

Review article

Role of antibiotics in periodontal therapy

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Abstract

Loeshe in 1976 propounded the 'Specific Plaque Hypothesis' and efforts have been done since, to formulate a periodontal treatment regimen based on targeting of specific microorganisms. Antibiotics have gained importance as an arsenal in the treatment of periodontitis. This review takes a concise view on the role of antibiotics in periodontics. This review puts importance of antibiotics in a nutshell as a quick reference for the general practitioners in treating periodontal diseases. The selection and indication for the use of antibiotics is given with a note on resistance

Key words: Periodontitis, antibiotics.

Introduction

Periodontal diseases are caused by interaction between host and bacteria¹. Bacteria begin reattaching to the crowns of teeth soon after the teeth have been cleaned. Overtime, this supragingival plaque becomes more complex, leading to a succession of bacteria that are more pathogenic. Bacteria grow in an apical direction and become subgingival, and eventually as bone is destroyed, a periodontal pocket is formed. In a

periodontal pocket the bacteria form a highly structured and complex biofilm¹. As this process continues, the bacterial biofilm extends so far subgingivally that the patient cannot maintain optimum oral hygiene. Effective control of destructive periodontal disease depends upon the identification and treatment of established infection and subsequent prevention of recurrence². It is also most important that periodontitis be

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recognized and treated in the early stages, when the manifestations are most easily reversed and major damage to the periodontium has not yet occurred. Approaches to periodontal treatment range from non-surgical versus surgical, resective versus regenerative, professional emphasis versus patient emphasis, and mechanical versus chemical therapy (systemic or local)¹.

Rationale for use of antibiotics in periodontal disease

The use of systemic antimicrobials as a part of the therapy in the management of periodontal diseases has been accepted as an adjunctive therapy for decades³. Several studies have concluded that in specific clinical situations, such as with patients with deep pockets, patient with progressive or active diseases or with specific microbiological profiles, antimicrobial therapy adjunctive to scaling and root planing could be clinically relevant. However, there is a lack of clear protocol for the use of antibiotics which may be due to specific properties of biofilm, which make subgingival periodontal pathogens more difficult to target, and, therefore, the development of strategies specifically designed to treat the subgingival microflora, as a biofilm, is highly desirable⁴.

Current periodontal therapy strongly emphasizes suppressing or eradicating specific periodontal pathogens. However, present treatment modalities differ in their ability to eliminate periodontal pathogens. Non-surgical scaling and root planing may remove subgingival *Campylobacter rectus* but is frequently ineffective against

Porphyromonas gingivalis, *Prevotella intermedia*, *Bacteroides forsythus* and enteric rods and may not significantly reduce *Actinobacillus actinomycetemcomitans* or *peptostreptococcus*⁴. Microbial debridement may fail to remove pathogenic organism because of their location in subepithelial gingival tissues, crevicular epithelial cells, altered cementum, radicular dentinal tubuli or furcation or other anatomic features complicating adequate instrumentation. Moreover, periodontal pathogens frequently colonize oral mucosa, tongue dorsum, tonsils and may translocate from non-periodontal sites to periodontal crevices⁵. Systemic antibiotics enter the periodontal tissues and periodontal pocket via serum and can affect microorganisms outside the reach of cleaning by instrument or topical antiinfective chemotherapeutics. Systemic antibiotic therapy can also potentially suppress periodontal pathogens residing on the tongue or other oral surfaces, thereby delaying subgingival recolonization of pathogens⁵.

Selection of antimicrobials

The periodontal clinical status, the composition of the periodontopathic microbiota, the patient's medical status, potential adverse drug reactions and possible drug interactions determine the choice of antimicrobial agent⁶. Bactericidal rather than bacteriostatic drugs are preferred because their effectiveness is independent of a functioning host defenses in the periodontal site. A combination of

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antibiotics is indicated in patients harboring several pathogens that, combined, fail to show sensitivity to any single antibiotic.

Before any antimicrobial agent can be recommended for periodontal therapy a number of basic and important conditions have to be fulfilled –

1. Drug must show in vitro activity against the organisms considered most important in the etiology.
2. It should be demonstrated that a dose sufficient to kill the target organism can be reached within the subgingival environment.
3. At that dose the drug should not have major local or systemic adverse effects.
4. Organisms should not be resistant to the antimicrobial agents.
5. Antibiotic should be specific for periodontal pathogens and not in general use for treatment of other diseases and should be inexpensive.

There are two major routes of drug delivery of antibiotics: i) Systemic antibiotic therapy and ii) local drug

delivery with its respective advantages and disadvantages.

Antimicrobial agent may be delivered by direct placement into the periodontal pocket or via systemic route. Local drug delivery allows the application of antimicrobial agents at levels that cannot be reached by systemic route⁷. Local drug delivery may be particularly successful if the presence of target organism is confined to clinically visible lesions. On the other hand, systemically administered antibiotics may reach widely distributed microorganisms⁶. Disadvantages of systemic therapy relates to the fact that the drug is dissolved by dispersal over the whole body, and a small portion of the total dose actually reaches the subgingival microflora in the periodontal pocket. Local drug delivery systems are means of drug application to confined areas. For the treatment of periodontal diseases, local delivery of antimicrobial drug ranges from simple pocket irrigation, placement of drug containing ointment and gels in the pockets to sophisticated devices for sustained release of antimicrobial agents⁷.

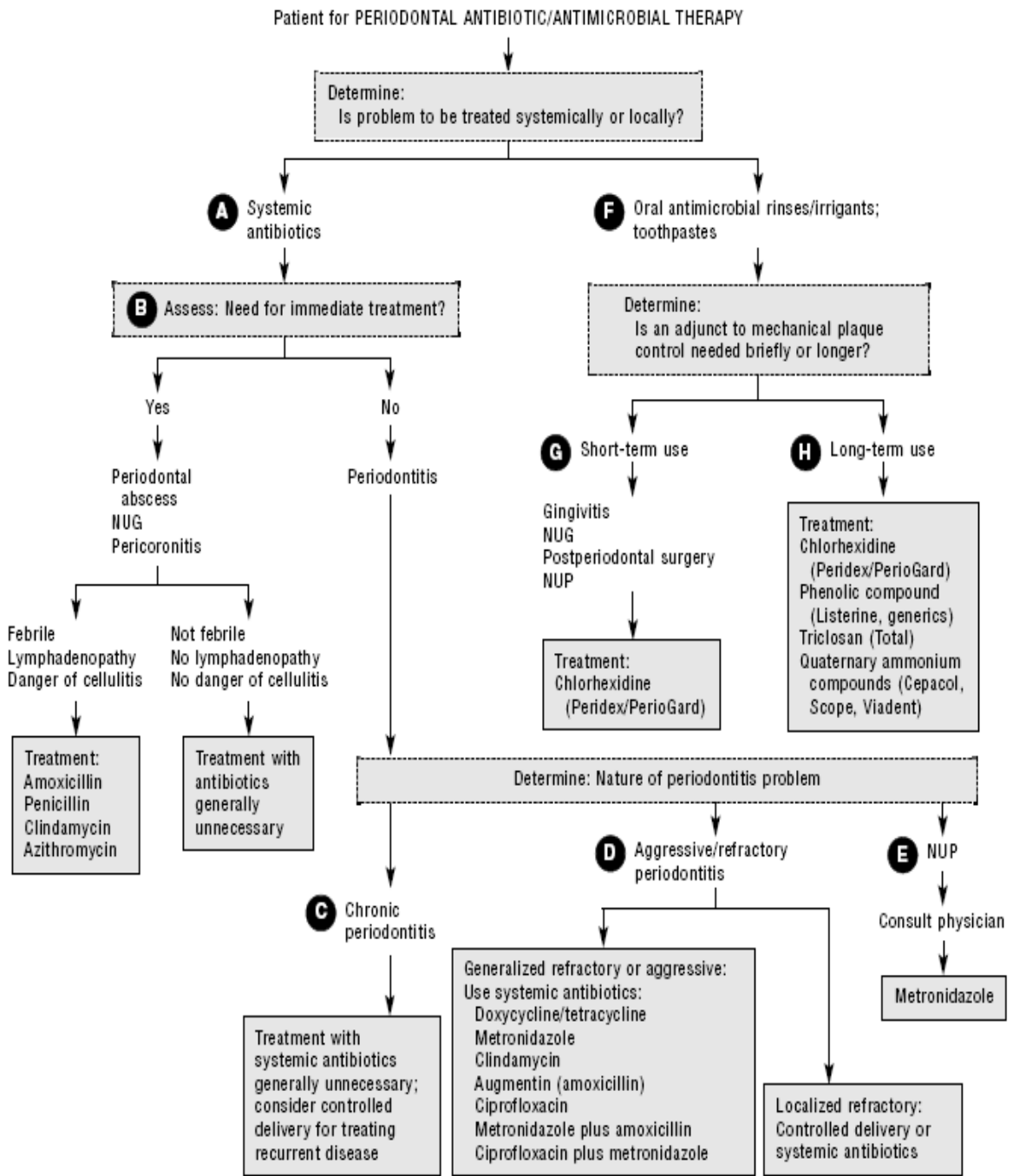


Figure 1: Protocols for usage of antibiotics in patients with periodontal disease

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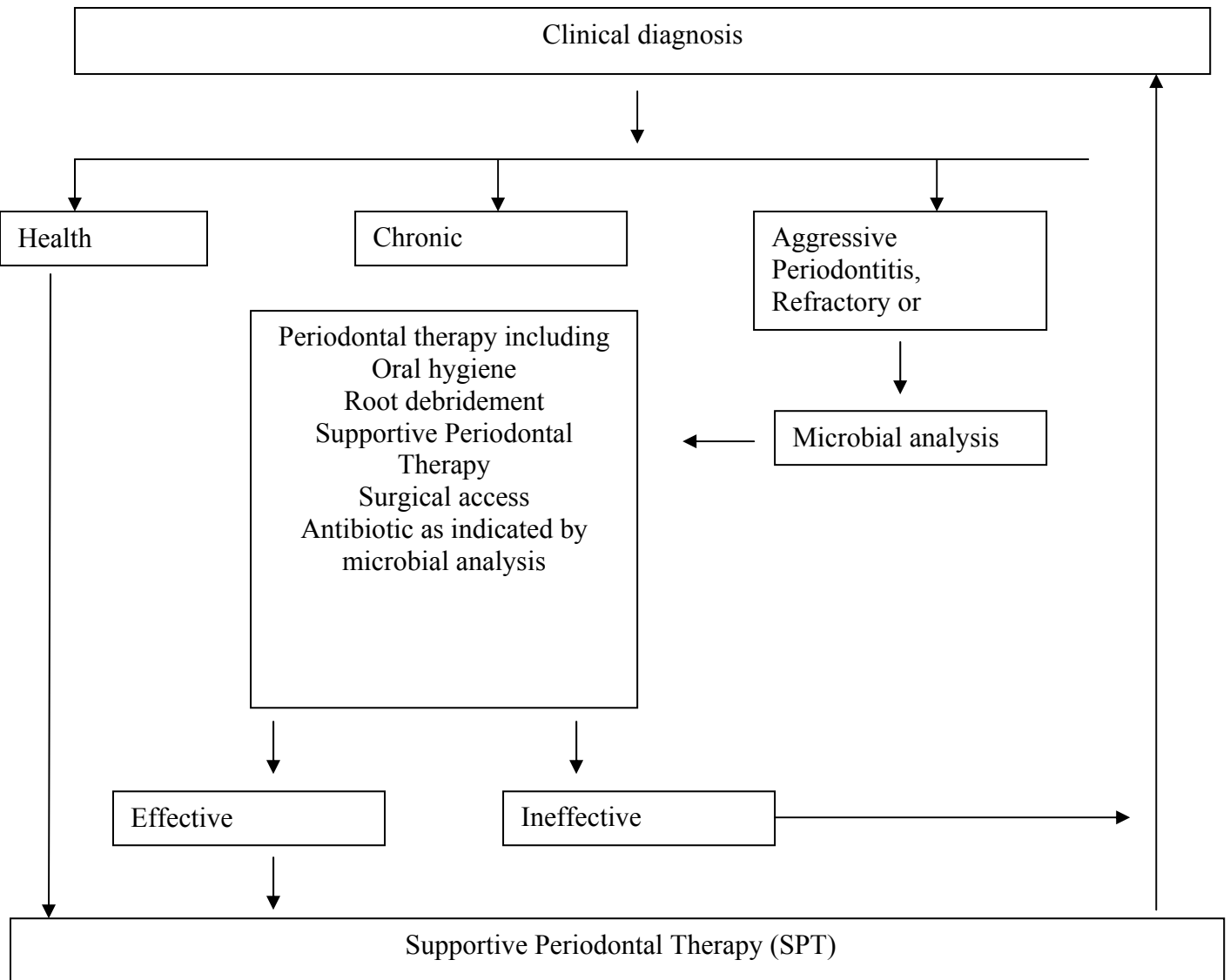


Figure 2: Guidelines for usage of antibiotics in patients with periodontal disease

Table 1: Systemic antibiotics used in periodontal therapy

CATEGORY	NAME	FEATURES
Penicillin	Amoxicillin	- Extended spectrum of antimicrobial activity, used systemically.
	Augmentin	- Effective against penicillinase producing microorganism, used systemically.
Tetracycline	Minocycline	-Effective against broad spectrum of microorganism, used systemically and locally.
	Doxycycline	- Effective against broad spectrum of microorganism, used systemically and locally.
	Tetracycline	- Effective against broad spectrum of microorganisms
Quinolone	Ciprofloxacin	- Effective against gram-ve rods, -Promotes health-associated microflora. Used systemically.
Macrolide	Azithromycin	- Concentrates at sites of inflammation Used systemically
Lincomycin	Clindamycin	- used against penicillin-allergic patients - effective against anaerobic bacteria -used systemically
Nitroimidazole	Metronidazole	- Effective against anaerobic bacteria, used systemically and locally.

Table 2: Common antibiotic regimens

Monotherapy	Regimen	Dose/Duration
Amoxicillin	500 mg	-Thrice daily for 8 days
Azithromycin	500 mg	- Once daily for 4 – 7 days
Ciprofloxacin	500 mg	-Twice daily for 8 days
Clindamycin	300 mg	-Thrice daily for 10 days
Doxycycline/Minocycline	100 -200 mg	-Once daily for 21 days
Metronidazole	500 mg	- Thrice daily for 8 Days
Combination Therapy		
Metronidazole and Amoxicillin	- 250 mg each	-Thrice daily for 8 days
Metronidazole and Ciprofloxacin	500 mg each	- Twice daily for 8 days

Patient selection

Antimicrobial treatment of patient with gingivitis or stable periodontitis is thought to afford little or no additional benefit over mechanical periodontal therapy and supragingival plaque control. In cases of periodontitis in which bacteria have been shown to invade gingival connective tissues (as in cases of aggressive periodontitis), antimicrobial therapy is warranted. Likewise patients with acute abscess, severe or rapidly progressive periodontal disease may also benefit from systemic antimicrobial treatment⁵(Figure 1).

Microbial resistance to antibiotics

When considering an antimicrobial treatment regimen, the possibilities of producing antimicrobial resistant strains of bacteria cannot be discounted. Bacterial drug resistance can occur via two mechanisms –

- Intrinsic resistance is result of an inherent cellular feature, usually a gene product such as an active drug export mechanism.
- acquired resistance results from either a mutation of existing genetic material or the insertion of genetic sequences that code for antibiotic resistance.

Guidelines for use of antimicrobial therapy (Figure 2).

Antimicrobial agent

Many semisynthetic and natural (i.e. antibiotic) compounds inhibit microbial growth, however not all are useful as chemotherapeutic agents. To be therapeutically beneficial, a compound should not only inhibit microbial growth in vivo, but also be harmless to the host.

Antimicrobial agents produce their effect by interfering with one or more of the following processes –

1. Protein synthesis
2. Cell wall synthesis
3. Maintenance of cell wall integrity

4. Nucleic acid structure and function
5. Essential cellular metabolism (such as folic acid and lipid biosynthesis).

Antibiotic agents commonly used as adjuncts in periodontal therapy (Table 1). Various antimicrobials have been used successfully in the treatment of periodontal disease. Some of the commonly used antimicrobials are discussed below: The dosages of commonly used antibiotics are enumerated in Table 2.

Tetracycline group

These are a group of antibiotics produced naturally from certain species of streptomyces or derived semisynthetically. These are bacteriostatic and more effective against gram +Ve than gram –Ve bacteria. It is effective in treating periodontal diseases because their concentration in the gingival crevice is 2-10 times higher than in serum². It is used in cases of refractory periodontitis, aggressive periodontitis and in host modulation². Tetracycline is used in dosage of 250 mg four times daily for 2 weeks.

Minocycline

It is effective against a broad spectrum of microorganisms. It suppresses spirochetes and motile rods. It is used in dosage of 200mg/day for 1 week.

Doxycycline

It has the same spectrum of activity as minocycline and may be equally as effective. Dosage of 100 mg twice daily on the 1st day then 100 mg once daily⁸.

Metronidazole

It is a nitroimidazole compound. It is bactericidal to anaerobic organisms and disrupts bacterial DNA synthesis. Usually it is not effective against *A. actinomycetemcomitans* but becomes effective when used in combination with other antibiotics³. It is also effective against anaerobes such as *P. gingivalis* and *P. intermedia*. Used in cases of gingivitis, ANUG, chronic periodontitis, aggressive

periodontitis and in cases of refractory periodontitis along with amoxicillin. Dosage of 250 mg orally four times daily for 7 days.

Beta-lactam antibiotics (Penicillin, amoxicillin and cephalosporins)

Penicillin acts by inhibition of bacterial cell wall production. Limited use in periodontal disease. Amoxicillin: It is a semisynthetic penicillin with extended spectrum of organisms including gram +ve and gram-ve bacteria. Indicated in aggressive periodontitis and periodontal abscess³. Dosage is 500 mg three times daily for 8 days.

Cephalosporins: Cephalosporins have similar structure and action as that of penicillins. However, cephalosporins are generally not used to treat dental-related infections. The penicillins are superior to cephalosporins in their range of action against periodontal pathogenic bacteria. Cephalosporins show cross- allergenicity to penicillin group of drugs.

Azithromycin

It is effective against anaerobes and gram -ve bacilli. The concentration of azithromycin in tissue specimens from periodontal lesion is significantly higher than that of normal gingival. It has been proposed that azithromycin penetrates fibroblasts and phagocytes in concentration 100–200 times greater than that of extracellular compartment⁹. The azithromycin is actively transported to sites of inflammation by phagocytes, released directly into the sites of inflammation as the phagocytes rupture during phagocytosis⁹. Azithromycin is used in dosage of 500 mg once daily for 3 days or single dose of 250 mg after an initial loading dose of 500 mg.

Ciprofloxacin

It is a quinolone, active against gram -ve rods, including all facultative and some anaerobic putative periodontal pathogens. It demonstrates minimal effect on

streptococcus species, which are associated with periodontal health. Ciprofloxacin therapy may facilitate the establishment of a microflora associated with periodontal health. At present, ciprofloxacin is the only antibiotic in periodontal therapy to which all strains of Actinomycetemcomitans are susceptible¹⁰. It can be used in combination therapy with metronidazole. Ciprofloxacin is used in cases of aggressive periodontitis in dose of 500 mg twice daily for 8 days.

Clindamycin

It is effective against anaerobic bacteria. It is effective in situations in which the patient is allergic to penicillin. Indicated in patients allergic to penicillin. Dosage is 300 mg twice daily for 8 days.

Serial and combination therapy

Because periodontal infection may contain a wide diversity of bacteria, no single antibiotic is effective against all putative pathogens. This 'mixed' infection can include a variety of aerobic, microaerophilic and both Gram +ve and gram -ve anaerobic bacteria. In this case it may be necessary to use more than one antibiotic, either serially or in combination¹¹.

Clinical use: Antibiotics that are bacteriostatic (eg tetracycline) generally require rapidly dividing microorganisms to be effective. They do not function well if a bactericidal antibiotic (e.g. amoxicillin) is given concurrently. When both types of drugs are required, they are best given serially not in combination. Combination of ciprofloxacin and metronidazole is well effective against mixed infections¹¹. Metronidazole targets obligate anaerobes and ciprofloxacin targets facultative anaerobes.

Local drug delivery of antimicrobials

The limitations of mouth rinsing and irrigation have prompted research for the development of alternative drug delivery systems. Recently, advances in drug

delivery technology have resulted in the controlled release of drugs⁷. The requirements for treating for periodontal disease include a means for targeting an anti-infective agent to infection sites and sustaining its localized concentration at effective levels for a sufficient time. While concurrently evoking minimal or no side effects.

Use of local delivery systems in dental practices –

1. Scaling and root planing is extremely effective treatment modality for controlling early to moderate periodontitis. Although all sites treated do not respond totally, the majority do. This would then leave a minority of sites requiring more aggressive treatment, which would include locally delivered antimicrobials.

2. Recurrent pockets in the periodontal maintenance patient are an excellent place in a dental practice to use any controlled local delivery system.

3. Not all types of inflammatory periodontitis are amenable for controlled local delivery of antimicrobials. When conventional treatment is not totally effective, additional and usually more aggressive treatment is necessary. If after scaling and root planing or scaling and root planing with controlled local delivery there are localized sites that did not respond, controlled local delivery of antimicrobials may be appropriate.

4. The ailing or failing implant may be an appropriate situation for local delivery of an antimicrobials.

5. Periodontal abscess.

6. In periodontal pockets before regenerative surgery is done.

Ideal characteristics of local drug delivery systems:

1. Inhibit or kill the putative pathogens.

2. It should reach the site.

3. Should have adequate concentration.

4. Be there long enough

5. Do no harm.

Tetracycline fibre (Actisite)

The actisite delivery system consists of a polymer, ethylene vinyl acetate, 25% saturated with tetracycline hydrochloride¹². In the marketed form, it is 23 cm in length and 0.5 mm in diameter and contains 12.7 mg of tetracycline hydrochloride. The fibre is flexible, can be placed into a periodontal pocket, and can be folded on itself to nearly fill the pocket. The fibre releases tetracycline at a constant rate for 14 days. The optimal sites for use of fibre are periodontal pockets of 5 mm or more in depth that bleed on probing and had not responded to mechanical therapy. The fibre should be held with cotton pliers and should place the fibre at the opening of the pocket to be treated. A gingival retraction cord packing instrument is used to place the fibre into the pocket gently at least 1mm apical to the gingival margin. Once the fibre placement is complete, the dentist isolates the area with cotton rolls, dried with the air syringe and applies a drop of tissue adhesive interdentially & facially & lingually. To avoid dislodging the fibre, the patient is instructed not to brush or floss the treated area until fibres are removed. Fibre should be kept for 7-14 days. The patient is placed on twice daily chlorhexidine rinse while the fibre is in place and for 1 week after their removal.

Chlorhexidine chip

The chlorhexidine chip (Periochip)¹³ is a small biodegradable film of hydrolyzed gelatin into which has been incorporated 2.5 mg of chlorhexidine gluconate. The chip resembles a baby's finger nail measuring approximately 4 into 5 mm and 0.35mm in thickness. The chip is easily placed into periodontal pockets that are 5mm or more. It is self-retentive and delivers chlorhexidine to the sites for at least 7 days. The chips should be grasped in a cotton forceps and gently inserted into the pocket. If the chip gets too wet, it may

become soft and even start to disintegrate. It is, therefore, advisable to dry the area. To avoid dislodging the chip, the patient is instructed not to brush or floss the treated area for 7 days.

Doxycycline polymer (Atridox)

A liquid biodegradable drug delivery system has been developed that hardens in the periodontal pocket and gives a controlled release of the incorporated agent¹⁴. This delivery system has been modified to incorporate and release the antimicrobial substance doxycycline. The liquid delivery system containing 10% doxycycline hyclate is contained within a syringe that has a blunt-ended 23 gauge canula attached. The canula has the diameter of a periodontal probe, is bent to resemble a periodontal probe, and is used in a similar diagnostic and tactile manner. In a site that qualifies for treatment, the tip of the cannula is introduced to the depth of the pocket¹⁴. The doxycycline hyclate is expressed into the pocket until it just overfills the pocket. As it begins to harden on contact with the moisture in the pocket and during the 1-2 minutes of hardening, it is packed into the pocket using the underside of a moistened curette or other blunt-ended instrument.

Minocycline microspheres (Arestin)

The FDA recently approved a new locally delivered sustained-release form of minocycline microspheres (Arestin) for subgingival placement¹⁵. The 2% minocycline is encapsulated into bioresorbable microsphere in a gel carrier.

Summary

Majority of periodontal diseases including the most destructive periodontal disease occur due to the presence of pathogenic microorganisms that colonize the subgingival biofilm. There is also evidence that suppression or eradication of these microorganisms results in an improvement of periodontal health. Mechanical removal of subgingival plaque is effective both in

reducing total bacterial load and in disrupting biofilm. However, for some patients and in certain situations, mechanical instrumentation of the infected area is not sufficient to control disease progression. Failure to obtain a favorable response may be due to inadequacy of the host's immune response, the ability of the pathogen to escape, either by invading gingival tissue or finding shelter in an unreachable site, limited access, instrument availability, operator skill, or a host of other possible factors. The incorporation of an appropriate chemotherapeutic agent in conjunction with mechanical instrumentation provides an additional effect to control disease¹⁶. It also should be remembered that antibiotics are not a panacea for all non responsive situations. Inappropriate use can lead to occurrence of resistance and ineffectiveness. Effective, appropriate and judicious use of antibiotics makes them an important agent in the treatment of periodontal diseases¹⁷.

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