Antibiotics vs Peroxide in a Post-Antibiotic Age

The Centers for Disease Control and Prevention (CDC) published a report at the end of 2019 that has been overshadowed by COVID-19. *Antibiotic Resistance Threats in the United States 2019* is a wake-up call to health care providers. In the introduction, the CDC Director implores us to "**Stop referring to a coming post-antibiotic era—**it's already here. You and I are living in a time when some miracle drugs no longer perform miracles and families are being ripped apart by a microscopic enemy."[1] And the report gives some startling statistics including that antibiotic resistant bacteria infect someone in the US every 11 seconds and kill someone every 15 minutes. That's nearly three million people infected each year with 35,000 annual deaths.

The problem is not going to be resolved soon. The biggest concern for public health experts is the rising resistant bacterial and fungal infections (the report does not include viral or parasitic infections) that are active in the community putting more people at risk and making it harder to identify and contain the threats. And those threats can be tricky to locate and isolate when the sources can spread through wastewater, food, contact with animals, and the environment.[2]

Treating the infections can be equally challenging. Take *Clostridium difficile* (*C diff*) infections as an example. This inflammation of the colon that causes diarrhea and colitis affects almost half a million people a year in the US.[3] The bacteria releasing the exotoxins that cause tissue damage colonize the gastrointestinal tract after the normal gut flora are altered, typically after antibiotic use. A lab test can confirm the infection, but there are few options to treat it, except for powerful antibiotics. The problem is that many patients contract *C diff* after taking antibiotics and the subsequent antibiotics they take to combat *C diff* are not particularly effective. 1 in 6 patients who get *C diff* will get it again in the next two months. For patients with healthcare-associated *C diff* infections who are over 65 years of age, 1 in 11 will die within a month of diagnosis.[4]

Because "poor antibiotic prescribing practices put patients at risk for *C. diff* infections,"[5] and because the general overuse and overreliance on antibiotics have led to significantly greater antibiotic resistant threats, prescribing practices are at the heart of the CDC antibiotic stewardship campaigns. In hospital settings, CDC estimates that 30-50% of antibiotics are unnecessarily or incorrectly prescribed. Fluent et al. identified similar numbers in dentistry.[6] It's important that dentistry take antibiotic resistance threats seriously since general and specialty dentists are the third-highest prescribers of antibiotics in all outpatient settings in the US.[7]

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[1] CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

[2] https://www.cdc.gov/drugresistance/about.html

[3] The 500,000 statistic was reviewed by CDC in March 2020 and is a significant increase over numbers cited just 10 years earlier when C diff infections were documented to affect 300,000 people in the US. Compare the numbers in https://www.cdc.gov/cdiff/what-is.html vs Yoo J, Lightner AL. Clostridium difficile Infections: What Every Clinician Should Know. *Perm J*. 2010;14(2):35-40.

[4] https://www.cdc.gov/cdiff/what-is.html. In 2017, 233,900 were hospitalized for C diff infections, and at least 12,800 people from those infections. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019, vii.

[5] https://www.cdc.gov/cdiff/clinicians/index.html

[6] Fluent MT, Jacobsen PL, Hicks LA; OSAP, the Safest Dental Visit. Considerations for responsible antibiotic use in dentistry. *J Am Dent Assoc*. 2016;147(8):683-686. Palmer NO, Woodward J.

[7] https://www.ada.org/en/publications/ada-news/2019-archive/october/new-ada-guideline-advises-against-prescribing-antibiotics-for-most-dental-pain-swelling.

The American Dental Association released a new guideline for antibiotic use at the end of 2019, advising against antibiotic use for most pulpal and periapical conditions and recommending instead only the use of dental treatment with acetaminophen or ibuprofen when needed. According to the new guideline, ***systemic antibiotics are warranted for these treatments only when the patient shows signs or symptoms of systemic infection such as fever or swollen lymph nodes***.[8]

This key remark in the guidelines bears emphasis since COVID-19 has overshadowed healthcare this year: "The use of antibiotics may result in little to no difference in beneficial outcomes (very low certainty) but likely result in a potentially large increase in harm outcomes (moderate certainty), warranting a strong recommendation against their use."[9] Put more succinctly: "Evidence suggests that antibiotics for the target conditions may provide negligible benefits and probably contribute to large harms. The expert panel suggests that antibiotics for target conditions be used only when systemic involvement is present and that immediate DCDT (definitive, conservative dental treatment) should be prioritized in all cases."

The harm message may need more attention to better filter down to wet-gloved dentists. The Minnesota Department of Public Health tracked 2176 *C diff* infections (CDIs) from 2009-2015 in 5 Minnesota counties. 1626 cases (75%) were confirmed, of which 57% were prescribed antibiotics prior to the CDI. 15% or 136 of these antibiotic prescriptions were written by dentists. The median age of dental patients was 57 years old and the most frequently prescribed drug was clindamycin. The authors conclude that "Dental antibiotic prescribing rates are likely underestimated. ***Stewardship programs should address dental prescribing and alert dentists to CDI subsequent to antibiotics prescribed for dental procedures."***[10]

In dentistry, many bacterial-based diseases result from biofilm induced inflammation. Gum disease, the most prevalent and still most underdiagnosed dental disease, is a classic example. Periodontitis, like other biofilm-based diseases, is "refractory to antibiotic agents and host defenses because the causative microbes live in complex communities that persist despite challenges that range from targeted antibiotic agents to phagocytosis."[11] It's not just that the bacteria have built up resistances to the drugs, but that the biofilm community itself actively resists antibiotics. Researchers suggest that "The regular delivery of nontargeted antibiofilm agents may be an effective strategy for treating biofilms, especially if these agents include oxidative agents that dissolve the biofilm matrix."[12]

And oxidative agents work well. The delivery of hydrogen peroxide effectively reduces bleeding, inflammation, pocket depths, and gram-negative bacterial loads when administered by prescription trays. [13]

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[8] https://jada.ada.org/article/S0002-8177(19)30617-8/fulltext?dgcid=PromoSpots_EBDsite_ABX

[9] Lockhart P et al. Evidence-based clinical practice guideline on antibiotic use for the urgen management of pulpal- and periapical-related dentalpain and intraoral swelling. A report from the American Dental Association. JADA 2019:150(11):906-921https://doi.org/10.1016/j.adaj.2019.08.020

[10] Bye M, Whitten T, Holzbauer S. Antibiotic Prescribing for Dental Procedures in Community-Associated *Clostridium difficile* cases, Minnesota, 2009–2015. *Open Forum Infect Dis*. 2017;4(Suppl 1):S1. Published 2017 Oct 4.

[11] Schaudinn C, Gorur A, Keller D, Sedghizadeh PP, Costerton JW. Periodontitis: an archetypical biofilm disease. *J Am Dent Assoc*. 2009;140(8):978-986.

[12] *Ibid*.

[13] Periogel® with 1.7% hydrogen peroxide and Perio Trays®, Perio Protect LLC, St. Louis, MO, USA. Putt MS, Mallatt ME, Messmann LL, Proskin HM. A 6-month clinical investigation of custom tray application of peroxide gel with or without doxycycline as adjuncts to scaling and root planing for treatment of periodontitis. *Am J Dent*. 2014;27(5):273-284. Putt MS, Proskin HM. Custom tray

While chlorine-based products and essential oils have shown efficacy,[14] the benefit of the tray delivery over rinse application is that the prescription tray can place and hold medication deep into the sulcus or periodontal pocket so that the medication can fight the infections deep below the gums where rinses cannot access. The benefit of hydrogen peroxide use is lost without the patented seal of the Perio Trays that allow oxygen to be retained below the gums to fight infection, particularly when biofilms are present, as well as anaerobic organisms.[15]

Low concentrations of hydrogen peroxide (e.g. Periogel® with 1.7% hydrogen peroxide) is particularly effective because it is a broad-spectrum antimicrobial, physically disrupting the biofilm matrix that protects biofilm communities, and because bacteria do not build up resistance to peroxide as they do to antibiotics. Bacteria can, however, develop resistance to hydrogen peroxide through increased production of degradative enzymes such as catalase. For anaerobic organisms, this would result in increased production of oxygen, which is deadly to anaerobes. Peroxide does more than just kill bacteria. Its release of oxygen – as it activates, peroxide turns into $O_2 + H_2O$ – changes the microenvironment of the periodontal pocket so that healthy bacterial species replace pathogenic ones.[16]

Let's be honest with patients and stop blaming them: more brushing and flossing is unlikely to help manage their disease better. Brushing, flossing (and rinsing) just can't get deep enough. Patients of course need to brush and floss, but, even when they do these acts well, these tools are insufficient to manage periodontitis or advanced gingivitis. Improving homecare is essential.

There are times when everything advocated – initial treatment, surgery, maintenance, homecare – fails, but we can do better and patients deserve better. Periodontal disease is one of the most under-diagnosed diseases in North America. It is always easier to address disease at the earliest stages. And it's always easier to maintain gingival health with effective homecare. Adding prescription tray delivery of hydrogen peroxide in an excellent choice in the post-antibiotic age.

Author Tanya Dunlap, PhD is the Managing Director of Perio Protect LLC. You can contact her via email tdunlap@perio-protect.com or call 314-256-0772.

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application of peroxide gel as an adjunct to scaling and root planing in the treatment of periodontitis: a randomized, controlled three-month clinical trial. *J Clin Dent*. 2012;23(2):48-56. Putt MS, Proskin HM. Custom tray application of peroxide gel as an adjunct to scaling and root planing in the treatment of periodontitis: results of a randomized controlled trial after six months. *J Clin Dent*. 2013;24(3):100-107. Cochrane RB, Sindelar B. Case Series Report of 66 Refractory Maintenance Patients Evaluating the Effectiveness of Topical Oxidizing Agents. *J Clin Dent*. 2015;26(4):109-114. Keller DC and Cochrane B. Composition of Microorganisms in Periodontal Pockets. JOHD 2019:2(2):123-36.

[14] Krayer JW, Leite RS, Kirkwood KL. Non-surgical chemotherapeutic treatment strategies for the management of periodontal diseases. *Dent Clin North Am*. 2010;54(1):13-33. Charles CH, Mostler KM, Bartels LL, Mankodi SM. Comparative antiplaque and antigingivitis effectiveness of a chlorhexidine and an essential oil mouthrinse: 6-month clinical trial. *J Clin Periodontol*. 2004;31(10):878-884.

[15] Dunlap T, Keller DC, Marshall MV, et al. Subgingival delivery of oral debriding agents: a proof of concept. *J Clin Dent*. 2011;22(5):149-15. Keller DC and Cochrane B. Composition of Microorganisms in Periodontal Pockets. JOHD 2019:2(2):123-36.

[16] *Ibid*. For more information on the chemistry and safety of hydrogen peroxide, see Marshall MV, Cancro LP, Fischman SL. Hydrogen Peroxide: A Review of Its Use in Dentistry. J Periodontol. 1995 Sept;66(9):786-96.