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Prophylactic and therapeutic application of antimicrobial agents in the oral cavity

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Antimicrobial substances are used for many prophylactic and therapeutic reasons in the oral cavity. They are used as mouthrinses, for the irrigation of specific oral locations, in form of gels, or varnishes. Different antimicrobial agents are available and some preparations are complex compositions of these compounds. Although it has been proven that several agents are suited to achieve a considerable reduction of oral microorganisms many questions concerning the clinical benefit are yet to be answered. This report summarises the evidence of the efficacy of oral antiseptics (especially chlorhexidine, pvp-iodine, and Listerine®) depending on different indications, which is the basis for clinical and practical recommendations.

1. Introduction

Antiseptics are used for various prophylactic and therapeutic reasons in the cavity. They are used as mouthrinses, for the irrigation of specific oral locations (e.g. the sulcus gingivalis), or in form of gels or varnishes. Different antimicrobial agents are available and some preparations are complex compositions of these compounds. Besides chlorhexidine, which has become the golden standard in view to plaque and gingivitis, other antimicrobials are applied in the oral cavity (Table 1).
This report summarises the evidence of the efficacy of oral antiseptics depending on different indications.

2. Reducing bacteremia due to oral surgery

It is well known that tooth extractions may cause bacteremia; literature data vary between 30% and 85% depending on the specific surgical operation, oral hygiene status, and the technique applied to identify bacteria in the blood [1, 2]. However, bacteremia does not only occurr during tooth extractions but also during the mechanical cleansing of the teeth and the interdental spaces (Table 2).
As a result it can be estimated that operations which do not touch the gingival sulcus cause bacteremia in 10–35%, whereas tooth extractions, injections, or dental scaling induce bacteremia in more than 50% of the treated patients [3].

Table 1: Antiseptic compounds used in oral mouthrinses, gels, or varnishes

Class of antimicrobial agent	Compound
Guanidine	Chlorhexidine Alexidine
Halogenes	PVP-iodine Tosylchloramidsodium (Chloramine T)
Cationic compounds	Cetylpyridiniumchloride Benzalkoniumchloride
Pyrimidine	Hexetidine
Bispyridine	Octenidindihydrochloride
Diphenylether	Triclosan
Fluoride	Aminfluoride, Tinfluoride
Others	Listerine® (cont.: thymol, menthol, eucalyptol and methylsalicylacid in a fix combination)

Several investigations have demonstrated the ability of oral mouthrinses to reduce these bacteremias (Fig. 1). However, it is doubtful if oral mouthrinses alone without additional treatment of the gingival sulcus are suited for the reduction of bacteremias following tooth extraction. Rinsing the oral cavity with chlorhexidine for example did not reduce post-extraction bacteremia [4, 5]. These findings are supported by Pitcher et al., who demonstrated by means of a coloured rinse that oral rinsing alone does not reach the subgingival plaque, which is achieved if the gingival sulcus is irrigated [6].
In accordance with these data increased effects concerning the reduction of bacteremia are reported if the gingival sulcus is irrigated in addition to an oral rinse (Fig. 2) [7].
The efficacy of a sulcus gingivalis irrigation prior to tooth extraction using PVP-iodine has been demonstrated (Fig. 2). The same is true for the application of Listerine if rinsing and irrigation are combined [8]. Chlorhexidine was less effective than PVP-iodine (Fig. 2), and hydrogen peroxide or cetylpyridiniumchloride had no significant effect [9, 10].
Although the clinical relevance of post-extraction bacteremia is discussed controversially, various societies recommend a prophylactic treatment prior to dental surgery for patients at risk of endocarditis [11–13]. These recommendations focus on the application of systemic antibiotics, the additional use of local antimicrobial agents was not considered [14–15]. Since the reduction of bacteremia by locally applied antiseptics is beyond any doubt, the additional use of these agents seems to be promising and is recommended by several organisations [2, 12]. Agent of choice for this particular indication is PVP-iodine. In the case of contra-indications chlorhexidine-based preparations or Listerine may be used instead. However, oral rinsing

Table 2: Frequency of bacteremia in different situations [2]

Situation	Cases under consideration	Frequency of bacteremia	
		A*	B*
Brushing teeth	385	0%	26%
Usage of dental floss	22	20%	58%
Usage of tooth picks	20	20%	40%
Usage of oral irrigator	90	7%	50%

* Gingival inflammation or trauma is moderate (A) or severe (B)

should be combined with an irrigation of the sulcus gingivals for example by ultrasonic scalers.

3. Prevention of wound infections following oral surgery

A professional tooth cleansing which includes the treatment of cariogenic lesions, gingivitis and periodontal pockets before elective surgery in the oral cavity is carried out is strongly recommended [16]. By means of additional application of antiseptic mouthrinses or varnishes 2 d prior to the surgical treatment until 2 d after removal of the suture material disturbances of the wound healing as well as wound pain may be reduced [17]. Chlorhexidine and Listerine seem to be equally efficient for this purpose [18, 19].

4. Reducing infectious aerosols in dentistry

The removal of supragingival and subgingival plaque generates aerosoles which transport microorganisms from the patient's oral cavity into the ambient air. Depending on the size of the droplets and particles these microorganisms can float in the air for hours. If they are not removed by a suction device or an adequate air exchange, they sediment and contaminate surfaces, unprotected instruments, and medical devices. Under particular conditions the aerosols contain considerably high counts of bacteria, similar to that found for coughing or sneezing [20]. Mohammed et al. demonstrated already in 1964, that the emission of microorganisms during dental procedures like scaling can be reduced significantly by means of an oral antimicrobial rinse [21]. Later studies affirmed this effect for cetylpyridiniumchloride [22] and Listerine [23, 24].
Therefore antiseptic mouthrinses prior to dental treatment are recommended by various authors [25, 26] and are meanwhile part of the "Clinical Guidelines for Infection Control in Dental Education Institutions" in the USA [27].

5. Preventing plaque and gingivitis

Numerous studies have investigated the efficacy of antiseptic mouthrinses to prevent plaque and gingivitis. Comparing these investigations it becomes obvious that daily rinsing with chlorhexidine [28, 29] or Listerine [30–32] provides a clear clinical benefit in regard to gingival health. If Listerine is directly compared with chlorhexidine, the latter provides better clinical results [33, 34]. However, before the daily use of antimicrobials for mouthrinses can be recommended, toxic side effects have to be excluded.
Several investigations have been carried out to identify side-effects which may occurr if chlorhexidine is used for a period of 2 years [35, 36]. Although only few negative

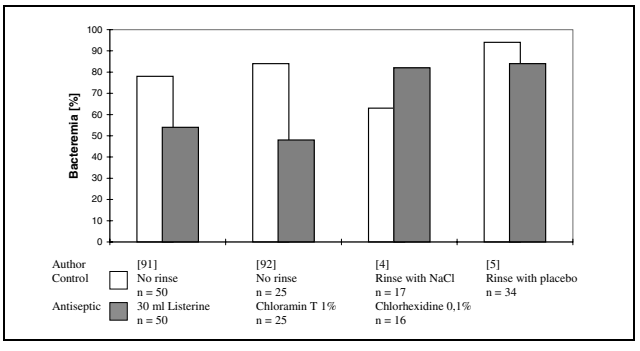

Fig. 1: Bacteremia following tooth extraction and a previously applied antiseptic mouthrinse

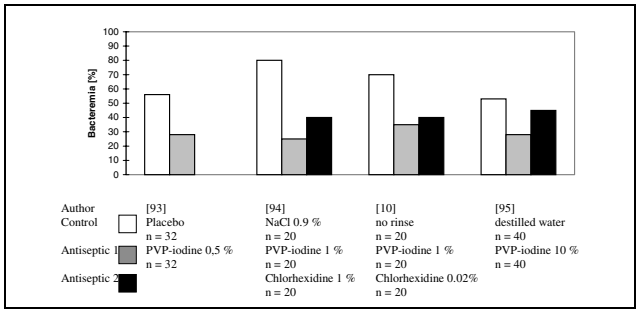

Fig. 2: Bacteremia following tooth extraction and a previously applied antiseptic mouthrinse combined with a sulcus gingivalis irrigation

effects were reported in these studies, it is strongly recommended to use the substance for a limited period of time even in countries, where it is available without prescription [37]. The most common side-effect of chlorhexidine is the so-called staining of teeth, tongue, and gingiva, which is probably caused by interactions with compounds of the nutrition (e.g. pigments in tea). Although this staining is completely reversible, it is an important argument against the daily use of chlorhexidine in mouthwashes [33, 38]. Other arguments are taste irritations, mutagenicity *in vitro* and in animal experiments [39], the induction of premalignant alterations, as well as neurotoxicity and the risk of anaphylactic reactions [40, 41].
Octenidindihydrochlorid exerts a strong antimicrobial effect in the oral cavity [42] and some studies indicate an anti-plaque activity [43, 44]. However, the agent has a very bitter taste and is not yet available as an oral mouth rinse [45].
In contrast, Listerine is quite untoxic and has an acceptable taste, but it also has a weak antimicrobial impact [45].
PVP-iodine has a strong immediate antimicrobial efficacy but seems to be of little value for the prevention of dental plaque [46–48].
The data about cetylpyridiniumchloride indicate a benefit in terms of plaque prevention, but the effects are smaller than those reported for chlorhexidine [49].
Triclosan [50, 51], hexetidine, [52], and the fixed combination aminfluorid/tinfluorid [53, 54] are of limited value in the prevention of plaque and gingivitis
As a conclusion it can be summarised that chlorhexidine remains the agent of choice if prophylaxis or treatment of plaque or gingivitis are desired for a limited period of time (e.g. during inability to clean the teeth mechanically due to mental disorder, high age, immobilisation of the mandibula etc.). However, daily rinsings as an adjunct to oral routine hygiene cannot be recommended because this would require that no side-effects at all occurr even if the antiseptic is used for several years.

6. Caries prevention with chlorhexidine

The importance of antimicrobial agents for caries prevention is growing. Parallel to a strong caries decline in the industrialised countries, caries prevalence in children and adolescents is becoming more polarised: About one quarter of the children exhibit 80% of the carious lesions and 80% of carious lesions is concentrated on molars [55]. In these cases, the conventional preventive measures such as oral hygiene training and fluoride usage are not effective enough. In contrast to this, chlorhexidine mouth rinses, varnish or gel applications achieve caries reductions of an average of 42% [56]. As caries is a site-specific disease varnishes can be applied at much lower doses and with fewer side effects than mouth rinses. Studies on a 1%

chlorhexidine and 1% thymol varnish (Cervitec/Vivadent) showed 76% fewer fissure caries in molars, 43% caries reduction in highly caries active children, 82% less mineral loss, and a 77% reduction of lesion depth in root caries [57–59]. Quarterly gel tray applications (1%) or gel brushing for intervals of 14 days reduced caries incidence in highly caries active children by up to 81% [56, 60]. Quarterly applications of varnish or gel seem to be sufficient, since recolonisation of cariogenic plaque needs up to 3 months [61, 62].
In summary, quarterly chlorhexidine gel or varnish applications should be used for patients or teeth with high caries risk, such as erupting teeth, active initial carious lesions, patients with high counts of *Streptococcus mutans*, root caries, or early childhood caries.

7. Maintaining oral hygiene in immunosuppressed patients

Patients treated with chemotherapy due to cancer and leucemia are immunosuppressed and have a considerable risk of infection, especially patients undergoing bone marrow transplantation because they become leucopenic for several days. Some patients are pancytopenic and, therefore, unable to clean their teeth mechanically since they might induce severe bleeding by tooth brushing. Some investigators estimate that 30–40% of all septicemias in cancer patients during chemotherapy are caused by microorganisms from the oral cavity [63–65]. In spite of these facts, there is no agreement concerning a recommendation how to maintain oral hygiene during chemotherapy [66, 67].
However, it is recommended to assess dental health prior to elective chemotherapy and to remove dental plaque by a professional in addition to the instructions for home-care [68–70]. Starting chemotherapy an oral antiseptic should be applied after meals and before sleeping. For this purpose an antiseptic agent with a strong remanent efficacy and high tolerability is desired.
Conflicting results are reported from authors using chlorhexidine in clinical studies. Since few patients were considered in these studies and other conditions concerning the application of the oral rinses (concentration of antimicrobial agent, frequency of daily rinsings) varied, it is difficult to compare the results. Some investigators observed a positive effect on mucositis, gingivitis, and plaque development if chlorhexidine was applied [71–73], others did not report a benefit [74–76].
Some authors found a microbial shift with an increase of gramnegative bacteria [73, 77]. Wahlin detected even an increase of *Pseudomonas* spp. [74], but these results were not significant.
However, at present only the application of chlorhexidine following a professional removal of dental plaque is investigated to prevent infections which may be caused by microorganisms of the oral cavity in chemotherapy patients. Due to the conflicting results of the studies with chlorhexidine, a clear recommendation cannot be given at present. Since side-effects and costs of oral antiseptics are very small, and the possible benefit for the patients is considerable, further studies including more patients and different antiseptic preparations are required.

8. Preventing and treating mucositis due to chemotherapy and radiotherapy

During local radiation therapy of cancer in the oral cavity or the oropharynx the mucous membranes are colonised with various non-indigenous mircroorganisms. Some of these microorganisms, e.g. *C. albicans*, can cause severe local infections and even septicemia, if they are not treated successfully. Therefore, rinsing of the oral cavity with an antiseptic seems to be promising.
It is difficult to give general recommendations for the application in this specific clinical situation, since only few studies have been carried out to elucidate the problem. Most investigators used chlorhexidine, but the results show that the benefit of this agent to alleviate mucositis is doubtful [78].
Foote reported even an increase of mucositis and severe disturbances of the sense of taste concluding that chlorhexidine is not suited for patients undergoing radiotherapy [79]. It is assumed that chlorhexidine does not exert its remanent antimicrobial effect because it cannot adhere to glycoproteins and mucins of the saliva since these patients suffer from severe xerostomia [77].
Other authors investigated benzydamine, a non-steroidal antiphlogistic with moderate antimicrobial activity, in these patients [80]. Samaranayake et al. observed no difference between benzydamine and chlorhexidine in view to mucositis, pain, and oral carriage of non-indigenous microorganisms [81].
Rahn [82] compared a PVP-iodine mouthrinse with sterile water in patients undergoing a combined radiochemotherapy because of head-and-neck cancer. In the active group 14/20 patients developed mucositis, whereas all patients (20/20) in the control group showed mucositis. Since the mucositis was considerably more severe in the control group, the application of PVP-iodine seems to be more effective in these patients and is accepted as a new indication by the German administration for drug safety (Bundesamt für Arzneimittelsicherheit).
However, summarising the published studies, the question how to prevent mucositis in radiotherapy patients is not sufficently answered yet.

9. Oral hygiene in artificially respirated patients

Respirated patients need a thorough oral hygiene because they are immunosuppressed (indepently from their basic diagnosis) and the natural cleaning mechanisms of the oral cavity and the oropharynx are disturbed due to reduced salivation. In addition, the mechanical cleansing of the patient's teeth is difficult for the nursing staff if the patient is intubated oropharyngeally. Another factor inreasing the patient's risk of infection is the high prevalence of gram-negative bacteria at most intensive care units and the application of antibiotics which disturb the indigenous flora of the mucous membranes. A frequently observed result of these predisposing factors is the colonisation of the oropharynx with *C. albicans* which can be the starting point of systemic complications.
Although the application of antiseptic mouthrinses seems to be very promising for these patients, up to now only few studies have been carried out to enlighten these problems.
DeRiso et al. assessed the benefit of a 0.12% chlorhexidine mouthrinse in 353 cardiosurgical patients at an intensive care unit in a double-blind, placebo-controlled study [83]. They reported a reduction of respiratory infections of 69% in the active group and a significant reduction of mortality (1.16% vs. 5.56% in the placebo group).
Therefore, the benefit of an oral antiseptic treatment of artificially respirated patients can be expected, but this evidence is quite weak, because it is based only on one study. It cannot be excluded that other antiseptics are bet-

ter suited for this purpose than chlorhexidine, and further studies are required to give clear recommendations on this issue.

10. Improving oral health conditions in elderly and handicapped persons

Some conditions make it almost impossible for the patients to maintain sufficient daily oral hygiene. This may be the case e.g. after polytrauma, in old age or due to mental disorder. These circumstances can justify the daily application of oral antiseptic mouthrinses to prevent plaque and gingivits.

Persson reported considerable benefit from daily as well as weekly rinsings with chlorhexidine in 42 elderly subjects [84]. The observed side-effects were acceptable, since only one person developed moderate staining after a 6-week period of daily rinsings. Surprisingly the daily rinsings were not significantly more efficent than the weekly application of the antiseptic.

The positive effects of daily rinsings in elderly patients are supported by an investigation of Yanover et al. who assessed the application of a daily rinsing with 10 ml chlorhexidine (0.2%) over a 6-month-period.

Positive results and very little side-effects are described by other authors who applied chlorhexidine in handicapped patients [85, 86].

Altogether, there is sufficient evidence to recommend the application of chlorhexidine for patients who are unable to carry out consequent daily oral hygiene. This is true for handicapped or elderly persons as well as for patients in specific clinical conditions, e.g. patients with an intermaxillary immobilisation due to fracture of the maxilla or mandibula.

However, chlorhexidine should not be applied for an unlimited period of time in daily mouth rinsings, since negative side-effects can never be excluded.

11. Antiseptic treatment of the mucous membranes prior to intraoral anesthesia

From a theoretical point of view a benefit of an antiseptic treatment of the mucous membranes prior to injections (e.g. prior to local anesthesia) may be expected. Since clinical data, which allow a comparison of the frequency of wound infections following intraoral injections with and without previous application of an antiseptic are not available, an evaluation of this treatment is impossible. However, the same is true for the application of skin antiseptics prior to intravenous injections: Controlled clinical studies showing an advantage of skin antiseptic prior to injections do not exist, but nobody doubts that skin antiseptic is useful and should be carried out.

Surface anaesthetics exert a moderate antimicrobial activity, but this effect is too weak to substitute an antiseptic treatment of mucous membranes [87].

12. Antiseptic treatment of the root canal

Clinical studies which prove a benefit of an antiseptic treatment of the root canal in terms of reducing postoperative infections are missing. On the other hand, in vitro studies showed significant reductions of bacteria in root canals and an irrigation solution is needed for the mechanical removal of loose debris [88, 89]. Therefore, endodontic treatment consists of a combination of mechanical and chemical cleansing of the root canal. Usually sodium hypochlorite or chlorhexidine solutions are applied to disinfect the root canal. Sodium hypochlorite also dissolves remaining pulpal tissue due to its proteolytic properties. Hydrogen peroxide should not be used because of its weak antimicrobial impact.

13. Conclusions

At present the following indications for the application of oral antiseptics can be summarised.

13.1. Applications with clear evidence based on controlled clinical studies

- Daily rinsings to support oral hygiene for a limited period of time in specific situations (e.g. during immunosuppression)
- To reduce plaque development and prevent gingivitis if proper mechanical cleansing of the teeth is not possible
- Quarterly chlorhexidine gel or varnish applications for teeth with high caries risk, such as erupting teeth, active initial carious lesions, patients with high counts of *Streptococcus mutans*, root caries, or early childhood caries

13.2. Applications with clear evidence from reports other than clinical studies or theoretical reasons

- To maintain oral hygiene in case of intermaxillar immobilisation (e.g. due to fracture of the jaw)
- Prior to or during dental treatment to reduce the generation of microbial aerosoles
- To prevent or reduce bacteremia in patients at risk of endocarditis (by rinsing and irrigation of the sulcus gingivalis) in combination with systemic prophylaxis
- To prevent infections in immunosuppressed patients (e.g. during chemotherapy or at intensive care units)
- First aid after accidental contamination of the oral cavity [90]

13.3. Applications with limited evidence but theoretical background

- Prior to and after intraoral surgery
- To prevent infections in artificially respirated patients
- To alleviate mucositis during radiotherapy or chemotherapie of head-and-neck cancer
- Prior to injections into the oral mucous membranes (e.g. for anesthesia)
- Prior to treatment of the root canal (e.g. filling)

13.4. Possible applications which have not been assessed yet

- Treatment of persons carrying multiresistant microorganisms (e.g. oropharyngeal colonisation with methicillin-resistant *S. aureus*)

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