What every dentist should know about antibiotic-resistant bacteria

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The emergence of antibiotic-resistant bacteria has complicated patient treatment and yielded poorer outcomes. This article provides an overview for dental professionals of the challenges posed by resistant microbial strains and the research efforts to overcome this significant obstacle.

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One of the greatest scientific discoveries of modern times, antibiotics are central to an intricate dilemma in healthcare. Some bacterial infections are no longer amenable to the usual medication protocol due to developed resistance. The US Centers for Disease Control and Prevention (CDC) estimated that, every year, more than 2 million people in the United States contract antibiotic-resistant infections and at least 23,000 affected persons die.[1] The World Health Organization (WHO) noted the obstacles posed by bacterial resistance on treatment of common infections, potentially leading to increased costs and delays in resolution.[2] Moreover, the WHO noted several "medical advances in recent years, such as chemotherapy for cancer treatment and organ transplantation, are dependent on the availability of anti-infective drugs."[2]

Microbiologic and evolutionary factors are key to the development of resistance traits in bacteria. The exposure of a bacterial population to an antibiotic yields the potential for the survival and propagation of genetically resistant bacteria. Thus, antibiotics are both the solution and the problem in treating bacterial infections.

The ongoing use of antibacterial agents in medicine, dentistry, and hygiene has contributed to a surge in antibiotic-resistant bacteria with dangerous consequences. For instance, some *Staphylococcus aureus* strains have become penicillin-resistant via enzymatic destruction of penicillin; *S aureus* infection can be associated with endocarditis, necrotizing fasciitis, and septicemia. Some resistant subtypes of *S aureus* include methicillin-resistant *S aureus* (MRSA) and vancomycin-resistant *S aureus* (VRSA). Previous studies implicated *S aureus* with oral infections around dental prosthetic implants, and MRSA has been detected in the oropharynx.[3,4] *S aureus* has been isolated from within the pharynx and the nares.[5] A Swiss study of 500 patients in a dental school practice found that 42% of patients had *S aureus* in locations such as the nose and/or pharynx; moreover, 2 samples were identified as MRSA.[6]

In a WHO statement, *S aureus* was classified as a priority 2 resistant bacterium.[7] The WHO determined that *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and Enterobacteriaceae are currently of the highest concern for low susceptibility to chemotherapeutics and are highly resistant to the β-lactam antibiotic carbapenem.[7]

Management of recalcitrant *S aureus* infections relies on laboratory methods to determine if the bacterial resistance is to a specific antibiotic. The polymerase chain reaction technique can be used to evaluate *Staphylococcus* samples for genetic evidence of targets such as *mecA*, *qac*, and *mupB*, which confer resistance.[8] This analytical tool can designate a specimen as resistant to antimicrobial substances such as methicillin, mupirocin, quaternary ammonium compounds, and chlorhexidine with excellent specificity and sensitivity.[8] In dentistry, polymerase chain reaction has been adapted to screen endodontic infections

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for resistant bacteria with genes such as bla_{TEM-1}, which confers penicillin resistance.[9]

The application of antibacterial technology and products to food production has also contributed to the rapid expansion of resistant bacteria. Overabundant antibiotic administration to ensure the healthy growth of livestock can risk indiscriminant destruction of bacteria and favors the development of resistant bacteria in human food and animal waste. In addition, the food given to livestock can be adulterated by bacteria and resistant bacteria.[10] Horizontal gene transfer between resistant strains enables multidrug resistance and, on human exposure, can promote additional challenges to antibiotic therapy. The CDC reports that "… more than 400,000 Americans get sick every year from infections caused by antibiotic-resistant foodborne bacteria."[11] In addition, the CDC estimates that "one in five resistant infections are caused by germs, such as *Salmonella* and *Campylobacter*, from food and animals."[11]

Prescriptions for dental conditions

Moderate- to high-risk fascial space infections can necessitate prescription of an antibiotic for management. Approximately 25 million, or 1 in 10, outpatient antibiotic prescriptions, mostly β-lactam penicillins, were provided to patients by dentists for oral healthcare in 2013.[12] The medical literature provides recommendations for prescribing antibiotics in the treatment of medically compromised patients. A 2015 clinical practice guideline from the American Dental Association Council on Scientific Affairs states that the uniform practice of providing prophylactic antimicrobial drugs to patients with a prosthetic joint implant is contraindicated; however, the guideline indicates that there can be situations in which antimicrobial prophylaxis is medically necessary, as deemed by the practitioner's clinical judgment.[13] The American College of Cardiology and American Heart Association jointly provided clinical guidelines for dentists treating patients with various cardiac disorders.[14] Antimicrobial prophylaxis in conjunction with dental therapy that will "involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa" may be considered valid for patients with prosthetic heart valves, certain patients with congenital heart disease, patients with a history of infective endocarditis, and heart transplant patients with regurgitation associated with valve malformation.[14]

Dentists are not the only healthcare professionals to prescribe antibiotics for dental conditions. In hospitals and urgent care facilities, physicians encounter patients seeking care for acute odontogenic pain and dental infections. Cohen et al reported that almost 30% of 272 survey participants who previously had tooth pain sought help from physicians or emergency department personnel.[15] These healthcare professionals often prescribe antibiotics and analgesics and instruct the patient to later seek the care of a dentist. A 1997-2007 National Hospital Ambulatory Medical Care survey disclosed that, in departments of emergency medicine, approximately half of all patients with nontraumatic dental conditions were given antibiotics.[16]

Another study noted differences in prescribing patterns between dentists and physicians.[17] The authors found that approximately 2 of 3 patients at medical offices were prescribed antibiotic therapy unlike at dental care settings.[17] In contrast, dentists prescribed 15%-40% fewer antibiotics—particularly broad-spectrum antibiotics—than physicians and were found to rely on other methods to address the chief complaints of the patient.[17]

Propagation of resistant bacteria

Antibiotic usage in food production has been shown to promote the growth of resistant bacteria. Antibiotics chemically similar to β-lactams, macrolides, and aminoglycosides have been administered to livestock for various food production reasons.[18] As a result, humans can consume foods contaminated with resistant bacteria and develop resistant infections. In the aquaculture industry (raising aquatic organisms for seafood), for example, antimicrobials are sometimes administered. Ryu et al detected *Escherichia coli* in approximately 7% of samples of South Korean retail and commercial seafood, demonstrating variable antimicrobial resistance in the presence of drugs such as ampicillin, tetracycline, and streptomycin.[19]

The influences of antibiotics are also present in animals raised for human consumption, such as cattle, pigs, and poultry. Since 1996, the US Department of Agriculture, the US Food and Drug Administration (FDA), and the CDC, along with other public health departments, have been working together under the National Antimicrobial Resistance Monitoring System to detect, evaluate, and publicize findings regarding foodborne-resistant bacteria.[1] The CDC strongly recommends against indiscriminant antimicrobial administration during food production because it could promote resistant bacterial infections and later zoonotic infections in humans.[1] Additionally, the WHO indicated that antibiotics used to treat humans generally should not have a secondary use in consumed animals.[2]

Another process that promotes antibiotic resistance is the use of antibacterial hygiene products. Specifically, triclosan, an additive in some soap and dentifrices, is included to induce either bactericidal or bacteriostatic effects against gram-negative or gram-positive bacteria.[20] Triclosan suppresses populations of *Porphyromonas gingivalis*, a key member of the red complex bacterial group.[21] In 2016, the FDA reviewed research on triclosan and determined that it may augment bacterial resistance.[22] Although triclosan products were registered by the US Environmental Protection Agency in 1969 and have been legally available for many years, the FDA concluded that not enough is known about the safety of triclosan.[22] One study indicated that a certain enoyl-ACP reductase protein potentiated resistance of *P aeruginosa* to triclosan.[23] More research is necessary to determine whether triclosan increases the risks of skin cancer and hormone interactions.[22]

Sewage management is another factor in the rise of antibiotic bacterial resistance. Some medications lightly processed by the human body are excreted into wastewater and eventually discharged after sewage management into the aquatic environment; the aquatic presence of more than 80 pharmaceutically active compounds has been confirmed in US and European investigations.[24] Antibiotics were also detected in all of the polluted water samples obtained near sewage treatment centers and medication production factories in the area around

Hyderabad, India, and the Musi River.[25] Enterobacteriaceae that were capable of destroying β-lactam drugs were discovered in the majority of these samples.[25]

Innovative antimicrobial technologies

Silver nanoparticles

Silver nanoparticle technology is an application that can disrupt and destroy several resistant and multidrug-resistant bacteria, such as MRSA and VRSA.[26] Silver particles eliminate bacteria by altering key cell structures, including the nuclear membrane and cell wall, through protein interactions.[26] In an investigation into improving dental adhesives, silver nanoparticles were incorporated and demonstrated the ability to mitigate cariogenic mutans streptococci populations, biofilm activity, and lactic acid release.[27] Thus, silver nanoparticle dental materials could reduce the incidence of secondary caries that would, without treatment, lead to destruction of tooth structure, pulpal necrosis, soft tissue infection, and a possible need for antimicrobial chemotherapeutics.

Despite this potential, there are ongoing concerns about silver toxicity. Humans absorb 18% of orally administered silver, leading to silver deposition in the intestine, skin (argyria), and stomach.[28] Animal studies have demonstrated dose-dependent reactions in the liver and immune system as well as weight loss and death.[28]

Functionalized dental implants

The modification of dental implant surfaces has led to a reduction of resistant bacterial proliferation. Lee et al evaluated the interaction between dental implants composed of non-thermal atmospheric pressure plasma jet functionalized titanium and titanium alloy and bacteria.[29] This innovative enhancement suppressed *Streptococcus sanguinis* adhesion to the implant through increased hydrophilicity and carbon cleaning.[29] Efforts that disrupt the attachment of bacteria to the implant surface could reduce the number of prescriptions for antimicrobials written by dental providers and, consequently, the development of resistant bacterial populations.

Ultrasound microbubbles

A biofilm is a complex bacterial ecosystem capable of achieving resistance to antimicrobial treatment. Dong et al reported that bactericidal ultrasound microbubbles generated pores in *Staphylococcus epidermidis* biofilms and that vancomycin could use these pores to access bacterial targets.[30] Furthermore, ultrasound microbubbles were found to be capable of modifying the genetic activity of *S epidermidis*, thus diminishing biofilm origination and augmenting neutrophil chemotaxis that degrades the bacteria.[31]

Quaternary ammonium

There are ongoing advances in antibiotic therapy to resolve resistant bacterial infections. Recently, the addition of a quaternary ammonium salt to a vancomycin analog yielded increased efficacy and potency against vancomycin-resistant enterococci through the obstruction of cell wall production and heightened cell wall penetrability.[32] The bacteria used in the study are normally resistant to many antibiotic types and are among the most resistant strains to the vancomycin D-Ala-D-Ala binding target.[32] The resistant bacteria also displayed relatively little or no increase in minimum inhibitory concentration when challenged with vancomycin counterparts that had more than 1 mechanism of action, signifying that antibiotics with multiple mechanisms of action could potentially achieve greater antimicrobial bioactivity.[32]

Conclusion

When treating bacterial infections, healthcare providers must consider the multitude of factors that favor antibiotic resistance. Dentists and physicians should only prescribe antibiotics when absolutely necessary. Healthcare providers should advise their patients about the risks of self-medication and stress the importance of completing a recommended antibiotic course. Furthermore, dental professionals should be aware of evolving technologies that have the potential to reduce the burden of antibiotic resistance, including silver nanoparticle science, functionalized dental implants, ultrasound microbubble techniques, and alternative (eg, triclosan-free) products for hygiene.

Addendum

Following the acceptance of this article for publication, the FDA in December 2017 issued a final rule regarding 24 biologically active ingredients, including triclosan, an over-the-counter antiseptic; triclosan was deemed not generally recognized as safe and effective due to insufficient data provided.[33] As a result, effective December 20, 2018, manufacturers cannot add triclosan or these other active ingredients to antiseptic products without premarket review.[33]

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