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Coping With Antimicrobial Resistance In The Context Of Periodontal Treatment: A Review

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ABSTRACT

Antimicrobial resistance is a significant barrier in periodontal treatment, representing a crucial point where traditional therapies meet the challenge of bacteria becoming more resilient. The introduction of antibiotics transformed the field of periodontal care by providing powerful methods to combat the bacterial infections at the root of gum diseases. However, the indiscriminate use and improper administration of antibiotics have precipitated a crisis of resistance, wherein bacteria develop mechanisms to thwart the very drugs intended to eradicate them. This increasing problem has led to a reassessment of treatment approaches, requiring a careful balance between controlling periodontal infections and addressing antimicrobial resistance. In this discourse, we delve into the complexities of coping with antimicrobial resistance within the context of periodontal treatment, exploring the multifaceted strategies required to navigate this intricate landscape and safeguard both oral health and the broader public welfare.

Keywords: Multifaceted strategies, Resistance mechanisms

INTRODUCTION

Antibiotics have revolutionized medical treatment by effectively combating bacterial infections that were once life-threatening. However, their widespread use and misuse have led to the emergence of antibiotic-resistant bacteria, posing a significant global health threat. Antibiotic resistance occurs when bacteria evolve mechanisms to withstand the effects of antibiotics, rendering these drugs ineffective against infections.

The increase in antibiotic resistance is a pressing concern worldwide, fuelled by factors such as inappropriate prescribing, inadequate infection control practices and widespread antibiotic use. Resistant bacteria can spread rapidly within healthcare settings and communities, complicating infection treatment and increasing the risk of illness and death.

The consequences of antibiotic resistance are severe, leading to longer hospital stays, higher healthcare costs and increased treatment failure rates. Some bacterial infections that were once easily treatable now require more potent and costly drugs with potentially severe side effects.[1]

Addressing antibiotic resistance requires a comprehensive approach, including promoting prudent antibiotic use, developing new antibiotics, improving infection prevention measures and raising awareness among healthcare providers and the public.

In the context of periodontal treatment, antibiotics are often used alongside local therapies to eliminate infection sources. However, their use should be judicious, considering potential risks such as toxicity, allergic reactions and the promotion of resistance.[1] Dentists frequently prescribe antibiotics empirically, based on suspected pathogens rather than specific microbial analysis. Resistance to primary antibiotic classes used in dentistry is increasing among bacteria isolated from dental infections.

With the escalating antibiotic use, it's crucial to investigate reservoirs of resistance, their genetic composition and the potential transfer of resistance genes to pathogenic microbes. The oral microbiota, a diverse array of microorganisms, including bacteria, fungi and protozoa that can serve as a reservoir for antibiotic resistance genes.

Biofilm formation on tooth surfaces plays a significant role in periodontal disease. Bacteria within biofilms exhibit distinct phenotypes and gene expression compared to planktonic cultures, impacting their response to antibiotics. The transfer of antibiotic resistance genes within the oral community underscores the importance of stringent antibiotic usage control.

To combat antibiotic resistance in periodontal treatment, novel antimicrobial strategies such as local drug delivery, host modulation therapy, monoclonal antibodies and targeted microbial peptides are being developed.[2] Additionally, antibiotic stewardship programs, infection control measures and surveillance systems are crucial for addressing antibiotic resistance effectively.

ANTIMICROBIALS IN DENTAL PRACTICE

In dental practice, infections of odontogenic origin are a common concern, often requiring dental intervention to effectively address the infection's root cause. While antibiotics are commonly prescribed, they are typically used in conjunction with local treatment, with the primary objective being the eradication of the infection's source. In fact, relying solely on antibiotics without addressing the local infection can worsen the condition and even pose risks of airway compromise in acute cases.

However, there are scenarios where antibiotic use is necessary, but several factors need to be taken into account, including the risk of antibiotic toxicity, potential allergies and the emergence of antibiotic resistance.

In dental practice, antibiotic prescribing is often based on clinical judgment rather than specific microbiological investigations of the infection site. Penicillin are among the most frequently prescribed antibiotics in dentistry. Studies have shown varying levels of resistance to penicillin among bacteria isolated from dental abscesses, ranging from 5% to 20% with an increasing trend over time.[3]

Periodontitis poses a significant challenge in dental practice due to its chronic inflammatory nature and potential for irreversible damage to the supporting structures of the teeth. Common antibiotics such as amoxicillin, amoxicillin/clavulanic acid, tetracyclines, clindamycin and metronidazole are used to combat bacterial growth in the gingival crevicular fluid.[4]

A systematic review examined the use of antibiotics in the treatment of periodontitis, incorporating both clinical trials and observational studies. Various antibiotics, including tetracyclines, metronidazole and amoxicillin, were assessed either alone or in combination regimens. The review evaluated outcomes such as reduction in probing depth, gain in clinical attachment level and microbial changes. The findings indicated that antibiotics offer additional benefits as adjuncts in periodontitis treatment, particularly in specific patient groups or disease presentations.[5]

While antibiotics are valuable tools in dental care, their mis-use poses a serious risk such as anti-microbial resistance. Dental practitioners must adhere to the guidelines, prescribe judiciously and educate patients. Collaboration, public awareness and policy reforms are essential to safeguard oral health and combat antibiotic misuse.

ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR) refers to the ability of microorganisms, such as bacteria, viruses, fungi, and parasites, to resist the effects of antimicrobial drugs, including antibiotics, antivirals, antifungals and antiparasites. This resistance occurs when these microorganisms evolve mechanisms that render the drugs ineffective in killing or inhibiting their growth.[6]

Over time, the proliferation of resistant bacterial strains, particularly against penicillin and other antibiotics, has escalated into a critical concern. Among these, Methicillin-resistant *Staphylococcus aureus* (MRSA) stands as a glaring example of extensively resistant bacteria. Additionally, there's a concerning increase in resistance prevalence among other species like vancomycin-resistant *Enterococcus* (VRE), with Australia witnessing notably elevated rates of vancomycin-resistant *Enterococcus faecium*.

Dental practitioners significantly contribute to overall antibiotic usage, accounting for approximately 3%–11% of all prescribed antibiotics.[7] However, surveys have revealed a concerning lack of awareness among dentists regarding antimicrobial resistance (AMR) and its impact on their prescribing habits.

Studies were conducted to investigate the use and misuse of antibiotics in dentistry in India. It was carried out on Indian populations evaluating the prescription of prophylactic or therapeutic antibiotics by dental practitioners or other healthcare providers, along with antibiotic self-medication by the general population. A total of 1377 identified and screened, 50 meeting the inclusion criteria for the review. Findings revealed a widespread misuse of antibiotics in Indian dentistry, characterized by unnecessary prescriptions, inappropriate drug selection and inadequate adherence to clinical guidelines. Factors contributing to antibiotic misuse included patient demand, lack of awareness among dental practitioners and systemic barriers to accessing dental care. Thus, raising an urgent need for targeted interventions, including educational programmes and policy reforms, to promote judicious antibiotic use.[8]

Bacteria, whether within a group or species, do not uniformly exhibit susceptibility or resistance to specific antimicrobial agents. The levels of resistance can vary significantly even among closely related bacterial groups. Susceptibility and resistance are typically assessed by determining the minimum inhibitory concentration (MIC), which refers to the lowest concentration of a drug required to inhibit bacterial growth.
Susceptibility is not an absolute value but rather a range of average MICs observed for a particular drug across the same bacterial species. If the average MIC falls within the resistant end of this range, the species is considered intrinsically resistant to that drug. Additionally, bacteria have the ability to acquire resistance genes from related organisms. The extent of resistance acquired can vary depending on the specific bacterial species and the genes obtained through horizontal gene transfer.

Resistance can manifest in two main forms:

1. **Natural resistance:**
- Intrinsic resistance is consistently expressed within a bacterial species and is independent of prior antibiotic exposure or horizontal gene transfer. It is a trait universally shared within the species.
- Examples include reduced permeability of the outer membrane in gram-negative bacteria and the activity of efflux pumps which expel antibiotics from bacterial cells reducing their effectiveness.

2. **Acquired resistance:**
- Acquired resistance can occur through various mechanisms collectively known as horizontal gene transfer (HGT) which includes conjugation, transduction and transformation.

A significant challenge posed by antimicrobial resistance is that the use of these drugs often leads to increased resistance. Even low concentrations of antimicrobials, known as sub-inhibitory concentrations, can select for high-level resistance in successive bacterial generations. Additionally, antimicrobial use can increase the mutation rate, facilitate the acquisition of resistance to other antimicrobial agents, and promote the movement of mobile genetic elements, exacerbating the spread of resistance.[9]

MECHANISMS OF ANTIMICROBIAL RESISTANCE

1. **Limiting Uptake of a Drug**: Bacteria reduce or prevent the entry of antimicrobial agents into cells through various methods:
- Thickened Cell Wall: Some bacteria produce thicker cell walls, hindering drug penetration.
- Changes in Porin Channels: Alterations in porin channels limit drug uptake, as observed in *Enterobacteriaceae*.
- Mutations within Porin Channels: Mutations can confer resistance to specific antibiotics.
- Biofilm Formation: Bacteria within biofilms are protected from antimicrobials due to the biofilm matrix and reduced metabolic activity.

2. **Modifying a Drug Target**: Bacteria alter the structure or function of target molecules to render antibiotics ineffective:
- Resistance to β-lactam Drugs: Bacteria modify penicillin-binding proteins (PBPs) to resist β-lactam antibiotics.
- Resistance to Glycopeptides: Changes in peptidoglycan structure reduce vancomycin binding.
- Resistance to Lipopeptides: Mutations alter the cell membrane's charge inhibiting drug action.

3. **Inactivating a Drug**: Bacteria produce enzymes that chemically modify antimicrobial agents rendering them inactive:
- Drug Hydrolyzation: Enzymes like β-lactamases hydrolyze antibiotics like penicillin.
- Transfer of Chemical Groups: Bacteria transfer chemical groups to drugs leading to inactivation.

4. **Beta-lactamases**: Bacteria resist β-lactam drugs through various mechanisms, including preventing interaction with PBPs, efflux pumps and hydrolysis by β-lactamases.
- Altered Penicillin-Binding Proteins (PBPs): Some bacteria modify existing PBPs or acquire new ones preventing the interaction between β-lactam drugs and their target PBPs, thus reducing drug efficacy.

- Efflux Pumps: Bacteria possess efflux pumps that expel β-lactam drugs from within the cell, reducing drug concentration and contributing to antibiotic resistance.

- Hydrolysis by β-lactamases: Bacteria produce β-lactamases, enzymes that hydrolyze the β-lactam ring structure of β-lactam drugs. This hydrolysis reaction renders the drug ineffective against its target PBPs by opening the ring.

5. **Drug Efflux**: Bacteria expel antibiotics from cells using efflux pumps reducing intracellular drug concentration and efficacy.[10]

COPING WITH ANTIMICROBIAL RESISTANCE

The World Health Organization (WHO) identified twelve bacteria, including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacteriaceae*, *Enterococcus faecium* and *Staphylococcus aureus*, as significant concerns due to their resistance to multiple antibiotics. Six of these bacteria are known as ESKAPE pathogens often associated with nosocomial infections and resistant to antibiotic treatment.

1. **Modifying Old Antibiotics**:
- Examples include omadacycline and cefiderocol which have been designed with modifications to evade common resistance mechanisms.
- Vancomycin modifications such as the maxamycins group show promise against vancomycin-resistant bacteria.
2. **Improved Efficacy of Antibiotics**:
- Stimulating metabolic pathways or inhibiting metabolic processes can increase bacterial susceptibility to antibiotics.
- Inhibition of metabolic pathways, such as limiting intracellular adenine levels can enhance antibiotic efficacy.
3. **Antibiotic Delivery Systems**:
- Nanoparticle carriers including polymer nanoparticles, liposomes and biomimetic nano delivery systems like outer membrane vesicles (OMVs) offer improved antibiotic delivery to difficult-to-reach areas.
- Aptamer-mediated delivery, targeting specific bacterial surfaces shows promise in enhancing antibiotic activity.
4. **Vaccines:**
- Vaccines play a crucial role in preventing infections and reducing the need for antibiotics.
- Challenges remain in developing effective vaccines against nosocomial pathogens like ESKAPE bacteria.
5. **Locally Delivered Antibiotics**:
- Administering antibiotics locally such as in periodontal disease treatment can improve efficacy while minimizing systemic side effects.
6. **Antimicrobial Photodynamic Therapy (aPDT):**
- aPDT offers a potential alternative for local antimicrobial treatment utilizing photosensitizers activated by specific wavelengths of light to target pathogens.
7. **Host Modulation Therapy**:
- Agents like sub-antimicrobial dose doxycycline (SDD) modulate the host response to infection without exerting selective pressure on bacteria.
8. **Antimicrobial Peptides (AMPs):**
- AMPs show promise in treating polymicrobial infections although challenges such as susceptibility to degradation and toxicity need to be addressed.
9. **Monoclonal Antibodies**:
- Cytokine inhibitors such as anti-TNF-α antibodies have shown potential in modulating the inflammatory response in periodontal disease.[11]

These strategies collectively aim to address the multifaceted challenge of antimicrobial resistance through various approaches including the development of new therapies, optimization of existing antibiotics, and modulation of host responses to infection.

CONCLUSION

Antimicrobial resistance presents a significant challenge in managing periodontal diseases. However, by adopting a comprehensive approach integrating antimicrobial stewardship, host modulation and innovative therapeutic modalities we can overcome these challenges and optimize treatment outcomes. Continued research and collaboration are vital for developing and implementing novel strategies to cope with antimicrobial resistance in periodontal treatment ultimately improving oral health and patients' quality of life**.**

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