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Role of Antimicrobial Therapy in Periodontics and Peri-Implantitis - A Review

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Abstract

Periodontal disease encompasses inflammatory conditions affecting the gingiva, periodontal ligament, cementum, and alveolar bone[1]. It is initiated by a complex microbial biofilm and influenced by host immune responses and environmental factors[2]. Although scaling and root planing (SRP) remains the cornerstone of periodontal therapy[3], adjunctive antimicrobial therapy is indicated in certain clinical situations to enhance clinical outcomes[4]. Locally or systemically delivered antimicrobial agents suppress periodontal pathogens, reduce inflammation, and promote periodontal healing[5]. This article reviews the rationale, classification, indications, and mechanisms of action, clinical applications, advantages, limitations, and adverse effects of antimicrobial therapy in periodontics, with an emphasis on evidence-based practice.

Keywords: Periodontitis, Local drug, Antimicrobials, Scaling and root planning, Peri-Implantitis.

Introduction

Periodontal diseases are primarily caused by pathogenic microorganisms present in the subgingival biofilm[6]. Key periodontal pathogens such as Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Tannerella

forsythia, and Treponema denticola play a critical role in the initiation and progression of periodontitis [7,8]. Although mechanical plaque control effectively reduce microbial load, complete elimination of pathogens from inaccessible areas is often difficult [3]. Antimicrobial therapy serves as an adjunct to mechanical treatment, particularly in aggressive forms of periodontitis, refractory cases [9] and in Peri-implantitis. Recent advances focus on antimicrobial implant surface modifications along with adjunctive modalities like photodynamic therapy and probiotics to enhance biofilm control and peri-implant healing

Rationale for Antimicrobial Therapy in Periodontics

The use of antimicrobial agents in periodontal therapy is based on the following principles[10]:

- Periodontitis is an infectious disease with specific microbial etiology [7]
- Certain periodontal pathogens can invade gingival tissues and are inaccessible to mechanical instrumentation [11]
- Some bacteria may recolonize periodontal pockets after SRP[12]
- Antimicrobials can suppress or eliminate specific pathogens and modulate disease progression [13]

Classification of Antimicrobial Therapy

Antimicrobial therapy in periodontics can be broadly classified into[14]

- **Local Antimicrobial Therapy (Local Drug Delivery – LDD)**

Local antimicrobial agents are delivered directly into periodontal pockets, achieving high drug concentrations at the site of infection with minimal systemic effects.[15]

Commonly used local agents:[16]

- Chlorhexidine
- Tetracycline fibers
- Doxycycline gel
- Minocycline microspheres
- Metronidazole gel

- **Systemic Antimicrobial Therapy**

Systemic antimicrobials are administered orally and distributed throughout the body via the bloodstream, reaching periodontal tissues and other oral niches.[17]

Commonly used systemic antimicrobials:[18]

- Tetracyclines (Tetracycline, Doxycycline, Minocycline)
- Penicillins (Amoxicillin)
- Nitroimidazoles (Metronidazole)
- Macrolides (Azithromycin)
- Combination therapy (Amoxicillin + Metronidazole)

- **Local Antimicrobial Therapy**

Local drug delivery (LDD) systems are increasingly used as adjuncts to conventional periodontal therapy to enhance antimicrobial impact directly at the site of disease [15,16].

Chlorhexidine Chip

Mechanism of Action

- Chlorhexidine is a cationic bisbiguanide with two biguanide groups, giving it a positive charge [19].
- This structure allows strong binding to negatively charged bacterial cell walls [19], disrupting membrane integrity and increasing permeability [20].
- The resulting leakage of essential cellular components ultimately leads to microbial cell death [20].
- Chlorhexidine gluconate is incorporated into a biodegradable chip e.g., PerioChip inserted into periodontal pockets, where it slowly releases over about 7–10 days.[21]

Clinical Evidence

- As an adjunct to SRP, chlorhexidine chips provide additional reduction in Pocket Probing Depth (PPD)

and clinical attachment level (CAL) compared to SRP alone [21,22].

- Meta-analyses suggest chlorhexidine chips may yield modest improvements in PD and gingival index relative to some other LDD agents, but outcomes vary by study [23].
- Chlorhexidine gel formulations also show benefit but may be less persistent than chips.[24]

Advantages

- Broad-spectrum antimicrobial effect [19]
- Sustained release minimizes the need for repeated applications [21]

Limitations

- May cause extrinsic tooth staining and calculus formation with long-term use [25]
- Effects sometimes smaller than other antimicrobials LDD agents in certain outcomes [23]

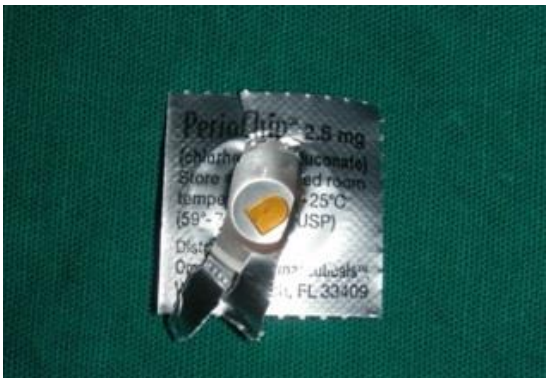

Figure 1: Chlorhexidine chip (Periochip containing 2.5mg of Chlorhexidine gluconate) [61]

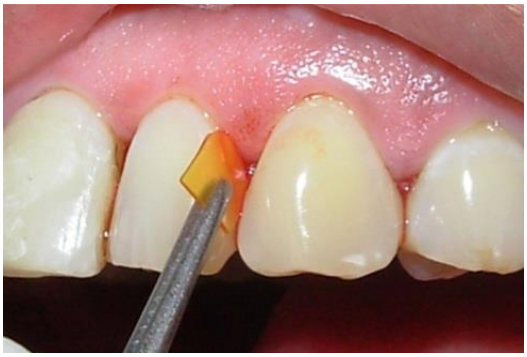

Figure 2: Placement of Periochip into Periodontal pocket after SRP [61]

- DOSE in Mouth Rinses -0.12% to 0.2% [26]

Tetracycline Fibers

Mechanism of Action:

- Inhibit bacterial protein synthesis by reversibly binding to the 30S ribosomal subunit [27]
- Bacteriostatic against a wide range of gram-positive and gram-negative bacteria [27]
- Inhibit collagenase activity and matrix metalloproteinases (MMPs), reducing connective tissue breakdown [28]
- Concentrate in gingival crevicular fluid (GCF) at levels 2–10 times higher than serum [29]

Tetracycline fibers are non-biodegradable fibers impregnated with tetracycline, placed sub gingivally and retained for up to 7–10 days. [30]

Clinical Evidence

- Multiple trials have demonstrated significant improvements in PPD and inflammatory parameters when tetracycline fibers are used adjunctively with SRP compared to SRP alone. [30,31]
- Some studies show greater pocket probing depth reduction compared to chlorhexidine chips, though results vary. [32]

Advantages

- Strong bacteriostatic effects on periodontal pathogens [27]
- May contribute to fibroblast attachment and inhibit collagenase activity [28]

Limitations

- Fibers require removal after release completion [30]
- Uneven release kinetics compared to biodegradable matrices [16]

Figure 3: Periodontal Plus AB AND Tetracycline fibre container with fibre [62]

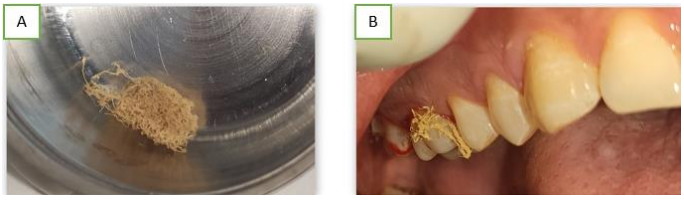

Figure 4: A: Tetracycline fibers; B: Fibers are placed in interdental area and sulcus [62]

Doxycycline Gel

Mechanism of action

- Doxycycline is a bacteriostatic drug.[27]
- They inhibit protein synthesis by binding to 30S subunit of ribosome of the susceptible organism reversibly.[27]
- Thereby preventing the binding of aminoacyl transfer RNA [27]

Doxycycline gel is a biodegradable polymer that releases doxycycline over ~21 days. The marketed formulation Atridox is most commonly studied. [33]

Clinical Evidence

- Doxycycline locally delivered as gel has been shown to improve PPD and CAL when used as an adjunct to SRP. [33,34]
- Doxycycline's inhibition of matrix metalloproteinases may provide additional host-modulating benefits. [28,35]

Advantages

- Sustained release with longer residence time [33]
- Good patient compliance due to no need for removal [34]

Limitations

- Cost and availability can be barriers in some settings [16]

Figure 5: Atridox gel [63]

Figure 6: Atridox applied locally

Metronidazole Gel

Mechanism of Action:

- Enters anaerobic bacterial cells and is reduced to cytotoxic metabolites [36]
- Causes DNA strand breakage and inhibition of nucleic acid synthesis [36]
- Bactericidal against obligate anaerobes [36]

Clinical Evidence

- Studies have demonstrated reductions in PPD and CAL when used with SRP compared to SRP alone.[37,38]

- Some meta-analyses suggest mixed results compared with other LDD agents, particularly regarding plaque index and gingival inflammation. [23]

Advantages

- Broad-spectrum activity against gram-negative anaerobes which predominate in periodontal infections [36]

Limitations

- May require multiple applications depending on formulation [37]

Figure 7: Elyzol gel

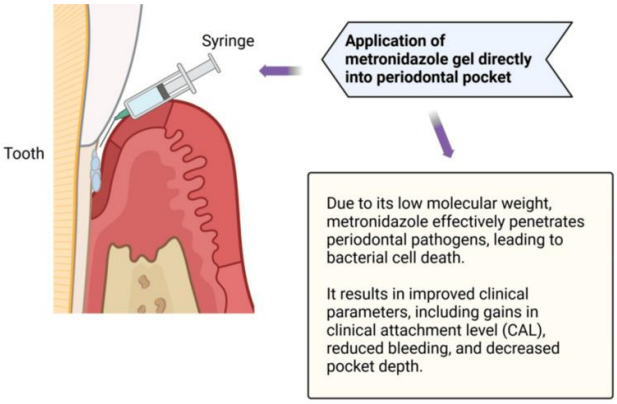

Figure 8: Application of metronidazole as a local drug delivery agent [64]

Minocycline Microspheres

Mechanism of Action

Minocycline is delivered in biodegradable microspheres e.g., Arestin which release the drug over ~14–21 days. [39]

Clinical Evidence

- Clinical trials show that minocycline microspheres as an adjunct to SRP significantly reduce PD and promote CAL gain versus SRP alone. [39.40]
- Studies often compare favorably with metronidazole gel, although direct comparisons with all agents remain limited.[41]

Advantages

- Convenient, biodegradable delivery [39]
- Sustained therapeutic levels in pocket environment [40]

Limitations

- Cost considerations and availability [16]

Figure 9: Arestin

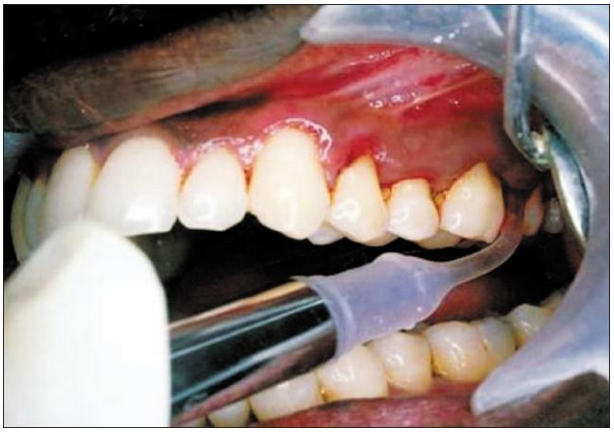

Figure 10: Application of minocycline microspheres [65]

➢ **Systemic Dosage Of Antimicrobials**

Tetracyclines (Tetracycline, Doxycycline, Minocycline)

Dosage and Administration:

- Tetracycline: 250 mg four times daily for 14 days [42]

- Doxycycline: 100 mg once daily for 14–21 days [43]
- Minocycline: 100 mg once daily for 14 days [43]
- Subantimicrobial dose doxycycline (SDD): 20 mg twice daily for 3–9 months (host modulation) [35]

Clinical Applications:

- Aggressive periodontitis with pocket probing depths of 4-6 mm and 7-10 mm [44]
- Refractory periodontitis with pocket probing depths of 4-6 mm and 7-10 mm [44]
- As host-modulatory therapy (SDD) is generally recommended for Pocket probing depth of greater than 5mm [35]

Metronidazole

Dosage and Administration:

- 400 mg three times daily for 7 days [45]

Clinical Applications:

- Necrotizing periodontal diseases [46]
- Periodontitis associated with anaerobic flora (*P. gingivalis, T. forsythia*) [45]
- Periodontal abscess [46]
- Often used in combination with amoxicillin [47]

Amoxicillin

Mechanism of Action:

- Inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins [48]
- Bactericidal against actively dividing bacteria [48]

Dosage and Administration:

- 500 mg three times daily for 7–10 days [47]

Clinical Applications:

- Aggressive periodontitis [44]
- Acute periodontal infections [46]
- Used synergistically with metronidazole [47]

Amoxicillin–Metronidazole Combination

Mechanism of Action:

- Broad-spectrum activity against facultative and obligate anaerobes [47]
- Synergistic bacterial elimination including *Aggregatibacter actinomycetemcomitans* [47,49]

Dosage and Administration:

- Amoxicillin 500 mg + Metronidazole 400 mg, three times daily for 7 days [47,49]

Clinical Applications:

- Generalized aggressive periodontitis [44,49]
- Severe chronic periodontitis not responding to SRP [18]

Azithromycin

Mechanism of Action:

- Binds to the 50S ribosomal subunit, inhibiting protein synthesis [50]
- Exhibits anti-inflammatory and immunomodulatory effects [51]
- High uptake by fibroblasts and phagocytes with sustained tissue levels [51]

Dosage and Administration:

- 500 mg once daily for 3 days [50]

Clinical Applications:

- Chronic periodontitis [50]
- Patients allergic to penicillin [50+]Cases requiring short-duration therapy [51]

➢ **Antimicrobial Therapy in Dental Implants**

Antimicrobial therapy serves as an adjunct to mechanical debridement in managing peri-implant diseases, particularly peri-implantitis driven by dysbiotic biofilms similar to periodontitis [66] .Systemic antibiotics, commonly amoxicillin (500 mg) with metronidazole (400–500 mg) for 7–14 days, provide modest additional reductions in probing pocket depth (PPD) and bleeding on probing (BOP), but routine use is discouraged due to limited long-term benefit and concerns of antimicrobial resistance (Table 1) . Local antimicrobial delivery, including minocycline microspheres, doxycycline gel,

and chlorhexidine, improves clinical parameters when used adjunctively (Table 1). Recent advances include antimicrobial surface modifications of implants using silver nanoparticles, titanium dioxide coatings, antibiotic-loaded hydrogels, and antimicrobial peptides to inhibit biofilm formation while promoting osseointegration (Table 2-6) .[67] Adjunctive approaches such as photodynamic therapy and probiotics are emerging.

Post-Surgical Antimicrobial Therapy in Dental Implants [68,69,70,71]

Table 1: Post-Surgical Antimicrobial Therapy in Dental Implants

Systemic/Local Antimicrobials	Dosage (Post Surgical Use)	Commonly Affected Implant Sites	Outcomes In Peri-Implant Conditions
Amoxicillin + Metronidazole	Amoxicillin 500 mg + Metronidazole 400 mg Three Times A Day (TID) for 7–14 days	Posterior maxilla, molar implant sites	Reduced Pocket Probing Depth (PPD), Reduced Bleeding on Probing (BOP), improved infection control in peri-implantitis
Amoxicillin (alone)	500 mg TID for 5–7 days	Immediate implants, posterior regions	Reduced early post-operative infection risk
Azithromycin	500 mg once daily for 3 days	Posterior maxilla, molar implant sites	Anti-inflammatory effect, reduction in peri-implantitis
Metronidazole (alone)	400 mg TID for 7 days	Posterior maxilla, molar implant sites	Reduced Anaerobic bacterial load
Minocycline microspheres (Local)	1 mg placed in pocket; repeat after 2–4 weeks if needed	Peri-implant pockets (≥5 mm)	Reduced PPD, Reduced BOP
Doxycycline hyclate gel (Local)	8.5% gel; single application, repeat if required	All implant sites	Reduced clinical attachment loss
Chlorhexidine Gel (Local)	0.12–0.2% gel or rinse twice daily for 2–3 weeks	All implant sites	Reduced Plaque accumulation, Reduced inflammation

Recent Advances in Antimicrobial Therapy for Peri - implantitis

Photodynamic Therapy in Peri-Implantitis

Table 2: Photodynamic Therapy in Peri-Implantitis

Type of Photodynamic Therapy (PDT)	Photosensitizer Used	Wavelength (Nm)	Mode Of Application	Clinical Outcome
Conventional PDT [72]	Methylene Blue,Toluidine Blue O	630–660 nm (diode laser),630–685 nm	Application of dye + fiber optic tip insertion into peri-implant pocket	Significant reduction in bleeding on probing (BOP) and pocket probing depth (PPD)
Indocyanine Green (ICG) mediated PDT [73]	Indocyanine Green	805–810 nm	Photosensitizer irrigation into pocket + near-infrared diode laser	Significant reduction in bleeding on probing (BOP) ,reduction in microbial load

Antimicrobial Peptides in Peri-Implantitis

Table 3: Antimicrobial Peptides in Peri-Implantitis

Antimicrobial Peptide	Source/Type	Mode of Action	Usage In Peri-Implantitis	Clinical Outcome
LL-37	Human cathelicidin	Disrupts bacterial membranes	Studied in peri-implant crevicular fluid and surface functionalization	Reduced biofilm formation; modulates inflammation
Human β-defensins (hBD-2, hBD-3)	Endogenous epithelial peptides	Disrupts bacterial membranes	Studied in peri-implant crevicular fluid and surface functionalization	Lower levels associated with peri-implantitis; experimental antimicrobial potential
Histatin-5	Salivary peptide	Disrupts bacterial membranes	Experimental coating on titanium implants	Inhibits peri-implant pathogen adhesion
Synthetic AMPs (e.g., GL13K)	Designer peptide derived from parotid secretory protein	Disrupts bacterial membranes	Experimental coating on titanium implants	Significant reduction in peri-implant biofilm formation

Nanoparticles in Peri-Implant Antimicrobial Therapy

Table 4: Nanoparticles in Peri-Implant Antimicrobial Therapy

Nanoparticle	Form / Combination	Mechanism Of Action	Application In Peri-Implantitis	Clinical Outcome
Silver nanoparticles (AgNPs) [74]	AgNP-coated titanium implants	Disruption of bacterial cell membrane; Reactive Oxygen Species (ROS) generation; inhibition of DNA replication	Implant surface modification	Significant reduction in peri-implant biofilm formation; broad-spectrum antibacterial effect
Titanium dioxide nanoparticles (TiO_2)	TiO_2 + UV activation (photocatalysis)	ROS-mediated bacterial killing	Photocatalytic implant surfaces	Decreased biofilm accumulation under light activation
Silver + Chitosan	AgNPs incorporated in chitosan matrix	Synergistic membrane disruption	Implant surface coating	Enhanced anti-biofilm activity

Probiotics in Peri-Implantitis Management

Table 5: Probiotics in Peri-Implantitis Management

Probiotic Strain	Form / Route	Proposed Mechanism	Clinical Outcome
Lactobacillus reuteri [75]	Lozenges (oral)	Competitive inhibition of pathogens; modulation of host inflammatory response	Reduced Bleeding on probing (BOP);
Lactobacillus brevis	Topical/oral administration	Anti-inflammatory cytokine regulation	Reduction in plaque and inflammatory markers

Host Modulation Therapy in Peri-Implantitis

Table 6: Host Modulation Therapy in Peri-Implantitis

Host Modulating Agent	Mechanism Of Action	Mode Of Use	Clinical Outcome
Subantimicrobial-dose doxycycline (SDD) [76]	Inhibits MMP-8 & MMP-9; decreases collagen breakdown;	Systemic adjunct to mechanical debridement	Reduced Pocket Probing depth (PPD); Reduced Bleeding on probing (BOP)
Omega-3 fatty acids [77]	Promotes pro-resolving mediators (resolvins); anti-inflammatory	Systemic adjunct to mechanical debridement	Shallower pockets and diminished gingival bleeding
Bisphosphonates (local delivery) [78]	Osteoclast inhibition; anti-resorptive	Systemic adjunct to mechanical debridement	Improved gingival inflammatory status with reduced bleeding on assessment

- **Antimicrobial therapy is indicated in the following situations:** [17,44]
  - Aggressive periodontitis
  - Refractory or recurrent periodontitis
  - Acute periodontal infections (e.g., necrotizing periodontal diseases, periodontal abscess)

- Patients with compromised host defense
- Deep periodontal pockets not responding adequately to SRP alone

➢ **Contraindications and Limitations**

- Not indicated as monotherapy [17]
- Risk of antimicrobials resistance [54]
- Adverse drug reactions and allergies [55]
- Alteration of normal oral and gut microflora [56]
- Patient compliance issues [17]

➢ **Adverse Effects of Antimicrobial Therapy**

- Gastrointestinal disturbances [55]
- Hypersensitivity reactions [55]
- Photosensitivity (tetracyclines) [42]
- Tooth discoloration (tetracyclines) [42]
- Development of resistant bacterial strains [54]

➢ **Clinical Considerations and Guidelines**

- Antimicrobials should always be used as an adjunct to mechanical therapy [17,44]
- Proper diagnosis and case selection are essential [17]
- Short, targeted antimicrobials regimens are preferred [18]
- Emphasis on plaque control and maintenance therapy [57]

Discussion

Periodontal and peri-implant diseases are biofilm-induced inflammatory conditions driven by pathogens such as Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Tannerella forsythia, and Treponema denticola [7,8]. While scaling and root planing (SRP) is the gold standard [3], adjunctive antimicrobials are beneficial in aggressive and refractory cases where pathogens persist [9,11,12].Local delivery systems provide high intra-pocket concentrations with minimal systemic effects and yield modest improvements in PPD and CAL [21,33]. Systemic amoxicillin with metronidazole shows synergistic benefits, particularly in aggressive periodontitis [47].In peri-implantitis, adjunctive antimicrobials reduce BOP and microbial load, though long-term results vary 66-71. Emerging therapies show promise but require further validation [72-78]. Careful case selection and antimicrobial stewardship remain essential for predictable outcomes [54-57].

Conclusion

Antimicrobial therapy plays a valuable adjunctive role in the management of periodontal diseases when used judiciously and in combination with mechanical debridement. [17,44] Proper case selection, understanding of pharmacological properties, and adherence to evidence-based guidelines are essential to maximize clinical benefits while minimizing risks. [18] Rational use of antimicrobial agents is critical in the era of increasing antimicrobials resistance. [54]

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