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MINI-REVIEW

Presence of non-oral bacteria in the oral cavity

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Abstract
A homeostatic balance exists between the resident microbiota in the oral cavity and the host. Perturbations of the oral microbiota under particular conditions can contribute to the growth of non-oral pathogens that are hard to kill because of their higher resistance to antimicrobials, raising the probability of treatment failure and reinfection. The presence of these bacteria in the oral cavity has been proven to be associated with several oral diseases such as periodontitis, caries, and gingivitis, and systemic diseases of importance in clinical medicine such as cystic fibrosis, HIV, and rheumatoid arthritis. However, it is still controversial whether these species are merely transient members or unique to the oral cavity. Mutualistic and antagonistic interactions between the oral microbiota and non-oral pathogens can also occur, though the mechanisms used by these bacteria are not clear. Therefore, this review presents an overview of the current knowledge about the presence of non-oral bacteria in the oral cavity, their relationship with systemic and oral diseases, and their interactions with oral bacteria.

Keywords Oral microbiota · Non-oral bacteria · Periodontitis · Systemic diseases

Introduction

The oral cavity is a complex and dynamic environment and is the primary gateway to the human body (Zarco et al. 2012; Craig et al. 2018). Various studies have identified over 1000 species from the oral cavity that forms the oral microbiota (Mahasneh et al. 2017; Gao et al. 2018). However, only a tiny fraction is causing oral infections such as dental caries and periodontitis (Kreth and Merritt 2009; Dewhirst et al. 2010). An imbalance of microbial flora contributes to the growth of various clinically important pathogens, that are generally considered ''non-oral'' bacteria, such as Gram-negative enteric rods (GNRs), enterococci, and staphylococci (Al-Ahmad et al. 2009; Van Winkelhoff et al. 2016). Non-oral bacteria are non-resident, super-infectious microorganisms that are not generally considered a common part of the oral microbiota. Their eradication from the dental biofilms seems to be more challenging due to their higher resistance to antimicrobials, raising the probability of treatment failure and reinfection (Souto et al. 2006). There has been a great deal of confusion in the literature regarding their natural reservoir and their ability to colonize the oral cavity. Previous studies have revealed that they may occur in high numbers and shift from transitory species to colonizers of the oral cavity in immunocompromised individuals (Simões-Silva et al. 2018; Arirachakaran et al. 2019). However, some studies have shown that they can colonize healthy subjects too (Ranganathan et al. 2017; Chinnasamy et al. 2019). Moreover, systemic colonization and infections associated with non-oral bacteria isolated from the oral cavity have been revealed (Arirachakaran et al. 2019; Ghapanchi et al. 2019), making the oral cavity an extra-hospital reservoir (Kearney et al. 2020).

Currently, there are a limited understanding and limited information regarding the pathogenesis of non-oral bacteria in the oral cavity. To the best of our knowledge, there are no reviews on the role of non-oral bacteria in the oral cavity and their relationship with the oral microbiota. Therefore, this review examines the current knowledge about the most extensively studied non-oral bacteria in the oral cavity and also provides an overview of the interactions between the oral microbiota and non-oral bacteria.

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Non-oral bacteria in the oral cavity: transitory species or colonizers?

Non-oral bacteria are commonly found in other parts of the human body (nares or gut). They can accidentally be introduced into the mouth by food, water, contact with animals, mouthing and chewing items, etc. Nevertheless, nowadays, there is a controversy about whether the oral cavity is an entry point or an important reservoir for this group of bacteria and whether they are merely transient or unique to this niche (Zuanazzi et al. 2010; Vieira Colombo et al. 2016).

There has been strong evidence that they might colonize the oral ecosystem (Souto and Colombo 2008a; Gonçalves et al. 2007a; Da Silva-Boghossian et al. 2011). Patients positive with certain subgingival non-oral species, most notably *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, are reported to show a higher percentage of periodontal sites with suppuration on probing (Silva-Boghossian et al. 2013), greater periodontal attachment loss (Da Silva-Boghossian et al. 2013; Van Winkelhoff et al. 2016) and much more aggressive forms of periodontitis. Furthermore, some of these bacteria isolated from the oral cavity, such as enterococci, were found to be genetically different from isolates from other parts of the human body (Vidana et al. 2011), which could potentially lead to another understanding of the ecosystem of the oral cavity.

The disturbance of the "equilibrium" (due to medical treatments, biological changes, or inadequate hygiene) between commensal bacteria and the host immune system could be the reason for the shift of non-oral bacteria from transitory species to colonizers (Handal et al. 2003; Dahlen 2009; Tada and Hanada 2010), and could enhance the subsequent morbid microbial communities in the compromised host (Botero et al. 2007a; Vieira Colombo et al. 2016). However, in normal oral health conditions, one should not expect these microorganisms to overcome in proportions the very well adapted oral species (Van Winkelhoff et al. 2016).

The most extensively studied species in the oral cavity are species of *Enterobacteriaceae*, *Staphylococcus aureus*, *Enterococcus faecalis, Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. The presence of unique and specific virulence factors can help in distinguishing between these different species.

Enterobacteriaceae

Enterobacteriaceae is a family of Gram-negative rods that have stood out in the healthcare environment due to the variety of severe infections that they can cause and their resistance to antibiotics (Leão-Vasconcelos et al. 2015). Their presence in the oral ecosystem is perhaps due to the ingestion of contaminated drinking water, food or poor personal hygiene (Barbosa et al. 2001; Gonçalves et al. 2007b). The prevalence of GNRs in the oral environment is extremely variable, and it is still not clear whether they are colonizing or merely transient bacteria. This is probably due to the use of single-sample techniques that do not allow the differentiation between transient presence and persistent presence (Martinez-Pabon et al. 2010). However, it has been shown that the prolonged transportation time of the samples may encourage the multiplication of GNRs, leading to higher positive results (Ali et al. 1996).

Moreover, numerous studies on GNRs pathogenesis in the oral ecosystem have shown that (1) they can persist within the subgingival environment after periodontal debridement and surgery (Slots et al. 1991), (2) they are implicated as key pathogens in cases of refractory periodontitis (Edwardsson et al. 1999), (3) they are detected at greater frequency and in higher proportions in patients with failing implants (Listgarten et al. 1999) and (4) they are usually associated with oral mucosal infections in immune-compromised patients. In these patients, oral mucosal infections may spread to the respiratory system and trigger life-threatening infections (Scannapecio et al. 2009; Tada and Hanada 2010). Furthermore, their virulence factors are conferred through several properties that give the ability to adhere and invade the host's tissues (Kazemian et al. 2017). Such as the release of enterotoxins and endotoxins, elaboration of extracellular leukotoxins, degradation of immunoglobulins IgG and IgA, suppression of lymphocyte proliferation and elaboration of collagenolytic and other proteolytic enzymes (Barbosa et al. 2001). Nevertheless, the GNRs are rarely identified at the species level, and they are referred to as "enterics" (Martinez-Pabón et al. 2010). However, the group is made up of a wide variety of bacterial species, which are incongruent in pathogenicity, virulence and antibiotic susceptibility (Arirachakaran et al. 2019). At the species level, some authors have found that some Gram-negative rods can dominate among oral species in some cases, like Pereira et al. (2013) who found that *K. pneumoniae* is the dominant bacterial species in cases wearing removable maxillary prosthesis with and without denture stomatitis lesions. Also, according to Zhu et al. (2008), there exists an important correlation between the presence of *K. pneumoniae* in the oral cavity and the risk of pneumonia by aspiration of these bacteria in people suffering from a stroke.

Moreover, its ability to degrade elastin (which is perceived to be a marker of *P. aeruginosa* in the aetiology of lower respiratory tract infections (Beatty et al. 2005)) could contribute to its virulence (Goncalve et al. 2007). Thurnheer and Belibasakis (2015) observed that when *Escherichia coli* are given the appropriate nutritional and environmental

conditions, they can endure and even dominate among oral species in a polymicrobial biofilm. However, Back-Brito et al. (2011) have found considerably higher numbers of enteric bacteria in the oral cavities of HIV-positive patients, and *Enterobacter cloacae* were the most frequently isolated species (Table 1, the search strategy is in the supplementary file, Table S1). Interestingly, it was found that the presence of *Candida albicans* in the oral cavity can increase the growth and the swarming activity of *Proteus mirabilis* (Kart et al. 2020).

Staphylococcus aureus

Although the anterior nares are considered the primary ecological niche for *Staphylococcus* (Kearney et al. 2020), their presence in the oral cavity is unquestionable (Soni et al. 2017) but controversial (Smith et al. 2001), as it is not clear whether they play a part in the ecology of the healthy oral flora or not (Smith et al. 2003a; Blomqvist et al. 2015).

However, many authors have indicated that the oral cavity functions as a potential reservoir for *S. aureus* infections in immunosuppressed patients (Agwu et al. 2015; Merghni et al. 2015) (Table 1) and might cause some oral diseases such as periodontitis and dental caries (Fritschi et al. 2008; Merghni et al. 2014); and systemic diseases such as heart disease, chronic kidney disease, orofacial granulomatosis and Crohn's disease (Gibson et al. 2000; Zuanazzi et al. 2010; Simões-Silva et al. 2018). Oral *S. aureus* has also been recognized as an aetiological factor of infective endocarditis (Carmona et al. 2002).

Persson and Renvert (2014) found that *S. aureus* is present at higher amounts in biofilms obtained from implants with peri-implantitis than peri-implant healthy subjects. Other studies have revealed that *S. aureus* was found at higher levels in the oral cavity and with greater prevalence in periodontitis than non-periodontitis subjects (Souto et al. 2006; Persson et al. 2008), while Fritschi et al. (2008) found higher levels of *S. aureus* in aggressive than chronic periodontitis subjects. Consequently, *S. aureus* was pointed out as a contributor to the microbial profiles that could differentiate between aggressive and chronic forms of the disease. Moreover, *S. aureus* was found at higher levels in the oral cavity of patients with rheumatoid arthritis than healthy controls (Jackson et al. 1999) and was the most frequently isolated species in the oral cavities of HIV-positive patients (Back-Brito et al. 2011). The ability of *S. aureus* to cause such a diverse array of problems is due to its arsenal of virulence factors that are coordinately expressed during different stages of infection, such as superantigens, toxins such as β-toxin, matrix-binding surface adhesins, biofilm formation and tissue-degrading enzymes such as proteases, lipases, nucleases, and collagenases (Lowy 1998; Merghni et al. 2014; Lima et al. 2019).

Enterococcus faecalis

E. faecalis is not yet considered a normal inhabitant of the oral cavity (Kouidhi et al. 2011) but has been isolated from various oral conditions, including periodontitis and dental caries (Zhu et al. 2010; Kouidhi et al. 2011) (Table 1). It is perceived to be the predominant infectious agent associated with primary and secondary endodontic infections (Vidana et al. 2011) because of its ability to reside within different layers of the oral biofilm, and co-aggregate with different saliva bacteria, which leads to failure of endodontic therapy (Al-Ahmad et al. 2010).

Moreover, it has been found that *E. faecalis* can preserve viability in root canals ex vivo for at least 12 months (Sedgley et al. 2005); this is perhaps due to its ability to form biofilms (Al-Ahmad et al. 2009, 2014) or colonize multi-species supragingival biofilms (Thurnheer and Belibasakis 2015). Furthermore, coexistence between enterococci and *C. albicans* has been observed in immunocompromised patients (Almståhl et al. 2001, 2008).

The origin of these opportunistic bacteria in the oral cavity is not yet clear. Wang et al. (2011) demonstrated that the prevalence of *E. faecalis* in the root canal system had been correlated with its occurrence in saliva. Meanwhile, some authors suggested nosocomial transmission from environmental surfaces in dental surgeries due to the robust nature of the microorganisms (Vidana et al. 2011; Lins et al. 2019), while others proposed foodborne transmission (Zehnder and Guggenheim 2009). However, Vidana et al. (2011) examined the genetic relationship between *E. faecalis* from root canals and isolates from different host sources and found that isolates from the root canals were not related to those from the typical gastrointestinal microflora, and none of these patients was recorded to have enterococci in their saliva. Likewise, Cole et al. (1999) did not find any members of this species in the saliva probes from 10 infants. Further investigations are needed to minimize the dissemination of virulent and multidrug-resistant clones to the oral cavity. In addition to their role in oral diseases, subsequent systemic colonization and infection associated with an oral source of enterococci have been found; Okui et al. (2015) reported a case of infective endocarditis of oral origin caused by *E. faecalis*, while Arirachakaran et al. (2016) isolated oral enterococci from HIV patients.

The most studied virulence factors of *E. faecalis* include biofilms, aggregation substance, gelatinase, lipoteichoic acid, the cytolysin toxin, surface adhesins, extracellular superoxide, sex pheromones, and hyaluronidase. Each of these factors might be associated with many phases of endodontic infections, periapical inflammation, and systemic diseases (Kayaoglu and Ørstavik 2004; Anderson et al. 2016; Komiyama et al. 2016).

Table 1 Summary of studies in which non-oral bacteria have been isolated in patients with systemic or oral diseases

Diseases	Non-oral bacteria	Study group/study type	Age	Prevalence of non-oral bacteria (%)	Specimen (s) collected	Country	References[a]
Periodontitis	GNRs[b] *S. aureus*	PG[c]: 535 patients A cross-sectional study	19–70 years	34.9% 6.2%	Periodontal pockets	Sweden	Dahlen and Wikström (1995)
	GNRs *Pseudomonas*	PG: 80 patients A cross-sectional study	17–58 years	18.8% 10.0%	Periodontal pockets	Brazil	Barbosa et al. (2001)
	GNRs	PG: 80 patients A cross-sectional study	35–60 years	20%	Periodontal pockets	Brazil	Gonçalves et al. (2007b)
	H. pylori	PG: 169 patients CG[d]: 56 healthy subjects A cross-sectional study	41 ± 14 34.3 ± 12	50% (PG) 11.4 (CG)	Subgingival plaque samples	Brazil	Souto and Colombo (2008b)
	E. faecalis	PG: 169 patients CG: 56 healthy subjects A cross-sectional study	41 ± 14 34.3 ± 12	47.8% (PG) 17.1% (CG)	Subgingival plaque samples	Brazil	Souto and Colombo (2008a)
	S. aureus	PG: 106 patients A cross-sectional study	≥ 18 years	24.6%	Subgingival plaque samples	Switzerland	Fritschi et al. (2008)
	Staphylococcus spp.	PG: 82 patients	18–70 years	42.7%	Subgingival plaque samples	Argentina	Cuesta et al. (2010)
	GNRs	PG: 63 patients CG: 45 healthy subjects A prospective cohort	33.29 ± 7.79 43.95 ± 8.97	16.7% (PG) 9.3% (CG)	Periodontal pockets	Colombia	Martínez-Pabón et al. (2010)
	E. faecalis	PG: 32 patients A prospective longitudinal study	≥ 18 years	40.6%	Root canal samples	China	Zhu et al. (2010)
	P. aeruginosa *Acinetobacter* spp.	PG: 169 patients CG: 55 healthy subjects A cross-sectional study	40.2 ± 14 31.1 ± 11	52.2% (PG), 11.4% (CP) 56.5% (PG), 31.4% (CP)	Periodontal pockets	Brazil	Souto et al. (2014)
	GNRs	PG: 102 patients A cross-sectional study	48 ± 13.2	42.9%	Subgingival plaque samples	Netherlands	Van Winkelhoff et al. (2016)
	GNRs *P. aeruginosa*	PG: 42 patients CG: 42 healthy subjects Case–control study	43.48 ± 12.46 29.36 ± 8.99	83.3% (PG), 71.4% (CG) 30.9% (PG), 28.5% (CG)	Subgingival plaque samples	India	Ranganathan et al. (2017)
Dental caries	*E. faecalis,* *E. faecium*	PG: 34 caries active subjects CG: 28 caries free subjects A cross-sectional study	4–12 years	46.9% (PG), 7% (CG) 9.5% (PG), 7% (CG)	Saliva	Tunisia	Kouidhi et al. (2011)
	S. aureus	PG: 105 healthy subjects A cross-sectional study	45.84 ± 15.82	20%	Dental abscess, caries and saliva	Tunisia	Merghni et al. (2014)

Table 1 (continued)

Diseases	Non-oral bacteria	Study group/study type	Age	Prevalence of non-oral bacteria (%)	Specimen (s) collected	Country	References[a]
Root canal infection	*E. faecalis*	PG: 100 patients CG: 100 healthy subjects A cross-sectional study	32–72 years	11% (PG) 1% (CG)	Oral rinse samples	USA	Sedgley et al. (2004)
	E. faecalis	PG: 41 patients A cross-sectional study	42.6 ± 15.3	10%	Oral rinse samples	USA	Sedgley et al. (2006)
	E. faecalis *Staphylococcus* spp *Pseudomonas* spp *A. baumannii*	PG: 50 patients A cross-sectional study	23–76 years	16% 2% 2% 2%	Root canal samples	Sweden	Vidana et al. (2011)
Cystic fibrosis (CF)	*P. aeruginosa*	PG: 31 patients CG: 31 healthy subjects	5–29 years	45.16% (PG) 3.22 (CG)	Oral cavity samples	Canada	Komiyama et al. (1985)
	P. aeruginosa	PG: 5 patients CG: 5 healthy subjects Case–control study	16–34 years 12–27 years	100% (PG) 0% (CG)	Sputum samples	France	Rivas Caldas et al. (2015)
Orofacial granulomatosis and Crohn's disease	*S. aureus*	PG: 450 patients A prospective cohort	13–29 years	0.8%	Oral rinse samples	UK	Gibson et al. (2000)
Oral cancer	*Staphylococcus* spp. *P. aeruginosa*	PG: 46 patients CG: 37 healthy subjects A cross-sectional study	67.4 ± 10.3 71.3 ± 9.9	43.7% (PG), 56.3% (CG) 57.1% (PG), 42.9% (CG)	Saliva and surgical scar	Japan	Yamashita et al. (2013)
	S. aureus *E. coli* *S. epidermidis*	PG: 40 patients A cross-sectional study	/	23.2% 15.62% 12.5%	Swabs over the cancerous lesion	India	Panghal et al. (2011)

Table 1 (continued)

Diseases	Non-oral bacteria	Study group/study type	Age	Prevalence of non-oral bacteria (%)	Specimen (s) collected	Country	References[a]
HIV	*S. aureus* *P. aeruginosa* *K. pneumoniae*	PG: 14 periodontitis patients A cross-sectional study	25–50 years	6.8% 6.7% 6.7%	Subgingival plaque samples	USA	Rams et al. (1991)
	GNRs	PG: 31 periodontitis patients CG: 32 healthy subjects A cross-sectional study	37.3 ± 9.3 22.8 ± 8.5	74.2% (PG) 18.8% (CG)	Subgingival plaque samples	Colombia	Botero et al. (2007b)
	S. aureus *S. epidermidis* *E. cloacae*	PG: 45 HIV subjects CG: 45 healthy subjects A cross-sectional study	22–66 years 23–66 years	92.4% (PG), 54% (CG) 47% (PG),61.8% (CG) 22.3% (PG), 18.1% (CG)	Oral rinse samples	Brazil	Back-Brito et al. (2011)
	P. mirabilis *S. aureus* *P. aeruginosa*	PG: 605 HIV subjects A cross-sectional study	1–60 years	16.4% 11.3% 8.6%	Oral lesions samples	Uganda	Agwu et al. (2015)
	Coliforms *Pseudomonas* spp. *S. aureus* Enterococci	PG: 221 HIV patients PG: 30 healthy subjects A cross-sectional study	8–69 years 27–47 years	15% (PG), 3% (CG) 11% (PG), 7% (CG) 14%(PG), 17% (CG) 2% (PG), 0% (CG)	Dorsum of the Tongue	Thailand	Arirachakaran et al. (2016)
	Pseudomonas spp. *Enterobacter* spp. *Klebsiella* spp. *Aeromonas* spp.	PG: 255 Thai HIV-positive adults on Highly active anti-retrovirus therapy (HAART) CG: 30 healthy subjetcs A cross-sectional study	/	9.01% (PG), 3.33% (CG) 4.31% (PG), 6.66% (CG) 5.49% (PG), 23.3% (CG) 3.92% (PG), 6.66% (CG)	Dorsum of the tongue, gingiva, periodontal pocket	Thailand	Arirachakaran et al. (2019)
Rheumatoid arthritis	*S. aureus*	PG: 111 patients CG: 83 healthy subjects A cross-sectional study	58.7 ± 11.64 55.9 ± 12.91	12.5% (PG) 3.6% (CG)	Oropharynx samples	USA	Jacobson et al. (1997)
	S. epidermidis *S. aureus*	PG: 25 patients CG: 50 healthy subjects A cross-sectional study	21–82 years 18–54 years	84% (PG), 88% (CG) 56% (PG), 24% (CG)	Oral rinse samples and tongue swabs	UK	Jackson et al. (1999)
Parkinson's disease	GNRs	PG: 50 patients A cross-sectional study	71–90 years	32%	A swab around the tonsillar area and soft palate	UK	Gosney et al. (2003)
Burns, skin, grafting and lacerations	*Staphylococcus* spp.	PG: 28 patients A cross-sectional study	14–84 years	53.57%	Supragingival plaque and oral rinse samples	UK	Smith et al. (2003a)

Table 1 (continued)

Diseases	Non-oral bacteria	Study group/study type	Age	Prevalence of non-oral bacteria (%)	Specimen (s) collected	Country	References[a]
Heart disease	*Staphylococcus* spp. *Pseudomonas* spp. *Acinetobacter* spp.	PG: 30 patients undergoing myocardium revascularisation surgery (Pre-surgery results) A prospective cohort	62.66 ± 4.01	85.7% 83.8% 53.3%	Saliva and subgingival plaque samples	Brazil	Zuanazzi et al. (2010)
Dyspepsia	*H. pylori*	PG: 30 patients CG: 20 healthy subjects A cross-sectional study	46.2 ± 11.44 44.5 ± 11.36	60% (PG) 15% (CG)	Subgingival plaque samples	India	Agarwal and Jithendra (2012)
Endocarditis	*E. faecalis*	PG:1 patient with arrhythmia A case report	67 years old	100% (PG)	A swab from Gingival mucosa	Japan	Okui et al. (2015)
Head and neck cancer	Gram-negative bacilli *S. aureus*	PG: 110 patients CG:50 healthy subjects A prospective case–control	20–80 years	63.6% (PG), 2% (CG) 8% (PG), 0% (CG)	Saliva	India	Soni et al. (2017)
Chronic kidney disease (CKD)	*S. epidermidis*	PG: 21 end-stage CKD adult patients CG:14 healthy subjects A cross-sectional study	46.8 ± 9.7 42.2 ± 14.5	89.5% (PG) 92.3% (CG)	Saliva	Portugal	Simões-Silva et al. (2018)
	P. aeruginosa	PG: 1 HIV-positive subject A case report	6 years old	100%	Biopsy of the gingival tissue	Brazil	Souza et al. (2018)
Chronic nail biting	GNRs	PG: 60 Nail biting subjects CG: 30 healthy subjects A cross-sectional study	11 ± 3.0 12 ± 3.5	75% (PG) 40% (CG)	Saliva	India	Chinnasamy et al. (2019)
Liver transplantation	*E. faecalis*	PG: 100 patients CG: 100 healthy subjects A cross-sectional study	10–67 years 10–77 years	2% (PG) 1% (CG)	Saliva	Iran	Ghapanchi et al. (2019)

[a]Inclusion and exclusion criteria and search strategy are in the supplementary file

[b]*GNRs* Gram-negative rods

[c]*PG* Patients group

[d]*CG* Control group

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a Gram-negative bacillus that most often affects the lower respiratory system and is associated with nosocomial infections (Watanabe et al. 2009). It can be part of the transient oral microbiota but seldom colonize the oral cavity, which is perhaps due to its strong aerobic character (Arirachakaran et al. 2019). However, studies using molecular biology methods have revealed that its presence in the oral cavity is underestimated and it is much higher in complex biofilms (Wade 2013; Souza et al. 2018).

Moreover, these species have many virulence properties such as the ability to adhere to and form biofilms on tissues and abiotic surfaces (Smith and Iglewski 2003b), along with their ability to produce and secrete extracellular enzymes and toxins (Smith and Iglewski 2003b; Pihl et al. 2010) as well as the expression of multiple antimicrobial resistance elements (Livermore 2002). *P. aeruginosa* has also been identified in the periodontal pockets of immunocompromised subjects (Nakou et al. 1997) and might be an important pathogen in periodontitis and gingivitis (Persson et al. 2008; Vieira Colombo et al. 2016) (Table 1).

Moreover, they are perceived to be the main pathogen in chronic obstructive pulmonary disease and biofilms on vehicles at intubation (Ewan et al. 2015). Their passage into the lungs may occur by passive aspiration of the bacterial microbiota released in saliva or eased by medical devices such as bronchoscopes and endotracheal tubes (Scannapieco et al. 2009). Lately, oral *P. aeruginosa* has been associated with oral squamous cell carcinoma (Al-Hebshi et al. 2017) and chronic kidney disease (Simões-Silva et al. 2018). Additionally, focal necrotizing lesions have been found in the oral mucosa of HIV-positive patients, which are different from periodontal disease patterns and are related to the presence of oral *P. aeruginosa* (Souza et al. 2018).

Acinetobacter baumannii

A. baumannii is a Gram-negative bacillus often found in the hospital environment. It is among the red list group of ESKAPE pathogens (*E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa,* and *Enterobacter* species) announced as a critical priority pathogen by World Health Organization (WHO) (WHO 2017).

There are not many reports on the incidence of *A. baumannii* in the oral cavity or its association with oral diseases; though some studies have found that it is significantly associated with suppuration in chronic periodontitis patients, aggressive periodontitis and root canal infections (Da Silva-Boghossian et al. 2013; Vidana et al. 2011; Souto et al. 2014), especially in patients with human immunodeficiency virus (Gonçalves et al. 2007a). Also, the likelihood of a subject being refractory to periodontal treatment increases when *A. baumannii* is present (Colombo et al. 1998). Furthermore, it is a major pathogen in ventilator-associated pneumonia, which is a massive problem in hospitals, particularly in intensive care units (Lee et al. 2012; Martinez-Lamas et al. 2014), and was isolated from patients suffering from heart disease (Zuanazzi et al. 2010).

Major virulence factors that were studied in *A. baumannii* isolated from the oral cavity are lipocalins production, biofilm formation, siderophore-mediated iron-acquisition system, outer membrane protein A, desiccation resistance and the ability to bypass the glucose metabolism, which can be considered as one of the key factors that help this bacteria survive in a nutrition-deficient environment (Richards et al. 2015; Priyadharsini et al. 2018).

Interactions between the oral microbiota and non-oral bacteria

In the oral cavity, where resources are limited, collaborations between species are needed to survive and endure. Some studies have shown the physical and metabolic interactions that exist between members of the oral microbiota and non-oral species; they can be mutualistic interspecies interactions (coaggregation) to form biofilms or antagonistic interactions to prevent the integration of a non indigenous bacterial species (Table 2). However, the biological mechanisms underlying these interactions are not yet clear.

Coaggregation is defined as cell-to-cell adhesion in which cells of a species adhere more or less specifically to different species (Kolenbrande 2000). This mechanism is involved in the establishment and maintenance of biofilms (Kolenbrander et al. 2010). For instance, in periodontitis patients, an association was found between GNRs and *Porphyromonas gingivalis* with *Tannerella forsythia*; both members of the "red complex" bacterial species are associated with severe forms of periodontitis (Socransky et al. 1998). Ardila et al. (2011, 2012) also reported a positive subgingival correlation between GNRs and *P. gingivalis,* and between GNRs and *Aggregatibacter actinomycetemcomitans*. Likewise, *E. faecalis* strains coaggregated with *Fusobacterium nucleatum* (Johnson et al. 2006), which was able to co-aggregate with *Helicobacter pylori* (Andersen et al. 1998) and *S. aureus* (Tawara et al. 1996; Lima et al. 2019). *Fusobacterium* is considered a key microorganism in the process of coaggregation among different genera and might work as a bridge between early and late colonizers (Andersen et al. 1998; Souto and Colombo 2008b). Previous studies have demonstrated that *F. nucleatum* utilizes the surface protein RadD to bind and form a dual-species biofilm with other oral species (Park et al. 2016; Lima et al. 2017). Moreover, Da Silva-Boghossian et al. (2011) demonstrated that

Table 2 Interactions between non-oral bacteria and oral microorganisms in the oral cavity

Non-oral bacteria	Oral bacteria	Type of interaction	References[a]
P. aeruginosa	*A. viscosus*	Coaggregation	Komiyama and Gibbons (1984)
P. aeruginosa	*S. sanguis, S. mitis* *A. naeslundii*		Komiyama et al. (1987)
S. aureus	*F. nucleatum*		Tawara et al.(1996)
H. pylori	*Fusobacterium*		Andersen et al. (1998)
GNRs	*P. gingivalis, T. forsythia*		Socransky et al. (1998)
S. aureus	*A. Naeslundii* *A. viscosus* *P. gingivalis*		Kamaguchi et al. (2003)
Weissella cibaria	*F. nucleatum*		Kang et al. (2005)
E. faecalis	*F. nucleatum*		Johnson et al. (2006)
GNRs	*P. gingivalis*		Ardila et al. (2011)
A. baumannii *P. aeruginosa*	*T. forsythia, P. gingivalis, T.denticola*		Da Silva-Boghossian et al. (2011)
GNRs	*A. actinomycetemcomitans*		Ardila et al. (2012)
S. aureus	*F. nucleatum, P. gingivalis*		Lima et al. (2019)
S. aureus	Viridans group streptococci		Uehara et al. (2001)
H. pylori	*S. oralis* *S. mutans* *S. sobrinus* *A. naeslundii* *P. intermedia* *P. nigrescens*	Antagonistic relationship	Okuda et al. (2003)
P. aeruginosa *A. baumannii*	*S. sanguinis*		Watanabe et al. (2009)
E. faecalis *S. aureus*	*A. actinomycetemcomitans*		Da Silva-Boghossian et al. (2011)
P. aeruginosa	*S. parasanguinis* *S. sanguinis* *S. gordonii*		Scoffield and Wu. (2015)
E. faecalis	*S. oris, S. mutans*		Thurnheer and Belibasakis (2015)

P. aeruginosa seemed to have synergism with *A. actinomycetemcomitans*, raising the risk of periodontal disease. Nonetheless, in the same study, the presence of *E. faecalis*, or *S. aureus* in association with *A. actinomycetemcomitans* decreased the risk of periodontal disease. However, other studies have revealed that *S. aureus* and *E. faecalis* were detected at higher levels and with greater prevalence in periodontitis than the non-periodontitis subjects (Fritschi et al. 2008; Persson et al. 2008). The differences in methods of detection and ecological variables may account for the data variability amongst these studies.

Antagonistic relationships are also detected in such intricate microbial communities. Nutritional competition between two early colonizers of the oral cavity and *E. faecalis* was observed. It was shown that the presence of *E. faecalis* in the oral plaque causes a significant reduction in the numbers of *Streptococcus oralis* and *Streptococcus mutans* (Thurnheer and Belibasakis 2015), which is in line with other studies demonstrating that *E. faecalis* dominates numerically over *S. mutans* in dual-species biofilms (Deng et al. 2009; Li et al. 2014).

Moreover, Okuda et al. (2003) found that *Streptococcus oralis*, *Actinomyces naeslundii, Streptococcus mutans*, *Prevotella intermedia, Prevotella nigrescens*, and *Streptococcus sobrinus*, produce bacteriocin-like inhibitory proteins against *H. pylori*. The fact that subjects with good oral hygiene harbor less *H. pylori* in their mouths could also be due to the inhibitory activity of the early colonizers of dental biofilms, such as oral streptococci, over that species (Anderson et al. 1998). Likewise, Watanabe et al. (2009) demonstrated that a substance called the ''new-antipseudomonal substance'' derived from *Streptococcus sanguinis* could have bactericidal activity against *A. baumannii* and *P. aeruginosa.* Nevertheless, these complex and dynamic interactions remain unknown. More profound studies focusing mainly on quorum sensing are needed to understand how non-oral bacteria regulate their genes and coordinate cooperative behaviors in the presence of oral bacteria.

Conclusion and future outlooks

The complex and dynamic interactions in the oral ecosystem between oral and non-oral bacteria are far from being wholly unraveled, and the pathogenetic mechanisms used by these microorganisms are still unclear. Nevertheless, it is clear that non-oral bacteria are not passive bystanders and could play an essential role in oral and systemic diseases. Some non-oral bacteria, such as those covered by this review, are becoming major microbes in the oral cavity and they are increasingly isolated from healthy subjects.

This review highlighted the possible role, versatility, and pathogenic potential of non-oral bacteria in the oral cavity. However, some studies that were used displayed some limitations. Most of the studies available on this subject were cross-sectional studies. Longitudinal studies are also needed to track the presence of these bacteria over an extended period. Assessing quantitatively, the presence of non-oral bacteria is of utmost importance and not just counting on presence/absence. Furthermore, molecular biology methods are also needed to see whether non-oral bacteria are genetically different from isolates from other parts of the human body.

Despite the limitations, the presence of non-oral bacteria in the oral cavity is clearly worrisome. It needs more attention to broaden our understanding of the oral ecosystem and develop novel and more adequate preventive and therapeutic approaches, as well as diagnostic applications so that we can control the spread of non-oral bacteria and render them incapable of damaging the host.

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