REVIEW ARTICLE OPEN ACCESS

Antibiotic Treatment in Oral Disease: A Review of Basic Mechanism of Antibiotics in Dentistry

Bunyanuch Rattanawongsaroj*, Sathid Aimjongjun**
*Satriwit School , Phra Nakhon , Bangkok , Thailand 10200
Email: jeen38174@gmail.com
** Department of Fundamental Science and Medical Science,
Pathumthani University, Mueang Pathum Thani District, Pathum Thani, Thailand12000
Email: sathid.a@ptu.ac.th

----------**********----------

Abstract:

Dentists commonly prescribe the antibiotics for controlling and treating the oral infections. Antibiotics had been helpful in treatment of infectious diseases considered dread for more than 100 years. Nowadays, there are many kinds of systemic antibiotics have been used in dental infection treatment. To reviewed the basic mechanism of antibiotic used in dentistry field, the dental antibiotic can interact on the cellular target by cell wall inhibition, protein DNA/RNA inhibition, antimetabolites inhibition, and/or cell membrane inhibition. Moreover, those antibiotics are also important used in dental procedures for prophylaxis in odontogenic, nonodontogenic, local/focal infection, and non-odontogenic infections treatment. However, widespread abuse of antibiotics in medical and dental field displays increased risk of adverse drug effect and importantly developmental propagation of antimicrobial resistant. Therefore, the present review focuses to summarize the basic mechanism of antibiotic therapy in dentistry. Moreover, indication of systemic dental antibiotic part also reviewed.

Keywords **—Antibiotics, Dentistry, Mode of action, Antimicrobial resistant, Odontogenic**

----------**********----------

I. INTRODUCTION

Middle of the last century, antibiotics were originally viewed as “wonder drugs” primarily because they were available to treat serious bacterial infections. Prior to 1940 infections were either treated with surgical drainage, antiseptics, silver compounds, arsenical, or with tincture [1]. Today more than 100 different kinds of antibiotics have been discovered, which humans had exploited these chemicals to cure various kinds of infectious diseases. In particular antibiotics are repeatedly used in dental practice. It has been approximated that 10 % of all common antibiotic prescriptions (beta lactams, macrolides, tetracyclines, clindamycin, metronida- zole) are related with dental infection and frequently ranked in the top 5 of antibiotic prescribers [2, 3]. Antibiotics are routinely prescribed in dental practice to control infections or to reduce the significance of infectious diseases [4]. Antibiotics are indicated for the treatment of odontogenic infections and oral non-odontogenic infections. They act as the prophylaxis against focal infection and local infection and also spreading prevention to surrounding tissues and neighbouring organs [4, 5]. Moreover, antibiotics are also crucial drug to control dental infections after surgical interventions such as incision, drainage, and pulp debridement [6].

The commonly prescribed antibiotics in dental practice include beta-lactam antibiotics containing a beta-lactam ring in their molecular structure such as penicillin. Most of gram-positive, gram-negative and anaerobic bacteria are susceptible to these anti-bacterial agents via cell wall synthesis inhibition[7, 8]. Nitroimidazoles or Metronidazole is the one of

the antimicrobial agents disrupting the DNA of the susceptible bacteria and inhibiting the cell wall protein synthesis used in therapeutic dentistry[9]. Those are specially administered to treat parasitic and anaerobic bacterial infections [10]. Moreover,bacteriostatic agents such as macrocyclic lactone ring can inhibit protein synthesis by modulate bacterial ribosomes which majorly act against gram positive beta-haemolytic streptococci [11]. Likes Macrolide, Erythromycin, Azithromycin, Clarithro- mycin, Lincosamides, and Clindamycin are the group of broad-spectrum antibiotics inhibit bacterial protein synthesis by targeting the 50s ribosomal protein [12]. Most of them are widely used to fight against both aerobic and anaerobic pathogens infected in oral disease. In addition, broad-spectrum bactericidal antibiotics such as Fluoroquinolones and its next generation, Ciprofloxacin and Moxi- floxacin mostly act against gram positive aerobic cocci, gram-negative bacilli, and anaerobic bacteria, by particularly preventing the bacterial DNA synthesis [13, 14]. Besides 50s ribosomal subunit targeting protein translation, Tetracycline is a bacteriostatic antibiotic that is energetic counter gram-positive and gram-negative bacteria by obstructing the protein synthesis through binding to the 30s ribosomal subunit [15, 16]. However, overabundantly using of antibiotics will lead to increase the unfavoured drug side effect and induce the development of antibiotics resistant bacterial species [17-19]. The spread of resistant infections is the severe global health problem that requires a global solution [19]. Therefore, there are many approaches aimed to protecting the emergence and spread of antibiotic resistant bacteria. Then, currently there are many research strategies aimed to develop new bacterial target antibiotics for the therapeutic approach. Alternatives to current antibiotic therapy also must be considered, either through the new drug classes development or through the use of vaccines, antibacterial substances or other return the ancient drug therapeutic strategies in dental practice [20, 21]

Thus, antibiotics have effectively remained the elective choice for treatment and precaution of the infectious diseases in medicine and dentistry sectors [22]. Curing only dental surgical removal method in patient without antibiotic treatment combination are absolutely fail to remedy the dental infection. Therefore, this present review attempts to update thecurrent knowledge and the summarize the antibiotics based on their mechanism of action used in dental prescribes which is providing further potential information and improvement of antibiotic stewardship in oral biology and medical sciences.

II. Basic Mechanisms of Antibiotic Action in Dental Practice

The common antibiotics used in dental practices are grouped on the basis of mechanism of action as described in Figure 1.

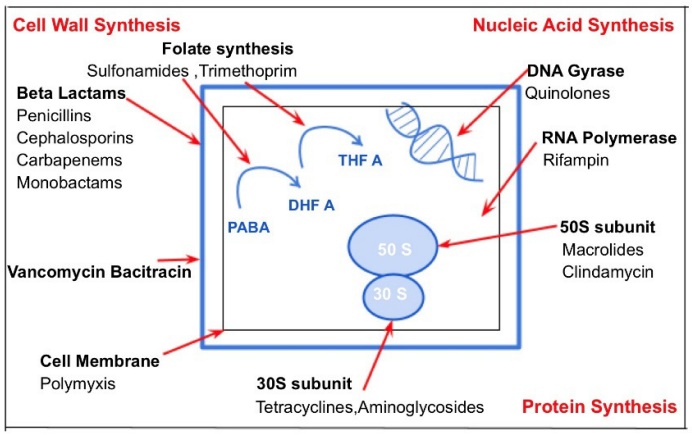

Figure 1.The basic mechanism action of antibiotics

Cell wall inhibition target

Peptidoglycan (also known as murein) is a rigid glycoprotein that makes up the cell wall in both gram-positive and gram-negative bacteria. Gram-positive bacteria, lack an outer membrane but are surrounded by layers of peptidoglycan which is thicker than the gram-negatives bacteria [23]. The function of peptidoglycan is the part of cell envelope and protects the cell from environmental stress rupturing and helps preserve cell shape. The biosynthesis peptidoglycan is also a main regulator of bacterial cell cycle [24]. The production of peptidoglycan occurred by the compose of polymerized glycan chains with cross-linked peptide substituents. The sugar component consists of alternating residues of β-(1,4) linked N-

acetylglu- cosamine (NAM) and N-acetylmuramic acid (NAG) [25]. Attached to the N-acetylmuramic acid is a peptide chain of three to five amino acids. The peptide chain can be cross-linked to the peptide chain of another strand forming the 3D peptido-glycan layer [26]. Maintenance of those layer is completed by the activity of transglycosylases and penicillin-binding proteins (PBPs; transpeptidases), which functions disaccharide pentapeptides to extend the glycan strands of existing peptidoglycan molecules adding and adjacent peptide strands of immature peptidoglycan cross-linking [27].

The most commonly used antimicrobial agents that inhibit cell wall biosynthesis include Beta - lactam antibiotics such as penicillins and cephalon-sporins. Beta-lactam antibiotics are classified into five classes: penicillin, cephalosporins, penems, carbapenems, and monobactams [1, 9]. The β-lactam antibiotics, which interfere with specific steps in homeostatic

cell wall biosynthesis by inhibit the transpep-tidation reaction resulting in cell shape and size morphology change, cell stress responses induction and eventually cell lysis [28]. The most common types of penicillin that used in dental infections are being administered odontogenic infections treatment including penicillin V, amoxicillin, and amoxi- cillin/clavulanic acid [10, 22]. They have been considered to be the gold standard for the first-line drug and the treatment of odontogenic infections [22]. Moreover, phenoxymethylpenicillin or amoxi- cillin has been administered for treatment gram-negative bacilli in nonallergic patients and used its combination of metronidazole or clavulanate to cure odontogenic bacterial infection [6]. To increase the treatment potency, the action of metronidazole can inhibit protein synthesis by interacting with DNA, and causes a loss of helical DNA structure and strand breakage [29]. In addition, clavulanic acid, the beta-lactamase inhibitors can work by precluding the penicillinase producing bacteria [30]. Therefore, those combinations are an appropriate option in the severe odontogenic infection cases, such as pulpitis and abscess [6]. Furthermore, cephalosporins and their combination with metronidazole also used to treat aerobic and anaerobic bacterial infected patient who are the penicillin allergy [31].

Cell membrane inhibition target

Bacterial membrane was considered to selective or disrupt multiple parts of the cell target for bacterial killing. The function of bacterial membrane provides selective permeability for cellular homeostasis and metabolic energy-transduction [32]. Basically, the bacterial membrane is arranged differently from a mammalian membrane is that an attractive target for new antibiotics development [33]. Gram-negative and Gram-positive bacteria contain phospholipids in their most including phosphatidylglycerol, phospha- tidylethanolamine and cardiolipin. Phosphatidyl- glycerol is normally found to be the most abundant of these three lipids and provided bacterial membrane stability[34]. These ability makes the bacteria membrane in anionic lipid and hence can be attract cationic peptides [35]. Polymyxin B or E is the peptide antibiotics can bind to lipid A anchoring for lipopolysaccharide in gram-negative bacteria [36]. Polymyxin B initially can accumulate in the outer membrane and consequently penetrates into the inner membrane and finally cause bacterial toxicity by interfering the outer membrane permeability [36]. Therefore, the commonly anti- biotic compounds used in implant dentistry such as polymyxin B and daptomycin. However, there are a lot of substance testing in clinical trial for membrane target drug discovery [37].

Antimetabolites target

In bacteria, one of their metabolisms is the folic acid biosynthesis. Folates are a family of molecules contain of three general elements: a core as central aromatic derived from para-amino benzoic acid (PABA), a modified pterin ring and a chain of one or more glutamates [38]. Many bacteria cannot take up folates directly into their cell however they can either make it by de novo reaction or take up the folate precursors such as para-amino benzoic acid (PABA) [39, 40]. The key for inhibit of the production of folate in bacterial cell is enzyme such as dihydropteroate synthase (DHP). In fact, sulfon-amides which is a substrate for that enzyme had been used to inhibit the THF biosynthesis at the site

of DHP by competition with p-aminobenzoic acid [41, 42]. In addition, Trimethoprim (TP) which is well known as antifolate drugs, inhibit dihydrofolate (DHF) reductase and are clinically used as antibacterial. In dentistry, sulfonamides are not used alone [43]. They can be applied in suppressive therapy of chronic UTI, for streptococcal pharyngitis, and gum infection [44, 45].

Protein DNA/RNA inhibition target

DNA, RNA and protein synthesis in the important requirement step for multiple cell division. Some antibacterial drugs work by inhibiting the synthesis of nucleic acid or interferes with DNA replication in bacterial cells [46]. Fluoroquinolones antibiotic class such as ciprofloxacin, ofloxacin, moxifloxacin is the broad spectrum that both against gram-positive and gram-negative bacteria [47]. Ciprofloxacin inhibits the replication of DNA by inhibiting bacterial DNA topoisomerase and DNA gyrase while ofloxacin action by inhibiting bacterial topoisomerase IV and DNA gyrase as well as moxifloxacin [48]. They are commonly prescribed for nonodontogenic infections, such as bacterial sinusitis, genitourinary tract, respiratory tract, joint, and bone infections [6]. In addition, moxifloxacin can be a good choice for both odontogenic and periodontal infections treatment [6]. Metronidazole is an DNA target antibiotic that is used to treat a wide variety of bacterial and parasitic infections. Their metabolites of metronidazole such as N-(2-hydroxyethyl) oxamic acid and acetamide can react with DNA and form adducts with guanosine leading to inhibit DNA synthesis [49].

Transcription is the process that the information of bacterial DNA can synthesize to messenger RNA. Rifampicin can Inhibits bacterial RNA polymerase activity and blocks transcription induce the bacterial cell death [50]. This drug can bind directly to in the polymerase subunit deep within the DNA/RNA complex, then facilitating direct blocking of the RNA elongation [50]. However, rifampicin is not a good choice for dental treatment or prophylaxis, it is used to recognized to prevent a risk of tuberculosis patients in dental management [51].

Finally, cellular bacterial protein can be translated from their messenger RNA by forming the complex of ribosome 50s and 30s catalysing subunits. Surely, the ribosomes found in bacterial cells (70S), are structurally specifical differed in animal cells ribosome (80S)[52]. The positively charged molecules of aminoglycosides (AG's) can attach to the outer membrane which is negatively charged leading to formation of large pores, and thus allow antibiotic up take in bacterial cells [53]. AG's can also directly interact with the 16S rRNA of the 30S subunit close to the A site leading cause misreading and premature termination of mRNA translation [54]. Tetracyclines, chlortetracycline, doxycycline, or minocycline can act upon directly the 16S r□RNA conserved sequences of the 30S ribosomal subunit to block binding of t-RNA to the A site of 30s [55]. 50S ribosome inhibitors include macrolides, lincosa- mides, streptogramins, amphenicols, and oxazolidi-none work by physically preventing either initiation of the translation of protein or blocking translocation of peptidyl tRNAs, which serves to inhibit the peptidyl transferase enzyme that nascent peptide chain elongation [56]. In the dental practice, azithromycin clarithromycin, or other in macrolide group is not recommend for the first line drug to treat the odontogenic infection, but they used for the patient who has allergised to the penicillin or its derivatives[4, 6].

III. Dental Antibiotic Indication

Antibiotic consider within the realm of dentistry has received growing attention with regards to both therapeutic and prophylactic therapy. The major use of antibiotic prophylaxis for dental procedures, are cases which cause bleeding in the oral cavity, has become a general practice among dentists [57]. Antibiotics are indicated in dental practice for treating immunocompromised patients, evident signs of systemic infection and if the signs and symptoms of infection progress rapidly[4, 57]. Moreover, following the guidance from the American Academy of Orthopedic Surgeons (AAOS) and the American Heart Association (AHA) recommendations prophylaxis antibiotic before dental visits was recommended in the past

for patients at high risk of some disease such as infective endocarditis (IE) and for patients with prosthetic joints to prevent prosthetic joint infections (PJIs)[58]. Additionally, the ADA developed guidelines for the management of dental pain and intra-oral swelling that largely considered against the use of more antibiotics for the treatment of infections without systemic involvement [58, 59].

Antibiotics for bacterial odontogenic infections

Odontogenic infection is the infection that basically originate in the teeth and/or their surrounding tissues. Normally the odontogenic infections cause mild symptoms and signs, however they can also develop into serious conditions. Despite the high incidence of odontogenic infections, there are no uniform criteria regarding the use of antibiotics to treat them [4]. Many oral diseases have been originated from odontogenic infection such as gum disease marginal periodontitis, apical periodontitis, pericoronitis, odontogenic maxillary sinusitis, osteomyelitis, necrotising fasciitis, Ludwig's angina and lemierre's syndrome [60]. In case of severe infection or serious disease that should be treated promptly by antibiotics because of the possibility of spread of infection via lymph and blood circulation, with the septicaemia development [61]. The most common species of bacteria found in odontogenic infections are the anaerobic gram-positive cocci such as *Streptococcus milleri, Strep- tococcus viridans Streptococcus anginosus Pepto- streptococci Prevotella Fusobacterium Porphy-romonas Bacteroides spp. Veilonella Actinomyces Propionobacterium Capnocytophaga*, and other uncommon pathogens including *Staphylococci spp* and enteric gram-negative bacilli [61].

Antibiotics for non-odontogenic infections

The non-odontogenic infections need to require a prolonged treatment. It is of utmost importance for dentists to be able to decide between infectious illnesses in the oral cavity and between having an oral or a nonoral origin. Those infections include tuberculosis, syphilis, leprosy and non-specific infections of bone [62]. New synthetic antibiotics such as fluoroquinolones are the drug of choice for management of non- odontogenic infections [6]. Fluoroquinones are firstly indicated for infection of bone and joint, infection of genitourinary tract, and respiratory tract infection [63]. Tuberculosis management recommends a long duration of antibiotic treatment which includes ethambutol, isoniazid, rifampicin, pyrazinamide and strepto-mycin [64]. Moreover, penicillin G is administered in the management of syphilis and clofazimine, dapsone and rifampicin are used for treating leprosy [65].

Antibiotic for prophylaxis of focal infection

The antibiotic prophylaxis refers to the antibiotics practice and administration for patients without signs of infection in order to reduce subsequent medical postoperative or post-treatment complications by the prevention of bacterial colonization. In dentistry, the most consideration for antibiotic prophylaxis have been to prevent infective endocarditis and prosthetic joint implant infection [57]. Infective endocarditis is an uncommon but serious and often life-threatening condition[6, 66]. The pathogenesis of infective endocarditis comprises of a complex sequence of events. Antibiotic prophylaxis for dental procedures may be appropriate for compromised immune systems person, artificial heart valves, histories with infection infective endocarditis, or heart transplants [67, 68].

Antibiotic for prophylaxis of local infection

Most commonly of dental local infection occur when bacteria invade the pulp and spread to nearby tissues. Traditionally the prophylaxis has been defined for preventing bacterial proliferation and dissemination in the surgical wound. The patient in case with removal of impacted teeth, periapical surgery, bone surgery, implant surgery, bone grafting and surgery for benign tumours have been risked of local infection [69, 70].

IV. ANTIBIOTICS RESISTANT IN DENTISTRY

Antibiotic resistance represents a worldwide public health risk that has the potential to increase the incidence of numerous morbidity and mortality due to unfolding of multi-resistant drug bacterial strains [71]. The discovery and more antibiotics usage are the major induction to natural selection for resistant bacteria [72]. In addition, many bacteria may also develop antibiotic resistance to

drug that used for treatment over time due to random chromosomal mutations [71]. However, these mutations can lead to changes in the gene product which lead in more resistant to the antibiotic than their parent [73]. Generally, the antibiotics prescribed most commonly dental practices are amoxicillin, penicillin and metronidazole [6]. These drugs have the potential to select for resistant bacteria within the commensal flora [74]. To assist efforts to reduce the unnecessarily and excessively usage, it is necessary that all healthcare workers or dentist must recognize and manage the dental infections to prevent the emergence and the spread of bacterial resistance.

V.FUTURE DIRECTION

This review suggests the following to improve appropriate use of antibiotics in the dental community. Firstly, to enhance education about the current and new antibiotic guidelines, recommend-dations and indications during both undergraduate and post graduate levels including more detail and deep information in dental antibiotic drug and resistance. Then to increase evidence-based research to document clinical benefits of antibiotic use, and to establish clinical practice guidelines.

VI. CONCLUSIONS

Antibiotic therapy is mandatory and essential in medicine and dentistry. In the past few years, there are a lot of data with a substantial increase in medical information, not only the mechanism of action that we mention, but also in the development of new inhibitors that could target on cellular strategies. Drug-resistant bacterial infections are becoming more prevalent and are a major health issue facing us today. Antibiotic usage has been linked to a variety of negative side effects, and the development of antimicrobial resistance. Understanding in bacterial resistant to antibiotic or how drug work is an important backgrounds training as well as in continuing in dental education programs to curb antibiotic abuse. Then, being able to explain the risks of antibiotics is a necessary part of consenting patients to treatment.

ACKNOWLEDGMENT

The authors wish to thank Treelearning coach team for helpful and suggestion of the manuscript.

REFERENCES

[1] Zinner, S.H., Antibiotic use: present and future. New Microbiol, 30(3): p. 321-5.2007.
[2] Hutchings, M.I., A.W. Truman, and B. Wilkinson, Antibiotics: past, present and future. Current Opinion in Microbiology, 51: p. 72-80, 2019.
[3] Durkin, M.J., et al., An evaluation of dental antibiotic prescribing practices in the United States. J Am Dent Assoc, 148(12): p. 878-886.e1. 2017.
[4] Oberoi, S.S., et al., Antibiotics in dental practice: how justified are we. International Dental Journal, 65(1): p. 4-10. 2015.
[5] Rocca, J.P., et al., Focal Infection and Periodontitis: A Narrative Report and New Possible Approaches. Int J Microbiol, p. 8875612. 2020.
[6] Ahmadi, H., A. Ebrahimi, and F. Ahmadi, Antibiotic Therapy in Dentistry. Int J Dent, p. 6667624. 2021.
[7] Sarkar, P., et al., A review on cell wall synthesis inhibitors with an emphasis on glycopeptide antibiotics. Medchemcomm, 8(3): p. 516-533. 2017.
[8] Ghooi, R.B. and S.M. Thatte, Inhibition of cell wall synthesis — is this the mechanism of action of penicillins? Medical Hypotheses, 44(2): p. 127-131. 1995.
[9] Qiu, W., et al., Application of Antibiotics/Antimicrobial Agents on Dental Caries. Biomed Res Int,p. 5658212. 2020.
[10] Kapoor, A., et al., Systemic antibiotic therapy in periodontics. Dent Res J (Isfahan), 9(5): p. 505-15. 2012.
[11] McCoy, L.S., Y. Xie, and Y. Tor, Antibiotics that target protein synthesis. WIREs RNA, 2(2): p. 209-232. 2011.
[12] Wilson, D.N., Ribosome-targeting antibiotics and mechanisms of bacterial resistance. Nature Reviews Microbiology, 12(1): p. 35-48. 2014.
[13] Stein, G.E. and E.J.C. Goldstein, Fluoroquinolones and Anaerobes. Clinical Infectious Diseases, 42(11): p. 1598-1607. 2006.
[14] Duggirala, A., et al., Activity of newer fluoroquinolones against gram-positive and gram-negative bacteria isolated from ocular infections: an in vitro comparison. Indian J Ophthalmol, 55(1): p. 15-9. 2007
[15] Chopra, I. and M. Roberts, Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev, 65(2): p. 232-60 ; second page, table of contents. 2001.
[16] Hamid, U. and A. Saqib, Classification of Anti - Bacterial Agents and Their Functions, in Antibacterial Agents, N.K. Ranjith, Editor, IntechOpen: Rijeka. p. Ch. 1. 2017 .
[17] Fair, R.J. and Y. Tor, Antibiotics and bacterial resistance in the 21st century. Perspect Medicin Chem, 6: p. 25-64. 2014.
[18] Chinemerem Nwobodo, D., et al., Antibiotic resistance: The challenges and some emerging strategies for tackling a global menace. Journal of Clinical Laboratory Analysis, 36(9): p. e24655. 2022.
[19] Ayukekbong, J.A., M. Ntemgwa, and A.N. Atabe, The threat of antimicrobial resistance in developing countries: causes and control strategies. Antimicrobial Resistance & Infection Control, 6(1): p. 47. 2017.
[20] Micoli, F., et al., The role of vaccines in combatting antimicrobial resistance. Nature Reviews Microbiology, 19(5): p. 287-302. 2021.
[21] Coates, A.R., G. Halls, and Y. Hu, Novel classes of antibiotics or more of the same? Br J Pharmacol, 163(1): p. 184-94. 2011.
[22] Guerrini, L., et al., Antibiotics in Dentistry: A Narrative Review of Literature and Guidelines Considering Antibiotic Resistance. The Open Dentistry Journal, 13: p. 383-398. 2019.
[23] Silhavy, T.J., D. Kahne, and S. Walker, The bacterial cell envelope. Cold Spring Harb Perspect Biol, 2(5): p. a000414. 2010.

[24] Vollmer, W., D. Blanot, and M.A. De Pedro, Peptidoglycan structure and architecture. FEMS Microbiology Reviews, 32(2): p. 149-167. 2008.
[25] Mihelič, M., et al., The mechanism behind the selection of two different cleavage sites in NAG-NAM polymers. IUCrJ, 4(Pt 2): p. 185-198. 2017.
[26] Irazoki, O., S.B. Hernandez, and F. Cava, Peptidoglycan Muropeptides: Release, Perception, and Functions as Signaling Molecules. Front Microbiol, 10: p. 500. 2019.
[27] Sauvage, E., et al., The penicillin-binding proteins: structure and role in peptidoglycan biosynthesis. FEMS Microbiology Reviews, 32(2): p. 234-258. 2008.
[28] Kong, K.F., L. Schneper, and K. Mathee, Beta-lactam antibiotics: from antibiosis to resistance and bacteriology. Apmis,118(1): p. 1-36. 2010.
[29] Uzlikova, M. and E. Nohýnková, The effect of metronidazole on the cell cycle and DNA in metronidazole-susceptible and -resistant Giardia cell lines. Molecular and biochemical parasitology, 198. 2015.
[30] Reading, C. and M. Cole, Clavulanic acid: a beta-lactamase-inhiting beta-lactam from Streptomyces clavuligerus. Antimicrob Agents Chemother, 11(5): p. 852-7. 1977.
[31] Nicolau, D.P., et al., Cephalosporin-metronidazole combinations in the management of intra-abdominal infections. Diagn Microbiol Infect Dis, 22(1-2): p. 189-94. 1995.
[32] Hurdle, J.G., et al., Targeting bacterial membrane function: an underexploited mechanism for treating persistent infections. Nat Rev Microbiol, 9(1): p. 62-75. 2011.
[33] John, T., et al., How kanamycin A interacts with bacterial and mammalian mimetic membranes. Biochimica et Biophysica Acta (BBA) - Biomembranes, 1859(11): p. 2242-2252. 2017.
[34] Sohlenkamp, C. and O. Geiger, Bacterial membrane lipids: diversity in structures and pathways. FEMS Microbiology Reviews, 40(1): p. 133-159. 2016.
[35] Murzyn, K., T. Róg, and M. Pasenkiewicz-Gierula, Phosphatidylethanolamine-phosphatidylglycerol bilayer as a model of the inner bacterial membrane. Biophys J, 88(2): p. 1091-103. 2005.
[36] Ayoub Moubareck, C., Polymyxins and Bacterial Membranes: A Review of Antibacterial Activity and Mechanisms of Resistance. Membranes (Basel), 10(8). 2020.
[37] Hughes, J.P., et al., Principles of early drug discovery. Br J Pharmacol, 162(6): p. 1239-49. 2011.
[38] Krátký, M., et al. 4-Aminobenzoic Acid Derivatives: Converting Folate Precursor to Antimicrobial and Cytotoxic Agents. Biomolecules, 10, DOI: 10.3390/biom10010009. 2020.
[39] Rossi, M., A. Amaretti, and S. Raimondi, Folate production by probiotic bacteria. Nutrients, 3(1): p. 118-34. 2011.
[40] Maynard, C., et al., A bacterial route for folic acid supplementation. BMC Biol, 16(1): p. 67. 2018.
[41] Cheong, M.S., et al., Influence of Sulfonamide Contamination Derived from Veterinary Antibiotics on Plant Growth and Development. Antibiotics (Basel), 9(8). 2020.
[42] Fernández-Villa, D., M.R. Aguilar, and L. Rojo Folic Acid Antagonists: Antimicrobial and Immunomodulating Mechanisms and Applications. International Journal of Molecular Sciences, 20, DOI: 10.3390/ijms20204996. 2019.
[43] Wróbel, A., et al., Trimethoprim and other nonclassical antifolates an excellent template for searching modifications of dihydrofolate reductase enzyme inhibitors. The Journal of Antibiotics, 73(1): p. 5-27. 2020
[44] Kaplan, E.L., et al., Macrolide Therapy of Group A Streptococcal Pharyngitis: 10 Days of Macrolide Therapy (Clarithromycin) Is More Effective in Streptococcal Eradication than 5 Days (Azithromycin). Clinical Infectious Diseases, 32(12): p. 1798-1802. 2001.
[45] Forbes, R., et al., ALternatives To prophylactic Antibiotics for the treatment of Recurrent urinary tract infection in women (ALTAR): study protocol for a multicentre, pragmatic, patient-randomised, non-inferiority trial. Trials, 19(1): p. 616. 2018.
[46] Kohanski, M.A., D.J. Dwyer, and J.J. Collins, How antibiotics kill bacteria: from targets to networks. Nat Rev Microbiol, 8(6): p. 423-35. 2010.
[47] Pham, T.D.M., Z.M. Ziora, and M.A.T. Blaskovich, Quinolone antibiotics. Medchemcomm, 10(10): p. 1719-1739. 2019.
[48] Hooper, D.C. and G.A. Jacoby, Topoisomerase Inhibitors: Fluoroquinolone Mechanisms of Action and Resistance. Cold Spring Harb Perspect Med, 6(9). 2016.
[49] Dingsdag, S.A. and N. Hunter, Metronidazole: an update on metabolism, structure–cytotoxicity and resistance mechanisms. Journal of Antimicrobial Chemotherapy, 73(2): p. 265-279. 2018.
[50] Campbell, E.A., et al., Structural Mechanism for Rifampicin Inhibition of Bacterial RNA Polymerase. Cell, 104(6): p. 901-912. 2001.
[51] Marais, S., et al., High dose oral rifampicin to improve survival from adult tuberculous meningitis: A randomised placebo-controlled double-blinded phase III trial (the HARVEST study). Wellcome Open Res, 4: p. 190. 2019.
[52] Bhavsar, R.B., L.N. Makley, and P.A. Tsonis, The other lives of ribosomal proteins. Hum Genomics, 4(5): p. 327-44. 2010.
[53] Kapoor, G., S. Saigal, and A. Elongavan, Action and resistance mechanisms of antibiotics: A guide for clinicians. J Anaesthesiol Clin Pharmacol, 33(3): p. 300-305. 2017.
[54] Chukwudi, C.U., rRNA Binding Sites and the Molecular Mechanism of Action of the Tetracyclines. Antimicrob Agents Chemother, 60(8): p. 4433-41. 2016.
[55] Brodersen, D., et al., The Structural Basis for the Action of the Antibiotics Tetracycline, Pactamycin, and Hygromycin B on the 30S Ribosomal Subunit. Cell, 103: p. 1143-54. 2001.
[56] Champney, W.S. and C.L. Tober, Specific inhibition of 50S ribosomal subunit formation in Staphylococcus aureus cells by 16-membered macrolide, lincosamide, and streptogramin B antibiotics. Curr Microbiol, 41(2): p. 126-35. 2000.
[57] Ramu, C. and T.V. Padmanabhan, Indications of antibiotic prophylaxis in dental practice- review. Asian Pac J Trop Biomed, 2(9): p. 749-54. 2012.
[58] Lockhart, P.B., et al., Prophylactic antibiotic prescribing in dental practice: Findings from a National Dental Practice-Based Research Network questionnaire. J Am Dent Assoc, 151(10): p. 770-781.e6. 2020.
[59] Lockhart, P.B., et al., Evidence-based clinical practice guideline on antibiotic use for the urgent management of pulpal- and periapical-related dental pain and intraoral swelling: A report from the American Dental Association. J Am Dent Assoc, 150(11): p. 906-921.e12. 2019.
[60] Chigurupati, R. and M. Shemkus, Complications of Odontogenic and Non-odontogenic Infections. p. 93-132. 2020.
[61] Siggins, M.K. and S. Sriskandan, Bacterial Lymphatic Metastasis in Infection and Immunity. Cells, 11(1). 2021.
[62] Frydrych, A.M. and C.S. Farah, Non-odontogenic Bacterial Infections, in Contemporary Oral Medicine: A Comprehensive Approach to Clinical Practice, C.S. Farah, R. Balasubramaniam, and M.J. McCullough, Editors. Springer International Publishing: Cham. p. 871-933. 2019.
[63] Frei, C.R., M.J. Labreche, and R.T. Attridge, Fluoroquinolones in Community-Acquired Pneumonia. Drugs, 71(6): p. 757-770. 2011.
[64] Sotgiu, G., et al., Tuberculosis treatment and drug regimens. Cold Spring Harb Perspect Med, 5(5): p. a017822. 2015.
[65] Smith, C.S., et al., Multidrug therapy for leprosy: a game changer on the path to elimination. Lancet Infect Dis, 17(9): p. e293-e297. 2017.
[66] Wilson, W., et al., Prevention of Infective Endocarditis. Circulation, 116(15): p. 1736-1754. 2007.
[67] Cloitre, A., et al., Antibiotic prophylaxis for the prevention of infective endocarditis for dental procedures is not associated with fatal adverse drug reactions in France. Med Oral Patol Oral Cir Bucal, 24(3): p. e296-e304. 2019.
[68] Brondani, M.A., Health Technology Assessment Fireside: Antibiotic Prophylaxis and Dental Treatment in Canada. J Pharm (Cairo), 2013: p. 365635. 2013.
[69] Annibali, S., et al., Local complications in dental implant surgery: prevention and treatment. Oral Implantol (Rome), 1(1): p. 21-33. 2008.
[70] Kim, J. and H. Jang, A review of complications of maxillary sinus augmentation and available treatment methods. J Korean Assoc Oral Maxillofac Surg, 2019. 45(4): p. 220-224.

[71] Peterson, E. and P. Kaur, Antibiotic Resistance Mechanisms in Bacteria: Relationships Between Resistance Determinants of Antibiotic Producers, Environmental Bacteria, and Clinical Pathogens. Frontiers in Microbiology, 9. 2018.
[72] Iskandar, K., et al., Antibiotic Discovery and Resistance: The Chase and the Race. Antibiotics (Basel), 11(2). 2022.
[73] Coculescu, B.I., Antimicrobial resistance induced by genetic changes. J Med Life, 2(2): p. 114-23. 2009.
[74] Verraes, C., et al., Antimicrobial resistance in the food chain: a review. Int J Environ Res Public Health, 10(7): p. 2643-69. 2013.

