Role of Oral Bacteria in Respiratory Infection*

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An association between oral conditions such as periodontal disease and several respiratory conditions has been noted. For example, recent evidence has suggested a central role for the oral cavity in the process of respiratory infection. Oral periodontopathic bacteria can be aspirated into the lung to cause aspiration pneumonia. The teeth may also serve as a reservoir for respiratory pathogen colonization and subsequent nosocomial pneumonia. Typical respiratory pathogens have been shown to colonize the dental plaque of hospitalized intensive care and nursing home patients. Once established in the mouth, these pathogens may be aspirated into the lung to cause infection. Other epidemiologic studies have noted a relationship between poor oral hygiene or periodontal bone loss and chronic obstructive pulmonary disease. Several mechanisms are proposed to explain the potential role of oral bacteria in the pathogenesis of respiratory infection: 1. aspiration of oral pathogens (such as Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, *etc.) into the lung to cause infection; 2. periodontal disease-associated enzymes in saliva may modify mucosal surfaces to promote adhesion and colonization by respiratory pathogens, which are then aspirated into the lung; 3. periodontal disease-associated enzymes may destroy salivary pellicles on pathogenic bacteria to hinder their clearance from the mucosal surface; and 4. cytokines originating from periodontal tissues may alter respiratory epithelium to promote infection by respiratory pathogens.* J Periodontol 1999;70:793-802.

KEY WORDS

Enzymes/adverse effects; periodontal diseases/microbiology; periodontal diseases/pathogenicity; respiratory tract infections/pathogenicity; oral hygiene; saliva/physiology; cytokines; saliva/enzymology.

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Recently, there has been a resurgence of interest in the interaction between oral conditions and a number of prevalent systemic diseases.[1,2] Among these interactions is that between oral infections such as periodontitis and respiratory disease. Respiratory diseases are responsible for significant morbidity and mortality in human populations. These diseases are widely prevalent and exact an extensive toll on human health and the cost of health care. Indeed, a recent report ranked lower respiratory infections as the third most common cause of mortality worldwide in 1990 (causing 4.3 million deaths), and chronic obstructive pulmonary disease (COPD) as the sixth leading cause of mortality (2.2 million deaths).[3] COPD was the fourth leading cause of death in the United States in 1996[4] claiming 100,000 lives, while pneumonia and influenza together caused almost 84,000 deaths.

This paper will first briefly describe the major respiratory diseases caused or influenced by bacteria. Secondly, the epidemiologic evidence that supports a role for oral bacteria in the process of respiratory infection will be reviewed. Finally, several mechanisms will be proposed to attempt to explain the potential role of oral bacteria in the process of respiratory infection.

Bacterial Pneumonia

This infection can be divided into community acquired- or hospital acquired (nosocomial) types depending upon the etiologic agent responsible.[5] Community-acquired pneumonia is typically caused by pathogens that normally reside on the oropharyngeal mucosa, such as *Streptococcus pneumonia, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumophila, Candida albicans*, and anaerobic species. In contrast, hospital-acquired, or nosocomial, pneumonia is often caused by bacteria that are not normally residents of the oropharynx but that enter this milieu from the environment, including Gram-negative bacilli (enterics such as *Escherichia coli, Klebsiella pneumoniae, Serratia* sps., *Enterobacter* sps.), *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

Respiratory infections are of particular concern in hospitals and other health care facilities such as nursing homes, especially in intubated patients. More than 5% of all hospital inpatients develop an infection, with 10 to 20% of these pneumonia. These infections often prolong hospital stays, increase patient care costs,

and cause significant morbidity and mortality. As many as 250,000 to 300,000 hospital-acquired respiratory infections occur in the U.S. each year,[6] with an estimated mortality rate of about 30%.[7] Pneumonia also contributes to a significant number of other deaths by acting as a complicating or secondary factor. Pneumonia is of special significance in the elderly population, accounting for the majority of admissions to hospitals from nursing homes.[8-10] Most of those fortunate to survive these serious infections still suffer severe morbidity. The cost of treating respiratory infections in the United States alone amounts to billions of dollars annually.

Chronic Obstructive Pulmonary Disease (COPD) and Emphysema

Another severe respiratory disease affecting a significant segment of the population is COPD. This condition is characterized by chronic obstruction to airflow with excess production of sputum resulting from chronic bronchitis (CB) and or emphysema.[11] CB is the result of irritation to the bronchial airway causing an expansion of the proportion of mucous-secreting cells within the airway epithelium. These cells secrete excessive tracheobronchial mucus sufficient to cause cough with expectoration for at least 3 months of the year over 2 consecutive years.[12] Emphysema is defined as the distention of the air spaces distal to the terminal bronchiole with destruction of the alveolar septa.

Chronic bronchitis is quite prevalent, with 20 to 30% of all adults over 45 years reporting a history of asthma or chronic bronchitis.[13] CB is more prevalent in men than in women, with about 20% of all adult males displaying some evidence of CB.[11] The prevalence of the disease in women is on the rise since more women are smoking than ever before. The incidence of emphysema is less well known since the main tool for non-invasive diagnosis (CT scanning) cannot be applied to population studies. It is interesting that it is rare to find lungs completely free of emphysema post mortem. However, the vast majority of individuals, while showing well defined histologic evidence of emphysema, will not have clinical symptoms of the disease.

Known risk factors for COPD include a history of prolonged cigarette smoking and genetic conditions such as the presence of a defective alpha 1-antitrypsin gene, variant alpha 1-antichymotrypsin, alpha 2-macroglobulin, vitamin D-binding protein, and blood group antigen genes.[14] Other environmental risk factors include chronic exposure to toxic atmospheric pollutants (e.g., second hand smoke).

One of the major complications of COPD is the occurrence of "exacerbations," or episodes in which there are objective signs that bronchitis has worsened as evidenced by increased sputum production showing a change in color and/or consistency. Increased cough, dyspnea, chest tightness, and fatigue may also accompany an exacerbation.

However, the factors responsible for the initiation of exacerbation are not completely known, although they are thought to be provoked in part by bacterial infection.[15,16] The organisms most closely associated with exacerbations are non-typeable *H. influenzae, S. pneumoniae* and *M. catarrhalis*. It should be pointed out that the frequency of exacerbations in COPD patients varies from individual to individual and the frequency of exacerbation is not related to the severity of lung disease. Although viral infections, fluid overload, and allergy have been suggested to enhance risk for exacerbation, no studies have yet proven the role of these factors in the disease process.[11]

Pathogenesis of Respiratory Bacterial Infection

In normal healthy adults, the pulmonary defense mechanisms maintain the infralaryngeal airway sterile. Infection is the result of either a defect in host defenses, challenge by a particularly virulent pathogen or by an overwhelming inoculum.[17] Lower respiratory infection begins by contamination of the lower airway epithelium by microorganisms contained in aerosolized droplets or by aspiration of oral secretions containing microorganisms. A critical step in this process is thus the colonization of oropharyngeal mucosal surfaces by respiratory pathogens and the shedding of attached bacteria from these surfaces into contiguous secretions that subsequently contaminate the lower respiratory tree.[17,18] Although colonization of the digestive tract has been suggested to be a source of hospital-acquired pneumonias,[19] recent evidence now supports the oropharyngeal region as the likely source of the bacteria.[20] Failure of host defense mechanisms to eliminate these pathogens from the lower respiratory surfaces results in their multiplication with subsequent infection and tissue destruction.[5,8,21] It is therefore possible that lower respiratory infection may be prevented by suppressing initial oropharyngeal respiratory pathogen colonization.

Risk Factors for Respiratory Infection

Not all individuals have equal risk for lower respiratory infection.[17] For example, community-acquired pneumonias are associated with conditions which increase the propensity for aspiration (alterations of consciousness due to stroke, seizures, dementia, alcohol abuse).

Cigarette smoking compromises the mucociliary barrier and phagocytic cell activity. Recurrent pneumonia suggests the presence of specific predisposing factors, such as congenital defects in host defense, cystic fibrosis, acquired immunodeficiency and other immunodeficiency syndromes, or COPD.

The risk for pneumonia is also dependent on environmental factors. The prevalence of community and nosocomial pneumonias are quite different. The prevalence of pneumonia in the community, although varying with locality, is approximately 0.1% of the population/year.[22] The prevalence of lower respiratory infection in hospitalized patients is higher, approaching 5% of all hospital admissions.[5,6] Certainly, the higher risk seen by hospitalized patients is due in part to immunologic or physiologic compromise compared to community dwelling individuals, and to the presence of antibiotic-resistant pathogens in the hospital environment.

Potential Role of the Oral Bacteria in Respiratory Infection

Recently, at least six studies have suggested a relationship between poor oral health and respiratory infection.[23-28] Two of these are cross-sectional epidemiologic studies that suggest an association between poor oral health and COPD.[24,26] The evidence gathered to date suggests that poor oral health may serve as a significant risk factor for lower respiratory infection, especially in high risk groups.

Oral Bacteria as Etiologic Agents of Aspiration Pneumonia

It is possible that the teeth and periodontium can serve as a reservoir for respiratory infection. Oral bacteria can be released from the dental plaque into the salivary secretions which are then aspirated into the lower respiratory tract to cause pneumonia (Fig. 1). Indeed, it has been long known that severe anaerobic lung infections can occur following aspiration of salivary secretions, especially in patients with periodontal disease.[17,18,29,30] Estimates have been made that 30 to 40% of all cases of aspiration pneumonia, necrotizing pneumonia, or lung abscess involve anaerobic bacteria.[31] A variety of oral anaerobes and facultative species have been cultured from infected lung fluids, including *Porphyromonas gingivalis, Bacteroides gracilus, Bacteroides oralis, Bacteroides buccae, Eikenella corrodens, Fusobacterium nucleatum, Fusobacterium necrophorum, Actinobacillus actinomycetemcomitans*, Peptostreptococci, Clostridium, and Actinomyces.[31-40] Most if not all of these organisms have been associated with periodontal disease.[41,42] It is also possible that viridans streptococci, thought to be exclusively benign members of the oral flora, may participate in the initiation and/or progression of pneumonia.[36,43-46]

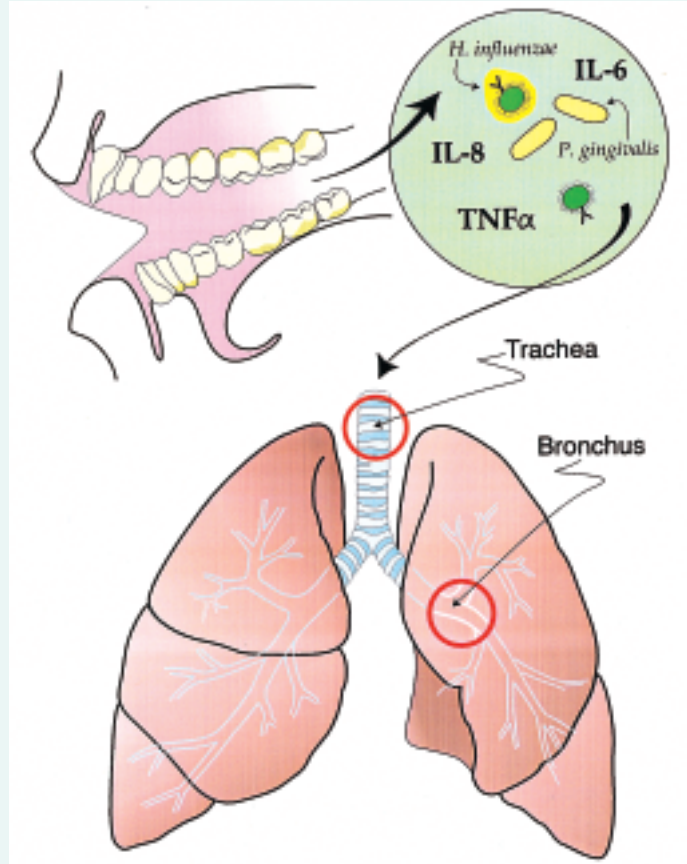

Figure 1.
*Oral bacteria, oral infection, and pneumonia. Bacteria that colonize the supra- or subgingival dental plaque are shed into the saliva. These pathogenic bacteria can be either those associated with periodontal disease (*P. gingivalis, Fusobacterium nucleatum, *etc.) or respiratory pathogens (*P. aeruginosa, Klebsiella pneumonia, *etc.). The saliva is aspirated into the lower respiratory tract (bronchus) where an infection can ensue. Cytokines from periodontally diseased tissues that enter the saliva from the gingival crevicular may be aspirated to stimulate local inflammatory processes that contribute to the initiation and/or progression of infection in the lung.*

Oral bacteria may also have a role in the exacerbations of COPD. For example, viridans streptococci were found to be the cause of pneumonia in 4% of COPD patients.[47]

Laboratory studies also suggest that oral anaerobes such as *P. gingivalis* can cause marked inflammation when instilled into the lungs of laboratory animals.[48] A relationship between the systemic humoral response to *Prevotella* species (bacteria associated with peri-

odontal disease) and ventilator-associated pneumonia in hospitalized patients has also been described. Thus, colonization of patients by *Prevotella* species may be associated with an infectious process leading to ventilator-associated pneumonia and a systemic humoral response.[49]

Dental Plaque as a Reservoir of Respiratory Pathogens

Ill patients are often unable to attend to oral hygiene. Several studies have documented that hospitalized individuals tend to have poorer oral hygiene than matched ambulatory, community dwelling controls.[23,27,28,50-52] Lack of attention to oral hygiene results in an increase in the mass and complexity of dental plaque, which may foster interbacterial interactions between indigenous plaque bacteria and acknowledged respiratory pathogens such as *P. aeruginosa* and enteric bacilli.[53] These interactions may result in colonization of the dental plaque by respiratory pathogens. Dental plaque may therefore provide a reservoir for respiratory pathogen colonization that can be shed into saliva. Contamination of the distal portions of the respiratory tree by saliva containing such organisms may result in pulmonary infections. It should also be pointed out that respiratory pathogens that establish in dental plaque may be difficult to eradicate. It is well known that bacteria in biofilms are much more resistant to antibiotics than planktonic bacteria.[54]

Previous studies have documented that patients admitted to medical intensive care units (MICU) have poorer oral hygiene than non-hospitalized patients and have a higher prevalence of respiratory pathogen colonization on the teeth and oral mucosa than do age and gender-matched outpatients.[23,55] In some cases, respiratory pathogens comprise up to 100% of the cultivable aerobic flora. In general, heavily colonized patients tend to be on antibiotic therapy. Respiratory pathogens are also more likely to colonize the oral cavities of patients with teeth or dentures than edentulous patients not wearing dentures. This finding suggests that respiratory pathogen colonization is favored by the presence of non-shedding surfaces and/or conditioning of mucosal surfaces by dental plaque.

Recently, a prospective study of 57 consecutive patients admitted to a MICU during a 3-month period assessed the colonization of dental plaque by respiratory pathogens.[27] The amount of dental plaque on the teeth of inpatients increased over time, as did the proportion of respiratory pathogens in their dental plaque. A high concordance was found between respiratory colonization of dental plaque by pathogens and the presence of the same pathogens in tracheal aspirate cultures, and between salivary and dental plaque cultures. Clinically, 21 patients developed a nosocomial infection in the ICU. Dental plaque colonization on days 0 and 5 was significantly associated with the occurrence of nosocomial pneumonia and bacteremia. In 6 cases of nosocomial infection, the pathogen was first isolated from the dental plaque.

Taken together, these results strongly suggest that patients admitted to ICUs have a significant risk for oral colonization by respiratory pathogens. Thus, the oral cavity may serve as an important nidus of infection for respiratory disease in high risk subjects, such as hospitalized or COPD patients.

It has been suggested that high risk patients in nursing home settings are also at risk for lower respiratory tract infection. The possibility therefore exists that, like the hospital intensive care environment, poor oral health may predispose nursing home residents to oral colonization by respiratory pathogens.[9,10] We recently studied the prevalence and distribution patterns of suspected respiratory pathogens in the dental plaque of older individuals living in a long-term care facility.[28] Findings from this group were compared to a similar number of age, race, and gender-matched community-dwelling subjects. Briefly, no differences were noted in the prevalence of colonization by respiratory pathogens between the chronic care facility subjects and dental outpatient subjects; 25% (7/28) of chronic care facility subjects were colonized with respiratory pathogens versus 27% (8/30) of dental clinic outpatients. However, when only those subjects who were positively colonized were considered (with the respiratory pathogen comprising ≥1.0 % of the total cultivable flora), there was a statistically significant difference between the prevalence of subjects who were colonized in each group (14% [4/28] of the chronic care facility subjects versus 0% [0/30] of the dental clinic outpatients). The proportion of respiratory pathogens in the plaque of chronic care facility subjects was much greater than that of the dental clinic outpatients who were colonized (42.88 ± 53.4 versus 0.02 ± 0.04).

These results suggest that nursing home subjects (who are at greater risk for lower respiratory infection) have a greater tendency for their dental plaque to be colonized by respiratory pathogens. This finding is substantiated by a recent report[25] that demonstrated that poor oral hygiene may be a major risk factor for respiratory tract infection in elderly institutionalized individuals.

Other oral factors may also play a role in initiating pneumonia in the elderly. A recent study evaluated the role played by dysphagia and a variety of medical and oral factors in aspiration pneumonia in 189 elderly subjects.[56] During a 4-year follow-up period, the best predictors for pneumonia were dependency for feeding, dependency for oral care, number of decayed teeth, tube feeding, more than one medical diagnosis, number of medications, and smoking. Dysphagia was concluded to be an important risk for aspiration pneumonia, but generally not sufficient to cause pneumonia unless other risk factors are present as well.

Oral Status and COPD

Although the evidence suggests a relationship between oral health and respiratory infection in high risk populations, what is the relationship between poor oral health and respiratory infection in the general population? To begin to assess potential associations between respiratory diseases and oral health in community-dwelling populations, data from the National Health and Nutrition Examination Survey I (HANES I) were analyzed.[26] This data base contains information on the general health status of 23,808 individuals. Of these, 464 individuals reported a suspected respiratory condition that was further assessed by a physician. These subjects were categorized as having a confirmed chronic respiratory disease (chronic bronchitis or emphysema), acute respiratory disease (influenza, pneumonia, acute bronchitis), or not to have a respiratory disease.

Significant differences were noted between subjects having no disease and those having a chronic respiratory disease confirmed by a physician. Individuals with a confirmed chronic respiratory disease had a significantly greater oral hygiene index (OHI) than subjects without a respiratory disease. Subjects with acute disease tended to have more decayed teeth than those without disease. No other statistical associations were noted between any of the other measures of oral health and acute respiratory disease. Also, no associations were noted between the periodontal index and either acute or chronic diseases.

To simultaneously control for multiple variables, gender, age, race, OHI, and smoking status were considered in a logistic regression model where predictors were dropped one by one until only significant predictors remained. The results suggest that for patients having the highest OHI values, the odds ratio for chronic respiratory disease was 4.5 (Table 1). These data are supported by the recent study of Hayes et al.,[24] who found periodontal disease, measured as alveolar bone loss assessed from periapical radiographs, to be an independent risk factor for COPD in adult males enrolled in the VA Normative Aging study.

Table 1.

OHI Odds Ratios (95% confidence intervals) (adjusted for smoking) of Having a Chronic Respiratory Disease for a Given OHI Value*

Percentile	OHI Value	Estimate of Odds Ratio	LCL	UCL
1	0	1.00	(1.00	to 1.00)
25	0.40	1.11	(1.00	to 1.22)
50	1.16	1.34	(1.01	to 1.77)
75	2.20	1.74	(1.02	to 2.94)
100	6.00	4.50	(1.06	to 18.99)

* From reference 26.
LCL = lower confidence limit.
UCL = upper confidence limit.

Although interesting, these data are limited in several ways. The data collected for the HANES study in the early 1970s utilized rather insensitive oral indices. Furthermore, the definitions of the respiratory diseases were likely imprecise. Longitudinal epidemiologic and interventional studies are required to definitely assess the role of oral disease in COPD progression.

Potential Mechanisms of Action of Oral Bacteria in the Pathogenesis of Respiratory Infection

Several mechanisms can be envisioned to help explain how oral bacteria can participate in the pathogenesis of respiratory infection: 1) aspiration of oral pathogens (such as *P. gingivalis, A. actinomycetemcomitans*, etc.) into the lung; 2) periodontal disease-associated enzymes in saliva may modify mucosal surfaces to promote adhesion and colonization by respiratory pathogens; 3) periodontal disease-associated enzymes may destroy salivary pellicles on pathogenic bacteria; and 4) cytokines originating from periodontal tissues may alter respiratory epithelium to promote infection by respiratory pathogens.

Periodontal Disease-Associated Enzymes in Saliva May Modify Mucosal Surfaces

Previous studies have shown that respiratory pathogens such as *P. aeruginosa* may adhere better to oral epithelial cells obtained from patients colonized by respiratory pathogens than to cells harvested from non-colonized patients.[56,57] Trypsin treatment of epithelial cells from non-colonized patients in vitro

resulted in increased adhesion by respiratory pathogens. These data suggest a mucosal alteration, perhaps the loss of fibronectin from the epithelial cell surface, promoted bacterial adhesion.[58] Buccal epithelial cells from gravely ill patients, all colonized by *P. aeruginosa*, interacted with greater numbers of bacterial cells in vitro, and possessed lesser amounts of surface fibronectin as determined by immunofluorescence. The removal of fibronectin (by exposure to proteases) may unmask mucosal surface receptors for respiratory pathogen adhesins. Other investigators have also pointed out an inverse relation between the amount of mucosal epithelial cell fibronectin and Gram-negative bacilli binding to these cells.[59]

Saliva contains a wide assortment of hydrolytic enzymes, and the amount of enzyme activity in saliva is related to the periodontal and oral hygiene status of the subjects tested.[60-62] For example, a direct relationship has been found between the ability of saliva to degrade fibronectin and oral hygiene status.[62] Subjects practicing meticulous oral hygiene (dental hygiene students) had very low levels of salivary fibronectin degrading enzymes. In contrast, saliva samples collected from laboratory workers having less than ideal oral hygiene had higher amounts of enzyme activity, and saliva collected upon awakening in the latter group had even higher levels. The source of these enzymes has been attributed to bacteria[60,61,63-65] or polymorphonuclear leukocytes which enter saliva from the gingival sulcus.[66] It is conceivable that in subjects having periodontal disease and elevated levels of proteolytic bacteria such as *P. gingivalis* and spirochetes, protease activity may alter the mucosal epithelium to increase the adhesion and colonization of respiratory pathogens (Fig. 2a). Such bacteria may also produce other enzymes such as mannosidase, fucosidase, hexosaminidase, and sialidase, known to be elevated in the saliva of such patients.[67,68] Exposure of epithelium and glycoproteins by such enzymes may increase the adhesion of Gram-negative bacteria to the mucosal surface by exposing normally "buried" adhesin receptors on the mucosal epithelium[69] which may foster increased adhesion and colonization by respiratory pathogens.

Destruction of Protective Salivary Pellicles by Oral Bacteria

Recent evidence suggests that the respiratory pathogen *H. influenzae* binds to mucins contained within mucosal secretions.[70-72] This binding may involve sialic acid residues.[70,73] In the context of COPD, it is possible that subjects with poor oral hygiene may have elevated levels of hydrolytic enzymes (e.g. sialidase) in their saliva. These enzymes may process mucins which reduce their ability to bind to and clear pathogens such as *H. influenzae* (Fig. 2b). Conversely, enzymes may process the respiratory epithelium to modulate adhesion of such pathogens to the mucosal surface (Fig 2c). Indeed, several studies have suggested that certain oral bacteria can breakdown a variety of salivary components.[74,75] Thus, increased dental plaque load from poor oral hygiene may result in elevated levels of salivary hydrolytic enzymes, which in turn may destroy protective domains of host secretory components (e.g., mucins) thus diminishing non-specific host defense against respiratory pathogens in high-risk subjects.

Salivary Cytokines May Alter Respiratory Epithelium

Periodontal disease (periodontitis) is a localized chronic inflammatory disease caused by infection of the periodontal tissues by bacteria in dental plaque resulting in destruction of supporting bone and connective tissues. In untreated periodontal disease, oral pathogens continuously stimulate cells of the oral tissues and periodontium (epithelial cells, endothelial cells, fibroblasts, macrophages, white cells) to release a wide variety of cytokines and other biologically active molecules.[76,77] Cytokines produced by epithelial and connective tissue cells in response to these bacteria including IL-1α, IL-1ß, IL-6, IL-8, and TNF.[77] Oral bacteria can also stimulate peripheral mononuclear cells to release cytokines (IL-1α and TNFα). In fact, oral streptococci (for example *Streptococcus sanguis*), which are abundant in dental plaque, stimulate the release of high levels of these cytokines from such cells.[78] Epithelial cells are also known to alter expression of various cell adhesion molecules on their surface in response to cytokine stimulation. Variation in expression of such adhesion molecules may alter the interaction of bacterial pathogens with the mucosal surface.[79]

One mechanism proposed for the gross airway epithelial damage observed in COPD involves release of proinflammatory cytokines (i.e., IL-8) from the respiratory epithelium, resulting in the recruitment and infiltration by neutrophils which subsequently release proteolytic enzymes and toxic oxygen radicals.[80,81] The release of cytokines from the respiratory epithelium may be the result of the binding of respiratory pathogens or their products to the respiratory epithelial cells. This mechanism has been demonstrated for medical pathogens such as *Strepto-coccus pneumoniae* and *Haemophilus influenzae*, which are also

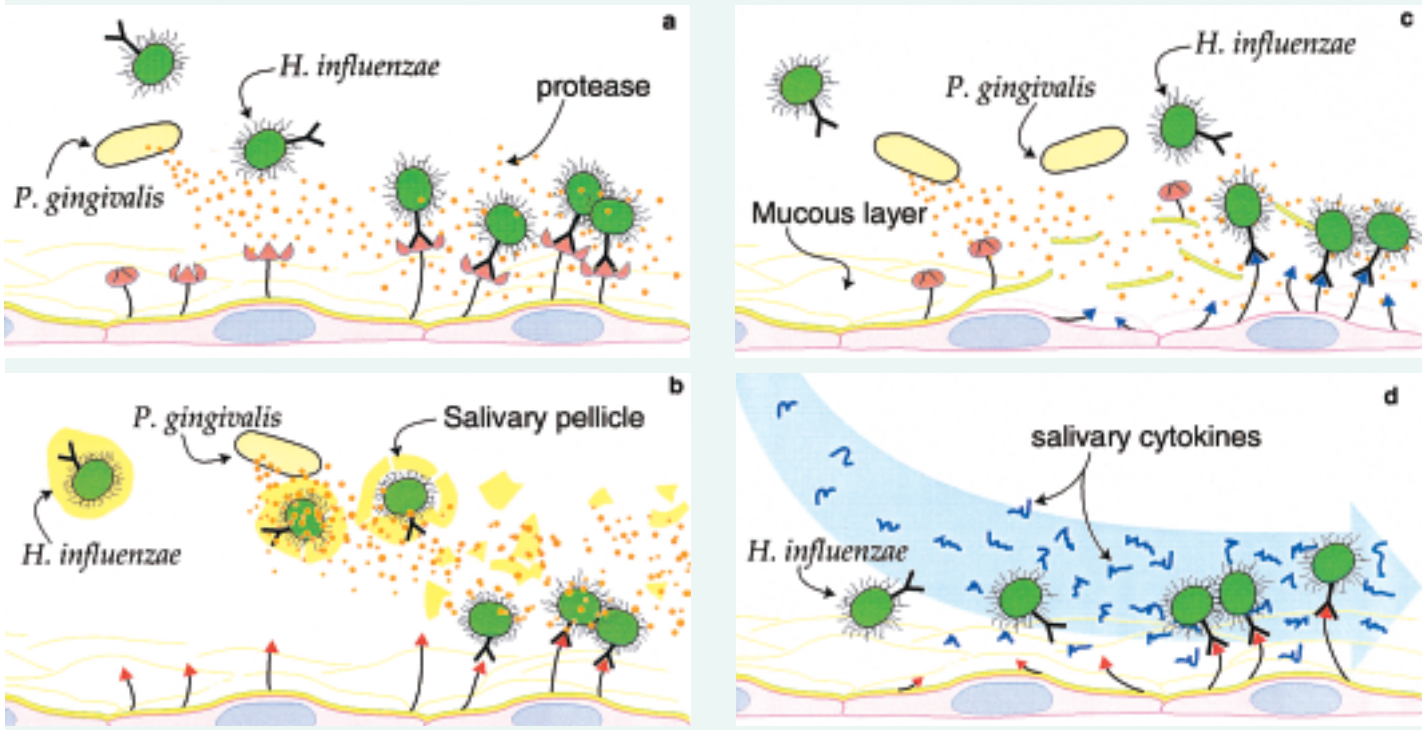

Figure 2.
a) Dental pathogens such as P. gingivalis *produce enzymes (such as proteases) that alter mucosal surface adhesion receptors for respiratory pathogens such as* H. influenzae, *which adhere, colonize and can subsequently be aspirated into the lung to cause infection.*
b) Oral bacteria such as P. gingivalis *produce enzymes that degrade the salivary molecules that normally form pellicle on the pathogens which prevents them from adhering to mucosal surfaces.*
c) Oral bacteria produce enzymes that degrade the salivary pellicle on the mucosal surface, thereby exposing adhesion receptors for respiratory pathogens.
d) Cytokines entering the saliva from inflamed periodontal tissues upregulate the expression of adhesion receptors on the mucosal surfaces to promote respiratory pathogen colonization.

known to attach to mucosal receptors and to stimulate cytokine production by the underlying cells.[82] It is also conceivable that oral bacteria in secretions in contact with respiratory epithelial surfaces may adhere to the mucosal surface. Oral bacteria are routinely cultivated, for example, from tonsillar epithelium.[83] These bound oral bacteria may stimulate cytokine production by mucosal epithelium. It is also possible that cytokines originating from the oral tissues (for example from the gingival crevicular fluids.[84-86] which exit the gingival sulcus to be mixed with whole saliva), may contaminate the distal respiratory epithelium to stimulate respiratory epithelial cells. The stimulated respiratory cells may then release other cytokines that recruit inflammatory cells (e.g., neutrophils) to the site. These inflammatory cells may release hydrolytic enzymes and other modifying molecules resulting in damaged epithelium that may be more susceptible to colonization by respiratory pathogens.

Oral bacteria may influence cytokine expression and effects in more novel ways. A recent paper by Darveau et al.[87] showed that IL-8 is secreted by gingival epithelial cells in response to components of the normal oral flora. In contrast, *P. gingivalis* strongly inhibited IL-8 accumulation from gingival epithelial cells. Inhibition was associated with a decrease in mRNA for IL-8. Antagonism of IL-8 accumulation did not occur in KB cells, an epithelial cell line that does not support high levels of intracellular invasion by *P. gingivalis*. Furthermore, a noninvasive mutant of *P. gingivalis* was unable to antagonize IL-8 accumulation. The authors concluded that invasion-dependent destruction of the gingival IL-8 chemokine gradient at sites of *P. gingivalis* colonization may impair mucosal defense. It is not yet known if *P. gingivalis* would have a similar effect on respiratory epithelium. Such an effect might result in perturbation of local cytokine networks and thus promote a destructive inflammatory lesion within the lung.

Conclusions

As described above, poor oral health, characterized by inadequate hygiene resulting in the formation of exten-

sive dental biofilms (plaque) may promote oral colonization of respiratory pathogens. Poor oral health may also influence the quality of respiratory epithelium resulting in increased susceptibility to respiratory infection. Oral secretions and/or oral bacteria may contain hydrolytic enzymes or cytokines that alter epithelial surfaces in ways that increase susceptibility to adhesion and colonization by respiratory pathogens. Thus, poor oral health may increase the risk for serious lower respiratory tract infection in susceptible subjects, including pneumonia in hospitalized subjects or exacerbation and progression of COPD.[1,24,27,55]

It is possible that factors responsible for poor oral health may be a determining factor influencing the frequency of respiratory infection in high risk groups. Further research defining the factors responsible for initiating the process of infection, the underlying conditions that may modulate the progression of the disease, and methods to improve its management are clearly needed. It is conceivable that improved oral health may decrease the prevalence of oropharyngeal colonization by respiratory pathogens and thereby reduce the risk of infection in high risk subjects.

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