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Detection of *Capnocytophaga canimorsus* and *Capnocytophaga cynodegmi* in dogs with periodontal disease of Brazil

Detecção de *Capnocytophaga canimorsus* e *Capnocytophaga cynodegmi* em cães com doença periodontal no Brasil

Detección de *Capnocytophaga canimorsus* y *Capnocytophaga cynodegmi* en perros con enfermidad periodontal en Brasil

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Abstract

Capnocytophaga canimorsus and *Capnocytophaga cynodegmi* are gram-negative bacilli found among the oral microbiota of dogs and cats, and are capable of infecting humans through bites, licks, or close contact with animals. Clinical manifestations in humans range from local inflammation of the lesion, to sepsis followed by death. The objective of this study was to detect *C. canimorsus* and *C. cynodegmi* in samples of subgingival curettage from dogs domiciled treated at a public veterinary hospital in Brazil, using PCR. Of a total of 121 samples were tested, the prevalence of *C. canimorsus* was 19% and that of *C. cynodegmi* was 66.94%. There was a significant association between the presence of *C. cynodegmi* and advanced periodontal disease. It is concluded that microorganisms are circulating in the oral microbiota of dogs domiciled in Brazil, which represents a risk to public health due to their zoonotic potential. Given the lack of studies on these microorganisms in the country, it is necessary to conduct research to understand the pathogenesis, clinical manifestations, diagnosis and treatment of infections by *C. canimorsus* and *C. cynodegmi* in Brazil, aiming at One Health.

Keywords: *C. canimorsus; C. cynodegmi*; PCR; Zoonosis; Domestic animals; One health.

Resumo

Capnocytophaga canimorsus e *Capnocytophaga cynodegmi* são bacilos Gram-negativos encontrados na microbiota oral de cães e gatos capazes de infectar humanos através de mordidas, lambidas ou contato próximo aos animais. As manifestações clínicas vão desde inflamação local da lesão a sepse, podendo ser seguida por óbito em humanos. O objetivo do trabalho foi detectar *C. canimorsus* e *C. cynodegmi* em amostras de curetagem subgengival de cães domiciliados atendidos em um Hospital Veterinário Público no Brasil, através da técnica de PCR. De 121 amostras testadas, a prevalência de *C. canimorsus* foi de 19% e de *C. cynodegmi* foi de 66,94%. Houve associação significativa entre a presença de *C. cynodegmi* e doença periodontal avançada. Conclui-se que os microrganismos estão circulantes na microbiota oral de cães domiciliados do Brasil, o que representa um risco à saúde pública devido ao seu potencial zoonótico. Visto a falta de estudos sobre esses microrganismos no país, se faz necessária a realização de pesquisas para compreender a patogenia, manifestações clínicas, diagnóstico e tratamento de infecções por *C. canimorsus* e *C. cynodegmi* no Brasil, visando a Saúde Única.

Palavras-chave: *C. canimorsus; C. cynodegmi*; PCR; Zoonose; Animais domésticos; Saúde única.

Resumen

Capnocytophaga canimorsus y *Capnocytophaga cynodegmi* son bacilos gramnegativos que se encuentran en la microbiota oral de perros y gatos capaces de infectar a humanos através de mordeduras, lamidos o contacto cercano con animales. Las manifestaciones clínicas van desde la inflamación local de la lesión hasta la sepsis, y pueden ser seguidas por la muerte en humanos. El objetivo de este trabajo fue detectar *C. canimorsus* y *C. cynodegmi* en muestras de legrado subgingival de perros domiciliados en un Hospital Veterinario Público de Brasil, utilizando la técnica de PCR. De las 121 muestras analizadas, la prevalencia de *C. canimorsus* fue del 19% y la de *C. cynodegmi* del 66,94%. Hubo una asociación significativa entre la presencia de *C. cynodegmi* y la enfermedad periodontal avanzada. Se concluye que los microorganismos están circulando en la microbiota oral de los perros domiciliados en Brasil, lo que representa un riesgo para la salud pública debido a su potencial zoonótico. Dada la falta de estudios sobre estos microorganismos en el país, es necesario realizar investigaciones para comprender la patogénesis, las manifestaciones clínicas, el diagnóstico y el tratamiento de las infecciones por *C. canimorsus* y *C. cynodegmi* en Brasil, apuntando a la Salud Única.

Palabras clave: *C. canimorsus; C. cynodegmi*; PCR; Zoonosis; Animales domésticos; Salud única.

1. Introduction

Pets are becoming more prevalent among the human population, being considered by many to be family members. According to the Brazilian Institute of Geography and Statistics (2019), 46.6% of households in the country have at least one dog, and 19.3% have at least one cat. Daily contact and proximity to animals increases the risk of zoonoses, diseases transmitted between humans and animals, rendering studies of the microorganisms that cause these diseases increasingly important (Silva et al., 2019). According to the United States Agency for International Development, more than 75% of emerging human diseases in the last century have been zoonoses (United States Agency for International Development, 2020), emphasizing that the concept of One Health should gain more and more traction when it comes to disease prevention, control, and eradication. The direct relationship between human, animal, and environmental health demands that professionals with diverse areas of expertise work together with the common goal of promoting health (Van Herten et al., 2019).

Capnocytophaga canimorsus (C. canimorsus) and *Capnocytophaga cynodegmi (C. cynodegmi)* are gram-negative bacilli found in the oral microbiota of dogs and cats, that are capable of infecting humans mainly as a result of bites (Brenner et al., 1989). The first reports of human infection by these organisms described a gram-negative bacillus that causes sepsis in humans (Bobo & Newton, 1976; Butler et al., 1977). These observations have been described several times in subsequent reports (Gosset et al., 2019; Knalb et al., 2020; Terashima et al., 2020). In 1989, Brenner et al., studying isolates from infections resulting from domestic animal injuries, identified the species *C. canimorsus* and *C. cynodegmi*, the first being detected mainly in blood cultures, and the second in cultures from infected lesion sites in humans. Subsequently, *C. canis*, *C. stomatis*, and *C. felis* were added to this genus, upon isolation from the oral microbiota of dogs and cats (Yamamoto et al., 1994; Frandsen et al., 2008; Renzi et al., 2015; Zangenah et al., 2016, Suzuki et al., 2020).

Both species of *Capnocytophaga* have slow and fastidious growth (Tanabe et al., 2019), and it is necessary to enrich the environment with 5 to 10% carbon dioxide (CO2) for its isolation, which may result in negative microbiological cultivation in many cases (Sakai et al., 2019).

Reported human infections are associated with sepsis, disseminated intravascular coagulation (DIC), meningitis, dermatological changes such as localized or disseminated purpura, and extremity necrosis, with the most common comorbidities including splenic dysfunction, alcoholism, smoking, and advanced (Butler, 2015; Cadre et al., 2018; Hannon et al., 2019; Galles et al., 2020), however there are reports of infection by *C. canimorsus* have been described in immunocompetent patients (Bialasiewicz et al., 2019; Kelly et al., 2019; Tani et al., 2019; Edlukudige Keshava et al., 2020). The bacteria has also been associated with infection with no history of bite, only by close contact with dogs (Hansen & Crum-Cianflone, 2019; Uçkai & Stirnemann, 2019).

The virulence factors of *C. canimorsus* include the presence of the enzyme catalase, which allows the survival of the bacteria inside phagocytes by the degradation of hydrogen peroxide and mechanisms that interfere in the coagulation cascade of the host contributing to the development of DIC, in addition to the capsule that confers resistance to the immune system and phagocytosis (Butler, 2015; Renzi et al., 2016; Hack et al., 2017). The genus has already been isolated from ceratitis in dogs with a history of bite in the ocular region and history of aggressive play with other dogs (Leadbetter et al., 2018), indicating that animals may also be affected.

Due to a lack of data on these microorganisms in this country, the objective of this study was to detect the presence of DNA from *C. canimorsus* and *C. cynodegmi* in the oral microbiota of dogs using subgingival curettage samples from animals treated at a public veterinary hospital in Brazil.

2. Methodology

Samples was performed on 121 DNA samples isolated from subgingival curettage from domestic dogs including different age groups, breeds, and sexes treated between May and August 2016 that presented at a public veterinary hospital in Brazil in healthy general condition according to blood counts and serum biochemistry. Periodontal disease (PD) was observed in animals and classified in the range of grade 1 (PD1) through grade 4 (PD4) according to the American Veterinary Dental College (AVDC). The Animal Use Ethics Committee (CEUA) approved this study.

Oligonucleotides CaL2 and CaR were used for detection of *C. canimorsus*, and CaL2 and CyR were used for detection of *C. cynodegmi* (Table 1), both primer pairs amplifying a 427 base pair (bp) sequence described by Suzuki et al. (2010). PCR reactions were performed with 10 ng of genomic DNA, 20 pmol of each oligonucleotide, 0.2 mM dNTPs, 1.87 mM $MgCl_2$, 0.1 volume 10x PCR buffer (200 mM Tris-HCl pH 8.4 and 500mM KCl), 1 U Taq DNA polymerase (Invitrogen), 3.75% DMSO, and ultrapure water to 20 μL final volume. Thermocycler conditions were initial denaturation at 95°C for 5 min, followed by 37 cycles of denaturation at 95°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 30 s, followed by a final extension at 72°C for 7 min. As positive controls were used sequenced DNAs of each bacterium (access to Genbank MN234238.1 and MN234247.1) and ultrapure water as negative control.

Amplified products were separated by electrophoresis in 1.5% agarose gels at 60V/cm, stained with red gel (Biotium), and visualized using a ChemiDocTM XRS system with ImageLab™ software. The two-sample PCR products used for controls were purified with commercial GFX PCR DNA and Gel Band Purification kits (GE Healthcare) and sequenced on an ABI-PRISM 3500 automatic sequencer (Life Technologies Corporation, USA) according to the manufacturer's recommendations. The sequences obtained were analyzed using the Basic Local Alignment Search Tool (BLAST) and deposited in GenBank.

Associations between presence of the bacteria *C. canimorsus* and *C. cynodegmi* and the degree of periodontal disease (PD), sex, and age, were assessed using Fisher's exact test or the Chi-square test, using Prism software (version 8.4.3).

Table 1 – Oligonucleotides used to amplify *C. canimorsus* and *C. cynodegmi*.

Oligonucleotides	**Sequence**
CaL2 (*foward*)	(5'-GTAGAGTGCTTCGGCACTTG-3')
CaR (*reverse*)	(5'-GCCGATGCTTATTCATACA-3')
CyR (*reverse*)	(5'-GCCGATGCTTATTCGTATG-3')

Source: Suzuki et al. (2010).

3. Results

Of the 121 samples, 19% (n = 23) were positive for *C. canimorsus*, and 66.94% (n = 81) were positive for *C. cynodegmi*. All samples positive for *C. canimorsus* were also positive for *C. cynodegmi*, while 47.93% (n = 58) were positive only for *C. cynodegmi*. The DNA sequences from *C. canimorsus* and *C. cynodegmi* obtained displayed 99.68% and 99.37% identity to reference sequences for these species, respectively (GenBank accession #CP032681.1 and #KT194087.1). Information and correlations with age, sex, and periodontal disease are shown in Table 2.

A significant association (p = 0.011) was observed between the presence of *C. cynodegmi* and the degree of periodontal disease, with the prevalence of *C. cynodegmi* in animals with grade PD4 (53/69) being 43.3% higher than its prevalence in animals with grade PD1 (28/52) (OR = 1.43; CI = 1.075 to 1.893). The probability of detecting *C. cynodegmi* in dogs with DP4 periodontal disease was 2.81 times higher than the likelihood of isolating this bacteria in dogs with PD1 (OR = 2.81; CI = 1.213 to 6.6). There was no statistically significant association between *C. cynodegmi* and other factors, including age and sex, and there was no significant association between *C. canimorsus* and periodontal disease, sex, or age.

Table 2 – PCR detection of *C. canimorsus* and *C. cynodegmi* according to the degrees of periodontal disease, sex and age.

Variable	***C. canimorsus***	***C. cynodegmi***
Periodontal disease grade		
PD1	19,23% (10/52)	53,84% (28/52)*
PD4	18,84% (13/69)	76,81% (53/69)*
Sex		
Female	20% (13/65)	60% (39/65)
Male	17,85% (10/56)	75% (42/56)
Age		
< 2 years	24,24% (8/33)	72,72% (24/33)
2-5 years	22,03% (13/59)	64,40% (38/59)
> 5 years	6,89% (2/29)	65,51% (19/29)

PD: periodontal disease
*p = < 0,05
Source: personal archive.

4. Discussion

The present study showed a high prevalence of *C. cynodegmi* in the oral microbiota of dogs domiciled in Brazil. More than half of the animals sampled were positive (66.94%), while *C. canimorsus* was present in 19% of the animals. In a literature review conducted by Butler (2015), the prevalence of *C. canimorsus* in dogs' oral microbiota ranged from 3% to 74%. The high variability was attributed to different diagnostic methods, since microbiological cultivation depends on factors that promote favorable atmospheric conditions, especially when it comes to the oral microbiota due to the predominance of microaerobic or anaerobic microorganisms, in addition to the need for rapid sampling for processing and use of appropriate means of transport, whereas molecular techniques such as PCR have greater sensitivity for detecting the genetic material of the agent of interest even in small amounts (Jardim Júnior et al, 2011), in addition to the ease in the conservation of the sample that can be frozen for long periods (Miernyk et al., 2017).

The means of collecting material can also influence the results, since studies that obtained samples through oral swab identified higher prevalences, which varied from 60% to 74% (Mally et al., 2009; Van Dam et al., 2009; Suzuki et al., 2010). Dilegge et al. (2011), using samples of dental plaque from dogs, detected *C. canimorsus* in 21.7% of tested animals, a value closer to that found in the present study, both of these values are lower than that seen in samples obtained by oral swab.

In a study of the human oral microbiota, Welch et al. (2019) showed that different species belonging to the same genus may be limited to inhabiting different geographic regions of the mouth, however this microbiota communicates through the saliva that circulates throughout the region leading microorganisms to places where they are not predominant, contributing to the mixture of microbial communities. Oral swab, because it covers a larger area of the mouth, may be responsible for a higher detection than through subgingival curettage, because the latter is done in a small region only.

Considering the zoonotic potential of *C. canimorsus* and *C. cynodegmi*, and the perspective of One Health, it is essential that owners perform oral hygiene for their pets and be aware of the potential for dog or cat bites (or pets licking an owner's wound) to become infected, as a 29.7% mortality rate is reported in severe cases of *C. canimorsus* infection (Mader et al., 2019). Pet owners are encouraged to seek professional healthcare if they experience symptoms including fever, headache, or mental confusion a few hours to a few days after a pet related injury has occurred, because these are the first clinical signs of infection with *C. canimorsus* (Taquin et al., 2017; Bialasiewicz et al., 2019; Hundertmark et al., 2019).

Although *C. cynodegmi* infections mainly remain local to lesion sites, Khawari et al. (2005) reported a case of sepsis and meningitis in a 72-year-old woman who had been bitten by her dog and had a history of diabetes mellitus and post-traumatic splenectomy. The patient presented purpura all over their body, coagulopathy, metabolic acidosis, and hypotension consistent with septic shock, with death occurring 48 h after the bite. The bacterium has also been attributed with cellulite, bacteremia, and pneumonia in a man two days after being bitten by a stray dog (Sarma & Mohant, 2001).

In addition to zoonotic risk, these micro-organisms impact pet health. There was a statistically significant association between the presence of *C. cynodegmi* and advanced periodontal disease. Periodontal disease is a common condition in dogs and cats. It can affect up to 80% of animals, where bacteria accumulate on dental surfaces with posterior damage and destruction of adjacent structures (Patel et al., 2016). The association of the genus *Capnocytophaga* with periodontal disease is controversial (Frandsen et al., 2008), however studies point to the genus as potential to cause gingivitis and periodontal disease in humans (Ciantar et al., 2005; Pudakalkatti et al, 2016; Kotrashetti et al. 2020), besides acting in synergism with periodontitis-causing microorganisms in the formation of bacterial biofilms also in humans (Okuda et al., 2012).

Correct education of pet owners regarding oral hygiene for pets is vital to preventing periodontal disease development (Bellows et al., 2019), which also contributes to human safety, decreasing the risk of transmission of zoonoses after bites or licking by these animals. In a study by Wallis et al. (2021), analyzing the subgingival microbiota of dogs from different countries, there was no significant association between the presence of *Capnocytophaga* spp. and periodontal disease, in

disagreement with what was found in the present study. Due to the scarcity and differences in data, further studies need to be done on the participation of the genus *Capnocytophaga* in periodontal disease in dogs demonstrating its role in this disease.

Factors such as diet, veterinary practices, animal genetics and oral hygiene of animals directly influence the composition of the oral microbiota as well as on the proliferation of potentially pathogenic microorganisms (Wallis et al., 2021). The correct guidance of tutors about oral hygiene of pets is important for the prevention of the development of periodontal disease (Bellows et al., 2019), which also contributes to their own safety, reducing the risk of zoonoses after bites or licks of these animals.

5. Conclusion

Through the present study it was possible to detect the circulation of *C. canimorsus* and *C. cynodegmi* in dogs in Brazil, alerting to possible risk in humans, besides indicating *C. cynodegmi* as a potential agent with participation in periodontal disease. Given the lack of studies on these microorganisms in the country, it is necessary to conduct research to understand the pathogenesis, clinical manifestations, diagnosis and treatment of infections by *C. canimorsus* and *C. cynodegmi*, besides the need to understand their real participation in periodontal disease in dogs.

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