PART 2 OF 3

Untreated periodontitis and COVID-19: What is the evidence?

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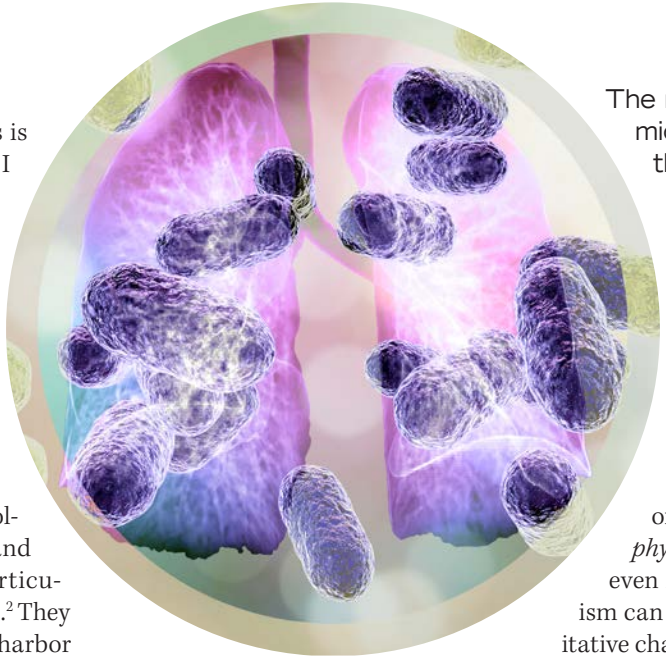
Presented in Part 2 of this series is a second biological mechanism I hypothesize may increase the risk for COVID-19 and/or its complications, namely how bacterial pathogens in the respiratory tract may predispose to influenza and other viral infection.[1] To reiterate what I wrote in Part 1, this is a hypothetical link; it has never been studied, and it is ripe for scientific investigation.

In their 2018 review, Shi and colleagues explored how bacteria and viruses impact each other, particularly during the infectious process.[2] They describe how mucosal surfaces harbor diverse microbial communities in complex ecosystems and how the bacterial portion of the microbiota influences the outcomes of many diseases, including infectious illnesses. In other words, the bacterial component of the resident microbiota plays a pivotal role in determining the outcome of an encounter with a new infectious organism. This evidence provides a compelling rationale for eliminating or reducing periodontal disease activity.

The oral microbiota is a reservoir for microorganisms implicated in respiratory infections, and anaerobic bacteria of the oral cavity have been identified in aspiration pneumonia and lung abscesses. We must acknowledge the large body of evidence that demonstrates that periodontitis increases the risk of pneumonia, especially in high-risk populations, such as the institutionalized elderly, patients hospitalized for extended lengths of time, and those undergoing long-term ventilation,[3-9] all of which are akin to the demographic hardest hit by COVID-19. In addition, periodontitis has been implicated in risk for chronic obstructive pulmonary disorder (COPD)—a known risk factor for COVID-19 infection.[10,11] Data from Wuhan reported that 7% of nonsurvivors had predisposing COPD.[10]



If only the periodontal microbiota could talk

The role of periodontal microbiota in subverting the immune response

In a healthy periodontium, the biofilm is symbiotic[i] with cooperative interactions between organisms within the microbial community. This produces host-microbe homeostasis.

However, accessory periodontal pathogens may pave the way for the introduction of the keystone pathogen,[ii] *Porphyromonas gingivalis*—meaning, even in low levels, this microorganism can initiate quantitative and qualitative changes in the oral microbiota to create an inflammatory environment.

Its virulence allows *P. gingivalis* to invade host cells, and once the organism is intracellular, it becomes protected from the immune response within the dysbiotic[iii] state of the microbiota.[12] Dysbiosis is an imbalance between the types of organisms present in a person's natural microflora that often contributes to damage of organs of the body. *P. gingivalis* is considered an inflammophilic[iv] organism, deriving its nutrients from the inflammation-enriched, dysbiotic microbiota. Here *P. gingivalis* has the potential to crowd out less competent microorganisms,[13] allowing this periodontal pathogen to replicate and increase its capacity to subvert the host immune response, both locally and systemically.

During this process, inflammophilic organisms, which normally are not harmful, become pathogenic in the subgingival niche. This cascade triggers infections downstream to other vulnerable mucosal surfaces, such as the lungs. The subversion of the host immune response locally eventuates periodontal destruction, especially in people with periodontal risk factors such as poorly controlled diabetes, obesity, and smoking.

Another periodontal microbe, *Fusobacterium nucleatum*, has the capacity to stimulate the production of proinflammatory cytokines that alter respiratory epithelium in such a way that it becomes primed for infection with respiratory pathogens,[14] including viruses.

Seeding the pathway for viral coinfection

When parts of periodontal microbiota are aspirated, they may seed vulnerable mucosal surfaces of the respiratory tract, increasing the risk of viral infections. The polymicrobial synergistic interactions seen in periodontitis might also occur in the lung tissue.[3] Fragmented microbiota carried to the lungs (and other organs) have the capacity to disrupt immune surveillance and the homeostasis of the tissue's ecosystem, causing a shift from a symbiotic microbiota to a dysbiotic one.

Virulent periodontal pathogens, *P. gingivalis* in particular, may interrupt homeostasis[15] of the commensal bacteria[v] of the upper respiratory tract, predisposing patients to pneumonia and priming the mucosal epithelium of the lungs for coinvasion by viruses such as SARS-CoV-2.

It's important to note that individual periodontal pathogens are more virulent when they are part of a commensal polymicrobial community, where they are protected.[16–20] Therefore, when the periodontal microbiota contains a mixed infection such as *P. gingivalis* and *Treponema denticola*, cases of aspiration pneumonia (animal model) have had significantly higher inflammatory responses, impaired bacterial clearance, and more severe lung pathology compared with a single infection with either microbe.[21]

Prevention of bacterial secondary infection should be an essential part of pandemic planning.

Individuals whose intrinsic immune system is competent may be able to resist a keystone pathogen's conversion of a symbiotic microbiota to a dysbiotic one, which may forestall the subversion of the immune system.[3]

Considering the COVID-19 pandemic

Prevention of bacterial secondary infection should be an essential part of pandemic planning.[22] Accordingly, given the high incidence of secondary infections of pneumonia in pandemic-scale influenza viruses, it's been suggested that vaccination against *Streptococcus pneumonia* should be considered as a preventive measure. That's a good idea. But how about treating sources of chronic infection that increase risk for pneumonia—such as periodontitis?

Early in the pandemic, Cox and colleagues[11] made a strong case for early diagnosis of coinfections. "Diagnosing coinfections is complex. The organism [coinfection] itself might be carried by the patient before the viral infection, might be part of an underlying chronic infection..."[11] Therefore, untreated periodontitis could be a coinfection that was established prior to the viral infection of SARS-CoV-2.

This makes sense, especially considering the risk periodontal disease poses to respiratory health. Consider the fact that many COVID-19 patients are kept on an invasive mechanical ventilator in an intensive care unit for multiple days, the length of time depending upon the severity of symptoms. This places them at significantly greater risk for ventilator-acquired pneumonia (VAP). Will untreated periodontitis escalate the risk for VAP in these patients? This makes for a compelling rationale for progressive diagnosis and treatment of periodontitis and minimizing the opportunity for new disease activity during periodontal maintenance.

Let's make sure to address untreated periodontitis in patients who have declined therapy in the past, and once treated, let's reduce the risk for dysbiotic disease activity in patients during periodontal maintenance.

For the public to recover from today's COVID-19, some researchers have suggested that testing patients for bacterial or fungal infections is critical in reducing the rate of secondary complications. How should this play out in our operatories? My answer is, let's make sure to address untreated periodontitis in patients who have declined therapy in the past, and once treated, let's reduce the risk for dysbiotic disease activity in patients during periodontal maintenance.

In Part 3 of this series, we'll explore the new therapeutic target, established in the 2017–2018 classification system, for patients with a reduced periodontium (after initial therapy)—lowering periodontal disease activity and reducing modifiable risk factors.

Comments are welcome. **RDH**

DISCLOSURE: *Florida Probe and Perio Protect provided unrestricted educational grants to Casey Hein for her research of this subject and writing of this article.*

NOTES

i. An environment where microorganisms communicate with one another and act together to stabilize their internal setting.

ii. The keystone pathogen hypothesis suggests that certain pathogens, in low abundance, are virulent enough that they can subvert host immunity in ways that favor the remodeling of a normal symbiotic microbiota into a dysbiotic and disease-provoking state.

iii. An imbalance between the types of organism present in a person's natural microflora that often contributes to damage of organs of the body.

iv. To have a propensity for or be attracted to inflammation.

v. Commensalism is a long-term biological interaction (symbiosis) in which members of one species gain benefits while those of the other species neither benefit nor are harmed. This is in contrast with mutualism, in which both organisms benefit from each other.

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