev G, Meltzer H, et al. The effect of naturally occurring chronic kidney disease on the micro-structural and mechanical properties of bone. *PLoS One* 2014;9:e110057.
13. Goldstein RE, Marks SL, Kass PH, et al. Gastrin concentrations in plasma of cats with chronic renal failure. *J Am Vet Med Assoc* 1998;213:826–828.
14. Lane M, Larson J, Hecht S, et al. Medical management of gastrinoma in a cat. *JFMS Open Rep* 2016;2.
15. Parente NL, Olivier NB, Refsal KR, et al. Serum concentrations of gastrin after famotidine and omeprazole administration to dogs. *J Vet Intern Med* 2014;28:1465–1470.
16. Parkinson S, Tolbert K, Messenger K, et al. Evaluation of the effect of orally administered acid suppressants on intragastric pH in cats. *J Vet Intern Med* 2014;29:104–112.
17. Tolbert MK, Graham A, Odunayo A, et al. Repeated famotidine administration results in a diminished effect on intragastric pH in dogs. *J Vet Intern Med* 2017;31:117–123.