Respiratory disease and the role of oral bacteria

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The relationship between oral health and systemic conditions, including the association between poor oral hygiene, periodontal disease, and respiratory disease, has been increasingly debated over recent decades. A considerable number of hypotheses have sought to explain the possible role of oral bacteria in the pathogenesis of respiratory diseases, and some clinical and epidemiological studies have found results favoring such an association. This review discusses the effect of oral bacteria on respiratory disease, briefly introduces the putative biological mechanisms involved, and the main factors that could contribute to this relationship. It also describes the role of oral care for individuals who are vulnerable to respiratory infections.

Keywords: pulmonary infection; periodontitis; oral biofilm; nosocomial pneumonia; oral hygiene

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The oral cavity hosts a highly diverse microbiota (1). Because of its humidity and temperature, the mouth provides an appropriate environment for the development of organized bacterial communities. These occur as biofilms on both hard surfaces (teeth) as well as the soft tissue of the stomatognathic system (2). It should be emphasized that these communities are complex organizations and include a wide variety of different species of bacteria with varying degrees of virulence (3).

Dental plaque biofilms containing periodontal pathogens may give rise to periodontal disease, the manifestation of which is determined by the virulence of the bacteria, the host immunological response, and environmental factors such as smoking (4).

Thus, it can be said that periodontal disease, which is a population-wide health problem, results from an imbalance between the bacteria and the host’s defense capacity modified by the presence of environmental factors. Investigations carried out in several countries have revealed that the more advanced forms of periodontal disease appear to affect some 5–20% of the population (5, 6).

Over recent years, oral bacteria and, especially, periodontal pathogens have been implicated as important agents with regard to causing other illnesses including respiratory diseases (7, 8, 10, 11). This hypothesis has been supported particularly by studies of patients receiving treatment in intensive care units: because of the cause of hospitalization, most patients present with an inadequate immunological response, and with reductions in salivation and the natural cleaning of the mouth that is promoted by mastication and tongue movement. This, together with the fact that oral care under these conditions is frequently negligent, facilitates bacterial colonization (9).

As yet however, it is unknown if oral bacteria plays a causal role in respiratory diseases. At present, only conjecture exists regarding this possibility; the present article will attempt to bring together the possible mechanisms and to compare the empirical findings from studies investigating the association.

Biological mechanisms involved in the possible association between oral conditions and respiratory diseases

Four possible mechanisms to explain the biological plausibility of an association between oral conditions and nosocomial respiratory infections have been described (7, 12).

1. Oral pathogens directly aspirated into the lungs.

There is evidence in the literature indicating that periodontal organisms such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans are involved in aspiration pneumonia (13–15). Furthermore, it is important to understand that the dental biofilm can be colonized by pulmonary pathogens, thus strengthening the idea that the oral cavity may constitute a reservoir for pathogens
that are responsible for aspiration pneumonia in high-risk patients (16–19).

2. Salivary enzymes associated with periodontal disease modify respiratory tract mucosal surfaces. In this hypothesis salivary enzymes associated with periodontal disease modify respiratory tract mucosal surfaces and promote adhesion and colonization by respiratory pathogens, with consequent aspiration into the lungs thereby causing infection. The possible mechanisms of mucosal surface modification leading to enhanced adhesion include: (a) modification of the mucosal epithelium due to high levels of proteolytic periodontal bacteria and their specific enzymes such as mannosidase, fucosidase, hexosaminidase, and sialidase; (b) loss of surface fibronectin, the protein that covers the mucosa resulting in de-masking of surface receptors; (c) removal of surface fibronectin by hydrolytic enzymes; and (d) release of cytokines. However, it is known that even though saliva contains a great variety of hydrolytic enzymes, salivary enzymatic activity is related to an individual’s oral hygiene and periodontal condition (20, 21). Moreover, the source of these salivary enzymes has been attributed to both the oral microbiota (20, 22–26) and to polymorphonuclear leukocytes entering the saliva from the gingival sulcus/pocket. Thus, the worse the oral hygiene and the poorer the oral condition, the higher the enzymatic activity will be and the greater the possibility of mucosal changes, thereby increasing the adhesion and colonization by respiratory pathogens (27).

3. Hydrolytic enzymes from periodontopathic bacteria may destroy the salivary film that protects against pathogenic bacteria. This may reduce the ability of mucins to adhere to pathogens such as *Haemophilus influenzae*, thus leaving them free to adhere to mucosal receptors in the respiratory tract. In turn, this results in fewer non-specific host defense mechanisms in high-risk individuals. *P. gingivalis*, for example, produces enzymes that degrade these salivary molecules as well as producing other enzymes that degrade the salivary film on the mucosal surface, thereby exposing adhesion receptors to respiratory pathogens. In the same way as cited previously, individuals with poor oral hygiene may have high levels of hydrolytic enzymes in their saliva.

4. The presence of a large variety of cytokines and other biologically active molecules continually released from periodontal tissues and peripheral mononuclear cells. In cases of untreated periodontal disease in high-risk individuals, the presence of a large variety of cytokines and other biologically active molecules continually released from periodontal tissues and peripheral mononuclear cells may alter the respiratory epithelium and promote colonization by respiratory pathogens via the upregulation of adhesion receptor expression on the mucosal surfaces, thereby resulting in infection.

Evidence from clinical and epidemiological studies

Recent studies have identified the bacteria present in the oral cavity and dental biofilm as potential pathogens in the etiology of nosocomial infection of the respiratory tract, notably in patients undergoing orotracheal intubation in intensive care units (26, 28–30). Such individuals have thus been recognized as a group that is vulnerable to this respiratory infection, given that they commonly present with neglected oral hygiene.

Among the groups that are vulnerable to this infection, geriatric patients stand out, since such individuals present with lowered levels of neuromotor activity in relation to deglutition and cough reflex, incompetent lower esophageal sphincter (31), and greater prevalence of dental caries (especially radicular caries) and periodontitis. The presence of poor oral health in individuals who are susceptible to bronchoaspiration may lead to states of infection of the respiratory tract, especially if these patients are in hospital environments (32–34).

Certain contributing factors need to be taken into consideration in analyzing the possible association between oral conditions and respiratory diseases. These include advanced age, the nature of the dental biofilm, the number of periodontally compromised teeth, the length of hospital stay, the use of antibiotics, oral care methods, and certain lifestyle habits such as smoking and alcohol consumption.

With respect to age, as noted above, it is believed that elderly individuals have a greater susceptibility to chronic inflammatory diseases and microbial infections such as periodontitis and pneumonia due to aspiration of oral organisms. It has also been suggested that, with advanced age, phagocytes may undergo significant changes in terms of signal transduction pathways thus affecting their capacity to regulate the inflammatory response or to perform certain antimicrobial functions (35). Some authors have also suggested that the frequency of hospital bacterial infection increases with age, not because of a greater hospitalization rate, but because of an increased risk per day of hospital stay (36).

With regard to colonization of the dental biofilm, 1 mm³ of plaque contains more than 10⁶ bacteria with 300 different anaerobic and facultative anaerobic species (37). Studies have shown that this combination of bacterial deposits and salivary constituents form a reservoir of respiratory pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* that are capable of provoking pneumonia and pulmonary abscesses in
individuals hospitalized in intensive care units (16, 17). Bacteria such as *P. gingivalis* and *S. aureus* have been identified in saliva as predictors of respiratory disease (38), independent of the presence or absence of teeth. Some studies have also suggested that the quantity of aspirated bacteria is more important than the type (39).

The number of teeth present and the degree to which the tooth surfaces and periodontal tissue have been compromised are important components in assessing the factors associated with respiratory infection. Teeth with caries constitute reservoirs for cariogenic organisms such as *Streptococcus sobrinus*, which has been shown to be associated with aspiration pneumonia in hospitalized functionally dependent individuals (38). In addition to its cariogenic potential, *S. sobrinus* seems to be associated with xerostomia, which is another contributing element to the incidence of pneumonia (40).

It is known that the oral microbiota of individuals with teeth is very different from that of individuals without teeth. Although, on the one hand, there is a lower prevalence of anaerobic bacteria in the absence of teeth and greater concentration of lactobacilli and fungi (41), it needs to be emphasized that the use of poorly cleaned prostheses, especially by dependent elderly results in a reservoir for respiratory pathogens. When such pathogens are aspirated, they may cause unexpected infections (42, 43).

The severity of periodontal disease seems to have a dose-response effect, although there is a scarcity of studies demonstrating this relationship. Notwithstanding, Scannapieco and Ho (44) and Hayes et al. (45) found a tendency toward diminished pulmonary function with increasing clinical attachment loss. In a retrospective longitudinal study, Awano et al. (46) demonstrated that individuals with at least 10 teeth and periodontal pockets greater than 4 mm presented with a higher incidence of mortality due to pneumonia than did those without any teeth with periodontal pockets, indicating that the greater the number of periodontally compromised teeth and, consequently, the greater the quantity of oral bacteria, the greater the risk of mortality due to pneumonia. In the light of similar evidence, Bgi et al. (33) suggested that evaluation of the periodontal condition could be a method for identifying individuals who were at high risk of developing nosocomial pneumonia.

Another point in this context is the relationship between an individual's length of hospital stay and their salivary flow. It is known that salivary secretion has a significant role in maintaining oral health and that its suppression or diminution leads to difficulty in swallowing and increases the risk of developing opportunistic infections. Amerongem et al. (47) stated that the presence of certain immunoglobulins and antimicrobial enzymes in saliva such as lactoferrin, lysozyme, and lactoperoxidase is of fundamental importance in maintaining health.

Sedating patients in intensive care centers and the length of their hospital stay interferes with salivary secretion and promotes changes in the oral microbiota in a matter of a few weeks. This favors the growth of Gram-negative bacteria and consequently increases the risk of aspiration of these pathogens (16, 17).

Increased colonization of the dental biofilm by respiratory bacteria in individuals exposed to antibiotics has also been shown (48). However, it needs to be emphasized that because the inability of antibiotics to penetrate the dental biofilm subgingival infection may persist after antibiotic therapy. Thus, mechanical cleaning and disruption of the biofilm are still essential in periodontal therapy (49).

Further, it is recognized that ventilation equipment often becomes contaminated with the patient's own bacteria such that the use of such equipment may represent a significant risk factor in the etiology of nosocomial pneumonia.

It has been increasingly observed that the use of toothbrushes as a means of removing dental plaque among hospitalized individuals is more efficient than the use of foam swabs, especially when used at an appropriate frequency (50, 51). Abe et al. (52) observed that elderly people who received professional oral hygiene care presented lower prevalence of respiratory pathogens such as *Candida albicans* than did individuals who did not receive such oral care. In another prospective study, it was noted that the mortality rate due to aspiration pneumonia was lower among elderly people who had been included in an oral care program than among those who had not participated in the program (53).

Behavioral aspects of inappropriate oral hygiene such as the brushing method adopted, lack of knowledge regarding oral care, and irregular visits to the dentist for supragingival scaling have all been shown to be associated with occurrences of chronic obstructive pulmonary disease (54), thus emphasizing the importance of oral care.

In a meta-analysis conducted in 2003, Scannapieco et al. (55) concluded that antimicrobial agents such as chlorhexidine have an effect in reducing the risk of respiratory infections. Good oral hygiene seems to diminish the levels of enzymes that degrade fibronectin, which originate in the dental biofilm or polymorphonuclear leukocytes found in saliva (23, 56). Chlorhexidine, which is widely used for inhibiting the formation of the dental biofilm and controlling gingivitis and oral ulceration, leads to changes in bacterial retention and growth thereby resulting in reductions in bacterial colonization on teeth.

In this context, DeRiso et al. (57) tested oropharyngeal decontamination using 0.12% chlorhexidine digluconate in patients who would be undergoing surgical procedures. They obtained a reduction in the nosocomial infection rate of 65%. More recently, Munro et al. (58) examined the effects of brushing, the use of chlorhexidine, and a
combination of both on the development of pneumonia associated with mechanical ventilation in 547 hospitalized patients. Their results showed that independent of brushing and 0.12% chlorhexidine reduced the incidence of pneumonia on the third day among individuals without infection at the baseline. In another clinical trial, Scannapieco et al. (59) showed that topical application of chlorhexidine once or twice a day was effective against S. aureus in the dental biofilm of individuals undergoing mechanical ventilation, but that it did not significantly reduce the frequency of Gram-negative pathogens. However, these authors attributed this lack of association to the greater sensitivity of S. aureus to chlorhexidine and to the small sample size of their study.

Alcohol intake also seems to be related to a higher frequency of pneumonias. Alcohol adversely affects the respiratory and immune systems, alters the mechanism of respiratory clearance (depression of the glottic reflexes: glottis, cough, and ciliary action), and in excess increases the risk of altered consciousness, convulsions, and vomiting with aspiration. Smoking has also been reported to be a residual confounding factor in studies of associations between oral conditions and respiratory infections, given that this compromises the mucociliary barrier and phagocyte activity. Some studies have shown that the worse the periodontal condition, the greater the risk of chronic obstructive pulmonary disease among smokers (54, 60).

In general, however, relatively few randomized controlled clinical trials have investigated the association between oral health and respiratory disease. In any such studies, it is extremely important to define the type of respiratory disease as well as the specific diagnostic criteria used for both the exposure measurement (periodontitis) and outcome measurement (respiratory infection).

In terms of periodontal disease, measurements such as the probing depths, bleeding on probing, clinical attachment levels, and alveolar bone levels are generally used. However, these measurements are surrogates that do not reflect the current disease activity. Beck and Offenbacher (61) suggested that the ideal would be to use a measurement that would portray both exposure and bacterial activity as well as levels of acute-phase inflammatory or reactive mediators.

Although bacteria are necessary for respiratory infection, they are insufficient alone to cause disease. Other factors such as the degree of neurological control over deglutition and respiration and smoking are involved and need to be taken into consideration.

In summary, it seems that there is still a significant knowledge gap regarding the association between poor oral health and pneumonia. This lack of evidence has made it difficult to carry out more elaborate intervention studies. Additional studies evaluating the role of the bacterial load in the oral cavity and the effectiveness of topical treatment for preventing hospital respiratory infections are needed.

Conclusion
So far there is no consensus regarding the hypothesis that oral bacteria might contribute to the etiology of respiratory diseases. Nevertheless, a number of theories have been put forward. These can be summarized as follows:

1. Oral bacteria that colonize the oropharynx may be aspirated through the lower respiratory tract, particularly in individuals at high risk of infection such as hospitalized patients.
2. Salivary enzymes associated with periodontal disease may modify the mucosal surfaces along the respiratory tract, thus facilitating colonization by pathogens.
3. Hydrolytic enzymes as a result of periodontal disease may destroy salivary films and consequently make bacteria elimination difficult, thus promoting the possibility of aspiration of these pathogens into the lungs.
4. Inflammatory molecules and peripheral mononuclear cells present in saliva may modify the respiratory epithelium and promote colonization by respiratory pathogens.

Although the association is not fully established and the biological mechanisms not yet fully understood, it is important to realize that oral diseases are preventable and protocols should be developed to prevent even the possibility of such an association. The history of health sciences presents episodes such as the classic example of puerperal fever, in which the problem was not fully understood nor a biological basis established, but where control or even preventive measures were adopted on a population-wide basis.

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The authors declare that there are no conflicts of interest relating to this study.

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