

***Helicobacter* spp. in domestic cats: identification and relationship with anatomical and histopathological gastric changes in animals of blood group A¹**

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ABSTRACT- Sousa D.A., Cascon C.M., Mello M.F.V., Leite J.S., Medeiros M.A., Fonseca A.B.M. & Ferreira A.M.R. 2017. ***Helicobacter* spp. in domestic cats: identification and relationship with anatomical and histopathological gastric changes in animals of blood group A.** *Pesquisa Veterinária Brasileira* 37(12):1467-1473. Departamento de Patologia e Clínica Veterinária, Faculdade de Veterinária, Universidade Federal Fluminense, Rua Vital Brazil 64, Niterói, RJ 24230-340, Brazil. E-mail: anatopatovet@vm.uff.br

The aim of this study was to evaluate the presence of gastric *Helicobacter*-like organisms and the endoscopic and histopathological changes in domestic cats with blood type A. Samples from the stomach antrum, body and fundus were collected from 32 mixed-breed stray domestic cats using gastroscopy. Urease testing and cytological analysis were performed in fresh samples. Tissue sections were processed and stained with hematoxylin and eosin (H&E) and the Warthin-Starry (WS) silver staining methods for histopathological examination. *Helicobacter* spp. were detected in 100% of samples subjected to silver staining and cytological analysis, and in 96.9% of samples subjected to urease testing. In 87.5% of the cats, mononuclear inflammatory-cell infiltrates were identified. The graduation and distribution of inflammatory infiltrates in these cats revealed mild (78.1%) to moderate (9.4%) inflammatory changes in at least one gastric region. These changes were independent of the colonization score. Hyperplasia of the lymphoid follicles was detected in three cats. Cats of blood group A are often colonized by *Helicobacter* spp. and the macroscopic and microscopic findings are consistent with studies in domestic cats reported to date, concluding that the most common blood group in cats is not associated with high susceptibility to symptomatic gastritis.

INDEX TERMS: *Helicobacter* spp., domestic cats, blood group A, endoscopy, feline, gastritis, histopathology.

RESUMO.- [*Helicobacter* spp. em gatos domésticos: identificação e relação com alterações gástricas anatômicas e histopatológicas em animais de sangue tipo A.] O ob-

jetivo deste estudo foi avaliar a presença de organismos semelhantes a *Helicobacter* e as alterações endoscópicas e histopatológicas em estômago de gatos domésticos de sangue tipo A. Amostras de antro, corpo e fundo gástricos foram coletadas de 32 gatos, sem raça definida, não domiciliados através de gastroscopia. Teste de urease e análise citológica foram realizados em amostras frescas. Secções teciduais foram processadas e coradas com hematoxilina e eosina e pela prata pelo método de Warthin-Starry para avaliação histológica. *Helicobacter* spp. foi detectado em 100% das amostras submetidas às análises citológicas e coloração pela prata e em 96,9% das amostras submetidas ao teste de urease. Em 87,5% dos gatos foi identificado infiltrado inflamatório mononuclear. A graduação e distribuição do infiltrado inflamatório nestes gatos revelaram alterações leves (78,1%) a moderada (9,4%) em pelo menos uma região gástrica. Estas alterações eram independentes do escore de

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colonização. Hiperplasia de folículos linfóides foram detectadas em 3 gatos. Gatos do grupo sanguíneo A são frequentemente colonizados por *Helicobacter* spp. e os achados macro e microscópicos são consistentes com estudos em gatos domésticos realizados até a presente data. Conclui-se que o grupo sanguíneo mais comum em gatos não está associado com uma alta susceptibilidade a gastrite sintomática causada por *Helicobacter* spp.

TERMOS DE INDEXAÇÃO: *Helicobacter* spp., felinos, grupo sanguíneo A, endoscopia, gastrite, histopatologia, endoscopia.

INTRODUCTION

Because *Helicobacter pylori* (*H. pylori*) has been described as a cause of gastric diseases in humans, the number of studies on the pathophysiology of these disorders were quite intensified, leading to the description of various related bacterial species in different mammals. The studies in humans have demonstrated an association of the ABO blood group system with susceptibility and/or resistance to such diseases (Coelho & Diniz 2010). In individuals belonging to the blood group O of the ABO system, it was observed a greater predisposition to the development of gastric diseases caused by *H. pylori* (Mattos et al. 2010, Jaff 2011). The gastric *Helicobacter* spp. infection in mixed-breed cats has also demonstrated a high association with mild to moderate gastritis (Geyer et al. 1993, Papasouliotis et al. 1997, Neiger et al. 1998, Araujo et al. 2010). Nevertheless, up to this day, there have been no studies in the literature including the description of *Helicobacter* spp. infection, gastric lesions and specific blood types in domestic cats. In 1950, it was reported the existence of a blood group system in felines, which consists of two kinds of naturally occurring alloantibodies. These two types received the nomenclature A and B, and later on, in 1980, a third blood type was described in cats, and named as AB. There are no reports of cats that do not have erythrocytary antigens - blood type O or zero, and studies in different countries show that most mixed-breed cats belong to blood group A (Jaff 2011). Therefore, the aim of the present study was to evaluate the presence of gastric *Helicobacter*-like organisms (GHLOs) and endoscopic and histopathological changes in domestic undomesticated cats with blood type A.

MATERIALS AND METHODS

Ethics statement. This study was approved by the Ethics Committee on Animal Use (CEUA, Comitê de Ética no Uso de Animais) of Universidade Federal Fluminense, Niterói, Brazil, under the protocol number 48/2011.

Animals. Thirty-two undomesticated domestic cats (12 males and 20 females), with body weight ≥ 2.0 kg, from a shelter for abandoned animals, underwent gastroscopy before the sterilization routine.

Collection and blood typing. A sample of 1.0 mL of blood was collected from the cephalic or femoral vein of cats and was sent, in a test tube containing EDTA, to a clinical lab for blood typing. For each sample, 30 μ L of blood was mixed with 30 μ L of wheat germ lectin (*Triticum vulgaris* lectin) in a test tube, in order to induce agglutination of cat blood of type B and AB. Samples from the cats whose blood did not undergo agglutination were selected for this study, because they belonged to blood group A.

Gastroscopy and gastric biopsy. The cats were fasted for 12 h before procedure. The induction and maintenance of anesthesia were performed with tiletamine-zolazepam association (Zoletil® 100). For induction it was used the dose of 3.75 mg/kg (0.075 mL/kg) intramuscular (IM) and for maintenance a dose of 2.5 mg/kg (0.05 mL/kg) intravenous (IV), diluted in 3 mL of saline solution, and reapplied when the animal presented superficialization signals. The assessment and collection of gastric mucosa samples were performed using a pediatric endoscope (Pentax FG-28C) of 9.0-mm diameter, with a 2.0-mm biopsy channel. The evaluation of the gastric mucosa was based on the WSAVA International Gastrointestinal Standardization Group (Washabau et al. 2010). At least two samples of the mucosa from the gastric body, antrum, and fundus were collected and individually stored. Between the procedures performed on different animals, all endoscopes, biopsy forceps, and cytology brushes were sterilized by immersion in glutaraldehyde for 20 min and then rinsed under tap water.

Rapid urease test. The mucosa samples from the stomach antrum, body, and fundus of each cat were collected and individually placed in a microtube of Renylab Uretest® commercial kit (Renylab Chemicals & Pharmaceuticals) according to the manufacturer's instructions. Samples that had changed color from yellow to magenta were considered positive for *Helicobacter* spp. The reading of results was performed at three time points (30 min, 2 h, and 8 h) and the timing of color changes was analyzed for a possible association with the amount of bacteria in the sample.

Cytopathology. Samples for cytological examination were obtained during gastroscopy via insertion of a cytology brush into the biopsy channel and brushing on the mucosa with a subsequent preparation of the smear material for microscopy on slides. Samples of each gastric region were separately collected and were air dried for later immersion in carbol fuchsin for 60 s and followed by washing in distilled water. The samples were examined under a light microscope with a 40 $\times$ objective in search of pink stained GHLOs. The sample was considered positive when there was at least one bacterial cell with morphology matching to the genus *Helicobacter*.

Histopathology. Immediately after collection, the samples were fixed in 10% buffered formalin for 24 to 48 hours for processing and paraffin embedding. Histological sections 3–5 μ m in thickness were stained with hematoxylin and eosin (HE) and the Warthin-Starry (WS) silver staining method. The presence and intensity of inflammatory cells were evaluated in H&E stained tissue sections under a light microscope with a 40 $\times$ objective. The type of inflammatory infiltrate was characterized and the cells were counted and classified according to the following scale: 0 (no change), up to 20 inflammatory cells per field; 1 (mild gastritis), 11–50 inflammatory cells per field; 2 (moderate gastritis), 51–100 inflammatory cells per field; and 3 (severe gastritis), >100 inflammatory cells per field (Day et al. 2008). Spiral and black GHLOs were counted in five fields of WS silver staining histological sections. The colonization density of GHLOs was scored according to Araujo et al. (2010) as: 0 (no infection), 1 (up to 10 GHLOs), 2 (from 10 to 50 GHLOs), 3 (from 51 to 100 GHLOs), 4 (from 101 to 200 GHLOs), 5 (>200 GHLOs).

Statistical analysis. The chi-square test, McNemar's test and the Cramer coefficient was used. Level of significance was set to 5%.

RESULTS

Endoscopic appearance of the gastric mucosa

Of the 32 animals evaluated, eight (25%) showed alterations in the gastric mucosa. Of these, six had mild endos-

copic gastritis and the other two animals showed moderate endoscopic pangastritis (Table 1). The other 24 (75%) animals had intact gastric mucosa with pale pink color and soft folds in the region of the stomach body.

Rapid urease test

In the urease test, 31cats (96.9%) showed positive results in the samples of the three gastric regions studied and one cat (3.1%) had negative results in the three samples tested (Table 2).

Table 1. Changes observed in different gastric regions of domestic cats during gastroscopy

Animal ID	GF	GB	GA
1	-	-	HY (1)
2	-	-	HY (1)
3	HY (1)	-	-
4	-	ER/UL (1)	-
5	ER(1)	-	-
6	ER (1)	-	-
7	HY/ED (2)	HY/ED (2)	HY/ED (2)
8	HY/ED (2)	HY/ED (2)	HY/ED (2)

GF = gastric fundus, GB = gastric body, GA = gastric antrum, HY = hyperemia, ED = edema, ER = erosion, UL = ulcer; 1 = mild, 2 = moderate.

Table 2. Urease test results. The relationship between time elapsed until a color change and the percentage of samples of each gastric region of domestic cats showing positivity for *Helicobacter* spp.

Color change	Gastric region		
	Antrum	Body	Fundus
Up to 30 min	17 (54.8%)	12 (38.7%)	19 (61.3%)
From 30 min to 2 h	5 (16.1%)	10 (32.2%)	5 (16.1%)
From 2 h to 8 h	9 (29.1%)	9 (29.1%)	7 (22.6%)
Negative	1	1	1

Min = minutes, b- h = hours.

Table 3. The frequency of colonization density of GHLOs in the gastric regions of the cats

Gastric Region	The score corresponding to the amount of <i>Helicobacter</i> spp. found				
	1	2	3	4	5
Antrum	3.1 %	21.9 %	21.9 %	31.2 %	21.9 %
Body	6.3 %	15.6 %	9.4 %	21.9 %	46.8 %
Fundus	3.1 %	15.6 %	12.5 %	34.4 %	34.4 %

Cytopathology

In all samples, the cytological examination showed the presence of at least one bacterial cell with morphology resembling the genus *Helicobacter* (Fig.1); these data indicate 100% of positive results among the studied cats.

Histopathology

In the histopathological analysis of the inflammatory infiltrate, 4 cats (12.5%) showed no changes in any of the examined gastric regions. Mononuclear cells infiltrates were identified in 28 cats (87.5%). In 25 cats (78.1%), there was a mild infiltrate and in 3 cats (9.4%) there was a moderate infiltrate in at least one gastric region. This assay revealed the presence of lymphocytes and plasma cells (Fig.2). Eight samples from the antrum, 11 from the body, and nine from the fundus had a score of 0. The score of 1 was assigned to 24 samples from the antrum, 20 samples from the body, and 21 samples from the fundus. The score of 2 was assigned to only one sample from the body and two from the fundus. The score of 3 was not assigned to any of the samples. Therefore, the samples were classified as either mild lymphoplasmacytic gastritis (score 1) or moderate lymphoplasmacytic gastritis (score 2).

In the assessment of the lymphoid follicles, only two samples from the antrum, one from the body, and three from fundus showed hyperplasia of lymphoid follicles. These samples were from only four animals.

Regarding the quantification of GHLO stained using the WS method, the body region showed the largest number of bacterial cells, followed by the gastric fundus and the gastric antrum as described in Table 3.

All samples of the mucosa from the gastric antrum, body, and fundus that were stained with WS revealed the presence of bacteria with morphology resembling the genus *Helicobacter*, confirming the results observed in the cytological assay (Fig.3).

Relation between diagnostic methods

Urease and WS stain. When comparing the urease test and histological analysis with the WS stain using Cramer's V statistic, the *p* value was 0.000 in the antrum, 0.010 in the body, and 0.000 in the fundus, showing a correlation between the time elapsed before a color change in the urease test and the number of gastric GHLOs in each region (Fig.4).

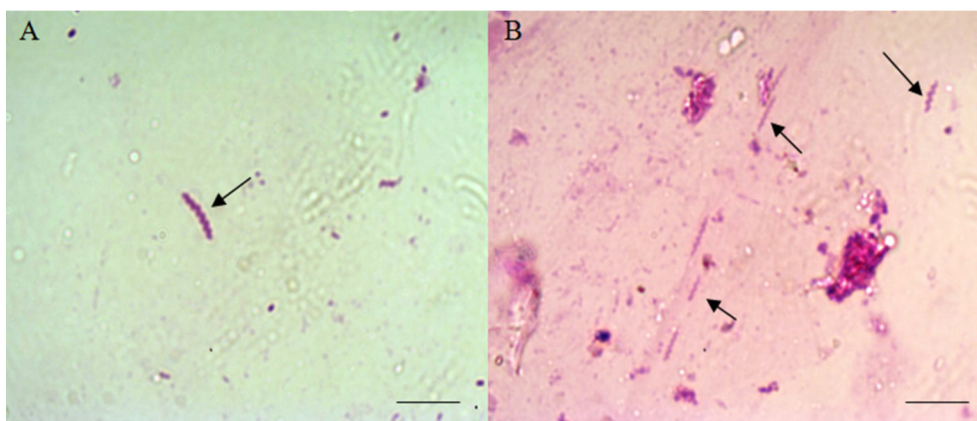


Fig.1. Gastric *Helicobacter*-like organism in domestic cats cytological smear (arrows). Carbol Fuchsin staining, scale bar = 10µm.

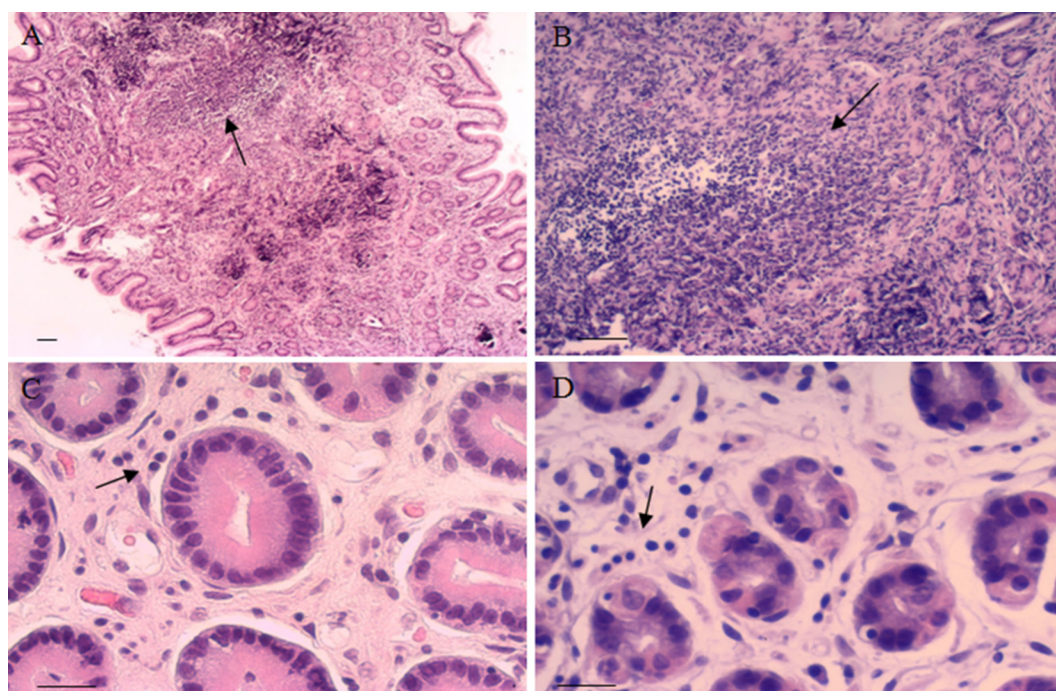


Fig.2. Inflammatory cells in the gastric mucosa of domestic cats. Hematoxylin and eosin staining. (A,B) Lymphoid follicle. (C,D) Lymphocytic inflammatory infiltrate in the lamina propria of the mucosa. (A) Bar = 50µm. (B,C,D) Bar = 20µm.

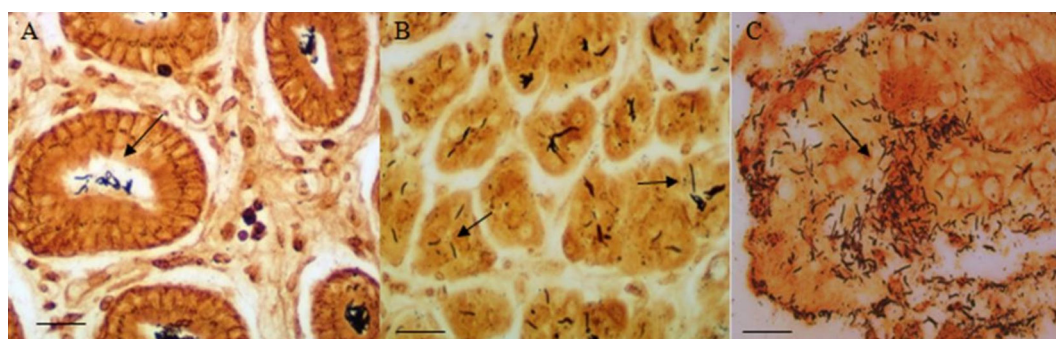


Fig.3. Colonization by gastric *Helicobacter*-like organisms (GHLOs) in the gastric mucosa of domestic cats. Warthin-Starry Silver staining. (A) Fundus region showing GHLOs in the glandular lumen. (B) Gastric body region showing GHLOs of varying sizes. (C) Fundus region, showing GHLOs marked in black on the surface mucus. (A,B,C) Bar = 20µm.

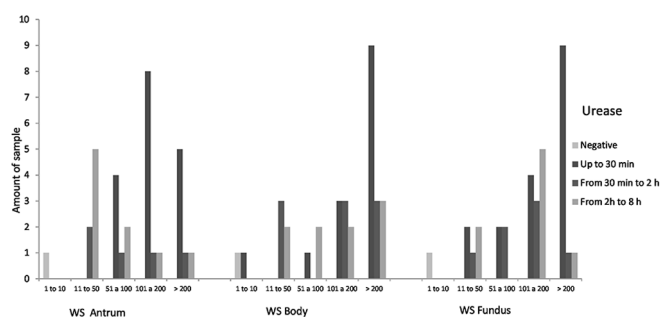


Fig.4. A histogram representing the relationship between time elapsed before a color change in the urease test and the colonization score (Warthin-Starry) in each sample of each gastric region of domestic cats.

HE and WS. The observation between histopathological samples stained with WS and HE using the Cramer's V statistic, was obtained $p=0.454$ in the antrum, $p=0.195$ in the body, and $p=0.501$ in the fundus; therefore, there was

no correlation between the inflammatory infiltration score and number of gastric GHLOs in each gastric region (Fig.5).

DISCUSSION

This study shows the occurrence of *Helicobacter* spp. in >90% of mixed-breed cats; this finding is in agreement with other studies in different countries (Papasouliotis et al. 1997, Akhtardanesh et al. 2006, Takemura et al. 2007, Araujo et al. 2010). One factor that may contribute to the spread of microorganisms among felines, including *Helicobacter* spp., is the habit of licking each other. One of the alleged routes of transmission of these bacteria is the direct oral route (Goh et al. 2011), which may explain the high percentage of infected animals found in different studies.

The urease test proved highly sensitive, detecting the presence of *Helicobacter* spp. in 31 of 32 cats. This negative cat had positive results for the cytological analysis and histopathology stained with silver (WS) show the presence

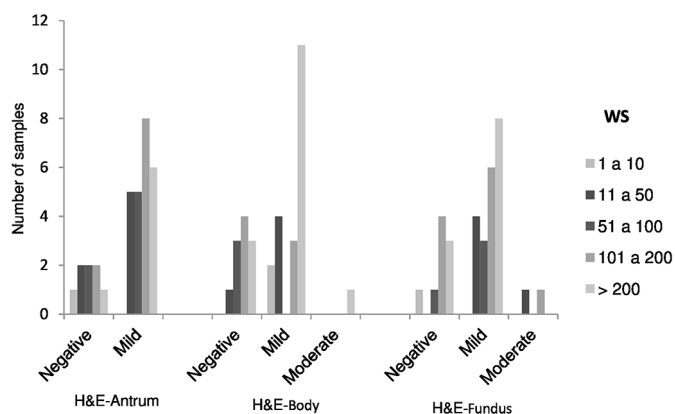


Fig.5. A histogram representing the relationship between the number of inflammatory cells and the score of colonization in each gastric region of domestic cats. Negative = up to 10 inflammatory cells per field; mild = 11–50 inflammatory cells per field; moderate = 51 to 100 inflammatory cells per field.

of GHLOs but with a very low number of bacteria reaching only score 1 in all samples. Over 70% of the samples of all gastric regions yielded positive results in the urease test within 2 h, and the color change occurred more rapidly in the samples with higher density of GHLOs. This finding leads us to the conclusion that the number of microorganisms influences the speed of degradation of the test urea, thereby showing a faster positive result (Fig.4).

In this study, all samples (100%) yielded a positive result in cytopathology and histopathological examination with silver staining (WS), showing that these tests have high sensitivity. This is in agreement with other studies showing that cytopathology and silver stained samples - (WS) are highly sensitive tests for detection of the genus *Helicobacter* (Takemura et al. 2007, Araujo et al. 2010).

The highest percentage of colonization by *Helicobacter* spp. in the gastric mucosa was observed in the body region followed by the fundus, which was in line with other studies in cats (Takemura et al. 2007, Araujo et al. 2010). In this study, >50% of all regions had the colonization scores 4 and 5, whereas only 6.3% of the samples from the body region and 3.1% from the antrum and fundus had a score of 1. Therefore, we can say that undomesticated cats have the gastric mucosa with colonization by *Helicobacter* spp. at the moderate to intense level.

The results of macroscopic evaluation by endoscopy, showed changes like hyperemia, edema, erosion and/ or ulcer in 25% of the animals. Nonetheless, when assessing microscopic changes, inflammatory infiltrate was observed in 87.5% of the animals. These data show that the macroscopic and microscopic results are not related in the evaluation of the presence of gastritis. This finding is in agreement with the results of obtained by Akhtardanesh et al. (2006), who observed macroscopic changes in only 26.3% of animals, while histopathological changes were found in 66.7% of the studied samples.

The presence of a mild to moderate inflammatory infiltrate found in different gastric regions is in line with other studies (Geyer et al. 1993, Takemura et al. 2007, Araujo et al. 2010). In the present research the inflammatory infil-

trate was not correlated with the density of colonization showing similar results reported by Akhtardanesh et al. (2006) and Neiger et al. (1998) but different from findings of other authors, who reported existence of this association (Otto et al. 1994, Happonen et al. 1996). This suggests that the different *Helicobacter* species can induce different intensities of inflammatory responses, since these studies there was no identification at the species level.

The hyperplasia of lymphoid follicles was found in only four animals; this incidence is lower than the incidence reported in studies with feline gastric samples collected during necropsy (Otto et al. 1994, Araujo et al. 2010). In the present study, the fact that the samples were collected using a pediatric endoscope may have contributed to the insufficient detection of hyperplastic lymphoid follicles. This may be due to the thickness of the samples that is much smaller compared with the samples collected during necropsy. The small samples were sufficient to obtain results in the rapid urease test and cytological and histopathological analysis with silver staining (WS) for evaluation of possible infection with *Helicobacter* spp. Some gastric samples did not have sufficient thickness to examine the entire length of the lamina propria; this situation may have reduced the actual number of detected hyperplastic lymphoid follicles. Some authors also reported that the detection sensitivity of hyperplasia of lymphoid follicles is lowest in samples collected using endoscopy (Neiger and Simpson 2000).

Some studies showed that several species of *Helicobacter* and different strains of the same species may not necessarily cause similar changes in gastric regions. The changes caused by *H. pylori* and *H. felis* are more pronounced than those caused by *H. heilmanni* (Scanziani et al. 2001). It is possible that the animals in this study were infected with less pathogenic species of *Helicobacter* spp. such as *H. heilmanni*, which is the most common *Helicobacter* species in cats.

In this study was observed that cats with blood group A are often infected with *Helicobacter* spp., but there was no correlation between the colonization score of the gastric regions and inflammatory infiltrate score observed. Studies in humans with gastric symptoms show that people with blood group O are more susceptible to infection with *H. pylori* and to relevant gastrointestinal complications and/ or have a cellular and immune response stronger than that of individuals with others blood types from the ABO group (Jaff 2011). Therefore, this study was conducted with only one blood group of the feline AB system. The group A was selected for the ease of finding individuals with this group, which was demonstrated in a study on blood groups of mixed-breed cats in the city of Rio de Janeiro; 94.8% of them belong to group A (Medeiros et al. 2008). Other studies have shown that most of mixed-breed cats in several countries also belong to this group (Hohenhaus 2004). In the present study, the more frequent blood group is often associated with colonization by GHLOs but the susceptibility of such cats to the relevant diseases is low.

Although the transmission of *Helicobacter* spp. from cats to human has been proposed (Dieterich et al. 1998, van Loon et al. 2003, Pregel et al. 2008, Haesebrouck et al.

2009), research shows that the incidence of GHLOs in humans is low (Baele et al. 2009). On the other hand, studies on undomesticated cats show that the most common *Helicobacter* species in humans, *H. pylori*, is not detectable in the gastric mucosa of undomesticated cats and is only found in pet cats; this finding is suggestive of anthroponosis (Erginsoy et al. 2006). In this study the identification of the species was not performed, but was observed large helicoidal bacterias suggesting that was GHLOs.

Research involving the genus *Helicobacter* and its species in various colonized animals, shows that the pathogenic potential of these bacteria varies, however with ability to cause changes in the gastric mucosa that can lead to more serious conditions such as cancer. De Bruyne et al. (2012) demonstrated the ability of *H. suis* to cause gastritis in piglets, and Lee et al. (1992) demonstrated the ability of *H. felis* to cause gastritis in dogs. Studies show that the stomach of nonhuman primates is colonized by *Helicobacter* spp. but their pathogenic potential is still under study (De Mello et al. 2005, Lopes et al. 2013). In studies involving *H. pylori*, it was possible to show that this species is the most common *Helicobacter* in the human stomach (Baele et al. 2009) and to demonstrate its ability to cause gastritis, ulcers, and neoplasia (Backert and Clyne 2011). In this study, 87.5% of the animals showed histopathological changes in the gastric mucosa. Of these, 78.1% achieved mild score and 9.4% moderate score. No animal had severe score, being probable that the studied cats were more adapted to the *Helicobacter* species present in their gastric mucosa, being less affected. However, other studies show that not only the most common species that colonizes a population can cause gastric lesions but so can other species, as demonstrated by Joosten et al. (2013), who reported the ability of *H. suis* to cause gastritis in humans. As studies are being conducted, a greater understanding is achieved of how gender influences the phenomena in question. This knowledge is expected to facilitate the development of better gastritis treatments for various species.

CONCLUSIONS

Cats of blood group A are often colonized by *Helicobacter* spp. and the macroscopic and microscopic changes are similar to those reported in other studies on cats.

The presence of inflammatory infiltrate found in cats of blood A group infected by *Helicobacter* sp., show no correlation between the colonization score of the gastric regions, which is the same results observed in others researches.

According to our present results, the blood group most common in cats is not associated with high susceptibility to symptomatic gastritis.

Despite the low transmission rate between humans and felines, deep understanding of GHLOs should result in the development of effective gastritis treatments for the various mammals that are infected with these bacteria.

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