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Taming the bacterial battlefield: unlocking the power of antibiotics in periodontal therapy- A review

[1]Dr. Sanjay Vasudevan, HOD &Professor, Army College of Dental Sciences, Secunderabad, India

[2]Dr. P. Ajay Reddy, Reader, Army College of Dental Sciences, Secunderabad, India

[3]Dr. Abhinav Atchuta, Reader, Army College of Dental Sciences, Secunderabad, India

[4]Dr. B. Manisha, Senior lecturer, Army College of Dental Sciences, Secunderabad, India

[5]Dr. Anahita Punj, Senior lecturer, Army College of Dental Sciences, Secunderabad, India

Corresponding Author: Dr. B. Manisha, Army College of Dental Sciences, Secunderabad, India

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Introduction

Periodontal disease is caused by a chronic bacterial infection that inflames the supporting structures of the teeth. Conventional treatment modalities for these diseases include mechanical debridement or surgical procedures to eradicate the subgingival microbial flora.It was in the late 1970s that antibiotic therapy as an additive to stand periodontal therapy fascinated dental professionals andis primarily aimed at suppressing and eliminating specific putative periodontal microflora. Therapeutic strategies typically involve administering antimicrobial agents, such as tetracyclines, macrolides, nitroimidazole compounds, quinolones, penicillins, and cephalosporins, either systemically or locally.

These drugs are specifically designed to kill or inhibit infective organisms with minimal effect on the recipient, making them particularly important in developing countries where infectious diseases are prevalent.

In the last 40 years, the focus has shifted from discovering new organisms that produce antibiotics to creating semi-synthetic derivatives with different spectrums of activity or more desirable properties.Adjunct anti-microbial therapy can help treat periodontitis in patients who are systemically compromised, have an acute or severe infection, or do not respond to mechanical treatment.

Thus, this paper intends to throw more light on antibiotics as 'a therapeutic double-edged sword' in periodontitis.

The Whys and Wherefores

- Periodontitis is a plaque-induced inflammatory condition. Mechanical treatment is needed initially to disrupt the biofilm and adjunctive systemic antibiotics are given to eliminate bacteria.

- The inability to eliminate pathogens like A. actinomycetemcomitans by mechanical debridement alone makes using antibiotics necessary.
- Inaccessible areas like furcation areas, root concavities, etc where periodontal instruments are not easily reached.
- Prevention of the recolonization of the treated sites by pathogens from the non- dental sites such as the dorsum of the tongue and the tonsils.
- In medically compromised patients as a prophylactic measure.
- Cases of Recurrent periodontitis.
- For the dual purpose of antibiotics. For instance, tetracycline is an antibiotic that reduces collagen and bone destruction by inhibiting collagenase.

Table 1: Antibiotic regimens used commonly in the treatment of periodontitis.[1]

Disease	Drug of choice
Chronic periodontitis	Doxycycline, tetracycline, metronidazole, azithromycin, augmentin, metronidazole (MET) +amoxicillin (AMX)
Aggressive periodontitis	Metronidazole+amoxicillin
Necrotizing periodontal disease	Amoxicillin, metronidazole, or its combination
Periodontal abscess	Amoxicillin, Azithromycin (AZM), Clindamycin

Antibiotics are an essential component in non-surgical periodontal therapy

The microbial plaque becomes more complex over time, necessitating the administration of adjunct systemic antibiotics in controlling bacterial infections as mechanical therapy alone is ineffective. The American Academy of Periodontology (AAP)in 2004, proposed antibiotics administration in patients who are unresponsive towards conventional therapy, patients who are medically compromised, or with periodontal infections that pose a threat to oral and systemic health.[2]

Studies have shown that drugs like metronidazole and clindamycin are effective in reducing microbial count, improving the host response, and promoting attachment gains as compared to mechanical therapy and doxycycline alone. Some tetracyclines, such as doxycycline, when given at sub-antimicrobial doses (SDD) of 20mg, are associated with better periodontal health. This is because they can inhibit collagenolytic MMPs in gingival tissues and fluid. SDD has no detrimental effect or antibiotic resistance on the periodontal microflora. As the periodontal pocket pathogens react differently, drug combinations may be effective. A recent systematic review has stated that superior results were obtained on prescribing amoxicillin + metronidazole (250 mg q8h) for 8 days with additional benefit in sites with PD >6mm as an adjunct to NSPT. However, the duration and the dosage of the protocol are still controversial. The study recommends using a full-mouth approach in one or two sessions within 24 hours to prevent recontamination of the treated areas.[3]A randomized controlled trial conducted in 2018 has noticed a decrease in the probing depth(PD) treated with scaling and root planning (SRP) and additional drug therapy of oral clarithromycin 500mg, thrice a day for a week.[4]

Actinobacillus actinomycetemcomitans (AA), a gram-negative anaerobic bacillus was analysed by Carlos[5] in a 6-month follow-up study. MOX or AMX + MET was used as an adjunction showing a significant reduction in the AA counts. However, only MOX reduced the counts to unnoticeable levels.

Locally delivered antibiotics such as Chlorhexidine, povidone-iodine, sodium hypochlorite, hydrogen

peroxide, and tetrapotassium peroxy diphosphate show effective concentrations up to 100 times greater in the periodontal pockets as compared to the systemically delivered drugs with promising therapeutic results. A systematic review (2005) found hydrogen peroxide to be the most effective antimicrobial for reducing pocket depth(PD), while tetracycline and minocycline were shownto be the best local therapeutic agents. Contradicting this, AAP did not recommend subgingival antimicrobial irrigation due to insufficient evidence.

The spreading of some acute lesions such as a periodontal abscess, endo-perio lesions, and necrotizing lesions may cause systemic involvement necessitating the use of systemic drugs along with scaling and root planing.

Antibiotics in surgical periodontal therapy

In cases where chronic periodontitis is severe or moderate, periodontal surgery may be necessary.[6] The success of such procedures is greatly influenced by the prevention of infection. To achieve this, it is important to follow strict aseptic protocols and anti-infective measures. These steps can eliminate the need for prophylactic antibiotics.[7]

Some authors argue that systemic antibiotics may not be effective in reducing post-operative complications. However, others believe that they can enhance healing, and reduce septicemia, pain, inflammation, and swelling after surgery. [8,9,10,11,12]

Newer biomaterials such as bone substitutes, EMD, and growth factors could affect surgeons' decisions on whether to use antibacterials or antimicrobials during the surgical period, which in turn, could lead to changes in the infection rate. Trials have been conducted to evaluate the use of antibiotics following SRP. There were no noteworthy variations detected in the perception of pain between the three groups (Amoxicillin, Doxycycline, and control groups).[13]In a randomized crossover clinical trial[14] involving 70 patients, they were divided into three groups: prophylactic, therapeutic, and no antibiotic. The study concluded that individuals who received prophylactic antibiotics experienced less pain. Furthermore, the inflammatory parameters in the prophylactic group were found to have reduced to an insignificant level.

Mouth rinses and supragingival irrigation have limited ability to deliver medications into the periodontal pocket.[15]Subgingival irrigation of antimicrobials has shown positive results. Still, drawbacks include a small drug reservoir and a shortened period of effective drug concentration due to exponential kinetics. Silva et al[16] reported that a combination of calcium hydroxide and saline irrigation had no impact on bacterial growth inhibition while chlorhexidine and tetracycline showed zones of inhibition in 70% and 40% of specimens, respectively.

Antimicrobials are commonly while placing an implant. A pre-procedural rinse with 0.1% CHX reduces bacteria by 10x.[17]Non-surgical therapy and at-home irrigation can help treat peri-implant mucositis. The effectiveness of systemic antimicrobials is uncertain in peri-implantitis studies.[18] Commonly prescribed antimicrobials include AMX, MET, and Augmentin. According to a meta-analysis of surveys, practitioners prescribe amoxicillin with clavulanic acid, penicillin V, AZM, clindamycin, or MET[19]. In 2013, an evidence-based Cochrane review recommended a prophylactic regimen of amoxicillin, 2 grams orally, to be taken one hour before implant placement.[20]

In general, when antibiotics are administered, they may not penetrate the bone tissue efficiently. For example, beta-lactam antibiotics can only reach 10 to 20% of serum concentrations in bone tissue.[21] This can increase

the likelihood of treatment failure if the microorganisms are less sensitive to the antibiotics or appear to be resistant to them. Positive clinical and radiographic changes were observed for up to 12 months after the use of minocycline microspheres as an adjunctive local delivery method for treating peri-implantitis. These effects can be attributed to successful non-surgical, surgical, and supportive periodontal therapies that were administered before the implant placement. This is demonstrated by the relatively low mean scores for full-mouth plaque and bleeding, shallow residual periodontal pockets, and minimal loss of clinical attachment (CAL).[22]The combination of VTA (Vancomycin Tobramycin Allograft) with a collagen membrane has yielded positive outcomes, resulting in an increase in radiographic bone fill, reduction in PD, and attachment gain after 12 months.[23] However, the rough surfaces of implants and prostheses make mechanical debridement challenging, so clinicians should consider the pros and cons of using antibiotics during surgery.

Photodynamic therapy (PDT) is a preferable alternative to administering systemic antimicrobial agents, as it reduces the risk of overdoses and associated side effects. Moreover, the controlled clinical studies suggest that PDT, when used in conjunction with SRP, leads to greater gains in clinical attachment level and reduction in bleeding on probing (BOP) and PD. PDT also helps prevent bacterial resistance from occurring.[24]A double-blinded clinical trial found that repeated application of PDT, when used alongside periodontal surgery, significantly reduced PD inchronic periodontitis after 150 days. CAL gain and the number of subgingival microbiota remained the same between the groups.[25]

Antibiotics in medically compromised patients

Certain medical conditions can have an impact on oral structures and the delivery of dental care. Studies suggest that there may be a link between oral health and coronary artery disease. However, many medical conditions that are said to affect dental care lack an evidence base and are often overstated. While the association between oral health and coronary artery disease is convincing, the causal relationship has not been established yet. If this relationship can be confirmed, it will provide a significant impetus for the promotion of oral health and the delivery of dental care.[26]Lockhart et al[27] conducted a review of the situations that dentists commonly consider for the possible use of antibacterial agents. They aimed to decide the existing evidence about the use of such drugs for preventing the transmission of oral bacteria to other parts of the body and reducing local infections caused by treatment interventions. It is inferred that relatively few situations require antibiotic prophylaxis. There is no agreement among experts on the necessity of prophylaxis, except for cases of endocarditis and late prosthetic joint infections.

Research has shown that the use of antibiotics can significantly improve the periodontal health of patients with diabetes and periodontitis in the long term. Systemic antibiotics have been found effective in reducing pocket depth (PD) and clinical attachment loss (CAL). Additionally, topical antibiotics have also proven to be beneficial in improving PD. However, using systemic antibiotics in the short term did not yield significant improvements in periodontal status. While periodontal treatment with or without adjuvant antibiotics did improve the periodontal status, it did not have any effect on the regulation of HbA1c.[28]

Pre-operative antibiotics have been proposed to prevent infection during and after implantation in diabetic patients with periodontitis.[29] Studies have shown that using antibiotics can significantly reduce the risk of

implant failure. However, before using antibiotics in periodontal treatment, a clinical evaluation should be performed to determine the benefits and risks.

Combination antiretroviral therapy has significantly decreased the occurrence of opportunistic infections in persons infected with HIV. For individuals who have experienced effective immune recovery, as evidenced by an increased CD4 cell count, discontinuing antibiotic prophylaxis can lead to lower toxicity, fewer drug interactions and costs, and better compliance with antiviral regimens. Consequently, in 2002, the US Public Health Service/Infectious Disease Society of America (USPHS/IDSA) revised their recommendations, to specify similar or slightly cautious CD4 count thresholds for discontinuing and initiating prophylaxis.[30]

Contraindications and adverse effects

Antimicrobial drugs are widely prescribed in medical practice and will likely continue to be so. It appears that a significant number of healthcare professionals who prescribe medications may not have sufficient knowledge regarding the potential negative impacts of said drugs on patients. It is important to prescribe antimicrobials for the shortest possible duration and only when the benefits outweigh the risks. Although some antibiotics are not commonly used because of their harmful side effects (such as aminoglycosides), even the antimicrobials commonly prescribed in community settings can cause adverse effects.[31]Though penicillin is generally safe, there are potential adverse effects associated with its use. These can range from mild reactions like rashes, urticaria, dermatitis, and joint pains, which are encountered in approximately one in every 10,000 patients, to more serious complications like hypersensitivity and anaphylactic reactions, as well as pseudomembranous colitis. While fatal reactions are rare, they can occur in about 10% of patients who experience serious adverse effects.[32]

Broad-spectrum antibiotics can lead to overgrowth of Candida species, particularly in individuals with diabetes. Infections from Clostridium difficile are commonly caused by antibiotics such as ampicillin, amoxicillin, clindamycin, third-generation cephalosporins, and fluoroquinolones. Teng et al 's[33]study on the FDA adverse reporting system found that C. difficile infections have a high risk with drug usage, especially quinolones. Thus, drugs should be prescribed only when necessary and for short durations to avoid adverse effects.

When prescribing antibiotics, it's important to be cautious in patients with impaired kidney or liver function. Additionally, a detailed medical history may rule out any allergies or anaphylactic reactions to antibiotics like penicillin. This is because contraindications for antibiotics are based on their pharmacokinetic and pharmacodynamic properties.[34]

Drug interactions and antimicrobial resistance

Certain commonly used antibiotics when combined with beta-blockers may interact and affect each other’s efficacy predisposing elderly and compromised patients to significant hypotension. Hence, knowing the medication history prior may prove beneficial in prescribing the drug combinations.[35] As there is a free and quicker movement of people, food, etc between the borders, thereby transporting the resistant bacteria across the globe, bacterial resistance has now emerged as a global issue.[36]

The development of antimicrobial resistance (AMR) is due to the mutations that bring changes in the genetic product. Typically, such mutations may bring low to moderate resistance to various antibiotics.[37]This concept

was first suggested by Dr. Fleming in the 1920s when he published his discovery of penicillin.[38]

Penicillin resistance was observed within two years of its introduction in the mid-1940s. Vancomycin resistance (VRE) emerged in 1987 and spread quickly in the following years, leading to surging sources of life-threatening infections in hospital wards. VRE has five necessary and sufficient genes for high-level resistance. In 1994, three clinical cases highlighted the importance of microbial surveillance. Despite several surgeries and antibiotics, periodontal abscesses and bone loss persisted. Microbiological analysis and sensitivity testing were performed extensively, and appropriate antibiotics were administered along with conservative therapy. The result was a remarkable improvement in disease progression lasting at least 2 1/2 years. The increasing prevalence of antibiotic resistance among human pathogens necessitates a conservative and restrictive approach to systemic antibiotics.[39]

Antibiotics in pregnancy

Pregnancy causes physiological changes that may pose challenges in dental care. Certain principles must be considered to provide safe and effective care to the mother while minimizing risk to the fetus. Most antibiotics have the potential to affect the fetus as they can cross the placenta. However, certain drugs like Amoxicillin, Metronidazole, Erythromycin, Penicillin, Cephalosporins, Gentamycin, Clindamycin are considered safe during pregnancy and lactation,but with certain restrictions. For example, Gentamycin has been linked to fetal ototoxicity, tetracycline can lead to tooth discoloration, and Chloramphenicol may cause maternal toxicity or fetal death. It is important to be aware of these limitations before taking any medication during pregnancy or lactation.[40]The macrolides and clarithromycin, classified as class C (US FDA category), do not significantly cross the placenta. Therefore, the use of such drugs is acceptable and beneficial.

Conclusion

Periodontal and peri-implant diseases are usually controlled with manual instrumentation to lower microbial counts and enhance the patient's ability to maintain oral hygiene at home. However, if the patient fails to take adequate responsibility for home care and other compliance issues, the disease is likely to recur. In such cases, antibiotics can be used as a therapeutic strategy to treat the disease. Post-surgical infections following certain surgical procedures may be controlled or prevented by antibiotics. However, their inappropriate use may lead to ineffective drugs and develop antibiotic resistance.

Antimicrobial use can be beneficial in specific surgical procedures to prevent post-surgical infections. However, inappropriate use can result in resistance and inefficacy. The effective and prudent use of antibiotics makes them an essential tool in treating periodontal diseases and individuals with weakened immune systems.

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