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Ecological therapeutic opportunities for oral diseases

Anilei Hoare[1], **Philip D. Marsh**[2], and **Patricia I. Diaz**[1]

[1]Division of Periodontology, Department of Oral Health and Diagnostic Sciences, UConn Health, Farmington, CT, USA

[2]Division of Oral Biology, School of Dentistry, University of Leeds, Leeds, UK

SUMMARY

The three main oral diseases of humans, that is caries, periodontal diseases and oral candidiasis, are associated with microbiome shifts initiated by changes in the oral environment and/or decreased effectiveness of mucosal immune surveillance. In this review we discuss the role that microbial-based therapies may have in the control of these conditions. Most investigations on the use of microorganisms for management of oral disease have been conducted with probiotic strains with some positive but very discrete clinical outcomes. Other strategies such as whole oral microbiome transplantation or modification of community function by enrichment with health-promoting indigenous oral strains may offer more promise but research in this field is still in its infancy. Any microbial-based therapeutics for oral conditions, however, are likely to be only one component within a holistic preventive strategy that should also aim at modification of the environmental influences responsible for the initiation and perpetuation of microbiome shifts associated with oral dysbiosis.

INTRODUCTION

The oral microbiome is formed by hundreds of microbial species, including bacteria, fungi, archaea and viruses, which coexist in specific and organized arrangements in the different habitats of the oral cavity (1, 2, 3, 4, 5, 6, 7, 8). Oral sub-habitats include the mucosa, covered by keratinized and non-keratinized stratified squamous epithelium, the papillary surface of the tongue dorsum and the hard structures of teeth, which are comprised by those above (supragingival) and below (subgingival) the gingival margin. The distinct environmental characteristics found in each of these habitats promote the development of unique microbial communities that, although living in close proximity, can be clearly discriminated from each other (9, 10, 11, 12). Moreover, the microbial composition of these communities is critical to oral health with the main oral diseases characterized by deleterious alterations in microbiome community structure at specific sub-habitats (13, 14).

As in other human mucosal compartments, an understanding of the composition of health and disease-associated communities, together with the development of treatments to attempt the restoration of healthy communities in diseased individuals, has been the subject of increasing research. In this review, we present an overview of the main oral diseases and a critical evaluation of potential microbial-based therapies. We conclude with a perspective on what we believe are key points regarding the etiology of oral diseases that need to be taken into account when developing microbial-based therapeutics for oral conditions.

1. Ecological factors mediating the assembly of oral communities

The oral cavity sub-habitats are colonized by uniquely adapted microbial communities. As other accessible surfaces of the human body, like skin, upper respiratory tract, gastrointestinal tract and vagina, the oral cavity is colonized soon after birth (15). The oral microbiome is one of the most complex and diverse microbial communities, harboring hundreds of species (2, 16). The distribution of such species within oral sub-habitats is determined by a number of factors such as: (i) the characteristics of the surfaces available for attachment, (ii) oxygen availability, (iii) exposure to nutrients from the diet of the host, and (iv) exposure to host products delivered by saliva and gingival crevicular fluid. Microbial successions and inter-species interactions also shape the development of oral communities.

Two different types of surfaces, hard and soft, are available for colonization in the oral cavity. The presence of hard, non-shedding surfaces is a unique feature of the mouth as tooth surfaces (and dentures) allow the development of permanent communities and substantial biomass unless disrupted by regular oral hygiene; in contrast, soft mucosal surfaces promote constant community turnover due to epithelial cell shedding. Both types of surfaces are constantly bathed by saliva, with salivary glycoproteins and proteins adsorbing in a selective way to create a conditioning film. The glycoproteins and proteins in the conditioning film serve as ligands attracting specific species from the genera *Streptococcus*, *Actinomyces*, *Capnocytophaga*, *Eikenella*, *Haemophilus*, *Prevotella*, *Propionibacterium* and *Veillonella*, among others, which are considered early colonizers (17, 18). These microorganisms possess specific arrangements of surface ligands (usually proteins) that allow their adherence (19). Species such as *Streptococcus mitis* and *Streptococcus sanguinis* recognize sialic-acid residues present in adsorbed salivary mucins (20, 21, 22, 23). Other species, such as *Actinomyces* spp. produce enzymes that actively modify adsorbed glycoproteins exposing specific saccharide residues (cryptic receptors), which mediate their own attachment (24, 25). Aditionally, most of the indigenous streptococci express polypeptides of the AgI/II family that mediate the recognition of salivary glycoproteins such as gp-340 and their adhesion to epithelial cells (26, 27, 28). This group of peptides is also involved in streptococcal attachment to extracellular matrix components such as fibronectin, collagen and laminin (29, 30), which are exposed when epithelial integrity is disrupted. Thus, selective recognition by early colonizers of molecules exposed at the different surfaces determines and confers specificity to early microbial colonization events.

The attachment of early colonizers to tooth surfaces provides new ligands for the colonization of other species that successively adhere giving place to the formation of a biofilm (31). Interspecies communication and microbial succession also constitute important aspects of community assembly at different oral surfaces. Classic studies on the physical interactions (coaggregation and coadhesion) among oral species have demonstrated that bacterial/bacterial and fungal/bacterial cell recognition and attachment are highly specific (32, 33, 34, 35, 36). Indeed, analysis of dental plaque shows that oral microbial assemblages are specifically organized structures in which individual taxa are arranged in a way suggestive of their functional niche in the consortium (6, 8, 37, 38). For example, in a 9-taxa consortium recently identified in supragingival plaque, filamentous corynebacteria occupied the central position with other taxa radially arranged around them. Anaerobic taxa tended to

be in the interior, whereas facultative or obligate aerobes were located at the periphery of the consortium. Consumers and producers of certain metabolites, such as lactate, tended to be near each other (6). Such highly organized spatial arrangements are likely to result from and facilitate a great variety of inter-species interactions, including the formation of metabolic networks (17).

Interactions among neighboring microbial species in oral communities could be synergistic or antagonistic in nature. One example of synergism in the oral cavity is the collective degradation of salivary glycoproteins by microbial consortia, in which complementary enzymatic activities allow the utilization of mucins in saliva as energy source, as no microorganism possesses the diverse array of enzymes needed for their complete breakdown (39). Also, several examples of food chains in which a metabolic product of one species is utilized as primary energy source by a partner species have been documented (40, 41, 42). Antagonistic interactions mediated by the production of bacteriocins and hydrogen peroxide may also affect community assembly (43, 44, 45, 46, 47, 48).

The interaction of communities with the host also plays a key role in community development. Multiple factors found in the mucosa, saliva and gingival crevicular fluid (GCF), a serum-like exudate constantly flowing between the gingiva and teeth, modulate the growth of the resident microbiota at the different surfaces (49, 50, 51, 52). Antimicrobial peptides of the β-defensin family (hBDs) are found in various locations of the oral cavity such as oral mucosa, gingiva, tongue epithelium, and salivary glands (53). These peptides are believed to selectively control the growth of resident microorganisms (49). In saliva, multiple antimicrobial activities have been described such as the inhibitory effect of histatins against *Candida* and *Streptococcus*; the antimicrobial activity of cystatins on *Porphyromonas gingivalis*, and cathelicidin LL-37 activity against *Candida* spp. (54, 55, 56, 57). Other molecules such as lactoferrin, lysozyme, and a variety of antimicrobial peptides present in saliva may also influence the composition of the microbial community (for a review see Marsh et al. (52)). Finally, elements of the complement system found in GCF may modulate colonization of the subgingival sulcus (50, 58).

Depending of the location in the oral cavity, the sources of nutrients for microorganisms also differ. In exposed surfaces such as tongue, mucosa and supragingival surfaces of teeth, dietary products as well as saliva components are the main available nutritional sources, while in the subgingival crevice the resident microorganisms obtain nutrients mainly from GCF. Saliva contains glycoproteins such as mucins, amylase, and immunoglobulin (Ig) A (52, 59), while GCF contains many serum-derived proteins, such as hemoglobin-derived peptides, IgM, IgG and albumin, which serve as nutrients for sub-gingival species (50, 60, 61, 62). Bacteria from supragingival plaque use host glycoproteins as a major energy source and function as a microbial community to sequentially degrade these structurally complex molecules (39, 63). Enrichment cultivation studies in serum and evaluation of the growth of bacteria in the presence of serum proteins suggest that the protein and iron-rich GCF promotes the growth of Gram-negative anaerobic proteolytic taxa, which characterize subgingival plaque (61, 64, 65, 66). In contrast, dietary carbohydrates mostly affect the community structure of supragingival plaque with their frequent intake promoting an

enrichment of species with an efficient carbohydrate metabolism and an ability to grow well at acidic pH values (67, 68).

Oxygen availability is another important factor driving the selective colonization of microbes in the oral cavity, since it varies widely among the different surfaces found in the mouth. The gingival crevice constitutes a highly reduced area with E_h levels as low as −300 mV as a consequence of low tension of oxygen (69, 70, 71). Therefore, this environment selects mostly obligately anaerobic species, while supragingival plaque is enriched with aerobic and facultative microorganisms. Anaerobic bacteria also are found in greater proportions in the tongue crypts, which serve as an anaerobic "pocket-like" reservoir for microbes (72).

2. Ecological aspects of oral disease etiology

The three main oral diseases, that is caries, periodontal diseases and oral candidiasis, are associated with dysbiosis of the resident oral microbiome. In the three conditions there is an overgrowth of certain indigenous microorganisms, which become the dominant species at the affected site at the expense of health-associated taxa. Figure 1 summarizes the factors mediating microbiome shifts in these three conditions.

Caries—Caries is the localized demineralization of dental hard tissues by acidic by-products derived from bacterial fermentation of dietary carbohydrates (73). If not controlled, the disease progresses resulting in the cavitation of the affected tooth, potentially allowing microbial colonization of the tooth pulpal tissue (74). Dental caries is a multifactorial disease in which the frequent intake of dietary carbohydrates and the subsequent generation of a low environmental pH drive alterations in the composition and metabolic properties of the bacterial communities in dental plaque, leading to the enrichment of acid producers (acidogenic) and acid-tolerant (aciduric) microorganisms (39, 75). The ecological plaque hypothesis, proposed to explain caries etiology, summarizes these dynamics (39). Prior to the onset of the disease, acidogenic bacteria present in the dental biofilm metabolize dietary fermentable sugars. The acid produced changes the local environment driving an ecological shift in the resident microbiota that favors the selection of aciduric species, which are able to tolerate, grow and continue to produce acid in low-pH environments. With the frequent intake of dietary sugars, and a more acidogenic and aciduric microbiome, the plaque pH is therefore maintained at low levels, promoting enamel demineralization (76).

Despite inter-subject variability, cariogenic plaques are enriched by a common but limited number of acidogenic/aciduric species compared to healthy subjects. Among these species, *Streptococcus mutans* shows the greater correlation with both onset and progression of caries (14, 77, 78, 79). However, besides *S. mutans*, increased abundance of other streptococci as well as species of *Actinomyces, Atopobium, Lactobacillus, Bifidobacterium*, *Propinibacterium* and *Scardovia* has also been associated with caries lesions (14, 77, 80, 81, 82, 83, 84, 85, 86, 87). A recent microbiome evaluation by Gross et al. (14) reported that *S. mutans* was the dominant species in many, but not all, subjects with caries. A different species from the Mutans group of streptococci (MS) (*Streptococcus sobrinus*), a phylotype from the Salivarius group of streptococci (*Streptococcus vestibularis*/*salivarius*) and a

species from the Mitis group of streptococci (*Streptococcus parasanguinis*) were also found in high levels in subjects with caries, especially in individuals with no or low levels of *S. mutans* (14). These findings indicate that the acidogenic activity of plaque is probably more important for lesion development than the presence of specific bacterial species. Thus, given the right ecological pressure, other species different from *S. mutans*, but with aciduric and acidogenic characteristics, could become significant contributors to the disease.

Periodontal diseases—Periodontal diseases are inflammatory conditions that affect the supporting structures of teeth. The interplay between biofilms that accumulate at the gingival margin and the resulting local immune responses results in gingival inflammation, that is, gingivitis. Further inflammation, as observed in periodontitis, results in destruction of the connective tissue attachment, alveolar bone resorption and eventual tooth loss (88). Periodontitis can be broadly classified as aggressive or chronic, based on clinical presentation and progression rate. Chronic periodontitis is generally detected in older subjects compared to more aggressive forms, has slower rates of progression and destruction, and is associated with ticker and more complex biofilms (89). Aggressive periodontitis is further divided into localized and generalized forms, the former typically affecting specific teeth (90).

The transition from health to periodontitis is characterized by shifts in the community structure of the subgingival microbiome, probably as a result of the interaction between resident communities and the inflammatory response of the host (13, 88, 91). Health-associated subgingival communities are enriched in Gram-positive taxa such as *Rothia* spp. and *Actinomyces* spp., while gingivitis communities are enriched with mostly Gram-negative species from the genera *Prevotella*, *Selenomonas* and *Fusobacterium*, among others (92, 93, 94). Further microbiome shifts occur as periodontitis develops with the establishment of a highly diverse community enriched in species such as *P. gingivalis*, *Tannerella forsythia, Treponema* spp., *Filifactor alocis*, and *Fretibacterium* spp., among many others (13, 95, 96, 97). Moreover, the aggressive form of periodontitis is characterized by elevated proportions of *Aggregatibacter actinomycetemcomitans* in addition to some of the mentioned bacterial species typically enriched in chronic periodontitis (98, 99, 100, 101, 102).

The exact mechanisms behind microbiome shifts associated with periodontal diseases have not been completely elucidated, but is likely that both microbial and host forces drive the community structure changes. Currently, the most accepted hypothesis of periodontal disease etiology is the polymicrobial synergy and dysbiosis model (88, 103). According to this model, low levels of keystone species such as *P. gingivalis* enhance microbial community virulence by disabling immune surveillance mechanisms in the gingival sulcus, allowing overall community overgrowth, which promotes inflammation. Inflammation further modifies the community selecting for “inflammophilic” organisms, which are those capable of metabolism of proteinaceous substrates derived from tissue breakdown and from GCF, the flow of which is increased in disease. Inflammation and dysbiosis reinforce each other, eventually causing destruction of periodontal tissues (88). Several mechanisms have been described to mediate the keystone pathogen-driven dysregulation of the host response. *P. gingivalis* has been shown to dysregulate pro-inflammatory signals in epithelial cells such

as the neutrophil chemokine IL-8 and the T-cell chemokine CXCL10/IP-10 (104, 105). Also *P. gingivalis*, together with *Prevotella intermedia* and *T. forsythia*, dysregulate via several mechanisms the complement pathway (88, 106, 107, 108, 109), with animal models showing that complement plays an essential role in the pathogenesis of periodontitis (110). Therefore, synergic interactions between species in the community, the decreased effectiveness of host surveillance mechanisms and the resulting enhancement of overall community growth with subsequent inflammatory responses conducive to connective tissue attachment and bone loss are likely to contribute to the onset of periodontitis.

Oral candidiasis—Oral candidiasis is the superficial inflammation of the oral mucosa due to the overgrowth of *Candida* spp. (111). Clinical presentations of the primary forms of oral candidiasis include: (i) acute pseudomembranous candidiasis; (ii) chronic erythematous candidiasis; (iii) acute erythematous candidiasis; and (iv) chronic hyperplastic candidiasis (112). *Candida albicans* is the most predominant species associated with oral candidiasis, followed by *Candida glabrata, Candida tropicalis, Candida parapsilosis, Candida kefyr*, *Candida dubliniensis*, *Candida lusitaniae* (currently *Clavispora lusitaniae*), *Candida krusei* (currently *Pichia kudriazevii* and *Issatchenkia orientalis*), and *Candida guilliermondii* (currently *Meyerozyma guilliermondii*) (113). However, the sole presence of these species in the oral cavity is not enough for disease onset. Oral candidiasis development is mostly driven by conditions that compromise the systemic immune response such as organ transplantation, HIV infection, chemotherapy, radiotherapy and advanced age. Other local contributory factors that may promote *Candida* overgrowth include wearing a removable prosthesis, poor oral hygiene, tobacco use and hyposalivation (111). Saliva seems to be a key element in the control of *Candida* overgrowth, since it has components such as soluble IgA and mucins that bind and clear the fungi from the oral cavity, as well as histatin 5 and calprotectin that have potent antifungal activities (114).

Contrary to other mucosal compartments, no clear relationship between the disruption of the bacterial component of the oral microbiome by the use of antibiotics and the overgrowth of *Candida* spp. in the oral cavity has been established. Our current understanding of fungal-bacterial ecology in relation to oral health and disease is limited. Current in vitro studies and animal models suggest that the interactions between *C. albicans* and bacterial partners such as oral streptococci may be synergistic rather than antagonistic (115, 116, 117). However, no longitudinal studies exist in humans evaluating fungal and bacterial microbiome interactions during oral candidiasis progression.

3. Overview of mechanisms behind common microbial therapeutic approaches

Microbial therapeutics include several approaches aimed at restoring the ecological balance through the use of viable cells. Such strategies have been applied with successful results mainly in gastrointestinal diseases and range from targeting specific species to the replacement of the entire microbiota. Among the strategies that use live cells as therapeutic agents and have been considered in the context of oral diseases are: (i) probiotics, (ii) bacterial replacement, and (iii) predatory bacteria and bacteriophages.

Probiotics—The World Health Organization, and the Food and Agriculture Organization of the United States define probiotics as “Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host”. Some of the desirable characteristics of a probiotic strain include: non-pathogenic and safe for the patient, genetically stable, and able to survive processing and administration conditions. Other characteristics such as being able to adhere to mucus and/or human epithelial cells, having antimicrobial activity against potentially pathogenic bacteria and/or the ability to reduce pathogen adhesion to surfaces may also be desirable (118).

Although the exact molecular mechanisms of action of probiotics are largely unknown, proposed mechanisms can be summarized in three general areas: (i) enhancement of mucosal barrier function, (ii) modulation of the immune response, and (iii) antagonism of pathogens either by the production of antimicrobial compounds or through competition for mucosal binding sites (119, 120). The enhancement of the mucosal barrier is thought to be mediated by the interaction of microorganism-associated molecular patterns (MAMPs) with specific epithelial cell receptors (119). Also, several specific bacterial molecules have been shown to direct the expression of tight-junction proteins protecting epithelial cells from apoptosis and promoting cellular proliferation (121), suppress intestinal inflammation through the activation of the histamine H2 receptor (122), and reduce the recruitment of T helper 17 (Th17) cells down-regulating interleukin 17 (IL-17) cytokine production (123). Fungal probiotics such as *Sacharomyces boulardii* have been shown to improve gut barrier function and decrease the inflammation tone reducing body weight, fat mass, and hepatic steatosis in obese and Type 2 diabetic mice (124, 125, 126, 127). Another example of an immunomodulatory probiotic effect is the production of a cell surface-associated exopolysaccharide (EPS) by *Bifidobacterium breve* that protects against infection with enteric pathogens in mice by inducing alterations in antibody production (128).

The direct antagonist effects of probiotics on potentially pathogenic species are possibly mediated by competition for nutrients or adherence, and via direct antimicrobial activity (129, 130, 131, 132). Although some direct probiotic-pathogen interactions have been documented, whether probiotics need to change the composition of the microbiota to exert their effect remains controversial. Probiotic-induced changes in microbial composition towards beneficial bacteria have been shown in both obesity and hepatocellular carcinoma models (123, 124), while McNulty et al. (133) showed that the metabolic function of the community changed without alterations in community membership after treatment of mice with a mixture of probiotics.

A list of diseases in which probiotic use is most accepted as some beneficial effect has been found includes: treatment of infectious childhood diarrhea, prevention of antibiotic-associated diarrhea, prevention and maintaining remission in pouchitis, treatment and maintenance of remission in ulcerative colitis, treatment and prevention of atopic eczema associated with cow’ s milk allergy, and hepatic liver disease. The recommendations for use of probiotics are strain specific and mostly include *Lactobacillus* and *Bifidobacterium* spp. (134, 135, 136).

Bacterial replacement therapies—Bacterial replacement therapies are based on the utilization of indigenous bacteria, usually genetically modified, to colonize human tissues and thereby prevent the outgrowth of disease-associated microorganisms (137, 138). The "effector" bacterial strain is normally an isolate from a human reservoir modified using genetic tools with the purpose of incorporating some benefitial properties. Desirable characteristics for an effector microbial strain have been summarized as: (i) to be specifically active against target pathogens without significantly disturbing the balance of the existing microbial ecosystem, (ii) indigenous and able to survive in the selected habitat and/or ecosystem and not elsewhere, (iii) non-pathogenic (or weakly opportunistic) for the host species, (iv) susceptible to low-risk antibiotics such as penicillin so that the strain can be later eliminated if desired, (v) easily propagated and readily prepared in a stable form for commercial distribution, (vi) easily identifiable among the resident microbiota, (vii) not causing systemic toxicity or immunological sensitization in the host or leading to selection of resistant microorganisms, (viii) capable of persisting in the host tissues to effect long-term protection (138).

In comparison to probiotics, less research has been conducted to create and evaluate genetically modified effector strains to prevent or treat human disease. Examples of studies using this approach include the evaluation of the role of genetically modified strains of *S. mutans* in the prevention and/or treatment of caries (139, 140). Additionally, studies have been published evaluating the effect of non-genetically modified strains that may out-compete pathogens when administered; for example, a nasal spray containing a mixture of *S. sanguinis*, *S. mitis* and *S. oralis* showed promise as a therapeutic alternative for acute otitis media in children (141).

A relatively new strategy that utilizes the bacterial replacement principles for the treatment of dysbiotic disorders is whole microbiome transplantation, also called ecotherapeutics. This strategy has been mainly directed towards the restoration of the intestinal microbiota after antibiotic treatment, which alters the indigenous community structure and allows colonization by pathogens such as *Clostridium difficile* (142). Ecotherapeutics include mostly fecal transplantation, which consists of administration of stool from a healthy donor to the symptomatic patient (143). Fecal transplantation has been tested as a therapy for *C. difficile*-associated diarrhea with excellent clinical results, showing restoration of bacterial diversity in stool samples and a decrease in symptomatology with a much more superior performance than vancomycin treatment, which has been the standard of care (144, 145). Also, some promising results have been obtained for other conditions such as metabolic syndrome, obesity, ulcerative colitis and irritable bowel syndrome (146, 147, 148, 149, 150).

Transplantation of selected members of the community also appears as a future viable alternative for the treatment of some dysbiotic diseases. The identification of specific strains with a probiotic-like capacity within the indigenous microbiome and subsequent administration seems a promising strategy. Experiments in mice have shown that oral administration of a cocktail of human intestinal clostridia is able to induce regulatory T (Treg) cells and anti-inflammatory molecules, and attenuated disease in models of colitis and allergic diarrhea (151). Another approach involves the identification of indigenous microorganisms that confer resistance to infection by exogenous pathogens after antibiotic

treatment, and that could thus be administered prophylactically with the aim of enriching them in the microbiome. For instance, the bile acid 7α-dehydroxylating intestinal bacterium, *Clostridium scindens*, has been shown to be associated with resistance to *C. difficile* infection when it forms part of the native gut microbiome, and enhances resistance to post-antibiotic infection when administered exogenously (152). These studies highlight the possibility of using indigenous effector bacteria that specifically modulate the inflammatory response and/or antagonize pathogenic strains and are habitat-specific.

Predatory bacteria and bacteriophages—Predatory bacteria consist of a diverse group of obligatory predators widely distributed in aquatic and terrestrial environments (153). The most studied strain is *Bdellovibrio bacteriovorus* HD100, which is a predator for Gram-negative species. After attaching to its prey, the predator invades its periplasmic space and multiplies while destroying its cytoplasm. Once the multiplication cycle is completed, the predator destroys the rest of the prey' s cell and releases its progeny (154).

Beside *B. bacteriovorus*, a number of strains of predatory bacteria called Bdellovibrio-and-like-organisms (BALOs) have received attention as antibacterial agents for the control of pathogenic bacteria. Among the characteristics that make these species good candidates for the control of diseases are: (i) non-pathogenic and non-toxic in several mammalians models; (ii) potentially well tolerated by humans; (iii) able to attack a wide range of Gram-negative bacteria; (iv) able to attack both planktonic and biofilm cells; (v) able to attack their prey even in presence of Gram-positive bacteria (155).

The characteristics listed above make BALOs candidate antibacterial agents for the treatment of a number of Gram-negative associated diseases. Several studies have reported killing activity of BALOs against a wide range of bacteria such as *Helicobacter pylori* and *Campylobacter jejuni* (156), as well as against bacteria associated with ocular infections (157), and periodontitis (158, 159). However, no human studies have been performed with BALOs, and only one study has demonstrated efficacy *in vivo*, showing that both cecal inflammation and colonization by *Salmonella enterica* serovar Enteritidis was reduced in chicken treated with *Bdellovibrio* (160).

Bacteriophages are viral particles that infect bacteria leading either to lytic or lysogenic cycles. Lytic (virulent) phages once replicated and assembled, rapidly destroy the bacterial cell, releasing their progeny (161). Because of their ability to kill bacteria, lytic phages have been historically used for treating infectious diseases such as dysentery, skin and urinary tract infections, among others (reviewed by Abedon et al. (162)). Several studies have been conducted with phages to prevent the formation of in vitro biofilms of *Pseudomonas aeruginosa*. Although initially promising results were obtained in one of these studies, regrowth of the biofilm after 24 hours of phage administration was observed (151). As an alternative, cocktails of phages or combinations of the viral particles with other antimicrobial agents were investigated with better efficiency at destroying biofilms (163, 164, 165). The efficacy of phage cocktails has also been tested in human trials for otitis and wound infections, which showed some clinical improvements and no adverse effects (166, 167).

4. Application of microbial-based therapies to oral diseases

Current strategies for treatment of caries and periodontal diseases are focused on the mechanical removal of dental plaque and associated deposits, complemented with the use of antimicrobial compounds and, in the case of caries, with diet modification, topical fluoride application and, if needed, restoration of damaged tooth structures (73, 168, 169, 170). The main limitation of such strategies is that only a temporary modification of the pathogenic communities is achieved after therapy with the disease-associated microbiota, in some individuals, recovering shortly after the initial therapeutic intervention (86, 171, 172). It is also not clear whether the oral microbiome is completely restored, even short-term, by these treatment strategies to a composition similar to that of a healthy subject that never experienced the disease. Oral candidiasis is mostly treated with antifungal agents, some of which select for strains of *Candida* spp. resistant to such antimicrobial agents (173, 174). Therefore, there is a current need for preventive and therapeutic strategies for oral diseases that aim at restoring a healthy microbiome and increase its resistance to dysbiotic perturbations.

Microbial therapeutics for caries—Attempts have been made to apply replacement therapies for the management of dental caries using potential effector strains with decreased acidogenicity, such as an *S. mutans* strain defective in intracellular polysaccharide (IPS) metabolism (140), a non-cariogenic *S. salivarius* strain called TOVE-R (175), and an *S. mutans* strain deficient in lactate dehydrogenase activity (176). These strains were used in studies that evaluated their antagonistic activity against native acidogenic *S. mutans* and other caries-associated species, their ability to persistently colonize the oral cavity, their safety and non cariogenicity, and the possibility to be eradicated if needed (139, 175, 177, 178).

The group of Jason M. Tanzer conducted studies with both an *S. mutans* defective in IPS metabolism and the non-cariogenic *S. salivarius* TOVE-R. The IPS-deficient *S. mutans* mutant was shown to prevent the colonization by two caries-associated strains of *S. mutans* and *S. sobrinus*, in *S. mutans*-free conventional rats (140), but no further studies were conducted. *S. salivarius* TOVE-R was demonstrated to partially displace both *S. mutans* and *S. sobrinus* pathogenic strains in a rat model, accompanied by a decrease in caries experience (175, 179). Some *in vitro* studies were conducted to characterize its mechanism of action (180) but, probably because of lack of genetic information on the strain, further studies in humans were not performed.

The group of Jeffrey D. Hillman isolated the *S. mutans* strain JH1001 which produced a bacteriocin, mutacin 1140, able to inhibit the in vitro growth of a wide range of bacteria including caries-associated species of *Streptococcus*, *Actinomyces* and *Lactobacillus* (176, 181). The effector strain failed to consistently colonize the human oral cavity, thus a mutant that produced higher levels of mutacin 1140 was constructed, thereby improving its colonization and competition with indigenous *S. mutans* (177, 182). Subsequent genetic modifications of the bacteriocin-producing strain were conducted, obtaining a less cariogenic strain due to deletion of lactate dehydrogenase activity (139). Further mutations were later introduced consisting of the deletion of the *dal* gene, involved in D-alanine

biosynthesis, and the *comE* gene involved in the uptake of environmental DNA (178). This last strain (A2JM) was expected to be non-cariogenic, able to displace oral cariogenic microorganisms, less prone to transformation and dependent on the exogenous addition of D-alanine, a property to allow control of its growth in the host via the exogenous administration of the amino acid. Although subsequent studies showed it was possible to eradicate the effector strain A2JM in a rat model, the genetically-modified strain did not have greater genetic stability than the parental strain and no studies in humans have been reported (178).

The evaluation of the effectiveness of probiotics as anticariogenic agents has been subject of high attention for the last 20 years. Despite an increasing number of publications in the field, only a small proportion of these studies have evaluated the effects of probiotics in human clinical trials. Stensson et al. (183) showed that the administration of *Lactobacillus reuteri* during the first year of life was associated with a decrease in caries prevalence at 9 years of age. Moreover, studies have shown that the administration of *Lactobacillus* and/or *Bifidobacterium* strains has a positive short-term effect decreasing MS counts in saliva (184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199). Other studies, however, have found that MS counts in plaque and/or saliva samples do not change or increase after probiotic intake (200, 201, 202, 203, 204). Also, changes in acidogenicity were not observed in plaque or saliva after probiotic use (201, 202). Long-term evaluation of probiotic administration has also shown contradictory results. While a reduction in caries incidence and/or MS counts was shown to occur after 10 or 12 months of ingestion of lactobacilli (205, 206), intervention early in life with *Lactobacillus* or *Bifidobacterium* spp. had no effect on occurrence of caries and/or on MS counts up to 4 years after the administration (207, 208). Even though the study of potentially probiotic bacteria focuses mostly on lactobacilli, other human indigenous species from the genera *Pediococcus*, *Leuconostoc*, and *Streptococcus* have also been proposed to have probiotic effects against caries (209, 210). *S. salivarius* M18 and a mouthwash containing a mixture of *S. oralis* KJ3sm, *Streptococcus uberis* KJ2sm and *Streptococcus rattus* JH145 (a spontaneous lactic acid deficient mutant) have been shown to decrease levels of MS (211, 212). Gruner et al. (213) recently performed a meta-analysis with the data available from randomized controlled trials published between 1967 and June of 2015, regarding the use of probiotics in caries, considering human studies that included a control group of either placebo or alternative treatments. Although, the analysis showed that probiotics were associated with reductions in the counts of *S. mutans*, the authors found no significant reduction in caries experience, concluding that currently there is no sufficient evidence for recommending probiotics in either prevention or treatment of caries.

More recently, investigations on caries have focused on finding a rationally-designed strategy to alter tooth plaque metabolism towards that of a microbial community compatible with health. Clinical studies in children with different caries experience have shown that plaque alkali production may be related to caries susceptibility with plaque from healthy children showing a greater ability to produce alkali via the arginine deaminase system (ADS) than plaque from children with caries lesions (214, 215). A limited number of oral species are capable of metabolizing arginine via the ADS with alkali generation. Most species identified belong to the genus *Streptococcus* with *S. sanguinis* strains being very

prevalent among ADS-positive isolates (216). Moreover, a highly arginolytic strain of *Streptococcus* belonging to a potentially novel species was isolated from supra-gingival plaque of a caries-free individual. The strain not only expressed the ADS pathway at high levels under a variety of conditions but also effectively inhibited the growth and two intercellular signaling pathways important in *S. mutans* (217). These studies show that strains capable of alkali production via arginine may be important contributors to the stability of healthy communities and have prompted investigators to consider if the exogenous administration of arginine may have a beneficial effect in enriching for a health-compatible dental plaque community. Indeed, a clinical study showed that the use of an arginine-containing toothpaste significantly increased ADS activity in plaque of caries-active individuals and shifted the bacterial composition to a healthier community, more similar to that of caries-free individuals (218). These investigations show that arginine could potentially serve as an anti-cariogenic agent and that perhaps the combination of exogenous arginine administration and enrichment of the microbiome with ADS-positive strains could potentially have a health benefit.

In summary, the management of caries with bacterial replacement therapies based on genetically modified strains has not advanced into clinical trials. Meanwhile, several clinical studies have been conducted with various probiotic combinations but results are mixed and so far are insufficient for recommending their use in caries management. The use of probiotics for caries prevention does not seem to be derived from a clear rationale as probiotics may not antagonize the local acidogenic microbiota, and the strains themselves have a potential for acidogenicity. Recent efforts focused on defining the metabolic properties of microbial communities associated with health seem to offer more promise, with therapies aimed at the enrichment of alkali production via arginine metabolism representing a more rational alternative.

Microbial therapeutics for periodontal diseases—In the case of periodontal diseases, oral or exogenous probiotic strains have been evaluated under the assumption that they could help in the suppression of periodontitis-associated species by the production of antimicrobial substances or via competitive exclusion mechanisms, and also contribute to modulation of immune responses (219, 220). Different bacterial strains have shown beneficial immunomodulatory effects with respect to the periodontium. These include species like *S. salivarius* and *Streptococcus cristatus* in *in vitro* studies (221, 222, 223), and *Lactobacillus brevis* CD2 in animal models and in humans with periodontitis (224, 225). *S. cristatus* has been shown to attenuate the expression of cytokines such as IL-8, IL-1α, IL-6 and tumor necrosis factor-α (TNF-α) in epithelial cells in response to *Fusobacterium nucleatum* (222, 223), while *S. salivarius* K12 has been shown to inhibit the secretion of IL-8 in response to several MAMPs (221). In both mice and humans, *L. brevis* has been shown to decrease levels of inflammatory markers like prostaglandin E-2 (PGE-2), γ-interferon (IFN- γ), TNF-α, IL-1β, IL-6 and IL-17A (224, 225).

The antimicrobial effects of probiotic-like strains against bacterial species associated with periodontal diseases have also been studied. Among these, a hydrogen peroxide-producing *S. sanguinis* strain has been shown to suppress *A. actinomycementcomitans* in vitro and antagonize its colonization in gnobiotic rats (226). In vitro studies have also shown that

species such as *S. sanguinis*, *S. cristatus*, *S. salivarius* and *S. mitis* inhibit colonization of epithelial cells by *A. actinomycetemcomitans* (227, 228), while in another study *S. sanguinis*, *S. salivarius*, *S. mitis*, *Actinomyces naeslundii*, and *Haemophilus parainfluenzae* reduced the adhesion of *P. gingivalis* to the bottom plate of a parallel plate flow chamber, but failed to significantly inhibit *A. actinomycetemcomitans* (229). Bifidobacteria species isolated from saliva samples of periodontally healthy individuals have also been shown to inhibit *P. gingivalis* growth possibly by competing for vitamin K (230).

Human clinical studies on the effect of *Lactobacillus* spp. probiotics in the treatment of chronic periodontitis have reported statistically significant improvements in periodontal clinical parameters such as plaque index, bleeding on probing and pocket depth and/or reduction of periodontitis-associated species when utilized alone (231, 232), or as an adjunct to periodontal treatment, in comparison to a control group (232, 233, 234). However, another study reported that the adjunctive use of a probiotic tablet, containing *Streptococcus oralis* KJ3, *Streptococcus uberis* KJ2 and *Streptococcus rattus* JH145, did not significantly improve the therapeutic outcomes of scaling and root planing when compared to the placebo group (235). In subjects with gingivitis, the use of probiotics has shown a positive clinical effect in some studies (236, 237, 238), while Iniesta et al. (239) reported decreased levels of *P. intermedia* in saliva, and *P. gingivalis* in subgingival plaque, but no improvements in plaque and gingival indexes after probiotic administration. Moreover, in healthy children subjected to complete oral prophylaxes followed by probiotic administration in the form of curd, no differences in gingival health were observed in comparison to the control (240). Other studies report that probiotic administration has a positive effect reducing inflammatory markers in GCF or decreasing levels of periodontitis-associated microorganisms (241, 242, 243).

The previously mentioned meta-analysis by Gruner et al. (213) of data available on probiotics trials between 1967 and June of 2015 also included periodontal diseases as an outcome. This evaluation revealed that while the use of probiotics for periodontal disease management did not significantly affect the counts of *A. actinomycementcomitans*, *P. gingivalis* and *P. intermedia*, it improved two clinical markers indicative of inflammation, that is bleeding-on-probing and gingival index and helped in reduction of pocket probing depth (213). In summary, most studies report a small but potentially beneficial effect of the use of probiotics in reducing risk factors associated with periodontal diseases, or when used as adjuncts to periodontal therapy, with most positive outcomes associated with the use of lactobacilli.

Attempts to recolonize the subgingival environment with health-associated bacteria as part of periodontal therapy were conducted by Teughels et al. (244), who evaluated the effect of administering a mixture of *S. sanguinis*, *S. salivarius* and *S. mitis* strains as adjuvants in subgingival artificially-created pockets in beagle dogs. Four months after the pockets were induced, different treatments consisting of either subgingival scaling and root planning (Rp), root planning and a single topical application of the streptococci mixture (Rpsingle), or root planning followed by three successive topical applications of the bacterial mixture (Rpmulti) were evaluated. The effect of each treatment was evaluated after 12 weeks and the results were compared with an untreated control group. Although significant reductions in pocket

depth, bleeding on probing, and clinical attachment level were observed in the three treatment groups, the improvements were greater in the Rp_{multi} group. The Rpmulti dogs also showed the most dramatic reduction in anaerobic and black-pigmented species including *Porphyromonas gulae* (a canine form of *P. gingivalis*), *P. intermedia* and *Campylobacter rectus*, and a lesser tendency for reemergence of these pathogens after 12 weeks (244), together with a significant increase in bone density (245). Although the authors did not evaluate whether the streptococci actually colonized the subgingival environment, it is worth noting that streptococci represent a minor genus in dogs (246, 247), and therefore the administration of human streptococci to dogs could be considered an exogenous microbial implantation rather than a restoration of indigenous microbiota. These experiments constitute perhaps one of the few attempts to evaluate if enrichment of the microbiome with species associated with periodontal health could have a beneficial effect.

Despite the knowledge that periodontitis is associated with a profound dysbiosis of the subgingival microbiome, no attempts at whole subgingival microbiome transplantation as a treatment of periodontal disease are found in the literature. Only one report shows research towards a possible application of microbiota transplantation in the oral cavity (248). In this study the authors tested an antimicrobial approach to decrease oral bacterial load in preparation for future whole microbiome transplantation. The report shows that the use of sodium hypochlorite was effective at reducing the numbers of oral bacteria and its antimicrobial effect could be inactivated by a non-toxic sodium ascorbate – ascorbic acid buffer.

A potentially interesting approach that has been evaluated in the context of periodontal diseases is the use of BALOs since periodontitis-associated dysbiosis is mostly due to an overgrowth of Gram-negative species. *B. bacteriovorus* HD100 has been shown to significantly reduce the number of viable *A. actinomycetemcomitans* both in planktonic and biofilm in vitro cultures (249). The eradication of *A. actinomycetemcomitans* from biofilms by predators, however, is not complete, but the combination of BALOs with an exopolysacharide-hydrolysing enzyme has been shown to be more effective at decreasing the levels of *A. actinomycetemcomitans* (158). Other studies have shown that different strains of *B. bacteriovorus* may be required to effectively antagonize other Gram-negative species such as *P. intermedia*, *P. gingivalis* and *Capnocytophaga sputigena* (158, 159). Moreover, the presence of saliva and other non-target bacteria such as the Gram-positive health-associated *A. naeslundii* have been shown as non-inhibitory to the predatory activity (159). The effect of *Bdellovibrio* has also been tested in a more complex context such as a 6-species community formed by *P. intermedia*, *A. actinomyctemcomitans*, *P. gingivalis*, *F. nucleatum*, *S. mitis* and *A. naeslundii*, as well as against saliva or subgingival plaque samples. In both cases, although it was observed that the efficiency of predation decreased as the complexity of the models increased, the predator was effective at decreasing the levels of *F. nucleatum* and *A. actinomycetemcomitans* but other species such as *P. gingivalis* were not affected (250). Importantly, the predatory activity of BALOs was shown to be completely abolished under oxygen-limiting conditions since BALOs are strict aerobes (159, 251). This is a relevant aspect and questions their true potential to eliminate periodontitis-associated species in the reduced conditions that exist in periodontal pockets. In summary, although BALOs

show promising in vitro results, especially in the control of *A. actinomycetemcomitans*, their effectiveness has not been tested *in vivo*.

Evaluations of the oral virome have revealed that the oral cavity harbors a great amount of bacteriophages (252, 253, 254). Although some efforts have been conducted to elucidate the contribution of viruses in the shifts associated with oral diseases, their role in dysbiosis remains unknown (255, 256). Differences in virome community structure were found between health and periodontal disease, in both subgingival and supragingival plaque but not in saliva, with higher proportions of lysogenic *Syphoviridae* in health while lytic viruses from the *Myoviridae* family were enriched in disease (256). These observations suggest that an altered virome is part of the dysbiosis associated with periodontitis. Despite the potential use of phages as antimicrobial agents against oral pathogens, only a few studies have focused on discovering phages for the control of periodontal dysbiosis (257, 258). Phages isolated from saliva and waste water from dental chair drainages showed antimicrobial activity against planktonic *F. nucleatum* or *A. actinomycetemcomitans* in in vitro biofilms, suggesting a potential application in gingivitis or aggressive periodontitis, which are diseases associated with these respective species (257, 258).

Microbial therapeutics for oral candidiasis—Several in vitro studies show probiotics may affect the virulence potential of *C. albicans*. *Lactobacillus* spp. and *S. salivarius* have been shown to negatively impact *C. albicans* yeast-to-hyphae differentiation and/or biofilm formation (259, 260). The mechanism of action would not depend on probiotic-yeast contact, because the use of sterile-filtered supernatant obtained from *S. salivarius* and *Lactobacillus* spp. significantly down regulates, in *C. albicans*, genes critical for the yeast–hyphae transition, biofilm formation, host cell invasion and virulence (261, 262). Also, the treatment of an engineered human oral mucosa tissue model with *Bacillus subtilis* has been shown to decrease *C. albicans* attachment (263).

Animal models have been used to demonstrate potential antagonistic effects of probiotic-like strains on *C. albicans*. *L. acidophilus* protected *Galleria mellonella* larvae against experimental candidiasis (262), while in immunosuppressed mice, *L. rhamnosus* reduced oral *C. albicans* colonization to a higher extent than the antifungal nystatin (264). Moreover, oral administration of *L. acidophilus* to mice has been shown to significantly shorten the duration of *C. albicans* colonization in the mouth, possibly due to an immunomodulatory effect (265). It has also been shown that the application of heat-killed *Enterococcus faecalis* to the tongue of immunosuppressed mice reduces both symptoms and *Candida* counts (266).

Human studies support the mentioned in vitro and animal studies, with positive reported effects for probiotic intake with regards to the risk of developing oral candidiasis. Salivary levels of yeast in elderly subjects have been shown to decrease compared to basal levels after probiotic intake (267, 268, 269), together with a significant increase in anti-*Candida* IgA levels (269). In patients diagnosed with oral candidiasis, the local administration of a mixture of *Bifidobacterium longum*, *Lactobacillus bulgaricus* and *Streptococcus thermophilus* was shown to improve oral pain and reduced the prevalence of *Candida* spp. compared with conventional antifungal therapies (270). Moreover, in asymptomatic denture

wearers harboring oral *Candida* spp., yeast detection was reduced in the probiotic group compared to placebo (271).

5. Limitations of current microbial therapeutic approaches for oral diseases and perspectives for development of new strategies

Positive but discrete results have been reported for the management of oral diseases using microbial-based therapies. Most microbial-based therapies evaluated in clinical studies are in the probiotic category with studies showing some small clinical benefits but lack of defined mechanisms of action. The use of probiotic-like strains seems more beneficial for periodontal diseases and oral candidiasis than for caries (213, 270, 271). Both periodontal diseases and candidiasis are associated with an increased inflammatory response (88, 111), and it is likely that probiotic-mediated immune modulation mediates such favorable effects. It is not clear, however, if the probiotic strains are indeed incorporated into the local microbiota, whether their effect is related to their direct interaction with oral tissues or if their effects are related to interactions with distant mucosal cells in the gastrointestinal tract and systemic immune modulation. It is also worth noting that although most clinical studies reviewed showed trends towards a positive effect of probiotics as adjuncts to periodontal therapy and in reducing oral yeast carriage, adequately powered and high quality clinical studies are scarce. Furthermore, the effect size in all studies testing probiotics seems rather small questioning the clinical relevance of their administration.

The development of more rationally-designed microbial-based therapies for oral diseases is still in its infancy but offers more promise than the indiscriminate use of non-specific probiotic strains. Oral diseases are associated with dysbiosis and therefore, preservation or restoration of the homeostatic state promoted by a health-associated community is the ultimate preventive and therapeutic goal. As reviewed in Figure 1, unique mechanisms mediate the microbiome shifts associated with caries, periodontal diseases and oral candidiasis. It is conceivable to think that microbial therapeutics could contribute to the prevention and treatment of these conditions via promotion of the growth of a health-associated community. The implantation of selected oral strains representing health-associated taxa, or the re-implantation of a sample from the same patient but enriched with health-promoting strains are alternatives together with whole microbiome transplantation. One of the challenges, however, of using microbial-based therapies in the mouth compared to the gut, is the potential for their rapid loss from the oral cavity by swallowing before they have had a chance to become established and/or exert an effect. The potential advantage of using indigenous oral species as microbial therapeutics is their greater potential to colonize the specific habitat from which were they were extracted, compared to exogenous strains. It is however clear that even if a health-associated community is obtained via such transplantation approaches or through selected killing of disease-associated species, a long-term effect would not be attained unless the environmental and host-related risk factors shown in Figure 1 are modified. Microbial therapeutics are therefore conceivable only within the context of a more holistic preventive approach involving several strategies.

In the case of caries, research involving microbial-based therapies has focused on competition and/or suppression of *S. mutans.* However, it is important to recognize that in

the absence of *S. mutans*, other acidogenic/aciduric species could become enriched given the right environmental pressure (frequent carbohydrate intake). Thus, more attention should be put on the control of the acidification of dental biofilms rather that in the elimination of specific species. A conceivable microbial-based therapy for caries could be the enrichment of the microbiome with indigenous strains that counter-act acid-production and therefore promote health-associated species, such as the recently isolated arginolytic strain of *Streptococcus* (217). Exogenous administration of such strains together with arginine oral supplementation may prove beneficial for caries prevention. The question, however, is whether such a strain, although native to the oral cavity of humans, can effectively colonize another host with an already assembled, organized and interacting microbiome community in which the specific niche is already occupied. Also, since the highly arginolytic strain is also a streptococcus it is possible that under carbohydrate pressure it may become acidogenic. It is thus clear that even if such a microbial-based therapy becomes a reality for caries management, it should be part of a holistic preventive approach with a focus on carbohydrate intake modification (see Figure 2).

In the case of periodontal diseases, current traditional therapies are directed towards controlling the subgingival microbial load. The use of mechanical and chemical means to control biofilm accretion is effective at preventing gingivitis and maintaining periodontal stability after therapy in most patients suffering from the disease but constitutes by no means a highly effective strategy as it depends on patient compliance. Desirable microbial-based therapeutics for periodontal diseases would be those that prevent the microbiome shifts associated with dysbiosis. In this respect strategies to antagonize the establishment of keystone pathogens such as *P. gingivalis* are desirable; however, more knowledge is required regarding inter-bacterial interactions in subgingival plaque and the identification of antagonistic species. For instance, *P. gingivalis* has the ability to sense extracellular arginine deiminase produced by *S. cristatus* and *S. intermedius*, responding by down-regulating the expression of key surface structures required for colonization (272, 273). Indeed, a negative correlation between the distribution of *S. cristatus* and *P. gingivalis* has been observed in subgingival plaque, suggesting that this antagonistic interaction may be important during *in vivo* community maturation (274). Moreover, understanding subgingival microbiome metabolic dynamics could uncover species that are important for overall community stability and increase the resilience of a health-associated community. This implies the application of a systems biology approach to study the microbiome focusing on the construction and analysis of *in silico* system-level metabolic models (275). Our field currently has information derived from omic' s studies that can be used to reconstitute the metabolic frameworks of oral bacteria in relation to oral diseases. Such metabolic models may allow prediction of the role that each species may have in the health- and/or disease-associated consortia (5, 276, 277, 278). As with caries, however, microbial therapeutics for periodontal diseases may be just a part of a broader approach that should also include immune modulation, as it seems microbiome shifts associated with periodontitis are initially the result of immune dysregulation and are perpetuated by uncontrolled inflammation (Figure 2). Examples of targeted anti-inflammatory strategies against periodontitis include resolvins, anti-complement and anti-IL17, which directly address the disease immune-mediated pathophysiology (110, 279).

Although highly experimental, whole oral microbiome transplantation is a strategy that should be tested in the context of oral diseases. Such treatment may have an application in the restoration of homeostasis in patients suffering from periodontitis in which a profound microbiome shift has led to the establishment of a resilient pathogenic community. It should be considered, however, that the transplantation of an entire community may generate unexpected outcomes such as nonspecific immune responses either locally as result of the community implantation in the oral cavity, or systemic if certain species migrate to extra-oral sites. Another non-desired effect may be unexpected interactions between the implanted microbiota components and the indigenous species that could favor the growth of potentially pathogenic species. The question about what constitutes a healthy community is also an aspect that needs to be considered. Both community composition and function in the donor needs to be evaluated before transplantation, but there are no defined thresholds to define a health-promoting microbiome. On the other hand, an advantage of whole microbiome transplantation is that an entire community may have more chances to establish and compete with a pathogenic community than the administration of selected species. Disruption of the native pathogenic community would probably be necessary for the establishment of the transplanted one and therefore whole microbiome transplantation should be part of a treatment approach aimed at decreasing the microbial load by mechanical means or antimicrobial strategies. Also important for the long-term stability of the transplanted health-associated community would be that environmental factors such as the inflammatory exudate are controlled as eventually the newly established community could also become dysbiotic.

In the case of oral candidiasis, little knowledge is available regarding the role of other microbiome members on *Candida* overgrowth. While it is clear that immune dysregulation at the oral mucosal barrier promotes the outgrowth of *C. albicans*, the main species associated with candidiasis, it is less clear whether bacteria or other oral fungi contribute to or antagonize *Candida*. Such information can be obtained from longitudinal studies evaluating microbiome dynamics during oral candidiasis and would be essential for the possible development of microbial-based therapeutic adjuvants to prevent or treat candidiasis. Once again, such microbial adjuvants would require enhancement of mucosal immunocompetence in a combined strategy to prevent candidiasis (Figure 2).

6. Concluding remarks

In this review we discussed current approaches based on the use of live microbial strains for the manipulation of oral microbial populations to maintain host-microbe homeostasis. Novel strategies that consider not only the composition of communities associated with disease, but also the pathogenic functions may be more promising for the management of oral dysbiosis. However, the design of such strategies necessitates a deeper understanding of the inter-microbial interactions involved in the transitions from health to disease and those interactions important to maintain the stability and that confer resilience to health-associated communities. Any microbial-based therapeutic strategy aimed at oral conditions, however, should be part of a holistic approach to control the environmental factors that are primarily responsible for microbiome shifts.

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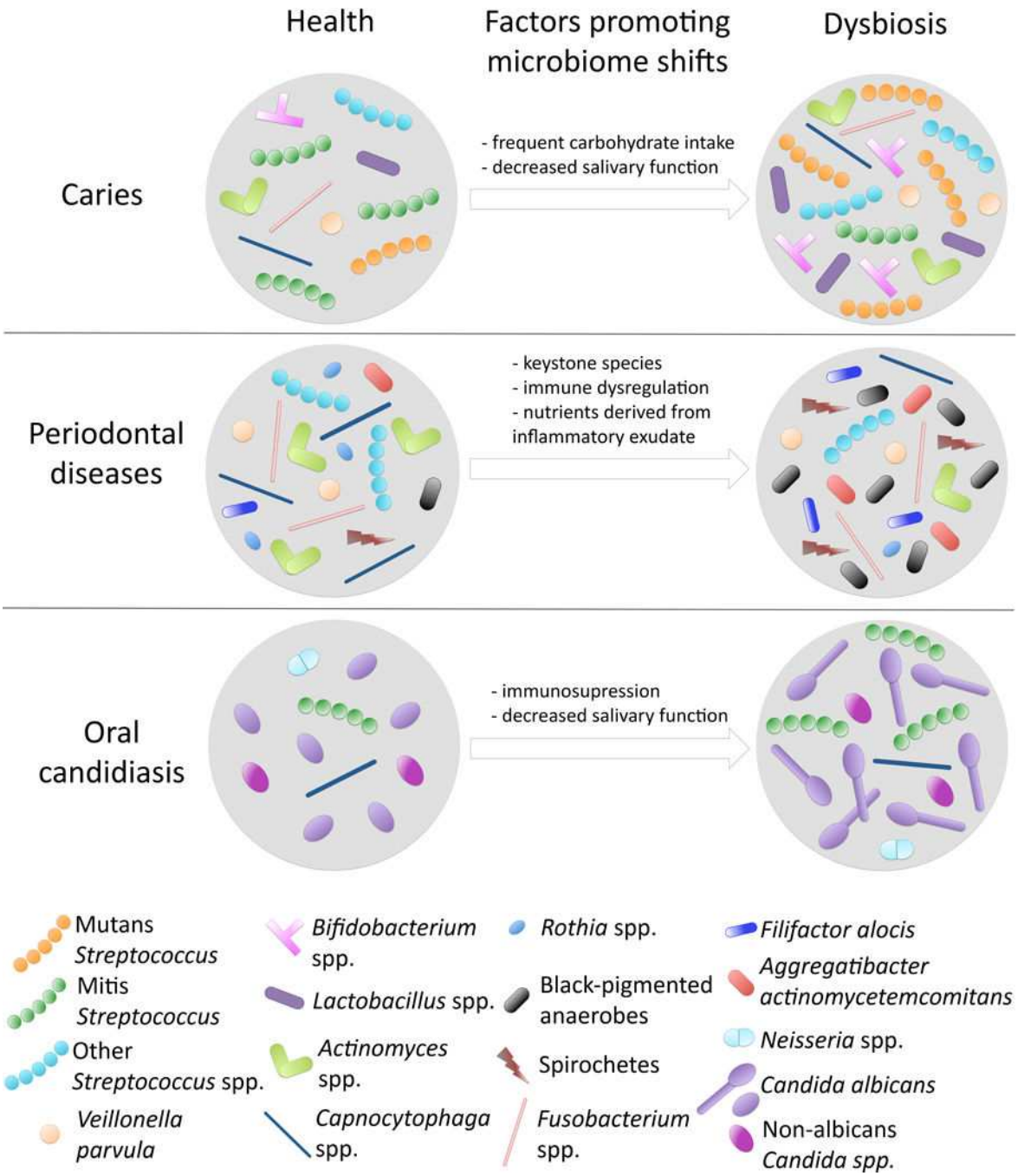

Figure 1.

Dsybiotic changes associated with oral diseases. Oral diseases are associated with changes in microbiome community structure. Examples of microbiome community shifts and the main factors promoting the establishment of the dysbiotic microbiota are depicted for caries, periodontal diseases and oral candidiasis.

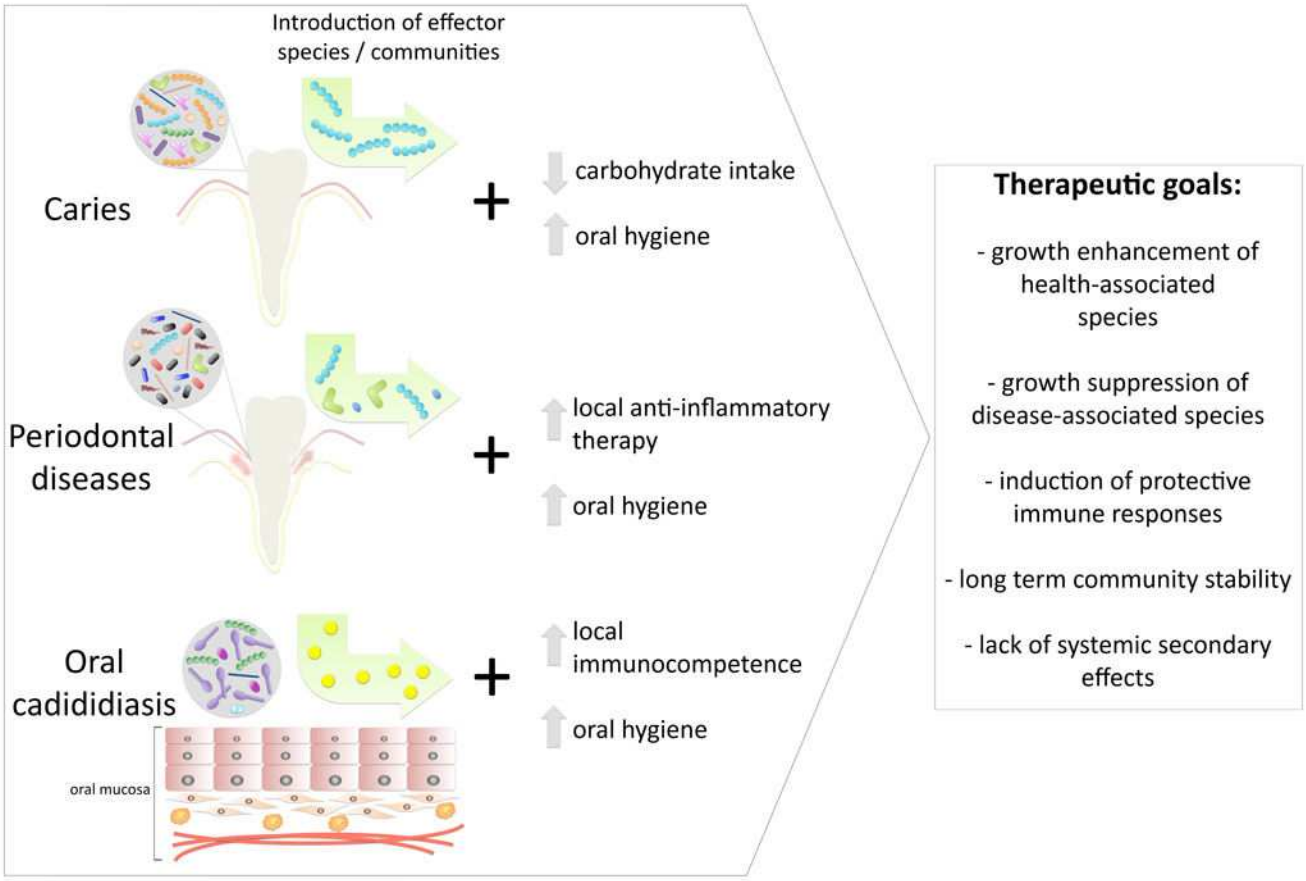

Figure 2.

Potential beneficial effects of microbial therapies in the management of oral diseases. The desirable effects of the introduction of effector species/communities together with complementary therapies are shown for caries, periodontal diseases and oral candidiasis.