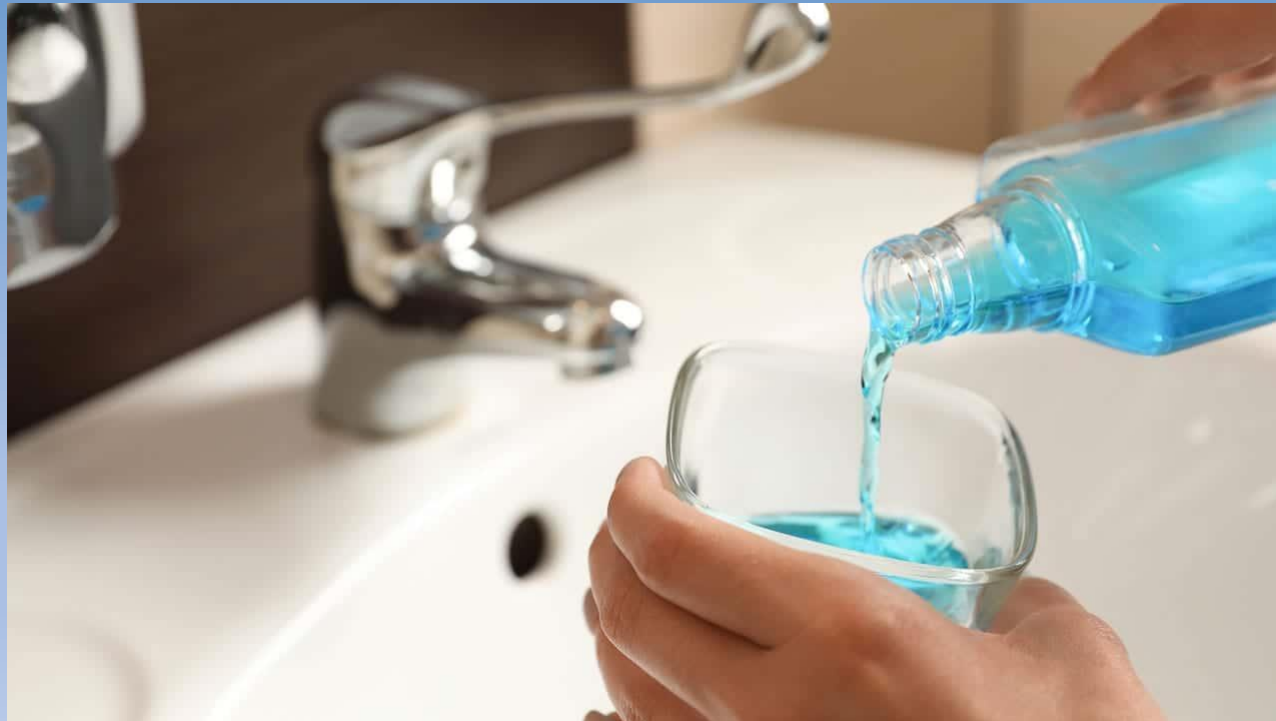
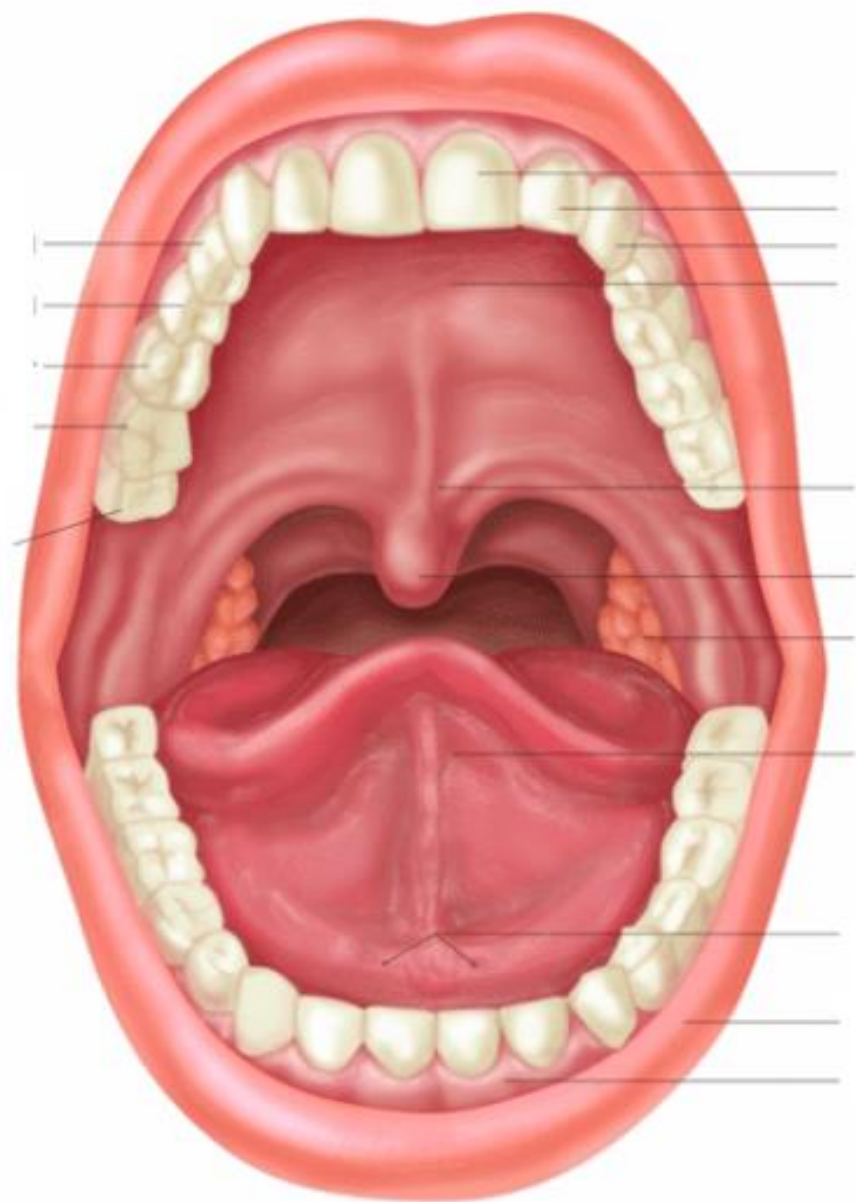


Antiseptic Mouthwashes : An Illustrated Review





- The oral cavity has a vast and complex biodiversity up to 800 microbial species.
- Plaque biofilm is the major etiologic factor causing gingivitis provides the justification for the use of antimicrobial mouth rinses.
- There is a wide range of commercially available MWs with antimicrobial properties for the treatment of oral diseases.

Why Chemical Control of Plaque

- Effective mechanical biofilm control requires time, willingness, and related skills. This may not be feasible in patients who are mentally or physically disabled, as well as in postsurgical situations where oral hygiene becomes almost impossible.

An Ideal Antiseptic Mouthwash

- Substantivity
- Safety : not toxic , allergic , irritant , resistance inducing
- Efficacy : for antiseptic : reducing inflammation
- Specificity : for antiseptic : efficient on oral pathogenic flora
- Taste
- Cost

Salivary Clearance

- 0.5 – 1.5 liter/d flow
- Clearance speed

Healthy

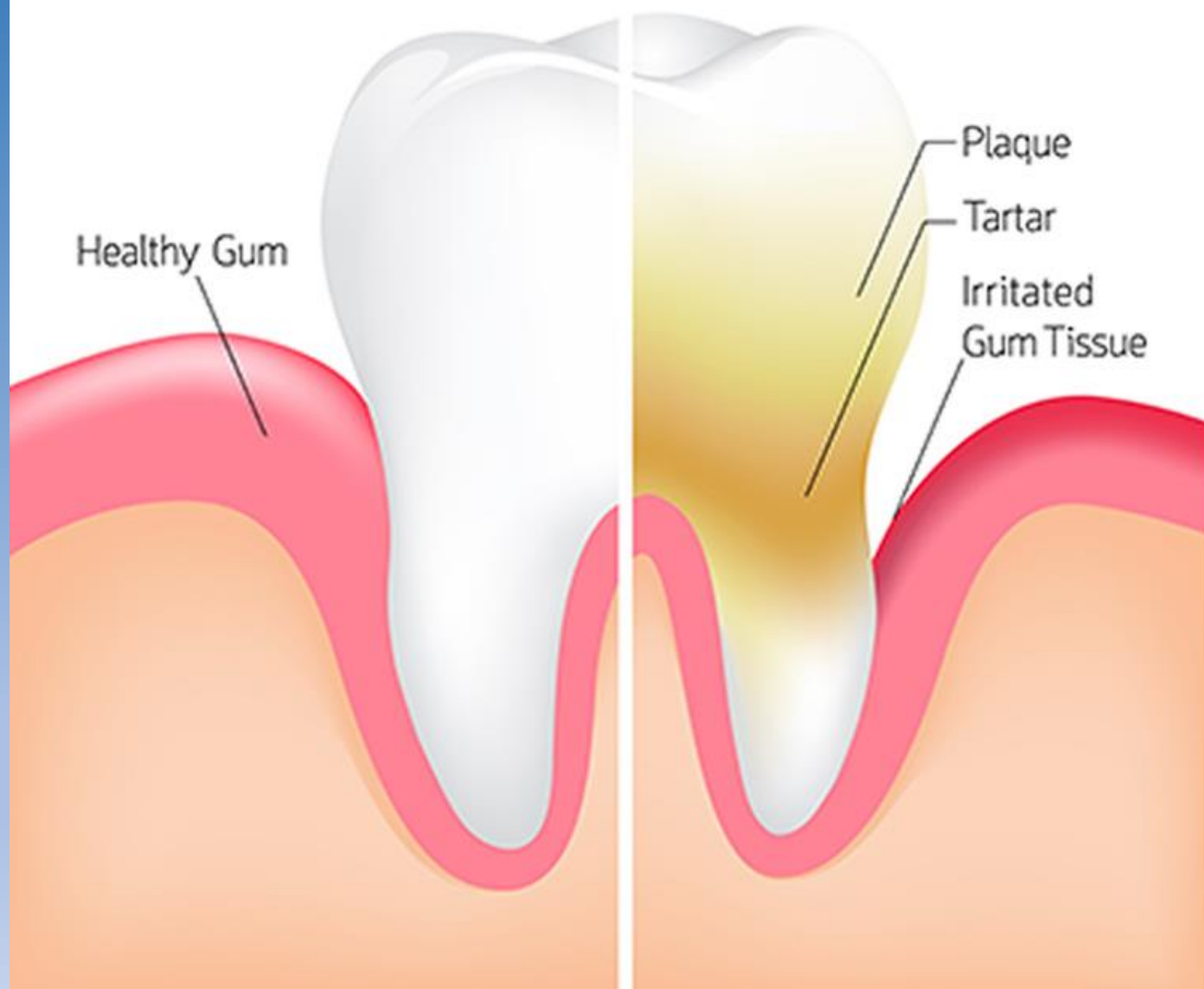
Unhealthy

Healthy Gum

Plaque

Tartar

Irritated
Gum Tissue



Mouthwash Structure

- Surfactant
- Alcohol
- Tasting
- Glycerin
- Benzoic acid
- Zinc chloride

- The practice of mouth rinsing has been in use by humans for more than 2000 years.
- The first MW advocated for dental plaque reduction seems to be urine from a newborn baby !!!
- In the 1880s, Miller (a dentist trained in microbiology) was the first to suggest the use of an antimicrobial MW to combat gingival inflammation.

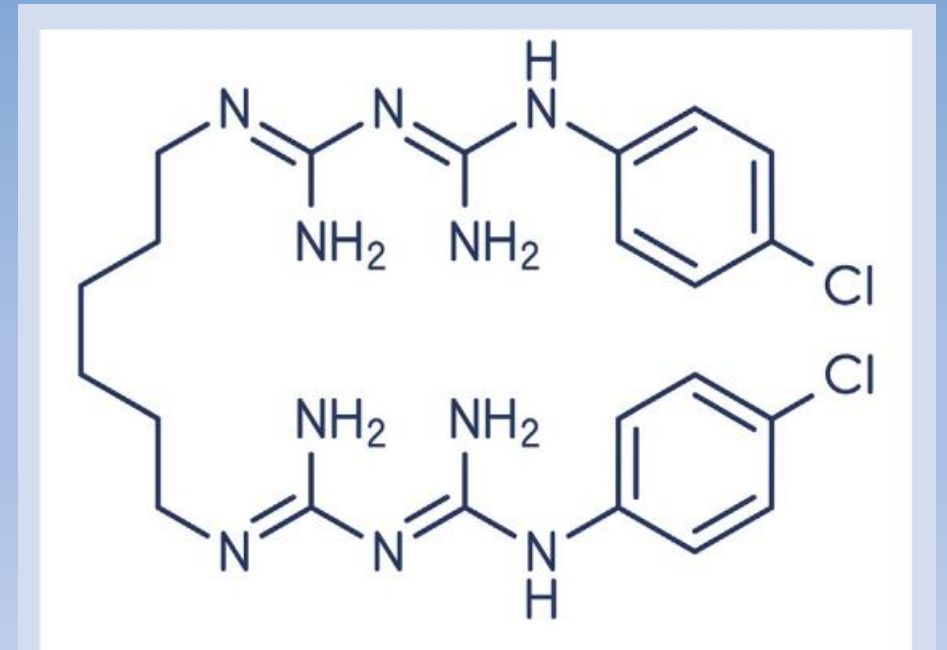
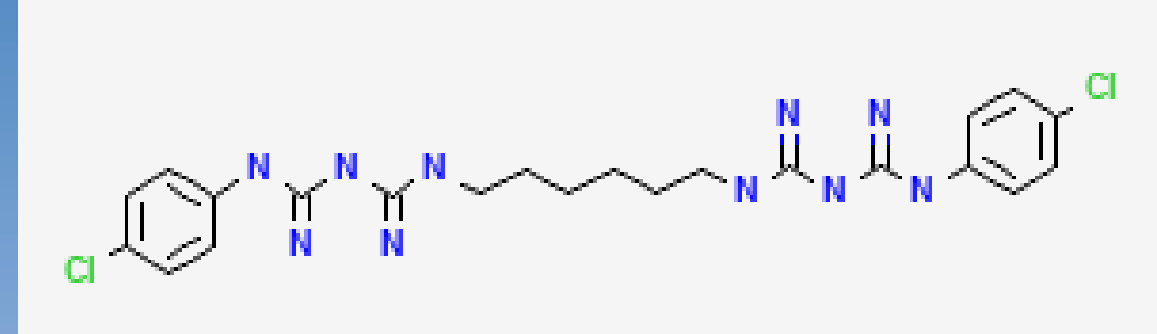
- Over the past decades, the use of MW has become customary, usually following mechanical plaque biofilm control.
- MW are an ideal vehicle in which to incorporate chemicals and are appreciated by the public because of their ease of use, reduction of plaque biofilm, and breath-freshening effect. CHX MW is the most potent chemotherapeutic agent and gold standard in reducing S mutans and oral biofilm.

Background

- It was introduced as a general disinfectant in the UK in the early 1954. At the time, this substance was called “Hibitane,”
- By 1976 it was available as a MW.
- Currently, CHX is one of the most effective, most popular antiseptic substances used in dentistry.

CHX Molecule Structure

- Two symmetrical structure with chlorophenyl rings and 2 synthetic **bis-biguanide** groups linked by a central hexamethylene bridge ($C_{22}H_{30}Cl_2N_{10}$).
- Is a cationic molecule with basic properties on both sides.
- Its biological activity owes single chlorine atoms on both phenolic rings.



Compounds

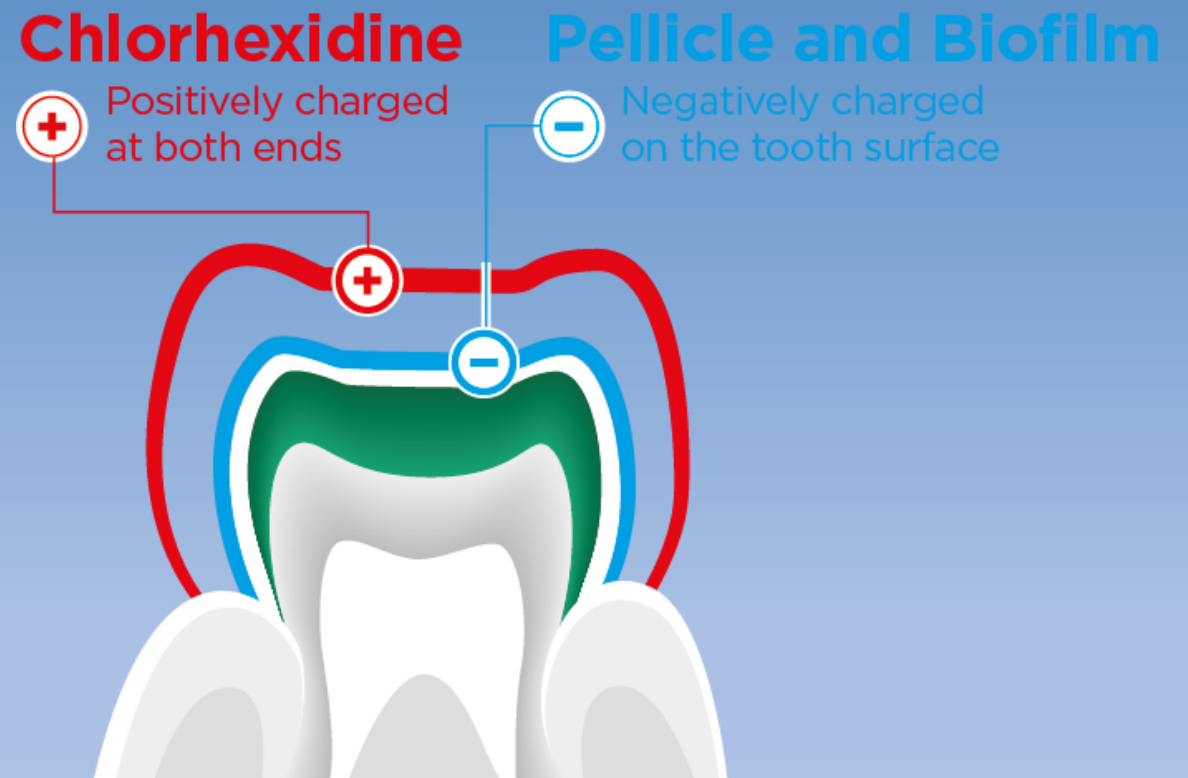
- A strong alkali practically insoluble in water. To make it water-soluble, the substance must be salified with gluconic acid.
- Salts of CHX have been applied in 3 formulations: acetate, digluconate and hydrochloride.
- Gluconate is almost colorless or pale-yellow liquid.

Effects on CHX Activity

- Heating to 100°C does not cause decay. During long-term storage under the influence of light and air CHX solution gradually darkens.
- Activity is dependent on the pH of the environment (optimal range=5-8).
- Activity is reduced in the presence of blood , pus & soaps.

- CHX MW only advised for topical use, and never for systemic administration.
- Being cationic, it binds to skin & mucosa 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.
- Poorly absorbed from the GI , even when large volumes are ingested.

- Due to the negative charge of most oral surfaces (including mucous membranes, teeth, and salivary glycoproteins), the cationic nature of CHX molecules exhibits good adherence to these surfaces and therefore interferes with bacterial adhesion, allowing for up to 12 hours.

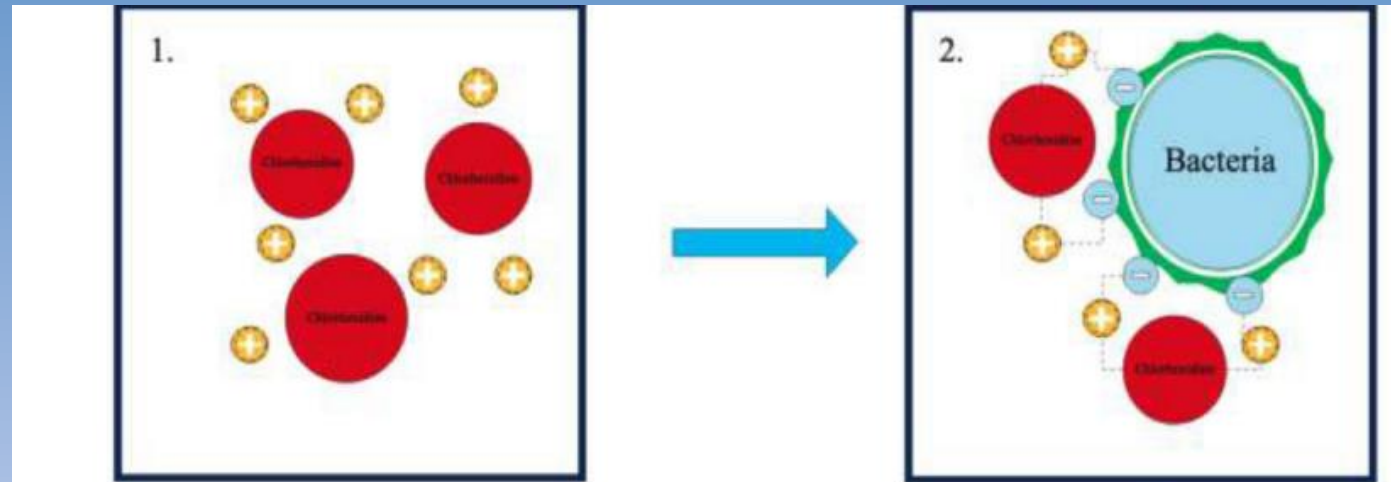


CHX Mode of Action

- The antimicrobial effect is dose-dependent.
- At low concentrations (0.02%-0.06%) has bacteriostatic activity, whereas at higher concentrations ($> 0.12\%$) acts bactericidal.
- CHX is lipophilic and positively charged. These two properties enable the interaction of CHX with bind nonspecifically to negatively-charged membrane phospholipids of bacteria.

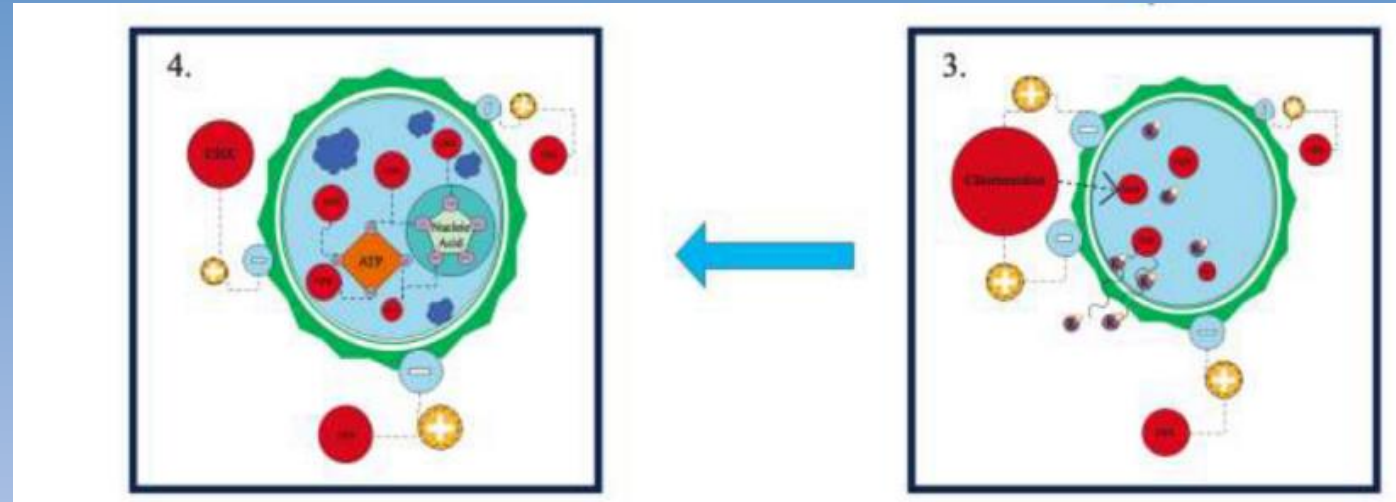
At Low Concentration

- Affects the change in the osmotic balance of the bacteria cell.
- This leads to cell wall damage , release and leakage of potassium , leads to a loss of as much as 50% of potassium ions; it may be reversible, on condition of removing the compound .



At High Concentration

- CHX enters the plasma membrane , release of intracellular components including nucleotides, coagulation of cytoplasmic proteins, formation of phosphate compounds, Increasing the bacterial cell membrane permeability , which in turn leads to lysis and cell death.



Spectrum of Action

- CHX is a broad-spectrum biocide
- CHX is most effective against Gram + and, to a lesser degree G- bacteria and fungi.
- This is due to the presence of the outer membrane in Gram – bacteria and the complexity of the cell wall in fungi that limits intracellular perfusion of CHX.

Spectrum of Action

- Against Staphylococcus , Actinomyces & Enterococcus in infected root canal systems.
- Eliminated also anaerobic perio-pathogens: Porphyromonas & Prevotella.
- Fungi can be inhibited by low concentrations of CHX but are less susceptible at higher concentrations.

Similarity with Antibiotics

- It was observed a correlation between the sensitivity of microorganisms to antibiotics and susceptibility to CHX.
- Resistance of Gram-negative bacteria for such ciprofloxacin and gentamicin, was accompanied the increase in resistance to CHX.

Activity against Virus

- Rapidly inactivated enveloped lipophilic viruses (HSV, influenza virus, CMV).
- No significant virucidal activity against small non-enveloped viruses (HPV).

Against COVID_19

- Findings regarding the effect of CHX on SARS-CoV-2 are conflicting.
- Earlier reports suggested lower CHX virucidal activity against SARS-CoV-2 on inanimate surfaces.
- The strategy with MW was to reduce the salivary load of the SARS-CoV-2 virus; thus, many substances such as povidone-iodine were analyzed.
- Due to the small sample size in the existing trials, more studies are still needed to prove the effectiveness of CHX on SARS-CoV-2.
- The COVID-19 pandemic increased CHX sales dramatically.

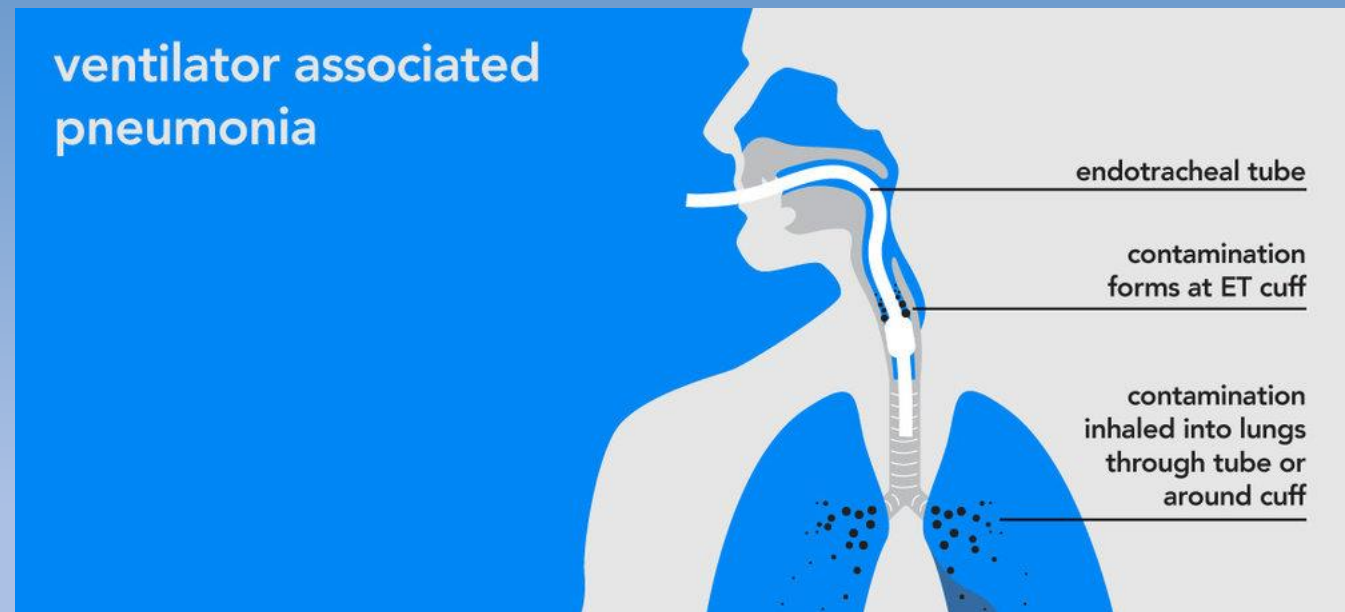
Formulations

- 0.2% & 0.12%
- 18 to 20 mg per application can be achieved with these concentrations.
- 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.



Wide Spectrum of Indications in Different Fields of Medicine

- To prevent hospital-acquired infections
- Hand hygiene in health care personnel.
- In bladder irrigation
- Pre-operative skin disinfection
- Impregnation of medical devices such as catheters & in ventilated patients.
- Disinfection of surfaces.



The Effects of Antimicrobial Oral Hygiene Treatment on Outcomes of Pulmonary Disease

- There is a high quality of evidence in the literature that the use of CHX adjunct to mechanical oral hygiene procedures exerts a substantial effect on the reduction in the amount of dental plaque in these patients.
- Minimizing the risk of complications of HAP in patients with periodontitis.
- The results of the other studies showed that improved periodontal health leads to improved clinical outcomes of COPD.



Meta-Analysis

> J Bras Pneumol. 2021 Jan 20;47(1):e20190286.

doi: 10.36416/1806-3756/e20190286. eCollection 2021.

Efficiency of different protocols for oral hygiene combined with the use of chlorhexidine in the prevention of ventilator-associated pneumonia

Protocols that include the mechanical removal of oral biofilm in combination with the use of chlorhexidine can reduce the incidence of VAP among ICU patients

- CHX cord application significantly reduces neonatal sepsis and mortality in developing countries. Therefore, we stress the importance of including CHX cord application into the essential newborn care in the setting with high burden of neonatal mortality.

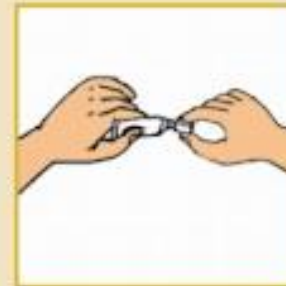
Gelano et al. Systematic review and meta-analysis (2019)

4% Chlorhexidine Gel (Navi Malam)

Use of 4% Chlorhexidine to prevent infection in newborn



- CHX can prevent cord infection in newborn babies
- Apply CHX immediately after cord cutting
- Single application is adequate
- Use the all gel of the tube



1. Use the sharp protuberance of the lid to break the inner shield of the tube



2. Wash hands properly with soap and water before application of CHX



6. Apply 4% CHX gel on the stump and the surrounding areas of the cord



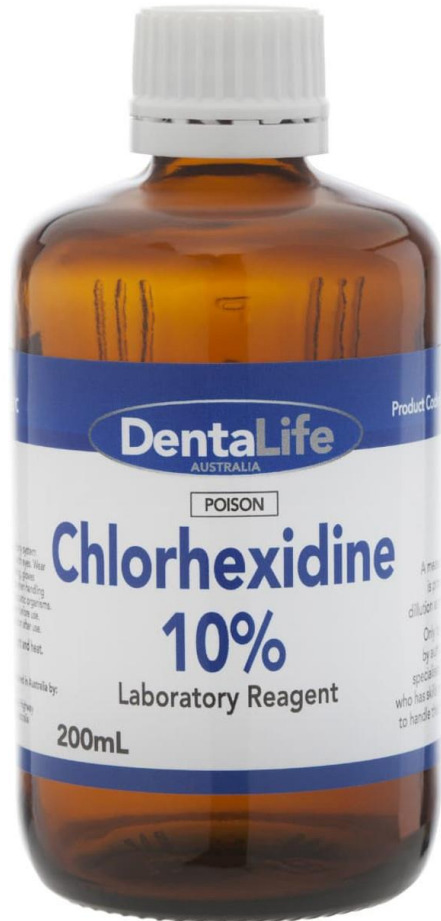
4. Spread the gel gently on the stump and surrounding areas using index finger



5. After applying CHX gel, apply nothing on the cord and keep the cord clean and dry

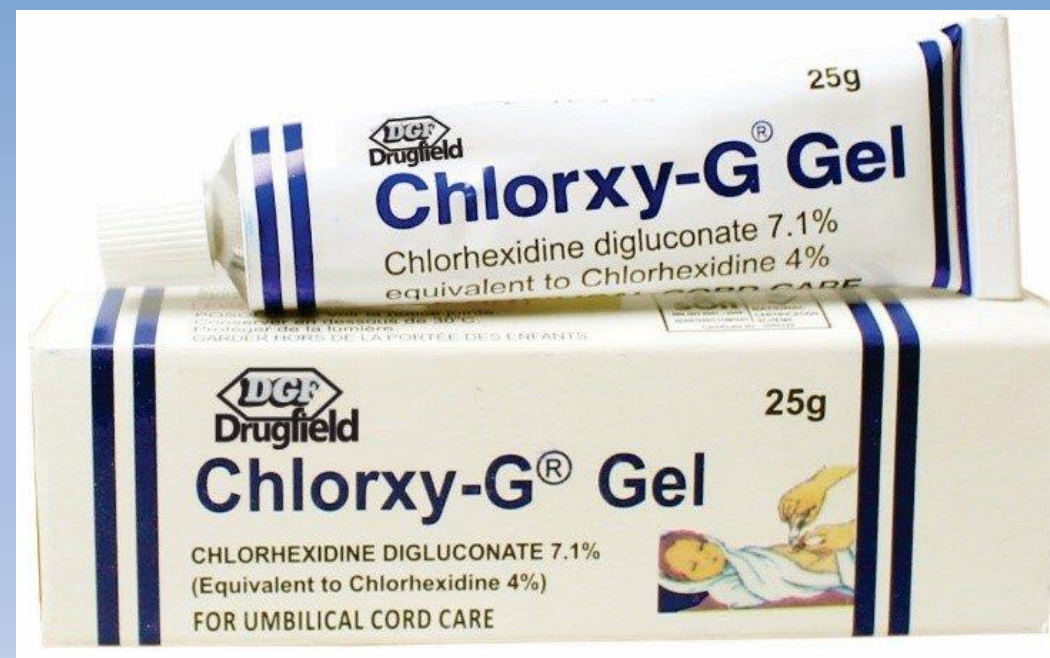
Evidences in Medicine

- 1- Preoperative skin preparation with 0.5-2% CHX associated with lower rates of surgical site infections (SSIs) before and after the insertion of venous access. The only other skin disinfectants is 10% iodopovidone.
- 2- Bathing with CHX can reduce the number of hospital-acquired infections greater as compared to bathing with soap and water (2% cloths)
- 3- CHX can be used for prevention of infection following caesarean section.



In Dentistry (The Most Widely Application)

- Available as MW, spray formulations (0.12-0.2%), gels (0.12-1%) and dental varnishes (1%, 10%, 40%). Can be found in toothpastes (0.05%), gels for cleaning teeth and dental flosses.



Gingivitis & Periodontitis

- Using of 0.12-0.2% concentrations of CHX in MW results in significant **reduction of gingivitis and plaque indexes** , Adjunct to SRP.
- 4-6 weeks of daily rinsing with 0.2% CHX reduced clinical signs in several studies.
- Not effective with reducing moderate to severe periodontitis, even as an adjunct.
- 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.
- CHX can be more effective in an alkaline environment of gingivitis rather than in acidic periodontitis.

- To reduce oral bacterial flora (Pre-surgical).
- Using of 0.12% CHX , 7 days post-operatively have preventive effect on dry socket.
- CHX is used also in prevention of tooth caries. It acts against S. mutans but the role in preventing dental caries is controversial.
- Solutions containing different concentrations of CHX have been suggested for the irrigation of infected root canals .

- Have impact in the **treatment of halitosis**, especially in reducing the levels of anaerobic bacteria related with halitosis.
- Used in the phases **following oral surgery**.
- If toothbrushing is not possible due to postoperative pain from implant placement, it is recommended that a 1-minute rinse of 0.2% CHX is used 3 times a day for 7 days or until sutures are removed.
- **Treatment of Peri-implantitis.**
- **During orthodontic treatment.**

MRONJ

- 0.12-0.2% CHX mouthwash should be used twice daily during the week before extractions and then twice daily for up to 2 months to facilitate healing in cancer patients at high risk of MRONJ.
- CHX can also be used to treat MRONJ (stage1).

Infective Endocarditis

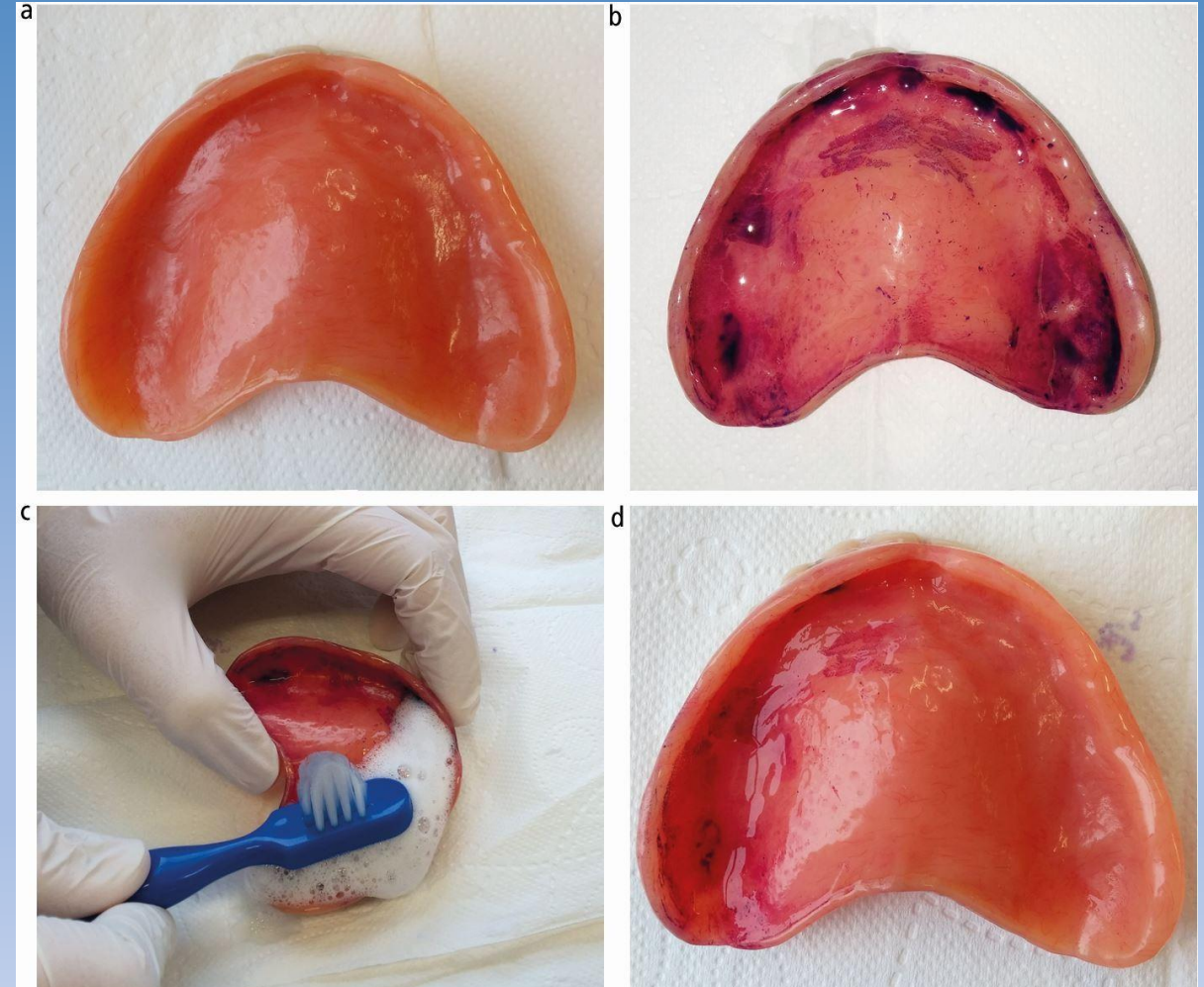
- A 1-minute pre-operative rinse of 0.2% CHX is recommended to reduce the bacterial load.
- Updated protocols do not support CHX use for this reason.

How to Use CHX MW?

- For all formulations, the advice is to rinse with 10-15 ml twice daily for 30 seconds & spit out.
- Under 12 years it is use only to be used on the advice of a healthcare professional.
- It is also advised for short-term use only : 2-4 weeks.
- Rx: Chlorhexidine gluconate MW 0.12%.
- No statistically significant differences in antiseptic effectiveness
- Avoid rinsing or eating for 30 min following treatment.
- Rinse after breakfast and at bedtime.

CHX in Treatment of Oral Lesions

- CHX gel can also be applied 1-2 times a day to affected areas to treat Candidiasis and aphthous ulcers, particularly in immunocompromised patients who are more susceptible to overgrowth of *Candida albicans*.
- In patients with DS, dentures may also be soaked in MW once or twice daily for 15 minutes.



Chemotherapy of Head & Neck Cancers

- It is more likely that HNCC patients may be using CHX rinses at home, due to its claims to improving plaque control and reducing gingivitis. In patients undergoing chemotherapy & radiotherapy who had developed oral mucositis, the use of CHX may elevate symptoms of mucositis.

In Special Care Dentistry

- Application of 1% CHX gel as a potentially effective adjunct for reducing periodontal disease, if applied at home daily in individuals with Down Syndrome.
- 0.12 % for periodontal diseases in HIV (LGE & NUG).
- In patients suffering from low salivary flow, chlorhexidine gluconate should be used concurrently with artificial saliva.
- Leukemia , hemophilia.

Cytotoxic Activity to Human Cells

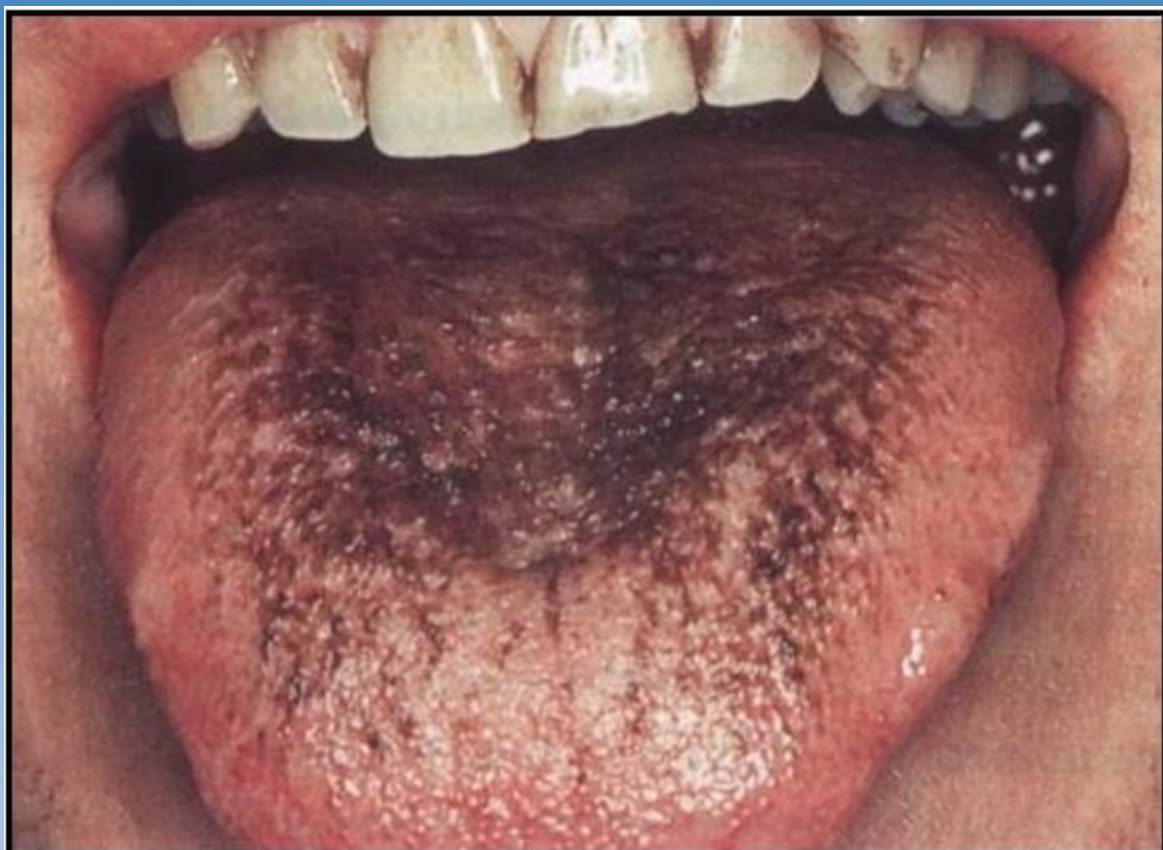
- To human gingival fibroblasts, periodontal ligament cells , alveolar bone cells , and osteoblastic cell line , which is time- and dose-dependent.
- Concentrations $\geq 0.02\%$ produces total loss of ATP in human dermal fibroblasts.
- In vitro : can stimulate apoptosis and cell death.
- Cytotoxic activity of CHX to human cells in vivo is recently not fully known and requires further studies.

Side Effects

- The most unwanted outcome is probably tooth staining.
- Used for more than 2 weeks in dental treatment most often causes **discoloration** of the teeth, tongue (coated) and fillings made of composite materials and glass ionomer. this is because CHX is able to attack the enamel film to remove it and thus makes the enamel susceptible to pigments in food or beverages.
- Maillard reaction: production of pigmented metal sulphide formation.



- Formulations of CHX are now available to prevent tooth staining, where an anti-discoloration system (ADS) has been added.
- ADS does not effect the ability of CHX to reduce to gingival inflammation.
- CHX is applied before the dentifrice, the staining will decrease.



- Xerostomia
- Hypogeusia , specifically salt and bitter.
- Increased calculus formation has also been reported with 0.12% CHX MW.
- Other less common side effects include burning sensations (glossodynia), desquamation of the oral mucosa, swelling of the parotid gland and oral paresthesia.

Allergy?

- CHX allergy has been reported (Some severe).
- All patients with suspected hypersensitivity reactions should be considered for CHX allergy testing and allergist consultation.
- perioperative allergy

Hypersensitivity reaction of the gingiva to chlorhexidine



3. Follow-up. Normal appearance of the gingiva 2 weeks after discontinuation of chlorhexidine-containing toothpaste.

- CHX rinses may interact with the anionic components of many toothpastes, and reduce the beneficial effects of fluoride on the remineralization of enamel lesions.
- Some components of toothpaste like sodium lauryl sulphate (SLS) reduce the substantivity and overall effectiveness of CHX , maybe deactivate CHX.
- So, it would be appropriate to wait at least 30 min and ideally 2 hours between brushing and using MW.
- Its effectiveness can also be influenced by nutrition, so it is good to avoid drinks for at least an hour.

Prolonged Use?

- Below et al. used 0.2% CHX rinse three times a day for 5 days and reported a saliva concentration peak on the fourth day, which remained detectable 12 h after the last use. They also detected a high concentration of p-chloroaniline, which is potentially carcinogenic .
- FDA recommendation is to limit the use of CHX mouthwash to a maximum of 6 months.

Hypertension?

- Bescos et al. reported that CHX could shift the oral microbiome resulting in decreased saliva nitrate concentration, which may have a severe adverse impact on patients with high blood pressure.
- Tribble et al. reported that washing the mouth twice a day with a 0.12% CHX solution for a week significantly increased blood pressure in healthy subjects.

Essential Oils

- EOs are used in an OTC MW containing a mixed phenol-related EOs, thymol 0.064% and eucalyptol 0.092%, mixed with menthol 0.042% in a 22% alcohol vehicle.
- The antimicrobial mechanisms of action of EO against bacteria are complex. At high concentrations, there is disruption of the cell wall and precipitation of cell proteins, whereas at lower concentrations, there is inactivation of essential enzymes.

- Listerine, a MW composed of a mixture of essential oils, was created in 1879.
- Over the past 100 years, phenolic compounds (e.g. LISTERINE) have been acknowledged to be germicidal and effective in reducing plaque and gingivitis.



- Adding LISTERINE to the standard oral hygiene regimen may be beneficial for orthodontic patients in maintaining proper oral health, thus reducing the likelihood of developing white spot lesions and gingivitis.

The Active Ingredients of Antimicrobial Rinses

Active Ingredient	Active Ingredient	Active Ingredient
EO (essential oils)	CPC (cetylpyridinium chloride)	0.12% CHX (chlorhexidine)
Description	Description	Description
Fixed combination of: 1. Eucalyptol (0.092%) 2. Menthol (0.042%) 3. Methyl salicylate (0.060%) 4. Thymol (0.064%)	Quaternary ammonium compound	A bactericidal bisbiguanide antiseptic, prescription in the US
Marketed Product	Marketed Product	Marketed Product
LISTERINE® Antiseptic	Crest® Pro-Health™ (Procter & Gamble) ACT® Total-Care™ (Chatterm) Colgate Total® Advanced Pro-Shield™ (Colgate-Palmolive)	Peridex® (3M ESPE) PerioGard™ (Colgate-Palmolive)

- Also, anti-inflammatory action has been proposed based on antioxidant activity.
- First Choice : CHX
- The most reliable alternative for plaque control is EO. No difference between CHX and EO with respect to gingivitis was observed.

Triclosan

- TCL is a chlorinated aromatic compound that has functional groups representative of both ethers and phenols. It has antibacterial properties , applied in consumer products, including soaps and detergents.
- In mouthwash products it is combined with zinc sulfate.



Cetylpyridinium chloride

- (CPC) is a cationic quaternary ammonium compound with surface-active properties.
- Its mechanism of action relies on the hydrophilic part of the CPC molecule interacting with the bacterial cell membrane leading to loss of cell components, disruption of cell metabolism, inhibition of cell growth, and finally cell death.
- It has a broad antimicrobial spectrum, with rapid killing of gram-positive pathogens in particular.

- The search retrieved 3 systematic reviews concerning the efficacy of CPC evaluating the adjunctive effect to toothbrushing in the prevention of plaque accumulation and gingival inflammation.
- Very limited.
- 0.025-0.075%



Oxygenating agents

- (OAs), such as hydrogen peroxide (H_2O_2)(1.5-3%) , carbamide peroxide (10-11%) & sodium perborate (3-6%) have been recommended for short-term use as disinfectants. (ANUG)
- They exert antimicrobial effects through the release of oxygen.



Povidone-Iodine

- PVP-I presents a significant virucidal activity against SARS-CoV-2 in saliva.
- A 30- or 60-s pre-procedural rinse of 0.5/1% PVP-I could be beneficial to reduce the risk of cross-infection in healthcare settings in diagnosed, suspected, or asymptomatic COVID-19-positive patients.
- Concentrations of 2% did not show statistically significant changes in salivary load.



Alcohol

- Alcohol in MWs is used to enhance flavor impact, to solubilize the flavor and some active ingredients, to provide some preservative power, and improve the transport of active ingredients into the dental plaque biofilm.
- Alcohol vehicle solution does not contribute to the efficacy of the MW.
Although the accumulated effects of MW usage with a high percentage of alcohol and ingestion of alcohol could theoretically predispose toward oral or pharyngeal carcinoma, the contributory effects of alcohol in these rinses are unclear and not considered proven by FDA.

- More recently, for various reasons, there has been an increase in the demand for alcohol-free MWs.
- Alcohol has been shown to cause mucosal irritation in some patients.
- An important determination is whether the inclusion or exclusion of alcohol could affect the activity of the MWs.

Rinse Duration and Volume

- The manufacturers of MWs recommend different durations for the rinsing procedure.
- The subjects preferred the shorter rinsing time, which raises the question of whether shorter rinsing times can be sufficient for effective plaque control.
- Minimal difference between rinsing for 30 or 60 seconds on plaque scores.
- The most pleasant volume of mouthwash is 15 mL.

Cost Effectiveness

- At present prices, the cost of mouthwashes would be far greater than that of toothbrushes and dentifrice. This may be prohibitive for many individuals, and dentifrice is thus still the best vehicle for delivering antiplaque agents.
- Nonetheless, if a MW is highly effective in terms of oral health gain, the additional cost of its use may be a price worth paying.

Conclusion

- As emerged out of this review, this would apply particularly to CHX and EO mouthwashes.
- The long-term use of antiseptics has raised concerns about the possibility of undesirable changes in the composition of the complex oral microflora, spot colonization and the emergence of resilience.
- Any mouthwash should be an adjunct rather than replacement for brushing.

Clinical Indications for CHX

- Short-term applications (Pre-surgical , healing phase of different oral surgeries , therapy for RAS , DS ...)
- Intermittent short-term applications (adjunct to periodontal maintenance care , high caries activity ,dental implants)
- Long-term applications (medically compromised , physical or mental handicapped patients)

