The Oral-Lung Axis: The Impact of Oral Health on Lung Health

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Poor oral health has long been recognized as a clinical risk factor for developing lung infections. Recent data using culture-independent techniques assessing the microbiome in healthy subjects have demonstrated that chronic microaspiration establishes a very similar microbial community between the mouth and lung, suggesting these 2 anatomic regions are closely intertwined. Dental disease is driven and aided by a dysbiosis in the oral microbiome, and evidence is mounting that implicates the microbiome in a variety of lung diseases including asthma, COPD, pulmonary fibrosis, and pneumonia. This review describes common dental conditions and potential mechanisms by which poor oral health may contribute to lung disease. We also review the current literature drawing associations between poor oral health and lung disease.

Introduction

Poor oral health has systemic health consequences, and the dental health of patients with lung disease is overall severely underappreciated. Although most physicians identify an aspiration event as a cause of pneumonia, there are more insidious ways that dental disease may affect the lungs and contribute to a variety of lung diseases. Studies using bacterial 16S ribosomal RNA gene sequencing reveal that the mouth and lung have similar microbiomes, emphasizing how interrelated these 2 anatomic regions are.[1] Numerous studies have suggested a relationship between oral hygiene and both acute and chronic respiratory diseases including asthma, COPD, and pneumonia.[2,3] Despite these data, the biologic mechanisms behind these associations remain poorly understood and are inextricably confounded by effects of tobacco use and comorbid illness.[4] This review intends to introduce common dental conditions, describe how the oral cavity and lungs are closely related as it pertains to the microbiome, and provide potential mechanisms for how dental disease may impact lung disease. Additionally, we review the current clinical evidence for associations between oral health and common pulmonary conditions.

Dental Disease Primer

Gingivitis

Gingivitis is an inflammatory disease that is triggered by bacteria in dental plaque, driven by the innate host response, and characterized clinically by swollen, red, and tender gums that bleed easily.[5] It starts at the gingival margin of the tooth as a reaction to the accumulation of bacteria-laden dental plaque. Gingival epithelial cells, neutrophils, and the complement system are all active early on as part of the host's innate defense. This response produces pro-inflammatory cytokines (eg, interleukins IL-1, IL-6, IL-8, tissue necrosis [TNF]-α, RANTES), antimicrobial peptides (eg, calprotectin, cathelicidin, defensins), proteolytic enzymes (eg, matrix metalloproteinases, collagenases), and activated complement, but the protective plaque biofilm makes it difficult to fully eliminate bacteria.[6,7] Gum disease is clinically evident after 10–21 d.[7] Normal health can be restored to the gum line by mechanical plaque removal (ie, manual tooth brushing).

Periodontitis

Chronic inflammation from gingivitis can eventually lead to periodontitis, which is characterized by loss of ligamentous connective tissue holding the tooth in place, bone resorption, and formation of a clinically evident periodontal

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pocket between the tooth and gingiva.[5] This is severe gum disease that can result in tooth loss. It is unclear why some individuals with gingivitis progress to periodontitis while others do not, but it is likely related to a combination of the oral microbiome, the host immune response, and other environmental factors (eg, smoking).[5,7] Increases in IL-1, IL-6, TNF-α, and prostaglandin E2 are found in gingivocrevicular fluid, and some cytokines correlate with disease severity (IL-1β, IL-8, IL-17, IL-18, MIP-1a).[8-10] Gram-negative bacteria such as *Porphyromonas gingivalis*, *Treponema denticola*, and *Actinobacillus* species are the bacteria traditionally described in periodontal pockets and are believed to drive the host inflammatory response. In fact, it is probably not a single bacterium that is responsible for the development of periodontitis, but an overall dysbiosis of the microbiome. In contrast to other diseases where the microbiome is characterized by decreased bacterial diversity, periodontitis has increased diversity and richness.[6]

Caries

Dental caries (also called cavities) are caused by bacteria that metabolize starches to create a local acidic environment that eventually demineralizes the hard surfaces of the tooth. This initially presents as white spots on the tooth, but in its most severe form can lead to tooth decay.[11] *Streptococcus mutans* and *Lactobacilli* have been reported as causative bacteria, although some reports argue that this view may be too simplistic and a more complicated interplay of the entire oral microbiome may be responsible.[6,12] Caries do not represent an inflammatory condition such as gingivitis or periodontitis; however, if left untreated, caries can develop into serious infectious complications such as a periapical abscess.[13]

Because bacteria drive the inflammatory response in the mouth and subsequent pathology, it is worth considering how this microbial continuum from the mouth to the lung may prompt the development or exacerbations of lung disease.

The Oral-Lung Axis: A Physiologic Rationale for Association

Aspiration Is the Source of the Healthy Lung Microbiome

Early studies of the healthy lung microbiome analyzed from bronchoalveolar lavage fluid noted significant similarity between the oral and lung microbiota.[1] This similarity is biologically plausible because the 2 anatomic sites are contiguous and microaspiration is common even among healthy adults.[14] Interestingly, compared to the oropharyngeal microbiota, the nasal microbiota shares
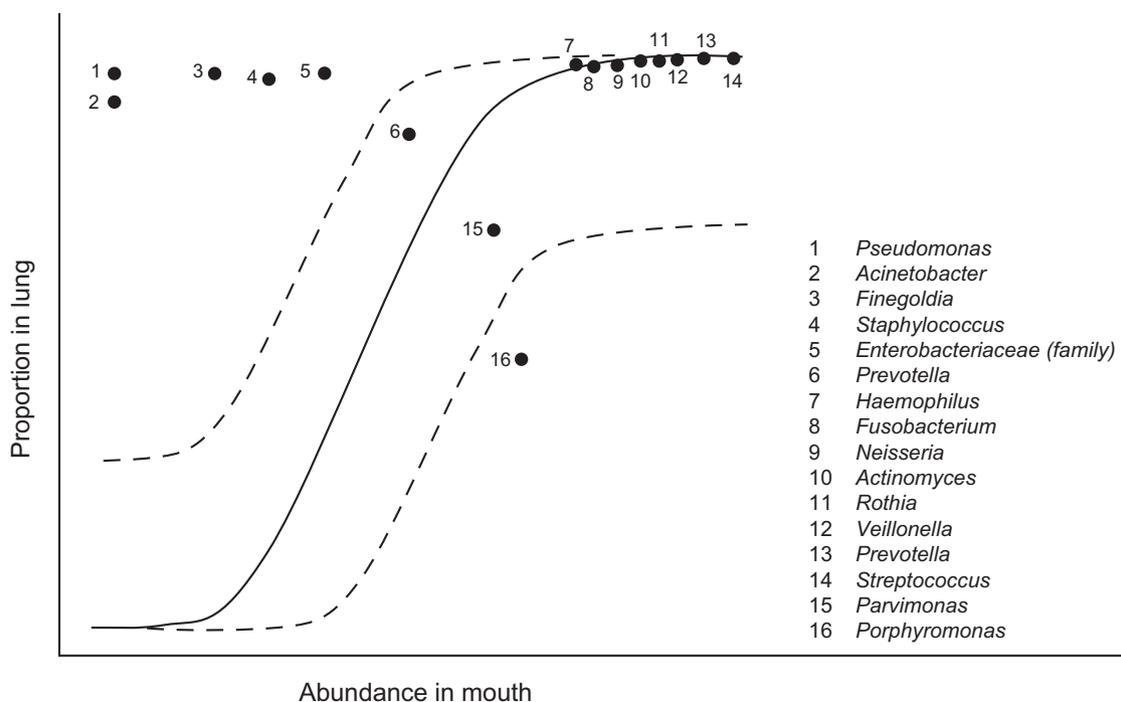
Fig. 1. Neutral theory model of oral wash and lung tissue specimens of subjects with COPD. The solid black line represents a best fit line, and the dashed lines represent 95% CIs. Numbered data points indicate the abundance of select taxa in oral and lung samples. Taxa 1–5 (*Pseudomonas*, *Acinetobacter*, *Finegoldia*, *Staphylococcus*, and *Enterobacteriaceae*) illustrate non-neutral behavior with overrepresentation in the lung microbiota (in comparison to neutral theory predictions based on the oral microbiota abundance). Taxa 6–15 (*Prevotella*, *Haemophilus*, *Fusobacterium*, *Neisseria*, *Actinomyces*, *Rothia*, *Veillonella*, *Streptococcus*, and *Parvimonas*) follow the neutral theory model; their presence in the lung microbiota is consistent with the neutral theory prediction based on their oral microbiota abundance. Taxa 16 (*Porphyromonas*) demonstrates non-neutral behavior with underrepresentation in the lung microbiota (in comparison to neutral theory prediction based its oral microbiota abundance). Adapted from Reference 18.

fewer similarities with the lung microbiota.[15] This supports the role of salivary flow and microaspiration as the main mechanisms that foster the population of the lung microbiome. Although the composition of the oral and lung microbiota are very similar, the lung likely harbors its own resident bacteria and may eliminate other common oral bacteria such as *Prevotella* species.[15-19]

The composition of the healthy lung microbiota is consistent with an ecological model known as the neutral theory of community ecology. This theory, adapted to the lung, proposes that the lung microbiota is the result of random immigration of bacteria from the oral microbiota, random bacterial reproduction in the lung, and random elimination of lung bacteria. In the lung, immigration is the result of microaspiration, inhalation of bacteria from the air, and mucosal dispersion. Elimination results from coughing, mucociliary clearance, and immune/host defenses. The neutral theory holds that the lung environment holds less influence over which lung taxa survive or die following immigration to the lung than do the random events of immigration, growth, or elimination. Therefore, if the lung microbiota follows the neutral theory, the lung microbiota composition should closely reflect the source (oral) microbiota composition.

Any lung taxa abundance that is not consistent with stochastic microbial immigration from the oropharynx or elimination represents "non-neutral" reproduction or elimination of that taxa in the lung environment. One large study utilizing all the datasets of the Human Microbiome Project found that only ~1% of human bacterial communities followed the neutral theory.[20] Interestingly, the healthy lung appears to be one of the few human sites to follow the neutral theory, supporting the interconnected microbial niche of the mouth and lungs.[1,15-19] With this evidence, it is now generally accepted that the composition of the healthy lung microbiota is heavily influenced by repeated microaspiration of oropharyngeal contents.

Architectural Lung Changes May Alter the Oral-Lung Axis

Other ecological models have also added to our understanding of the lung microbiota. The adapted island model of lung biogeography holds that the number of taxa in the lung microbiota decreases as the distance from the upper airway increases. This is due to increased frequency of immigration between 2 adjacent sites compared to sites that
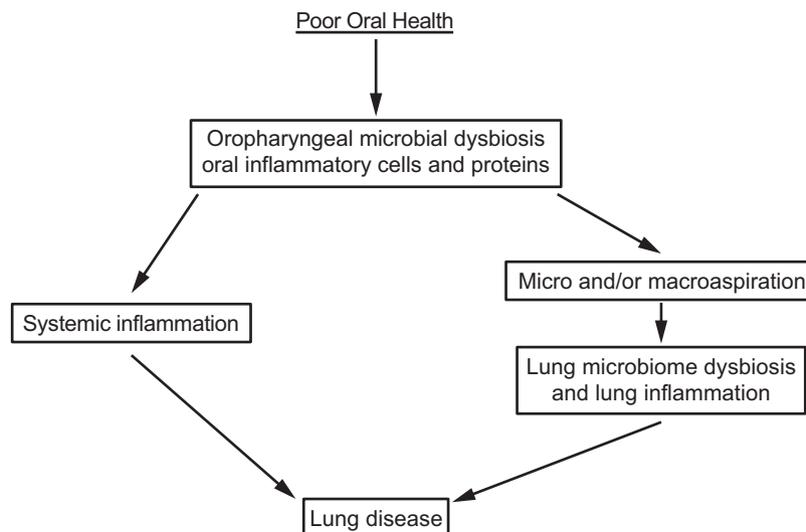
Fig. 2. General framework delineating potential mechanisms of how poor oral health may cause or contribute to lung disease.

are farther apart. For example, the number of taxa in the lung microbiota is greater in right upper lobe than in the right middle lobe—which coincides with a greater distance between the right middle lobe (compared to the right upper lobe) and the upper airway.[21,22] Lung architecture influences the lung microbiota composition in health, but it also appears to have a large impact on the microbiota in lung disease. As one could imagine, changes such as oxygen tension or mucociliary clearance mechanisms in emphysema or bronchiectasis may cause active environmental selection that leads to preferential growth or elimination of select taxa. This causes the oral-lung axis to exhibit non-neutral behavior as the lung begins to sustain a more unique microbiota compared to the mouth (Fig. 1).[19] An early study of the lung microbiome in subjects with advanced COPD showed that distinct microbiota could be identified within the same lung lobe based on micro-anatomic differences.[23] Another study of lung tissue obtained at the time of lung extirpation during transplantation also revealed notable shifts in the microbiota in the setting of end-stage lung disease.[24] Although anatomic changes such as bronchiectasis or blebs may be directly responsible for these microbiota shifts in chronic lung disease, these findings could also be due to other confounding effects such as treatments for lung disease (eg, antibiotics, steroids) or other exposures related to chronic illness. Whereas early lung microbiome studies have surveyed how changes in the microbiota and oral-lung axis are associated with lung disease, if and how the microbiota plays a causal role in chronic lung disease is still being explored.[25,26] Additionally, the effect of microbial dysbiosis in caries or periodontal disease on the lung microbiome has not been carefully studied.

The Oral-Lung Axis: Potential Mechanisms of Disease Pathogenesis

We have just described a biologic rationale for the oral-lung axis in health. There is also evidence to support the association between oral health and respiratory disease states. A number of hypotheses have provided biologic plausibility to strengthen this association. The leading ones are discussed here (Fig. 2).

Aspiration of Oral Bacteria

The most straightforward example of the oral-lung axis is aspiration of bacteria directly into the lung to cause disease. As noted above, there is overlap between common oral bacteria and lung bacteria. It has been classically taught that aspiration of oral secretions can lead to pneumonia, pulmonary abscess or empyema. Early microbiologic studies implicated numerous anaerobic oral bacteria such as *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*, and *Prevotella* with these pulmonary conditions.[27,28] More recent data regarding aspiration pneumonia pathogens reveal a predominance of aerobic organisms, both in the community and in the hospital.[29] Studies examining dental plaque show that biofilms harbor commonly recognized pulmonary pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*.[30-32] It is not entirely known how aspiration of bacteria leads to infection in some patients and not others. It is likely a combination of factors including the frequency and volume of aspirated material, efficacy of airway and lung clearance mechanisms, comorbid conditions, the patient's immune system, bacterial

virulence, and the degree of dysbiosis in the lung microbiome.[29,33]

Although it is well recognized that aspirated bacteria can lead to the acute illnesses listed above, the extent to which chronic microaspiration contributes to lung disease is unclear. In a cohort of healthy individuals, the enrichment of the oral flora *Veillonella* and *Prevotella* in bronchoalveolar lavage fluid has been associated with increased pulmonary inflammation as measured with number of inflammatory cells and exhaled nitric oxide.[34] A study of the bronchial microbiome of subjects with atopic asthma found only 4 taxa that were uniquely associated with asthma. Two of these were the periodontal pathogens, *Fusobacterium* and *Porphyromonas*.[35] *Prevotella* species have been associated with protracted bacterial bronchitis in children.[36] In a study of subjects with stable COPD, increased bacterial burden in the airways was associated with FEV_1 decline over time. The common bacteria that were cultured from sputum included *Streptococcus viridans*, *Nesseria spp.*, *Corynebacterium*, as well as *Hemophilus spp.*, all of which are normal oral flora.[37]

Aspiration of Inflammatory Proteins

Numerous different cytokines and enzymes are elevated in the saliva of subjects with periodontal disease compared to controls.[38] Many of the inflammatory proteins associated with periodontitis, which were outlined in the dental primer, have also been reported in chronic lung diseases such as COPD, asthma, and pulmonary fibrosis. For example, TNF-α has been shown to be increased in the sputum of patients with COPD, and it is also increased at the time of COPD and asthma exacerbations.[39-41] Matrix metalloproteinases, such as MMP-9, have been implicated in the destruction of periodontal connective tissue and enamel, as well as lung parenchyma, which may aid in the pathogenesis of asthma, COPD, and idiopathic pulmonary fibrosis.[42-44] IL-6 in the sputum is associated with a more rapid decline in lung function as well as frequent exacerbations of COPD.[45] The persistent aspiration of these molecules from an inflamed oral cavity may aggravate daily respiratory symptoms, lead to exacerbations of disease, or destroy the lung parenchyma.

Systemic Inflammation

Patients with periodontitis have high levels of systemic inflammatory markers, such as C-reactive protein.[46] Regular periodontal treatments can decrease levels of C-reactive protein and IL-6, suggesting that a local inflammatory process can have systemic effects.[47] This information, among other supporting observational and animal model data, has led investigators to link periodontal disease to other systemic illness such as cardiovascular disease,

rheumatoid arthritis, pregnancy complications, and osteoporosis.[48-51] A causal relationship is not established in these diseases, but there are mounting data indicating that systemic dissemination of periodontal inflammatory proteins, repeat episodes of bacteremia, and provocation of autoimmune pathways could provide this mechanistic link.[52,53] Systemic inflammation is also present in lung diseases such as asthma and COPD, with C-reactive protein levels inversely correlating with FEV_1.[54,55] Little is known about how dental care affects systemic inflammation in patients with chronic respiratory illness, and this provides a potential area of investigation.

Oral Health and Pulmonary Disease

Obstructive Lung Disease

COPD. There is great interest in the relationship between oral health and COPD. Most studies have been cross-sectional analyses, making it difficult to fully control for certain shared risk factors such as smoking, which limits conclusions. While a few studies have found no association between oral health and COPD after smoking status is considered, more studies have shown that periodontitis is associated with a diagnosis of COPD and may even be an independent risk factor.[56-58] Additionally, several studies have shown that oral health correlates with other measures of COPD, such as lung function and exacerbations.[59,60]

Using the NHANES III database of nearly 14,000 subjects, a correlation was demonstrated between loss of attachment of periodontal tissue and chronic bronchitis or emphysema, with an odds ratio of 1.45 (95% CI 1.02–2.05) once the attachment loss was > 3 mm. This correlation persisted after controlling for demographic data including smoking history and socioeconomic status.[61] A meta-analysis of 14 observational studies (3,988 subjects with COPD and 22,871 control subjects) reported an association between periodontitis and a diagnosis of COPD with a pooled odds ratio of 1.78 (95% CI 1.48–2.91), adjusted for age, smoking status, dental habits, and socioeconomic status.[56] One study attempted to establish causation by looking at incident diagnosis of COPD, defined as an $FEV_1 < 65\%$ predicted, over a 25-y follow-up.[62] Periodontitis that was present at baseline examination, as assessed with radiographic alveolar bone loss, was linked to increased odds of developing COPD (odds ratio 1.6, 95% CI 1.2–2.0) during the follow-up period.

Other COPD outcome measures associated with oral health include the BODE index (ie, body mass index, airflow obstruction, dyspnea, exercise capacity), spirometry, and exacerbation rates. In a case-control study of 581 subjects with COPD and 438 control subjects, higher BODE scores were associated with worse periodontal indices (eg, bleeding index, alveolar bone loss, and number of teeth),

with the plaque index having the highest likelihood for an association with COPD (odds ratio 9.01, 95% CI 3.98–20.4).[63] Peter et al[60] evaluated the relationship between FEV_1 and periodontal indices and reported that a worse clinical attachment level, probing depth, and gingival index correlated with a decreased FEV_1.[60] Exacerbation phenotype may also correlate with oral health. COPD frequent exacerbators have ≥ 2 exacerbations per year, while infrequent exacerbators have 0 or 1 exacerbations per year. After adjusting for smoking and lung obstruction severity, those with frequent exacerbations had fewer teeth, brushed their teeth less, and had more dental plaque, suggesting that poor oral hygiene may be a risk factor for COPD exacerbation.[59]

Poor oral hygiene is common in people with COPD. COPD patients have few remaining teeth, more dental plaque, and worse oral health-related quality of life.[64,65] Additionally, COPD patients do not brush their teeth, use dental floss, or visit the dentist as frequently as those without COPD.[64,66] Whether these correlations, which are likely multifactorial, play a causative role in COPD pathogenesis is unknown.

Despite evidence that periodontitis and poor oral hygiene practices are associated with COPD, there are limited data indicating whether improving oral health translates into better COPD outcomes. Two small trials evaluated the impact of periodontal treatments on COPD exacerbation rates. Kucukcoskun et al[67] randomized 40 COPD frequent exacerbators with comorbid moderate to severe chronic periodontitis to a periodontal treatment group, which included oral hygiene instructions, full mouth scaling, and root planning, or to a control group that received only oral hygiene instructions. At the 1-y follow-up, there was a significant reduction in COPD exacerbations in the treatment group (ie, from a mean of 3 per year to 2 per year), whereas there was no change in the exacerbation rate of the control group. Similarly, Zhou et al[68] conducted a randomized trial comparing periodontal treatment with scaling and root planning to no periodontal treatment in 60 subjects with COPD. After 2 y of treatment, the odds ratio for developing a COPD exacerbation in the treatment group compared to the control group was 0.29 (95% CI 0.10–0.84) after adjusting for age, gender, body mass index, smoking status, and baseline exacerbations. Although these trials are suggestive of the potential benefits of periodontal therapies in reducing COPD exacerbations, larger prospective trials are still needed.

Asthma. Most of the literature on the relationship between asthma and oral health is in the pediatric population. Notably, saliva production, which has protective properties for oral health, is decreased by the use of β-agonist inhalers, which are commonly prescribed for asthma treatment.[69] There is also evidence to suggest that inhaled corticosteroids promote caries.[70] Results of studies in subjects with asthma have been largely mixed but are suggestive of a higher rate of dental caries, gingivitis, and periodontitis in individuals with asthma.[3,71] One study reported a significant increase in plaque and gingivitis in subjects with asthma between the ages of 11 and 25 y compared to a control group.[72] Another 4-y follow-up study of similarly aged asthma subjects demonstrated decreased salivary flow as well as increased caries progression. A third study identified lower rates of salivary flow and higher rates of gingival inflammation and dental caries, again suggesting medication-induced dental disease.[73] Similar to the COPD literature, inferences regarding cause and effect from any of these studies are limited by study design, small number of subjects, and confounding effects of inhaler usage.

Bronchiectasis. Cystic fibrosis and non-cystic fibrosis bronchiectasis represent another spectrum of COPD characterized by inflamed and dilated airways. Studies examining the association between bronchiectasis-based pulmonary disease and oral health remain scarce. In fact, no data exist regarding oral health in non-cystic fibrosis bronchiectasis. Aspiration is commonly cited as a cause of bronchiectasis, but historically this has referred mainly to gastroesophageal reflux.[74] It is unknown whether chronic aspiration of oral bacteria and inflammatory proteins in the saliva eventually leads to bronchiectasis. Small studies in subjects with cystic fibrosis have noted decreased caries prevalence in children with cystic fibrosis compared to matched control groups. Despite these findings, dental enamel defects are relatively well described in individuals with cystic fibrosis.[75]

Non-Obstructive Lung Disease

Pneumonia. The relationship between oral health and pneumonia has been well described. A systematic review found an association between poor oral health, such as caries and periodontitis, and pneumonia with odds ratios ranging from 1.2 to 9.6, depending on the study.[2] As mentioned previously, aspiration of oropharyngeal secretions containing potential respiratory pathogens is thought to be a critical step in development of pneumonia. Studies support oral health as a factor in nursing home-, hospital-, and community-acquired pneumonia.[76-78] In one nursing home study, increased dental plaque was associated with more febrile days and episodes of pneumonia.[79]

It has been known for decades that the oropharyngeal flora of acutely ill hospitalized patients changes, with an emergence of Gram-negative organisms.[80] Mechanically ventilated patients' dental plaque is colonized with respiratory pathogens such as *S. aureus* and *P. aeruginosa,* and these organisms decrease in abundance after extubation.[81]

This shift in oropharyngeal flora in the hospitalized patient is thought to be a risk factor for developing nosocomial infections. Indeed, there are trials focused on oral care with the aim of preventing pneumonia. In a collection of randomized trials of nursing home residents and hospitalized subjects, regular oral care led to a 6.6–11.7% absolute risk reduction in the development of pneumonia compared to no oral care.[82]

Prevention of ventilator-associated pneumonia (VAP) with the use of topical oral chlorhexidine or selective decontamination of the orodigestive tract with antibiotics is controversial. A Cochrane review of 18 randomized controlled trials concluded that chlorhexidine-based oral care significantly decreased rates of VAP (relative risk 0.75, 95% CI 0.62–0.91) compared to placebo or usual care, but it did not affect duration of mechanical ventilation, length of stay, or mortality.[78] However, another systematic review reported a possible increase in mortality with the use of oral chlorhexidine.[83] Similarly, there is conflicting evidence regarding use of topical oral antibiotics and decontamination procedures in the ICU. Reviews of randomized trials on this topic have reported reduced incidence of VAP in subjects who received topical antibiotics.[84] On the other hand, there is also evidence that implementing oral decontamination protocols in the ICU may cause harm. The incidence of VAP in subjects, both in intervention and control groups, participating in randomized trials of oral decontamination is higher than known VAP incidence based on observational data, suggesting that the use of topical oral antibiotics may paradoxically be putting a population of ICU patients at risk.[85] Given the uncertain benefit for topical oral antibiotics or chlorhexidine in ventilated patients, guideline statements have not formally endorsed this practice, and further study is needed.

Interstitial Lung Disease. Interstitial lung disease represents a heterogeneous group of lung pathologies, and there has been interest in how the lung microbiome may shape disease progression. Currently, no studies describe oral health in interstitial lung disease. The only published study that reported the oral flora consisted of a varied group of subjects with interstitial lung disease in addition to subjects with *Pneumocystis* pneumonia and healthy controls.[86] There was no difference in diversity or composition of the lung microbiota between the groups. Additionally, only 7 of the 33 subjects had a lung microbiome that differed from the oral microbiome, and the clinical implications of this were unclear. In the whole cohort, the most common bacterial families identified in the lung were common oral flora such as *Prevotellaceae*, *Streptococcaceae*, and *Acidaminococcaceae*.

Further studies of the lung microbiome in subjects with idiopathic pulmonary fibrosis using bronchoalveolar lavage fluid demonstrate that the lung microbiome is associated with progression of disease. In one study, increased abundance of *Streptococcus* and *Staphylococcus* taxa correlated with disease progression.[87] Two other studies concluded that the total abundance of bacteria in the lung was coupled with progression of fibrosis.[25,26] Increasing amounts of bacteria in the lung resulted in a dysbiosis with a loss of bacterial diversity. In the study by Molyneaux et al,[26] no individual bacterial taxa could be linked with progression of fibrosis. Again, the common bacterial taxa noted in the lung included common oral flora such as *Haemophilus*, *Neisseria*, *Streptococcus*, and *Veillonella*. These intriguing studies offer a new potential therapeutic pathway in a lethal disease. Questions remain regarding the interplay between chronic microaspiration, replication, and the elimination of bacteria in aspirated oropharyngeal secretions, as well as the role of concomitant bronchiectasis in creating this increased bacterial burden in the lung. Additionally, how poor oral hygiene and dental disease may promote bacterial overgrowth in the setting of idiopathic pulmonary fibrosis is unknown and a compelling area for future research.

Potential Limitations

Despite the evidence suggesting an association between oral health and lung disease, there are limitations and confounders that require careful consideration. First of all, there are various definitions used for periodontitis and COPD in the literature.[4] Additionally, smoking is a clear risk factor for obstructive lung diseases and idiopathic pulmonary fibrosis, but it also is a risk factor for dental disease such as periodontitis.[88,89] NHANES data indicate that there is a dose-dependent relationship between tobacco smoke exposure and likelihood of periodontitis.[90] Whereas most studies looking at an independent association between COPD and periodontitis try to control for history of smoking, this is difficult to do in observational studies. Comorbid illnesses also confound the association between oral health and lung disease. Periodontitis aligns with cardiovascular disease, stroke, and diabetes.[49,91] COPD has a similar overlap of systemic disease comorbidities, which raises the possibility of an external factor driving the association between oral health and lung disease.[92] The role of respiratory medications affecting oral health must also be considered. Thrush is a well-known adverse effect of inhaled corticosteroids, representing a dysbiosis of oral flora, and β agonists decrease saliva production, which can lead to changes in pH and dental disease.[73] Geo-cultural and socioeconomic status may also play a role. There may be variability in diet or access to dental care across regions or cultures that affect the generalizability of studies. Socioeconomic status is independently correlated with the presence of periodontal disease and influences outcomes such as lung function, symptoms, and hospital admission in patients with COPD.[93,94] To resolve these confounding

issues, carefully conducted prospective studies are needed. Finally, there is currently no evidence that specifically targeting the oral microbiota with antibiotics leads to improved outcomes in chronic lung disease. Indiscriminate use of antibiotics to alter the oral microbiome comes with the risks of creating multi-drug-resistant organisms, adverse drug reactions, and dysbiosis of the microbiota, which may lead to complications such as *Clostridioides difficile* diarrhea.[95]

Summary

Aspiration has historically been recognized as a common inciting event in pulmonary disease. New diagnostic methods describing the oral-lung microbiome relationship, as well as numerous epidemiologic studies, have shown that the mouth and lung are more interconnected than previously recognized. The epidemiological data for these associations in chronic lung disease are inconsistent and evolving. Presently, we lack evidence to conclude that there is a causal link between oral disease and chronic lung disease pathogenesis. However, this prospect provides
a potential new therapeutic path that warrants further evaluation. Future prospective interventional trials to improve oral health are necessary to evaluate this potential relationship.

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