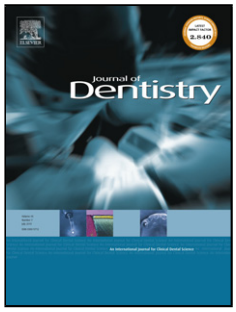
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Current uses of chlorhexidine for management of oral disease: a narrative review

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Short title: chlorhexidine and oral disease

Abstract

Objectives: Chlorhexidine (CHX) is a commonly used antiseptic mouthwash, used by dental practitioners and the public, due to its antimicrobial effects. The aim of this article was to provide a narrative review of current antimicrobial uses of CHX relevant to dentistry in the context of oral diseases, highlighting need for further studies to support its safe and appropriate use.
Study selection, data and sources: Randomised controlled trials, systematic reviews and national (UK and US) guidelines were consulted where available, with search terms for each subject category entered into MEDLINE, PubMed, Google Scholar and the Cochrane database.
Results: Some evidence existed to support adjunctive short-term use of CHX to manage dental plaque, and reduce clinical symptoms of gingivitis, dry socket, as well as reduce aerosolisation of bacteria. However, use must be weighed alongside the less desirable effects of CHX, including extrinsic staining of teeth, antimicrobial resistance to antiseptic agents and the rare, but fatal, allergic reactions to CHX. Conversely, evidence for the effectiveness of chlorhexidine to manage or

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prevent periodontitis, dental caries, necrotising periodontal diseases, peri-implantitis, and infections associated with extraction and aerosolised viruses remains less certain.
Conclusions: The use of CHX in dentistry and oral healthcare continues to be widespread and thus it is important that dental practitioners understand that, based on its differential mechanisms of action on different microbes, appropriate clinical and dental use of CHX should be oral disease specific. However, further scientific and clinical research is required before full recommendations can be made.

Key words: chlorhexidine, mouthwash, periodontitis, caries, bacteria, virus

Introduction

Chlorhexidine gluconate (1,1'-hexamethylene bi [5-(p-chlorophenyl) biguanide] di-D-gluconate) (CHX) is a gluconate salt; a biguanide compound, that has been around since the 1950s for clinical use. It is also a broad-spectrum anti-microbial agent, causing disruption of cellular membranes [1]. It is thus currently used as a disinfectant agent for cleaning non-living clinical surfaces and catheters. It is also generally biocompatible, being used orally as an antiseptic mouthwash by dental practitioners and the general public to prevent bacterial biofilm and plaque accumulation [2]. The latter are potentially causative for dental caries, plaque-induced gingivitis, periodontitis and oral soft tissue disease. Nevertheless, as discussed henceforth, CHX has differing effects on bacteria, viruses and fungi, and the potential to have more clinical benefit with some oral diseases than others. The aim of this article therefore, was to provide a narrative review of current antimicrobial uses of CHX relevant to dentistry, especially in the context of oral diseases caused by microbes, highlighting need for further studies to support its safe and appropriate use. Search terms for each subject category were entered into MEDLINE, PubMed, Google Scholar and the Cochrane database. The hierarchical system of evidence based medicine was then applied through the review, such that Cochrane review and systematic reviews with randomised trials were used as evidence supporting CHX use, followed by individual randomised controlled trials [3]. If only individual case controlled or laboratory based studies were available these were then reported. National guidelines were also included to provide a sense of current opinion. This article was not intended to be a systematic review and therefore recommendations were not made as such. This was largely because more research is required in this field, and we consider that this article importantly uses the best available evidence to demonstrate this need.

Formulations and uses

For oral use CHX comes in several different formulations. In the United Kingdom (UK) and Europe 0.2% CHX mouthwash (Corsodyl™) is available over the counter (OTC), as either an alcohol-containing or non-alcohol formulation. 0.2% tends to be recommended for short-term intensive plaque control, whereas 0.06% is referred to as a daily rinse. In the United States (US) CHX is also

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prescribed as a 0.12% mouthwash (Paroex™). For all mouth rinse formulations, the advice is to rinse with 10ml twice daily for 30 seconds, but under 12 years it is use only to be used on the advice of a healthcare professional (under 18 years in the US). It is also advised for short-term use only; 2-4 weeks, only being licensed for 30 days of use in the UK [4,5]. In patients with oral candida, dentures may also be soaked in Corsodyl™ mouthwash once or twice daily for 15 minutes [6].

CHX mouthwash is near-neutral solution (pH range 5-7), only advised for topical use, and never for systemic administration. Being cationic, it binds to skin, mucosa and tissues, which in turn make it poorly absorbed across these membranes. After a single rinse, 30% may remain in saliva for up to 5 hours, and on the oral mucosa for up to 12 hours, with plasma levels being undetectable [7,8]. This is because CHX is poorly absorbed from the gastrointestinal tract, even when large volumes are ingested. It is generally considered safe for oral use, but some side effects and complications have been reported, as later eluded to.

For oral use, CHX digluconate is also available in gel formulations, for example, 1% CHX (Corsodyl™), 0.2% CHX (Perio Kin™) and 0.5% CHX (Curasept™) gel being available for oral use in the UK, including OTC. These gels can also contain other chemicals that assist with muco-adhesion, for example carboxymethyl- (CMC), hydroxypropylmethyl- (HPMC) and hydroxypropyl- (HPC) cellulose in varying combinations. 2% CHX gels or ointments may be used on the skin, and this may actually preferred to 70% alcohol or povidone-iodine when applied prior to insertion of venous catheters [9]. Much like mouthwash, these oral gels can be used topically for management of caries and as an adjunct to mechanical plaque control for gingivitis and periodontitis as well as for use for oral candida (including denture stomatitis, applied to the denture surface and or the oral mucosa) and aphthous ulcers. In these situations, approximately 2cm of gel may be applied to the site once or twice daily. CHX sprays (0.14 ml of 0.2% Corsodyl™) may also be applied twice daily to gingival or mucosal surfaces, to treat gingivitis, candidiasis and ulcers in a similar manner.

In addition, available to oral and dental clinicians are Periochip™ or PerioCol™-CG, formulated as biodegradable ‘chips’, soaked in 2.5 mg of CHX digluconate, which can be inserted into periodontal pockets in combination with sub-gingival debridement. These products may produce better clinical outcomes for periodontitis patients, although their success has yet to be fully elucidated [10,11]. The numbers of other CHX dental products continue to expand, to currently include toothpastes with 0.05% CHX, such as Curapsept™ and Corsodyl™. These are also sodium lauryl sulphate-free (SLS free), the foaming agent, known to be an allergen and cause mucosal irritation and desquamation in some patients [12]. Toothbrushes and floss coated in CHX are also now commercially available. However, no appropriate meta-analyses or systematic reviews of the clinical effectiveness of such dental products could be identified at this time.

Antimicrobial activity

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As an antiseptic mouthwash, CHX has an anti-microbial effect on bacteria, fungus and viruses causative for a number of different oral diseases. *In vitro*, the anti-bacterial effects of CHX all relate to altered cell membrane permeability [1]. At low concentrations (0.02%-0.06%) CHX causes displacement of $Ca^{2+}$and Mg^{2+} and loss of K^{+} from the cell wall, resulting in a bacteriostatic effect [1,13]. At high concentrations (>0.1%) CHX causes leakage of all the main intracellular components out of the cell, resulting in a bactericidal (cell lysis and death) effect [1,13]. The anti-viral effects of CHX are also due to altered cell membrane permeability and ultimately CHX can inactivate enveloped viruses, such as herpes simplex virus, which are associated with cold sores [14,15]. However, CHX has little virucidal activity on non-enveloped viruses, including HUMAN papilloma viruses (HPV), which may be associated with oral cancers [15,16]. The anti-fungal effects of CHX however, relate to the prevention of biofilm formation on both biological and non-biological surfaces, by species such as *Candida*, rather than disrupting the structure or cellular membrane of the microbe. For example, CHX can reduce the amount of *Candida albicans* adhering to the surface of dentures [17], as well decrease the numbers of *Candida albicans* residing on soft tissues *in vivo*, such as the oral mucosa [18].

The communities of bacteria, fungi and viruses residing within different niches of the oral cavity comprise the oral microbiome [19,20]. A diverse oral microbiome is essential for maintaining good oral (and systemic) health [20]. However, when it becomes less diverse, for example with antiseptics such as CHX, it can become dysbiotic [20,21]. Bacterial oral dysbiosis and has been linked to oral diseases, including caries, periodontitis, oral cancer, peri-implantitis and mucosal diseases [19]. Thus, in recent years, the potential for CHX to induce dysbiosis, including increased prevalence of disease-causing species *in vivo* [21], has come to be considered just as important direct bactericidal effect of CHX reported in the laboratory *in vitro* [1,12]. Thus, whilst full exploration is beyond the scope of the current manuscript, understanding of the oral microbiome is important for any discussion of the anti-microbial effects of CHX *in vivo.*

Side effects, contraindications and allergic reactions

Returning to clinical uses, CHX as a mouthwash or topical oral gel is not without adverse effects, some of the most common being dry mouth (xerostomia), altered taste sensations (hypogeusia), specifically salt and bitter, and a discoloured or coated tongue. Despite anti-plaque properties, increased calculus formation has also been reported with 0.12% CHX mouthwash [22]. Other less common side effects include burning sensations (glossodynia), desquamation of the oral mucosa, swelling of the parotid gland and oral paraesthesia [23]. However the most unwanted outcome, that deters patients using of CHX mouthwash, is probably tooth staining [24]. This is common once usage exceeds more than several weeks, due to non-enzymatic browning (Maillard reaction) and the production of pigmented metal sulphide formation in the pellicle [25]. This in turn can also allow tin and iron binding reactions with dietary aldehydes and ketones that enhances precipitation of food components onto teeth [26]. Nevertheless, formulations of CHX are now available to prevent

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tooth staining, for example 0.2% Curasept ADS™, where an anti-discoloration system (ADS) has been added to reduce tooth surface staining, via inhibition of the Maillard reaction and protein denaturation. There is also now evidence from systematic review that ADS does not effect the ability of CHX to reduce to gingival inflammation and plaque scores [27].

The more potentially serious side effects associated with the oral use of CHX are the possible Type IV and Type I hypersensitivity reactions accompanied by severe anaphylaxis. For CHX, these are reported at an incidence of 0.78 per 100,000 exposures [28,29]. There are also case studies reporting that CHX mouthwash can lead to respiratory arrest and death due to severe anaphylactic responses [30]. Hence, although rare, and of limited numbers, such reported allergic reactions have influenced the usage of CHX amongst clinicians in recent years, and must have some bearing when considering risk *versus* benefit for appropriate use of CHX in the management of all relevant oral conditions. It is unlikely that these reactions are associated with any other components within the mouthwash, which comprises of Glycerol, Macrogolglycerol Hydroxystearate, Sorbitol liquid (non-crystallising) and purified water, although some formations do contain menthols that does have the potential to irritate mucosal tissues in rare cases [31]. In the UK, the current British National Formulary (BNF) guidelines do not contra-indicate the use of CHX in pregnancy, and commercial data sheets have not identified any adverse effects on the foetus. However it is suggested that mothers may choose to avoid those formulations containing alcohol. The advice is more cautious in the US, as the Food and Drug Agency (FDA) state that CHX may be best avoided, especially Periochip™, due to the lack of evidence confirming its use is safe during pregnancy and breast feeding.

Another emerging issue with CHX is that of Antimicrobial resistance (AMR), whereby the micro-organisms it is designed to kill, adapt and become resistant, which means that the mouthwash becomes less effective [32]. There are several mechanisms by which this may occur, including mutation in or the addition of genetic material, leading to changes in cell membrane structure (increased expression of efflux pumps) and promoting the cross-resistance of other bacteria to antibiotics, including amongst the most multi-drug resistant species [14,33,34]. In addition to allergies and staining, AMR must also therefore be considered when recommending CHX use.

Uses for oral disease

CHX is used broadly in dentistry and common usage includes (but is not limited to) (i) the management of oral hygiene, dental plaque and caries with or without underlying conditions; (ii) to assist in the management of gingivitis, periodontitis and peri-implant disease; (iii) as an irrigant during root canal therapy; (iv) management of oral surgery and associated complications; (v) management of oral mucosal disease and (vi) as a pre-rinse to reduce aerosolisation of microbes during dental procedures. These applications can involve use by the public as an over the counter mouth rinse, or as a mouth rinse, gel and slow release form (chips) used by dental practitioners.

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The next sections focus on the suitability of current uses of CHX in the management of specific oral diseases.

Caries

Dental caries involves the build-up of plaque, containing bacteria such as *Streptococcus mutans* and *lactobacilli spp* that produce lactic acid in the presence dietary carbohydrates, to cause dissolution of tooth enamel and dentine [35]. In the UK CHX (Corsodyl™ 0.2%) can be used as a daily mouthwash, as it is known to reduce the amount of plaque on teeth [5,36]. However, despite CHX reducing plaque, Cochrane review considered eight clinical trials in adolescents and children, to conclude it does not concurrently reduce caries [37]. In support of this, 0.2% CHX gel also did not reduce *S. Mutans* when applied to the surface of teeth in longitudinal studies [37,38]. Furthermore, systemic review of CHX varnishes applied to the surface of teeth also did not identify any strong evidence that CHX reduces rates of dental caries [39]. For caries prevention rather, 0.05% sodium fluoride daily oral rinse is currently suggested [40,41].

Nevertheless, if mouthwash is to be utilised for plaque reduction, national guidelines state that mechanical tooth brushing and interdental cleaning are the preferred method for effective plaque removal, and that any mouthwash should be an adjunct rather than replacement for brushing [41,42]. The interval between tooth brushing and CHX mouthwash, should also be greater than 30 minutes, and ideally more than 2 hours [43]. This not only because a mouthwash could potentially wash the fluoride from toothpaste away, but because CHX rinses may interact with the anionic components of many toothpastes, such as SLS and sodium monoflurophosphate, and reduce the beneficial effects of fluoride on the remineralisation of enamel lesions [44].

Gingivitis and periodontitis

Gingivitis and periodontitis are ‘gum diseases’ caused by the host inflammatory response to bacteria at or within the gingival crevice/periodontal pocket. The most significant levels of disease involve *Gram*-negative anaerobic species, such as *Porphyrmonas gingivalis, Fusobacterium nucleatum, Prevotella spp* and *Treponema denticola* [45,46]. CHX is not a ubiquitous agent recommended for all plaque-induced gingival and periodontal diseases [47] rather, as an adjunct strategy for early gum disease (gingivitis) and periodontitis [48].

CHX may confer some clinical benefit in managing gingivitis, as a systematic review demonstrated that 4-6 weeks of daily rinsing with 0.2% CHX reduced clinical signs in several studies [34]. However, the recent European Federation of Periodontology (EFP) consensus guidelines make it clear that such antiseptic products should be used as an *adjunct* to mechanical tooth brushing and interdental cleaning [48]. The EFP guidelines also cited the most effective adjunctive agents for controlling plaque and gingival inflammation, contained CHX, essential oils and cetylpyridinium chloride [49,50].

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For established periodontitis, adjunctive physical or chemical agents may also be employed alongside mechanical measures [48,51]. The EFP guidance suggests that '*adjunctive antiseptics may be considered, specifically CHX mouth rinses for a limited period of time, in periodontitis therapy, as adjuncts to mechanical debridement, in specific cases'*. Furthermore, the EFP document states '*locally administered sustained-release CHX as an adjunct to subgingival instrumentation in patients with periodontitis may be considered.'* This has been supported by systematic review from ten studies demonstrating that Periochip™ as an adjunct to root surface debridement, also caused small decreases in both periodontal pocketing and clinical attachment loss (<1mm) [52-54].

It is important to note that the EFP guidelines apply to the treatment of Stage I-III periodontitis and not for Stage IV (very severe) periodontitis. Related to this level of disease, Cochrane reviews concluded that use of 0.2% CHX mouthwash was not effective with reducing moderate to severe periodontitis, even as an adjunct [5,55-58]. One possible reason could be that CHX used as a mouth rinse does not penetrate deep periodontal pockets, where anaerobic bacteria reside and modulate periodontal disease, as well as shifts in the oral microbiome to bacteria associated with oral disease [21].

Necrotising Periodontal Diseases

Necrotizing gingivitis (and more rarely necrotizing periodontitis) is mostly observed in patients who are temporarily and/or moderately compromised with risk factors such as poor oral hygiene, host immune suppression and the accumulation of anaerobic bacteria, such as *Prevotella intermedia*, *Fusobacterium*, plus spirochetes such as *Treponema* [59,60], stress, poor nutrition and smoking etc. The bacteria that cause the gingiva to become inflamed and swollen are associated with characteristic grey sloughing and halitosis [61]. First line treatment involves oral hygiene, and antibiotics such as metronidazole or amoxicillin, but NICE and SDCEP guidelines currently recommend 0.12% or 0.2% CHX, or 6% hydrogen peroxide, mouthwashes as an adjunct [42,47]. This may be related to anti-bacterial effects of CHX on some *Gram* negative bacteria such as *Prevotella Intermedia* [62]. More clinical studies and systematic reviews however, are necessary before providing recommendations, especially as CHX can shift the oral microbiome to biofilms where *Fusobacterium* can predominate [63]. Rarely seen in the developed world are necrotising gingivitis, necrotising periodontitis, which may be seen in chronically and severely compromised patients with such underlying conditions such as HIV [60,61].

Peri-implantitis

With respect to dental implants, chlorhexidine has indications at several different stages:

- Pre-surgical mouth rinse (0.12% or 0.2% Chlorhexidine) to reduce oral microbial load for 7-10 days prior to surgery and immediately prior to surgery [64,65];

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- Post-operative protocols involving application of pressure for 30 minutes with gauze soaked in chlorhexidine [65] and rinse and during 7-14 days after surgery to aid healing [66,67] and for treatment of post-operative infections;
- Reduction of implant biofilm formation post-surgery [68] this may not necessarily relate to long improved outcomes in terms of preventing or managing longer term infections such as peri-implantitis
- As a mouth rinse during implant maintenance and for treatment of peri-implant disease, where high levels of plaque control are important. Including, irrigation with 0.12-0.2% chlorhexidine, plus topical chlorhexidine gel for 10 days, as an adjunct to mechanical debridement, may be beneficial [69].
- As a local delivery system adjunct where multi-centre trails have also suggested that 6 months uses of Periochip™ could reduce implant pocketing depth [70].

Current UK guidelines suggest that management of peri-implantitis could include '*non-surgical debridement with carbon fibre or plastic curettes and irrigate the pocket with 0.2% CHX*' [47]. However, a more recent systematic review from eight studies has concluded that, the bleeding on probing and pockets depth reductions observed with mechanical debridement of implants alone, were not improved by the adjunct use of CHX over 10-14 days, either as a 0.12% and 0.2% mouth rinse, or a 1% gel [71].

For the surgical management of peri-implantitis involving re-contouring the implant surface, implant debridement and apically repositioned flap found that irrigation with 0.12% or 2% CHX as chemical adjunct, reduced microbial decontamination, yet did not improve clinical outcomes [72]. Further studies and refinements on current guidelines for management of peri-implantitis are thus needed.

Oral surgery and oral medicine

Medication-related osteonecrosis of the jaw (MRONJ), is a healing defect associated with the use of several groups of medications including bisphosphonates, RANKL inhibitors and anti-angiogenic agents [73,74]. NHS England guidelines (2015) state that 0.2% CHX mouthwash should be used twice daily during the week before extractions and then 24 hours post-operatively, and twice daily for up to 2 months to facilitate healing [75]. Elsewhere in Europe and the US, 0.12% CHX mouthwash has been similarly be advised 3 times a day for 7 days before, and then 15 days after, extractions in cancer patients at high risk of MRONJ [76]. However, NHS England guidelines have since been superseded by Scottish guidelines, advising not to use of CHX mouthwashes prior to extraction in patients categorised as either low or high risk of MRONJ, stating that there is insufficient evidence to support the use [74,75]. Nevertheless, CHX can also be used to treat MRONJ once it has developed. Indeed, the American Association of Oral and Maxillofacial Surgeons suggest the use of CHX mouthwash, in the early management of MRONJ (Stage 1) [77]. Cochrane review also concluded that more research was required regarding CHX use with MRONJ

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[78], and thus global agreement on the use of CHX, both prophylactically and as part of management, awaits full confirmation.

Infective endocarditis

Historically, CHX pre-rinses were considered for individuals who are at higher risk of infective endocarditis following dental procedures [79]. In 2015, NICE reviewed the evidence from randomised controlled trials, including studies using 10ml 0.2% CHX mouthwash for 1 minute prior to extraction [80-82], to conclude that pre-rinsing had no beneficial effect on any subsequent bacteraemia. This was supported by a more recent systematic review and meta-analysis, also demonstrating that CHX has little effect on the bacteraemia induced by tooth extraction [83]. In the UK, the updated SCDEP and latest NICE/BNF do *not* recommend CHX prophylaxis [80,84].

Root canal treatment

Irreversible pulpitis and periapical periodontitis are caused by bacteria entering the root canal system, including *Gram*-positive *Enterococcus faecalis,* which is arguably the most resistant bacteria to disinfection and unresolved periapical infections [85]. Cochrane review found no conclusive evidence with clinical outcomes, namely pain and swelling, to advise that CHX, compared to other antiseptics, is the superior irrigant of choice for root canal therapy [86,87]. Data are conflicting however. For example, using the secondary outcome measures of microbial culture *in vitro*, 2% CHX had superior bactericidal properties to sodium hypochlorite (2.5%) on *Enterococcus faecalis* [88]. Conversely, after longer periods of irrigation for 20-minutes, 2.5% sodium hypochlorite was more effective at preventing bacterial growth than 2% CHX [89]. A sufficient exposure time is therefore important with sodium hypochlorite use. Higher concentrations (5.25%) of sodium hypochlorite are also more effective than lower concentrations (1%) [90], but 2% sodium hypochlorite remains the irrigant of choice amongst dentists for root canal therapy, due to being less tissue toxic than 5.25% [90]. Furthermore, sodium hypochlorite more successfully dissolves inorganic matter compared to CHX, which if left compromises the quality of the seal within the root canal filling, leading to possible failure [91]. Nevertheless, the SDCEP suggest 0.2% CHX for whole mouth oral disinfection, as an adjunct to healing of perio-endo lesions after RCT has been completed [3,47].

Tooth Extractions

CHX is recommended by the SDCEP as a mouthwash during dental infections leading to periodontal abscesses [47]. However, dental abscesses are polymicrobial in nature and it is difficult to find any evidence as to how effective CHX is at reducing the clinical symptoms *in vivo*, and/or the mechanisms by which it may do so [92]. CHX may also sometimes be used as a mouth rinse post-tooth extraction, to reduce post- operative bacterial infections, even though salt water rinses tend now to be the first line post- operative approach [93]. Recent studies however, have demonstrated that pre-rinsing reduces post-operative bacteraemia after extraction, which peaks at 1-5 minutes afterwards, by only 12% [83]. Nevertheless, CHX does remain in use as a pre- and

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post-rinse for surgical third molar extractions, supported by Cochrane review and the UK Faculty of General Practitioners (FGDP) [94], for rinsing either pre- or post-extraction with 0.2% CHX, or placing 0.12% CHX gel in the socket post extraction. This appeared to reduce clinical symptoms of post-operative alveolar osteitis (dry socket) by up to 58% [95-97]. This is interesting because the cause of alveolar osteitis is not thought to be bacterial; rather it is caused by premature disruption of the clot after extraction allowing bone to be exposed to the oral environment [98].

Oral infections

Denture stomatitis is a disease largely caused by the presence of the fungi *Candida albicans* within the oral cavity due to poor denture hygiene, and thus options for disinfecting dentures may include CHX [99]. CHX gel can also be applied 1-2 times a day to affected areas of the oral mucosa to treat *Candidiasis* and apthalous ulcers, particularly in immunocompromised patients who are more susceptible to overgrowth of *Candida albicans* [100,101], with some *in vivo* evidence to supporting its ability to reduce this fungi in saliva, biofilms and the gingival crevice [102,103]. Current guidelines advise the use of CHX twice daily for mucosal inflammation and ulceration with secondary infection relating to oral herpes simplex virus infection [3,100,104]. This guidance is supported by longstanding evidence that CHX mouthwash is antiviral for many enveloped viruses that may colonise the oral cavity, including herpes simplex virus (HSV), cytomegalovirus (CMV), influenza A, parainfluenza and hepatitis B (HBV) [105,106].

Pre-rinsing to reduce microbial aerosols

In response to dental procedures, including the use of the high speed drill, 3 in 1 air and ultrasonic scaler, microbes can aerosolise and splatter up to 6 feet away from the dental chair [107,108]. Recent systematic review has demonstrated moderate evidence that pre-procedural mouth rinsing with antiseptics can reduce dentally generated aerosolisation of viable microbes [109]. This includes 0.2% CHX reducing the number of colony forming units (CFUs) of bacteria produced (approximately 70%) in response to ultrasonic scaling, as measured on an agar plate placed within the dental surgery [110-112]. Randomised controlled trials have also shown that compared to pre-rinsing with 0.2% CHX, herbal mouth rinses are less effective - in the region of 30% [111]. Therefore, pre-existing 2003 CDC guidelines recommending pre-rinsing with CHX gluconate, essential oils, or Povidone-Iodine to reduce microorganisms in aerosols and spatter produced by dental procedures still appear to be appropriate [113].

However, these aerosolisation studies mainly pertain to bacterial cultures. CHX may also be more anti-virucidal against enveloped than non-enveloped viruses [114,115], thus much research is still required in this area. The emerging virus Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), causative for the ongoing COVID-19 pandemic, also resides in the oral cavity, due to the high expression levels of the Angiotensin Converting Enzyme-2 receptor (ACE2) in oral soft tissues, as well as saliva [115-117]. Despite SARS-CoV-2 being enveloped, latest publications provide conflicting evidence as to whether CHX pre-rinses reduce viral loads within saliva [118-

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120]. We therefore advise caution assuming any benefits of CHX pre-rinses for reducing dentally-induced aerosolisation of viruses. 1% hydrogen peroxide appears to be a more effective anti-viral agent and therefore, at this time, appears the pre-rinse of choice for reducing salivary load and aerosolisation of oral microbes [119-120]. Povidone-Iodine, 20-30% ethanol and herbal mouthwashes, such as Listerine, may also have some emerging evidence of antiviral properties, but further studies are required, and this field is rapidly changing [119-120].

Uses in secondary care

Oral cancer patients

The Royal College of Surgeons of England (RCS, Eng.) guidance states CHX may be used prior to and during cancer therapy, including radiotherapy and chemotherapy of head and neck cancers (HNCC), or other cancers such as leukaemia, where maintaining oral hygiene and tooth brushing may be difficult, with the aim of reducing oral bacterial load [121]. Anecdotal evidence suggests CHX is not widely used within hospital maxillofacial departments for this purpose. It is more likely that HNCC patients may be using CHX rinses at home, due to its aforementioned claims to improving plaque control and reducing gingivitis [5]. There are no studies advocating the use of CHX to prevent caries, gingivitis and periodontal disease in HNCC patients, rather effective oral hygiene, and a 0.2% fluoride daily mouthwash, would be preferred, as the xerostomia-associated caries [122]. Oral mucositis is a recognised complication of radiotherapy for HNCC [122]. Recent systemic review however, did not identify benefit of CHX for reducing the clinical symptoms oral mucositis [123,124]. Indeed, in patients undergoing cancer chemotherapy with neutropenia who had developed oral mucositis, the use of CHX appeared to actually induce more mucosal inflammation, and elevate symptoms of mucositis [125].

Inter-maxillary fixation and orthodontic devices

It has long been established that intra-oral appliances, including inter-maxillary fixation devices and orthodontic appliances, impair oral hygiene and thus render patients at a higher risk of plaque accumulation, and in turn dental caries [126,127]. Individual studies have demonstrated that 0.2% CHX mouthwash can reduce plaque indices and the incidence of white spot lesions with fixed appliances [128,129]. However, a systematic review by Tang et al (2016), although detecting significant reductions in *S. Mutans* with CHX mouthwashes, only found weak evidence that CHX use related to clinical benefits with reduced caries for individuals wearing fixed orthodontic appliances [130]. With a different purpose, 1% CHX gel also appeared to be effective at removing *Staphylococcus aureus* from removable orthodontic retainer devices [131], perhaps mirroring finding with dentures. However, at present, the British Orthodontic Society (BOS) patient

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information leaflets recommend daily alcohol-free fluoride mouth rinses, rather than CHX, for prevention of caries [132], and due to it's concurrent staining associated with longer-term use. Therefore, at this time, it would be unlikely for dental practitioners to recommend CHX for plaque control with orthodontic appliances.

Uses in special care dentistry

Public Health England (PHE) figures have estimated 1 million people in the UK with learning disabilities, to include Downs Syndrome, autism and head injuries. Such conditions can lead to physical and psychological difficulties that make effective oral hygiene routines more challenging (PHE). Indeed there is increased caries risk, increased gingivitis and a high prevalence of periodontal disease amongst individuals with learning difficulties [133,134]. The British Society of Periodontology (BSP) also advocate that the use of *'antiplaque agents like CHX are useful for managing acute periods when cleaning is difficult but not needed as a routine'* [4], such as those with special needs who find mechanical tooth brushing physically difficult or painful [47]. Although it must be noted that use of CHX mouthwash is licensed for 30 days of use [41].

The most recent Clinical Guidelines for the Oral Health Care of People with Learning Disabilities (2012) mention the application of 1% CHX gel as a potentially effective adjunct for reducing periodontal disease, if applied at home daily in individuals with Down Syndrome [135]. However, although CHX in its various formulations may be effective in reducing gingivitis in systemically healthy individuals [5], for those with learning disabilities systematic review could not find any good evidence that CHX reduced gingivitis or periodontal disease [136]. An explanation proposed for this was that these individuals experienced more severe levels of gingival inflammation [136], and thus fluoride use with improved manual oral hygiene continue to be first line, as reported for healthy individuals, but with adapted techniques, tools and increased supervision [41].

Evidence supporting current use and future studies

The purpose of this review was to use available evidence and guidelines to highlight possible appropriate uses of CHX for clinical management of oral disease. In summary, there is an evidence base to suggest that CHX may be effective for plaque control and gingivitis, alveolar osteitis (not caused by microbes), prevention of bacterial aerosolisation and symptomatic management of some viral infections of the oral cavity. However, these indications must always be weighed alongside staining of teeth, emerging antimicrobial resistance and the rare anaphylactic reactions to CHX. Conversely, the effectiveness of CHX (alone) for preventing or managing chronic periodontitis, dental caries, ANUG, peri-implantitis, infections associated with extraction and aerosolisation of viruses is less well supported by the literature. We propose that more clinical studies investigating the mechanism of action of CHX on oral microorganisms *in vivo* are urgently needed, as the oral use of CHX should be targeted and disease and, preferably, microbe specific.

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Periodontal Condition (using 2017 Classification/Terminology)	Examples of clinical uses for CHX
Periodontal Health & Gingival Health, Periodontal abscesses, endodontic-periodontal lesions, peri-implant health, peri-implantitis	As a short-term adjunct to mechanical plaque control. During immediate post-operative phase after ressective periodontal surgery e.g. crown lengthening.
Gingivitis: Dental Biofilm induced, Peri-implant mucositis	Short-term management of plaque-induced gingival inflammation as an adjunct to mechanical plaque control. As an adjunct in management of Drug-influenced gingival enlargement / Fixed orthodontic appliance therapy
Gingival Diseases: Non-dental biofilm induced	Management of self-harming traumatic lesions e.g. gingivitis artefacta. Management of specific infections or Inflammatory and immune conditions with erosive/ulcerative tissues Post biopsy/excision of neoplasms
Necrotising Periodontal Diseases	As a short-term adjunct to (or temporary replacement for) mechanical plaque control.
Periodontitis	As a short-term adjunct to mechanical plaque control. Sub-gingival adjunctive irrigant (mouth rinse), gel or local delivery system to conventional sub-gingival debridement Following periodontal surgery
Periodontitis as a manifestation of systemic disease, traumatic occlusal forces, tooth and prosthesis related factors	As a short-term adjunct to mechanical plaque control. Sub-gingival adjunctive irrigant (mouth rinse), gel or local delivery system to conventional sub-gingival debridement Following periodontal surgery
Systemic diseases or conditions affecting the periodontal supporting tissues	As a short-term adjunct to mechanical plaque control. Sub-gingival adjunctive irrigant (mouth rinse), gel or local delivery system to conventional sub-gingival debridement Following periodontal surgery
Periodontal Abscesses	See periodontitis and also for pericoronal abscess / pericoronitis
Endodontic-periodontal lesions	See periodontitis Intra-canal irrigant where sodium hypochlorite unavailable/contraindicated
Muco-gingival deformities and conditions	As a short-term adjunct to mechanical plaque control in defect or following corrective muco-gingival surgery
Traumatic occlusal forces	See periodontitis
Tooth and prosthesis related factors	See periodontitis Removable prosthesis cleansing
Peri-implant health	See Periodontal Health & Gingival Health
Peri-implant mucositis	See Gingivitis: Dental Biofilm induced
Peri-implantitis	See periodontitis
Peri-implant soft and hard tissue deficiencies	As a short-term adjunct to mechanical plaque control to facilitate post-extraction healing

Table 1. Periodontal conditions where CHX mouthwash could be used currently, in alignment with the 2017 Classification of Periodontal Diseases.

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	Key causative microbes	Formulation	Supporting information
Dental caries	*Streptococcus Mutans* *Lactobacillus*	Not recommended	May reduce prevalence of *S. Mutans* and amount of gingival plaque, but unlikely to reduce incidence of dental caries Early indications mouthwash may result in more acid saliva and microbiome shift to caries causing bacteria
Orthodontics	See dental caries	Not recommended	See dental caries
Pre-extraction	Mixed	Not recommended	Pre-rinsing no beneficial effect on any subsequent bacteraemia
Post-extraction	Mixed	Not recommended	Saltwater mouth rinse preferred post-operatively
Dry socket	None - inflammatory	0.12 or 0.2% daily mouthwash	Evidence to support use as oral rinse pre- or post-extraction, may have benefit on reducing clinical symptoms
MRONJ	None - inflammatory	Not recommended	Most recent guidelines, not recommended in UK prior to extraction Outside UK 0.12% or 0.2% daily mouthwash may be used to manage stage 1 symptoms of MRONJ
Root canal procedures	*Enterococcus faecalis* (most persistent)	0.2 - 2% peri-operative irrigant	May have some benefit on pathogens causative for persistent periodontal periodontitis after root canal therapy, but hydrogen peroxide considered superior
Bacterial aerosolisation	Mixed	10 ml of 0.12 or 0.2% mouthwash for 1 minute prior to procedure	Reduces aerosolisation by 70-90%

Table 2. Dental hard tissue diseases and procedures where CHX could be used under current UK guidelines and narrative review of recent published evidence.

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	Key causative microbes	Formulation	Supporting information
SYSTEMIC			
Infective endocarditis	Streptococcus *Viridans* *Streptococcus Salivarius*	Not recommended	Pre-rinsing no beneficial effect on any subsequent bacteraemia
VIRAL AND FUNGAL			
Viral infections (enveloped)	Herpes Simplex -1 Herpetic gingivostomatitis	1- 2% CHX gel topically (prescription only)	May have some virucidal properties as evidenced *in vitro*, but more clinical studies and systematic review needed More research required particularly for emerging viruses, as limited evidence for effectiveness Use with caution.
Viral infections (non-enveloped)		Not recommended	
Viral aerosolisation		Not recommended	Insufficient evidence to conclude that pre-rinse reduces aerosolisation of any viruses during dental procedures. More studies required
Denture stomatitis	*Candida albicans*	0.12 or 0.2% daily mouthwash 1-2% CHX gel to mucosa	Mouthwash recommended for denture stomatitis, supported by studies confirming CHX reduces oral *C. albicans* load A number of also studies suggesting mouthwash prevents binding of Candida to teeth and dentures (reduces biofilms)
ORAL MUCOSA			
Mucositis	None- inflammatory	Not recommended	May increase mucosal inflammation
Poor oral hygiene due to underlying condition	Mixed	Not recommended	Improved oral hygiene preferred for caries prevention and to improve periodontal health, with 0.2% fluoride daily oral rinse if adjunct mouthwash required

Table 3. Other systemic conditions, including oral mucosal viral and fungal conditions, where CHX could be used under current UK guidelines and narrative review of recent published evidence. Underlying conditions may include physical and psychological disabilities.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflicts of interest

None

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