Antibiotics in Periodontal Therapy

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The majority of inflammatory periodontal diseases is caused by bacteria. Mechanical removal of bacterial deposits from the teeth by the patient (individual oral hygiene) and mechanical debridement by the dentist (professional tooth cleaning, antiinfective periodontal therapy, periodontal surgery) are effective in treatment of most cases of plaque-induced gingivitis and periodontitis. However, in particular risk patients (e.g. under elevated risk for bacterial endocarditis) periodontal procedures that cause transitory bacteremia require systemic antibiotic prophylaxis. Further, in severe cases of necrotising ulcerative gingivitis and periodontitis local therapy has to be supported by systemic antibiotics. In cases of aggressive and generalised severe chronic periodontitis that show subgingival infection with particular periodontal pathogens, especially by *Actinobacillus actinomycetemcomitans,* successful therapy requires systemic antibiotics adjunctively to mechanical antiinfective therapy. Therapy of persisting pockets during supportive periodontal therapy may additionally benefit from application of locally delivered antibiotic devices.

Key words: adjunctive systemic and local antibiotic therapy, periodontitis therapy, prophylaxis of bacterial endocarditis, necrotising ulcerative gingivitis/periodontitis

INTRODUCTION

Perforation of teeth through the continuous epithelial lining of the oral cavity is a singular anatomical situation. The dental surface consists of hard tissues that lack the potential to renew themselves and to shed their superficial layer. The microecologic system of the oral cavity is colonised by more than 400 different bacterial species (Moore and Moore, 1994). Approximately 150 or more different species may be detected and cultivated from the oral cavity of a single individual. Some bacteria are capable of adhering to and colonising dental surfaces, thereby preparing the ground for the colonisation by other microorganisms. The layer that is generated in this manner is called **dental plaque**, **bacterial plaque**, or **biofilm**. Biofilm is the name of organised aggregations on solid surfaces (e.g. on teeth but also ship bodies, artificial heart valves, water pipes etc.) that consist of microorganisms, extracellular bacterial macromolecules, and products originating from the surrounding medium (e.g. saliva or sulcus fluid). Bacterial plaque is the particular oral form of biofilm. The structure of biofilm not only hinders diffusion of growth factors into bacterial plaque but also forms an effective barrier against host defence (e.g. antibodies, lysozyme, lactoferrine) and antimicrobial substances (e.g. mouth rinses, antibiotics).

In contrast to the epithelial surfaces of the body, teeth are not capable of shedding their superficial layers with the adhering microorganisms. Hence, gingivitis and periodontitis are characterised by inflammatory and immune response to the oral microflora, particularly that part that adheres to the tooth surface or has been established subgingivally. The primary etiologic factor of most inflammatory periodontal diseases (plaque-induced gingivitis, chronic and aggressive periodontitis) is bacterial plaque. The removal of supra- and subgingival biofilm that is required for therapy of periodontal diseases is accomplished mechanically by profes-

antibiotic prophylaxis (e.g. with increased risk of endocarditis)
NUG/NUP (American Academy of Periodontology, 2001)
adjunctive antibiotic therapy in presence of specific periodontal pathogens in – aggressive periodontitis (American Academy of Periodontology, 2000b) – generalised severe chronic periodontitis – refractory periodontitis (American Academy of Periodontology, 2001) – moderate to severe periodontitis with systemic diseases or immune deficiencies (American Academy of Periodontology, 2000b)
periodontal abscess spreading into adjacent tissue loges, with fever and/or severe lymphadenopathia (American Academy of Periodontology, 2001)

Table 1 Indications for systemic use of antibiotics in periodontal therapy (Beikler et al, 2003).

sional tooth cleaning and subgingival instrumentation of root surfaces in the course of antiinfective therapy in most cases.

In some particular cases, however, additional adjunctive use of systemic (Table 1) or local antibiotics is reasonable and required.

Historically the term **antibiotic** referred to antimicrobial agents that were produced by living microorganisms (bacteria, fungi). Penicillin that was derived from the fungus *penicillium notatum* is an example for this. Synthetical antimicrobial agents originally are called antimicrobial chemotherapeutics (e.g. metronidazole). However, today most natural antibiotics are chemically modified (semisynthetic) to improve their pharmacokinetics or to widen their range of effect. Thus, usually today and in this article the term antibiotic is used for both groups of substances - natural antibiotics and antimicrobial chemotherapeutics (van Winkelhoff and Vandenbrouke-Grauls, 2001).

ANTIBIOTIC PROPHYLAXIS

Prophylaxis of Bacterial Endocarditis

Bacterial endocarditis fortunately is a rare (incidence of 20–60 cases per ONE million) but dangerous disease. Untreated bacterial endocarditis is lethal in 100% of cases. However, even properly treated, depending on the microbial flora lethality ranges from 5–76% (Jeserich and Just, 2001). Endocarditis develops if bacteria that have got access to blood circulation (**bacteremia**) colonise the internal surface of the heart and cause symptoms of infection (sepsis, septicemia). Sepsis in general and infection of the endocard in particular are facilitated by primary or secondary deficiency of host defence. General or local defective host defence is generally found in immunesuppressed patients after organ transplantation, leukaemia and cardiac defects (e.g. heart and valvular defects or heart valve prostheses) (Tables 2 and 3).

In 25% of patients who develop bacterial endocarditis medical history reports recent dental treatment or orofacial infection. A risk for endocarditis exists with all dental procedures that cause bacteremia, i.e. gingival, pulpal, and periapical bleeding. Periodontal procedures that are likely to elicit bacteremia are pocket probing, scaling and root planing, supportive periodontal therapy, periodontal surgery, subgingival application of antibiotic slow and controlled release devices as well as prophylactic cleaning of teeth and implants if gingival bleeding is to be expected (Table 4). Thus, these procedures require antibiotic prophylaxis (Table 4) in patients with moderate and high endocarditis risk (Table 2). In many cases patients at elevated risk for bacterial endocarditis have a so-called heart passport that gives information about the required antibiotic prophylaxis. Table 5 shows a prophylactic regime that is applicable under normal conditions; in uncertain cases it is advisable to contact the particular patient's physician.

Prophylaxis after Radiation Therapy in the Maxillofacial Region

Therapy of malignant craniomandibular neoplasias in most cases includes radiotherapy. Salivary glands, jaws and teeth are located in the field of radiation. The high radiation doses that normally are applied result in a severely reduced vitality of

Table 2 Cardiac conditions that require antibiotic endocarditis prophylaxis (Dajani et al, 1997)

High risk	Moderate risk
Prosthetic cardiac valves	Congenital cardiac malformations that are not listed under high or negligible risk
Previous bacterial endocarditis	Aquired valvar dysfunction (e.g. rheumatic heart disease)
Complex cyanotic congenital heart disease (e.g. single ventricle states, transposition of the great arteries, tetralogy of Fallot)	Hypertrophic cardiomyopathy
Surgically constructed systemic pulmonary shunts or conduits	Mitral valve prolapse with valvar regurgitation and/or thickened leaflets

Table 3 Cardiac conditions that do not require antibiotic endocarditis prophylaxis (Dajani et al, 1997).

Negligible risk (no greater risk than the general population)
Isolated secundum atrial septal defect
Surgical repair of artrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residua beyond 6 months)
Previous coronary artery bypass graft surgery
Mitral valve prolapse without valvar regurgitation
Physiologic, functional, or innocent heart murmurs
Previous Kawasaki disease without valvar dysfunction
Previous rheumatic fever without valvar dysfunction
Cardiac pacemakers (intravascular and epicardial) and implanted defibrillators

maxillary and mandibular bone. Thus, a high risk of infected osteoradionecrosis is a consequence for persisting epithelial defects related to dentoalveolar surgery (e.g. flap surgery). In such cases a perisurgical antibiotic prophylaxis (e.g. amoxicillin) is required at latest 24 hours before surgery (Grötz, 2002).

Drug-Induced Immunesuppression

In immunesuppressed patients (e.g. after organ transplantation or in autoimmune diseases) the reduced host response to infectious agents results in the risk for transvasal translocation of microorganisms via bacteremia and thus abscesses in various regions of the body. In these cases antibiotic prophylaxis is required for periodontal therapy also. Many patients under cyclosporine A medication after organ transplantation are in need of frequent periodontal care to treat and even better prevent drug-induced gingival overgrowth (Dannewitz and Eickholz, 2002a, b). In consideration of various interactions with other medications and altered pharmacokinetics in patients after kidney transplantation it is advisable to have antibiotic prophylaxis chosen and prescribed by the patient's physician or internal specialist.

Endocarditis prophylaxis recommended	Endocarditis prophylaxis not recommended
– Dental extractions	– Restorative dentistry (operative and prothodontic) with or without retraction cord
– Periodontal procedures including surgery, scaling and root planning, probing, and recall maintenance	– Local anesthetic injections (nonintraligamentary) – Intracanal endodontic treatment; post placement and build up – Placement of rubber dams
– Dental implant placement and reimplantation of avulsed teeth	– Postoperative suture removal
	– Taking of oral impressions
– Endodontic (root canal) instrumentation or surgery only beyond the apex	– Placement of removable prosthodontic or orthodontic appliances
– Subgingival placement of antibiotic fibers or strips	– Fluoride treatments
	– Taking oral radiographs
– Initial placement of orthodontic bands but not brackets	– Orthodontic appliance adjustment
	– Shedding of primary teeth
– Intraligamentary local anaesthetic injections	
– Prophylactic cleaning of teeth or implants where bleeding is anticipated	

Table 4 Dental therapy and endocarditis prophylaxis (Dajani et al, 1997)

Standard:	Allergic to penicillin:
amoxicillin	**clindamycin**
Adults: 2g orally	Adults: 600mg orally
Children: 50mg/kg orally	Children: 20mg/kg orally
1 hour before procedure	1 hour before procedure

Table 5 Antibiotic endocarditis prophylaxis for oral procedures (Dajani et al, 1997; Jeserich and Just, 2001).

Diabetes Mellitus

A patient has diabetes mellitus if glucose concentration in blood plasma has been assessed twice to be 126 mg/dl or higher in sober patients or at least 200 mg/dl two hours after oral intake of glucose (hyperglycemia) (American Diabetes Association, 1997). For differentiation between good and poor glycemic control in diabetics the so called hemoglobin-A_{1c} value (HbA_{1c}) is used. HbA_{1c} assesses control of blood glucose within the past one to two months. In healthy adults it is 4.3–5.8% and in well controlled diabetics 6–7%. Under poor glycemic control in diabetics HbA_{1c} values between 8–10% are found. For a HbA_{1c}

value of more than 10% there is a high risk for acute diabetic decompensation (Allolio and Schulte, 1996).
In almost all well-controlled diabetics conventional periodontal therapy may be performed. However, some particular aspects should be taken into consideration. Diabetics generally are predisposed to bacterial infections, which vice versa may disturb metabolic control severely. If periodontal surgery is planned in well-controlled diabetes mellitus antibiotic prophylaxis should be considered from case to case (Seymour and Heasman, 1992). However, up to now there are no evidence-based studies that advocate obligate antibiotic medication in well-controlled diabetics in general (Rees and Otomo-Corgel, 1992; Rees, 2000).
In poorly controlled or uncontrolled diabetes mellitus elective dental and periodontal procedures should not be performed, at least temporarily (Alexander, 1999). If oral or periodontal surgery is required in cases of emergency due to acute processes, antibiotic prophylaxis is required in any case to minimise the risk of postsurgical infections and complications of wound healing (American Dental Association, 1994).

HIV Infection

In patients with asymptomatic HIV infection any dental therapy may be performed (Little and Falace, 1991). Whether antibiotic prophylaxis should be applied in asymptomatic HIV patients or not has to be considered very carefully. It has been demonstrated that particularly HIV patients in more advanced stages of the disease show allergic reactions to prescribed antibiotics in high frequency (Glick, 1994).
According to the guidelines of the American Heart Association (AHA) and of the Council on Dental Therapeutics of the American Dental Association (ADA) (Dajani et al, 1997), antibiotic prophylaxis for dental treatment is required in patients at risk of a subacute bacterial endocarditis unrelated to HIV status.
In AIDS patients with severe immune suppression and neutropenia as well as thrombocytopenia, dental and periodontal treatment should be limited to dental emergencies. Elective treatments under these conditions are contraindicated in general. Emergency therapy that cannot postponed from a medical point of view should be performed as conservatively as possible. Analgetics and antibiotics should only be used or prescribed after consultation of the patient's physician. If surgical treatment is required, antibiotic prophylaxis should be considered to avoid hematogenic spread of infections due to frequent transitory bacteremias. This applies in particular in cases of severe neutropenia with cell counts below 500/mm^3 (Glick, 1994).
Periodontal surgery may be performed safely even in HIV-positive patients with low CD4$^+$ cell counts. However, careful medical history taking and consultation with the patient's physician or internal specialist are required. In cases with CD4$^+$ cell counts below 100/mm^3, severe neutropenia with less than 500 neutrophil granulocyts/mm^3 has to be considered and controlled for (Glick, 1994).
In HIV-infected patients some particular aspects have to be considered regarding choice of suitable antibiotics. In cases of severe neutropenia, bactericidal antibiotics are required (e.g. penicillin, amoxicillin, cephalosporin), whereas bacteriostatic antibiotics (e.g. erythromycin, clindamycin, tetracycline) are not indicated. If bacteriostatic antibiotics are used, bacteremia may persist after prophylaxis has been finished and possibly result in even increasing bacterial counts. Additionally, in HIV patients the risk for overgrowth of *Candida albicans* has to be considered after antibiotic medication for longer periods. Thus, systemic use of antibiotics in HIV patients is always combined with local application of antimycotic drugs. Further, in HIV patients suffering from severe immune suppression systemic antifungal prophylaxis is advisable (Ryder, 2000).

SYSTEMIC ANTIBIOTIC THERAPY

Necrotising Ulcerative Gingivitis (NUG) and Periodontitis (NUP)

Necrotising ulcerative gingivitis starts interdentally at the gingival papillae. Linear erythema is pathognomic (a fiery red line), which delineates the region of yellowish gray fibrin-covered necrosis from healthy gingival tissue (attempt of demarcation) (Fig 1). Patients complain of intense pain and report that the process had appeared quite suddenly. In many cases halitosis, regional lymphadenopathy, and in some cases symptoms of general disease (e.g. fever), are reported.
Table 6 shows the risk factors that predispose for NUP/NUG ('trench disease': widespread disease

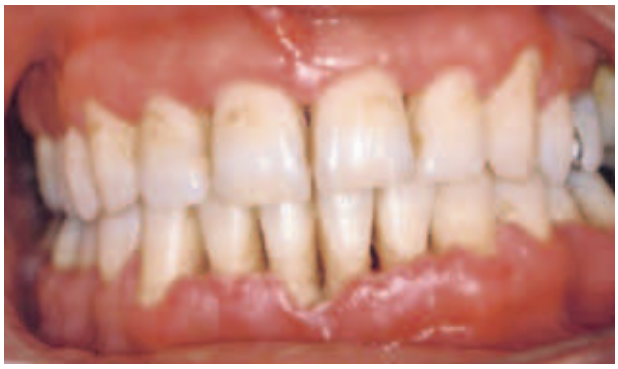


Fig 1 Necrotising ulcerative gingivitis and periodontitis exhibiting necrosis of papillas in the mandibular anterior region, linear erythema, and supragingival bacterial deposits.

Existing plaque-induced gingivitis	
Nicotine abuse	weakened host
Psychosocial stress	
HIV infection	
Malnutrition (e.g. drug addiction)	

Table 6 (*right*) Risk factors for NUG/NUP.

in soldiers during the First World War; deficient [oral] hygiene, cigarette smoking, stress [drum fire], malnutrition). The constantly found part of microflora related to NUG/NUP consists of Treponema spp. (spirochetes), Selemonas spp., Fusobacterium spp., and *Prevotella intermedia*.

Acute therapy includes supragingival depuration and chemical plaque control using 0.1–0.2% chlorhexidine digluconate mouth rinse. Patients are seen for control on a daily basis, and local therapy may be repeated. If local therapy fails to result in a significant improvement 24 hours after initiation of therapy or if there are signs for spread of infection (lymphadenopathy, fever), systemic antibiotics are required (American Academy of Periodontology, 2001): 250 mg metronidazole three times daily for three to five days (Holmstrup and Westergaard, 2003). Patients with clinical symptoms of NUG/NUP should be referred to a physician or internal specialist for examination of general infection status (e.g. HIV infection) and of the hematopoetic system (for exclusion of leukemia). If NUG is not treated in time, gingival necroses may spread within a short time and result in attachment as well as bone loss (NUP).

Adjunctive Antibiotic Therapy Targeting Specific Periodontal Pathogens

In general, use of antibiotics may follow two rationales: in acute infection where therapy must not be postponed unspecific broad spectrum antibiotics or specific antibiotics that are known to be effective in the particular disease (e.g. NUG/NUP: metronidazole) should be used without delay (expectative antibiotic therapy). In chronic infections the pathogen is first identified by microbiological examination and then, according to the result of microbiological analysis, an antibiotic is chosen that is appropriate (i.e. effective) for the particular identified microorganism. Periodontitis is characterised by chronic progression. The vast majority of cases (mild to moderate chronic periodontitis) can be treated successfully by mechanical debridement of subgingival bacterial deposits alone (antiinfectious and surgical therapy). However, because of the infectious character of periodontitis use of antibiotics may be considered. Today **microbiological diagnosis** is available for daily practice by commercial DNA- and RNA-probe tests. The indication for microbiological tests depends on the respective clinical diagnosis (Table 7). Tests for antibiotic sensitivity, i.e. antibiograms, are advisable if a preceding adjunctive antibiotic therapy has failed (Beikler et al, 2003).

Treatment of the forms of periodontitis listed in Table 7 is complex. Thus, after clinical diagnosis referring the respective patients for treatment to a periodontal specialist should be considered.

Even **aggressive and severe chronic periodontitis** may be treated successfully in many cases, despite detection of subgingival microorganisms that are closely related to periodontitis etiology (*Porphyromonas gingivalis, Tannerella forsythensis, Eikenella corrodens, P. intermedia, Prevotella nigrescens, Treponema denticola*) by mechanical debridement alone (subgingival scaling and root planning, flap surgery). An exception is ***Actinobacillus actinomycetemcomitans*** which has the character

Table 7 Indications for microbiological diagnostics and possibly adjunctive systemic use of antibiotics in periodontal therapy (Flemmig et al, 1998; Beikler et al, 2003).

– early onset periodontitis (**aggressive periodontitis***)
– severe generalised adult periodontitis (> 50% bone loss > 14 teeth) (**generalized severe chronic periodontitis***)
– periodontitis exhibiting progessive attachment loss despite appropriate therapy (**refractory periodontitis**)
– moderate to severe periodontitis with systemic diseases (particularly dysfunctions of neutrophils, diabetes mellitus, HIV infection with CD4 < 200/mm^3) (**periodontitis as symptom of systemic disease***)

* actual classification (Armitage, 1999)

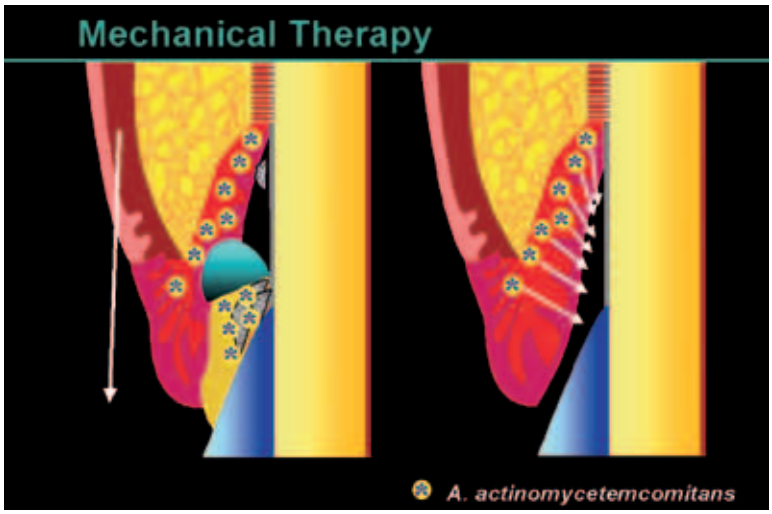


Fig 2a,b Exclusive mechanical therapy of a periodontal lesion infected by *Actinobacillus actinomycetemcomitans*: a) subgingival deposits inclusive *A. actinomycetemcomitans* are removed from the root surface. However, the periodontal pathogen persists within soft tissues, b) from where it recolonises the pocket again.

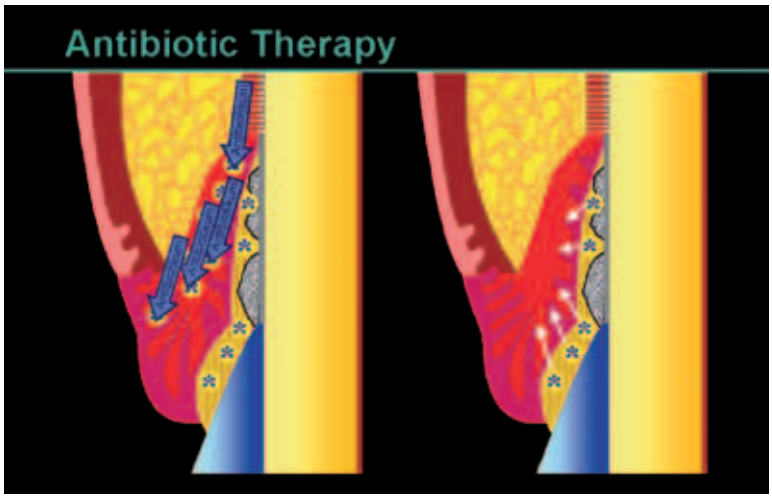


Fig 3a,b Exclusive systemic antibiotic therapy of a periodontal lesion infected by *Actinobacillus actinomycetemcomitans*: a) the antibiotic kills *A. actinomycetemcomitans* within soft tissues. However, it fails to penetrate the biofilm that adheres to the root surface. *A. actinomycetemcomitans* persists with the biofilm, b) from where it recolonises the soft tissues again.

of an exogenic pathogen (Slots and Ting, 2002) and which, in most cases, cannot be eradicated or suppressed below the detection limit by mechanical treatment alone (Christersson et al, 1985; Müller et al, 1993; Mombelli et al, 1994). *A. actinomycetemcomitans* is capable of leaving the pocket and invading the tissues or colonising extraperiodontal habitats (e.g. tongue, tonsils). In those retreats the microorganism cannot be reached be mechanical instrumentation of the root surfaces (Fig 2). Treatment with systemic antibiotics alone would eliminate those bacteria that have invaded the tissues. However, the effect on the biofilm at the root surface would be insufficient (Fig. 3). If *A. actinomycetem-*

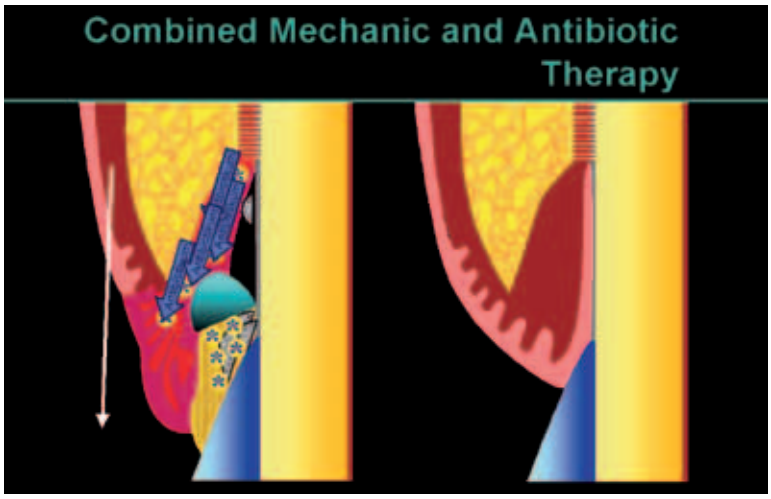


Fig 4a,b Combined mechanical and antibiotic therapy of a periodontal lesion infected by *Actinobacillus actinomycetemcomitans*: a) subgingival deposits including *A. actinomycetemcomitans* are removed from the root surface. The antibiotic kills A. actinomycetemcomitans within the soft tissues. Mechanical instrumentation destroys the biofilm,
b) resolution of infection, remission of inflammation and establishment of a long epithelial attachment.

Table 8 Adjunctive systemic antibiotic therapy of *Actinobacillus actinomycetemcomitans* (van Winkelhoff et al, 1989; Beikler et al, 2003).

Standard amoxicillin 375–500mg metronidazole 250–400mg	Allergic to penicillin ciprofloxacin 250mg metronidazole 250–500mg
3x daily for one week parallel to mechanical therapy (subgingival instrumentation)	

comitans is not eradicated or at least significantly reduced, remission will not be obtained and periodontal destruction will further progress (Christerrsson et al, 1985). Systemic use of tetracyclines adjunctively to mechanical therapy results in a reduction of *A. actinomycetemcomitans*, but eradication is not achieved (Müller et al, 1993). After combined use of **amoxicillin and metronidazole** adjunctively to subgingival scaling and root planing the periodontal pathogen could not be detected in 21 of 22 cases of aggressive and generalised severe chronic periodontitis (van Winkelhoff et al, 1989) (Table 8) (Fig 4). Amoxicillin and metronidazole three times daily for one week parallel to mechanical subgingival instrumentation are effective against *A. actinomycetemcomitans* in aggressive periodontitis, periodontitis in Papillon-Lefèvre syndrom, generalised severe chronic and refractory periodontitis (Slots and Ting, 2002). However, this combination is not effective against *Pseudomonas* and enterobacteria, which are found in approximately 14% of advanced lesions in the USA. Cultural tests for the detection of subgingival pseudomonads and enterobacteria is available commercially. In patients who are allergic to penicillin, amoxicillin may be replaced by the gyrase inhibitor ciprofloxacin. Ciprofloxacin and metronidazole also are effective against *Pseudomonas* and enterobacteria (Slots and Ting, 2002). These combinations of bactericidal antibiotics result in stable clinical and microbiological long-term results. Detection of periodontal pathogens alone after combined mechanical and systemic antibiotic therapy is no indication for renewed systemic antibiotic therapy if clinical results are favourable. Not only occurrence but also counts of e.g. *A. actinomycetemcomitans* and *P. gingivalis* at a single site are decisive for further attachment loss. An elevated risk of further attachment loss is associated with bacterial counts of at least 3×10^4 for *A. actinomycetemcomitans* and of 6×10^5 for *P. gingivalis*, respectively (Haffajee et al, 1983).

To achieve optimal efficacy the intake of systemic antibiotics should start immediately after mechanical instrumentation is finished and, thus, the biofilm is disintegrated (Beikler et al, 2003). It should be kept in mind that, after adjunctive systemic antibiotic therapy, maintenance of effective individual hygiene by the patient and compliance with supportive periodontal therapy are required to maintain a stable periodontal status on long-term.

Independently from microbiological detection of periodontal pathogens before therapy systemic intake of 250 mg tetracycline four times daily parallel to nonsurgical instrumentation in patients suffering from severe periodontitis for a period of three weeks

resulted in more favorable clinical results (attachment gain) than mechanical therapy alone. Over a period of 12 years after therapy attachment loss was observed in both groups. However, the tetracycline group maintained better clinical results for the whole observation period (Ramberg et al, 2001). In contrast to metronidazole, tetracycline is an antibiotic that does not play an important role in general medicine. However, tetracycline may cause systemic adverse effects, e.g. photosensitivity. Hence, for adjunctive application of antibiotics in nonsurgical treatment of severe periodontitis that is not associated with *A. actinomycetemcomitans* perhaps topically subgingival application of antibiotics may be favoured.

Periodontal Abscess with Tendency to Spread

Therapy of choice in localised and generalised periodontal abscesses is subgingival instrumentation of the affected pocket or pockets under local anesthesia. This type of therapy eliminates the acute cause of the process and provides marginal pus drainage. After mechanical instrumentation subgingival irrigation with 0.1 to 0.2% chlorhexidine solution or instillation of 1% chlorhexidine gel are appropriate. If the respective site is controlled, remission of complaints is mostly found the following day and consequent case-related therapy of the cause of abscess (vertical root fracture, subgingival food impaction, subgingival infection in deep pockets, furcation involvement, infrabony defects, or marginal epithelial attachment after superficial instrumentation with persisting subgingival infection) may be initiated (systematic periodontal therapy, resective furcation therapy). However, systemic antibiotic therapy adjunctive to local treatment is required in those rare cases in which a spreading of the abscess into adjacent compartments threatens or fever and/or significant lymphadenopathia is found (antibiotic of first choice: amoxicillin with clavulanic acid 500 mg 3 p.d.; in cases of penicillin intolerance: clindamycin 300 mg 3 p.d.) (Wagner and Shah, 2002).

LOCAL ANTIBIOTIC THERAPY

The **risk** of causing allergies and the development of **resistencies** (development of bacteria that are no longer sensitive to a particular antibiotic) belong to the disadvantages of use of antibiotics in general and in periodontal therapy. Thus, in periodontics ideally only antibiotics that do not play an important role in general medicine, and particularly intensive care, should be used (e.g. tetracyclines). However, systemic use of antibiotics has further disadvantages: systemic adverse events (e.g. drug exanthema) (Fig 5) and effects on extraoral bacteria (e.g. enteric flora). These disadvantages have led to the development of local applications of antibiotics which are intended to exclusively affect bacteria within the periodontal pocket. Sulcus fluid flow causes an exchange of the volume of a 5 mm deep pocket 40 times an hour (Goodson, 1989). This high rate of exchange results in a rapid dilution of the concentration of subgingivally applied agents. Hence, applications had to be developed that establish a stable subgingival depot from which effective antibiotic concentrations are released continuously. Local subgingival delivery devices that release an active agent (antibiotic) for up to 24 hours are called **sustained release devices**. In contrast, **controlled release devices** set free effective concentrations for more than 24 hours (American Academy of Periodontology, 2000a).

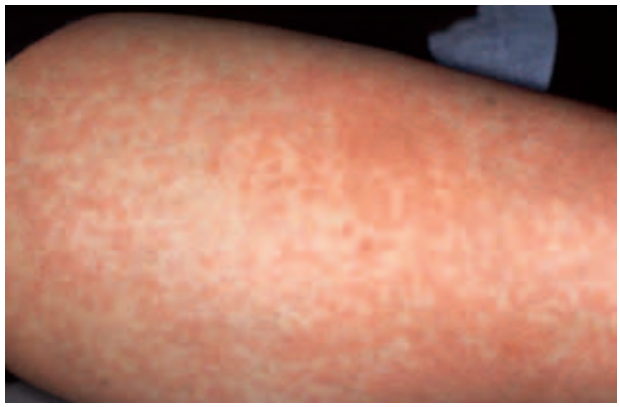


Fig 5 Drug induced exanthema (red rush) after systemic intake of amoxicillin.

Local application of antibiotics aims at three targets: 1) Support of nonsurgical mechanical antiinfective therapy (application adjunctive to scaling and root planing to increase the efficacy of therapy), 2) support of reinstrumentation during supportive periodontal therapy (application adjunctive to scaling and root planning to increase the efficacy of therapy), and 3) as alternative to subgingival reinstrumentation during supportive periodontal therapy (application instead of scaling and root planing to achieve the same effect).

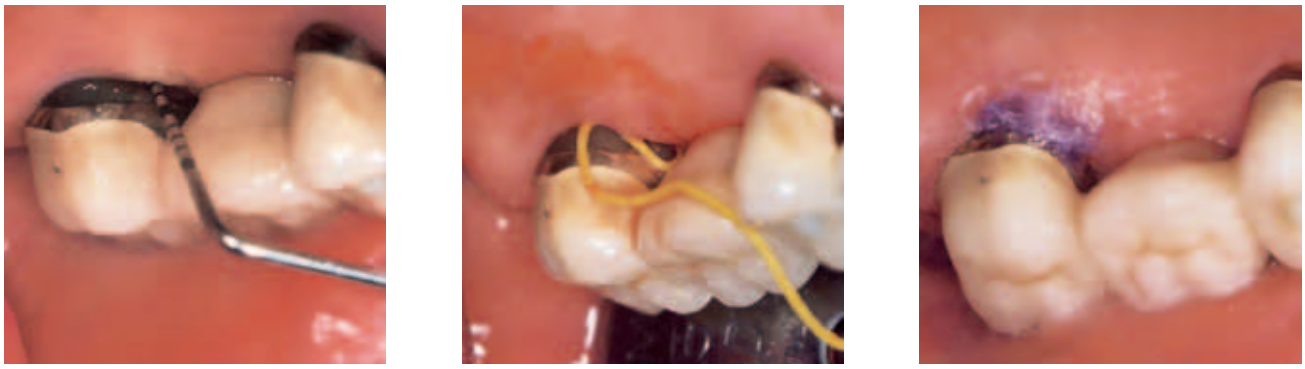


Fig 6a–c Actisite fibre: persisting pocket mesiolingual of a second maxillary left molar during supportive periodontal therapy: a) probing pocket depth 7 mm, b) subgingival application of actisite fibre, c) closure of pocket using cyanoacrylate.

Fig 7 Applicator for Elyzol dental gel.

A meta-analysis comparing the efficacy of surgical and nonsurgical periodontal therapy with or without topical subgingival application of antibiotics demonstrated better clinical results after topical subgingival antibiotics adjunctive to nonsurgical mechanical therapy than after mechanical instrumentation alone (Hung and Douglass, 2002).
For adjunctive systemic antibiotic therapy aimed at specific periodontal pathogens, metronidazole (the antibiotic of first choice in anaerobic infections) and ciprofloxacin may be used. These are antibiotics that have important significance in general medicine. However, these antibiotics regularly are used only for one therapy cycle. Local antibiotics possibly are used again and again within the same patient over years of supportive periodontal therapy. Thus, only those antibiotics should be used for local application that have no or only minor significance in general medicine and particularly intensive care (e.g. tetracyclines).
One of the first available devices was the **Actisite®** fiber (not available any more), a nonresorbable monolithic ethylene vinyl acetate polymer fibre (Ø 0.5mm, length 35cm) that was loaded with 25% tetracycline HCl. After mechanical instrumentation of the lesion the tetracycline fiber was placed subgingivally using a periodontal probe or a retraction fibre applicator (Fig 6). Finally the pocket had to be closed using cyanoacrylate to prevent expulsion of the fibre by crevicular fluid flow (Fig 6c). The fibres have to be removed in a second appointment seven to 13 days after application. The tetracycline fibre had good pharmacokinetic properties: for a period of seven days after application a mean tetracycline concentration of more than 1300 µg/ml was detected (controlled release device) (Tonetti et al, 1990). One Actisite fibre is sufficient for the treatment of three to five lesions, depending on depths and extension of the respective pockets. However, application is difficult and time-consuming. Additionally, a second appointment is required to remove the device. Thus, slow-release devices were sought that on one hand can be easily applied and on the other hand are bioabsorbable. A bioabsorbable slow-release device is **Elyzol®** 25% dental gel (Colgate-Palmolive Company, New York, NY, USA). The gel consists of 250mg metronidazole benzoate in a matrix consisting of glyceryl mono-oleat and sesame oil in 1g gel (Norling et al, 1992). The gel comes in capsules or disposable applicators (Fig 7). Two applications of the agent with a one-week interval are recommended. On contact with crevicular fluid the gel is transformed into a highly viscous and adhesive substance. While dissolving, the agent continuously releases metronidazole. However, concentration of metronidazole in crevicular fluid drops exponentially after application of the gel (Stoltze, 1992). One applicator provides material for the treatment of three to five lesions, depending on depth and extent of periodontal pockets.

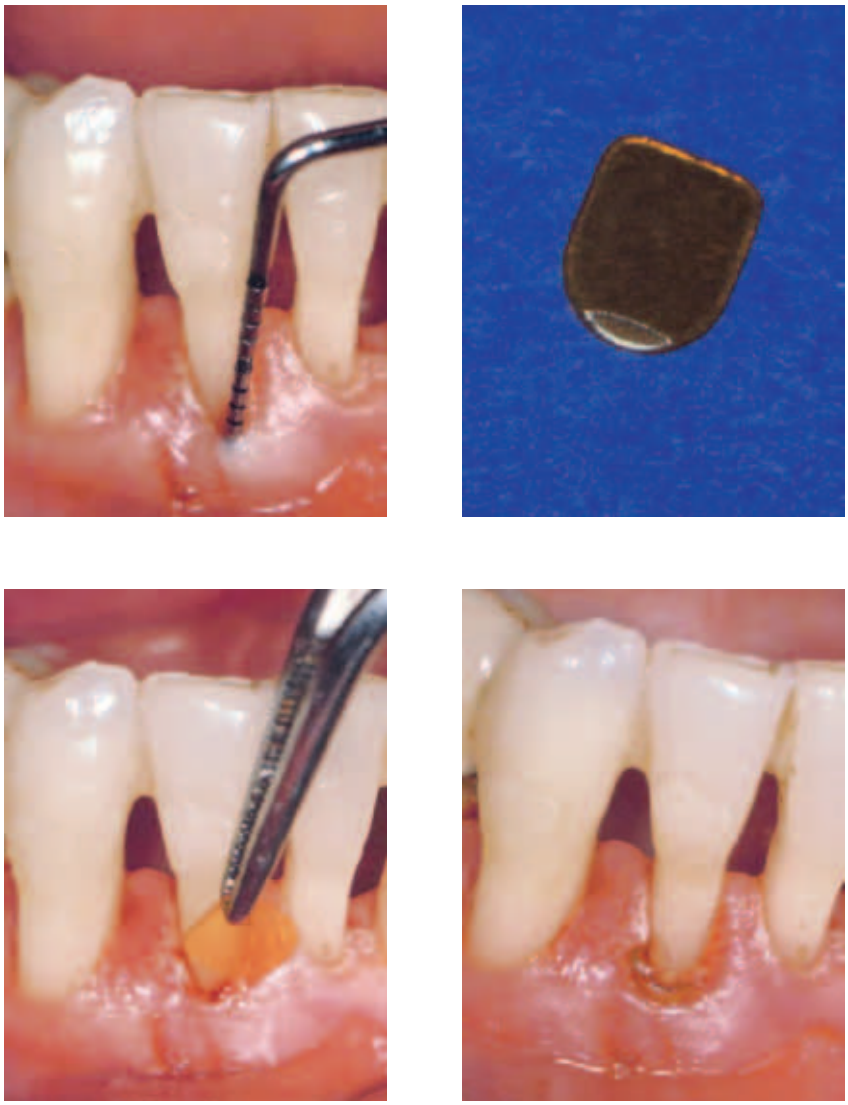


Fig 8a–d PerioChip: persisting pocket buccal of a lateral mandibular left incisor during supportive periodontal therapy: a) probing pocket depth 6 mm, b) PerioChip, c) subgingival application of PerioChip using a dental forceps, d) PerioChip in situ.

Minocycline ointment (Dentomycine®, Lederle, UK; Periocline®, Sunstar, Japan) is a biodegradable agent consisting of 2% minocycline HCl in a matrix of hydroxyethyl-cellulose, aminoalkyl-methacrylate, triacetine and glycerine. The ointment is instilled subgingivally, using a special applicator. The agent is biodegradable and releases minocycline during biodegradation.

Minocycline microspheres (Arestine®, OraPharma Inc., Warminster, PA, USA) is a powder of microspheres that encapsule minocycline hydrochloride in a bioabsorbable polymer (polyglycolide-co-DHLI lactide). This powder is dispensed subgingivally to the base of the pocket by means of a disposable plastic cartridge affixed to a stainless-steel handle. Immediately upon contact with moisture, the polymer begins to hydrolyse and to release minocycline (Williams et al, 2001).

PerioChip® (Dexxon Ltd., Hadera, Israel) is a bioabsorbable slow-release device that is not loaded with an antibiotic but with an antimicrobial agent. The chip has a square shape with round edges at one of the short sides with 5 mm length, 5 mm width and 1 mm thickness (Fig 8a). The bioabsorbable matrix consists of gelatine glutaraldehyd polycondensate, glyceryl and purified water. This vehicle is loaded with 34% chlorhexidine-bis-D-gluconate. Periochip is applied using dental forceps (Fig 8b–d). After contact with fluids the chip becomes very sticky. Thus, sometimes under application it must be sheared off the forceps into the pocket with another instrument. One PerioChip can be used for the treatment of one lesion.

There are two slow-release devices for topical subgingival application using doxycycline as active antibiotic agents. **Atridox®** (Atrix Laboratories, Fort Collins, CO, USA) is a bioabsorbable gel contain-

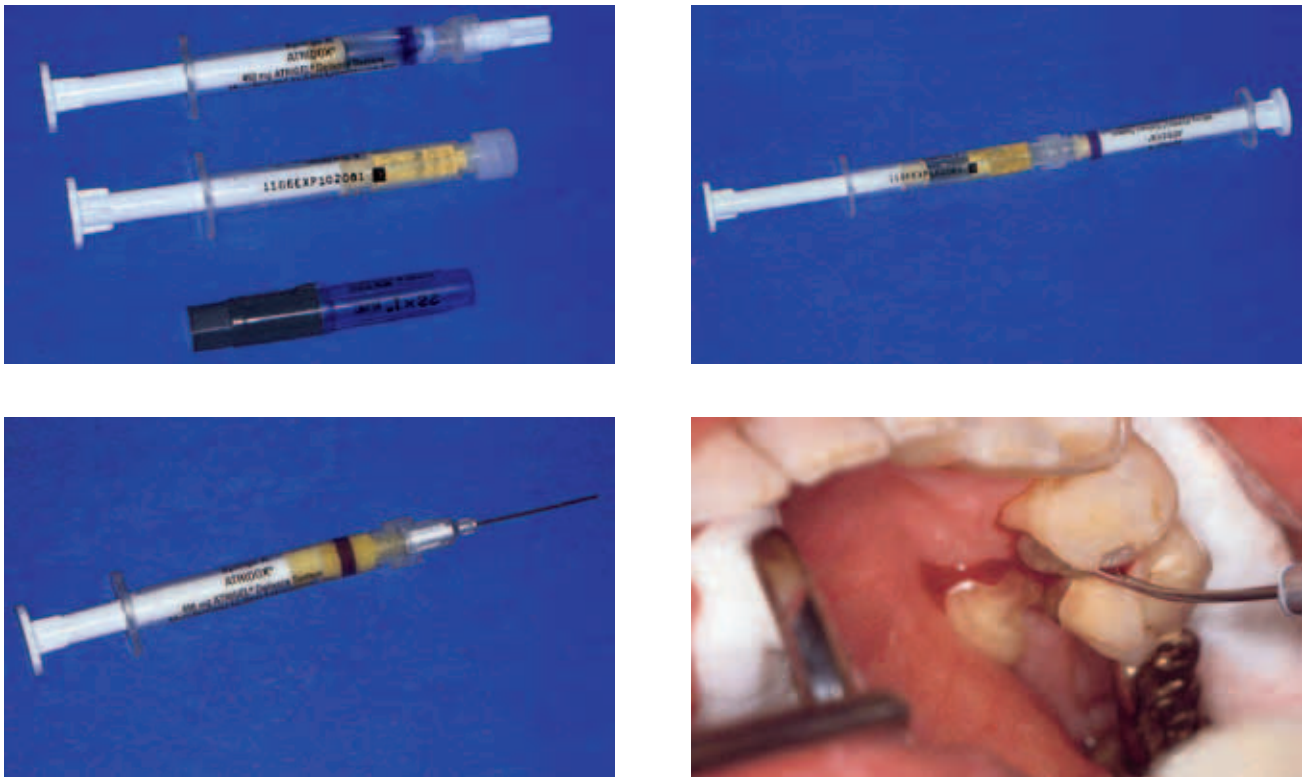


Fig 9a–d Atridox: a) from above to below: application syringe containing the polymer, syringe containing the doxycycline powder, blunt needle, b) syringes with polymer and doxycycline screwed together for mixing, c) application syringe with gel mixed from polymer and doxyxycline powder, d) subgingival application of Atridox gel.

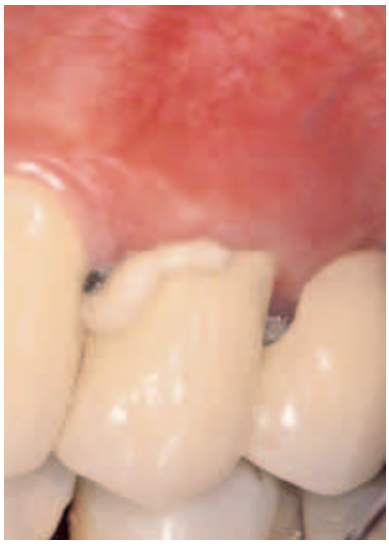
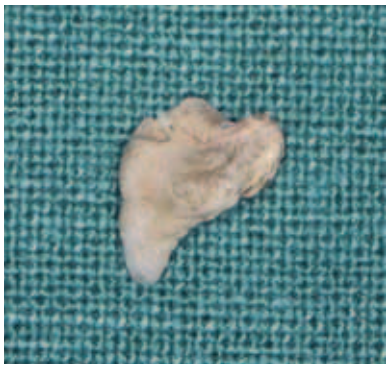


Fig 10 Atridox 14 days after subgingival application and gingival recession.

ing 10% by weight doxycycline, 33% by weight poly (DL-lactide) and 57% by weight N-methyl-2-pyrrolidone. The antibiotic agent comes as powder that has to be mixed with the polymer immediately before use (Fig 9a–c). Having contact with tissue fluid the light-flowing gel is applied using a blunt syringe, which transformes it to a highly viscous substance (Fig 9d). The syringe is pushed to the bottem of the pocket and, moving the syringe slowly coronally, gel is pressed into the pocket until overflow is visible at the gingival margin. After this overflow has hardened it can be pushed apically into the pocket. In some cases the highly viscous gel does not degrade totally and remnants have to be removed using a curette at another appointment (Fig 10, 11). Another 14% doxycycline gel for topical subgingival use, based on a synthetical biodegradable polymer vehicle, has been evaluated (Eickholz et al, 2002; Kim et al, 2003). Pharmacokinetic profiles of both agents are comparable: five days after subgingival application of the 14% doxycycline gel without closure of the pocket concentration in crevicular fluid was 126.47 ± 38.10 µg/ml (Kim et al, 2002). Five days after subgingival application of Atridox with closure of the periodontal pockets using tissue glue or dressing doxycycline concentration in crevicular fluid was 361.92 ± 92.32 µg/ml and 533.37 ± 202.19 µg/ml, respectively (Stoller et al, 1998). Eight days after subgingival

Table 9 Antibiotics in periodontal therapy (Ciancio and van Winkelhoff, 2001).

penicillin	**bactericidal**, mainly active against gram-positive bacteria; **adverse effects:** hypersensitivity (0.6% to 10%), Herxheimer reaction
amoxicillin	broad spectrum, β-lactamase sensitive; **adverse effects:** gastrointestinal disturbances, diarrhea, skin reactions (exanthema) in 20% of cases; colitis ulcerosa
amoxicillin & clavulanic acid	broad spectrum, β-lactamase stable; **adverse effects:** as amoxicillin
tetracyclines	**bacteriostatic**, broad spectrum, collagenase inhibitory effect, numerous bacterial resistancies; **adverse effects:** photosensitivity reactions, gastrointestinal disturbances, oral candidiasis, allergic reactions are uncommon, at high doses: hepatotoxicity and nephrotoxicity; permanent discolouration of teeth if taken during tooth formation; reversible vertigo (only minocycline)
tetracycline	4 doses a day
minocycline	semisynthetical tetracycline derivative; 2 doses a day
doxycycline	strongest collagenase inhibitory effect of all tetracyclines; 1 dose a day
metronidazole	**bactericidal**, active against strict anaerobic bacteria, synergistic effect with amoxicillin against *A. actinomycetemcomitans*; **adverse effects:** metallic taste, vertigo, nausea (12%), disulfiram (antabus) reaction, at high doses peripheral neuropathy **Cave: important antibiotic in general medicine**
clindamycin	**bacteriostatic**; **adverse effects:** diarrhea, gastrointestinal disturbances (thus, intake together with food recommended); colitis ulcerosa
ciprofloxacin (fluoroquinolone)	**bactericidal**; **adverse effects:** gastrointestinal disturbances, diarrhea, nausea, vomiting, oral candidiasis, headaches, dizziness, drowsiness, insomnia, allergic reactions, hyperpigmentation, photosensitivity; **Cave: important antibiotic in general medicine**



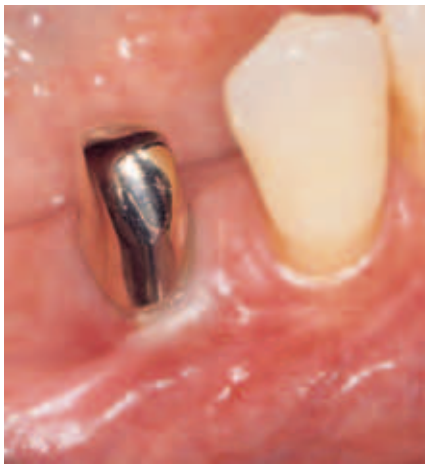


Fig 11a, b Atridox 14 days after subgingival application: a) the fastened agent in situ, b) after removal by a curett.

application the respective values were 115.25 ± 37.83 µg/ml (14% doxycycline gel) (Kim et al, 2002) and 36.32 ± 14.02 as well as 15.72 ± 10.73 µg/ml (Atridox) (Stoller et al, 1998). Direct comparison of both agents in a further study confirmed these results (Kim et al, 2004). Thus, both agents may be classified as controlled-release devices.

Efficacy of local antibiotics was mostly studied in chronic periodontitis. Patients with chronic and aggressive periodontitis were included only in a few clinical trials (Eickholz et al, 2002; Kim et al, 2003). Topical subgingival application adjunctive to nonsurgical instrumentation of untreated and recurrent pockets resulted in better clinical results than mechanical therapy alone or after adjunctive topical application of the vehicle gel (placebo): 2% minocycline ointment (van Steenberghe et al, 1993; 1999), PerioChip (Soskolne et al, 1997), minocycline microspheres (Williams et al, 2001), 25% metronidazole (Stelzel and Flores-de-Jacoby, 2000), 14% doxycycline gel (Eickholz et al, 2002). Whereas a single application of 14% doxycyline gel was sufficient to achieve these results after six months (Eickholz et al, 2002), up to three PerioChips had to be applied into single pockets over the observation period of nine months (Soskolne et al, 1997). Early studies on minocycline microspheres showed more favorable probing depth reduction for minocycline adjunctive to mechanical therapy than for mechanical debridement alone. However, more attachment gain was observed after exclusivly mechanical therapy than after adjunctive minocycline (Jones et al, 1994). A recently published systematic review reveals an additional benefit of use of subgingivally delivered topical antibiotics regarding probing depth reduction but not regarding attachment gain (Hanes and Purvis, 2003).

For therapy of persisting or recurrent pockets during supportive periodontal therapy (SPT), topical subgingival application of antibiotics adjunctive to mechanical instrumentation resulted in better clinical outcomes after use of Actisite (Kinane and Radvar, 1999) and minocycline microspheres (Meinberg et al, 2002), wheras adjunctive use of 25% metronidazole failed to show an additional benefit (Stelzel and Flores-de-Jacoby, 2000). After exclusivly subgingival application of slow-release devices for treatment of persisting or recurrent pockets during SPT, insignificantly inferior or equally clinical results were reported in comparison to scaling and root planing: Elyzol (Stelzel and Flores-de-Jacoby, 1992), Atridox (Garrett et al, 1999), 14% doxycycline gel (Kim et al, 2003).

Use of local antibiotics seems to be appropriate, particularly for SPT, in patients who exhibit persisting pathological pockets (probing depths ≥ 5 mm with bleeding on probing) after accomplishment of active periodontal therapy (root surfaces free of mineralised deposits). In these patients repeated subgingival scaling in the long term may result in hard-tissue loss and often root sensitivity. Use of subgingivally applied slow-release devices may be a possible strategy to avoid this discomfort and to treat persisting pockets with a concept different from the mechanical therapy that had failed to resolve pockets at those respective sites.

Anti-infectious therapy of untreated periodontitis by locally subgingival application of doxycycline gel and mechanical instrumentation of root surfaces has been proposed recently under the name

pharmaco-mechanic infection control (PMIC). According to this concept, root surfaces in all pathologically deep pockets (probing depths ≥ 5 mm) are debrided roughly mechanically using ultrasonic instruments without local anesthesia. After that doxycycline gel is applied subgingivally. After re-evaluation three months later, persisting pockets are instrumented thoroughly under local anesthesia by hand instruments. Clinical success is similar to the traditional rationale, which follows a sequence vice versa: as a first-step anti-infectious therapy is performed under local anesthesia by thorough mechanical instrumentation (scaling and root planning), and in a second step after re-evaluation or during SPT persisting pockets are reinstrumented and local antibiotics are applied. In a first clinical study with 101 patients PMIC was revealed to be less time-consuming than the traditional concept: PMIC took a total of two hours, conventional therapy took more than three hours (Wennström et al, 2001). At present it is not clear whether the amount of time saved by the concept of PMIC outweighs the cost of the doxycycline gel. However, other clinical trials demonstrate the clinical efficacy of local subgingival application of doxycycline gel additional to nonsurgical mechanical therapy of untreated periodontitis (Eickholz et al, 2002). The additional clinical effect that has been reported after systemic use of tetracycline adjunctive to nonsurgical periodontal therapy (Ramberg et al, 2001) might also be achieved by topical subgingival application of tetracycline or its derivatives without systemic adverse effects. However, the risik of **allergies and resistance** cannot be avoided by local application of antibiotics. Additionally, up to now it is not quite clear how many pockets may be treated by local application of antibiotics without systemic effects. In patients with untreated generalised chronic severe or aggressive periodontitis in many cases almost all teeth have pathological pockets and, thus, according to the concept of PMIC, would be treated with local antibiotics. Before PMIC is looked upon as standard treatment option, further studies – particularly investigating pharmacokinetics – have to be performed.

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