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Antimicrobial Mouthwashes: An Overview of Mechanisms—What Do We Still Need to Know?

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ABSTRACT

This narrative literature review is the first in a 6-section supplement on the role of mouthwashes in oral care. This introduction briefly summarises current knowledge on antimicrobial mechanisms, relating to some of the most common over-the-counter mouthwash products available worldwide: chlorhexidine, hydrogen peroxide, cetylpyridinium chloride, povidone iodine, and essential oils. The aim of this first article is to describe how mouthwashes "kill" pathogenic microbes when used adjunctively and thus provide a basis for their widespread use to manage key oral diseases, namely caries, gingivitis, and periodontal disease. This article therefore sets the scene for subsequent, more detailed exploration of mouthwashes regarding their clinical effectiveness, impact on the oral microbiome, and possible effects on systemic health as well as natural alternatives and future directions. Other than the clinical effectiveness (for certain agents) of mouthwashes, on many topics there remains insufficient evidence for systematic review or formulation of robust national guidelines. The supplement, therefore, compiled by an international task team, is aimed at general dental practitioners across the globe, as an easy-to-read guide for helping to advise patients on mouthwash use based on the current best available evidence.

Background

The sales of antimicrobial mouthwashes are big business worldwide, available over-the-counter (OTC) or via prescription from dental practitioners, as part of the armoury against a variety of oral diseases caused by bacteria, viruses, and fungi that exist on oral hard and soft tissues. Fluoride mouthwashes are also widely used to improve remineralisation of hard tissues and prevent dental decay (caries). Currently available antimicrobial mouthwashes may "kill" pathogenic bacteria (bactericidal), whilst others may prevent bacterial growth (bacteriostatic) and the formation of biofilms (important for the formation of plaque), which contribute to dental caries, gingivitis, and periodontal disease. Their bactericidal approach is supported by decades of research, whereby antimicrobial agents studied in vitro or ex vivo destroyed bacteria at clinically usable concentrations. Subsequently, these agents have been used clinically, largely without toxicity to the host, to manage oral disease; that is, they are antiseptic.

A huge variety of chemical and natural antiseptic mouthwashes are currently available OTC to help manage bad breath (halitosis), dental decay, and gum disease, often used daily without the intervention of a dental clinician. These include chlorhexidine (CHX), hydrogen peroxide (H_2O_2), cetylpyridinium chloride (CPC), povidone iodine (PVP-I), and essential oils (EO). A common mechanism by which pathogenic bacteria are killed by many antimicrobial mouthwashes via by destruction of the microbe cell wall resulting in cell death. However, the mechanisms to achieve this by each commercially available mouth rinse may differ and will be introduced here. It is often assumed that antimicrobial mouthwashes work in a similar way against viruses, but much less is known about the antiviral properties of mouthwashes. It also remains surprising that few mouthwash studies have been performed in vivo, with lack of systematic reviews and national and international guidelines to advise the general public and dental practitioners across the globe on when and how to use mouthwashes. The aim of this supplement is therefore to provide dental clinicians with a greater understanding on the mechanisms of action and

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effectiveness of mouthwashes on microbes associated with oral disease by presenting the best current available evidence.

There is strong evidence, summarised via systematic review, that commonly used mouthwashes can reduce plaque and gingivitis, with CHX arguably being the most effective; thus, the effectiveness of CHX will be assessed in this supplement.[1–5] However, many antiseptic mouthwashes appear to be less effective with more severe forms of gum disease,[6] perhaps because mouthwashes used alone cannot reach the depth of the periodontal pockets where the anaerobic bacteria associated with periodontal disease reside. There is also strong evidence that sodium fluoride mouthwashes (NaF; 0.05% daily rinse or 2% daily rinse by prescription) can be used successfully for the management of dental caries, by increasing remineralisation of enamel.[7] With these proposed benefits, it is not surprising that people use OTC mouthwashes in their self-management of the first signs of dental decay, bleeding gums, or bad breath (halitosis). However, right from the outset, it must be emphasised that good oral hygiene practices should not rely on the use of oral antiseptics alone and their long-term use should be discouraged, due to possible adverse effects on oral and systemic health, discussed later in this supplement. Mouthwashes may also fail to be effective without accompanying tooth brushing, interdental cleaning, and professional plaque removal. Indeed, most guidelines across the globe recommend the use of mouthwashes as an "adjunct" to good oral hygiene,[8,9] leading to some small but significant clinical benefits in reduction of periodontal pocket depth, plaque, and bleeding scores.[6] Thus, most of the benefits this supplement describes henceforth must be considered in the context of this adjunctive use.

Commonly used mouthwashes, their constituents, and mechanisms

Chlorhexidine

Chlorhexidine has been used extensively in dentistry and medicine and is available OTC used as an antiseptic mouth rinse (0.12% and 0.2%) as well as used as a surface disinfectant (0.2%) > (2%) in dental care settings. It is a bis-biguanide agent with broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria, plus fungi and certain viruses. The antimicrobial effect of chlorhexidine is dose-dependent, being bacteriostatic at low concentrations of 0.02% to 0.06% and bactericidal at high concentrations of greater than 0.12%.[11] Biguanide compounds interact with negatively charged microbial cell membranes, disrupting the structure leading to spillage of cell contents; they can also penetrate the cell, condensing bacterial chromosomes and blocking DNA replication.[10] The initial use of chlorhexidine in dentistry was as a presurgical disinfection of the mouth, and it generally has low toxicity in humans (unless swallowed in large amounts), but it has common adverse reactions including temporary taste alteration and brown discolouration of the teeth and tongue.[10] However, new chlorhexidine mouthwashes are now available with antidecolouration systems that purportedly avoid staining, whilst also reducing plaque and gingivitis.[12]

As described, there is abundant robust evidence supporting the antibacterial, antiplaque, and antigingivitis effects of CHX mouthwash,[1] and the best available evidence for its effectiveness as an adjunct, for the management of oral disease, will be described in this supplement. CHX may also have some antiviral properties against certain viruses such as herpes simplex type-1, influenza A, and human coronavirus and severe acute respiratory syndrome-related coronavirus in vitro,[13,14] appearing to be more effective on enveloped than non-enveloped viruses, but with more research required in vivo to support this.[13] Although allergic reactions are very rare, there have been significant severe reactions when surgical equipment has been soaked in high concentrations of CHX preoperatively[15] and a reported case of anaphylaxis following the use of CHX mouthwash to irrigate a dry socket.[16] There is also emerging evidence of antimicrobial resistance (AMR) with the use of antiseptics such as CHX.[17,18] Therefore, current CHX use in dentistry should be confined to short-term use only (up to 1 month), at some other time than tooth brushing.[9,13]

Hydrogen peroxide

Hydrogen peroxide is a widely available OTC as a mouthwash (1.5%) and is a bleaching agent with a strong oxidising action that liberates oxygen free radicals and disrupts lipid microbial cell walls to "kill" obligate anaerobes. It also foams on contact with human tissues, with the release of water and oxygen, which may also contribute towards the destruction of anaerobic species of bacteria.[19,20] Hydrogen peroxide has been shown to be an effective mouthwash for reducing plaque and gingival bleeding without adverse effects.[21] However some studies have reported that concentrations greater than 5% may cause soft tissue damage, and so lower concentrations between 1% and 3% tend to be used in mouthwashes for their antibacterial effects. Concentrations of 0.5% Hydrogen peroxide have been shown to be virucidal to enveloped viruses, including coronavirus.[22] Hydrogen peroxide mouthwashes are broad-spectrum antimicrobials shown to reduce gingivitis and tooth staining[23] as well as acting as a soaking solution for dentures.[24]

CPC

CPC, a quaternary ammonium compound (QAC), can be used in mouthwashes in varying concentrations (0.045%–0.1%), with low toxicity to the human host. QACs are also found in several surface spray disinfectants. CPCs have broad-spectrum antimicrobial properties; they are antibacterial via a reaction with lipids and proteins of the cell membrane, which leads to disorganisation in its structure and the leakage of low-molecular components out of the cell.[25] QACs also release of autolytic enzymes leading to the lysis of the bacterial cell wall and loss of functional components. They are further antifungal, via reverse distribution of charges on the cell surface, and antiviral, via disruption or detachment of the viral envelope, with subsequent release of the nucleocapsid, but their effects on nonenveloped viruses are less certain.[26–28] CPCs seem to be effective for reducing plaque and gingivitis,[29,30] with some occasional reports of staining and temporary loss of taste.

Povidone iodine

Povidone iodine may be contained in mouthwashes (0.5% and 1.0%) and may be recommended as use as a gargle for sore throats due to its antiseptic properties. However, when gargled, povidone iodine may potentially cause serious adverse reactions, including altered thyroid function if ingested and anaphylactic-type allergic reactions in patients with a history of allergy to iodine or shellfish.[31] Its antimicrobial actions result from the release of iodine, which destabilises bacterial lipid membranes and lyses proteins. Povidone iodine has therefore proven to be bactericidal, fungicidal, and virucidal and is frequently used for skin and mucous membrane disinfection (eg, Betadine). It is therefore also commonly used as a hand wash, surgical scrub, and skin wipe solutions (7.5% and 10%), not just as a dental antiseptic.[32] Povidone iodine is similarly effective at killing most oral bacteria, including periodontal pathogens, fungi, mycobacteria, viruses, and protozoa,[33] with no cytotoxic effects on human cells.[34] For many years, therefore, povidone iodine mouthwash has been recommended for decontamination of periodontal sites before invasive procedures to reduce the risk of bacteraemia.[35] However, it is difficult to find up-to-date evidence with respect to reductions in plaque and gingivitis.[36]

EOs

EOs encompass many different natural oils extracted from plants and are directly antibacterial, antifungal, and antioxidant with relatively low toxicity.[37] Commonly used EOs in mouthwashes include eucalyptol, menthol, peppermint, clove, methyl salicylate, and thymol. Such compounds have broad-spectrum antimicrobial activity, and clinical short-term studies have demonstrated that EO mouthwashes reduce bacterial plaque biofilms and, in turn, gingivitis and halitosis.[38] However, as combinations of oils are often used, it is difficult to ascertain from the literature specifically which EO compounds are effective. Nevertheless, based on their antimicrobial actions, EO mouthwashes have been recommended as an adjunct to mechanical oral hygiene when oral hygiene is impaired, as well as for the support of gingival health around dental implants.[39] EOs are often held in concentrations of up to 26% alcohol in mouthwashes, together purported to kill microorganisms through penetration of the plaque biofilm. However, alcohol and the potential for accidental ingestion of high doses of alcohol should preclude the use of such EO mouthwashes for children as well as patients with dry mouths and oral mucosal ulcerative disease, who report worsening of their mucosal pain and oral dryness with alcohol mouthwash.

Alcohol

Alcohol has been used in health care for centuries, due to its potent antimicrobial actions, and is effective at 70% to 80% when used to "kill" microbes on surfaces. Alcohol is contained in mouthwashes for the same reason, in concentrations of up to 26%. It can also sometimes help to dissolve certain insoluble agents in medicinal products, so they can be held in solution. As stated, alcohol can be found in EO mouthwashes, such that it can be difficult to distinguish whether the EO or the alcohol is exhibiting the antimicrobial actions. One significant current concern over alcohol mouthwashes, however, is the possible links to oral cancer, due to the production of acetaldehyde,[40] as discussed in this supplement. Thus, many mouthwashes are now alcohol-free, with alcohol becoming less significant when considering how mouthwashes impact oral disease.

Triclosan

Triclosan is another synthetic antimicrobial agent, found in many brands of dentifrice at concentrations of 0.5%, to help reduce plaque and gingival bleeding.[41] It works by inhibiting the fatty acid biosynthetic pathway within microbial cells, disrupting lipid synthesis and resulting in cell death.[42] It is also found in OTC mouthwashes, in combination with NaF and other antiseptics agents (including CPCs), to make mouthwashes more efficacious at controlling plaque and reducing gingivitis, despite its clinical effectiveness as a mouthwash being uncertain.[41] There is also emerging evidence that use of triclosan may be associated with reproductive and endocrine dysfunction,[43] as well as contributing to antimicrobial resistance and toxicity within aquatic species.[44] For this reason, many countries, including the US (via the US Food and Drug Administration), have banned triclosan in cosmetics, wipes, and soaps.[42] Despite this, it can still be found worldwide in many oral hygiene products due to its potent antimicrobial properties. Thus, clinicians must consider whether the uncertain clinical beneficial effects, at the current time, may outweigh the emerging risks.

Commonly used mouthwashes and emerging mechanisms

It has been highlighted thus far that most commercially available mouthwashes are antimicrobial, underlying their beneficial effects on reducing plaque an gingivitis, and effectiveness using the highest level of evidence is covered in this supplement. However, recent evidence has questioned the dogma of indiscriminately "killing" microbes as the main desirable property of an effective antiseptic mouthwash, suggesting that the oral microbial ecosystem, or oral microbiome, should be considered an integral part of both oral and systemic health. Microbes within the oral cavity exist as a community, and certain species of bacteria are required for good oral health, whilst others are associated with disease (pathogenic). Indiscriminate destruction of all oral microbes may therefore hinder the effectiveness of mouthwash use, and any up-to-date discussions of mouthwash use must consider their effects on the oral microbiome and the immunologic response of the human host. There is also emerging evidence that the oral micro-environment may impact systemic health and when the oral microbiome shifts towards a predominance of certain pathogenic species (dysbiosis), there may be associations with systemic diseases such as cardiovascular disease, cancer, rheumatoid arthritis, diabetes, and Alzheimer's disease and even pregnancy outcomes.[45] It may be pertinent to therefore seek antimicrobial mouthwashes that "balance" the oral microbiome whilst combating oral

disease, but little is known about the mechanisms of not only the commonly used mouthwashes introduced here but the natural and developmental mouthwashes already available OTC and in may health food stores; hence, the evidence around these will also be discussed.

Summary

In summary, following on from this introduction of "how they work" at a microbial level, this supplement will now use in vivo evidence wherever possible to discuss the most commonly used antimicrobial mouthwashes in the context of:

1. their effectiveness, in the context of oral disease
2. the oral microbiome: the good, the bad, and the balanced
3. their effects on systemic health
4. alternatives and future directions

Based on these 4 articles, the intention of this supplement is therefore to make some concluding suggestions and recommendations for appropriate adjunctive mouthwash use for practitioners (existing and more natural/novel agents), specific to different oral diseases such as gingivitis, periodontal disease, caries, halitosis, and dry socket, based on their mechanisms of action and clinical effectiveness using the best available evidence. This will then be considered alongside remerging evidence relating to their effects on the oral microbiome and systemic health, to ultimately reconsider whether the oral health benefits still outweigh these emerging risks at the current time and highlight future directions for management of oral disease involving mouthwashes.

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Conflict of interest

None disclosed.

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