REVIEW ARTICLE

Antibiotics for Periodontal Infections: Biological and Clinical Perspectives

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Abstract

Aim: The review is to highlight the use of antibiotics in periodontal infections and prevent indiscriminate use of antibiotics.

Background: Periodontitis is the most common disease of the periodontal attachment apparatus, and its etiological factor can be related to the existence of virulent microorganisms in the dental plaque biofilm which harbors millions of microorganisms. In addition, the pathogenesis of this disease is greatly influenced by the host immune response that leads to the cyclic destruction and healing pattern.

Review results: Periodontitis is mostly treated through mechanical debridement using surgical and nonsurgical therapy. However, many times, this treatment does not render desired results due to poor patient compliance, altered immune response, or other host-related factors. This leads to the administration of antibiotics as an adjunct to mechanical debridement. Antibiotics are useful in eliminating periodontopathic microbes, but these agents should be cautiously used and prescribed only if indicated.

Conclusion: Indiscriminate use of antibiotics can lead to unforeseen adverse effects as well as the development of resistant strains of microorganisms.

Clinical significance: Hence, it is crucial for the dentists to know the indications, contraindications, undesirable effects, correct choice, and dosage of the antimicrobial agent before prescribing it to their patients thereby ensuring the success of periodontal therapy. Thus, the clinician should keep in mind that the antibiotics are merely adjuncts to mechanical therapy and not its replacement.

Keywords: Antibiotic, Periodontitis, Plaque control, Periodontal pathogen.

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Background

Dental plaque is "the nonmineralized microbial accumulation that adheres tenaciously to tooth surface, restorations, and prosthetic appliances, shows structural organization with predominance of filamentous forms, is composed of an organic matrix derived from salivary glycoproteins and extracellular microbial products, and cannot be removed by rinsing or water spray".[1] Biofilms are "matrix-enclosed bacterial population's adherent to each other and/or to surfaces or interfaces."[2] The extracellular polymeric component on interaction with the host tissue will result in disease.[3] The prolonged and unattended presence of the plaque in the oral cavity can lead to periodontitis and dental caries.[4]

The presence of dental plaque leading to disease in the oral cavity is explained by the following theories:

- Specific plaque hypothesis (Loesche 1976): this suggests that the presence of specific bacterial species within the dental plaque will lead to disease, and the absence of these species results in healthy mouth.[5]
- The nonspecific plaque hypothesis updated (Theilade 1986): describing the overall increase in the nonspecific microbial count in the dental plaque around teeth as a relatively homogeneous mass leads to gingivitis. However, some indigenous subgingival bacteria can be more virulent than others; they influence the host's defense mechanism.[6]
- Ecologic plaque hypothesis (Marsh 1994): this theory states that unique local environment influences the composition of oral microflora, and any disturbance in this balance may lead to increase in pathogenic microflora over harmless normal oral micro flora.[7]

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The periodontal disease is an inflammatory entity of microbial etiology affecting the periodontal apparatus leading to loss of attachment mostly seen in the elderly population. It is majorly classified into two types: gingivitis and periodontitis. Gingivitis is a reversible condition that affects the gingiva and is commonly seen among all age groups, whereas periodontitis affects the entire periodontal architecture leading to periodontal destruction, pocket formation, recession, and subsequently loss of a tooth. It has been postulated that pathogenesis of periodontitis occurs in a cyclic manner with periods of exacerbation, remission, and latency that is a result of the host immune response.[8]

The most common form of periodontitis is chronic periodontitis which leads to slow progression of bone loss and attachment loss.[9,10] Supra and subgingival deposits are the main causes of periodontal disease; hence, mechanical debridement is the first line of treatment as it reduces the microbial load. However, despite the mechanical plaque removal, the residual presence of microorganism persists, making the antibiotic therapy desirable to fight the pathogens and stop disease progression.[9,11]

The Rationale for the Prescription of Antibiotics in Periodontal Therapy

Diseases of the periodontium are divided into chronic periodontitis and aggressive periodontitis; both of which termed as localized or generalized depending on their site of occurrence. Furthermore, it is classified as: periodontitis associated with systemic diseases, necrotizing ulcerative gingivitis, and endodontic lesions.[12] Among all these above-mentioned entities, chronic periodontitis is the most commonly observed type in adults. The predisposing risk factors for periodontal disease are subgingival plaque accumulation, stress, smoking, immunological disorders, nutritional deficiency, traumatic occlusion, etc.[13] The subgingival plaque is a complex microbial ecosystem with more than 500 microbial species of microorganisms.[14] Some of these microbial species have been identified as the causative organisms for the periodontal disease under the effect of local and systemic causes. Among the oral flora, the most important are *Porphyromonas gingivalis* (seen in chronic periodontitis), *Aggregatibacter actinomycetemcomitans* (seen in aggressive periodontitis), *Bacteroides* sp., *Treponema* sp., *Fusobacterium* sp., *Prevotella* sp., *Campylobacter* sp., and *Eikenella.* The Socransky complexes, red and orange complex microorganisms, were commonly seen in 5 mm and more periodontal depth and attachment loss cases.[15–17]

These periodontal microorganisms play a vital role in the occurrence of the disease; however, it is not the only factor responsible. The host immune response plays a vital role in the pathogenesis of periodontal disease causing the cyclic pattern of remission and exacerbation.[18] The increased levels of inflammatory mediators, such as interleukin-1β, prostaglandins, and tumor necrosis factor α, lead to the chronic and persistent inflammation that causes the destruction of periodontal tissues.[19,20] These mediators result in the destruction of alveolar bone mediated by the activation of tissue degradation factors like polymorphonuclear serine proteases, plasminogen, and matrix metalloproteinases.[21,22]

Mechanical periodontal therapy, i.e., surgical and nonsurgical debridement of the dental plaque along with patient education for maintenance of good personal oral hygiene and follow-up and thereby removal of local irritating factors is the mainstay for treatment of periodontal disease. The strength and success of this approach have been proven time and again by longitudinal studies. The potency of the approach is evaluated by the resolution of clinical signs and symptoms, removal of periodontal microbes, and repopulation of the oral cavity by beneficial microorganisms. Conventional mechanical therapy does not yield favorable results with all patients or sites. The antibiotics use is recommended during certain kinds of periodontal disease because of their infective nature and the limitations of conventional mechanical therapy.[23,24]

The debate over the significance of an exclusive microbial etiology of periodontal infections may never be completely dissolved. Nevertheless, there is a slight question that certain specific microorganisms are related to certain phases of periodontal diseases.[6] The sustained and total elimination of periodontal pathogens is a very difficult endeavor as all these pathogens belong to the indigenous flora of the oral cavity; hence, there is immediate repopulation and oral biofilm formation soon after completion of mechanical periodontal debridement.[25–27] Nevertheless, in periodontitis, one of the specific manifestations is the faster loss of connective tissue leading to deep pockets with gram-negative and highly virulent strains of bacteria. In such cases, antimicrobials would prove to be valuable adjuncts to mechanical therapy as professional debridement alone may not be capable of effectively eliminating all the microbes in the periodontal tissues (Table 1).[28,29]

Ideal properties of antibiotic:

- The antibiotics can be targeted to specific virulent microorganisms;
- Targeted use of narrow-spectrum antibiotics results in the elimination of selective pathogen that does not disturb the normal microbiota;
- Desired high therapeutic index ratio, so that the drug can be administered without toxic effects;
- The antibiotics should have minimal or no drug reactions;
- The antibiotic should have different routes of administration like intravenous, intramuscular, oral administration;
- The antibiotics should possess desirable pharmacokinetics and pharmacodynamics properties;
- The antibiotics should not develop resistance or preferable slower emergence.

Antibiotic of Choice

The success of antibiotic therapy depends on the potency of the agent used against the culprit microbe. The choice of antibiotic regimen is difficult to periodontal disease as it is a mixed

Table 1: Classification of antibiotics on the basis of the mechanism of action[30]

Mechanism of action	*Example*
Inhibition of synthesis of bacterial cell walls	Penicillin and cephalosporin
Affecting permeability by interference with the cell membrane of the microorganism	Antifungal agents
Inhibition of protein synthesis by affecting the function of the 30S or 50S ribosomal subunits	Tetracycline, macrolides, and clindamycin
Blocking of important metabolic steps	Sulfonamides and trimethoprim
Interference with nucleic acid synthesis	Metronidazole and quinolones

microbe disease. Antibiotics are target specific, i.e., each acts on a particular part of the oral biofilm. For instance, *T. denticola*, *F. nucleatum*, *P. gingivalis*, and *B. forsythia*, belonging to the red and orange Socransky complexes are gram-negative strict anaerobes and are specifically targeted by metronidazole, whereas it marginally affects genera *Actinomyces*, *Streptococcus*, and *Capnocytophaga* that belong to the green complex.[30–32] Metronidazole also has a limited effect on facultative anaerobe, for example, *A. actinomycetemcomitans*. A broad-spectrum drug is amoxicillin that affects both gram-negative anaerobes and *Actinomyces* species.[31,33] A large array of antibiotics are used as adjuncts to nonsurgical and surgical therapy in the treatment of periodontal disease. The commonly used antimicrobials in periodontal therapy are tetracycline, metronidazole, penicillin, macrolides, ciprofloxacin, and clindamycin. Metronidazole and amoxicillin are reported to be the most commonly used combination antibiotic regimen.[31]

Duration, Dosage, and Timing of Antibiotics in Periodontal Therapy

An extensive search of the literature reveals that there is no agreement on the ideal regimen, dosage, and duration of antibiotic therapy for periodontal disease. According to the guidelines of antibiotic therapy, the onset of antibiotic therapy with respect to mechanical therapy is of high relevance. Indirect evidence hints, antibiotic therapy should begin on the last day of mechanical therapy and for a short time, except in patients with the immunocompromised state where prophylactic antibiotics are recommended.[31,34] Tab le 2 shows some of the commonly prescribed antibiotic regimes for periodontitis.

Importance of Patient Compliance in the Success of Antibiotic Therapy

The issue of patient consistency has been rarely tended in the literature, specifically in assessing the impacts of systemic antimicrobials. Studies have reported that merely 20% of patients conform to the regimen prescribed.[31,35] Azithromycin is preferred because of its long half-life and pharmacologic properties. One tablet (500 mg) every day for three continuous days instead of multiple antimicrobial regimens.[31,36] Compliance as far as oral cleanliness and upkeep consideration is ought to be understood. Studies where positive results emulating adjunctive anti-infection agents were accounted for, patients had received periodic maintenance and had acceptable oral hygiene. In the event where the patient is noncompliant with oral cleanliness measures, a positive treatment result taking after adjunctive antimicrobial agents may not be possible. Antibiotic therapy is not an alternative but only an adjuvant to good oral hygiene and regular maintenance.[31]

Table 2: Commonly prescribed antibiotic regimen for periodontitis

Antibiotic	*Dosage*
Metronidazole	500 mg/t.i.d./8 days
Clindamycin	300 mg//t.i.d./8 days
Doxycycline/minocycline	100–200 mg/q.d./21 days
Ciprofloxacin	500 mg/b.i.d./8 days
Azithromycin	500 mg/q.d./4–7 days
Metronidazole + amoxicillin	250 mg/t.i.d./8 days (each drug)
Metronidazole + ciprofloxacin	500/b.i.d./8 days (each drug)

Contraindications and Adverse Effects

An extensive literature search has revealed several lacunae in the area concerning reporting of adverse events following the use of antibiotic therapy in the treatment of periodontal disease. Most adverse effects account for minor gastrointestinal tract disturbances, such as diarrhea and nausea. However, genuine adverse occasions, for example, hypersensitive and anaphylactic response and pseudomembranous colitis, are reported, and patients have to be educated to the potential risks while prescribing systemic antibiotics. The adverse effects of penicillin witnessed are often mild like rashes, urticaria, dermatitis, and joint pains. The anaphylactic reaction in response to penicillin occurs approximately one in every 10,000 patients encountered, and about 10% of these prove to be fatal.[31,37] Utilization of antibiotics is ought to be painstakingly considered by selecting antimicrobials that expand antimicrobial action and minimize potential medication interactions and adverse effects. An extensive medicinal history should be taken preceding antibiotic prescription.

The most commonly prescribed pharmaceutical agents in the current medical practice are antibiotics, and it is imperative for a periodontist to be well aware of the contraindications and possible adverse effects of the antibiotics used in the treatment of periodontal diseases. The contraindications for use of antibiotics are related to their pharmacokinetics and pharmacodynamics properties. Hence, caution should be exercised while prescribing antibiotics to patients with impaired renal or hepatic functions. An exhaustive medical history will also help in ruling out the instances of allergies and anaphylactic reactions related to antibiotics such as penicillin.[38]

Antimicrobial Resistance in Biofilms

Biofilms have significantly high antimicrobial resistance when compared with their free-floating counterparts, which spawns severe concerns in the treatment procedure. Antimicrobial resistance of microorganisms inherent or arise as a result of the emergence of resistant strains of bacteria.[31] A few studies have evaluated the increase in antimicrobial resistance in oral biofilm post-antimicrobial therapy. Feres et al. have reported patients of chronic periodontitis treated by nonsurgical periodontal treatment followed by oral antimicrobial therapy to have antibiotic-resistant species in saliva and plaque samples.[39] An increase in microbial resistance has been reported in countries where antibiotics are sold over the counter without a prescription in comparison with where antibiotics sale is more restricted and only with prescription.[40] This highlights the significance of microbial resistance in antibiotics, thereby making it use more responsibly to prevent the spread of resistant microbial strains globally.[31]

Intrinsic, mutational, and acquired resistance are the three major mechanisms by which antimicrobial resistance occurs.[30,41,42] Intrinsic resistance is the inherent naturally occurring resistance of an organism to an antibiotic. Mutational resistance occurs due to the formation of a genetically different microbial population as a result of spontaneous chromosomal alteration. This kind of resistance has been observed for aminoglycosides and rifampin where a change in a single nucleotide base has occurred in microorganism.[30,41] Finally, acquired resistance occurs by transduction, transformation, or conjugation where there is horizontal acquisition of a genetic element. Transduction involves the intervention of a bacteriophage that facilitates the transfer of exogenous DNA from one microbe to

another, whereas during transformation, the microorganisms take up available DNA from the surrounding environment. Conjugation is the most common mechanism by which transfer of antibiotic resistance genes occurs, where there is a direct cell-to-cell contact for the transfer of genetic material.[30,41,42] Hence, the three main strategies used by bacteria for resistance to different antimicrobials are prevention of the drug from reaching its target, alteration of the target, and inactivation of the particular antimicrobial agent.[43–48]

Experts have postulated different mechanisms to explain the higher resistance of antibiotics in oral biofilms. The defensive mechanisms employed in the biofilm seem to be discrete from those, which are accountable for conventional antimicrobial resistance.

They all appear during the final stage of biofilm maturation.[49,50] The presence of enzymes, β-lactamases, leads to less penetration of the antibiotic in the oral biofilm. The secretion of the exopolysaccharide matrix further prevents penetration of antimicrobials by forming a protective coating or binding the antimicrobial.[49,51–54] Several authors have documented the presence of various microenvironments in the biofilms, and they differ in their metabolism, oxygenation, and pH, thereby providing evidence of the complex heterogeneity within biofilms.[55,56] The oral biofilm is a biologically programmed structural growth on a surface that has specific metabolic, interactive, physiological functions, and genetic expressions that are quite unique. This diversity is termed as the "biofilm phenotype" and is reported to be the underlying cause of antimicrobial resistance in biofilms.[57–60] Increased resistance to antimicrobials in biofilms is a result of a combination of all or some of these mechanisms acting together as a multilayered defense during biofilm maturation. These mechanisms function in a reversible and transient way adding to the higher antimicrobial resistance. The following factors have an influence on the development of drug resistance:

- Change in the metabolism;
- The presence of the extracellular polymeric substance;
- Genomic and proteomic regulation;
- Persister cells survive and repopulate after antibiotic therapy;
- High-stress response leads to the development of drug resistance;
- Poor antibiotic penetration and dosage can lead to the development of drug resistance.

Conclusion

Herrera et al. concluded that antibiotics should be used with periodontal therapy only when indicated and act as an adjunct to mechanical treatment.[34] Nevertheless, indirect evidence ropes in the disagreement that antibiotic therapy should be started on the last day of mechanical debridement and be for a brief duration of time (<1 week) to ensure patient compliance. Mechanical plaque control is the mainstay for the prevention and treatment of periodontal disease, but it requires immense patient cooperation and motivation; therefore, antimicrobial therapy acts as a useful adjuvant for achieving the desired results. Hence, it is imperative for the clinician to know the effect of these agents so that they can provide the patients with tailor-made prescriptions and make periodontal therapy a success.[61] Furthermore, antimicrobial therapy should be prescribed with caution keeping in mind the adverse effects and the increasing microbial resistance. There need to be standard guidelines in periodontal and peri-implant conditions.[62]

Clinical Significance

Hence, it is crucial for the dentists to know the indications, contraindications, undesirable effects, correct choice, and dosage of the antimicrobial agent before prescribing it to their patients, thereby ensuring the success of periodontal therapy. Thus, the clinician should keep in mind that the antibiotics are merely adjuncts to mechanical therapy and not its replacement.

References

1. Nolte WA. Oral ecology. In: Nolte WA, ed. Oral microbiology. 2nd ed., St. Louis: Mosby; 1973. p. 21.
2. Costerton JW, Lewandowski Z, DeBeer D, et al. Biofilms, the customized microniche. J Bacteriol 1994;176(8):2137–2142.
3. Hojo K, Nagaoka S, Ohshima T, et al. Bacterial interactions in dental biofilm development. J Dent Res 2009;88(11):982–990.
4. Axelsson P. Preventive material, methods, and programs, Vol. 4. Chicago: Quintessence Publishing Co. Inc.; 2004.
5. Loesche WJ. Chemotherapy of dental plaque infections. Oral Sci Rev 1976;9:65–107.
6. Theilade E. The non-specific theory in microbial etiology of inflammatory periodontal diseases. J Clin Periodontol 1986;13(10):905–911.
7. Marsh PD. Host defenses and microbial homeostasis: role of microbial interactions. J Dent Res 1989;68:1567–1575.
8. Pejcic A, Pesevska S, Grigorov I, et al. Periodontitis as a risk factor for general disorders. Acta Facult Med Naiss 2006;23(1):59–65.
9. Jenabian N, Moghadamnia A, Abdollahi Y, et al. Comparison of the efficacy of short-term and long-term azithromycin regimen with metronidazole and amoxicillin for treatment of moderate chronic periodontitis in adults. J Dent School 2013;31:37–43.
10. Bidault P, Chandad F, Grenier D. Systemic antibiotic therapy in the treatment of periodontitis. J Can Dent Assoc 2007;73(6):515–520.
11. Moeintaghavi A, Talebi-ardakani MR, Haerian-ardakani A, et al. Adjunctive effects of systemic amoxicillin and metronidazole with scaling and root planing: a randomized, placebo-controlled clinical trial. J Contemp Dent Pract 2007;8(5):51–59.
12. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4(1):1–6.
13. Van Dyke TE, Shailesh D. Risk factors for periodontitis. J Int Acad Periodontol 2005;7(1):3–7.
14. Paster BJ, Boches SK, Galvin JL, et al. Bacterial diversity in human subgingival plaque. J Bacteriol 2001;183(12):3770–3783.
15. Nishihara T, Koseki T. Microbial etiology of periodontitis. Periodontol 2000 2004;36:14–26.
16. Feng Z, Weinberg A. Role of bacteria in health and disease of periodontal tissues. Periodontol 2000 2006;40:50–76.
17. Slots J, Ting M. *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* in human periodontal disease: occurrence and treatment. Periodontol 2000 1999;20:82–121.
18. Schenkein HA. Host responses in maintaining periodontal health and determining periodontal disease. Periodontol 2000 2006;40:77–93.
19. Kinane DF, Lappin DF. Clinical, pathological and immunological aspects of periodontal disease. Acta Odontol Scand 2001;59(3): 154–160.
20. Madianos PN, Bobetsis YA, Kinane DF. Generation of inflammatory stimuli: how bacteria set up inflammatory responses in the gingiva. J Clin Periodontol 2005;32(Suppl 6):57–71.
21. Sorsa T, Tjäderhane L, Salo T. Matrix metalloproteinases (MMPs) in oral diseases. Oral Dis 2004;10(6):311–318.
22. Reynolds JJ, Meikle MC. Mechanisms of connective tissue matrix destruction in periodontitis. Periodontol 2000 1997;14:144–157.
23. Kaldahl WB, Kalkwarf KL, Patil KD. A review of longitudinal studies that compared periodontal therapies. J Periodontol 1993;64(4):243–253.
24. Kaldahl WB, Kalkwarf KL, Patil KD, et al. Long-term evaluation of periodontal therapy: I. Response to 4 therapeutic modalities. J Periodontol 1996;67(2):93–102.

25. Zambon JJ, Christersson LA, Slots J. *Actinobacillus actinomycetemcomitans* in human periodontal disease. Prevalence in patient groups and distribution of biotypes and serotypes within families. J Periodontol 1983;54(12):707–711.
26. Wolff LF, Liljemark WF, Bloomquist CG, et al. The distribution of *Actinobacillus actinomycetemcomitans* in human plaque. J Periodontal Res 1985;20(3):237–250.
27. van Palenstein Helderman WH. Is antibiotic therapy justified in the treatment of human chronic inflammatory periodontal disease? J Clin Periodontol 1986;13(10):932–938.
28. Gillett R, Johnson NW. Bacterial invasion of the periodontium in a case of juvenile periodontitis. J Clin Periodontol 1982;9(1):93–100.
29. Saglie R, Newman MG, Carranza Jr FA, et al. Bacterial invasion of gingiva in advanced periodontitis in humans. J Periodontol 1982;53(4):217–222.
30. Soares GM, Figueiredo LC, Faveri M, et al. Mechanisms of action of systemic antibiotics used in periodontal treatment and mechanisms of bacterial resistance to these drugs. J Appl Oral Sci 2012;20(3): 295–309.
31. Heitz-Mayfield LJ. Systemic antibiotics in periodontal therapy. Aust Dent J 2009;54(1 Suppl):S96–S101.
32. Socransky SS, Haffajee AD, Cugini MA, et al. Microbial complexes in subgingival plaque. J Clin Periodontol 1998;25(2):134–144.
33. Feres M, Haffajee AD, Allard K, et al. Change in subgingival microbial profiles in adult periodontitis subjects receiving either systemically-administered amoxicillin or metronidazole. J Clin Periodontol 2001;28:597–609.
34. Herrera D, Alonso B, León R, et al. Antimicrobial therapy in periodontitis: the use of systemic antimicrobials against the subgingival biofilm. J Clin Periodontol 2008;35(8 Suppl):45–66.
35. Llor C, Sierra N, Hernández S, et al. The higher the number of daily doses of antibiotic treatment in lower respiratory tract infection the worse the compliance. J Antimicrob Chemother 2009;63(2):396–399.
36. Foulds G, Shepard RM, Johnson RB. The pharmacokinetics of azithromycin in human serum and tissues. J Antimicrob Chemother 1990;25(Suppl A):73–82.
37. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the american heart association: a guideline from the american heart association rheumatic fever, endocarditis, and kawasaki disease committee, council on cardiovascular disease in the young, and the council on clinical cardiology, council on cardiovascular surgery and anesthesia, and the quality of care and outcomes research interdisciplinary working group. Circulation 2007;116(15):1736–1754.
38. Pejčić A, Kesić L, Obradović R, et al. Antibiotics in the management of periodontal disease. Sci J Fac Med Niš 2010;27(2):85–92.
39. Feres M, Haffajee AD, Allard K, et al. Antibiotic resistance of subgingival species during and after antibiotic therapy. J Clin Periodontol 2002;29(8):724–735.
40. van Winkelhoff AJ, Herrera D, Oteo A, et al. Antimicrobial profiles of periodontal pathogens isolated from periodontitis patients in The Netherlands and Spain. J Clin Periodontol 2005;32(8):893–898.
41. Walker CB. The acquisition of antibiotic resistance in the periodontal microflora. Periodontol 2000 1996;10:79–88.
42. Walker CB. Selected antimicrobial agents: mechanisms of action, side effects and drug interactions. Periodontol 2000 1996;10:12–28.
43. Nikaido H. Multidrug resistance in bacteria. Annu Rev Biochem 2009;78:119–146.
44. Nikaido H. Prevention of drug access to bacterial targets: permeability barriers and active efflux. Science 1994;264(5157):382–388.
45. Ince D, Hooper DC. Quinolone resistance due to reduced target enzyme expression. J Bacteriol 2003;185(23):6883–6892.
46. Spratt BG. Resistance to antibiotics mediated by target alterations. Science 1994;264(5157):388–393.
47. Davies J. Inactivation of antibiotics and the dissemination of resistance genes. Science 1994;264(5157):375–382.
48. Robicsek A, Strahilevitz J, Jacoby GA, et al. Fluoroquinolone-modifying enzyme: a new adaptation of a common aminoglycoside acetyltransferase. Nat Med 2006;12(1):83–88.
49. Sedlacek MJ, Walker C. Antibiotic resistance in an *in vitro* subgingival biofilm model. Oral Microbiol Immunol 2007;22(5):333–339.
50. Rickard AH, Gilbert P, High NJ, et al. Bacterial coaggregation: an integral process in the development of multi-species biofilms. Trends Microbiol 2003;11(2):94–100.
51. De Beer D, Srinivasan R, Stewart PS. Direct measurement of chlorine penetration into biofilms during disinfection. Appl Environ Microbiol 1994;60(12):4339–4344.
52. Suci PA, Mittelman MW, Yu FP, et al. Investigation of ciprofloxacin penetration into Pseudomonas aeruginosa biofilms. Antimicrob Agents Chemother 1994;38(9):2125–2133.
53. Stewart PS. Theoretical aspects of antibiotic diffusion into microbial biofilms. Antimicrob Agents Chemother 1996;40(11):2517–2522.
54. Stewart PS. Diffusion in biofilms. J Bacteriol 2003;185:1485–1491.
55. Wimpenny J. Laboratory models of biofilm. In: Heman HN, Wilson M, ed. Dental plaque revisted: oral biofilms in health and disease. Cardiff: Bioline; 1999. pp. 89–110.
56. de Beer D, Stoodley P, Roe F, et al. Effects of biofilm structures on oxygen distribution and mass transport. Biotechnol Bioeng 1994;43(11):1131–1138.
57. Mah TF, O'Toole GA. Mechanisms of biofilm resistance to antimicrobial agents. Trends Microbiol 2001;9(1):34–39.
58. Sauer K. The genomics and proteomics of biofilm formation. Genome Biol 2003;4(6):219.
59. Brooun A, Liu S, Lewis K. A dose-response study of antibiotic resistance in Pseudomonas aeruginosa biofilms. Antimicrob Agents Chemother 2000;44(3):640–646.
60. Mah TF, Pitts B, Pellock B, et al. A genetic basis for pseudomonas aeruginosa biofilm antibiotic resistance. Nature 2003;426(6964): 306–310.
61. Hai JH, Lee C, Kapila YL, et al. Antibiotic prescribing practices in periodontal surgeries with and without bone grafting. J Periodontol 2019. DOI: 10.1002/JPER.19-0195. [Epub ahead of print].
62. Ong A, Kim J, Loo S, et al. Prescribing trends of systemic antibiotics by periodontists in Australia. J Periodontol 2019;90(9):982–992.