Could Periodontitis Be an Overlooked Co-Infection in the Fight Against COVID-19?

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The overwhelming threat we face from COVID-19 conveys to us a responsibility to find ways to prevent and combat this deadly disease.

It wasn't long after the World Health Organization declared COVID-19* a global pandemic that the surge of SARS-CoV-2 information began getting published. The plethora of articles included clinical case reports, profiling of the molecular structure of the virus, and analysis of biological data harvested from pandemic hot spots. Hypotheses abounded, most related to identifying COVID-19 risk factors, mapping the infection's pathway, and figuring out prophylactic and therapeutic blueprints. What is noticeably missing is research on how low-grade chronic infections such as periodontitis—one of the most prevalent diseases in the world—may influence the trajectory of COVID-19. This includes the possibility that periodontitis could be a predisposing factor with the potential to increase the risk for complications of COVID-19, precipitating life-threatening respiratory sequelae.

This article proposes the hypothesis that untreated or unstable periodontitis may be a significant yet overlooked source of pre-COVID-19 co-infection that may add to the body's inflammatory burden and consequently exacerbate risk for this deadly virus and its complications. Oral healthcare providers (OHCPs) will be urged to become more vigilant in diagnosing and treating periodontitis and stabilizing the reduced periodontium during long-term periodontal maintenance, and specific recommendations for progressive periodontal intervention will be proposed.

The Case for a Link Between Periodontitis and COVID-19 and Its Complications

Evidence that many persistent infections can alter immunity to unrelated pathogens, such as a new virus or bacteria, has been emerging for many years.[1] Could this include periodontitis? Maybe. Called "bystander" chronic infections, these persistent infections also adversely impact the effectiveness of vaccines in people who have been infected with new viruses.[1] Does that mean untreated or unstable periodontitis may negatively influence the effectiveness of vaccines for COVID-19? Like many other questions surrounding the nebulous science of this pandemic, the answer isn't clear yet.

*COVID-19 is the disease caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), originally known as the "2019 novel coronavirus". WHO. Accessed at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it.

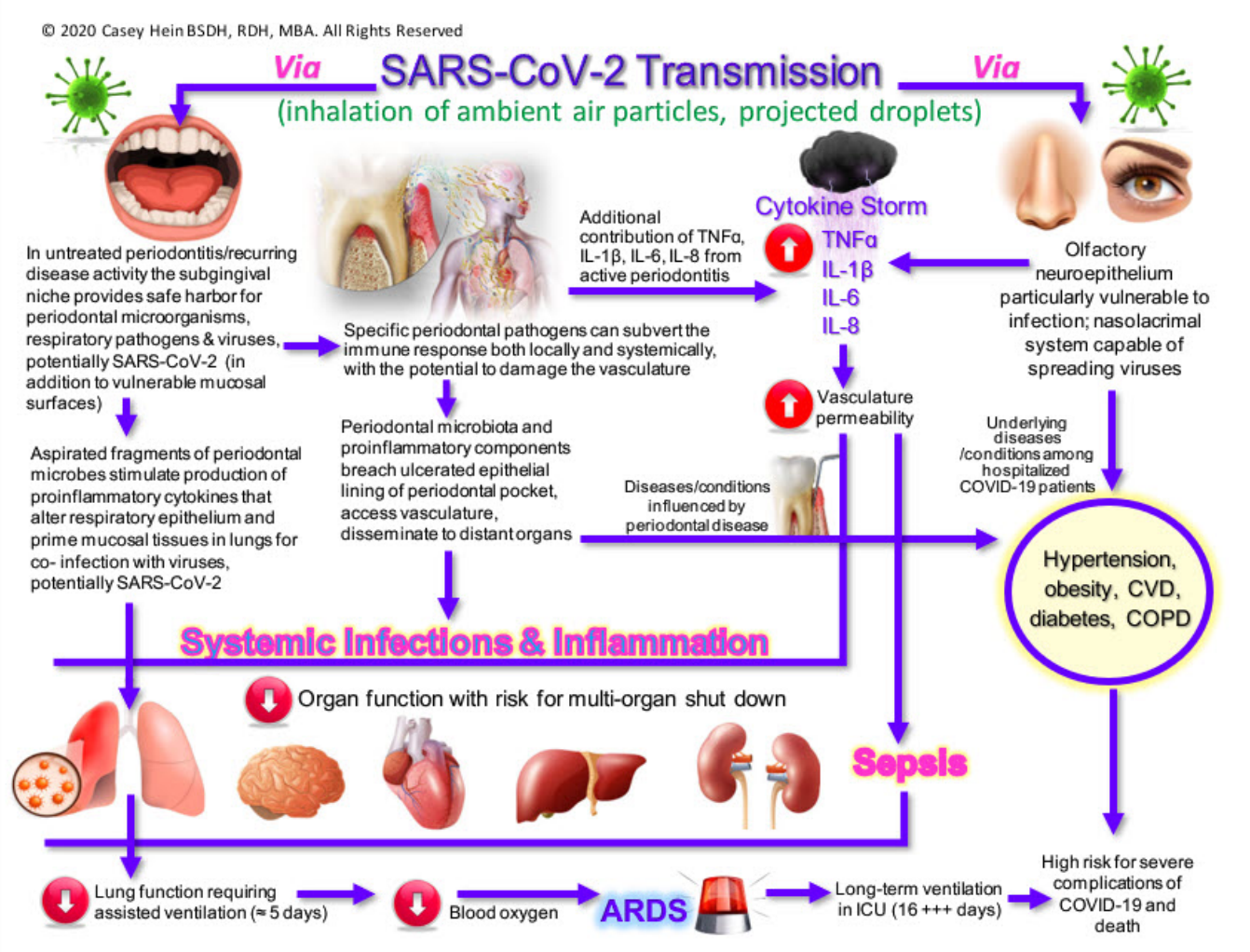


Figure 1—Biologic mechanisms that underpin the hypothesis that untreated or unstable periodontitis may play a role in susceptibility to SARS-CoV-2, and/or complications of its associated disease, COVID-19.

Soon after the SARS-CoV-2 pandemic began, Cox and colleagues suggested that it was important to diagnose co-infections as early as possible: "The organism [co-infection] itself might be carried by a patient *before the viral infection*, might be part of an underlying chronic infection…"[2] Though periodontitis was not discussed in the article, there are a number of biological pathways that hypothetically link untreated periodontitis as a source of co-infection established prior to the infection of SARS-CoV-2. The interplay between bacteria and viruses in the trajectory of infectious illnesses is well recognized.[3] As an example, we know that mucosal surfaces are reservoirs for diverse microbial communities that thrive and multiply in complex ecosystems. The

bacterial component of these microbiomes play a central role in defining the outcome of an encounter with a new infectious organism, including viruses. This evidence, along with other intriguing information, challenges us to explore, in depth, the potential for periodontitis, as a co-infection, to undermine immunity for viral infections like COVID-19, and/or influence the severity of its complications.

Figure 1 provides a synopsis of biologic mechanisms that underpin the hypothesis that untreated or unstable periodontitis may play a role in susceptibility to SARS-CoV-2, or complications of its associated disease, COVID-19, as follows below.

The first contact viruses make with human hosts is usually mucosal surfaces.[3] Evidence to date suggests that the primary entry of SARS-CoV-2 is by inhalation of ambient air particles and projected droplets that have an affinity for mucosal surfaces of the oral cavity, nose, and eyes.[4] Whether pathology develops depends on the integrity of mucosal surfaces and the immunocompetence of the individual. If the host cannot mount sufficient immune defense and the mucosa is vulnerable, the virus colonizes in these tissues. As SARS-CoV-2 enters through the nose, the olfactory neuroepithelium, which is particularly vulnerable to infection, provides a safe harbor for the virus.[5] In eye contamination, the virus is thought to spread through the nasolacrimal system.[6] It's important to mention these alternative routes of transmission; however, the subject of this paper is viral transmission via the oral cavity.

When the integrity of mucosal surfaces within the oral cavity is compromised, this presents the ideal environment for viral infection. The periodontal pocket (PP) with recurring disease activity offers an inflammation-rich substrate in an ecosystem which is highly compatible for viruses to survive and proliferate. It's important to note that not just bacteria reside in the PP; viruses also inhabit this niche. The most frequently detected viruses in PPs are herpes simplex, Epstein-Barr, and human cytomegalovirus with a median prevalence in PPs of 26-78%, 46-58%, and 42-58%, respectively.[4] Like bacteria, viruses have the capacity to translocate via the periodontal capillary system in the ulcerated epithelial lining, then enter the systemic vasculature to set up focal infections in organs distant to the oral cavity.[7] In addition, the oral cavity is a reservoir for respiratory pathogens; *Chlamydia pneumoniae* has been found in the plaque of patients who have periodontitis.[8] It is possible that SARS-CoV-2 may be another virus that thrives within the PP.

We also must acknowledge the compelling body of evidence that establishes periodontitis as a risk factor for pneumonia. This is especially true for high-risk individuals such as the institutionalized elderly, patients hospitalized for extended lengths of time, and those undergoing long-term ventilation,[9-15] all of whom are also at greatest risk for COVID-19. In addition, periodontitis has been implicated in risk for chronic obstructive pulmonary disease (COPD), a known risk factor for COVID-19 infection.[16]

The cytokine release syndrome (CRS) is thought to be responsible for many of the life-threatening sequelae of COVID-19. Also known as "cytokine storm," it is activated by the immediate response of the innate immune system to assaults to the body, such as influenza, pneumonia, and sepsis, which triggers an uncontrolled and excessive release of proinflammatory cytokines, specifically TNFα, IL-1ß, IL-6 and IL-8 throughout the body. This cascade of events produces high levels of systemic inflammation, and when inflammation escalates to a high enough level, vascular permeability increases, paving the way for sepsis and multiorgan shutdown. Of note, in-vitro evidence suggests that the keystone pathogen, *Porphyromonas gingivalis*, is capable of damaging the vasculature,[17] potentially exacerbating the sequelae of the cytokine storm, including harming the kidneys, liver, heart, brain, and lungs. The very same cytokines that flood the body during a cytokine storm (i.e., TNFα, IL-1ß, IL-6, and IL-8), are also released in the PP with ongoing periodontal disease activity. Beyond their local effect, these cytokines contribute to the avalanche of systemic inflammation from the cytokine storm. The question is: Does the additional release of cytokines from unstable periodontitis as a co-infection portend more severe complications of COVID-19?

Respiratory failure, specifically the acute respiratory distress syndrome (ARDS), is the leading cause of morbidity in COVID-19 patients.[18] Consequently, it is critical that we reognize the capacity of specific periodontal pathogens such as *P. gingivalis* to subvert the host immune response, both locally and systemically, and *F. nucleatum* to upregulate proinflammatory cytokines that alter the epithelium of the respiratory tract, priming the mucosa for respiratory infections of viral or bacterial origins.[19] This places patients at risk for secondary co-infection, leading to pneumonia.

The risk for post-virus secondary bacterial co-infection, such as *Streptococcus pneumoniae*, rises as pulmonary function declines, causing a reduction in blood oxygen levels that necessitates assisted ventilation. This often leads to ARDS, usually requiring long-term ventilation in intensive care units, lasting 16 days or longer. Long-term ventilation is recognized as a significant factor in the survivability of COVID-19, and the possibility that active periodontitis may amplify that risk is a variable that must be considered. Among those COVID-19 patients who were admitted to the hospital in Wuhan, about 42% developed ARDS, 52% of whom died.[20]

Hypertension, obesity, CVD, diabetes, and COPD have all been cited as underlying diseases and conditions among patients hospitalized with COVID-19.[21-23] These are all diseases/conditions that are influenced by periodontal disease.

Treating periodontitis has always been essential to sustaining oral health. But, given the evidence presented above, delaying treatment of periodontitis, for whatever reason, may pose a risk for those who defer care, especially for those individuals who have underlying diseases or conditions that place them at greater risk for severe complications of COVID-19. Taken all together, the influence of untreated or unstable periodontitis on the progression of biological events associated with COVID-19 as described above, may potentiate more damage than the SARS-CoV-2 virus itself. In light of these biological possibilities, the importance of progressive diagnostics, therapeutics, and long-term stabilization strategies in the treatment of periodontitis cannot be overstated.

Recommendations for Progressive Diagnostics, Therapeutics, and Long-Term Stabilization of the Reduced Periodontium†

Some old and some new ideas for stepping up the diagnosis, treatment, and long-term stabilization of the periodontium follow:

1. More important than ever before, OHCPs must help patients minimize bacterial load in the oral cavity by re-emphasizing how essential oral hygiene is in staying healthy. Poor oral hygiene may be a factor in infection of SARS-CoV-2.

   Over 25 years ago, researchers discovered that only 20% of the risk of developing periodontitis is plaque related, and that host factors such as smoking, poor glycemic control, and genetics were more predominate determinants in periodontal risk assessment.[24] That said, the cornerstone of periodontal health has always been good oral hygiene.[25] In our current environment, reducing bacterial burden, anyplace in the body, is even more important.

   Perhaps the most valuable contribution to the 2017 system for Classification of Periodontal and Peri-Implant Diseases and Conditions is the framework that was established to assess metrics like the rate of periodontal disease destruction, the future risk for recurring disease activity, and the potential impact of periodontitis or its treatment on overall health. Collectively, these metrics comprise the diagnostic term "grading." To this point, Lang and Bartold suggested that "for periodontal health to be attained, or maintained, the composition of the subgingival microbiota needs to be redirected toward one compatible with gingival health."[25] Motivating patients to better care for their mouths is fundamental in this regard. A handout with patient education tips can be found in Figure 2.

   A systematic review published in 2015 found that a key predictor of compliance to oral hygiene self-care instruction is patients' understanding of the seriousness of periodontal disease.[26] Consequently, it follows that if patients realize the potential threat that untreated or unstable periodontitis poses to overall health, compliance to self-care and treatment recommendations would improve. In this pandemic, patients are well primed to learn ways they can bolster their immune system. Patient education may include the possibility that untreated periodontitis could influence susceptibility to viruses and/or escalate the severity of related complications of viral illnesses, such as COVID-19; however, whatever we say must be grounded in science. The intention is not to scare patients into treatment, but rather to help those who have questioned the benefit of periodontal treatment understand the threat untreated periodontitis poses to overall health. Here are some sound bites that may be useful.

   - One of the strongest defenses we have against viruses is a robust

†Reduced periodontium is the term used to describe the status of periodontal tissue with reduced connective tissue attachment and alveolar bone height following active periodontal treatment

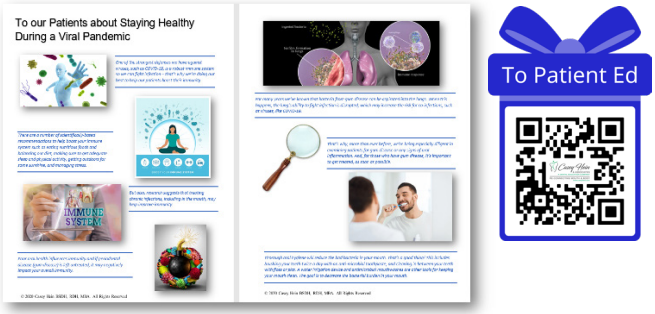


Figure 2—Handout for patient education and QR code to download copy.

immune system so we can fight infection.

- There are a number of scientifically based recommendations to help boost the immune system such as eating nutritious foods and balancing our diet, making sure to get adequate sleep and physical activity, getting outdoors for some sunshine, and managing stress.
- Research also suggests that treating chronic infections, including in the mouth, may help improve immunity. Poor oral health influences immunity, and if periodontal disease is left untreated, it may negatively impact overall immunity.
- For many years, we've known that bacteria from periodontal disease can be aspirated into the lungs. When this happens, the lungs' ability to fight infection is disrupted, which may increase the risk for co-infections such as viruses like SARS-CoV-2.
- That's why we must be especially diligent in examining patients for periodontal disease or any signs of oral inflammation. And, for those who have periodontal disease, it's important to get treated as soon as possible.
- Thorough oral hygiene will reduce the amount of pathogenic bacteria in the mouth. This includes brushing teeth twice a day with an antimicrobial toothpaste, and cleaning in between teeth with floss or picks. A water irrigation device and antimicrobial mouthwashes are other tools for keeping the mouth clean. The goal is to decrease the bacterial burden in the mouth.

2. Boost probing accuracy to improve periodontal disease diagnoses and to assess periodontal stability by utilizing an automated probing system.

The progression of periodontal destruction is not a straight line. From long-established research, we know there are periods of dormancy and bursts of disease activity. This was addressed in the 2017 classification system with the proposal that for patients with a reduced periodontium there be a new therapeutic target: The goal must be to achieve stability or remission/control.[25] Clinical parameters that inform the level of disease activity follow below in Figure 3. Two types of treatment outcomes were defined: stability or remission/control. In periodontal disease stability there is either no or very minimal bleeding upon probing (BOP), and modifying factors[‡], and predisposing factors[§] are controlled or remedied. In disease remission/control, although significantly reduced, there is still BOP, and modifying and predisposing factors are not fully controlled.[27]

Assessment of the status or stability of the case provides essential information to help determine treatment plans and to establish the best

[‡]Modifying factors are dynamic systemic changes that influence the level of disease activity. A good example is an HbA1c of greater than 7.0%, which would increase the risk for periodontal disease activity.

[§]Predisposing factors are more local factors that increase the probability of disease occurrence or reoccurrence such as things that promote retention of dental plaque including calculus, overhanging margins, subgingival restorations, tilted/rotated/crowded teeth.

	Periodontal disease stability	Periodontal disease remission/control
Bleeding upon probing	No/Minimal	Significantly reduced
Modifying factors	Controlled	Not fully controlled
Predisposing factors	Controlled	Not fully controlled

Figure 3—Clinical parameters for assessing the level of periodontal disease activity in a reduced periodontium.[25]

strategies and intervals for periodontal maintenance.

Florida Probe**, an automated probing technology, is essential in operationalizing the new 2017 diagnostic framework. The system has a very strong track record for greater probing accuracy, increased clinician efficiency and patient acceptance of periodontal treatment plans, and beautifully rendered charts that detail results of periodontal exams. The system's ability to track key metrics that help determine staging, grading, and the level of disease activity in a reduced periodontium makes this an indispensable tool in assisting clinicians with implementing the new diagnostic classification framework. In Figure 4, samples of two Florida Probe charts demonstrate a comparison of clinical metrics before treatment and five months after treatment. The callouts show how the Florida Probe technology automatically calculates a summary of the key metrics, such as the number of sites with pockets less than 4 mm, sites with pockets between 4 and 5 mm in depth, and sites with pockets greater than 5 mm, in addition to the number of sites that BOP, and sites of suppuration. The line graphs on the bottom indicate the changes that occur such as pocket depths and BOP at subsequent examinations.

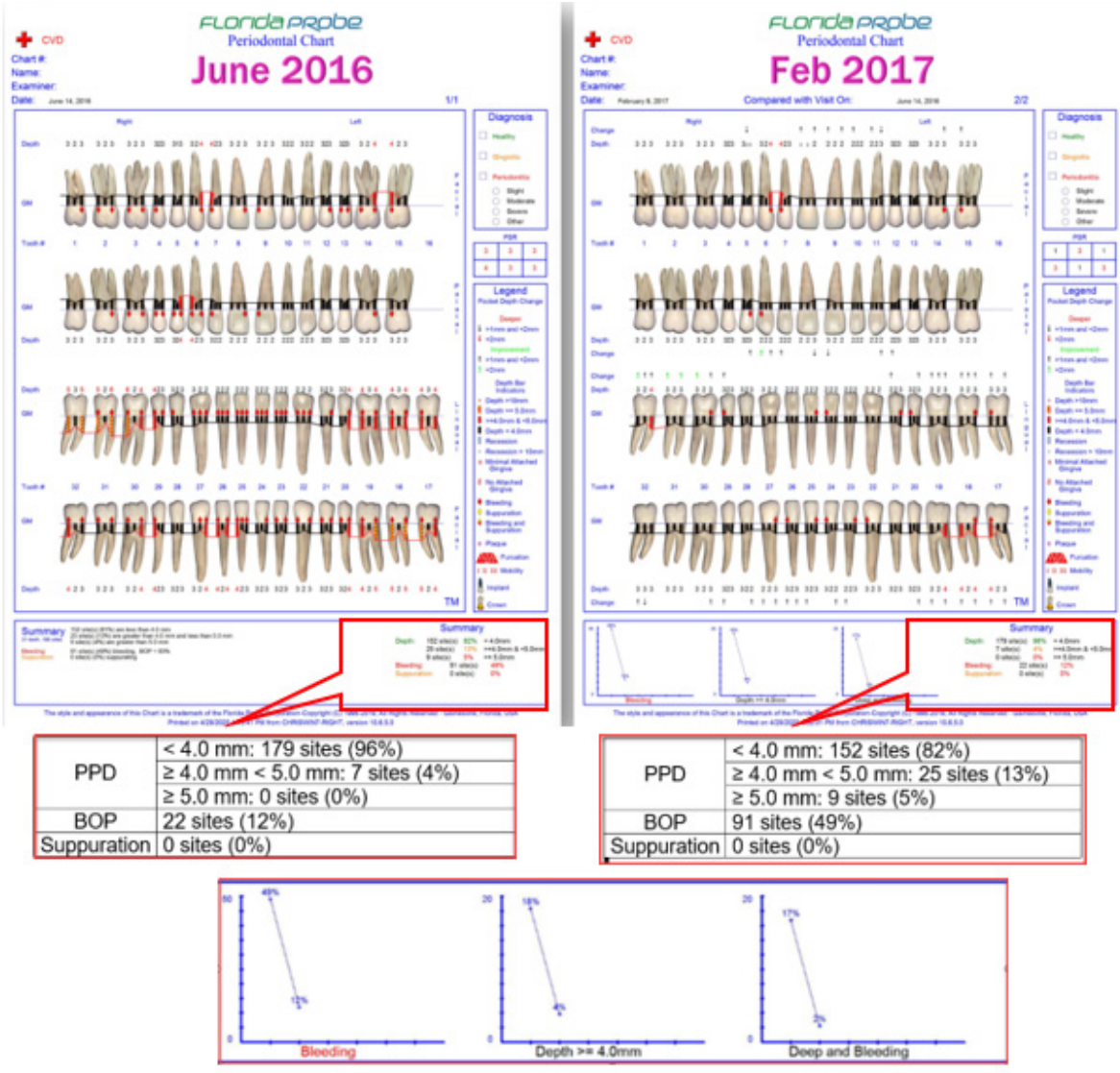
Among Florida Probe's best features are its sophisticated software that bridges to most practice management systems, and its VoiceWorks, a wireless USB headset that allows voice recording of periodontal metrics, a lower-cost, easier-to-implement option of the Florida Probe system.

3. Utilize adjunctive therapies for patients in periodontal maintenance that facilitate periodontal disease stability in a reduced periodontium. After initial periodontal treatment, consider two therapeutic strategies:
   1) Host-modulatory therapy with subdose doxycycline to reduce degradation of collagen within the periodontium.
   2) FDA-cleared prescription Perio Trays to deliver hydrogen peroxide gel into the periodontal pocket aimed at disrupting subgingival biofilms and creating ecological conditions that are incompatible for proliferation of gram negative anerobic organisms known to be associated with periodontal disease activity.

Use of Subdose Doxycycline in Host Modulatory Therapy

It was over two decades ago when Golub and colleagues discovered that tetracyclines had a role in modulating the host response

**Florida Probe Corporation. Gainesville, FL



PPD	< 4.0 mm: 179 sites (96%)
	≥ 4.0 mm < 5.0 mm: 7 sites (4%)
	≥ 5.0 mm: 0 sites (0%)
BOP	22 sites (12%)
Suppuration	0 sites (0%)

PPD	< 4.0 mm: 152 sites (82%)
	≥ 4.0 mm < 5.0 mm: 25 sites (13%)
	≥ 5.0 mm: 9 sites (5%)
BOP	91 sites (49%)
Suppuration	0 sites (0%)

Figure 4—Periodontal charts from the Florida Probe® system that document key metrics before and after treatment, which is essential in operationalizing the 2017 Classification of Periodontal & Peri-Implant Diseases and Conditions.

to periodontal bacteria.[28] They found that in low doses, tetracycline and its derivatives could inhibit connective tissue breakdown and thus help preserve the collagen content of the periodontium. Subsequent studies confirmed that the use of subantimicrobial doses of doxycycline, as an adjunct to scaling and root planing (SRP), improved clinical parameters beyond what can be achieved by SRP alone.[29-30]

Doxycycline at a dose as low as 20 mg twice a day does not reach the minimum inhibitory concentration necessary to cause an antimicrobial effect. This allows its long-term use in helping to stabilize the reduced periodontium. Originally produced under the label

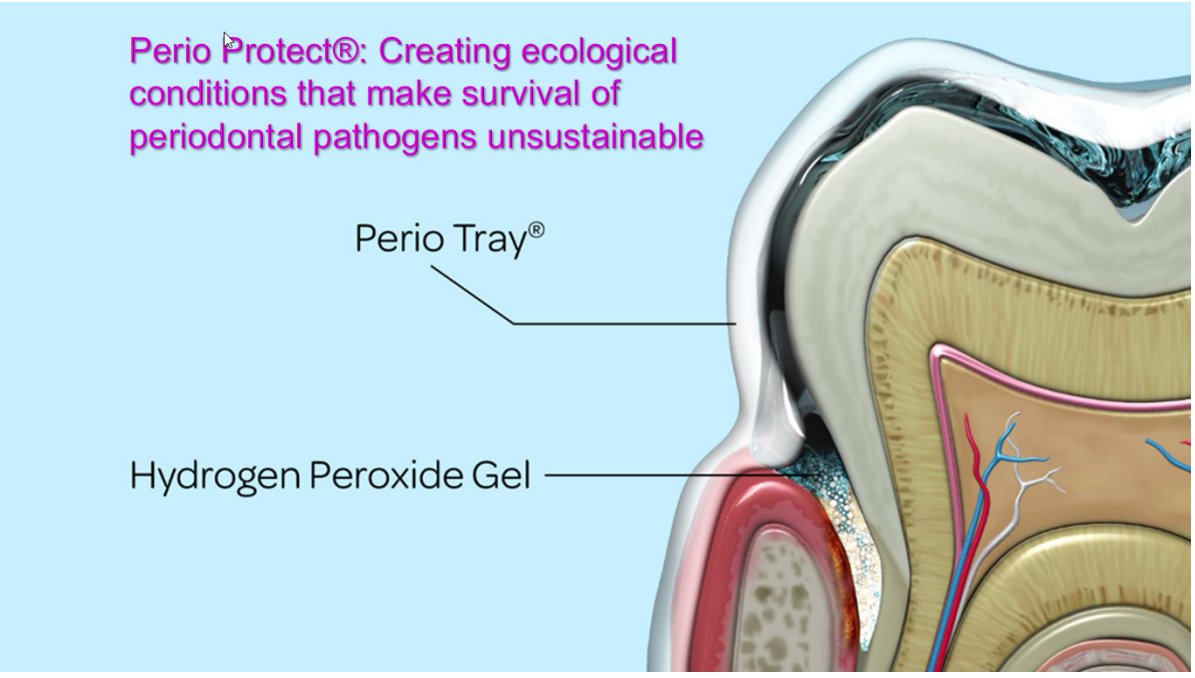


Figure 5—Illustration of dispersion of Perio Gel from a Perio Tray

Periostat, subdose doxycycline, as an adjunct for periodontal therapy is still marketed under this name. An alternative is generic doxycycline, at 20 mg twice a day. Although host modulatory therapy with subdose doxycycline has shown success in stabilizing the periodontium, it is an underutilized treatment option. Periostat (and its generic equivalent) has a robust evidence base that qualifies it as a valuable adjunctive therapy to SRP.

Use of a Custom-Fabricated Tray System With Hydrogen Peroxide Gel

One of the most valuable modalities to preserve homeostasis within the subgingival niche following SRP is an FDA-cleared tray delivery that disperses and sustains optimal levels of hydrogen peroxide in periodontal pockets as deep as 9 mm. Perio Trays** are designed with a patented internal peripheral seal and extension system, which is characterized as a gasket to prevent hydrogen peroxide gel (Perio Gel) from leaking into the mouth. To ensure the medication is delivered to patient-specific sites, the trays are customized.

Perio Gel contains hydrogen peroxide at a concentration of 1.7%. Once activated, the hydrogen peroxide lyses cell walls of pathogenic bacteria, killing the cells, and oxygenating subgingival tissues. This process modifies the substrate within the PP that makes survival of periodontal pathogens unsustainable (Figure 5).

**Perio Protect LLC. St. Louis, MO

As a result, there is an ecological shift in the PP, which paves the way for microbial symbiosis where bacteria associated with periodontal health can colonize, thrive, and repopulate at the expense of periodontal pathogens.

When used daily, the Perio Protect system reduces the potential for disease activity, which is the new therapeutic target for a reduced periodontium. Inflammation is reduced locally to support successful maintenance of periodontal tissue health, diminishing the risk of pathogenic bacteria and viruses breaching the ulcerated epithelium of the PP and entering the vasculature. Downstream, this may mitigate the threat posed by vascularly disseminated periodontal bacteria known to invade organ tissues. With today's concern about bacterial resistance from overprescription of antibiotics, Perio Gel's lack of bacterial resistance is another reason to consider this adjunct in stabilizing the reduced periodontium.[31-35]

Conclusion

As we commit our best efforts to halt the relentless spread of SARS-CoV-2, navigate its economic and social consequences, and wait for an effective vaccine, people in high-risk groups must be protected. OHCPs have a major role to play in safeguarding individuals who may be compromised from untreated or unstable periodontitis, which may predispose them to SARS-CoV-2 infection and/or complications of COVID-19. This is especially important for those who have co-morbid diseases and conditions such as diabetes, cardiovascular disease, chronic obstructive pulmonary disease, and obesity.

Acquiring and analyzing data from patients who have COVID-19 and periodontitis is critical in determining if untreated/unstable periodontitis is among chronic infections that may activate the over-exuberate inflammatory pathways associated with the cytokine storm. If so, intervention of periodontitis may attenuate the severity of COVID-19, which would be a significant breakthrough in the fight against this virus.

Currently being studied is the question about whether SARS-CoV-2 can be reactivated after recovering from the initial infection. Consider this: Testing for COVID-19 has been through nasopharyngeal and oropharyngeal swabs. Could it be that the PP is an unrecognized niche that could harbor SARS-CoV-2, in either active or latent states? Periodontal pockets are not tested in medical settings, but we do know that viruses such as these thrive in the inflammation-rich environment of the subgingival niche. If left untreated, could periodontitis reactivate COVID-19 after recovery from its initial infection? Is this a missing piece in the pandemic?

The possibility that untreated or unstable periodontitis could increase the risk for COVID-19 and/or its complications is not really a reach. We have a professional obligation to figure this out. Following MERS, and then SARS, SARS-CoV-2 is the third coronavirus that has led to an epidemic in the 21st century, and there is little doubt that other lethal viral assaults are on the way. Treatment for chronic infections such as periodontitis may be preemptive strategy for mitigating the risk for infection of future viruses like SARS-CoV-2.

The notion that periodontitis is an infection limited to the oral cavity without systemic consequences precludes us from assuming the responsibility (and accountability) we must take for the overall health of our patients. Almost 20 years

ago, in another publication, I wrote, "The science indicates that as individual clinicians, we have the potential to profoundly change the course of serious inflammatory diseases." Never could I have imagined a time when this statement would be even more relevant.

Comments Are Welcome

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