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► To cite this version:

Anne Jolivet-Gougeon, Martine Bonnaure-Mallet. Screening for prevalence and abundance of Capnocytophaga spp by analyzing NGS data A scoping review. Oral Diseases, 2021, 27 (7), pp.1621-1630. <10.1111/odi.13573>. <hal-02930404>

HAL Id: hal-02930404

<https://hal.science/hal-02930404v1>

Submitted on 11 Sep 2020

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HAL Authorization

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Article type : Review Article

**Screening for prevalence and abundance of *Capnocytophaga* spp
by analyzing NGS data. A scoping review.**

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Running title: *Capnocytophaga*, NGS and diseases

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Date of resubmission: July, 2020

Abstract

Background. *Capnocytophaga* spp. are commensal bacteria of the oral cavity and constitute a genus of the core microbiome.

Objective. This genus is responsible for many local and systemic conditions in both the immunocompetent and immunocompromised, but its beneficial or deleterious role in the microbiota has been little explored.

Design. Online databases were used to identify papers published from 1999 to 2019 based on next-generation sequencing (NGS) data to study comparative trials. Work using other identification methods, case reports, reviews, and non-comparative clinical trials were excluded.

Results and conclusion. We selected 42 papers from among 668 publications. They showed a link between the abundance of *Capnocytophaga* spp. in the oral microbiota and various local pathologies (higher for gingivitis and halitosis; lower in active smokers, etc.) or systemic diseases (higher for cancer and carcinomas, IgA nephropathy, etc.). After discussing the limits inherent to the NGS techniques, we present several technical and biological hypotheses to explain the diversity of results observed between studies, as well as the links between the higher or lower abundance of *Capnocytophaga* spp and the appearance of local or systemic conditions and diseases.

Keywords: *Capnocytophaga* spp., NGS, cancer, carcinoma, gingivitis, halitosis, smoker, periodontitis, caries, 16SrRNA gene.

INTRODUCTION

More than 700 commensal bacterial species are present in the human oral cavity (Paster, 2001). The proliferation of other species, or dysbiosis, is associated with the development of various pathologies. Within the oral cavity, there are bacteria associated with periodontitis, belonging to the "red complex" (*Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia*) or the orange complex (*Prevotella intermedia*, *Fusobacterium nucleatum*, etc), and bacteria considered to be non-pathogenic, belonging to the "green complex" (*Eikenella corrodens*, *Campylobacter gracilis*, *Aggregatibacter actinomycetemcomitans*) (Socransky, 1998) or blue complex (*Actinomyces viscosus*) (Topcuoglu & Kulekci, 2015). *Capnocytophaga* spp. are long, thin, slow-growing Gram-negative bacilli with a gliding ability on agar media. They are preferentially anaerobic and require enrichment with CO₂ (5-10%) for optimum growth (capnophilic). Clinical isolates of *Capnocytophaga* spp. are generally isolated from (1) the human oral cavity (*C. gingivalis*, *C. granulosa*, *C. haemolytica*, *C. leadbetteri*, *C. ochracea*, and *C. sputigena*) and (2) the oral cavities of dogs and occasionally cats (*C. canimorsus*, *C. cynodegmi*, *C. canis*, and *C. stomatis*). Several species remain unclassified according to sequence analysis of the 16S rRNA gene, such as AHN9607/AHN9576/AHN9798/AHN8471/ChDC. According to publications, *Capnocytophaga* species are most often located within the green complex (Carrouel, 2016), but sometimes within the orange complex, without clear arguments for classifying them as pathogenic or beneficial. Sometimes they are not even mentioned (Topcuoglu & Kulekci, 2015), although they represent more than 6% of the oral flora (Al-Hebshi, 2019) and up to 15% in some pathologies (Ehrmann, 2014). Therefore, *Capnocytophaga* spp. are often isolated from complex flora in the oral cavity (Zaura, 2009). The question of oral hygiene is still a subject of debate: some authors find no influence on the abundance of *Capnocytophaga* spp., regardless of the quality of oral hygiene (Mashima, 2017), whereas others find a higher abundance of *Capnocytophaga* spp. in the event of poor oral hygiene (Pereira, 2012). Several authors have even reported a lower abundance of *Capnocytophaga* from throat swab samples from healthy Chinese volunteers, aged 18 to 21 years, during the winter heating period in polluted areas (Li, 2019). However, these bacteria can also be involved in local and systemic infections, both in immunocompetent and immunosuppressed patients (Sixou, 2006). In addition, certain strains are resistant to 3rd-generation cephalosporins and/or fluoroquinolones

(Jolivet-Gougeon, 2000, Jolivet-Gougeon, 2005, Ehrmann, 2017) and can be a reservoir of resistance genes (Dupin, 2015), adding to their pathogenicity.

In recent years, many NGS studies have been carried out and there are numerous publications reporting the use of NGS to qualitatively and semi-quantitatively describe and characterize the various microbiota. They have been mainly based on sequencing of the hypervariable regions of the 16S rRNA gene and several methods have been used, such as the Illumina or Ion Torrent Personal Genome Machine techniques (Campisciano, 2017) or pyrosequencing 454. *Capnocytophaga* spp. are generally reported to be commensal bacteria of the oral cavity and usual inhabitants of the oral "core microbiome" (Jiang, 2014, Xu, 2014, Johansson, 2016). However, the relative abundance of *Capnocytophaga* spp. has been reported to be variable within the oral microbiota, in particular in cases of local or systemic pathologies.

The aim of this scoping review was to gather arguments to highlight the role of *Capnocytophaga* spp. within complex oral flora, using NGS techniques, through a literature review spanning 20 years (1999-2019). Clinical trial analysis is performed and the limits of NGS techniques in this context analyzed. We then present hypotheses to explain the possible link between the proliferation of *Capnocytophaga* spp. and several local and systemic pathologies.

DESCRIPTION OF THE METHOD

We chose to conduct a scoping review of the literature because our goal was to provide an overview of a potential relationship between the abundance of *Capnocytophaga* spp., determined by NGS methods, and local or systemic disease (Grant & Booth, 2009).

Our protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA—ScR) (Tricco, 2018). We performed an online search of the Medline/PubMed database of all international publications containing "*Capnocytophaga*" published between the period of their first indexation, 1999, and 2019. Only clinical Conferences, clinical studies, clinical trials, controlled clinical trials, meta-analysis, multicenter studies and randomized controlled trials were selected in PubMed search, and the keyword "*Capnocytophaga canimorsus*" was excluded. The words "oral microbiome", "oral microbiota", "next-generation sequencing", "Illumina", "metagenomic", "454", and "Ion Torrent" were

selected, and crossed with previous "*Capnocytophaga*" selection. The final search results were exported into Zotero 3.0, and the duplicates were removed. Some articles were excluded with reasons (Supplementary data 1- Full-text articles excluded with reasons). Search concepts and keywords were summarized in Table 1. The selected publications were entered into an Excel spreadsheet and organized by authors, types of pathologies involved [local (gingivitis, periodontitis, halitosis, caries) or systemic (smokers and alcohol abusers, cancers and carcinoma, HIV and others)], populations studied (control/healthy and pathology), type of sample(s) collected, primers used, software used for data production and analysis, sequencing technique and abundance of *Capnocytophaga* spp. in the microbiota.

A data-charting form was jointly developed by two reviewers to determine which variables to extract, refine them, and ensure that all relevant data were captured. The study authors first reviewed the titles and abstracts, and secondarily entirely read the selected articles. A health sciences librarian assisted with the search strategy and one reviewer (AJG) selected the final articles for inclusion, with a second author reviewing the final selection (MBM). The two reviewers independently charted the data, discussed the results, and continuously updated the data charting form in an iterative process.

RESULTS

All international publications (*Capnocytophaga*; n=1287) published between the period of their first indexation, 1999, and 2019 (n = 668) were screened. The term *Capnocytophaga canimorsus* was excluded (n = 456). These articles were all crossed with "oral microbiome" (n = 122), "oral microbiota" (n = 112), next-generation sequencing (n = 16), Illumina (n = 10), metagenomic (n = 9), 454 (n = 6), and Ion Torrent (n = 2). The full electronic search strategy is presented Figure 1. The final search results (n = 277) were exported into Zotero 3.0 and duplicates removed (n = 131). Some articles were excluded with reasons (Supplementary data 1- Full-text articles excluded with reasons n=89 and Figure 1). A calibration exercise was carried out using these 131 citations for title and abstract screening (step1). The irrelevant articles were removed: animal studies (n = 5), case reports, reviews, sequencing of a single strain (n = 10), non-comparative clinical trials (microbiome development, single pathology, oral hygiene, etc.) (n =

25) and other methods (checkboard DNA-DNA hybridization techniques, specific microarrays, specific PCR, electrophoresis, serum antibodies, or cultures) (n = 49). Indeed, such methods detect only a limited number of oral pathogens, without considering the numerous commensal species that can interfere with detection, nor the totality of *Capnocytophaga* species. In total, there were 42 studies, meeting the inclusion criteria, selected for final analysis (Figure 1). An overview of the reviewed articles is presented in Table 2 and Table 3 (Supplementary data). Among the 42 studies selected, 19 studies concerned local pathologies [gingivitis (n = 2), periodontitis (n = 6), halitosis (n = 2), and caries (n = 9)] and 23 systemic pathologies [smokers / alcohol abusers (n = 6), cancer / carcinoma patients (n = 11), HIV patients (n = 1) and others (n = 5)].

***Capnocytophaga* in healthy patients**

Numerous studies have demonstrated the presence of various *Capnocytophaga* species in the oral cavity of healthy individuals, particularly in "control" patients from various clinical studies (Table 2 and Table 3, Supplementary data). Their presence has often been reported associated with eubiosis or their prevalence even elevated in healthy individuals (Tsai, 2018, Chen, 2018, Xi, 2019). Studies based on culture-based analysis have shown varying roles, depending on the species of *Capnocytophaga* under consideration. During the formation of dental plaque, for example, *C. gingivalis* is found the first day, whereas *C. sputigena* is isolated after even days (Teles, 2012). By NGS, *Capnocytophaga* spp. are more often found in higher abundance in control or healthy patients than in sick individuals (Shchipkova, 2010, Xu et al., 2014, Jiang et al., 2014, Camelo-Castillo, 2015, Tsai et al., 2018, Wu, 2016, Xiao, 2016, Chen et al., 2018, Pimentel, 2018, Xi et al., 2019). However, NGS studies have too rarely differentiated between the species concerned within the genus *Capnocytophaga*.

Overall, it can therefore be concluded that many NGS studies have shown the presence of *Capnocytophaga* spp. in the oral cavity and core microbiome in healthy patients.

***Capnocytophaga* and disease**

Local pathologies

Capnocytophaga spp. are found in significantly greater abundance in patients with gingivitis, whether in the general population (Park, 2015) or in patients with AIDS (Zhang, 2015).

For patients with periodontitis, the results differ depending on the study. In several studies (Tsai et al., 2018, Chen et al., 2018), the authors observed a higher abundance of the genus *Capnocytophaga* in individuals without a pathology other than localized periodontitis, including moderate local inflammation, shown by slight bleeding (Camelo-Castillo et al., 2015). Park et al. (Park et al., 2015) compared to the microbiota of patients with chronic gingivitis and periodontitis and did not observe a difference in the case of periodontitis, whereas Acharya et al. (Acharya, 2019) showed that the abundance of *C. leadbetteri* was much higher in patients with periodontitis than healthy patients. Based on Traditional Chinese Medicine, gastric cancers and oral diseases can be diagnosed by the appearance of the tongue [white-thin coating (W-thin) group, white-thick coating (W-thick) group, yellow-thin coating (Y-thin) group, and yellow-thick coating (Y-thick) group]. The microbiota is closely related to oral diseases in cases of W-thin coating and only *C. leadbetteri* has been identified as a potential biomarker for this group (Xu, 2019).

The abundance of *Capnocytophaga* spp. has been shown to be significantly higher in patients with halitosis (Seerangaiyan, 2017). In preschool children, *C. ochracea* has been shown to be the most common species in supragingival plaque samples (Ren, 2016).

In patients with caries, all authors agree that the abundance of *Capnocytophaga* spp. is higher in subjects free from caries (Xu et al., 2014, Jiang et al., 2014, Xiao et al., 2016, Xi et al., 2019). Gross et al. (Gross, 2010) showed that the abundance of *C. gingivalis* decreases as the caries disease progresses, whereas Kahharova et al. (Kahharova, 2020) observed a gradual decrease in the abundance of *C. sputigena* and Schoilew et al. (Schoilew, 2019) a decrease in the abundance of *C. ochracea*. Only one study has reported higher colonization by *Capnocytophaga* in Swedish adolescents with active caries (characterized by the intake of sweet products) (Johansson et al., 2016).

Most studies have shown that the abundance of *Capnocytophaga* spp. is lower in active tobacco smokers than non-smokers (Shchipkova et al., 2010, Bizzarro, 2013, Wu et al., 2016, Pimentel et al., 2018). The same result was observed in marijuana users with head and neck squamous cell carcinoma (HNSCC): *Capnocytophaga* was found at only low levels on the

tongue (Newman, 2019). However, Thomas et al. (Thomas, 2014) showed a significantly higher abundance of *Capnocytophaga* spp. in smokers using the Ion Torrent technology and samples from the dorsum and laterals of the tongue, regardless of their level of alcohol consumption.

A high prevalence of *Capnocytophaga* spp. has also been found in patients with carcinomas or oral cancers (Mager, 2005, Perera, 2018, Liu, 2019, Takahashi, 2019), especially during radiotherapy (Vesty, 2019).

In conclusion, the prevalence of *Capnocytophaga* spp. in periodontal diseases or caries appears to depend on the species involved and the association with other factors, such as age, alcohol consumption, or being a cigarette smoker. However, studies are in agreement concerning the higher prevalence of *Capnocytophaga* spp. in patients with gingivitis, carcinoma, or oral cancers.

Systemic pathologies

Oral microbiota can also be modified in systemic diseases (Graves, 2019).

A high prevalence of *Capnocytophaga* spp. has often been found in the oral microbiota of immunocompromised patients. This is true for cancer patients, especially those undergoing chemotherapy (Sixou et al., 2006) or antibiotic therapy (Jolivet-Gougeon et al., 2005, Jolivet-Gougeon, 2008). NGS studies have confirmed these results, showing an increase in their abundance during radiotherapy (Hu, 2013a, Hu, 2013b), lung cancer (Yan, 2015), and esophageal carcinoma (Elliott, 2017). Only one study reported a lower abundance of *C. ochracea* in cases of pharyngeal cancers (Panda, 2019). The oral microbiota has been studied in patients with other causes of immunosuppression, such as those with HIV infection. Fukui et al. (Fukui, 2018) showed a higher relative abundance of *Capnocytophaga* spp. in the oral microbiota of HIV patients, with a predominance of *C. ochracea*. Zhang et al. (Zhang et al., 2015) found a predominance of *Capnocytophaga* spp. only in HIV patients with gingivitis. Similarly, a combination of *C. ochracea* and HPV virus has only been observed in patients with periodontitis (Chowdhry, 2019, Ganly, 2019). *Capnocytophaga* spp. are also isolated in higher quantities when periodontitis is associated with an autoimmune disease, such as IgA nephropathy (Cao, 2018).

The link between *Capnocytophaga* spp. and metabolic diseases has also been studied. In a study of Kelsen et al. (Kelsen, 2015), this genus was more abundant in the oral microbiota of

patients with Crohn's disease than those without. The results are less clear cut for obesity: Wu et al. (Wu, 2018) showed a lower abundance of *Capnocytophaga* spp. in an obese population than in normal-weight individuals. Previous NGS studies, using the DNA–DNA hybridization checkerboard technique, have found *C. ochracea* to be at significantly higher levels ($P < 0.001$) in obese than non-obese women (Silva-Boghossian, 2018). This difference in the results could be explained by the sex of the population studied. Indeed, Yeo et al. (Yeo, 2019) reported a higher relative abundance of *Capnocytophaga* spp. in women than men in a study of the microbiota of a semi-industrialized indigenous tribe by the Illumina technique. Although numerous culture-based studies (Mashimo, 1983), techniques using 16S rRNA gene cloning and sequencing (Casarin, 2013), and DNA-DNA hybridization (Rodriguez-Hernandez, 2019) have largely shown a predominance of *Capnocytophaga* spp. in diabetes, few studies of the oral microbiota by NGS have been conducted to confirm these results (Ganesan, 2018).

The search for *Capnocytophaga* sp, as an oral marker for other diseases has been attempted, without success, such as for the occurrence of atherosclerosis (Fak, 2015) or the exacerbation of chronic obstructive pulmonary disease (COPD) (Tan, 2014). The presence of *Capnocytophaga* spp. in large quantities has only been negatively associated with cholesterol and Low Density Lipoprotein levels (Fak et al., 2015), and no difference could be shown between gingival plaques and tracheal aspirations (Tan et al., 2014).

In summary, the prevalence of *Capnocytophaga* spp. in metabolic diseases is still unclear and may depend on other factors, such as sex, weight, etc. Further studies are necessary to confirm or refute the role of *Capnocytophaga* spp. in these diseases. A high prevalence has however been demonstrated in patients with an autoimmune disease or those who are immunocompromised (particularly HIV patients and those undergoing radiotherapy).

DISCUSSION

Before the extensive use of high-throughput sequencing, culture-based methods and DNA-DNA hybridization checkerboard-based techniques were widely used and already affirmed the predominance of *Capnocytophaga* spp. in gingivitis (Testa, 2016), diabetes (Rodriguez-Hernandez et al., 2019), and cancer (Jolivet-Gougeon et al., 2005, Jolivet-Gougeon et al., 2008,

Hu et al., 2013a, Hu et al., 2013b). This bibliographic study has shown the role of *Capnocytophaga* spp. as a potential biomarker for local and systemic diseases, particularly cancer. We will first discuss the limits of NGS techniques, and then attempt to explain the link between variations in the abundance of *Capnocytophaga* spp. in the oral microbiota, and the occurrence of some diseases.

Search limitations

One might think that restricting the research period (only after 1999) could be a limiting factor in this study, but before this date few data existed about NGS, and none about *Capnocytophaga* and NGS (or related words (next generation sequencing, Illumina, 454, Ion torrent, metagenomic).

We used only one database for this study (PubMed) and we have already had 41 studies to describe. Extending this research to other databases would have further increased the power of this literature review.

Technical bias

Prior to NGS, bacterial culture was the “gold standard” because these capnophilic species are easily cultivated. This has often led to an overestimation of their abundance in the oral flora (Ali, 1996), because non-cultivable bacteria could not be enumerated. Although generally more exhaustive, the analysis of various NGS studies, seeking to estimate the relative abundance of *Capnocytophaga* spp. within the oral flora often come up against technical biases that need to be considered.

Genomic analyses have made it possible to discover many other species and numerous studies have been published to describe the various microbiota of patients and animals under various physiological and pathological conditions. However, these studies, which make extensive use of bioinformatics, are rarely completed by qPCR studies and even less so by culture-based studies to validate the bioinformatics results.

Patients selected as "healthy" in these studies are often very different in terms of age, gender, and measurable hormonal status, as well as parameters that are more difficult to analyze, such as their diet, whether or not they consume alcohol, whether or not they exercise, their degree of stress, etc. Xenobiotics can also play an important role and not all the studies mention the exclusion of patients who consume xenobiotics (especially antibiotics, antiseptics, and anxiolytics).

Such errors could be rectified by studies of large populations, which would facilitate more precise statistical analysis. However, with few exceptions (Wu et al., 2016), most studies showing differences in the prevalence of *Capnocytophaga* spp. compared cohorts of patients with a small number of individuals (< 100), which inevitably leads to conclusion bias.

In addition, although the results obtained in each study (if taken individually) are potentially informative, they remain difficult to compare. The sampling techniques used were different, depending on the study: saliva samples or different locations of plaques, washing or not before sampling, different washing products and different doses, and stimulation (e.g. with chewing gum) or not (Table 2 and Table 3, Supplementary data).

The analysis techniques for the samples have also differed, such as the sequencing technology and analysis (in particular software versions) (Table 2 and Table 3, Supplementary data).

Hypotheses to explain the link between abundance of Capnocytophaga spp. and diseases

Despite the shortcomings of the existing body of studies, links have been shown between the variation in the abundance of *Capnocytophaga* spp. and local pathologies, such as gingivitis and halitosis, or systemic diseases, such as cancer (\pm radiotherapy or chemotherapy), diabetes, and concomitant infection (HIV) (Pereira, 2014). Several possibilities can be suggested to explain these links.

Gum damage, especially with bleeding, promotes the growth of *Capnocytophaga* spp., which require iron. Certain oral organisms are able to acquire iron from serotransferrin and genes involved in such iron capture systems have been detected in *Capnocytophaga* spp. (Manfredi, 2015). *Capnocytophaga* spp. have also been associated with iron-overload in humans, mainly due to their impaired ability to acquire host iron (Weinberg, 2000). Hattori et al. (Hattori, 1996) also reported sequences of FNR family homologues identified in oral *C. ochracea* and *C. sputigena*. Finally the abundance of *Capnocytophaga* spp. in the oral microbiota has also been reported to be higher in non-anemic than anemic patients (Xi et al., 2019).

In smokers, the occurrence of mucositis and peri-implantitis ranges from 44.9 to 63.4% and 11.2 to 18.8%, respectively (Rinke, 2011, Atieh, 2013). Sun et al. (Sun, 2016) examined the metabolic response of *C. sputigena* to smokeless tobacco extract and alterations in nicotine and nicotine metabolism using a LC/MS-based metabolomics approach. They showed that *C.*

sputigena only metabolizes nicotine to a minor extent (0.05% for hydroxy-nicotine and 1.39% for cotinine N-oxide (CNO)), but that it can degrade minor alkaloids, including nornicotine, anatabine, and anabasine. They also demonstrated a decrease in bacteria-related metabolites, which could explain (at least in part) the lower abundance of *Capnocytophaga* spp. observed in smokers. Of note, many compounds are those that induce oxidative stress (e.g., oxygen, nitrogen radicals or non-radical species, reactive carbonyl compounds), which can cause damage by binding to biological macromolecules, resulting in disruption of the cell structure or cell dysfunction, which may further induce physical damage (e.g., periodontitis).

Capnocytophaga spp. are bacteria of which the growth is largely facilitated in the presence of glucose (Spratt, 1996) and thus diabetes could favor their expansion. Ohara-Nemoto et al. (Ohara-Nemoto, 2018) showed that *Capnocytophaga* spp. can produce dipeptidyl peptidase (DPP) 4, DPP5, DPP7, and DPP11, which are expressed in the periplasmic space and crucial for energy production, of which some, such as DP-4, are involved in the regulation of blood glucose levels via the degradation of incretins. Chang et al. (Chang, 1988) demonstrated that experimental diabetes in rats is followed by increased production of collagenase by the gingival tissues, within weeks, and proved that *Capnocytophaga* spp. are able to induce collagenase production by gingival tissues of germ-free mice.

The presence of *Capnocytophaga* spp. in high quantities has been demonstrated during chemotherapy in cancer (Sixou, 1998, Sixou et al., 2006, Villafuerte, 2018). Antibiotics (Jolivet-Gougeon et al., 2008, Campisciano et al., 2017), frequently used during cancer treatment, may also play a role because they can lead to the selection of resistant *Capnocytophaga* spp. strains that produce broad-spectrum enzymes capable of inhibiting the action of 3rd-generation cephalosporins (Jolivet-Gougeon et al., 2005) or fluoroquinolones (Ehrmann et al., 2017). The presence of mucositis and gingivitis is often associated with these diseases and their treatment (Vesty et al., 2019), which could induce dysbiosis, conducive to the growth of *Capnocytophaga* spp. In a comparison of HPV⁺ and HPV⁻ cases, Chowdhry et al. (Chowdhry et al., 2019) demonstrated dominance of *C. ochracea*. At the same time, the mismatch repair pathway and nucleotide excision repair were altered in the HPV⁺ samples, suggesting greater formation of DNA adducts, which can lead to the process of carcinogenesis. Similarly, the presence of *C. gingivalis* has recently been shown to strongly correlate with oral cancer (Karpinski, 2019).

Certain diseases (cancers, diabetes, rheumatoid arthritis, and systemic lupus erythematosus) are associated with inflammatory processes, and differences in the abundance of *Capnocytophaga* spp. have often been associated with them. These systemic diseases also increase susceptibility to destructive periodontal diseases (Graves et al., 2019). The link between the presence of *Capnocytophaga* spp. and the inflammatory reaction can be explained by several mechanisms. The presence of pathogenic bacteria positively correlates with the level of systemic inflammation, such as serum C-reactive protein or elevated levels of cytokines in saliva (Correa, 2017). Yoshimura et al. (Yoshimura, 1997) showed an increase in the levels of beta IL-1, TNF-alpha, and IL-8 released from cells stimulated with *C. ochracea* LPS. As for other bacteria in the oral cavity, the activation of NF-κB and inhibition of cellular apoptosis is a possibility, although this has never been shown for the genus *Capnocytophaga*. Finally, certain proinflammatory responses caused by *Capnocytophaga* spp. can be procarcinogenic. Indeed, microbial metabolites can contribute to inflammatory process and influence the balance of proliferation and cell death in tissues (Garrett, 2015, Perera et al., 2018, Vergara, 2019). For example, the abundance of *C. leadbetteri* was shown to be significantly elevated in oral squamous cell carcinoma (OSCC) patients and the expression of genes involved in bacterial chemotaxis, flagellar assembly, and lipopolysaccharide (LPS) biosynthesis were significantly elevated, suggesting a potential association between these bacteria and OSCC (Zhang, 2019). An effect of *Capnocytophaga* spp. on the immune system has also been shown (Jansen, 1994, Ochiai, 1998), which could provide a link with autoimmune or viral diseases (Chowdhry et al., 2019).

CONCLUSION

Variations in the abundance of *Capnocytophaga* spp. are associated with the appearance of local or systemic pathologies, with a particular higher level of this organism in some diseases at certain stages of development of periodontal diseases, diabetes, or certain types of cancer.

ACKNOWLEDGMENTS

We dedicate this work to Pr Michel Cormier, who taught us so much in Microbiology, and who was a recent victim of Covid-19. We salute his dynamism and his humanity, and we thank him for his renewed encouragement.

We thank Adina Pascu for helping us to format the manuscript.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

FUNDING

This study received no funding.

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FIGURE AND TABLE LEGENDS

Figure 1

The full electronic search strategy and article selection.

*NGS: next generation sequencing

Table 1

Search concepts and keywords.

Table 2 (Supplementary data)

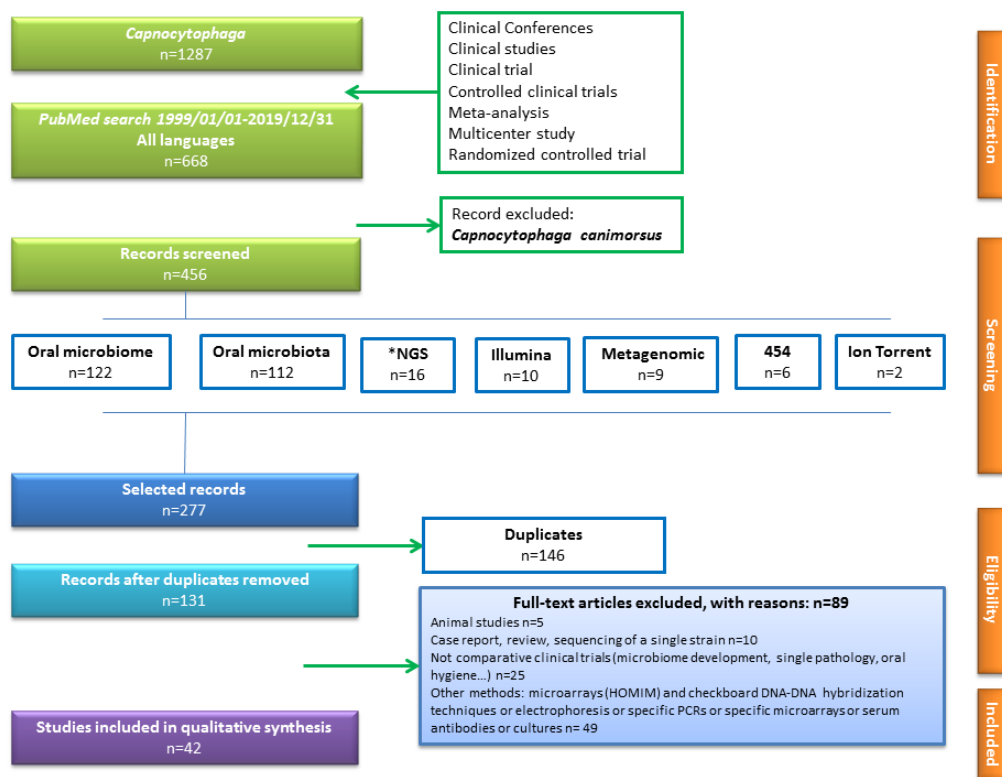
Summary of the included studies assessing the presence/abundance of *Capnocytophaga* spp. in gingivitis, periodontitis, caries, and halitosis by next-generation sequencing from 1999 to 2019 (n = 19).

Table 3 (Supplementary data)

Summary of the included studies assessing the presence/abundance of *Capnocytophaga* spp. in systemic pathologies (excluding gingivitis, periodontitis, caries, and halitosis) by next-generation sequencing from 1999 to 2019 (n = 23).

Table 1.

Concept	Controlled and natural keywords
<i>Capnocytophaga</i>	<i>Capnocytophaga</i> [NOT] <i>canimorsus</i>
Oral microbiota	« Oral microbiota » or Oral microbiome »
NGS	« Next generation sequencing » or « Illumina » or « 454 » or « Ion torrent » or « metagenomic »
Database	<i>Selection:</i>
PubMed	Clinical Conferences, Clinical studies, Clinical trial, Controlled clinical trials, Meta-analysis, Multicenter study, Randomized controlled trial
Limits	<i>Excluded:</i>
1999/01/01-2019/12/31	<p>Animal studies</p> <p>Case report, review, sequencing of a single strain</p> <p>Not comparative clinical trials (microbiome development, single pathology, oral hygiene...)</p> <p>Other identification methods: microarrays (HOMIM) and checkboard DNA-DNA hybridization techniques or electrophoresis or specific PCRs or specific microarrays or serum antibodies or cultures</p>



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