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Low-cost periodontal therapy

Jørgen Slots

Periodontitis is a common and often lifelong infectious disease that is defined by loss of periodontal ligament and alveolar bone (81). The disease proceeds with periods of exacerbation and remission. Some types of periodontitis arrest spontaneously within a relatively short period of time, while other disease types undergo a prolonged course of tissue destruction that may lead to excess tooth mobility and edentulism (22). Periodontitis can also affect and be affected by the systemic health (33, 298). Periodontitis occurs with increased frequency in immunocompromised and low-income individuals (8, 40, 66, 79, 327), and the disease may be associated with specific genetic variants (167, 172, 204, 327, 386) and is particularly severe in patients with various Mendelian (monogenic) diseases that primarily affect nonoral tissues (122, 125).

Periodontitis is associated with and probably caused by a combination of virulent bacteria, mammalian viruses and proinflammatory host responses (303). The most prominent putative periodontal pathogens are gram-negative anaerobic rods and herpesviruses (303). Virtually all cases of aggressive periodontitis involve an active herpesvirus infection, which has the potential to impair periodontal host defenses and induce an overgrowth of pathogenic bacteria (304). Slowly progressing or stable types of periodontitis may occur in subjects who demonstrate plaque accumulation of low-grade pathogenic bacteria, or who possess protective immunity against the major periodontal pathogens.

The key to combating periodontitis is easy-to-follow preventive guidelines and early disease intervention with effective and safe antimicrobial therapy that is implemented cooperatively by the dental professional and the patient (29). Lack of patient compliance with disease-preventive measures can undermine an otherwise successful treatment by the dental professional (165). Basic periodontal treatment includes removal of dental biofilms and biofilm-retentive calculus by mechanical means and by antimicrobial medication. However, the ability of mechanical treatment alone (scaling and root planing, periodontal surgery) to resolve destructive periodontal disease was probably overestimated in the past. The chemotherapeutic option became increasingly important after the recognition of the microbial specificity of periodontitis, and the use of topical and systemic antimicrobial agents is now the rule rather than the exception in the treatment of severe periodontitis. Proper management of periodontal disease must also consider follow-up treatment after initial therapeutic success, and contemplate alternative modes of intervention in the event of therapeutic failure.

This article reviews current periodontal therapeutic intervention, with emphases on the treatment needs of low-income individuals, putative periodontal pathogens and their antibiotic-susceptibility profiles, professional mechanical and chemotherapeutic options, and affordable patient self-care. The article concludes with proposing a multifaceted approach to periodontal treatment that possesses high efficacy and tolerability and can be implemented in virtually all parts of the world using low-cost local resources.

Periodontal disease and low-income populations

Contemporary periodontal healthcare is centered on evidence-based diagnosis and therapy (212, 376) and is directed towards both individuals (25) and societies (157, 365). It takes into account the socioeconomic status and the expectation of patients (344), and the cost-benefit and cost-effectiveness ratios of the periodontal treatment (112, 355). The basic approach to allocating healthcare resources most efficiently is to relate change in financial costs to change in therapeutic outcome (126). It is reasonable to expect higher costs of initial periodontal treatment for older than for younger individuals, as more severe disease is generally present in older patients. Younger periodontitis patients may incur higher expenses in the

long term because of lifelong maintenance care. Risk-stratification schemes and structured treatment guides may help to optimize the outcome of periodontal therapy (105).

Periodontitis is a major health problem in low-income populations (7, 230, 231). Classical risk factors for periodontitis, such as immunocompromising diseases / conditions (228, 332) and tobacco use (66, 362), are prevalent in developing countries. Other risk factors for periodontitis are obesity (261) and diabetes (77, 201, 339), which have assumed almost epidemic proportions in many countries of the world, including regions of Asia (66). Also, infection with periodontopathic herpesviruses occurs at a higher prevalence in less-developed countries than in affluent countries (4), and the herpesvirus seroprevalence in high-income countries exhibits racial, educational and socioeconomic disparities (382). Taken together, low-income individuals in developing countries tend to demonstrate a high level of risk factors for periodontal disease (110, 217), and are at increased risk of developing severe periodontitis (7, 26, 27, 336) and even potentially fatal oral infections such as noma (cancrum oris) (41, 220).

The world's population is currently 7 billion and estimated to grow by 33% in the next 40 years with the greatest expansion occurring in low-income countries (349). Income levels vary widely among residents within a country, across countries in the same region and between regions, and pockets of poverty extend into middle- and high-income countries (320). The 2008 poverty data from the World Bank estimated that 1.4 billion people (one in four; more than the combined population of Europe and the USA) in 115 low-income countries were living in extreme poverty, as measured by the US$ 1.25-a-day poverty line of purchasing power (375). The poverty rate in sub-Saharan Africa is as high as 50%. In 2011, the United States Department of Agriculture determined that 802 million people in 70 developing countries were chronically hungry ('food-insecure') and that 43% of the world's hungry population lived in sub-Saharan Africa (266).

The great majority of low-income individuals have little or no access to good-quality dental care, and inequity in the delivery of dental services is particularly pronounced in the developing world (27, 161). People living in poverty can generally not afford dental treatment in a private office, and the dental healthcare supported by governments or development agencies is frequently underfunded or fails to reach the majority of the poorest people (365). Resource-poor countries are faced with allocating scarce funds to several competing healthcare programs and may not identify dentistry for the poor as a high-priority item. Dentists in countries with no formal healthcare delivery system must often resort to compromised treatment options, such as extraction of symptomatic teeth and tooth replacement with removable dentures (101, 363).

Successful periodontal healthcare of low-income populations must be based upon affordable professional therapy and self-care techniques with proven efficacy and safety. Even so, most models for prevention and treatment of periodontal disease have not been tested or compared in controlled studies, and periodontal disease management of low-income individuals is particularly understudied (161, 222). Also, traditional models of dental education produce dental professionals in quantities or with skills that are inadequate to meet the oral healthcare needs of low-income communities.

Despite a lack of a consensus approach to affordable periodontal healthcare, it is unanimously accepted that removal of dental biofilm microorganisms is essential for maintaining a healthy periodontium. Self-management of periodontal disease is of utmost importance for individuals with limited access to professional dental services (24). A sizable majority of dental patients in developing countries already rely on self-medication, mostly analgesics, but the general public demonstrates a lack of understanding of the management of oral infectious diseases (6). Healthcare information shared via electronic media may eventually improve oral health literacy globally (211).

Periodontal pathogens

Knowledge of the periodontal microbiota is critical for implementing successful periodontal therapy. Periodontal pockets contain as many as 400 species of bacteria (226), which are organized in biofilms to gain protection against physical removal and assault from toxic substances, immune responses and antimicrobial treatment (171). The subgingival microbial community differs markedly in periodontal health and in periodontitis (296). Alpha-hemolytic streptococci and actinomyces species predominate in periodontal health or slight gingivitis and after successful periodontal therapy (120, 296, 309). These gram-positive bacteria exhibit little periodontopathic potential and may even protect against colonization of more pathogenic species. A caveat is that some gram-positive plaque bacteria (mutans streptococci

and *Actinomyces naeslundii*) can cause enamel or cemental caries (170, 263).

Most periodontal pathogens belong to gram-negative anaerobic or microoxic genera, although various gram-positive bacteria and gram-negative facultative rods can also contribute to periodontal breakdown (21, 323). Complex inter-relationships of symbiosis, antagonism and commensalism among periodontal bacteria determine the aggressiveness of periodontal infections (245, 324). Major periodontopathic species include the gram-negative species *Porphyromonas gingivalis, Tannerella forsythia, Dialister invisus/pneumosintes*, *Prevotella intermedia, Treponema denticola*, *Fusobacterium* species, *Campylobacter rectus*, *Aggregatibacter actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*) and unnamed species/phylotypes identified by nonculture molecular techniques (21). A specific *A. actinomycetemcomitans* genotype, termed the JP2 clone, exhibits increased periodontopathogenicity (131) and was found to strongly predominate in subjects who converted from a healthy periodontal state to localized aggressive (juvenile) periodontitis (87, 88). The pathogenicity of the *A. actinomycetemcomitans* JP2 clone may be a result of its high cytotoxic activity against human neutrophils (338). The JP2 clone has the characteristics of an exogenous human microorganism (166, 338) and thus potentially can be eradicated by antibiotic therapy (353). The clone is prevalent in North and West Africa (166) and among Black people in the Americas (64), but not among people of European or Asian ancestry (64, 277). *A. actinomycetemcomitans* strains not belonging to the JP2 clone can also be involved in aggressive periodontitis in African teenagers (97).

Gram-positive periodontopathogens include *Eubacterium* species and *Parvimonas micra* (previously *Peptostreptococcus micros* or *Micromonas micros*) (21). *Staphylococcus aureus* and coagulase-negative staphylococci inhabit approximately 50% of gingivitis and periodontitis lesions (67, 243), and most *S. aureus* strains show leukocidal activity (146). Beta-hemolytic streptococci (other than *Streptococcus pyogenes*) may occur in one-third of advanced periodontitis lesions and comprise, on average, 10% of total isolates in culture-positive sites (75, 106). Superinfecting organisms, such as multiple-drug-resistant *Enterococcus faecalis* (244, 333) and enteric gram-negative rods, pseudomonads and *Candida albicans* (70, 308), can colonize periodontal pockets, especially in immunocompromised and elderly individuals (308) and in patients with previous exposure to antibiotics (130). Enteric gram-negative rods are frequent periodontal organisms in the population of developing countries (10, 133, 311), probably because of consumption of contaminated drinking water, superinfection induced by a high frequency of antibiotic-requiring infectious diseases, or user- or healthcare provider-related misuse of antibiotics (47). Classical periodontal pathogens, as well as staphylococci, enteric gram-negative rods and *C. albicans*, are also implicated in peri-implantitis (9, 99, 128, 267, 337). Periapical lesions of endodontic origin that expand into an existing periodontal pocket (123) can be an additional source of periodontal pathogens (272). Parasites can also colonize the mouth, and systemic protozoal infections may affect the oral cavity of individuals in subtropical and tropical countries (e.g. leishmaniasis) (38).

Most individuals experience periodontitis in relatively few teeth and predominantly at interdental surfaces in spite of a heavy load of periodontopathic bacteria in saliva (284). As suggested previously (301), the restricted occurrence of periodontitis lesions may be a result of the participation of both bacteria and herpesviruses in the disease process. Studies have linked Epstein–Barr virus and cytomegalovirus to marginal periodontitis (304), peri-implantitis (147), apical periodontitis (314), and oral ulcers and cancers (118, 302). Epstein–Barr virus is also associated with pregnancy gingivitis and other types of gingivitis (100), and is an etiologic agent of oral hairy leukoplakia and lymphoid and epithelial malignancies (315). Cytomegalovirus is involved in severe types of periodontitis (179, 299) and in embryopathosis affecting tooth morphogenesis (148, 328), osteogenesis of the jaws (31, 149) and salivary gland development (203). Herpesvirus infections may trigger an overgrowth of periodontopathic bacteria (303) and, paradoxically, anti-herpesvirus immune responses may contribute to both tissue destruction and the arrest of periodontal breakdown (63). Herpesvirus infections can also affect the systemic health (302). The notion of a herpesvirus etiology of periodontitis may accommodate both local and remote cause hypotheses of the disease (143).

Periodontal treatment concepts

Microbiology studies from the 1970s and 1980s linked specific bacteria to periodontitis and changed the paradigm of periodontal treatment (296, 321). Periodontics adopted generally accepted principles for the treatment of infectious diseases, including the use of antiseptics and antibiotics (77, 253). The

discovery of cross-infection of periodontal pathogens among individuals in close contact argued for the treatment of entire family units (23, 168, 316). Professional periodontal therapy became centered on mechanical debridement, periodontal pocket irrigation with a potent antiseptic agent, and systemic antibiotics and/or surgery for advanced disease. Patients with severe periodontitis will receive a broader and more powerful antimicrobial treatment than patients with mild periodontitis, but the optimal type of antimicrobial therapy is still a topic of debate.

The morphological and infectious complexity of periodontitis lesions suggest that a pure mechanical approach to periodontal therapy may not resolve all cases of the disease. Indeed, a 30-year epidemiologic study in Sweden found that the current mode of periodontal treatment and maintenance care had increased the percentage of periodontally healthy individuals from 8% to 44%, paralleling a decrease in the percentage of patients with gingivitis and moderate periodontitis, but had not been able to reduce the prevalence of 6–8% of advanced periodontitis (141). A study in Norway found that the proportion of 35-year-old individuals with no alveolar bone loss had increased from 46% in 1973 to 76% in 2003 but that severe periodontitis remained unchanged, at 8.1% (293). Apparently, cases of advanced periodontitis have an etiology, perhaps related to herpesviruses, that is largely unresponsive to conventional periodontal therapy and maintenance care.

Efficacious periodontal self-care should be directed toward both supragingival and subgingival control of pathogens, and this entails the daily removal of dental plaque by mechanical means and the frequent rinsing of periodontal pockets with an antiseptic agent. In contrast to a rapid bacterial recolonization after supragingival cleaning, subgingival pathogens may remain suppressed for several months after periodontal pocket debridement (120, 309), probably because of potent antimicrobial defenses in the serumal gingival crevice fluid (95).

Methodologies of periodontal antimicrobial therapy

The primary goal of periodontal therapy is to achieve a periodontal environment free of pathogenic microorganisms. Mechanical debridement and pharmacotherapy are both important components of periodontal treatment. The presence of subgingival calculus renders chemotherapy partly ineffective, underscoring the need for mechanical removal of calculus (137). On the other hand, scaling and root planing alone may not eliminate a substantial portion of subgingival pathogens, especially in deep periodontal sites (348). 'Routine scale' (≈supragingival scaling) and polishing performed without the use of subgingival chemotherapeutic agents, root planing or periodontal surgery have little effect on destructive periodontal disease (35).

Calculus removal

Calculus contributes to the development of periodontitis by providing a porous reservoir for bacterial retention and growth (150). Although minor amounts of subgingival calculus may be compatible with nonprogressing disease, major calculus deposits will invariably sustain gingival inflammation and pose a risk for further loss of periodontal attachment (52). A thorough mechanical debridement of the teeth of patients with periodontitis may take as long as 2 h (221).

Scaling and root planing comprise the principal mode through which subgingival calculus is removed, although alternative methods of calculus removal are available. The limitation of scaling and root planing is well recognized and was illustrated on extracted teeth coated with fingernail polish to mimic dental deposits (227). Clinical studies showed that scaling removed all calculus and biofilm in only 11% of periodontal pockets deeper than 5 mm (331, 357). Hand instrumentation failed to eliminate subgingival calculus in 10% of periodontal pockets with a depth of < 5 mm, in 23% of pockets with a depth of 5–6 mm and in 35% of pockets with a depth of > 6 mm (239). Another scaling study detected residual calculus in 19% of periodontal pockets with a depth of < 4mm, in 38% of pockets with a depth of 4–5 mm, in 43% of pockets with a depth of > 5 mm and in 10% of single-rooted teeth and in 30% of multirooted teeth (111). Disappointingly and underappreciated, even scaling performed in conjunction with access flap surgery may fail to remove all calculus in 24% of periodontal sites with a depth of 4–6 mm and in 50% of sites with a depth of > 6 mm (48).

Power-driven scalers are equipped with a working tip that oscillates at ultrasonic (25–42 kHz) or sonic (6–8 kHz) frequencies (177). Ultrasonic oscillation is generated by the process of piezoelectricity or magnetostriction, and sonic oscillation is generated by the passage of compressed air over an eccentrically vibrating rod. Power-driven instrumentation provides a similar degree of calculus removal as hand instrumentation (150), but at a faster pace (195). Subgingival

calculus was present after ultrasonic scaling in 50% of maxillary molars and in 44% of mandibular molars in one study (219), and in 34% of single-rooted teeth and in 24% of molar teeth in another study (44). Subgingival ultrasonic debridement can be improved by substituting water with an antiseptic cooling fluid (270), or by modifying the working tip of the scaler (177), such as using slim tips to reach deeper into periodontal pockets (92, 195) or furcation areas (42, 90). Even so, it is unclear if scaling with slimmer tips actually improves clinical outcome (281).

Effective periodontal debridement presupposes a reliable identification of calculus. Direct visualization and tactile perception have traditionally been used for calculus detection, but these methods often fail to identify all subgingival accretions (202, 225). New technologies for calculus removal include detection-only systems (a miniaturized endoscope-device based on light reflection; laser-activated fluorescence of the tooth surface) and combined systems for calculus detection and elimination [an ultrasonic-based combined calculus detection and treatment device; an indium-gallium-arsenide-phosphate-based diode laser combined with an erbium-doped yttrium aluminum garnet (Erbium:YAG) laser] (202). Calculus removal by these methods shows promise in laboratory and initial clinical studies (202), but their ability to eliminate calculus in deep periodontal pockets is still unclear.

Adverse outcomes of aggressive scaling and root planing, especially if performed by inexperienced operators, include patient discomfort or outright pain, unwarranted removal of cementum and dentin, and increase in tooth sensitivity (150). Ultrasonic scalers used at medium power seem to produce less root-surface damage than hand instrumentation or sonic scalers (94). Vigorous debridement should be avoided in periodontal sites that probe < 3 mm, as this can traumatize the periodontal attachment and give rise to gingival recession, tooth sensitivity and subsequently root-surface caries (181, 233).

Nonconventional devices

Lasers, photodynamic therapy, air-polishing instruments and hyperbaric oxygen therapy may aid in the antimicrobial treatment of periodontal lesions. Although capable of killing bacteria, the adjunctive or alternative use of these devices to scaling has not gained widespread acceptance because of a lack of consistent data regarding clinical effectiveness, the experimental nature of some of the techniques and high acquisition costs.

Lasers comprise perhaps the most promising new type of device for treatment of periodontal and periimplant infections. Periodontal lasers include YAG lasers, diode lasers and CO_2 lasers (285). Ongoing research aims to identify the type of laser, the wavelength and the dosage that safely and effectively kills microbes and enhances periodontal healing (18, 145, 285). Laser treatment offers good hemostasis, but there is insufficient evidence to indicate that laser treatment provides antimicrobial and healing outcomes that are superior to those of more traditional periodontal therapies (145, 285, 294). Lasers have relatively high patient acceptance, but carry high purchasing costs.

Photodynamic therapy is a minimally invasive procedure that attempts to kill microbes via the process of oxidation (325, 340). The photodynamic action relies on the combination of action of three components: a nontoxic photosensitizer molecule such as porphyrin derivatives, 5-aminolevulanic acid, or phenothiazinium dyes (methylene blue, toluidine blue O); the delivery of activating long-wavelength visible light (red light) or near-infrared light via endoscopes or fiber-optic catheters; and molecular oxygen that is converted to reactive oxygen species, primarily superoxide or singlet oxygen. Photodynamic therapy has been used to treat a variety of cancers and infections in medicine, but may not kill more than one-third of the bacteria in oral biofilms (107) and may not substantially suppress major periodontal pathogens in subgingival sites (215).

Air-polishing devices employ slurries of air, water and sodium bicarbonate or glycine powder to disrupt the subgingival microbiota (232). Air-polishing devices are available as stand-alone units or as handheld devices to be connected to the high-speed tubing of the dental unit. Sodium bicarbonate-based air-polishing, applied for 10 s at a 90° angle towards the supragingival surface of teeth with a pocket depth of 5–7 mm, reduced the total subgingival pathogen counts from 26% to 5% and motile morphotypes from 13% to 2% (252). Interest in air-polishing was renewed recently with the introduction of a low-abrasive glycine powder for subgingival biofilm removal (232). The glycine-based slurry delivered with a low-air-pressure device may help to minimize adverse gingival events from air-polishing (234), and facial emphysema has only been documented in 12 patients out of more than one million air-polishing applications (235). To minimize the introduction of live bacteria into gingival tissue, subgingival irrigation with povidone-iodine may precede the air-polishing procedure. However, glycine-based

air-polishing may not significantly reduce the amount of major periodontal pathogens (206). Periodontal patients on maintenance care may benefit from air-polishing, but the clinical outcome of air-polishing vs. other types of antimicrobial treatment has yet to be determined.

Hyperbaric oxygen therapy refers to the medical use of oxygen at a level higher than atmospheric pressure with formation of free oxygen radicals. Hyperbaric oxygen acting as a bactericidal / bacteriostatic agent is applied in hard-fixed or soft-portable chambers. Hyperbaric therapy has been used in the treatment of necrotizing fasciitis, gas gangrene, chronic refractory osteomyelitis, mucormycosis, intracranial abscesses and infected foot ulcers in patients with diabetes (158), but has only demonstrated short-term effectiveness in the treatment of periodontitis (214).

Probiotics refers to the implantation of live microorganisms to replace or inhibit the growth of pathogenic microbes (330, 342). Lactobacilli and bifidobacteria have historically been the most commonly used probiotic bacteria, and oral administration of probiotic lactobacilli has reduced the total count of five periodontopathic species (199). Noncariogenic streptococci may also serve as probiotic bacteria in the oral cavity (136). It is not known if probiotic microorganisms can be sustained at the expense of periodontal pathogens for an extended period of time. The use of probiotics for the prevention or treatment of periodontal disease needs to be evaluated in properly designed studies (85) and is still in the exploratory phase of research (84).

Pharmacotherapeutics

Scalers of even the slim type cannot access the most apical part of periodontal lesions, which harbors high loads of pathogens (323), and thus may not eliminate periodontopathic bacteria in deep probing sites (73, 91) and in furcation defects (191). In contrast, microbicidal antimicrobials applied through the orifice of the periodontal pocket, or antibiotics delivered systemically, can penetrate throughout the subgingival area and represent an important adjunct to mechanical periodontal therapy (253, 360). Periodontics employs microbe-targeting strategies based on both microbe-nonspecific and microbe-specific drugs.

Antiseptics

Cost-concerns and the worldwide increase of antibiotic-resistant bacteria have created interest in using inexpensive, safe and highly bactericidal / virucidal antiseptics in periodontal therapy. Antiseptics attack multiple components of infectious agents, practically eliminating the risk of resistance development, and do not interact with prescription medications. Antiseptics are especially important in the treatment of biofilm infections, which may be unresponsive to even high concentrations of antibiotics (262). Also, as relatively small amounts of antimicrobial agents are applied subgingivally, and the content of inflamed periodontal pockets is emptied into the oral cavity every 90 s (113), the risk of antiseptics entering the gingival tissue and causing systemic damage is virtually nonexistent. The high degree of safety allows a frequent and broad use of antiseptics in periodontal treatment. Povidone-iodine (e.g. Betadine®, Iodopax®, generics), dilute sodium hypochlorite (chlorine bleach) and chlorhexidine gluconate exert wide spectra of microbicidal and virucidal activity, even after only a few minutes of application (297), and when used together with subgingival scaling are more effective than scaling alone in reducing periodontal pathogens (270) and in improving clinical attachment (253, 270, 271) and alveolar bone mass (271). The limitations of topical antimicrobials are the inability to eradicate microbes residing within the gingival tissue and the risk of cytotoxicity and hypersensitivity reactions.

Halogen-based antiseptics. Halogen-releasing antiseptics are important anti-infective agents in medicine and dentistry. Iodine- and chlorine-based compounds constitute some of the most powerful microbicidal agents for both antiseptic and disinfective purposes (297). Fluorine compounds exert comparatively little antiseptic effect and are mostly used in dentistry to protect against acid attacks by cariogenic bacteria. Bromine compounds are too toxic to be used in anti-infective therapy.

Iodine. Iodine is a bactericidal, fungicidal, trichomonacidal and virucidal agent. The antimicrobial activity occurs through the oxidation of amino (NH^-), thiol (SH^-) and phenolic hydroxyl (OH^-) groups in amino acids and nucleotides. Iodine is used in hospitals for the disinfection of skin and mucous membrane before surgery, for cleansing open wounds, for operative wound infection antisepsis, for adjunctive burn treatment and for the treatment of vaginitis. Iodine kills virtually all bacteria in planktonic growth, but may not reach and kill all sessile bacteria in biofilm formations (17). Aqueous (Lugol's iodine) and tincture (iodine in alcohol) solutions of iodine have been employed as dental antiseptics for more than

150 years, but the early iodine formulations caused surface staining and irritation of mucosa and skin. Some plastics absorb elemental iodine and assume a brownish stain.

Iodophors ('iodine carriers' or 'iodine-releasing agents') developed in the 1950s largely overcame these negative aspects of iodine treatment (287). Iodophors are 7.5–10% solutions of iodine complexed with an organic carrier, such as polyvinylpyrrolidone (povidone), to provide a controlled release of iodine. The most common commercial form of povidone-iodine is a 10% solution in water yielding 1% (10,000 ppm) available iodine. Povidone-iodine is generally nontoxic and nonirritating to mucous membranes, can easily be washed off with soap and water with no residual staining and is available globally at low cost, making it an excellent choice for oral antiseptic use. Povidone-iodone exerts high antimicrobial activity under acidic conditions, but is inactivated by excessive amounts of blood and sputum, underscoring the necessity of removing these fluids before treatment. For optimal effectiveness, povidone-iodine needs to be applied for at least 5 min.

Povidone-iodine can give rise to allergic reactions, including itching, burning, reddening and blistering in the area of treatment, and patients' history of allergy to iodine or shellfish needs to be evaluated. Severe allergenic reactions may require medical attention. As prolonged iodide intake may inhibit synthesis of the thyroid hormone and cause goiter, myxedema or hyperthyroidism, povidone-iodine should not be used routinely in patient self-care, or in patients with thyroid dysfunction. In the USA, hyperthyroidism occurs in 1.3% (clinical = 0.5% and subclinical = 0.7%) of the population and hypothyroidism occurs in 4.6% (clinical = 0.3% and subclinical = 4.3%) of the population, with a considerable ethnic variation (139). Also, iodine treatment is not recommended during pregnancy or breast-feeding because of the potential for iodine to cross the placenta or to enter breast milk, causing iodide overload and transient hypothyroidism in the fetus or the newborn infant (319).

Povidone-iodine is a valuable antiseptic in the treatment of periodontal disease and a variety of other oral infections (297). Povidone-iodine kills all major periodontopathic bacteria *in vitro* within 15–30 s (210, 291), and exhibits a wide virucidal spectrum, covering both nonenveloped and enveloped viruses (163), including the periodontopathic cytomegalovirus (216). Studies have shown a measurable improvement in the periodontal status after treatment with povidone-iodine (240, 258, 278). Huong et al. (137) studied the effect of subgingival irrigation with povidone-iodine in deep periodontal pockets with radiographic evidence of subgingival calculus. At 5 weeks post-treatment, a 95–100% reduction in total subgingival pathogen counts was observed in 44% of pockets after irrigation with povidone-iodine plus scaling and root planing, but in only 6–13% of pockets after povidone-iodine irrigation alone, scaling and root planing alone, or water irrigation alone ($P = 0.02$) (137). The average decrease in pocket depth was 1.8 mm at week 5 after povidone-iodine irrigation plus scaling and root planing (137). Von Ohler et al. (356) found that a single subgingival irrigation with povidone-iodine led to a 12–90% decrease in total subgingival microbial counts at 1 month post-treatment. Rosling et al. (268) reported that patients who received a whole-mouth application of povidone-iodine at the time of initial therapy exhibited less periodontitis for up to 13 years post-treatment. Remarkably, povidone-iodine lavage, together with thorough debridement of necrotic tissue, arrested the progression of noma in eight HIV-infected patients (56).

The American Heart Association and the American Dental Association (71) and others (55) have recommended rinsing periodontal sites with povidone-iodine before dental-invasive procedures to reduce the risk of bacteremia. Povidone-iodine may be applied subgingivally using a thin syringe capable of reaching close to the base of periodontal pockets. Povidone-iodine rinsing or gauze soaked in povidone-iodine can also be used in acute open wounds or body cavities, such as with infectious complications following tooth extraction (254). Also, of potentially great clinical significance, povidone-iodine shows promise in the prevention of dental caries. Caries-prone children who received a povidone-iodine application to their entire dentition every 2–3 months experienced a marked reduction in new caries lesions compared with controls (80, 193, 292, 347).

Chlorine. Sodium hypochlorite (NaOCl) is a highly active cytotoxic oxidant that is recognized to be one of the most potent antiseptic and disinfectant agents against bacteria, fungi and viruses. Sodium hypochlorite is hydrolyzed in water to form hypochlorous acid (HOCl) and the less active hypochlorite ion (OCl^-). Hypochlorous acid is split into hydrochloric acid (HCl) and the oxygen atom (O), which is a strong oxidator. The equilibrium between hypochlorous acid and the hypochlorite ion permits the neutral-charged and small-sized hypochlorous acid molecule to diffuse through the microbial cell wall and change

the oxidation–reduction potential of the cell. Sodium hypochlorite reacts with proteins, nucleic acids and lipids, and inactivates enzymes essential in the energy-yielding metabolism of microorganisms. As sodium hypochlorite occurs naturally in human neutrophils, monocytes and macrophages (124), it does not evoke allergic reactions, is not a mutagen, carcinogen or teratogen, and has a century-long safety record (45). Sodium hypochlorite, at concentrations of 5–6%, can cause irritation to the skin, mucous membranes and the eyes, although the irritant effect is reversible.

Sodium hypochlorite is used in hospitals, animal facilities and in the human drinking water supply, and serves as a bleaching agent and a food additive (275). Undiluted (5.25–6.0%) sodium hypochlorite can eradicate and prevent the transmission of HIV from needles of intravenous drug users (264). Sodium hypochlorite is available globally, at exceptionally low cost, as a household bleach at concentrations of 5–6% and as an industrial bleach at concentrations of 10–50%. To minimize decomposition, commercial solutions of sodium hypochlorite contain sodium hydroxide to maintain a pH of 11–13. Sodium hypochlorite is inactivated by organic material, deteriorates with exposure to light and heat, and is corrosive to certain metals, such as chrome-cobalt alloy and aluminum. Household bleach stored in the original container has a shelf-life of at least 6 months.

Sodium hypochlorite has been used as an antiseptic agent in dentistry for more than a century, and remains a widely used root canal irrigant at concentrations of 1.0–5.25% (385). Sodium hypochlorite rinsing exerts broad antimicrobial activity against experimental oral biofilms (46, 53, 115, 326) and has demonstrated an 80-fold decrease in biofilm endotoxin compared with a water control (282). De Nardo et al. (76) found in prison inmates, who for 21 days abstained from oral hygiene but performed supervised twice-daily 0.05% sodium hypochlorite oral rinse, 48% reduction in Plaque Index score, 52% reduction in Gingival Index score and 39% reduction in bleeding on probing sites compared with water rinse. Lobene et al. (187) studied, in college students abstaining from oral hygiene, the clinical effect of investigator-administered rinsing of tooth surfaces with 0.5% sodium hypochlorite (Carrel-Dakin solution) in a water-pressure cleansing device. The sodium hypochlorite rinse, perhaps because of substantivity to tooth surfaces, produced a 47% greater reduction in dental plaque amount compared with water-rinsing, and low pretreatment gingivitis scores were maintained around teeth receiving the sodium hypochlorite rinse, whereas the gingivitis score increased by 50% in water-treated sites (187). Lobene et al. (187) also found that the sodium hypochlorite rinse interfered, at least for 24 h, with the ability of dental plaque to produce an acid environment after a sucrose challenge. As described by Zou et al. (387), sodium hypochlorite can also penetrate into and potentially kill cariogenic bacteria within dentinal tubules. Thus, similarly to the findings for povidone-iodine (80, 193, 292), frequent oral rinsing with sodium hypochlorite may exert an important anti-caries effect. Furthermore, dentin hypersensitivity can be reduced by the application of 0.5% sodium hypochlorite with a cotton swab onto the affected tooth surface (own unpublished findings).

The American Dental Association Council on Dental Therapeutics has designated dilute sodium hypochlorite as a 'mild antiseptic mouthrinse' and suggested its use for direct application to mucous membranes (16). Dilute sodium hypochlorite (household bleach) has a basic pH and does not pose a risk of tooth erosion and does not corrode titanium implant surfaces (own unpublished data). A histological study found that concentrated sodium hypochlorite solution applied subgingivally exhibited no detrimental effect on periodontal healing (159). Dilute sodium hypochlorite has no contraindications.

The lowest concentration of sodium hypochlorite solution that reliably inactivates bacteria *in vitro* is 0.01% (274). A suitable concentration of sodium hypochlorite for periodontal pocket irrigation is ≤ 0.5%, dependent on the taste tolerance of the patient. This is equivalent to 10 ml (two teaspoonfuls = two-thirds of a tablespoon) of 6.0% household bleach in 125 ml (one half-glass) of water. Special measuring spoons are available that hold exactly 5 ml. Patients are advised to rinse orally for 30 s, two or three times a week, with 8 ml (two reduced teaspoonfuls) of 6% chlorine (household) bleach diluted in 250 ml of water (full glass), to yield a sodium hypochlorite concentration of 0.2%. More frequent rinsing may produce a brown-black extrinsic discoloration of the teeth (76), probably stemming from food or beverage chromogenic products (366) or from overgrowth of nonperiodontopathic *Actinomyces* species (295).

Other types of chlorine-based antiseptics have not gained broad acceptance in dentistry. Chlorine dioxide produced from acidic sodium chlorate exerts significant antimicrobial activity and can be stabilized as an oral rinse preparation (373). Acidified sodium chlorite used as a mouthrinse has demon-

strated a plaque-inhibitory action equivalent to that of chlorhexidine (380). Chloramine-T has been used as a periodontal pocket irrigant (135), but chloramine-T can induce severe respiratory hypersensitivity in dental personnel (236).

Fluorine. Fluorine compounds exhibit little ability to prevent or reduce dental plaque formation or periodontal disease (74, 223). However, as periodontal therapy promotes a shift towards gram-positive dental plaque microorganisms, including cariogenic bacteria (309), patients with newly exposed low-fluoride root surfaces should receive intensive fluoride treatment. Recommended treatments include 0.05% sodium fluoride rinses, 1.1% sodium fluoride gel or 0.4% stannous fluoride gel applied with a toothbrush or via a delivery tray.

Chlorhexidine. Chlorhexidine, a bisbiguanide antiseptic, is used extensively in dental and medical treatment. Chlorhexidine was developed in the 1940s and marketed as a topical antiseptic for skin wounds in 1954. Chlorhexidine was later employed in obstetrics, gynecology and urology. In dentistry, chlorhexidine was initially used in endodontics and for presurgical disinfection of the mouth. Chlorhexidine exerts broad activity against bacteria, yeasts, fungi and enveloped viruses, although some periodontal bacteria are only moderately susceptible (312). The positively charged chlorhexidine molecule reacts with the negatively charged cell surface of microorganisms and damages the microbial cell envelope. Allergic contact reactions from chlorhexidine are rare but, when occurring, may cause severe tissue reactions (114). Chlorhexidine is inactivated by organic serum compounds in the gingival crevice fluid, and subgingival placement produces little change in microbial and clinical variables (39, 72, 367). Chlorhexidine can potentially impair fibroblasts and normal periodontal healing (197).

Chlorhexidine has remained an important oral antiseptic for more than 40 years (152). In 1970, Löe & Schiott (188) demonstrated the plaque-inhibitory effect of chlorhexidine. Numerous studies and meta-reviews have later confirmed the anti-plaque and anti-gingivitis effects of chlorhexidine (3). The ability of chlorhexidine to adhere to the dental pellicle and oral mucosa extends its anti-plaque effect. Chlorhexidine gluconate is used in dentistry as a 0.12–0.2% mouthwash applied in a volume of 15 ml for 30 s twice a day. Rather than purchasing expensive chlorhexidine oral rinse products, patients may acquire low-cost generic chlorhexidine at concentrations of ≥2% and dilute with water to the concentration desired for oral use. Chlorhexidine is also available as a spray or as a dental gel for application to teeth or oral ulcers, and as a varnish to be used in dental caries prophylaxis.

A major disadvantage of chlorhexidine is its propensity to dark-stain tooth surfaces. Dark staining gaps along the margin of tooth-colored restorations may necessitate the replacement of affected restorations. Also, the cationic chlorhexidine is incompatible with anionic surfactant compounds in toothpastes, which neutralize its antimicrobial action, and therefore chlorhexidine should not be used in conjunction with toothbrushing (152). Chlorhexidine usage may temporarily alter the taste sensation.

Chlorhexidine is an efficient antiseptic in combating halitosis. Severe halitosis can be socially unacceptable and numerous remedies for oral malodor have been proposed throughout history (286). Persistent halitosis is caused by the volatile sulfur compounds produced by anaerobic bacteria that mainly reside on the dorsum of the tongue (121, 190, 259). Halitosis can be markedly reduced by applying 4% chlorhexidine to the most posterior part of the tongue dorsum using a toothbrush or a cotton swab tip (own unpublished data). The ability of chlorhexidine to bind to and be slowly released from the mucosal surface of the tongue makes it the preferred antiseptic agent against halitosis bacteria (132).

Miscellaneous antiseptics. Hydrogen peroxide in concentrations up to 1.5% induces no adverse effects, even with daily use over an extended period of time (140), but exhibits only a modest effect on subgingival bacteria and clinical periodontal disease (182, 367). Prolonged subgingival application of 3% hydrogen peroxide may suppress periodontopathic bacteria (370). Hexetidine, a methylhexahydropyrimidine, is used in mouthwashes and may show antiplaque activity, but can give rise to dark extrinsic tooth staining and sensitivity of the oral mucosa (5). Phenolic agents, in concentrations of 1–5%, quaternary ammonium compounds, in concentrations of 0.1–2%, and ethyl and isopropyl alcohol in concentrations of 50–70%, exert moderate bactericidal activity *in vivo*. Phenol (350) and alcohol (200) in mouthwashes may constitute health risks, especially in smokers (151), although adverse effects have been difficult to establish in epidemiological studies (62). Botanical extracts and naturally occurring cationic peptides that protect various animals from infection are used in periodontal healthcare (335), but limited scientific data exist on the clinical efficacy and safety of natural products for oral use.

A combination of microbicidal agents with different mechanisms of action may be more effective than single antiseptics. A hydrogen peroxide-sodium hypochlorite combined solution potentiated the killing and removal of *Pseudomonas aeruginosa* cells and experimental biofilm (82). A mixture of sodium chloride, sodium bicarbonate (baking soda) and hydrogen peroxide ($NaCl\text{-}NaHCO_3\text{-}H_2O_2$) applied subgingivally during scaling followed by subgingival irrigation with povidone-iodine significantly enhanced the microbiological and clinical effects of mechanical debridement (271), but did not result in clinical improvement in unscaled sites (269). Chlorhexidine and sodium hypochlorite may not be combined as such a combination can lead to the formation of the carcinogenic products parachloroaniline (32) and 1-chloro-4-nitrobenzene (36).

Topical antibiotics

Antibiotic products with high drug content for direct placement in periodontal pockets are commercially available (93, 153). The microbiological and clinical effects of subgingivally applied tetracyclines and metronidazole are modest, transient or nonexistent (39, 238). The chief drawbacks of topical antibiotic therapy are an insufficient range of antimicrobial activity for even broad-spectrum antibiotics and the risk of resistance development to the antibiotic employed and to multiple drugs. Also, commercial antibiotic products directed towards bacteria do not target viruses and yeasts, can be cumbersome to place in deep periodontal lesions, carry a high acquisition cost, and are not sold in several countries. Periodontal treatment by topical antibiotics would appear to be a less desirable option than povidone-iodine or sodium hypochlorite from the standpoint of efficacy, safety, costs and availability.

Systemic antibiotics

Systemic antimicrobial drug therapy of periodontitis aims at reducing or eradicating specific periodontopathic bacteria that are not readily reached by topical therapy, such as pathogens in gingival tissue, furcation defects, the base of periodontal pockets, and on the tongue, tonsils and buccal mucosa (99, 351). The two major periodontopathic bacteria *A. actinomycetemcomitans* and *P. gingivalis* may invade gingival epithelial cells and connective tissue (102, 173, 343, 346), thereby escaping the antimicrobial effect of subgingival mechanical debridement (256), but both species can be suppressed by systemic antibiotics (317). Untreated, *A. actinomycetemcomitans* may persist in periodontal sites for decades (273).

The selection of effective and safe antibiotics can be challenging because periodontitis lesions usually harbor a constellation of periodontopathic bacteria with diverse susceptibility profiles and because of a growing resistance to common antibiotics (359). Emergence of antibiotic resistance is a result of the overuse or misuse of antibiotics in human and animal medical practice and in food production, and to a largely unregulated access to antibiotics in some countries. Antibiotic therapy may need to be adjusted to local susceptibility data (19). An emerging concern is the increasing number of immunocompromised hosts who often exhibit a reduced response to antibiotic therapy. Dentists can play a role in halting antimicrobial resistance by adhering to prudent principles for the prescription of antibiotics (310).

Systemic antibiotic therapy can confer considerable clinical benefits to the 10–15% of periodontitis patients who experience aggressive / advanced disease (207, 318, 341). Systemic antibiotics are rarely needed for mild and moderate types of chronic periodontitis. As periodontal pathogens reside in biofilm formations (171, 198), which protect the resident pathogens from the action of antibiotics (322, 360), subgingival biofilms should be broken up by mechanical or antiseptic means before antibiotic therapy (189). The subgingival biofilm of periodontitis lesions is loosely arranged with a high content of motile microorganisms and disintegrates more easily than the tenacious supragingival plaque (183, 184, 369). The negative aspects of systemic antibiotic therapy include reliance on patient compliance, a limited spectrum of antimicrobial activity, the possibility of inducing resistance, interactions with concurrent medications and the risk of triggering hypersensitivity (134, 288). Lapses in adherence to an antibiotic regimen can prevent therapeutic success and hasten the development of drug-resistant strains.

Periodontal antibiotic therapy should be limited to the shortest effective time possible to avoid hypersensitivity development, toxicity and excess expense. Even short-term antibiotic therapy will increase, at least transiently, the percentage of resistant subgingival bacteria (103, 242, 309). The tradition in dentistry is to treat empirically, in other words, to institute antibiotic therapy based on the 'best estimate' of the most probable pathogen(s) and the usual antibiotic susceptibility pattern of the suspected pathogen(s). However, the diversity of the periodontal microbiota complicates the selection of antibiotics, and periodontal antibiotic therapy should preferably be based on identification of the periodontal pathogens of individual patients and

antimicrobial susceptibility testing (155, 290, 300). Microbiological testing allows dentists to move from a 'trial and error' approach to the more predictable 'targeted therapy'. Unfortunately, antimicrobial susceptibility testing currently depends on expensive culture methodology, and proficient oral microbiology reference laboratories are only available in a few countries. Diagnostic techniques used in oral microbiology include direct microscopic examination, microbial culture, rapid biochemical and antigen testing, serologic identification, and a variety of novel molecular methodologies (54, 383). Some of these diagnostic procedures lend themselves to point-of-care testing.

Table 1 shows the antibiotics frequently prescribed to treat periodontitis. The mode of action and the unwanted effects of antibiotics are detailed elsewhere and not discussed in this review (288, 289). Most antibiotics listed have a broad therapeutic window and can be acquired at low cost. The dosage recommendations are for systemically healthy adults with a normal weight and must be adjusted for body size to ensure optimal therapeutic effectiveness and safety. Interactions with other medications, toxicity and hypersensitivity may restrict antibiotic use in individual patients.

Metronidazole is a potent antibiotic against anaerobic bacteria and protozoa with little propensity to developing resistance. The advantages of metronidazole include a high percentage of sensitive anaerobes in periodontitis lesions, rapid bacterial killing, good penetration into gingival tissue, proven effectiveness in periodontal treatment, availability in oral dosage forms, low potential to induce serious adverse reactions, and low acquisition cost (109, 358). Also, by exerting activity against *Clostridium difficile*, treatment with metronidazole reduces the risk of pseudomembranous colitis, although metronidazole-resistant *C. difficile* strains are emerging (28). Clindamycin is active against anaerobic bacteria and beta-hemolytic streptococci and has demonstrated efficacy in the treatment of refractory periodontitis, but should be prescribed with caution because of the risk of pseudomembranous colitis from superinfection with clindamycin-resistant *C. difficile* (358). Penicillin / amoxicillin is inexpensive, has a long history of use in dentistry, and can be safely prescribed to pregnant women and to children, but amoxicillin, with or without clavulanic acid (a beta-lactamase inhibitor), shows little efficacy as a single drug treatment of periodontitis (300). Tetracyclines are inexpensive and exert the least toxicity of all antibiotics, but are poorly absorbed after oral administration in 50% of individuals (279). Tetracyclines are effective against *A. actinomycetemcomitans* in localized aggressive (juvenile) periodontitis (313), but may not provide sufficient suppression of pathogens in mixed periodontal infections of adults (353). Ciprofloxacin, a fluoroquinolone, is effective against enteric gram-negative facultative rods and pseudomonads (30, 307), which are frequent inhabitants of periodontitis lesions of older patients (308) and of periodontal sites of the general population in developing countries (311). Ciprofloxacin should not be prescribed to individuals younger than 18 years of age because of the potential for articular chondrotoxicity (329), and patients receiving ciprofloxacin should refrain from strenuous exercise owing to an increased risk of Achilles tendinitis or partial tendon

Table 1. Systemic antimicrobial agents in periodontal therapy

Antimicrobial agents	Prescription (orally)*	Indication
Metronidazole	500 mg / TID / 8 days	Anaerobes, protozoa
Clindamycin	300 mg / TID / 8 days	Anaerobes, beta-hemolytic streptococci
Doxycycline	100–200 mg / QD / 21 days	Mixed infection
Ciprofloxacin	500 mg / BID / 8 days	Facultative enteric rods
Azithromycin	250–500 mg / QD / 4–7 days	Mixed infection
Amoxicillin-metronidazole	250 mg amoxicilllin-250 mg metronidazole / TID / 8 days	Advanced periodontitis microorganisms
Ciprofloxacin-metronidazole	500 mg of each / BID / 8 days	Advanced periodontitis microorganisms
Fluconazole	100 mg / QD / 14 days	*Candida*
Valacyclovir hydrochloride (Valtrex®)	500 mg / BID / 10 days	Herpes simplex virus, Epstein–Barr virus, cytomegalovirus (?)

BID, twice daily; TID, three times daily; QD, once daily.
*For systemically healthy adults of normal body weight.

rupture (354). Interest in azithromycin, a macrolide antibiotic, in managing periodontitis has grown over the past decade (205, 300). Azithromycin exhibits good penetration into gingival tissue and periodontal pockets and is usually taken only once a day for 4–7 days. Fluconazole may be prescribed for oral candida infections (224, 280, 371). Valacyclovir may resolve periodontal infections by Epstein–Barr virus and perhaps also by other herpesviruses (334).

Antibiotic combination therapy with two or more antibiotics is employed in periodontics to take advantage of the different mechanisms of action of antimicrobials. Indications for combination antibiotic therapy include: (i) empirical treatment of severe infections, (ii) treatment of polymicrobial infections, (iii) prevention of the emergence of bacterial resistance, and (iv) increased effectiveness from antibiotic synergism (more than additive) (276). The disadvantages of combination therapy include: (i) increased risk of adverse drug reactions, (ii) superinfections with *Candida* or other microbes owing to major suppression of the indigenous microbiota, and (iii) a diminution of antibiotic effectiveness with improperly selected antibiotics (e.g. bactericidal and bacteriostatic antibiotics may be used sequentially, but not concomitantly) (276). Bactericidal antibiotics include penicillins, cephalosporins, metronidazole, ciprofloxacin and aminoglycosides, and bacteriostatic antibiotics include tetracyclines, erythromycin, clarithromycin, azithromycin, clindamycin and sulfonamides (134).

Amoxicillin-metronidazole (250 mg of amoxicillin and 250 mg of metronidazole, three times daily for 8 days) is the most common antibiotic combination in periodontics. Amoxicillin exerts antimicrobial synergy with metronidazole against periodontal pathogens (229), and amoxicillin-metronidazole is particularly effective against *A. actinomycetemcomitans* infections (318). The amoxicillin-metronidazole combination therapy used as the sole periodontal treatment has yielded a clinical outcome similar to that of scaling and root planing (194). Adverse reactions of amoxicillin-metronidazole combination therapy are infrequent and relatively minor, except for patients who are allergic to beta-lactam drugs (300). Amoxicillin-metronidazole antibiotics may interact with some medications, but generally without serious consequences (300).

The combination of ciprofloxacin and metronidazole (500 mg of each drug, twice daily for 8 days) is indicted for periodontitis involving a mixture of enteric gram-negative facultative rods and anaerobes. The ciprofloxacin-metronidazole combination therapy also constitutes a valuable alternative for penicillin-allergic periodontitis patients. The ciprofloxacin-metronidazole combination provides unique antimicrobial benefits in its own right. Nonperiodontopathic viridans streptococci exhibit resistance to both ciprofloxacin and metronidazole and dominate the periodontal microbiota post-treatment (307). By interacting antagonistically with major periodontal pathogens (136), the viridans streptococci can delay pocket colonization by pathogenic species and thereby extend the therapeutic benefit of the antibiotic treatment. As cariogenic streptococci of the mutans group may also overgrow, it is recommended that caries-prone individuals, especially those with exposed root surfaces, receive anti-caries fluoride treatment as part of the periodontal therapy.

Patient self-care

Patient self-care constitutes the most cost-effective approach to the management of periodontal disease. Periodontal self-care aims to preserve a healthy periodontium or at least to minimize disease activity through the mechanical or chemotherapeutic removal of dental biofilms. Oral hygiene instructions should emphasize subgingival and interdental cleaning and brushing with fluoride toothpaste. However, even if adherence to oral hygiene practice is recognized to be of critical importance in periodontal maintenance, the mode of self-care performed by most individuals fails to sustain a long-term improvement in the periodontal status (257). Educational intervention targeting dental plaque and gingival health frequently has only a short-term effect (364). The difficulty in altering oral hygiene habits may be due to a lack of motivation or problems with understanding and implementing the prescribed oral hygiene procedures (160, 257, 372). Also, low-income individuals may not employ proper oral hygiene measures because of the prohibitive expense of self-care products. Moran (208) pointed out that individuals in developing countries or in lower social groups of industrialized countries may not be able to afford the relatively high costs of commercial mouthrinses and other oral products.

Oral hygiene products and techniques have a 6000-year-long history and are still evolving (104, 368). Brushing with toothpaste is the preferred oral hygiene practice in industrialized countries (49). However, an almost sole reliance on toothbrushing for preventing periodontitis is problematic (142). A single, self-performed toothbrushing with a manual brush only reduced the average plaque scores by 43%

(352), and plaque was left behind on 85% of interdental surfaces (233). Also, no specific toothbrush design seems to be superior to any other in the maintenance of gingival health (61), and overzealous and improper use of the toothbrush can damage dental tissues and gingiva (1). Powered toothbrushes removed 7–17% more plaque on supragingival (352) and on interdental surfaces (61) than manual brushes, but are generally too expensive for low-income individuals. Even if performed correctly, a toothbrush reaches only 0.9–1.5 mm into the periodontal pocket (233). However, a sustained regimen of supragingival plaque removal affects the subgingival ecology and may reduce periodontopathogen counts in pockets up to 5 mm in depth (69, 129, 379).

Interdental brushes, toothpicks and dental floss may reach 2.5–3.5 mm into interdental subgingival sites (233), but toothpicks (138) and dental floss (37) fail to eliminate all interdental plaque and gingival inflammation, especially in teeth with exposed furcations, root surface concavities and grooves. Also, these oral hygiene products are only used by 5–10% of the population (233). An oral irrigator used together with toothbrushing may be able to reduce gingival bleeding scores more efficiently than dental floss plus toothbrushing (265) or toothbrushing only (144). Chewing sticks prepared from roots, twigs and stems of local plants are utilized in many countries (377), and may be equal to or more efficacious than a manual brush in reducing interdental plaque (15) and subgingival pathogens (14).

Popular toothpastes and mouthrinses contain triclosan (2′-hydroxy-2,4,4′-trichlorodiphenyl ether), essential oils dissolved in alcohol, quaternary ammonium compounds (cetylpyridinium chloride), sodium bicarbonate, zinc citrate or zinc chloride, amine fluoride/stannous fluoride, or stannous fluoride/sodium hexametaphosphate (to control calculus and extrinsic tooth staining) (57, 68, 378). The efficacy of oral hygiene products are reviewed elsewhere (1, 209), but in general, toothpastes may not significantly enhance the plaque-removing properties of toothbrushing alone (2) and exert, at best, only a limited effect on periodontal disease (74). Even if triclosan-containing toothpaste may aid in combating dental plaque and periodontal disease (59), which is disputed in some studies (176), the possible long-term systemic effect of chronic exposure to triclosan is unresolved (96). Triclosan serves as a microbicide in a variety of household and personal care products and is detected in plasma, urine and maternal milk in a large segment of different populations (12, 13). Brushing with 2 cm of triclosan-containing toothpaste for 3 min twice a day for 14 days increased the plasma triclosan concentration from 0.009–0.81 to 26–296 ng/g (13). There is also emerging evidence of co-resistance and cross-resistance of triclosan (381) and of quaternary ammonium compounds (127) with clinically important antibiotics and disinfectants. Bioaccumulation of triclosan in wastewater and soil affects microbial processes and may upset the balance of ecosystems (169).

Self-administered supragingival and subgingival application of antimicrobial agents offers a valuable supplement to mechanical plaque removal, yet remains underutilized in patient self-care (213). Syringes and irrigators are convenient devices for subgingival delivery of antimicrobials. The pocket penetration by powered oral irrigation devices was found to be 71% for shallow sites, 44% for moderately deep sites and 68% for deep sites, with a maximum pocket penetration of 4–5 mm (58). By using special irrigation tips placed 1 mm subgingivally, irrigants can access 90% of the depth of 6 mm pockets and 64% of the depth of pockets exceeding 7 mm (58). Irrigation with an antimicrobial solution, such as dilute sodium hypochlorite, provides greater microbiological and clinical effects than irrigation with plain water (60, 270).

Treatment protocols

The periodontal diagnosis, the health-seeking behavior and the socioeconomic status of the patient are key factors in therapeutic decision-making. Basic components of periodontal therapy include oral hygiene instruction, mechanical depuration and topical application of antiseptics. Patients with severe periodontitis may receive additional systemic antibiotic therapy and perhaps surgical intervention (156). Periodontal mechanical debridement combined with systemic antibiotics gives rise to greater gains of clinical attachment than mechanical debridement alone (119). A lack of oral health motivation by patients can complicate periodontal treatment decisions. In individuals who are unwilling or unable to make major changes in their oral hygiene habits, periodic scaling and subgingival irrigation with a potent antiseptic may be able to retard periodontal disease progression.

Basic periodontal therapy

Figure 1 depicts the steps of basic periodontal therapy. Simple gingivitis and moderate periodontitis are

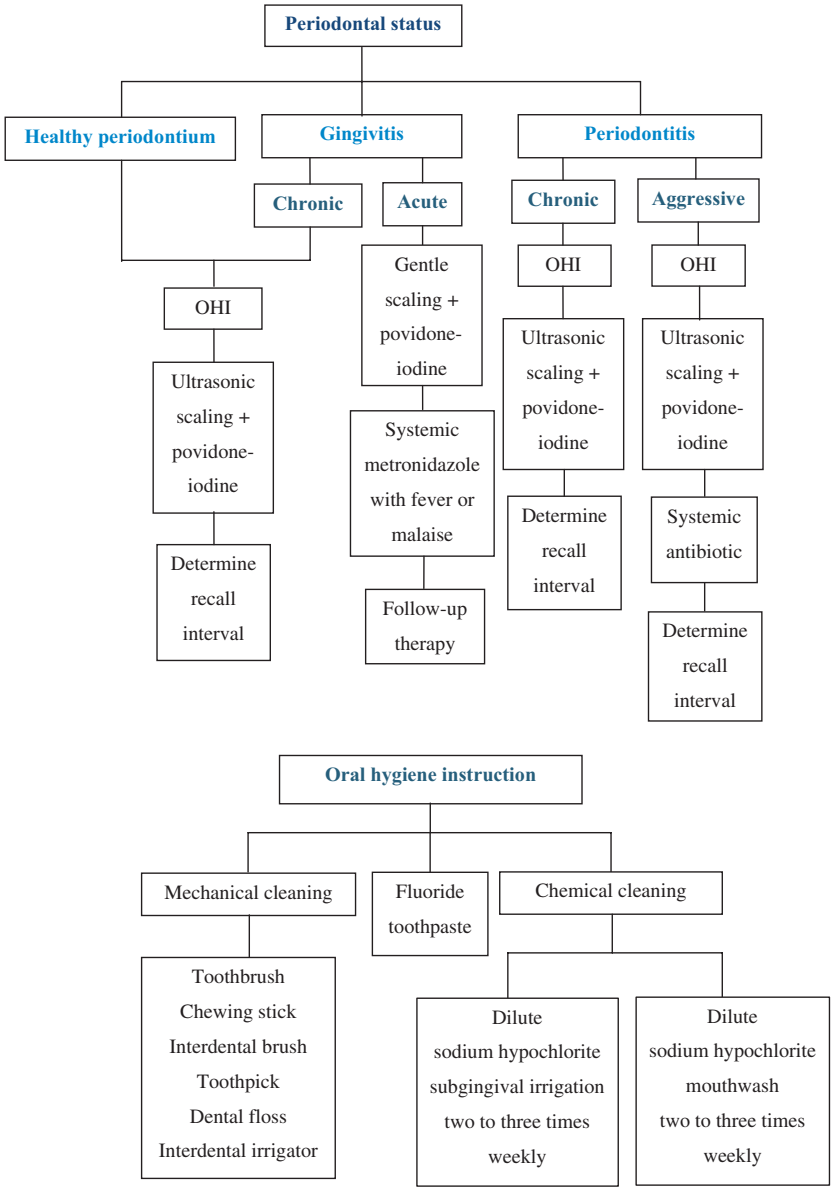

Fig. 1. Outline of antimicrobial treatment of periodontal diseases. OHI, oral hygiene instruction.

treated with mechanical depuration, antiseptics and attention to oral hygiene. Ultrasonic scaling is commonly used because it produces a clinical outcome equal to that of hand instrumentation but with a shorter treatment time (345, 361). In periodontal pockets of >4 mm, the mean probing depth was reduced by 1.7–1.9 mm after ultrasonic scaling and by 1.2–2.3 mm after hand instrumentation (116). Ultrasonic scaling may be followed by hand instrumentation to obtain a better tactile perception of calculus. Definitive scaling of deep periodontal pockets may be carried out a few weeks following the initial therapy to benefit from reductions in gingival inflammation and probing depth (137). Dental professionals may limit scaling to pockets with calculus and suspected calculus, and rely on antiseptics for eradication of pathogens in sites free of calculus. Scaling should be performed gently or avoided altogether in shallow periodontal sites to prevent permanent attachment loss (233).

Subgingival irrigation by 10% povidone-iodine for 5 min is recommended prior to mechanical debridement in order to reduce bacteremia and following mechanical debridement to eradicate any remaining pathogens (55, 241). The initial povidone-iodine treatment also reduces the dispersion of viable microorganisms in aerosols from ultrasonic scaling. Blood and pus inhibit the antimicrobial effect of povidone-iodine and ought to be eliminated from periodontal pockets before povidone-iodine application (384). Povidone-iodine is applied to both scaled and nonscaled sites using, for example, a 3-ml

endodontic syringe with a 23-gauge cannula that has a blunt end and side ports. The syringe is inserted into the base of the periodontal pocket to ensure maximum delivery of antiseptic (154). A single course of subgingival irrigation of the entire dentition may take 1.5 min and should be performed three times for a total application time of about 5 min. Ultrasonic scaling performed with 0.5% povidone-iodine instead of plain water has produced additional clinical improvement in some (270), but not in all (78, 178), studies. Povidone-iodine may also be applied supragingivally to the entire dentition to reduce oral *Streptococcus mutans* counts and caries risk. Subjects who are allergic to iodine or are pregnant may be treated with dilute sodium hypochlorite.

Patients with aggressive periodontitis should receive systemic antibiotic therapy to reduce or eradicate pathogens that invade gingival tissue or colonize difficult-to-reach subgingival and extradental sites (346). *A. actinomycetemcomitans*, for example, invades periodontal tissue and may not be eliminated from subgingival sites by mechanical debridement or by periodontal surgery alone (256), but can be eradicated by systemic antibiotics (318). Valuable antibiotic therapies are amoxicillin-metronidazole (250 mg of amoxicillin and 250 mg of metronidazole, three times daily for 8 days) for young and middle-aged patients, and ciprofloxacin-metronidazole (500 mg of each, twice daily for 8 days) for older patients and for patients in developing countries with subgingival enteric rods (308, 311). Prescribing antibiotics without the guidance of a microbiological analysis carries the risk of overgrowth of antibiotic-resistant pathogens, but repeat subgingival and oral rinsing with dilute sodium hypochlorite during the course of antibiotic therapy may control resistant pathogens.

The periodontal load of herpesviruses, which reside in inflammatory cells (65), can be markedly reduced by resolving gingival inflammation through scaling or chemotherapeutics (86, 117, 303). Also, povidone-iodine, sodium hypochlorite and chlorhexidine are potent antiviral agents. Systemic valacyclovir (500 mg, twice daily for 10 days) has suppressed high periodontal counts of Epstein–Barr virus and markedly improved the clinical status of periodontitis lesions that were refractory to conventional periodontal therapy (334). Future vaccines against periodontopathic herpesviruses represent a promising approach to the control of periodontal disease, in both developed and developing countries.

Patients are instructed to rinse subgingivally with 0.2% sodium hypochlorite using a syringe or an oral irrigator and to use the 0.2% sodium hypochlorite solution as a mouthrinse two or three times weekly. Oral irrigation also enhances the removal of interdental plaque (265). The sodium hypochlorite treatment loosens the attachment of microorganisms to dental surfaces and thus facilitates mechanical cleaning. Common household bleach containing 6.0% sodium hypochlorite, diluted 1:30 with tap water, as described above, is a convenient way of obtaining dilute sodium hypochlorite. Dilute sodium hypochlorite loses activity over time and may be discarded after 24 h.

Recall appointments are decided based on the periodontal diagnosis and the ability of the patient to maintain a disease-free dentition. However, despite the importance of professional anti-infective therapy, the long-term benefit and the cost-effectiveness of routine periodontal recall programs are not well established. The optimal interval between periodontal debridement sessions is ill-defined (34), and the usual 3–6 months between recalls may be extended for patients practicing good oral self-care or harboring low levels of periodontal pathogens (186).

Periodontal recall intervals may be determined based on the estimated risk for future periodontal breakdown. Lang et al. (175) found that periodontal sites showing bleeding on probing at one out of four consecutive recall visits had a 3% risk of breakdown, whereas sites exhibiting bleeding at four consecutive maintenance visits had a 30% risk of losing attachment. Also, periodontitis patients with fewer than 10% of sites with bleeding in the dentition generally have a low risk for progressive disease, whereas patients with more than 25% of sites with bleeding should be scheduled for recall more frequently (175). In a series of studies, Rams and co-workers found that low (0–2) sextant scores in the Community Periodontal Index of Treatment Need (CPITN) screening system provided a presumptive identification of nonprogressive periodontal disease, but high scores were not predictors of disease-active periodontitis (248); that the lack of periodontitis disease progression at Ramfjord's six index teeth (teeth nos: 3, 9, 12, 19, 25 and 28) was suggestive of a low risk of progressive disease in the entire dentition (251); and that periodontitis sites with a radiographically intact crestal lamina dura exhibited virtually no risk of disease progression for at least 2 years (positive predictive value = 100%) (246). The absence of radiographic crestal lamina dura in angular periodontal defects (247) and in peri-implantitis lesions (337) is frequently an indicator of progressive disease.

Specific periodontopathic bacteria may be better predictors of attachment loss than various clinical variables (306). *P. gingivalis* and *A. actinomycetemcomitans* occurred in periodontal lesions that exhibited ongoing loss of attachment after treatment, whereas these and other periodontal pathogens were either absent or present at low levels in periodontal sites that remained disease-inactive (43, 249, 270). A simple differential microscopic count of subgingival bacterial morphotypes (183) or a quantification of saliva-borne periodontal pathogens (284) can aid in the assessment of the probability of progressive disease. In the future, identification of infectious agents by fully automated diagnostic systems may help to determine the likelihood of periodontal disease progression and serve as a guide for periodontal treatment (237, 316).

Treatment of advanced / refractory periodontitis

Figure 2 outlines a treatment protocol for advanced periodontitis. The efficacy of treatment of disease-active periodontitis may not be well established, as most studies have investigated chronic periodontitis / adult periodontitis or 'burned out' aggressive periodontitis, which pathologically may merely constitute gingivitis in disease-stable deep probing sites. Nonprogressing periodontitis sites may respond well to treatment despite a significant prior loss of attachment. Another concern is the overdiagnosis ('diagnostic creep') of moderate / stable cases of periodontitis, which may lead practitioners to institute overly aggressive therapy. Lindhe et al. (180) found that only 12% of untreated periodontitis lesions experienced additional attachment loss over a 6-year period. The majority of breakdown occurred in 8% of the study subjects (180). Renvert et al. (255) studied intraosseous periodontal defects with probing depths of ≥6 mm, which were treated by either scaling and root planing alone or by flap surgery, and which received no further subgingival treatment for 5 years. Nonsurgically and surgically treated sites exhibited similar attachment gains, and relapses first occurred at the end of the 5-year study period (255). Owing to the uncertainty of periodontal diagnostics and the intrinsically low incidence of disease-active periodontitis, it may be prudent to adopt a wait-and-watch strategy after efficaceous nonsurgical therapy and only intervene surgically if there is a high risk or compelling evidence of periodontal disease progression.

The data implicating herpesviruses in periodontal breakdown seem sufficiently strong to prescribe systemic anti-herpesvirus medication in severe cases of periodontitis (305). The anti-herpesvirus drug

Day 0:
(Microbiological sampling)
Povidone-iodine subgingival irrigation (prior to scaling)
Ultrasonic scaling
Povidone-iodine subgingival irrigation (postscaling)
Valacyclovir (500 mg, twice daily for 10 days)

Self-care: Subgingival irrigation and oral rinsing with dilute (0.2%) sodium hypochlorite, two to three times weekly (lifelong)

Day 10:
Povidone-iodine subgingival irrigation (prior to scaling)
Ultrasonic scaling
Povidone-iodine subgingival irrigation (postscaling)
Amoxicillin-metronidazole (250 mg of amoxicillin and 250 mg of metronidazole, three times daily for 8 days) for young and middle-aged patients
Ciprofloxacin-metronidazole (500 mg of each, twice daily for 8 days) for older patients and for patients in developing countries

Fig. 2. Treatment of advanced / refractory periodontitis.

valacyclovir hydrochloride (Valtrex®; GlaxoSmith-Kline) has eliminated high loads of Epstein–Barr virus from refractory periodontitis lesions and arrested disease progression (334). As the periodontal herpesvirus infection promotes upgrowth of periodontopathic bacteria (303), the antiviral therapy is instituted prior to antibiotic therapy against bacterial pathogens (Fig. 2).

Treatment of periodontitis-affected molars

Molar teeth tend to experience more attachment loss than single-rooted teeth (185), and furcation-involved molars have traditionally been assigned a guarded or poor prognosis. Teeth with furcation involvement are frequently treated with pocket elimination or root-resective surgery, and tooth extraction with implant placement is gaining in importance (50, 83). However, the prognosis of teeth affected by periodontitis can be difficult to define and is often assessed too pessimistically for furcation-involved molars. Forty-nine adult periodontitis patients on a 3-month maintenance care program in a 3-year study showed a similar rate of recurrent attachment loss in furcations as in flat molar surfaces, and in molars with a baseline Grade 2–3 vs. a Grade 0–1 furcation involvement (250). The equal rate of periodontal disease progression in furcation sites as in flat surface sites questions the notion of an inherently low resistance in the furcation area. Also, as the total root surface area of molars is two to three times larger than that of incisors and premolars, and as molars with divergent roots offer better periodontal support than single-rooted teeth with the same lengthwise loss of attachment, molars will experience increased mobility much later in the disease process than single-rooted teeth. A less favorable treatment outcome has been reported for furcation-involved molars than for nonfurcated teeth (174, 192), but with proper professional treatment and patient self-care, molars with furcation involvement have been maintained for 10–20 years or even longer (51, 196, 218). Teeth with 80–90% loss of periodontal attachment have served successfully as abutments in cross-arch restorations (89).

Molar replacement is performed in partially edentulous patients who have special esthetic needs or are at risk for supraeruption of unopposed maxillary molars, but the routine replacement of missing molars with partial dentures or implants may not be desirable or necessary (98). Of concern are the reports that 12% of implants (in 28% of subjects with implants) that have been in function for at least 5 years may experience progressive bone loss (108), and as many as 53% of subjects who are smokers and have a history of periodontitis may develop peri-implantitis (260).

Käyser (164) described 'the shortened dental arch therapy', which has the preservation of functional dental arches as the limited treatment goal. The functional demands of a dentition vary from individual to individual and change with time, but are usually met in middle-aged individuals with 10 or even fewer well-positioned pairs of occluding teeth. In other words, the masticatory and esthetic requirements of a dentition can be satisfied by the anterior and the premolar regions ('the ultimate occlusal preservation target'). The shortened dental arch concept is accepted by many dentists and patients, and is an important therapeutic option for low-income individuals (11, 20, 162, 283, 374).

Concluding remarks

Individual and healthcare-delivery factors play important roles for the long-term success of periodontal treatment, and the patient and the dental professional should jointly make the decision about the specific type of therapy. The needs of people seeking periodontal treatment may be divided into two main categories: considerate and useful advice about affordable treatment choices; and accessibility to treatment where scientific knowledge forms the basis for the therapeutic choice. Decision about the optimal periodontal therapy then involves balancing the benefits, the risks and the financial costs of treatment in a real-world setting.

The underlying concept of the periodontal therapy proposed here is that periodontitis is an infectious disease caused by specific pathogenic bacteria and herpesviruses, and that a treatment which markedly reduces or eradicates the pathogens is able to arrest progression of the disease. The additional theme of this article is treatment simplification to avoid therapies that may be curative but are too complex and expensive to serve the needs of low-income individuals. Several new antimicrobial devices in periodontal healthcare carry considerable acquisition costs and may not be a realistic option in low-income communities. A truly low-cost treatment is a prerequisite for improving the periodontal disease status among poor people of the world.

This article presents an efficacious, highly safe, minimally invasive, practical and inexpensive therapy for the prevention and treatment of periodontitis. The

major elements of the proposed therapy are mechanical pocket debridement, periodontal pocket irrigation with potent antiseptics, treatment of advanced disease with systemic antibiotics, and attention to proper self-care. Well-tolerated antimicrobial agents, each exhibiting significant antimicrobial activity against periodontal pathogens, are administered in ways to affect pathogens residing in different oral ecological niches. The agents produce greater antimicrobial effect when used concomitantly rather than sequentially. As monotherapies, the individual components of the proposed therapy may not be able to control destructive periodontal disease. The chemotherapeutics recommended here are readily available throughout the world, have been used in periodontal therapy for decades, offer significant benefits for individuals with very limited financial resources, and are well accepted by most dental professionals and patients. Employment of common antiseptics with excellent antibacterial and antiviral properties may obviate the need for expensive commercial anti-plaque products and for surgical intervention. It appears that povidone-iodine and dilute sodium hypochlorite have all the characteristics for becoming the first-choice antiseptics in the treatment and prevention of periodontal disease. However, even though the benefit of antimicrobial periodontal therapy is indisputable, studies are still needed to identify the most cost-effective method of managing periodontitis and the long-term therapeutic outcome. Implementation of efficacious and low-cost periodontal healthcare is urgently needed in many parts of the world.

References

1. Addy M. Oral hygiene products: potential for harm to oral and systemic health? *Periodontol 2000* 2008: **48**: 54–65.
2. Addy M, Hunter ML. Can toothbrushing damage your health? Effects on oral and dental tissues. *Int Dent J* 2003: **53**: 177–186.
3. Addy M, Moran JM. Clinical indications for the use of chemical adjuncts to plaque control: chlorhexidine formulations. *Periodontol 2000* 1997: **15**: 52–54.
4. Adjei AA, Armah HB, Gbagbo F, Boamah I, Adu-Gyamfi C, Asare I. Seroprevalence of HHV-8, CMV, and EBV among the general population in Ghana, West Africa. *BMC Infect Dis* 2008: **8**: 111.
5. Afennich F, Slot D, Hossainian N, van der Weijden G. The effect of hexetidine mouthwash on the prevention of plaque and gingival inflammation: a systematic review. *Int J Dent Hyg* 2011: **9**: 182–190.
6. Afolabi AO, Akinmoladun VI, Adebose IJ, Elekwachi G. Self-medication profile of dental patients in Ondo State, Nigeria. *Niger J Med* 2010: **19**: 96–103.
7. Albandar JM. Global risk factors and risk indicators for periodontal diseases. *Periodontol 2000* 2002: **29**: 177–206.
8. Albandar JM, Rams TE. Global epidemiology of periodontal diseases: an overview. *Periodontol 2000* 2002: **29**: 7–10.
9. Alcoforado GA, Rams TE, Feik D, Slots J. Microbial aspects of failing osseointegrated dental implants in humans. *J Parodontol* 1991: **10**: 11–18.
10. Ali RW, Bakken V, Nilsen R, Skaug N. Comparative detection frequency of 6 putative periodontal pathogens in Sudanese and Norwegian adult periodontitis patients. *J Periodontol* 1994: **65**: 1046–1052.
11. Allen PF, Witter DJ, Wilson NH. A survey of the attitudes of members of the European Prosthodontic Association towards the shortened dental arch concept. *Eur J Prosthodont Restor Dent* 1998: **6**: 165–169.
12. Allmyr M, Adolfsson-Erici M, McLachlan MS, Sandborgh-Englund G. Triclosan in plasma and milk from Swedish nursing mothers and their exposure via personal care products. *Sci Total Environ* 2006: **372**: 87–93.
13. Allmyr M, Panagiotidis G, Sparve E, Diczfalusy U, Sandborgh-Englund G. Human exposure to triclosan via toothpaste does not change CYP3A4 activity or plasma concentrations of thyroid hormones. *Basic Clin Pharmacol Toxicol* 2009: **105**: 339–344.
14. Al-Otaibi M, Al-Harthy M, Gustafsson A, Johansson A, Claesson R, Angmar-Månsson B. Subgingival plaque microbiota in Saudi Arabians after use of miswak chewing stick and toothbrush. *J Clin Periodontol* 2004: **31**: 1048–1053.
15. Al-Otaibi M, Al-Harthy M, Söder B, Gustafsson A, Angmar-Månsson B. Comparative effect of chewing sticks and toothbrushing on plaque removal and gingival health. *Oral Health Prev Dent* 2003: **1**: 301–307.
16. American Dental Association. *Accepted dental therapeutics*. Chicago IL: American Dental Association, 1984, p. 326.
17. Anderson RL, Vess RW, Panlilio AL, Favero MS. Prolonged survival of *Pseudomonas cepacia* in commercially manufactured povidone-iodine. *Appl Environ Microbiol* 1990: **56**: 3598–3600.
18. Aoki A, Sasaki KM, Watanabe H, Ishikawa I. Lasers in nonsurgical periodontal therapy. *Periodontol 2000* 2004: **36**: 59–97.
19. Ardila CM, Granada MI, Guzmán IC. Antibiotic resistance of subgingival species in chronic periodontitis patients. *J Periodontal Res* 2010: **45**: 557–563.
20. Arigbede AO, Ajayi DM, Akeredolu PA, Onyeaso CO. Attitudes and perception of Nigerian dentists about shortened dental arch therapy (SDAT). *Odontostomatol Trop* 2009: **32**(126): 13–19.
21. Armitage GC. Comparison of the microbiological features of chronic and aggressive periodontitis. *Periodontol 2000* 2010: **53**: 70–88.
22. Armitage GC, Cullinan MP, Seymour GJ. Comparative biology of chronic and aggressive periodontitis: introduction. *Periodontol 2000* 2010: **53**: 7–11.
23. Asikainen S, Chen C, Slots J. Likelihood of transmitting *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* in families with periodontitis. *Oral Microbiol Immunol* 1996: **11**: 387–394.
24. Axelsson P, Albandar JM, Rams TE. Prevention and control of periodontal diseases in developing and industrialized nations. *Periodontol 2000* 2002: **29**: 235–246.
25. Baehni PC. Translating science into action: prevention of periodontal disease at patient level. *Periodontol 2000* 2012: **60**: 162–172.

26. Baelum V, Scheutz F. Periodontal diseases in Africa. *Periodontol 2000* 2002: **29**: 79–103.
27. Baelum V, van Palenstein Helderman W, Hugoson A, Yee R, Fejerskov O. A global perspective on changes in the burden of caries and periodontitis: implications for dentistry. *J Oral Rehabil* 2007: **34**: 872–906.
28. Baines SD, O'Connor R, Freeman J, Fawley WN, Harmanus C, Mastrantonio P, Kuijper EJ, Wilcox MH. Emergence of reduced susceptibility to metronidazole in *Clostridium difficile*. *J Antimicrob Chemother* 2008: **62**: 1046–1052.
29. Baker KA. The role of dental professionals and the patient in plaque control. *Periodontol 2000* 1995: **8**: 108–113.
30. Barbosa FC, Mayer MP, Saba-Chujfi E, Cai S. Subgingival occurrence and antimicrobial susceptibility of enteric rods and pseudomonads from Brazilian periodontitis patients. *Oral Microbiol Immunol* 2001: **16**: 306–310.
31. Baskar JF, Stanat SC, Huang ES. Congenital defects due to reactivation of latent murine cytomegaloviral infection during pregnancy. *J Infect Dis* 1985: **152**: 621–624.
32. Basrani BR, Manek S, Sodhi RN, Fillery E, Manzur A. Interaction between sodium hypochlorite and chlorhexidine gluconate. *J Endod* 2007: **33**: 966–969.
33. Beikler T, Flemmig TF. Oral biofilm-associated diseases: trends and implications for quality of life, systemic health and expenditures. *Periodontol 2000* 2011: **55**: 87–103.
34. Beirne P, Clarkson JE, Worthington HV. Recall intervals for oral health in primary care patients. *Cochrane Database Syst Rev* 2007: **4**: CD004346.
35. Beirne P, Forgie A, Worthington HV, Clarkson JE. Routine scale and polish for periodontal health in adults. *Cochrane Database Syst Rev* 2005: **1**: CD004625.
36. Below H, Lehan N, Kramer A. HPLC determination of the antiseptic agent chlorhexidine and its degradation products 4-chloroaniline and 1-chloro-4-nitrobenzene in serum and urine. *Microchimica Acta* 2004: **146**: 129–135.
37. Berchier CE, Slot DE, Haps S, Van der Weijden GA. The efficacy of dental floss in addition to a toothbrush on plaque and parameters of gingival inflammation: a systematic review. *Int J Dent Hyg* 2008: **6**: 265–279.
38. Bergquist R. Parasitic infections affecting the oral cavity. *Periodontol 2000* 2009: **49**: 96–105.
39. Bonito AJ, Lux L, Lohr KN. Impact of local adjuncts to scaling and root planing in periodontal disease therapy: a systematic review. *J Periodontol* 2005: **76**: 1227–1236.
40. Borrell LN, Crawford ND. Socioeconomic position indicators and periodontitis: examining the evidence. *Periodontol 2000* 2012: **58**: 69–83.
41. Bourgeois DM, Leclercq MH. The World Health Organization initiative on noma. *Oral Dis* 1999: **5**: 172–174.
42. Bower RC. Furcation morphology relative to periodontal treatment. Furcation entrance architecture. *J Periodontol* 1979: **50**: 23–27.
43. Bragd L, Dahlén G, Wikström M, Slots J. The capability of *Actinobacillus actinomycetemcomitans*, *Bacteroides gingivalis* and *Bacteroides intermedius* to indicate progressive periodontitis; a retrospective study. *J Clin Periodontol* 1987: **14**: 95–99.
44. Breininger DR, O'Leary TJ, Blumenshine RV. Comparative effectiveness of ultrasonic and hand scaling for the removal of subgingival plaque and calculus. *J Periodontol* 1987: **58**: 9–18.
45. Bruch MK. Toxicity and safety of topical sodium hypochlorite. *Contrib Nephrol* 2007: **154**: 24–38.
46. Buergers R, Rosentritt M, Schneider-Brachert W, Behr M, Handel G, Hahnel S. Efficacy of denture disinfection methods in controlling *Candida albicans* colonization in vitro. *Acta Odontol Scand* 2008: **66**: 174–180.
47. Byarugaba DK. A view on antimicrobial resistance in developing countries and responsible risk factors. *Int J Antimicrob Agents* 2004: **24**: 105–110.
48. Caffesse RG, Sweeney PL, Smith BA. Scaling and root planing with and without periodontal flap surgery. *J Clin Periodontol* 1986: **13**: 205–210.
49. Cancro LP, Fischman SL. The expected effect on oral health of dental plaque control through mechanical removal. *Periodontol 2000* 1995: **8**: 60–74.
50. Carnevale G, Pontoriero R, Hürzeler MB. Management of furcation involvement. *Periodontol 2000* 1995: **9**: 69–89.
51. Cattabriga M, Pedrazzoli V, Wilson TG Jr. The conservative approach in the treatment of furcation lesions. *Periodontol 2000* 2000: **22**: 133–153.
52. Chapple IL. Periodontal diagnosis and treatment- where does the future lie? *Periodontol 2000* 2009: **51**: 9–24.
53. Chávez de Paz LE, Bergenholtz G, Svensäter G. The effects of antimicrobials on endodontic biofilm bacteria. *J Endod* 2010: **36**: 70–77.
54. Chen C, Slots J. Microbiological tests for *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*. *Periodontol 2000* 1999: **20**: 53–64.
55. Cherry M, Daly CG, Mitchell D, Highfield J. Effect of rinsing with povidone-iodine on bacteraemia due to scaling: a randomized-controlled trial. *J Clin Periodontol* 2007: **34**: 148–155.
56. Chidzonga MM. Noma (cancrum oris) in human immunodeficiency virus/acquired immune deficiency syndrome patients. Report of eight cases. *J Oral Maxillofac Surg* 1996: **54**: 1056–1060.
57. Ciancio SG. Chemical agents: plaque control, calculus reduction and treatment of dentinal hypersensitivity. *Periodontol 2000* 1995: **8**: 75–86.
58. Ciancio SG. Nonsurgical chemical periodontal therapy. *Periodontol 2000* 1995: **9**: 27–37.
59. Ciancio SG. Controlling biofilm with evidence-based dentifrices. *Compendium* 2011: **32**: 70–76.
60. Ciancio SG, Mather ML, Zambon JJ, Reynolds HS. Effect of a chemotherapeutic agent delivered by an oral irrigation device on plaque, gingivitis, and subgingival microflora. *J Periodontol* 1989: **60**: 310–315.
61. Claydon NC. Current concepts in toothbrushing and interdental cleaning. *Periodontol 2000* 2008: **48**: 10–22.
62. Cole P, Rodu B, Mathisen A. Alcohol-containing mouthwash and oropharyngeal cancer. *J Am Dent Assoc* 2003: **134**: 1079–1087.
63. Contreras A, Botero JE, Slots J. Biology and pathogenesis of cytomegalovirus in periodontal disease. *Periodontol 2000* (in press).
64. Contreras A, Rusitanonta T, Chen C, Wagner WG, Michalowicz BS, Slots J. Frequency of 530-bp deletion in *Actinobacillus actinomycetemcomitans* leukotoxin promoter region. *Oral Microbiol Immunol* 2000: **15**: 338–340.
65. Contreras A, Zadeh HH, Nowzari H, Slots J. Herpesvirus infection of inflammatory cells in human periodontitis. *Oral Microbiol Immunol* 1999: **14**: 206–212.

66. Corbet EF, Leung WK. Epidemiology of periodontitis in the Asia and Oceania regions. *Periodontol 2000* 2011: **56**: 25–64.
67. Cuesta AI, Jewtuchowicz V, Brusca MI, Nastri ML, Rosa AC. Prevalence of *Staphylococcus* spp and *Candida* spp in the oral cavity and periodontal pockets of periodontal disease patients. *Acta Odontol Latinoam* 2010: **23**: 20–26.
68. Cummins D. Vehicles: how to deliver the goods. *Periodontol 2000* 1997: **15**: 84–99.
69. Dahlén G, Lindhe J, Sato K, Hanamura H, Okamoto H. The effect of supragingival plaque control on the subgingival microbiota in subjects with periodontal disease. *J Periodontol* 1992: **19**: 802–809.
70. Dahlén G, Wikström M. Occurrence of enteric rods, staphylococci and *Candida* in subgingival samples. *Oral Microbiol Immunol* 1995: **10**: 42–46.
71. Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, Gewitz MH, Shulman ST, Nouri S, Newburger JW, Hutto C, Pallasch TJ, Gage TW, Levison ME, Peter G, Zuccaro G Jr. Prevention of bacterial endocarditis: recommendations by the American Heart Association. *J Am Dent Assoc* 1997: **128**: 1142–1151.
72. Daneshmand N, Jorgensen MG, Nowzari H, Morrison JL, Slots J. Initial effect of controlled release chlorhexidine on subgingival microorganisms. *J Periodontal Res* 2002: **37**: 375–379.
73. Darby IB, Hodge PJ, Riggio MP, Kinane DF. Clinical and microbiological effect of scaling and root planing in smoker and non-smoker chronic and aggressive periodontitis patients. *J Clin Periodontol* 2005: **32**: 200–206.
74. Davies RM. Toothpaste in the control of plaque / gingivitis and periodontitis. *Periodontol 2000* 2008: **48**: 23–30.
75. De La Garza-Ramos MA, Galán-Wong LJ, Caffesse RG, González-Salazar F, Pereyra-Alférez B. Detection of *Porphyromonas gingivalis* and *Streptococcus intermedius* in chronic periodontitis patients by multiplex PCR. *Acta Odontol Latinoam* 2008: **21**: 163–167.
76. De Nardo R, Chiappe V, Gómez M, Romanelli H, Slots J. Effect of 0.05% sodium hypochlorite oral rinse on supragingival biofilm and gingival inflammation. *Int Dent J* 2012: **62**: 208–212.
77. Deas DE, Mealey BL. Response of chronic and aggressive periodontitis to treatment. *Periodontol 2000* 2010: **53**: 154–166.
78. Del Peloso Ribeiro E, Bittencourt S, Ambrosano GM, Nociti FH Jr, Sallum EA, Sallum AW, Casati MZ. Povidone-iodine used as an adjunct to non-surgical treatment of furcation involvements. *J Periodontol* 2006: **77**: 211–217.
79. Demmer RT, Papapanou PN. Epidemiologic patterns of chronic and aggressive Periodontitis. *Periodontol 2000* 2010: **53**: 28–44.
80. DenBesten P, Berkowitz R. Early childhood caries: an overview with reference to our experience in California. *J Calif Dent Assoc* 2003: **31**: 139–143.
81. Dentino A, Lee S, Mailhot J, Hefti AF. Principles of periodontology. *Periodontol 2000* 2013: (in press).
82. DeQueiroz GA, Day DF. Antimicrobial activity and effectiveness of a combination of sodium hypochlorite and hydrogen peroxide in killing and removing *Pseudomonas aeruginosa* biofilms from surfaces. *J Appl Microbiol* 2007: **103**: 794–802.
83. DeSanctis M, Murphy KG. The role of resective periodontal surgery in the treatment of furcation defects. *Periodontol 2000* 2000: **22**: 154–168.
84. Devine DA, Marsh PD. Prospects for the development of probiotics and prebiotics for oral applications. *J Oral Microbiol* 2009: **1**(Suppl.).
85. Dhingra K. Methodological issues in randomized trials assessing probiotics for periodontal treatment. *J Periodontal Res* 2012: **47**: 15–26.
86. Ding F, Meng HX, Li QQ, Zhao YB, Feng XH, Zhang L. Effect of periodontal mechanical treatment on herpesviruses in gingival crevicular fluid of patients with chronic periodontitis. *Zhonghua Kou Qiang Yi Xue Za Zhi* 2010: **45**: 426–430 (in Chinese).
87. DiRienzo JM, Slots J. Genetic approach to the study of epidemiology and pathogenesis of *Actinobacillus actinomycetemcomitans* in localized juvenile periodontitis. *Arch Oral Biol* 1990: **35**(Suppl.): 79S–84S.
88. DiRienzo JM, Slots J, Sixou M, Sol MA, Harmon R, McKay TL. Specific genetic variants of *Actinobacillus actinomycetemcomitans* correlate with disease and health in a regional population of families with localized juvenile periodontitis. *Infect Immun* 1994: **62**: 3058–3065.
89. Donos N, Laurell L, Mardas M. Hierarchical decisions on teeth vs. implants in the periodontitis-susceptible patient: the modern dilemma. *Periodontol 2000* 2012: **59**: 89–110.
90. dos Santos KM, Pinto SC, Pochapski MT, Wambier DS, Pilatti GL, Santos FA. Molar furcation entrance and its relation to the width of curette blades used in periodontal mechanical therapy. *Int J Dent Hyg* 2009: **7**: 263–269.
91. Doungudomdacha S, Rawlinson A, Walsh TF, Douglas CW. Effect of non-surgical periodontal treatment on clinical parameters and the numbers of *Porphyromonas gingivalis*, *Prevotella intermedia* and *Actinobacillus actinomycetemcomitans* at adult periodontitis sites. *J Clin Periodontol* 2001: **28**: 437–445.
92. Drisko CH. Root instrumentation. Power-driven versus manual scalers, which one?. *Dent Clin North Am* 1998: **42**: 229–244.
93. Drisko CH. Nonsurgical periodontal therapy. *Periodontol 2000* 2001: **25**: 77–88.
94. Drisko CL, Cochran DL, Blieden T, Bouwsma OJ, Cohen RE, Damoulis P, Fine JB, Greenstein G, Hinrichs J, Somerman MJ, Iacono V, Genco RJ, Research, Science and Therapy Committee of the American Accademy of Periodontology. Position paper: sonic and ultrasonic scalers in periodontics. *J Periodontol* 2000: **71**: 1792–1801.
95. Ebersole JL. Humoral immune responses in gingival crevice fluid: local and systemic implications. *Periodontol 2000* 2003: **31**: 135–166.
96. Edwardsson S, Burman LG, Adolfsson-Erici M, Bäckman N. Risker och nytta med triklosan i tandkräm (Risks and benefits with triclosan containing toothpastes). *Tandläkartidningen* 2005: **97**: 58–64 (Swedish with English summary).
97. Elamin A, Albandar JM, Poulsen K, Ali RW, Bakken V. Prevalence of *Aggregatibacter actinomycetemcomitans* in Sudanese patients with aggressive periodontitis: a case-control study. *J Periodontal Res* 2011: **46**: 285–291.
98. Elias AC, Sheiham A. The relationship between satisfaction with mouth and number and position of teeth. *J Oral Rehabil* 1998: **25**: 649–661.

99. Emrani J, Chee W, Slots J. Bacterial colonization of oral implants from nondental sources. *Clin Implant Dent Relat Res* 2009: **11**: 106–112.
100. Ereş G, Altıok E, Ozkul A, Açıkel CH. Subgingival Epstein-Barr and cytomegalovirus occurrence in pregnancy gingivitis. *J Periodontal* 2011: **82**: 1676–1684.
101. Esan TA, Olusile AO, Akeredolu PA, Esan AO. Socio-demographic factors and edentulism: the Nigerian experience. *BMC Oral Health* 2004: **4**(1): 3.
102. Feng Z, Weinberg A. Role of bacteria in health and disease of periodontal tissues. *Periodontol 2000* 2006: **40**: 50–76.
103. Feres M, Haffajee AD, Allard K, Som S, Goodson JM, Socransky SS. Antibiotic resistance of subgingival species during and after antibiotic therapy. *J Clin Periodontol* 2002: **29**: 724–735.
104. Fischman SL. The history of oral hygiene products: how far have we come in 6000 years? *Periodontol 2000* 1997: **15**: 7–14.
105. Flemmig TF, Beikler T. Decision making in implant dentistry: an evidence-based and decision-analysis approach. *Periodontol 2000* 2009: **50**: 154–172.
106. Flynn MJ, Slots J. Beta-hemolytic streptococci in advanced periodontitis. *Oral Microbiol Immunol* 1993: **8**: 295–297.
107. Fontana CR, Abernethy AD, Som S, Ruggiero K, Doucette S, Marcantonio RC, Boussios CI, Kent R, Goodson JM, Tanner AC, Soukos NS. The antibacterial effect of photodynamic therapy in dental plaque-derived biofilms. *J Periodontal Res* 2009: **44**: 751–759.
108. Fransson C, Lekholm U, Jemt T, Berglundh T. Prevalence of subjects with progressive bone loss at implants. *Clin Oral Implants Res* 2005: **16**: 440–446.
109. Freeman CD, Klutman NE, Lamp KC. Metronidazole. A therapeutic review and update. *Drugs* 1997: **54**: 679–708.
110. Garcia RI, Nunn ME, Dietrich T. Risk calculation and periodontal outcomes. *Periodontol 2000* 2009: **50**: 65–77.
111. Gellin RG, Miller MC, Javed T, Engler WO, Mishkin DJ. The effectiveness of the Titan-S sonic scaler versus curettes in the removal of subgingival calculus. A human surgical evaluation. *J Periodontol* 1986: **57**: 672–680.
112. Gjermo PE, Grytten J. Cost-effectiveness of various treatment modalities for adult chronic periodontitis. *Periodontol 2000* 2009: **51**: 269–275.
113. Goodson JM. Gingival crevice fluid flow. *Periodontol 2000* 2003: **31**: 43–54.
114. Goon AT, White IR, Rycroft RJ, McFadden JP. Allergic contact dermatitis from chlorhexidine. *Dermatitis* 2004: **15**: 45–47.
115. Gosau M, Hahnel S, Schwarz F, Gerlach T, Reichert TE, Bürgers R. Effect of six different peri-implantitis disinfection methods on in vivo human oral biofilm. *Clin Oral Implants Res* 2010: **21**: 866–872.
116. Greenstein G. Nonsurgical periodontal therapy in 2000: a literature review. *J Am Dent Assoc* 2000: **131**: 1580–1592.
117. Grenier G, Gagnon G, Grenier D. Detection of herpetic viruses in gingival crevicular fluid of patients suffering from periodontal diseases: prevalence and effect of treatment. *Oral Microbiol Immunol* 2009: **24**: 506–509.
118. Grinde B, Olsen I. The role of viruses in oral disease. *J Oral Microbiol* 2010: **2**: 2127.
119. Haffajee AD, Socransky SS, Gunsolley JC. Systemic anti-infective periodontal therapy. A systematic review. *Ann Periodontol* 2003: **8**: 115–181.
120. Haffajee AD, Teles RP, Socransky SS. The effect of periodontal therapy on the composition of the subgingival microbiota. *Periodontol 2000* 2006: **42**: 219–258.
121. Haraszthy VI, Zambon JJ, Sreenivasan PK, Zambon MM, Gerber D, Rego R, Parker C. Identification of oral bacterial species associated with halitosis. *J Am Dent Assoc* 2007: **138**: 1113–1120.
122. Haritha A, Jayakumar A. Syndromes as they relate to periodontal disease. *Periodontol 2000* 2011: **56**: 65–86.
123. Harrington GW, Steiner DR, Ammons WF. The periodontal-endodontic controversy. *Periodontol 2000* 2002: **30**: 123–130.
124. Harrison JE, Schultz J. Studies on the chlorinating activity of myeloperoxidase. *J Biol Chem* 1976: **251**: 1371–1374.
125. Hart TC, Atkinson JC. Mendelian forms of periodontitis. *Periodontol 2000* 2007: **45**: 95–112.
126. Heasman PA, Vernazza CR, Gaunt FL, Pennington MW. Cost-effectiveness of adjunctive antimicrobials in the treatment of periodontitis. *Periodontol 2000* 2011: **55**: 217–230.
127. Hegstad K, Langsrud S, Lunestad BT, Scheie AA, Sunde M, Yazdankhah SP. Does the wide use of quaternary ammonium compounds enhance the selection and spread of antimicrobial resistance and thus threaten our health? *Microb Drug Resist* 2010: **16**: 91–104.
128. Heitz-Mayfield LJA, Lang NP. Comparative biology of chronic and aggressive periodontitis vs. peri-implantitis. *Periodontol 2000* 2010: **53**: 167–181.
129. Hellström MK, Ramberg P, Krok L, Lindhe J. The effect of supragingival plaque control on the subgingival microflora in human periodontitis. *J Clin Periodontol* 1996: **23**: 934–940.
130. Helovuo H, Hakkarainen K, Paunio K. Changes in the prevalence of subgingival enteric rods, staphylococci and yeasts after treatment with penicillin and erythromycin. *Oral Microbiol Immunol* 1993: **8**: 75–79.
131. Henderson B, Ward JM, Ready D. *Aggregatibacter* (*Actinobacillus*) *actinomycetemcomitans*: a triple A* periodontopathogen? *Periodontol 2000* 2010: **54**: 78–105.
132. Hennessey TD. Antibacterial properties of Hibitane. *J Clin Periodontol* 1977: **4**: 36–48.
133. Herrera D, Contreras A, Gamonal J, Oteo A, Jaramillo A, Silva N, Sanz M, Botero JE, León R. Subgingival microbial profiles in chronic periodontitis patients from Chile, Colombia and Spain. *J Clin Periodontol* 2008: **35**: 106–113.
134. Hersh EV, Moore PA. Adverse drug interactions in dentistry. *Periodontol 2000* 2008: **46**: 109–142.
135. Herzog A, Hodges KO. Subgingival irrigation with chloramine-T. *J Dent Hyg* 1988: **62**: 515–521.
136. Hillman JD, Socransky SS. Replacement therapy of the prevention of dental disease. *Adv Dent Res* 1987: **1**: 119–125.
137. Hoang T, Jorgensen MG, Keim RG, Pattison AM, Slots J. Povidone-iodine as a periodontal pocket disinfectant. *J Periodontal Res* 2003: **38**: 311–317.
138. Hoenderdos NL, Slot DE, Paraskevas S, van der Weijden GA. The efficacy of woodsticks on plaque and gingival inflammation: a systematic review. *Int J Dent Hyg* 2008: **6**: 280–289.
139. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T(4), and thyroid antibodies in the United States population

(1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002: **87**: 489–499.
140. Hossainian N, Slot D, Afennich F, van der Weijden G. The effects of hydrogen peroxide mouthwashes on the prevention of plaque and gingival inflammation: a systematic review. *Int J Dent Hyg* 2011: **9**: 171–181.
141. Hugoson A, Sjódin B, Norderyd O. Trends over 30 years, 1973–2003, in the prevalence and severity of periodontal disease. *J Clin Periodontol* 2008: **35**: 405–414.
142. Hujoel PP, Cunha-Cruz J, Loesche WJ, Robertson PB. Personal oral hygiene and chronic periodontitis: a systematic review. *Periodontol 2000* 2005: **37**: 29–34.
143. Hujoel P, Zina LG, Cunha-Cruz J, Lopez R. Historical perspectives on theories of periodontal disease etiology. *Periodontol 2000* 2012: **58**: 153–160.
144. Husseini A, Slot DE, van der Weijden GA. The efficacy of oral irrigation in addition to a toothbrush on plaque and the clinical parameters of periodontal inflammation: a systematic review. *Int J Dent Hyg* 2008: **6**: 304–314.
145. Ishikawa I, Aoki A, Takasaki AA, Mizutani K, Sasaki KM, Izumi Y. Application of lasers in periodontics: true innovation or myth? *Periodontol 2000* 2009: **50**: 90–126.
146. Iwase M, Slots J, Berthold P, Taichman NS. Leukocidal activity of staphylococci isolated from human periodontal lesions. *Oral Microbiol Immunol* 1990: **5**: 233–236.
147. Jankovic S, Aleksic Z, Dimitrijevic B, Lekovic V, Camargo P, Kenney B. Prevalence of human cytomegalovirus and Epstein-Barr virus in subgingival plaque at peri-implantitis, mucositis and healthy sites. A pilot study. *Int J Oral Maxillofac Surg* 2011: **40**: 271–276.
148. Jaskoll T, Abichaker G, Htet K, Bringas P Jr, Morita S, Sedghizadeh PP, Melnick M. Cytomegalovirus induces stage-dependent enamel defects and misexpression of amelogenin, enamelin and dentin sialophosphoprotein in developing mouse molars. *Cells Tissues Organs* 2010: **192**: 221–239.
149. Jaskoll T, Abichaker G, Sedghizadeh PP, Bringas P Jr, Melnick M. Cytomegalovirus induces abnormal chondrogenesis and osteogenesis during embryonic mandibular development. *BMC Dev Biol* 2008: **8**: 33.
150. Jepsen J, Deschner J, Braun A, Schwartz F, Eberhard J. Calculus removal and the prevention of its formation. *Periodontol 2000* 2011: **55**: 167–188.
151. Johnson NW, Jayasekara P, Amarasinghe AAHK. Squamous cell carcinoma and precursor lesions of the oral cavity: epidemiology and aetiology. *Periodontol 2000* 2011: **57**: 19–37.
152. Jones CG. Chlorhexidine: is it still the gold standard? *Periodontol 2000* 1997: **15**: 55–62.
153. Jorgensen MG, Aalam A, Slots J. Periodontal antimicrobials-finding the right solutions. *Int Dent J* 2005: **55**: 3–12.
154. Jorgensen M, Slots J. Locally delivered chemotherapeutic agents. In: Harpenau LA, Kao RT, Lundergan WP, Sanz M. editors. *Hall's critical decisions in periodontology*, 5th edn. Shelton CT, USA: People's Medical Publishing House (PMPH) Ltd., In press.
155. Jorgensen M, Slots J. Microbial analysis in periodontal diagnosis and treatment planning. In: Harpenau LA, Kao RT, Lundergan WP, Sanz M. editors. *Hall's critical decisions in periodontology*, 5th edn. Shelton CT, USA: People's Medical Publishing House (PMPH) Ltd., In press
156. Jorgensen M, Slots J. Periodontal systemic antibiotic therapy. In: Harpenau LA, Kao RT, Lundergan WP, Sanz M. editors. *Hall's critical decisions in periodontology*, 5th edn. Shelton CT, USA: People's Medical Publishing House (PMPH) Ltd., In press.
157. Jürgensen N, Petersen PE, Ogawa H, Matsumuto S. Translating science into action: periodontal health through public health approaches. *Periodontol 2000* 2012: **60**: 173–187.
158. Kaide CG, Khandelwal S. Hyperbaric oxygen: applications in infectious disease. *Emerg Med Clin North Am* 2008: **26**: 571–595.
159. Kalkwarf KL, Tussing GJ, Davis MJ. Histologic evaluation of gingival curettage facilitated by sodium hypochlorite solution. *J Periodontol* 1982: **53**: 63–70.
160. Kallio PJ. Health promotion and behavioral approaches in the prevention of periodontal disease in children and adolescents. *Periodontol 2000* 2001: **26**: 135–145.
161. Kandelman D, Arpin S, Baez RJ, Baehni PC, Petersen PE. Oral health care systems in developing and developed countries. *Periodontol 2000* 2012: **60**: 98–109.
162. Kanno T, Carlsson GE. A review of the shortened dental arch concept focusing on the work by the Käyser/Nijmegen group. *J Oral Rehabil* 2006: **33**: 850–862.
163. Kawana R, Kitamura T, Nakagomi O, Matsumoto I, Arita M, Yoshihara N, Yanagi K, Yamada A, Morita O, Yoshida Y, Furuya Y, Chiba S. Inactivation of human viruses by povidone-iodine in comparison with other antiseptics. *Dermatology* 1997: **195**(Suppl. 2): 29–35.
164. Käyser AF. Limited treatment goals-shortened dental arches. *Periodontol 2000* 1994: **4**: 7–14.
165. Kerry GJ. Supportive periodontal treatment. *Periodontol 2000* 1995: **9**: 176–185.
166. Kilian M, Frandsen EV, Haubek D, Poulsen K. The etiology of periodontal disease revisited by population genetic analysis. *Periodontol 2000* 2006: **42**: 158–179.
167. Kinane DF, Shiba H, Hart TC. The genetic basis of periodontitis. *Periodontol 2000* 2005: **39**: 91–117.
168. Kobayashi N, Ishihara K, Sugihara N, Kusumoto M, Yakushiji M, Okuda K. Colonization pattern of periodontal bacteria in Japanese children and their mothers. *J Periodontal Res* 2008: **43**: 156–161.
169. Kookana RS, Ying GG, Waller NJ. Triclosan: its occurrence, fate and effects in the Australian environment. *Water Sci Technol* 2011: **63**: 598–604.
170. Krasse B, Fure S. Root surface caries: a problem for periodontally compromised patients. *Periodontol 2000* 1994: **4**: 139–147.
171. Kuboniwa M, Lamont RJ. Subgingival biofilm formation. *Periodontol 2000* 2010: **52**: 38–52.
172. Laine ML, Crielaard W, Loos BG. Genetic susceptibility to periodontitis. *Periodontol 2000* 2012: **58**: 37–68.
173. Lamont RJ, Yilmaz O. In or out: the invasiveness of oral bacteria. *Periodontol 2000* 2002: **30**: 61–69.
174. Lang NP. Focus on intrabony defects – conservative therapy. *Periodontol 2000* 2000: **22**: 51–58.
175. Lang NP, Joss A, Tonetti MS. Monitoring disease during supportive periodontal treatment by bleeding on probing. *Periodontol 2000* 1996: **12**: 44–48.
176. Lang NP, Sander L, Barlow A, Brennan K, White DJ, Bacca L, Bartizek RD, McClanahan SF. Experimental gingivitis studies: effects of triclosan and triclosan-containing den-

tifrices on dental plaque and gingivitis in three-week randomized controlled clinical trials. *J Clin Dent* 2002: **13**: 158–166.
177. Lea SC, Walmsley AD. Mechano-physical and biophysical properties of power-driven scalers: driving the future of powered instrument design and evaluation. *Periodontol 2000* 2009: **51**: 63–78.
178. Leonhardt A, Bergström C, Krok L, Cardaropoli G. Healing following ultrasonic debridement and PVP-iodine in individuals with severe chronic periodontal disease: a randomized, controlled clinical study. *Acta Odontol Scand* 2006: **64**: 262–266.
179. Li X, Sun QF, Sun YD, Ge SH, Yang PS. Quantitative detection of human cytomegalovirus in aggressive and chronic periodontitis lesions. *Hua Xi Kou Qiang Yi Xue Za Zhi* 2011: **29**: 242–245 (in Chinese).
180. Lindhe J, Haffajee AD, Socransky SS. Progression of periodontal disease in adult subjects in the absence of periodontal therapy. *J Clin Periodontol* 1983: **10**: 433–442.
181. Lindhe J, Socransky SS, Nyman S, Haffajee A, Westfelt E. ''Critical probing depths'' in periodontal therapy. *J Clin Periodontol* 1982: **9**: 323–336.
182. Listgarten MA, Grossberg D, Schwimer C, Vito A, Gaffar A. Effect of subgingival irrigation with tetrapotassium peroxydiphosphate on scaled and untreated periodontal pockets. *J Periodontol* 1989: **60**: 4–11.
183. Listgarten MA, Helldén L. Relative distribution of bacteria at clinically healthy and periodontally diseased sites in humans. *J Clin Periodontol* 1978: **5**: 115–132.
184. Listgarten MA, Mayo HE, Tremblay R. Development of dental plaque on epoxy resin crowns in man. A light and electron microscopic study. *J Periodontol* 1975: **46**: 10–26.
185. Listgarten MA, Slots J, Rosenberg J, Nitkin L, Sullivan P, Oler J. Clinical and microbiological characteristics of treated periodontitis patients on maintenance care. *J Periodontol* 1989: **60**: 452–459.
186. Listgarten MA, Sullivan P, George C, Nitkin L, Rosenberg ES, Chilton NW, Kramer AA. Comparative longitudinal study of 2 methods of scheduling maintenance visits: 4-year data. *J Clin Periodontol* 1989: **16**: 105–115.
187. Lobene RR, Soparkar PM, Hein JW, Quigley GA. A study of the effects of antiseptic agents and a pulsating irrigating device on plaque and gingivitis. *J Periodontol* 1972: **43**: 564–568.
188. Löe H, Schiott CR. The effect of mouthrinses and topical application of chlorhexidine on the development of dental plaque and gingivitis in man. *J Periodontal Res* 1970: **5**: 79–83.
189. Loesche WJ, Giordano JR. Metronidazole in periodontitis V: debridement should precede medication. *Compendium* 1994: **15**: 1198, 1201, 1203 passim; quiz 1218.
190. Loesche WJ, Kazor C. Microbiology and treatment of halitosis. *Periodontol 2000* 2002: **28**: 256–279.
191. Loos B, Claffey N, Egelberg J. Clinical and microbiological effects of root debridement in periodontal furcation pockets. *J Clin Periodontol* 1988: **15**: 453–463.
192. Loos B, Nylund K, Claffey N, Egelberg J. Clinical effects of root debridement in molar and non-molar teeth A 2-year follow-up. *J Clin Periodontol* 1989: **16**: 498–504.
193. Lopez L, Berkowitz R, Spiekerman C, Weinstein P. Topical antimicrobial therapy in the prevention of early childhood caries: a follow-up report. *Pediatr Dent* 2002: **24**: 204–206.
194. López NJ, Socransky SS, Da Silva I, Japlit MR, Haffajee AD. Effects of metronidazole plus amoxicillin as the only therapy on the microbiological and clinical parameters of untreated chronic periodontitis. *J Clin Periodontol* 2006: **33**: 648–660.
195. Low SB. Clinical considerations in nonsurgical mechanical therapy. *Periodontol 2000* 1995: **9**: 23–26.
196. Lundgren D, Rylander H, Laurell L. To save or to extract, that is the question. Natural teeth or dental implants in periodontitis-susceptible patients: clinical decision-making and treatment strategies exemplified with patient case presentations. *Periodontol 2000* 2008: **47**: 27–50.
197. Mariotti AJ, Rumpf DA. Chlorhexidine-induced changes to human gingival fibroblast collagen and non-collagen protein production. *J Periodontol* 1999: **70**: 1443–1448.
198. Marsh PD, Moter A, Devine DA. Dental plaque biofilms: communities, conflict and control. *Periodontol 2000* 2011: **55**: 36–47.
199. Mayanagi G, Kimura M, Nakaya S, Hirata H, Sakamoto M, Benno Y, Shimauchi H. Probiotic effects of orally administered *Lactobacillus salivarius* WB21-containing tablets on periodontopathic bacteria: a double-blinded, placebo-controlled, randomized clinical trial. *J Clin Periodontol* 2009: **36**: 506–513.
200. McCullough MJ, Farah CS. The role of alcohol in oral carcinogenesis with particular reference to alcohol-containing mouthwashes. *Aust Dent J* 2008: **53**: 302–305.
201. Mealey BL, Ocampo GL. Diabetes mellitus and periodontal disease. *Periodontol 2000* 2007: **44**: 127–153.
202. Meissner G, Kocher T. Calculus detection technologies and their clinical application. *Periodontol 2000* 2011: **55**: 189–204.
203. Melnick M, Mocarski ES, Abichaker G, Huang J, Jaskoll T. Cytomegalovirus-induced embryopathology: mouse submandibular salivary gland epithelial-mesenchymal ontogeny as a model. *BMC Dev Biol* 2006: **6**: 42.
204. Meng H, Ren X, Tian Y, Feng X, Xu L, Zhang L, Lu R, Shi D, Chen Z. Genetic study of families affected with aggressive periodontitis. *Periodontol 2000* 2011: **56**: 87–101.
205. Merriam CV, Citron DM, Tyrrell KL, Warren YA, Goldstein EJ. In vitro activity of azithromycin and nine comparator agents against 296 strains of oral anaerobes and 31 strains of *Eikenella corrodens*. *Int J Antimicrob Agents* 2006: **28**: 244–248.
206. Moëne R, Décaillet F, Andersen E, Mombelli A. Subgingival plaque removal using a new air-polishing device. *J Periodontol* 2010: **81**: 79–88.
207. Mombelli A, Cionca N, Almaghlouth A. Does adjunctive antimicrobial therapy reduce the perceived need for periodontal surgery? *Periodontol 2000* 2011: **55**: 205–216.
208. Moran JM. Chemical plaque control–prevention for the masses. *Periodontol 2000* 1997: **15**: 109–117.
209. Moran JM. Home-use oral hygiene products: mouthrinses. *Periodontol 2000* 2008: **48**: 42–53.
210. Nakagawa T, Hosaka Y, Ishihara K, Hiraishi T, Sato S, Ogawa T, Kamoi K. The efficacy of povidone-iodine products against periodontopathic bacteria. *Dermatology* 2006: **212**(Suppl. 1): 109–111.

211. Nattestad A. Knowledge management systems for oral health in developing and developed countries. *Periodontol 2000* 2012: **60**: 156–161.
212. Needleman I, Moles DR. A guide to decision making in evidence-based diagnostics. *Periodontol 2000* 2005: **39**: 164–177.
213. Newman HN. Periodontal pocket irrigation as adjunctive treatment. *Curr Opin Periodontol* 1997: **4**: 41–50.
214. Nogueira-Filho GR, Rosa BT, David-Neto JR. Effects of hyperbaric oxygen therapy on the treatment of severe cases of periodontitis. *Undersea Hyperb Med* 2010: **37**: 107–114.
215. Novaes AB Jr, Schwartz-Filho HO, de Oliveira RR, Feres M, Sato S, Figueiredo LC. Antimicrobial photodynamic therapy in the non-surgical treatment of aggressive periodontitis: microbiological profile. *Lasers Med Sci* 2011.
216. Numazaki K, Asanuma H. Inhibitory effect of povidone-iodine for the antigen expression of human cytomegalovirus. *In Vivo* 1999: **13**: 239–241.
217. Nunn ME. Understanding the etiology of periodontitis: an overview of periodontal risk factors. *Periodontol 2000* 2003: **32**: 11–23.
218. Nyman SR, Lang NP. Tooth mobility and the biological rationale for splinting teeth. *Periodontol 2000* 1994: **4**: 15–22.
219. Oda S, Ishikawa I. In vitro effectiveness of a newly-designed ultrasonic scaler tip for furcation areas. *J Periodontol* 1989: **60**: 634–639.
220. Ogbureke KUE, Ogbureke EI. NOMA: A preventable ''scourge'' of African children. *Open Dent J* 2010: **4**: 201–206.
221. Oliver RC, Jackson Brown L, Löe H. Periodontal treatment needs. *Periodontol 2000* 1993: **2**: 150–160.
222. Pack AR. Dental services and needs in developing countries. *Int Dent J* 1998: **48**(3 Suppl. 1): 239–247.
223. Paine ML, Slots J, Rich SK. Fluoride use in periodontal therapy: a review of the literature. *J Am Dent Assoc* 1998: **129**: 69–77.
224. Pallasch TJ. Antifungal and antiviral chemotherapy. *Periodontol 2000* 2002: **28**: 240–255.
225. Parashis AO, Anagnou-Vareltzides A, Demetriou N. Calculus removal from multirooted teeth with and without surgical access. (I). Efficacy on external and furcation surfaces in relation to probing depth. *J Clin Periodontol* 1993: **20**: 63–68.
226. Paster BJ, Dewhirst FE. Molecular microbial diagnosis. *Periodontol 2000* 2009: **51**: 38–44.
227. Pattison AM. The use of hand instruments in supportive periodontal treatment. *Periodontol 2000* 1996: **12**: 71–89.
228. Pattni R, Walsh LJ, Marshall RI, Seymour GJ, Bartold PM. Periodontal implications of immunodeficient states: manifestations and management. *J Int Acad Periodontol* 2000: **2**: 79–93.
229. Pavicić MJ, van Winkelhoff AJ, de Graaff J. Synergistic effects between amoxicillin, metronidazole, and the hydroxymetabolite of metronidazole against *Actinobacillus actinomycetemcomitans*. *Antimicrob Agents Chemother* 1991: **35**: 961–966.
230. Petersen PE. Oral health. In: Heggenhougen K, Quah S editors. *International encyclopedia of public health*. San Diego: Elsevier, 2008: 677–685.
231. Petersen PE, Ogawa H. The global burden of periodontal disease: towards integration with chronic disease prevention and control. *Periodontol 2000* 2012: **60**: 15–39.
232. Petersilka GJ. Subgingival air-polishing in the treatment of periodontal biofilm infections. *Periodontol 2000* 2011: **55**: 124–142.
233. Petersilka GJ, Ehmke B, Flemmig TF. Antimicrobial effects of mechanical debridement. *Periodontol 2000* 2002: **28**: 56–71.
234. Petersilka G, Faggion CM Jr, Stratmann U, Gerss J, Ehmke B, Haeberlein I, Flemmig TF. Effect of glycine powder air-polishing on the gingiva. *J Clin Periodontol* 2008: **35**: 324–332.
235. Petersilka G, Panitz W, Weresch R, Eichinger M, Kern U. Air emphysema in periodontal therapy. A case series with critical literature overview. *Parodontologie* 2010: **21**: 165–175.
236. Piirilä P, Hodgson U, Estlander T, Keskinen H, Saalo A, Voutilainen R, Kanerva L. Occupational respiratory hypersensitivity in dental personnel. *Int Arch Occup Environ Health* 2002: **75**: 209–216.
237. Pozhitkov AE, Beikler T, Flemmig TF, Noble PA. High-throughput methods for analysis of the human oral microbiome. *Periodontol 2000* 2011: **55**: 70–86.
238. Quirynen M, Teughels W, De Soete M, van Steenberghe D. Topical antiseptics and antibiotics in the initial therapy of chronic adult periodontitis: microbiological aspects. *Periodontol 2000* 2002: **28**: 72–90.
239. Rabbani GM, Ash MM Jr, Caffesse RG. The effectiveness of subgingival scaling and root planing in calculus removal. *J Periodontol* 1981: **52**: 119–123.
240. Rahn R. Review presentation on povidone-iodine antisepsis in the oral cavity. *Postgrad Med J* 1993: **69**(Suppl. 3): S4–S9.
241. Rahn R, Schneider S, Diehl O, Schäfer V, Shah PM. Preventing post-treatment bacteremia: comparing topical povidone-iodine and chlorhexidine. *J Am Dent Assoc* 1995: **126**: 1145–1149.
242. Rams TE, Babalola OO, Slots J. Subgingival occurrence of enteric rods, yeasts and staphylococci after systemic doxycycline therapy. *Oral Microbiol Immunol* 1990: **5**: 166–168.
243. Rams TE, Feik D, Slots J. Staphylococci in human periodontal diseases. *Oral Microbiol Immunol* 1990: **5**: 29–32.
244. Rams TE, Feik D, Young V, Hammond BF, Slots J. Enterococci in human periodontitis. *Oral Microbiol Immunol* 1992: **7**: 249–352.
245. Rams TE, Flynn MJ, Slots J. Subgingival microbial associations in severe human periodontitis. *Clin Infect Dis* 1997: **25**(Suppl. 2): S224–S226.
246. Rams TE, Listgarten MA, Slots J. Utility of radiographic crestal lamina dura for predicting periodontitis disease-activity. *J Clin Periodontol* 1994: **21**: 571–576.
247. Rams TE, Listgarten MA, Slots J. Regards actuels sur les radiographies conventionnelles en parodontie. *J Parodontologie* 1994: **13**: 179–184 (in French).
248. Rams TE, Listgarten MA, Slots J. Efficacy of CPITN sextant scores for detection of periodontitis disease activity. *J Clin Periodontol* 1996: **23**: 355–361.
249. Rams TE, Listgarten MA, Slots J. Utility of 5 major putative periodontal pathogens and selected clinical parameters to

predict periodontal breakdown in patients on maintenance care. *J Clin Periodontol* 1996: **23**: 346–354.
250. Rams TE, Listgarten MA, Slots J. Risk of periodontitis recurrence by tooth surface location. *J Dent Res* 1999: **78** (special issue): 118 (Abstract 102).
251. Rams TE, Oler J, Listgarten MA, Slots J. Utility of Ramfjord index teeth to assess periodontal disease progression in longitudinal studies. *J Clin Periodontol* 1993: **20**: 147–150.
252. Rams TE, Slots J. Air polishing effects on subgingival microflora in human periodontal pockets. *J Periodontol* 1994: **65**: 986.
253. Rams TE, Slots J. Local delivery of antimicrobial agents in the periodontal pocket. *Periodontol 2000* 1996: **10**: 139–159.
254. Reimer K, Wichelhaus TA, Schafer V, Rudolph P, Kramer A, Wutzler P, Ganzer D, Fleischer W. Antimicrobial effectiveness of povidone-iodine and consequences for new application areas. *Dermatology* 2002: **204**(Suppl. 1): 114–120.
255. Renvert S, Nilvéus R, Dahlén G, Slots J, Egelberg J. 5-year follow up of periodontal intraosseous defects treated by root planing or flap surgery. *J Clin Periodontol* 1990: **17**: 356–363.
256. Renvert S, Wikström M, Dahlén G, Slots J, Egelberg J. On the inability of root debridement and periodontal surgery to eliminate *Actinobacillus actinomycetemcomitans* from periodontal pockets. *J Clin Periodontol* 1990: **17**: 351–355.
257. Renz ANPJ, Newton JT. Changing the behavior of patients with periodontitis. *Periodontol 2000* 2009: **51**: 252–268.
258. Ribeiro Edel P, Bittencourt S, Sallum EA, Sallum AW, Nociti Júnior FH, Casati MZ. Non-surgical instrumentation associated with povidone-iodine in the treatment of interproximal furcation involvements. *J Appl Oral Sci* 2010: **18**: 599–606.
259. Riggio MP, Lennon A, Rolph HJ, Hodge PJ, Donaldson A, Maxwell AJ, Bagg J. Molecular identification of bacteria on the tongue dorsum of subjects with and without halitosis. *Oral Dis* 2008: **14**: 251–258.
260. Rinke S, Ohl S, Ziebolz D, Lange K, Eickholz P. Prevalence of periimplant disease in partially edentulous patients: a practice-based cross-sectional study. *Clin Oral Implants Res* 2011: **22**: 826–833.
261. Ritchie CS. Obesity and periodontal disease. *Periodontol 2000* 2007: **44**: 154–163.
262. Roberts AP, Mullany P. Oral biofilms: a reservoir of transferable, bacterial, antimicrobial resistance. *Expert Rev Anti Infect Ther* 2010: **8**: 1441–1450.
263. Rodrigues A, Lussi A, Seemann R, Neuhaus KW. Prevention of crown and root caries in adults. *Periodontol 2000* 2011: **55**: 231–249.
264. Romanelli F, Smith KM, Pomeroy C. Reducing the transmission of HIV-1: needle bleaching as a means of disinfection. *J Am Pharm Assoc (Wash)* 2000: **40**: 812–817.
265. Rosema NA, Hennequin-Hoenderdos NL, Berchier CE, Slot DE, Lyle DM, van der Weijden GA. The effect of different interdental cleaning devices on gingival bleeding. *J Int Acad Periodontol* 2011: **13**: 2–10.
266. Rosen S, Peters M, Shapouri S. United States Department of Agriculture. International food security assessment, 2010 Update: Improved production mitigated impact of higher food commodity prices. http://www.ers.usda.gov/Publications/GFA2101/,2011.
267. Rosenberg ES, Torosian JP, Slots J. Microbial differences in 2 clinically distinct types of failures of osseointegrated implants. *Clin Oral Implants Res* 1991: **2**: 135–144.
268. Rosling B, Hellström MK, Ramberg P, Socransky SS, Lindhe J. The use of PVP-iodine as an adjunct to nonsurgical treatment of chronic periodontitis. *J Clin Periodontol* 2001: **28**: 1023–1031.
269. Rosling BG, Slots J, Christersson LA, Genco RJ. Topical chemical antimicrobial therapy in the management of the subgingival microflora and periodontal disease. *J Periodontal Res* 1982: **17**: 541–543.
270. Rosling BG, Slots J, Christersson LA, Gröndahl HG, Genco RJ. Topical antimicrobial therapy and diagnosis of subgingival bacteria in the management of inflammatory periodontal disease. *J Clin Periodontol* 1986: **13**: 975–981.
271. Rosling BG, Slots J, Webber RL, Christersson LA, Genco RJ. Microbiological and clinical effects of topical subgingival antimicrobial treatment on human periodontal disease. *J Clin Periodontol* 1983: **10**: 487–514.
272. Rotstein I, Simon JH. Diagnosis, prognosis and decision-making in the treatment of combined periodontal-endodontic lesions. *Periodontol 2000* 2004: **34**: 165–203.
273. Russo PA, Nowzari H, Slots J. Transmission and persistence of *Actinobacillus actinomycetemcomitans* in twins with advanced periodontitis. *J Calif Dent Assoc* 1998: **26**: 290–294.
274. Rutala WA, Cole EC, Thomann CA, Weber DJ. Stability and bactericidal activity of chlorine solutions. *Infect Control Hosp Epidemiol* 1998: **19**: 323–327.
275. Rutala WA, Weber DJ. Uses of inorganic hypochlorite (bleach) in health-care facilities. *Clin Microbiol Rev* 1997: **10**: 597–610.
276. Rybak MJ, McGrath BJ. Combination antimicrobial therapy for bacterial infections. Guidelines for the clinician. *Drugs* 1996: **52**: 390–405.
277. Rylev M, Bek-Thomsen M, Reinholdt J, Ennibi OK, Kilian M. Microbiological and immunological characteristics of young Moroccan patients with aggressive periodontitis with and without detectable *Aggregatibacter actinomycetemcomitans* JP2 infection. *Mol Oral Microbiol* 2011: **26**: 35–51.
278. Sahrmann P, Puhan MA, Attin T, Schmidlin PR. Systematic review on the effect of rinsing with povidone-iodine during nonsurgical periodontal therapy. *J Periodontal Res* 2010: **45**: 153–164.
279. Sakellari D, Goodson JM, Kolokotronis A, Konstantinidis A. Concentration of 3 tetracyclines in plasma, gingival crevice fluid and saliva. *J Clin Periodontol* 2000: **27**: 53–60.
280. Samaranayake LP, Keung Leung W, Jin L. Oral mucosal fungal infections. *Periodontol 2000* 2009: **49**: 39–59.
281. Sanz M, Teughels W. Innovations in non-surgical periodontal therapy: consensus report of the Sixth European Workshop on Periodontology. *J Clin Periodontol* 2008: **35**(Suppl. 8): 3–7.
282. Sarbinoff JA, O'Leary TJ, Miller CH. The comparative effectiveness of various agents in detoxifying diseased root surfaces. *J Periodontol* 1983: **54**: 77–80.
283. Sarita PT, Witter DJ, Kreulen CM, Creugers NH. The shortened dental arch concept-attitudes of dentists in Tanzania. *Community Dent Oral Epidemiol* 2003: **31**: 111–115.

284. Saygun I, Nizam N, Keskiner I, Bal V, Kubar A, Açıkel C, Serdar M, Slots J. Salivary infectious agents and periodontal disease status. *J Periodontal Res* 2011: **46**: 235–239.
285. Schwarz F, Aoki A, Sculean A, Becker J. The impact of laser application on periodontal and peri-implant wound healing. *Periodontol 2000* 2009: **51**: 79–108.
286. Scully C, Greenman J. Halitosis (breath odor). *Periodontol 2000* 2008: **48**: 66–75.
287. Selvaggi G, Monstrey S, van Landuyt K, Hamdi M, Blondeel P. The role of iodine in antisepsis and wound management: a reappraisal. *Acta Chir Belg* 2003: **103**: 241–247.
288. Seymour RA, Hogg SD. Antibiotics and chemoprophylaxis. *Periodontol 2000* 2008: **46**: 80–108.
289. Seymour RA, Rudralingham M. Oral and dental adverse drug reactions. *Periodontol 2000* 2008: **46**: 9–26.
290. Shaddox LM, Walker C. Microbial testing in periodontics: value, limitations and future directions. *Periodontol 2000* 2009: **50**: 25–38.
291. Shiraishi T, Nakagawa Y. Evaluation of the bactericidal activity of povidone-iodine and commercially available gargle preparations. *Dermatology* 2002: **204**(Suppl. 1): 37–41.
292. Simratvir M, Singh N, Chopra S, Thomas AM. Efficacy of 10% Povidone Iodine in children affected with early childhood caries: an in vivo study. *J Clin Pediatr Dent* 2010: **34**: 233–238.
293. Skudutyte-Rysstad R, Eriksen HM, Hansen BF. Trends in periodontal health among 35-year-olds in Oslo, 1973–2003. *J Clin Periodontol* 2007: **34**: 867–872.
294. Slot DE, Kranendonk AA, van der Reijden WA, van Winkelhoff AJ, Rosema NA, Schulein WH, van der Velden U, van der Weijden FA. Adjunctive effect of a water-cooled Nd:YAG laser in the treatment of chronic periodontitis. *J Clin Periodontol* 2011: **38**: 470–478.
295. Slots J. The microflora of black stain on human primary teeth. *Scand J Dent Res* 1974: **82**: 484–490.
296. Slots J. Subgingival microflora and periodontal disease. *J Clin Periodontol* 1979: **6**: 351–382.
297. Slots J. Selection of antimicrobial agents in periodontal therapy. *J Periodontal Res* 2002: **37**: 389–398.
298. Slots J. Update on general health risk of periodontal disease. *Int Dent J* 2003: **53**(Suppl. 3): 200–207.
299. Slots J. Update on human cytomegalovirus in destructive periodontal disease. *Oral Microbiol Immunol* 2004: **19**: 217–223.
300. Slots J. Systemic antibiotics in periodontics. *J Periodontol* 2004: **75**: 1553–1565.
301. Slots J. Herpesviruses in periodontal diseases. *Periodontol 2000* 2005: **38**: 33–62.
302. Slots J. Oral viral infections of adults. *Periodontol 2000* 2009: **49**: 60–86.
303. Slots J. Herpesviral-bacterial interactions in periodontal diseases. *Periodontol 2000* 2010: **52**: 117–140.
304. Slots J. Human viruses in periodontitis. *Periodontol 2000* 2010: **53**: 89–110.
305. Slots J. Herpesvirus periodontitis: infection beyond biofilm. *J Calif Dent Assoc* 2011: **39**: 393–399.
306. Slots J, Emrich LJ, Genco RJ, Rosling BG. Relationship between some subgingival bacteria and periodontal pocket depth and gain or loss of periodontal attachment after treatment of adult periodontitis. *J Clin Periodontol* 1985: **12**: 540–552.
307. Slots J, Feik D, Rams TE. In vitro antimicrobial sensitivity of enteric rods and pseudomonads from advanced adult periodontitis. *Oral Microbiol Immunol* 1990: **5**: 298–301.
308. Slots J, Feik D, Rams TE. Age and sex relationships of superinfecting microorganisms in periodontitis patients. *Oral Microbiol Immunol* 1990: **5**: 305–308.
309. Slots J, Mashimo P, Levine MJ, Genco RJ. Periodontal therapy in humans. I. Microbiological and clinical effects of a single course of periodontal scaling and root planing, and of adjunctive tetracycline therapy. *J Periodontol* 1979: **50**: 495–509.
310. Slots J, Pallasch TJ. Dentists' role in halting antimicrobial resistance. *J Dent Res* 1996: **75**: 1338–1341. Erratum in: *J Dent Res* 1996:75:811.
311. Slots J, Rams TE, Feik D, Taveras HD, Gillespie GM. Subgingival microflora of advanced periodontitis in the Dominican Republic. *J Periodontol* 1991: **62**: 543–547.
312. Slots J, Rams TE, Schonfeld SE. *In vitro* activity of chlorhexidine against enteric rods, pseudomonads and acinetobacter from human periodontitis. *Oral Microbiol Immunol* 1991: **6**: 62–64.
313. Slots J, Rosling BG. Suppression of the periodontopathic microflora in localized juvenile periodontitis by systemic tetracycline. *J Clin Periodontol* 1983: **10**: 465–486.
314. Slots J, Sabeti M, Simon JH. Herpesviruses in periapical pathosis: an etiopathogenic relationship? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003: **96**: 327–331.
315. Slots J, Saygun I, Sabeti M, Kubar A. Epstein-Barr virus in oral diseases. *J Periodontal Res* 2006: **41**: 235–244.
316. Slots J, Slots H. Bacterial and viral pathogens in saliva: disease relationship and infectious risk. *Periodontol 2000* 2011: **55**: 48–69.
317. Slots J, Ting M. *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* in human periodontal disease: occurrence and treatment. *Periodontol 2000* 1999: **20**: 82–121.
318. Slots J, Ting M. Systemic antibiotics in the treatment of periodontal disease. *Periodontol 2000* 2002: **28**: 106–176.
319. Smerdely P, Lim A, Boyages SC, Waite K, Wu D, Roberts V, Leslie G, Arnold J, John E, Eastman CJ. Topical iodine-containing antiseptics and neonatal hypothyroidism in very-low-birthweight infants. *Lancet* 1989: **2**(8664): 661–664.
320. Snow P, McNally ME. Examining the implications of dental treatment costs for low-income families. *J Can Dent Assoc* 2010: **76**: a28.
321. Socransky SS, Haffajee AD. Evidence of bacterial etiology: a historical perspective. *Periodontol 2000* 1994: **5**: 7–25.
322. Socransky SS, Haffajee AD. Dental biofilms: difficult therapeutic targets. *Periodontol 2000* 2002: **28**: 12–55.
323. Socransky SS, Haffajee AD. Periodontal microbial ecology. *Periodontol 2000* 2005: **38**: 135–187.
324. Socransky SS, Haffajee AD, Dzink JL. Relationship of subgingival microbial complexes to clinical features at the sampled sites. *J Clin Periodontol* 1988: **15**: 440–444.
325. Soukos NS, Goodson JM. Photodynamic therapy in the control of oral biofilms. *Periodontol 2000* 2011: **55**: 142–166.
326. Spratt DA, Pratten J, Wilson M, Gulabivala K. An in vitro evaluation of the antimicrobial efficacy of irrigants on biofilms of root canal isolates. *Int Endod J* 2001: **34**: 300–307.

327. Stabholz A, Soskolne WA, Shapira L. Genetic and environmental risk factors for chronic periodontitis and aggressive periodontitis. *Periodontol 2000* 2010: **53**: 138–153.
328. Stagno S, Pass RF, Thomas JP, Navia JM, Dworsky ME. Defects of tooth structure in congenital cytomegalovirus infection. *Pediatrics* 1982: **69**: 646–648.
329. Stahlmann R, Lode H. Toxicity of quinolones. *Drugs* 1999: **58**(Suppl. 2): 37–42.
330. Stamatova I, Meurman JH. Probiotics and periodontal disease. *Periodontol 2000* 2009: **51**: 141–151.
331. Stambaugh RV, Dragoo M, Smith DM, Carasal L. The limits of subgingival scaling. *Int J Periodontics Restorative Dent* 1981: **1**: 30–41.
332. Stanford TW, Rees TD. Acquired immune suppression and other risk factors / indicators for periodontal disease progression. *Periodontol 2000* 2003: **32**: 118–135.
333. Sun J, Song X, Kristiansen BE, Kjaereng A, Willems RJ, Eriksen HM, Sundsfjord A, Sollid JE. Occurrence, population structure, and antimicrobial resistance of enterococci in marginal and apical periodontitis. *J Clin Microbiol* 2009: **47**: 2218–2225.
334. Sunde PT, Olsen I, Enersen M, Grinde B. Patient with severe periodontitis and subgingival Epstein–Barr virus treated with antiviral therapy. *J Clin Virol* 2008: **42**: 176–178.
335. Surathu N, Arun KV. Traditional therapies in the management of periodontal disease in India and China. *Periodontol 2000* 2011: **56**: 11–24.
336. Susin C, Albandar JM. Aggressive periodontitis in an urban population in southern Brazil. *J Periodontol* 2005: **76**: 468–475.
337. Tabanella G, Nowzari H, Slots J. Clinical and microbiological determinants of ailing dental implants. *Clin Implant Dent Relat Res* 2009: **11**: 24–36.
338. Taichman NS, Simpson DL, Sakurada S, Cranfield M, DiRienzo J, Slots J. Comparative studies on the biology of *Actinobacillus actinomycetemcomitans* leukotoxin in primates. *Oral Microbiol Immunol* 1987: **2**: 97–104.
339. Taiyeb-Ali TB, Cheta Raman PC, Vaithilingam RD. Relationship between periodontal disease and diabetes mellitus: an Asian perspective. *Periodontol 2000* 2011: **56**: 258–268.
340. Takasaki AA, Aoki A, Mizutani K, Schwarz F, Sculean A, Wang CY, Koshy G, Romanos G, Ishikawa I, Izumi Y. Application of antimicrobial photodynamic therapy in periodontal and peri-implant diseases. *Periodontol 2000* 2009: **51**: 109–140.
341. Teles RP, Haffajee AD, Socransky SS. Microbiological goals of periodontal therapy. *Periodontol 2000* 2006: **42**: 180–218.
342. Teughels W, Van Essche M, Sliepen I, Quirynen M. Probiotics and oral healthcare. *Periodontol 2000* 2008: **48**: 111–147.
343. Thiha K, Takeuchi Y, Umeda M, Huang Y, Ohnishi M, Ishikawa I. Identification of periodontopathic bacteria in gingival tissue of Japanese periodontitis patients. *Oral Microbiol Immunol* 2007: **22**: 201–207.
344. Thomson WM, Sheiham A, Spencer AJ. Sociobehavioural aspects of periodontal disease. *Periodontol 2000* 2012: **60**: 54–63.
345. Torfason T, Kiger R, Selvig KA, Egelberg J. Clinical improvement of gingival conditions following ultrasonic versus hand instrumentation of periodontal pockets. *J Clin Periodontol* 1979: **6**: 165–176.
346. Tribble GD, Lamont RJ. Bacterial invasion of epithelial cells and spreading in periodontal tissue. *Periodontol 2000* 2010: **52**: 68–83.
347. Tut OK, Milgrom PM. Topical iodine and fluoride varnish combined is more effective than fluoride varnish alone for protecting erupting first permanent molars: a retrospective cohort study. *J Public Health Dent* 2010: **70**: 249–252.
348. Umeda M, Takeuchi Y, Noguchi K, Huang Y, Koshy G, Ishikawa I. Effects of nonsurgical periodontal therapy on the microbiota. *Periodontol 2000* 2004: **36**: 98–120.
349. United Nations. *World population prospects: the 2008 revision*. Geneva: Population Division of the Department of Economic and Social Affairs, United Nations, 2010.
350. U.S. Department of Health and Human Services. Agency for Toxic Substances and Disease Registry. *Toxicological profile for phenol*. September 2008.
351. van Assche N, van Essche M, Pauwels M, Teughels W, Quirynen M. Do periodontopathogens disappear after full-mouth tooth extraction? *J Clin Periodontol* 2009: **36**: 1043–1047.
352. van der Weijden F, Slot DE. Oral hygiene in the prevention of periodontal diseases: the evidence. *Periodontol 2000* 2011: **55**: 104–123.
353. van Winkelhoff AJ, Rams TE, Slots J. Systemic antibiotic therapy in periodontics. *Periodontol 2000* 1996: **10**: 45–78.
354. Vanek D, Saxena A, Boggs JM. Fluoroquinolone therapy and Achilles tendon rupture. *J Am Podiatr Med Assoc* 2003: **93**: 333–335.
355. Vernazza C, Heasman P, Gaunt F, Pennington M. How to measure the cost-effectiveness of periodontal treatments. *Periodontol 2000* 2012: **60**: 138–146.
356. von Ohler C, Weiger R, Decker E, Schlagenhauf U, Brecx M. The efficacy of a single pocket irrigation on subgingival microbial vitality. *Clin Oral Investig* 1998: **2**: 84–90.
357. Waerhaug J. Healing of the dento-epithelial junction following subgingival plaque control. II. As observed on extracted teeth. *J Periodontol* 1978: **49**: 119–134.
358. Walker CB. Selected antimicrobial agents: mechanisms of action, side effects and drug interactions. *Periodontol 2000* 1996: **10**: 12–28.
359. Walker CB. The acquisition of antibiotic resistance in the periodontal microflora. *Periodontol 2000* 1996: **10**: 79–88.
360. Walker CB, Karpinia K, Baehni P. Chemotherapeutics: antibiotics and other antimicrobials. *Periodontol 2000* 2004: **36**: 146–165.
361. Walmsley AD, Lea SC, Landini G, Moses AJ. Advances in power driven pocket / root instrumentation. *J Clin Periodontol* 2008: **8**(Suppl.): 22–28.
362. Walter C, Kaye EK, Dietrich T. Active and passive smoking: assessment issues in periodontal research. *Periodontol 2000* 2012: **58**: 84–92.
363. Warnakulasuriya S. Demand for dental care in Sri Lanka. *Community Dent Oral Epidemiol* 1985: **13**: 68–69.
364. Watt RG, Marinho VC. Does oral health promotion improve oral hygiene and gingival health? *Periodontol 2000* 2005: **37**: 35–47.

365. Watt RG, Petersen PE. Periodontal health through public health- the case for oral health promotion. *Periodontol 2000* 2012: **60**: 147–155.
366. Watts A, Addy M. Tooth discolouration and staining: a review of the literature. *Br Dent J* 2001: **190**: 309–316.
367. Wennström JL, Heijl L, Dahlén G, Gröndahl K. Periodic subgingival antimicrobial irrigation of periodontal pockets (I). Clinical observations. *J Clin Periodontol* 1987: **14**: 541–550.
368. West NX, Moran JM. Home-use preventive and therapeutic oral products. *Periodontol 2000* 2008: **48**: 7–9.
369. Westergaard J, Frandsen A, Slots J. Ultrastructure of the subgingival microflora in juvenile periodontitis. *Scand J Dent Res* 1978: **86**: 421–429.
370. Wikesjö UM, Reynolds HS, Christersson LA, Zambon JJ, Genco RJ. Effects of subgingival irrigation on *A. actinomycetemcomitans*. *J Clin Periodontol* 1989: **16**: 116–119.
371. Williams DW, Kuriyama T, Silva S, Malic S, Lewis MAO. *Candida* biofilms and oral candidosis: treatment and prevention. *Periodontol 2000* 2011: **55**: 250–265.
372. Wilson TG. Compliance and its role in periodontal therapy. *Periodontol 2000* 1996: **12**: 16–23.
373. Wirthlin MR, Marshall GW Jr. Evaluation of ultrasonic scaling unit waterline contamination after use of chlorine dioxide mouthrinse lavage. *J Periodontol* 2001: **72**: 401–410.
374. Witter DJ, van Elteren P, Käyser AF, van Rossum GM. Oral comfort in shortened dental arches. *J Oral Rehabil* 1990: **17**: 137–143.
375. The World Bank. Poverty data: A supplement to World Development indicators 2008. WDI08 2008: suppl. 1216: 1–26. (http://siteresources.worldbank.org/DATASTATISTICS/Resources/WDI08supplement1216.pdf).
376. Worthington H, Needleman I. Evidence-based periodontal disease prevention and treatment: introduction. *Periodontol 2000* 2005: **37**: 9–11.
377. Wu CD, Darout IA, Skaug N. Chewing sticks: timeless natural toothbrushes for oral cleansing. *J Periodontal Res* 2001: **36**: 275–284.
378. Wu CD, Savitt ED. Evaluation of the safety and efficacy of over-the-counter oral hygiene products for the reduction and control of plaque and gingivitis. *Periodontol 2000* 2002: **28**: 91–105.
379. Ximénez-Fyvie LA, Haffajee AD, Som S, Thompson M, Torresyap G, Socransky SS. The effect of repeated professional supragingival plaque removal on the composition of the supra- and subgingival microbiota. *J Clin Periodontol* 2000: **27**: 637–647.
380. Yates R, Moran J, Addy M, Mullan PJ, Wade WG, Newcombe R. The comparative effect of acidified sodium chlorite and chlorhexidine mouthrinses on plaque regrowth and salivary bacterial counts. *J Clin Periodontol* 1997: **24**: 603–609.
381. Yazdankhah SP, Scheie AA, Høiby EA, Lunestad BT, Heir E, Fotland TØ, Naterstad K, Kruse H. Triclosan and antimicrobial resistance in bacteria: an overview. *Microb DrugResist* 2006: **12**: 83–90.
382. Zajacova A, Dowd JB, Aiello AE. Socioeconomic and race/ethnic patterns in persistent infection burden among U.S. adults. *J Gerontol A Biol Sci Med Sci* 2009: **64**: 272–279.
383. Zambon JJ, Haraszthy VI. The laboratory diagnosis of periodontal infections. *Periodontol 2000* 1995: **7**: 69–82.
384. Zamora JL, Price MF, Chuang P, Gentry LO. Inhibition of povidone-iodine's bactericidal activity by common organic substances: an experimental study. *Surgery* 1985: **98**: 25–29.
385. Zehnder M. Root canal irrigants. *J Endod* 2006: **32**: 389–398.
386. Zhang J, Sun X, Xiao L, Xie C, Xuan D, Luo G. Gene polymorphisms and periodontitis. *Periodontol 2000* 2011: **56**: 102–124.
387. Zou L, Shen Y, Li W, Haapasalo M. Penetration of sodium hypochlorite into dentin. *J Endod* 2010: **36**: 793–796.