



Oral Care in A Post-Antibiotic Age: Problems and Treatment Options

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Abstract

Antibiotic overuse has created a problem with increased antibiotic resistance of disease-causing microorganisms. Prophylactic antibiotic usage in dentistry has contributed to this problem and to adverse events like *Clostridioides difficile* infection. Antibiotic prescribing practices need review, and so do treatment options for patient care in the post-antibiotic age. Hydrogen peroxide is an example of an antimicrobial that can treat anaerobic organisms and those found in biofilms to reduce periodontal disease and improve general health. The development and use of non-antibiotic, broad-spectrum antimicrobial and anti-inflammatory agents and narrowly targeted antibiotic prescription usage will improve dentistry.

Keywords: Antibiotic resistance; *Clostridioides difficile* infection; Periodontitis; Hydrogen peroxide; Prescription tray therapy

Abbreviations: Centers for Disease Control and Prevention (CDC); *Clostridioides difficile* (C. diff) *Clostridioides difficile* infection (CDI)

Introduction

As the first signs of COVID-19 infections were breaking out in late 2019, the Centers for Disease Control and Prevention (CDC) published a report on *Antibiotic Resistance Threats in the United States*. It was a clear warning that the post-antibiotic age had arrived and that we needed to pay greater attention to the overuse of antibiotics and to rising resistant bacterial and fungal infections [1]. The consequences of inaction were clear: more people will be infected with antibiotic resistance microbes and more people will die as a result of these infections.

This report built on the antibiotic stewardship movement dating to the 2014 publication of the *National Strategy for Combating*

Antibiotic Resistance. Significant progress has been made in raising general awareness of the health threats and challenges facing us, but prescribing practices are hard to change. In the decade before the COVID-19 pandemic, there were no observed declines in antibiotic use [2]. A more recent report examining outpatient visits in 2020-2021 for COVID-19 indicates that antibiotics were prescribed for 30% of patients in the investigation, even though these drugs-azithromycin, doxycycline, amoxicillin, and levofloxacin-are not known to have effect for viral patterns of symptoms [3]. Researchers warn that the overuse of these drugs will make treatment for other diseases ineffective. A case in point includes treatment for syphilis. *Treponema pallidum*, the causative pathogen of syphilis, is now notably resistant to azithromycin [4].

In addition to the increasing ineffectiveness of antibiotics, there are also the adverse consequences of taking antibiotics. Up to twenty percent of visits to Emergency Rooms in the United States are due to adverse events after taking antibiotics [5]. These events can be very difficult to resolve. Take *Clostridioides difficile* (C. diff) infections (CDI) as an example. This inflammation of the colon that causes diarrhea and colitis affects almost half a million people a year in the US [6]. 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 good options to treat it. Fecal microbiota transplants show promising results, but they are reserved for patients with repeat outbreaks [7]. The first course of treatment is typically antibiotics, but many patients contract CDI after taking antibiotics and the subsequent antibiotics they take to combat CDI are not particularly effective. 1 in 6 patients who get CDI will get it again in the next two months. For patients with healthcare-associated CDI who are over 65 years of age, 1 in 11 will die within a month of diagnosis [8].

Discussion

It's important that dentistry take antibiotic resistance threats and adverse events seriously since general and specialty dentists are the third-highest prescribers of antibiotics in all outpatient settings in the US [9]. In 2019, a study published in *JAMA Network Open* "found that antibiotic prophylaxis was prescribed in more than 168,000 dental visits from 2011 to 2015. In 90% of these visits, a procedure was performed that would require antibiotic prophylaxis only for cardiac patients considered at high risk for secondary infections," calculating that over 80% of these prescriptions are unnecessary [10].

Dentists are the number one prescribers of clindamycin in all outpatient settings (amoxicillin is the most frequently prescribed antibiotic by dentists), which is noteworthy "because clindamycin is associated with the highest risk of *Clostridioides difficile* infection" and "clindamycin was more likely to be unnecessarily prescribed compared to amoxicillin (OR, 1.10; 95% [CI], 1.05 to 1.15) [11]". Dental prescriptions for clindamycin have been directly linked to CDIs in patients, although deaths were not reported [12].

The American Dental Association released guidelines 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 guidelines, **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** [13].

This key remark in the guidelines bears emphasis since COVID-19 overshadowed healthcare: "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" [14]. 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" [15].

The American Academy of Orthopaedic Surgeons and the American Heart Association also revised their guidelines to narrow the use of oral antibiotics before dental procedures, in 2013 and 2007 respectively, but there is still no comprehensive antimicrobial stewardship program in dentistry. Individual practitioners are left responsible for keeping up to date on the changing recommendations.

Clearly antibiotic prescribing practices need review, and so do treatment choices so that wet-gloved clinicians have more antimicrobial options for patient care in the post-antibiotic age [16]. In dentistry, many bacterial-based diseases result from biofilm-induced inflammation. Periodontitis, the most prevalent and still most underdiagnosed dental disease, is a classic example. Like other biofilm-based diseases, periodontitis is "refractory to antibiotic agents and host defenses" [17]. It's not just that the bacteria have built up resistances to various drugs, but the biofilm community itself actively resists antibiotics, preventing them from penetrating the biofilm. 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" [18].

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 with an internal peripheral seal [19]. Low concentrations of hydrogen peroxide (e.g. Perio Gel™ 1.7% hydrogen peroxide) is particularly effective because it is a broad-spectrum antimicrobial that physically disrupts the biofilm matrix that protects biofilm communities, and because bacteria do not build up resistance to peroxide as they do to antibiotics. Peroxide does more than just kill bacteria. Its release of oxygen-as it degrades, peroxide turns into O_2+H_2O -changes the microenvironment of the periodontal pocket so that healthy bacterial species replace pathogenic ones [20].

The topical application and increased pressurization of oxygen deep into the sulcus or periodontal pocket as a result of sealed prescription tray delivery of hydrogen peroxide [21] is key to long-term health and healing. This approach follows new concepts in managing chronic wounds, like those underlying periodontal

disease. Guidelines from American Medical Association through the Wound Healing Society encourage the use of topical antimicrobial medications, hyperbaric oxygen and adjunctive medications to manage the cause of disease, followed by wound bed preparation such as debridement or surgery along with wound dressings and compression mechanics. The final step is prevention through long-term management [22].

It is always easier to address infection and disease at the earliest stages, and it's always easier to maintain gingival health with effective homecare. Brushing, flossing (and rinsing) just can't get deep enough. Patients of course need to brush and floss, but, even when used regularly and well, these tools are insufficient to manage periodontitis or advanced gingivitis, as is evident in the high rates of periodontal disease. Improving periodontal health will also provide protection from other diseases such as cardiovascular disease and diabetes [23]. Adding prescription tray delivery of the antimicrobial hydrogen peroxide is an excellent choice in the post-antibiotic age. Hydrogen peroxide is already part of the body's own defense mechanism, and tray delivery would provide local protection at the main area of interest that can also affect systemic health.

Conclusion

The development and use of non-antibiotic, broad-spectrum antimicrobial, and anti-inflammatory agents and narrowly targeted antibiotic prescription usage will improve dentistry. The first step is to raise awareness, and the harder step is to sustain attention to treatment choices.

Acknowledgment

None.

Conflict of Interest

Tanya Dunlap, PhD is the Managing Director of Perio Protect LLC. Duane C. Keller DMD is the Chief Scientific Officer of Perio Protect, LLC. Milton Marshall is a consultant for Perio Protect, LLC.

References

1. CDC (2019) Antibiotic Resistance Threats in the United States. Atlanta, GA: U.S. Department of Health and Human Services. See also <https://www.cdc.gov/drugresistance/about.html>
2. Petersen MR, Cosgrove SE, Quinn TC, Patel EU, Kate Grabowski M, et al. (2021) Prescription Antibiotic Use Among the US population 1999-2018: National Health and Nutrition Examination Surveys. *Open Forum Infect Dis* 13; 8(7): ofab224.
3. Tsay SV, Bartoces M, Gouin K, Kabbani S, Hicks LA (2022) Antibiotic prescriptions associated with COVID-19 outpatient visits among Medicare beneficiaries, April 2020 to April 2021. *JAMA* 327(20): 2018-2019.
4. Kow CS, Hasan SS (2020) Use of Azithromycin in COVID-19: A Cautionary Tale. *Clinical Drug Investigation* 40: 989-990. Bacteria develop a resistance to antibiotics through a variety of means, such as horizontal gene sharing, bacterial transformation, transduction, and conjugation. Quorum sensing along with bacterial intra-cellular and inter-cellular communications enable an increase in resistance to antibiotics, as well as the ability of some bacteria to invade host cells, thus protecting them from extracellular antibiotics or antimicrobials. The human immune system cannot keep up with microbial changes as microbes reproduce faster than human cells and are more adaptive to changing environments.
5. Fluent MT, Jacobsen PL, Hicks LA, OSAP, the Safest Dental Visit (2016) Considerations for responsible antibiotic use in dentistry. *J Am Dent Assoc* 147(8): 683-686.
6. 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 (2010) Clostridioides difficile Infections: What Every Clinician Should Know. *Perm J* 14(2): 35-40.
7. <https://www.cdc.gov/cdiff/pdf/Cdiff-progression-H.pdf>
8. <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 died. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019, vii.
9. <https://www.ada.org/en/publications/ada-news/2019-archive/october/new-ada-guideline-advises-against-prescribing-antibiotics-for-most-dental-pain-swelling>.
10. <https://www.cidrap.umn.edu/news-perspective/2019/05/study-finds-81-dental-antibiotic-prescribing-not-needed>
11. <https://www.cidrap.umn.edu/news-perspective/2019/05/study-finds-81-dental-antibiotic-prescribing-not-needed>.
12. 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." Bye M, Whitten T, Holzbauer S (2017) Antibiotic Prescribing for Dental Procedures in Community-Associated Clostridium difficile cases, Minnesota, 2009-2015. *Open Forum Infect Dis* 4(Suppl 1): S1.
13. [https://jada.ada.org/article/S0002-8177\(19\)30617-8/fulltext?dgcid=PromoSpots_EBDsite_ABX](https://jada.ada.org/article/S0002-8177(19)30617-8/fulltext?dgcid=PromoSpots_EBDsite_ABX)
14. Lockhart P (2019) Evidence-based clinical practice guideline on antibiotic use for the urgent management of pulpal- and periapical-related dental pain and intraoral swelling. *J Am Dent Assoc* 150(11): 906-921.
15. Ibid, 906.
16. These agents include hydrogen peroxide (e.g. Perio Protect), essential oils (e.g. PerioSciences), molecular iodine (e.g. Iotech), hypochlorous acid (GabrielScience), and other chlorine-based products. Lipoxins and resolvins (e.g. Forsyth Institute) to help resolve inflammation are promising and under investigation.
17. Schaudinn C, Gorur A, Keller D, Sedghizadeh PP, Costerton JW (2009) Periodontitis: an archetypical biofilm disease. *J Am Dent Assoc* 140(8): 978-986.
18. Ibid.
19. Perio Gel™ 1.7% hydrogen peroxide via Perio Tray™ delivery, Perio Protect LLC, St. Louis, MO, USA. Peroxide needs time to work. The optimal treatment time with Perio Tray™ delivery is 15-minute

- applications. Putt MS, Mallatt ME, Messmann LL, Proskin HM (2014) 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* 27(5): 273-284. Putt MS, Proskin HM (2012) Custom tray 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* 23(2): 48-56. Putt MS, Proskin HM (2013) 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* 24(3): 100-107. Cochrane RB, Sindelar B (2015) Case Series Report of 66 Refractory Maintenance Patients Evaluating the Effectiveness of Topical Oxidizing Agents. *J Clin Dent* 26(4): 109-114. Keller DC and Cochrane B (2019) Composition of Microorganisms in Periodontal Pockets. *JOHD* 2(2): 123-136.
20. Ibid (1995) 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* 66(9): 786-796.
 21. Dunlap T, Keller DC, Marshall MV, Costerton JW, Schaudinn C, et al. (2011) Subgingival delivery of oral debriding agents: a proof of concept. *J Clin Dent* 22(5): 149-158.
 22. Condensed from: A Barbul (2006) Clinical Treatment Guidelines, *Wound Rep Reg*. 14: 645-711.
 23. Hansen PR, Holmstrup P (2022) Cardiovascular Diseases and Periodontitis. *Adv Exp Med Biol* 1373: 261-280. Preshaw PM, Alba AL,