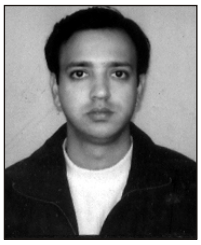
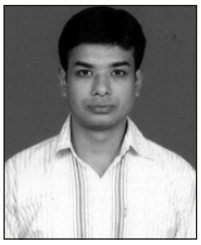
ANTIBIOTICS IN PERIODONTICS





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Introduction

Periodontal diseases comprise a group of oral infections whose primary etiological factor is dental plaque.Anaerobic and motile bacteria increase the gingival infection. In periodontitis, a proliferation of gram negative capnophilic and anaerobic bacteria (Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis and Bacteroides forsythus) and spirochetes takes place as the pockets deepen.

Types of periodontal pathogens divided into endogenous and exogenous sources of origin.

- Opportunistic infection it occur in a systemically or locally impaired host.
- Periodontal opportunistic infections may be associated with diabetes mellitus, malignancies, AIDS, stress, smoking.

Superinfection

- A new infection that complicates treatment of an existing infectious process.
- It involves indigenous or exogenous microorganisms.
- Enteric rods, pseudomonads, staphylococci, yeasts have been described as superinfecting organisms in periodontitis.

True infection

- It involves organisms that normally do not occur or have a very low carrier rate in healthy individuals.
- A. actinomycetemcomitans and P. gingivalis may be regarded as true infectious agents in periodontal disease.

Inflammatory periodontal diseases are treated primarily by mechanical debridement.

Despite these therapy, some individuals continue to experience periodontal breakdown, because some bacteria are deep seated in the connective tissue. So selective antimicrobial therapy may remove persistent periodontal pathogens.

Systemic antibiotic therapy in periodontal practice depends on

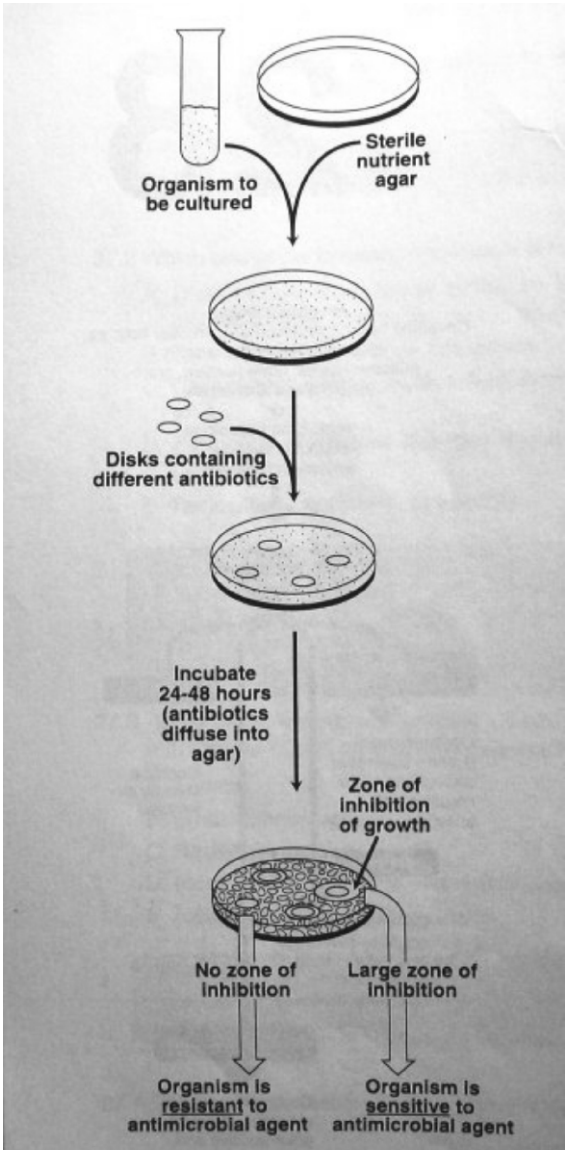
- Patient selection
- Microbiological analysis
- Sampling procedure
- Antimicrobial susceptibility testing

Identification and sensitivity of organism

"Characterization of organism" is central to the selection of the proper drug.

A rapid assessment of the nature of the organism can be made on the basis of Different stains such as Gram stain.

Culture the infective organism in order to arrive at a



conclusive diagnosis.

The disc diffusion technique provides only qualitative or semi quantitative information on the susceptibility of a given micro organism to anti microbial agent.

Classification of antibiotics

Inhibition of cell wall synthesis:

- Beta lectam ex- penicillins, cephalosporins.

Inhibition of protein synthesis:

- Tetracycline ex- doxycycline,minocycline.
- Macrolides ex- erythromycin, azithromycin.
- Aminoglycoside ex- streptomycin, gentamicin.

Inhibition of nucleic acid synthesis:

- Sulphonamide ex- sulfadiazine, sulfisoxazole.
- Quinolones ex- ciprofloxacin, norfloxacin.
- Azoles ex- metronidazole, ornidazole.

Beta lactam antibiotics

Penicillins

The penicillin are classified as beta lactam drug, because of their unique lactam ring.

Penicillin-G naturally obtained from fungus Penicillium notatum.

Semisynthetic penicillin ex phenoxymethyl penicillin, methicillin, cloxacillin, ampicillin, amoxicillin.

Mechanism of action

Penicillin like all beta lactam antibiotic, inhibit bacterial growth, by interfering with specific step in bacterial cell wall synthesis.

Cell wall is a rigid structure outside the cell membrane, it maintain the shape of the cell & prevent the lyses.

Bacterial cell wall contain polymer, polysaccharide and polypeptide.

Polysaccharide contain alternating amino sugar N-acyl glucosamine & N acetylmurmuric acid.

A five amino acid peptide is linked to the N acetyl muramic acid.

Penicillin binding proteins (PBP), catalyze the transpeptidase reaction, that removes the terminal alanine to form a crosslink with a nearby peptide which gives the cell wall structural rigidity.

Beta lactam antibiotics are structural analogue of the natural D-ala-D-ala substrate & they covalently bond by PBP at the active site.

After beta lactam antibiotic is attached to the transpeptidase, reaction is inhibited polypeptidoglycan synthesis blocked & cell dies.

This is why, penicillin and cephalosporin are bactericidal only if, cells are actively growing and synthesizing the cell wall.

Resistance - it is due to following mechanism

Inactivation of antibiotic by beta lactamase.

Impaired penetration of drug into target PBP.

Amoxicillin

- Similar to ampicillin but it has higher serum levels.
- Activity against many gram negative oral anaerobic bacteria.
- Susceptible to β-lactamases.
- Penetrates well into gingival crevicular fluid but rapidly hydrolyzed if significant levels of β-lactamases are present.
- designed specifically for oral administration.

Dose 250mg, 500mg TDS orally.

Clavulanic acid

- It has a β-lactam ring.
- It is a progressive inhibitor.
- It gets inactivated after binding to the enzyme.
- It permeates the outer layers of the cell wall of bacteria and inhibits the β-lactamase.

Use in Periodontics

- Periodontal abscess 250mg 2 tab immediately then 1 tab every 8 hrs.
- Aggressive periodontitis 500mg TDS for 8 days.
- Refractory periodontitis 500mg 2 tab immediately then 1 tab every 8 hrs.

Adverse reactions

Allergic hypersensitivity reactions

- Common.
- 0.6-10% patients having allergic reaction.
- Maculopapular rash, fever, bronchospasm, serum sickness, anaphylaxis.

Direct toxicity

- Rare.
- Prolonged therapy involving high doses administered intravenously.
- Occur in patients with impaired renal function.
- Nausea, diarrhea.

Cephalosporins

These are a group of semisynthetic antibiotics derived from cephalosporins-C obtained from a fungus Cephalosporium.Nucleus consists of a β-lactam ring fused to a dihydrothiazine ring.

First generation

- Developed in 1960.

- Highly active against gram positive but weaker against gram negative.
- Rapidly eliminated and only maintains adequate blood levels for 4 hours.
- Ex - cephalothin, cefazolin given parenteral. Cephalexin, cephadrin given orally.

Second generation

- More active against gram negative and anaerobes.
- Ex cefuroxime, cefoxitin given parenteral. Cefaclor, cefuroxime given orally.

Third generation

- Ex cefotaxime, ceftizoxime given parenteral. Cefixime given orally.

Fourth generation

- Ex cefepime, cefpirome given parentral.

Mechanism of action

- It is bactericidal.
- Mechanism of action same as penicillin.
- Inhibition of bacterial cell wall synthesis.

MACROLIDES.

Mechanism of action

Antimicrobial action of erythromycin may be inhibitory or bactericidal, particularly at higher concentration. Inhibition of protein synthesis occur, via binding to 50S ribosome subunits and interferes with translocation. Protein synthesis is inhibited, because amino acyl translocation reaction, & the formation of initiation compound, are blocked.

Resistance

- Reduced permeability of cell membrane.
- Production of esterase that hydrolyze macrolide.
- Modification of ribosomal binding site (ribosomal protection either by mutation or a macrolide inducible methylene.

Use in Periodontics

- Erythromycin does not concentrate in gingival tissue so not used.
- Spiramycin is active against gram positive organisms and is excreted in high concentration in saliva. It is used as an adjunct to periodontal treatment.

Dose 250-500mg 6 hourly.

Fluoroquinolones

First generation fluoroquinolones -

- Norfloxacin, ofloxacin, ciprofloxacin

Second generation fluoroquinolones

- Lomefloxacin, sparfloxacin

Mechanism of action

Fluoroquinolones inhibit the bacterial DNA gyrase. Which nicks double stranded DNA, introduces negative supercoils and then reseals the nicked ends. This is necessary to prevent excessive positive supercoiling of the strands when they separate to permit replication or transcription.

Resistance

It is because of chromosomal mutation producing a DNA gyrase with reduced affinity for fluoroquinolones. Reduced permeability of the bacterial membranes to these drugs.

Use in Periodontics

- It is the only antibiotic is which is effective against all strains of A.a.
- Recommended dosage is 500mg b.i.d.

Tetracycline

All tetracyclines are slightly bitter solids which are weakly water soluble, but their hydrochlorides are more soluble. Aqueous solutions are unstable. All have practically the same antimicrobial activity (with minor differences). The subsequently developed members have high lipid solubility, greater potency and some other differences. On the basis of chronology of development, as well as for convenience of description, they may be divided into 3 groups.

Mechanism of action

The tetracyclines are primarily bacteriostatic; inhibit protein synthesis by binding to 30S ribosomes in susceptible organism. Subsequent to such binding, attachment of aminoacyl-t-RNA to the mRNA-ribosome complex is interferred with. As a result the peptide chain fails to grow.

The sensitive organisms have an energy dependent active transport process which concentrates tetracyclines intracellularly. In gram negative bacteria tetracyclines diffuse through porin channels as well. The more lipid soluble members (doxycycline, minocycline) enter by passive diffusion also (this is partly responsible for their higher potency). The carrier involved in active transport of tetracyclines is absent in the host cells. Moreover, protein synthesizing apparatus of host cells is less sensitive to tetracyclines. These two factors are responsible for the selective toxicity of tetracyclines for the microbes.

Antimicrobial spectrum

When originally introduced, tetracyclines inhibited practically all types of pathogenic microorganisms except fungi and viruses; hence the name 'broad spectrum antibiotic. However, promiscuous and often indiscriminate use has gradually narrowed the field of their usefulness.

Clinical Use

Tetracyclines have been investigated as adjuncts in the treatment of localized aggressive periodontitis (LAP). A. actinomycetemcomitans is a frequent causative microorganism of LAP and is tissue invasive. Therefore mechanical removal of calculus and plaque from root surfaces may not eliminate this bacterium from the periodontal tissues. Systemic tetracycline can eliminate tissue bacteria and has been shown to arrest bone loss and suppress A. actinomycetemcomitans levels in conjunction with scaling and root planing. This combined form of therapy allows mechanical removal of root surface deposits and elimination of pathogenic bacteria from within the tissues. Increased post treatment bone levels have been noted using this method.

Long-term use of low doses of tetracyclines has been advocated in the past. One long-term study of patients taking low doses of tetracycline (250 mg per day for 2 to 7 years) showed persistence of deep pockets that did not bleed on probing. These sites contained high proportions of tetracycline-resistant, gram-negative rods (i.e., Fusobacterium nucleatum). After the antibiotic was discontinued, the flora was characteristic of sites with disease. Therefore it is not advisable to engage in long-term regimens of tetracyclines because of the possible development of resistant bacterial strains. Although commonly use in the past as antimicrobial agents, especially for localized aggressive periodontitis and other types of aggressive periodontitis, tetracyclines now tend to be replaced by more effective combination antibiotics.[13]

Function of tetracycline

- Collagenase inhibition
- Anti bone resorption effect
- Anti inflammatory actions
- Fibroblast attachment

Mechanism of action

Tetracycline enter into microorganism in part by passive diffusion & in part by an energy dependent process of active transport. Concentration of drug increases inside the cell. Inside the cell tetracycline bind reversibly to 30S subunit of bacterial ribosome. Block the binding of amino acyle t RNA to the acceptor site on in RNA ribosome complex .This prevent addition of amino acid to the growing peptide. Protein synthesis hampered.

Localized Aggressive Periodontitis

Systemic tetracyclines can eliminate tissue bacteria and arrest bone loss and suppressesn A.a levels in conjunction with scaling and root planing.

It is now well proven that a regimen of tetracycline 1g/day for 14 days given with a course of non surgical or surgical treatment can enhance the reolution of inflammation, gain of attachment and refill of bone in angular defects in patients with localized aggressive periodontitis. (**Lindhe 1982**).

Slots & **Rosling** (**1983**) showed that a gain in clinical attachments is most likely when A.a cannot be cultivated from treated sites, and they suggested that tetracycline administration should be extended for a third week to reduce the chance of repopulation with A.a in the short term.

Refractory periodontitis adjunctive systemic tetracycline therapy in the treatment of patients who do not respond to conventional treatment. In these so called refractory patients. A course of 1g tetracycline/day over 14-21 days given.

When patients receive regular maintenance care following systemic tetracycline, the clinical effects and the microbiological alterations in the subgingival flora can last for several years (**Lundstrom et al. 1984. Rams & Keyes 1985, Papli et al. 1989**).

Besides its antibacterial action tetracyclines also posses following properties.

- Collagenase inhibition
- Anti bone resorption effect
- Anti inflammatory actions

Collagenase inhibition

- Periostat 20mg capsule of doxycycline hyclate.

Mechanism of action

- Suppression of the activity of collagenase.

Doxycycline has been found to be more effective in blocking PMN type collagenase activity (MMP-8) than fibroblast type collagenase activity (MMP-1). **Golub et al. 1995.**

Doxycycline provides a safe therapeutic method for reducing pathologically elevated collagenase levels without interfering with normal connective tissue turnover.

Mechanisms

Doxycycline inhibits active MMPs directly by a mechanism that is dependent on its calcium and zinc binding properties (**Golub et al. 1998a**). Inhibit the HOCL from activating latent pro MMPs.

Anti Bone Resorption Effect

The antiproteolytic properties of the tetracyclines along with their specific anticollagenase activity has resulted in the application of these drugs to inhibit bone resorption. Tetracyclines inhibit bone resorption induced by parathyroid hormone, prostaglandins of E series and bacterial endotoxin in tissue cultures. Tetracyclines inhibit osteoblast and osteoclast derived MMPs, thereby inhibiting bone resorption

Anti Inflammatory Action

Tetracyclines have ability to suppress PMN activity by scavenging the reactive oxygen metabolities. Tetracyclines also inhibit eicosanoid synthesis (specially PGE2) by inhibiting phospholipase A2 activity.

Root Conditioning

Tetracycline bind strongly to the root surface and can be

released in an active form over extended periods of time. They are generally used as a 0.5% solution at a PH of 3.2 and is applied for 5 minutes.

Metronidazole

It is the prototype nitroimidazole introduced in 1959 for trichomoniasis and later found to be a highly active amoebicide. It has broad spectrum cidal activity against protozoa, including Giardia lamblia in addition to the above two. Many anaerobic bacteria, such as Bact.fragilis. Fusobacterium, Clostridium perfringens, Helicobacter pylori and anaerobic Streptococci are sensitive. Though it does not directly inhibit·the helminth· Dracunculus medinensis, extraction of the worm from under the skin is facilitated. It does not affect aerobic bacteria. Clinically significant resistance has not developed among the parasites for which it is used but decreased responsiveness of T vaginalis has been observed in some areas.

Chemical structure of Metronidazole

The mechanism of action of metronidazole is not well understood. After entering the microorganism by diffusion, its nitro group is reduced to intermediate compounds which cause cytotoxicity, probably by damaging DNA. Its selectively high activity against anaerobic organisms has suggested interference with electron transport from NADPH or other reduced substrates.

Metronidazole has been found to inhibit cell mediated immunity, to induce mutagenesis and to cause radio sensitization.

Pharmacokinetics

Metronidazole is almost completely absorbed from the small intestines: little unabsorbed drug reaches the colon. It is widely distributed in the body, attaining therapeutic concentration in vaginal secretion, semen, saliva and CSF. It is metabolized in liver primarily by oxidation and glucuronide conjugation, and excreted in urine. Plasma t½ is 8 hrs. [9]

Clinical Usage

Metronidazole has been used clinically to treat gingivitis, acute necrotizing ulcerative gingivitis, chronic periodontitis, and aggressive periodontitis. It has been used as monotherapy and also in combination with both root planing and surgery or with other antibiotics. Metronidazole has peen used successfully for treating necrotizing ulcerative gingivitis.

Studies in humans have demonstrated the efficacy of metronidazole in the treatment of gingivitis and periodontitis. A single dose of metronidazole (250 mg orally) appears in both serum and gingival fluid in sufficient quantities to inhibit a wide range of suspected periodontal pathogens. Administered systemically (750 to 1000 mg/day for 2 weeks), this drug reduces the growth of anaerobic flora, including spirochetes, and decreases the clinical and histopathologic signs of periodontitis. The most commonly prescribed regimen is 250 mg tid for 7 days. Loesche and co-workers found that 250 mg of metronidazole given three times daily for 1 week was of benefit to patients with a diagnosed anaerobic periodontal infection. In this study, an infection was considered anaerobic when spirochetes composed 20% or more of the total microbial count. Metronidazole used as a supplement to rigorous scaling and root planing resulted in a significantly reduced need for surgery when compared with root planing alone. The bacteriologic data of this study showed that only the spirochete count was significantly reduced currently, the critical level of spirochetes needed to diagnose an anaerobic infection, the appropriate time to give metronidazole, and the ideal dosage or duration of therapy is unknown.

As monotherapy (no concurrent root planing), metronidazole is inferior and at best only equivalent to root planing. Therefore if metronidazole is used, it should not be administered as monotherapy.

Metronidazole offers some benefit in the treatment of refractory periodontitis, particularly when used in combination with amoxicillin. The existence of refractory periodontitis as a diagnostic category indicates that some patients do not respond to conventional therapy, including root planing, surgery, or both. Soder and co-workers showed that metronidazole was more effective than placebo in the management of sites unresponsive to root planing. Nevertheless, many patients still had sites that bled on probing despite metronidazole therapy.

Studies have suggested that when combined with amoxicillin or amoxicillin-clavulanate potassium (Augmentin), metronidazole may be of value in the management of patients with localized aggressive or refractory periodontitis.[13]

Clinical trials assessing efficacy of metronidazole

Metronidazole as a monotherapy : Lekovic V et al. reported that metronidazole administered in the absence of scaling and root planing reduced mean probing depth .4 to 2.4mm. A limited gain of clinical attachment was attained and bleeding on probing was reduced, but never eliminated.

Several studies compared the ability of metronidazole to root planing to alter clinical and microbiologic parameters. These investigations indicated that drug therapy was inferior, or at best equivalent, to mechanical instrumentation.

Maintenance periodontally stable patients: Giedrys Leeper et al. reported that metronidazole did not enhance the effects of scaling and root planing in a relatively healthy patient population that presented for supportive therapy every 3 to 4 months.

Adult periodontitis : Probing depths 6mm or less **Loesche** et al. reported better results with combined therapy at sites 4 to 6mm deep when an anaerobic infection was confirmed. Combined therapy reduced probing depths 1.2 versus 0.75mm after root planing and attachment gain was 0.79 versus 0.32mm.

Adult periodontitis : Probing depth 7mm or more

Loesche et al. reported that combined therapy at pockets 7mm or more, resulted in a greater mean pocket reduction and gain of clinical attachment when compared to root planing.

Recurrent periodontitis : Gusberti et al. administered metronidazole in conjunction with hand instrumentation to patients demonstrating breakdown 1 to 3 years after surgery. This therapy decreased probing depths 2mm, gained 1mm of clinical attachment, and reduced bleeding on probing. Monitored microbes remained reduced for 9 months, but they tended to increase with time.

Lundstrom: et al. employed combined therapy on patients who deteriorated 2 to 10 years after treatment, despite supportive treatment every 3 to 6 months. Combined therapy resulted in a marked reduction of probing depths (2.5mm), reduced bleeding on probing and spirochetes.

Overall, adjunctive metronidazole therapy appeared to facilitate improved periodontal status in patients who developed recurrent disease.

Combination antibiotic regimen

Since the subgingival microflora in oral infections may consists of various putative pathogens that differ in antimicrobial susceptibility, the use of a combination of two or more antibiotics represent a valuable approach in chemotherapy.

Combination therapy may help

- To broaden the antimicrobial range of the therapeutic regimen beyond that attained by any single antibiotic.
- To prevent the emergence to bacterial resistance.

Metronidazole : When amoxicillin is combined with metronidazole, the combination is effective against aggressive and refractory periodontitis.

Ciprofloxacin: It is combined with metronidazole is used in the treatment of periodontitis associated with enteric rods and or pseudomonas.

Disadvantages of combination therapy

- Increased adverse reaction
- Antagonistic drug interactions with improperly selected antibiotics.

Guidelines for the use of systemic antibiotics in periodontal therapy.

- Antibiotics are not necessary in most cases of gingivitis and periodontitis.
- Antibiotics may be necessary for refractory/recurrent periodontal disease which does not respond to conventional therapy.
- Antibiotics may be necessary in aggressive periodontitis as an adjunct to conventional therapy.
- Antibiotics may be necessary in patients with systemic conditions.
- Antibiotics may be useful in patients with periodontal abscess that does not respond to conventional therapy and who have systemic involvement.
- Antibiotics may be useful in patients with acute necrotizing ulcerative gingivitis/periodontitis.
- Antibiotics may be necessary patients with rapidly progressive periodontitis.

Failures in antibiotic therapy

- Inappropriate choice of antibiotic (microorganism is not susceptible).
- Emergence of antibiotic resistant microorganisms.
- Too low a blood concentration of the antibiotic (faulty dosing).
- Slow growth rate of microorganisms (beta lactams require rapidly dividing organisms for activity; older abscesses have a slow microbial growth rate).
- Impaired host defences.
- Patients noncompliance.
- Inability of the antibiotic to penetrate to the site of infection.

Conclusion

Periodontal treatment aims at restoring a microbiota compatible with periodontal health. Mechanical periodontal treatment can reduce total supra and subgingival bacterial mass, but major pathogens may escape the effect of treatment due to their ability to invade periodontal tissues. Systemic periodontal antibiotic therapy aims to reinforce mechanical periodontal treatment and to support the host defense system.

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