Review Article

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Oral Bacterial Resistance to Antibiotics Used in Dentistry

Vaishali Jamdade[1*] Anshuman Jamdade[2] Nilesh Pardhe[3] Shashank Gupta[4] Satyapal Yadav[5] Neeraj Yadav[6]

[1]Senior Lecturer, Department of Oral and Maxillofacial Surgery, Mahatma Gandhi Dental College and Hospital, Jaipur, Rajasthan, India.
[2]Professor and Head, Department of Oral Medicine and Radiology, Mahatma Gandhi Dental College and Hospital, Jaipur, Rajasthan, India.
[3]Ex Professor and Head, Department of Oral and Maxillofacial Pathology, Mahatma Gandhi Dental College and Hospital, Jaipur, Rajasthan, India.
[4]Senior Lecturer, Department of Oral Medicine and Radiology, Mahatma Gandhi Dental College and Hospital, Jaipur, Rajasthan, India.
[5]Reader, Department of Oral Medicine and Radiology, Mahatma Gandhi Dental College and Hospital, Jaipur, Rajasthan, India.
[6]Reader, Department of Oral Medicine and Radiology, Mahatma Gandhi Dental College and Hospital, Jaipur, Rajasthan, India.

ABSTRACT

Background: Antibiotics marked the turning point in modern human medicine. Before them, infections had a much higher mortality rate. But indiscriminate use of antibiotics caused increased bacterial resistance and oral dysbiosis. Oral microbiome represents an ecological niche for a wide number of bacteria. The colonization of anaerobes is responsible for a large number of oral infections. However, multiple local as well as systemic factors also plays an important role in the bacterial resistance.

Keywords: Antibiotics, Bacterial, Resistance, Oral, Dentistry.

INTRODUCTION

Introduction of antibiotics changed everything, and mortality rates dropped tremendously. Rapid technological advancement allowed the discovery of other types of antibiotics and, with them, came the era of overuse and over prescription. Bacteria possess the ability to adapt to its environment, much like we can. They possess the so-called 'resistance genes' ('r' genes), which are transcripted into different antimicrobial resistance mechanisms. Scientists discovered something far worse: not only this resistance appeared quickly and simultaneously, *but it also had the capability to share its defense mechanisms to other sensitive strains*.[1] It's interesting to note that penicillinase (a type of β-lactamase) was discovered *before penicillin was mass marketed across the world*.[2] The purpose of this paper is to find out the efficacy of different antibiotics used in dentistry in terms of bacterial resistance.

Adaptability and Fitness

Microbiomes can develop compensatory mutations to overcome the challenges of antibiotics. It was also believed that newly synthetic antibiotics (trimethoprim, sulphonamides) not derived from naturally occurring sources, would represent a step that bacteria wouldn't overcome. Unfortunately, this wasn't the case. Bacteria continued making multiple mutations to battle against these pharmacological agents.

Normal Microbiome in the Oral Cavity

Amongst the most commonly isolated bacteria we have: α-hemolytic streptococci, coagulase-negative staphylococci, Gram-negative cocci belonging to the families Neisseriaceae and Veillonellaceae, lactobacilli, spirochaetes, corynebacteria and mycoplasmas. Pathogenic species isolated include the *Staphylococcus aureus*, *Enterococcus faecalis*, *S. pneumoniae*, *Streptococcus pyogenes*, *Neisseria meningitidis*, members of the family Enterobacteriaceae, *H. influenzae* and actinomycetes.[3]

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*Correspondence Dr. Nilesh Pardhe.
Department of Oral and Maxillofacial Pathology, Mahatma Gandhi Dental College and Hospital, Jaipur, Rajasthan, India.
Email: drpardhenilesh@hotmail.com
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The microbial composition is modified by a series of endogenous and exogenous factors, leading to a *dysbiosis* (i.e., the loss of the complex equilibrium between the host and its microbiome). These are: the use of antimicrobials, diseases (e.g., diabetes, hypertension), oral hygiene, salivary properties, oral temperature (e.g., it increases when you smoke), diet, immune and genetic characteristics of the host and environmental pollutants.[4]

Oral Health and Disease

Amongst all the most commonly found oral pathologies in the clinical practice, dental caries and periodontal diseases are the most common. For example, the incidence of caries sharply dropped after mass prescription of penicillin and other antibiotics. In a retrospective conducted in Norway, incidence of caries went from 81% to 52.2% in less than two decades.[5] Of course, this comes at the expense of over-prescription of antibiotics for any type of oral disease. The colonization of strict anaerobes with facultative anaerobes are responsible for a large number of oral infections, such as dentoalveolar infections, periodontitis, and pericoronitis.[6]

Multiple factors modify oral ecosystem that lowers the oral cavity's pH, allowing more pathogenic and acid producing bacteria to colonize and wreak havoc. Lack of proper oral hygiene, compounded by a high sugar intake (carbohydrates are fermented into lactic acid, lowering the pH), the growth of cariogenic bacteria in the biofilm. Of course, the pathogenesis of caries, gingivitis and periodontitis is very complex, involving inflammatory state, interactions between the host's immune system and the local bacteria and many others. Many hypotheses have been devised to explain these phenomenons.[7]

Commonly Used Antibiotics in Dentistry

Amoxicillin

One of the most commonly prescribed antibiotics in dentistry practice, and for good reasons. In a single study[8] 34 different strains of anaerobic bacteria were subjected to an analysis to test their sensibility or resistance to said antibiotics. All of them turned out to be vulnerable to it. Their susceptibility was increased when used alongside clavulanic acid, especially amongst gram-negative bacilli. However, from time to time, reports of a β-lactamase producing Prevotella sp., but the results are inconclusive.

Cephalosporins

Both gram-negative and positive bacteria have previously shown resistance to this family. Take, for example, the Enterococcus sp. Isolated from root canals and in peri-coronal infections, who have shown resistance to cephalosporins. Cephalosporins are divided into five generations, but the most commonly used are first to the third ones. These include cefadroxil, cefradine, cefazolin, cefuroxime and many others. Their wide-spectrum capabilities are what prompted the over-prescription of these, resulting in bacterial resistance. Some studies have indicated that resistance to first- and second-generation cephalosporins are pretty high, needing a *Minimum Inhibitory Concentration* (i.e. the minimum amount to kill bacteria/inhibit their growth) of even 128 mg/L.[9] Curiously, another study saw susceptibility of bacteria towards first and-second generation, but fourth-generation required higher MICs. This suggests that appropriate use of cephalosporins is pivotal. For *Prevotella sp*., *Fusobacterium sp.* and *Veillonella sp*. species, their resistance to cephalosporins have been previously documented. Even scarier is the evidence that antibiotic resistance can be transferred to S. pneumoniae.[10]

Clindamycin

Clindamycin is a strong option for patients allergic to penicillin. In both symptomatic treatment of local infections, most bacteria are eradicated by it. Only 10% of Streptococcus viridans have proven to be resistant to it.[11] Odontogenic and peri odontogenic diseases have multiple local and systemic complications if left untreated. For the latter, one of the scariest is infective endocarditis. Cleave in the surface epithelium allows bacteria to get into the bloodstream, reaching the heart cavities, colonizing and forming infected vegetations. To prevent this, and for patients allergic to β-lactamase, its use is recommended. However, there's a downside to its use: the adverse effects. Thus, it must be used with caution in patients with kidney and liver failure.

Metronidazole

In order to target both aerobic and anaerobic bacteria, metronidazole is prescribed along with other antibiotics, making the bacteria's resistance to it more alarming. For example, Roche & Yoshimori conducted a study to evaluate the sensibility of bacteria towards metronidazole, especially bacteria responsible for odontogenic abscesses. Out of the 97 isolates, only 8 were resistant (five isolates of *Lactobacillus* spp., two isolates of *Gemella morbillorum* and an isolate of *Actinomyces israelii*).[12] In another study, only 3,7% of the isolates turned out to be resistant to this antimicrobial.[13] Overall, facultative anaerobes prove to be the more resilient, due their capability of surviving under both aerobic and anaerobic conditions.

The possible mechanisms implicated are structural modifications of the binding site and entry of the drug, modifications of the enzymes responsible for the drug reduction and a bigger efflux capability.

Ciprofloxacin

Fluoroquinolones are the equivalent of 'bombs' in antibiotic therapy. Penicillin, cephalosporins and others are considered less damaging and aggressive, akin to low weight artillery. Once it's been tested that the responsible bacteria is resistant to these 'guns', clinicians move on to these more powerful agents. They work by inhibiting the acid folic metabolism in numerous steps, preventing its use by the bacteria. They are less commonly prescribed to avoid creating bacterial resistance and due to their adverse effects.

Documentation has shown that gram-positive and negative microorganisms are highly susceptible to ciprofloxacin. However, it's not the case for every microorganism. Approximately 65.62% of S. aureus (a highly pathogenic bacteria) isolates turned out to be resistant.[14]

Doxycycline

Member of the tetracyclines. Enzymatic modification of the drug, synthesis of efflux proteins that pump out the drug and proteinic protection of the bacterial ribosome have all been documented as the primary resistance mechanisms. The tetracycline resistance protein, transcripted by the tet (Q) gene, seems to be the culprit. Prevotella spp, such as *P. nigrescens, P. intermedia* and *P. gingivalis* isolate demonstrated expression of this gene. α-haemolytic streptococci are another example. Apparently, co-resistance of the tetracyclines family and the oral penicillin isn't rare. Around 50% Gram-negative oral anaerobes have shown resistance to both families, so this is something that clinicians need to look out for.[3]

CONCLUSION

Bacterial susceptibility was increased when Amoxicillin is used alongside clavulanic acid, especially amongst gram-negative bacilli. Bacterial resistance to first- and second-generation cephalosporins are high. However, fourth-generation Cephalosporins required higher *Minimum Inhibitory Concentration*. Clindamycin is a strong option for patients allergic to penicillin. However, it must be used with caution in patients with kidney and liver failure. In case of Metronidazole, facultative anaerobes are more resilient. Ciprofloxacin should be used less to avoid bacterial resistance and due to their adverse effects. Gram-negative anaerobes have shown resistance to Tetracycline family. Further research is required to be done on larger samples to estimate oral bacterial resistance to different antibiotics.

CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interest regarding this article

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