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A Performance Summary of Agents Used in Oral Care for Non-Ventilated and Mechanically-Ventilated Patients

Paula S. Lavigne and Mark C. Lavigne*

Global Clinical Affairs, Avanos Medical, Inc., 5405 Windward Parkway, Alpharetta, GA 30004, USA

***Corresponding Author:** Mark C. Lavigne, PhD, Global Clinical Affairs, Avanos Medical, Inc., 5405 Windward Parkway, Alpharetta, GA 30004, USA.

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Abstract

Background: Clinical settings can ironically exacerbate the conditions of patients by facilitating the development of non-ventilator hospital-acquired pneumonia (NV-HAP) and ventilator-associated pneumonia (VAP). The use of oral care agents may reduce oral and respiratory infections in patients. The intent of this broad information resource is to assist healthcare providers to make the best decisions possible about oral hygiene administration for critically ill and other patients.

Methods: Several scientific/medical databases were searched, as directed by the use of terms related to the content of interest for this work, for publications pertaining to the performance of multiple oral care agents on NV-HAP, VAP, and other oral care-relevant endpoints. Relevant publications were selected for incorporation into this work without bias, with information from each presented here according to agent name and corresponding endpoints addressed.

Results: Effects on NV-HAP and VAP incidence are dominated by studies involving chlorhexidine gluconate (CHG), which has shown significant effectiveness in adults, but not in children, and may cause mortality in some patient populations. To our knowledge, only cetylpyridinium chloride, sodium bicarbonate, and hydrogen peroxide have been compared to CHG with respect to the VAP rate. Similar anti-microbial effects of coconut oil (CO) to CHG suggest CO as an anti-NV-HAP and/or VAP agent, but this hypothesis has not been tested.

Conclusions: Thus, unmet needs in oral care are at least 2-fold, including to further investigate 1) a treatment to prevent pneumonia in hospitalized children and 2) CHG links to mortality. One or both of these goals may reveal a necessity to identify an oral care agent that can substitute for the anti-NV-HAP and/or -VAP effects of CHG.

Keywords: Oral Care; Agents; Medications; Nosocomial Pneumonia; Ventilator-Associated Pneumonia; Critical Care

Introduction

Despite the intent of a hospital environment to promote healthcare and recuperation from illness, it can paradoxically make patients more ill, commonly by facilitating infection. Kaneoka et al. (2015) conveyed that pneumonia is the second most common healthcare-associated infection worldwide and increases the cost of care and mortality [1]. Hospital-acquired, or nosocomial, pneumonia (NP) consists of two major types, non-ventilator hospital-acquired pneumonia (NV-HAP) and ventilator-associated pneumonia (VAP). Ventilator-associated pneumonia is defined as occurring >48 hours after endotracheal intubation and occurs as a consequence of mechanical ventilation (MV). Klompas (2017) indicated that the United States (US) Centers for Disease Control and Prevention (CDC) estimates that VAP currently affects approximately 6.6% of patients on MV, corresponding to approximately 50,000 cases per year in the US alone [2]. Non-ventilator hospital-acquired pneumonia is not present at the time of hospital admission but instead occurs 48 hours or more after admission [3]. Based on the 2012 US National Inpatient Sample, Giuliano et al. determined the overall incidence of NV-HAP to be 1.6%, which represents a rate of 3.63/1000 patient

days [4]. Non-ventilator HAP is associated with increased total hospital charges, a longer hospital length of stay, and a greater likelihood of death in comparison to other patient cohorts: pneumonia on admission, general hospital admissions, matched on mortality and disease severity, but not patients with VAP [4].

The microbial-contaminated oropharyngeal space is the origin of NP in patients. Bacterial colonization in dental plaque, which is a predecessor of gingivitis, is robustly associated with the development of nosocomial infections [5,6]. Moreover, the risk of VAP elevates as plaque burden increases [7]. Microbial colonization of the oropharyngeal space, whether derived from plaque and gingivitis or by some other means, such as accumulation of secretions in mechanically-ventilated (M-V) patients, is especially concerning for patients who are immunocompromised and those, due to a predicate mental or physical illness, who are unable to address these infectious threats through adequate oral care. Based on their analysis that emphasized the important link between oral health and NP, Amaral et al. (2009) concluded that a lack of oral care is a risk factor for NP incidence [8]. Indeed, oral care has been shown to significantly reduce the incidence of VAP among ICU patients [9], and decontamination of the oropharyngeal space with an antiseptic significantly decreased oropharyngeal colonization by aerobic pathogens [10] and reduced VAP risk [11] among M-V patients.

The outcomes of the studies immediately above illustrate that the neutralization of oral contaminants is beneficial toward preventing NP. As explained by Vilela et al. (2015), there are two ways to remove dental plaque and its associated microorganisms: 1) by means of mechanical, and/or 2) pharmacological interventions [12]. In a systematic review and randomized controlled trial (RCT), Vilela et al. (2015) and Munro et al. (2009), respectively, concluded that oral hygiene using a 0.12% solution of chlorhexidine gluconate (chlorhexidine; CHG), and not tooth brushing, seemed to be a more effective hygiene method [12,13]. Consistent with this, approximately 80% of hospitals' ventilator bundles include an antiseptic mouthrinse [2].

Oral care practices are important state-of-the-art strategies for healthcare professionals to reduce the incidence of pneumonia among non-ventilated and ventilated individuals. In this comprehensive review article, we aim to furnish healthcare providers with an information source that can be used to help them to achieve best-practice treatments for cleansing the oropharyngeal space of their patients, based on performances of multiple oral care agents, including CHG, cetylpyridinium chloride (CPC), sodium bicarbonate (NaHCO3), hydrogen peroxide (H2O2), mouth moisturizers, coconut oil (CO), and others that are discussed herein.

Methods

Literature concerning the performance of multiple oral care agents was identified with respect to their effects on NV-HAP, VAP, dental plaque, gingivitis, and other endpoints, among critically ill and healthy individuals. The bibliography that supported this work was derived from searches of PubMed (US; https://www.ncbi.nlm.nih.gov/pubmed/), EBSCO (US; https://www.ebsco.com/), the National Institute for Health and Care Excellence (NICE; United Kingdom; https://www.nice.org.uk/), Google Scholar (US; https://scholar.google.com/), and Google (US; https://www.google.com/) using terms such as "chlorhexidine and oral care", "hydrogen peroxide and oral care", "chlorhexidine and mortality", and "chlorhexidine and coconut oil". Titles and abstracts of citations produced were reviewed for relevance to the content of this report. Full publications of selected references and their bibliographies were inspected without bias for incorporation into this work according to the names of the agents and the endpoints that addressed the oral care performance of each.

Results

Chlorhexidine

Chlorhexidine is indicated as a topical antiseptic and as an anti-bacterial dental rinse to treat gingivitis and has activity against gram-positive and gram-negative organisms, facultative anaerobes, aerobes, and yeast; it is both bacteriostatic and bactericidal, depending on its concentration [14,15]. Chlorhexidine provides anti-microbial activity during oral rinsing. Microbiological sampling of plaque has shown a general reduction of counts of certain assayed bacteria, both aerobic and anaerobic, ranging from 54-97% through 6 months of use [14,16,17].

Following the use of a 0.12% topical oral solution (mouthwash or oral rinse) of CHG, approximately 30% of the drug is retained in the oral cavity [14,16,17]. This retained drug is slowly released into the oral fluids. Chlorhexidine is poorly absorbed in the gastrointestinal (GI) tract [14,16,17]. It is almost 100% eliminated without absorption [18]. Use of a CHG oral rinse in a 6-month clinical study did not result in any significant changes in bacterial resistance, overgrowth of potentially opportunistic organisms, or other adverse changes in the oral microbial ecosystem. Three months after discontinu

ing CHG use, the number of bacteria in plaque had returned to baseline levels, and the susceptibility of plaque bacteria to CHG was equal to that at baseline [14,16].

Chlorhexidine gluconate uses include treatment of gingivitis [14,16], periodontitis [19], prevention of dental caries [20], and oropharyngeal decontamination to reduce the risk of NV-HAP or VAP in critically ill patients [20], cardiac surgery patients [21,22], and mechanically-ventilated (M-V) patients [23,24]. Chlorhexidine gluconate is deactivated by anionic compounds, including the anionic surfactant, sodium lauryl sulfate, commonly used as a detergent in toothpaste and mouthwashes [25,26]. For this reason, CHG mouth rinses should be used at least 30 minutes after using dental products containing these ingredients [26]. There is no specific CHG dose recommended for use in M-V patients, due to the heterogeneous nature of the studies and paucity of conclusive data that have been reported about this issue [15].

Chlorhexidine Gluconate Properties and Effects in Oral Care

Anti-Infection

Fourrier et al. (2000; RCT) found that, compared to standard oral care (mouth rinsing with bicarbonate isotonic serum and then gentle oropharyngeal sterile aspiration 4 times/day), 0.2% CHG gel oral care applied 3 times daily significantly reduced dental plaque accumulation, colonization of such plaque with microorganisms, and the risk of nosocomial infection among ICU patients (N = 60; mean age = 51 years-old (years)) [27]. Later, as a consequence of their prospective, multicenter, double-blind, placebo-controlled efficacy study, Fourrier et al. (2005; N = 228; mean age = 61 years) reported that 0.2% CHG gel significantly reduced oropharyngeal colonization by aerobic pathogens compared to a placebo gel, but this did not manifest as a significant difference between study groups in the incidence of respiratory infections [28]. The test agent administration protocols and patient populations (non-edentulous, requiring endotracheal intubation and MV, with an anticipated length of stay >5 days) were similar in each of these studies by Fourrier and respective colleagues, and so the contrasting effects on nosocomial infection risk may be attributable to the fact that the former study occurred in one center, while the latter involved multiple clinical centers. Indeed, perhaps the variety of environments presented in the multi-center investigation introduced other variables (e.g., oral care compliance, technique differences, etc.) that could have impacted the ability of CHG oral care to meaningfully influence the nosocomial infection rate. As such, Ćabov et al. [29] (2010; N = 60 non-edentulous patients consecutively admitted to the surgical ICU and requiring a minimum stay of 3 days; mean age = 55 years) used the same methodological strategy (prospective, double-blind, placebo-controlled) for their RCT as Fourrier et al. did in 2005 [28], except that it was a single-center trial, as Fourrier et al. had conducted in 2000 [27]. And like the results of this latter report, Ćabov et al. observed that, compared to a placebo, 0.2% CHG gel oral care significantly decreased oropharyngeal colonization and the incidence of nosocomial infections [29].

Based on a retrospective analysis, Postma et al. (2012) reported that 2% CHG, compared to standard care with saline, reduced bacterial, but not fungal, oral cavity colonization among M-V ICU patients (N = 104; mean age = 68 years) [30]. Of the cultures produced by respiratory sampling from each cohort, 102 (55%) and 173 (62%) (no significant difference) contained pathogenic bacteria in the CHG and saline groups, respectively. In healthy volunteers (N = 45; age range = 18-38 years) of an RCT, Preus et al. (2013) found that a 0.2% CHG mouth rinse reduced gingivitis and dental plaque to a greater extent than that of essential oils (EOs) or hydro-alcohol oral care solutions [31]. Noted CHG-associated adverse events (AEs) were tooth discoloration, burning sensation, and reduced taste. Sharif-Abdullah et al. (2016) performed a double-blind, parallel-group RCT to assess microbial colonization among edentulous geriatric inpatients (N = 90) [32]. Oral care including 0.2% CHG mouthwash or thymol gargle (control group) was compared, with each provided to their respective recipients once daily for 7 days. Compared to baseline values, microbial colonization counts after 7 days of CHG were significantly less, while in contrast, thymol did not reduce oral microbial burden. Tuon et al. (2017) observed in their RCT that 2% CHG was more effective than placebo (0.9% sodium chloride (NaCl)) against multi-drug resistant (MDR) bacteria in M-V patients (N = 46; mean age = 46 years) [33]. Compared to the placebo, 2% CHG significantly reduced the prevalence of methicillin-resistant Staphylococcus aureus (MRSA) in dental plaque and the oral mucosa.

Effectiveness in Non-Mechanically- and Mechanically-Ventilated Patients

In order to test the hypothesis that twice-daily oropharyngeal cleansing with 0.2% CHG solution reduces the risk of NP in a mixed medical and surgical ICU population of non-ventilated and ventilated patients (N = 512; mean age = 36 years), Panchabhai et al. (2009; RCT) compared oropharyngeal

cleansing with 0.2% CHG to 0.01% potassium permanganate (control) solution [34]. Of the 471 subjects who completed the protocol, no significant difference in NP occurrence, median day of development of pneumonia, or mortality was observed. A systematic review and meta-analysis involving 22 randomized trials (N = 4277 patients) by Silvestri et al. (2014) revealed that CHG (0.12%, 0.2%, 1%, 2%) significantly reduced the incidence of NV-HAP and VAP [35]. Interestingly, a subgroup analysis revealed a significant benefit of CHG on NV-HAP in surgical patients only, most of whom, had cardiac surgery. The authors indicated that in critically ill, mainly surgical patients, oral CHG reduced NV-HAP, VAP, and NV-HAP due to Gram-positive and Gram-negative bacteria, and due to "normal" flora (community microorganisms), without affecting mortality. In a prospective observational examination, Chen et al. (2016) studied patients (N = 873; mean age = 62 years) who stayed >48 hours in an emergency ICU and were provided oral hygiene by swabbing with 0.08% metronidazole (MDE) twice daily until discharge or death during the first year (period M), whereas 0.2% CHG was applied during the following 3 consecutive years (periods C1-C3) [36]. Treatment with CHG during period C3 yielded significantly fewer episodes of NV-HAP compared to those in period M, and the time to initiation of NV-HAP in the ICU was significantly delayed during all CHG treatment periods compared to the MDE intervention time-frame. The incidence of VAP was significantly less during periods C2 and C3 compared to period M.

Effectiveness to Prevent Ventilator-Associated Pneumonia in Adults Versus "Control" Regimens

MacNaughton et al. (2004; RCT) explored the ability of 0.2% CHG mouth rinse to reduce the incidence of nosocomial lower respiratory tract infections (LRTIs) in intubated adult ICU patients (N = 179) who were predicted to require ventilatory support for at least 48 hours [37]. Chlorhexidine (0.2%) was compared to a placebo control solution (50% peppermint water, 50% sorbitol), with initial oropharyngeal suction to remove secretions, and then twice-daily applications of the test agents to respective patients' roof of the mouth, inside of cheeks, tooth surfaces, gums, tongue, and buccal cavity. Each of the oral care protocols continued until a patient was extubated or died. Treatment of patients with CHG made no significant impact on VAP incidence, as the occurrence of VAP in each study group was similar. In their RCT involving patients (N = 5) in a critical care unit, Bopp et al. (2006) assigned patients to twice-daily oral hygiene involving brushing the cheeks, teeth, and endotracheal tube with a suctioning toothbrush using 0.12% CHG (mean patient age = 40 years) or standard oral care 6 times per day consisting of use of a soft foam swab and half strength H2O2 (mean age = 74 years) [38]. One of the 3 patients in the non-CHG cohort was discharged with NP, but the 2 subjects in the CHG group did not develop NP. Munro et al. (2009) randomly assigned 547 patients (mean age = 48 years) in an RCT to 1 of 4 treatments: 0.12% CHG oral swab twice daily, toothbrushing 3 times daily, both toothbrushing and CHG, or control (usual care) to examine which intervention was best for preventing VAP in M-V patients [13]. While CHG, toothbrushing, or its combination had no effects on the entire patient pool, including those who did or did not have pneumonia upon day 1 of treatment, by day 3 of treatment, CHG had significantly reduced the incidence of VAP compared to those who did not receive CHG. Pobo et al. (2009) considered the effect that electric toothbrushing would have on the VAP rate [39]. The adult patients (N = 147; mean age = 54 years) in this prospective, simple-blind, randomized trial were intubated for >48 hours and received either standard oral care that included application of gauze containing 0.12% CHG to all dental pieces, tongue, and the mucosal surface, and 10 milliliters (ml) of 0.12% CHG was injected into the oral cavity, with aspiration after 30 seconds. In the toothbrush group, the same protocol as for the CHG group was performed and, in addition, brushing tooth by tooth, on anterior and posterior surfaces, and along the gumline, and brushing the tongue, was performed with an electric toothbrush. Whereas the study groups had similar rates of VAP, the authors concluded that adding electric toothbrushing to standard oral care with 0.12% CHG was not effective for the prevention of VAP. Scannapieco et al. (2009) conducted a RCT to compare CHG-based oral care to that with a vehicle control (treatments: vehicle only 2x/day, vehicle 1x/day + 0.12% CHG 1x/daily, or 0.12% CHG 2x/day) among M-V ICU patients (N = 146; age range = 18-88 years) [40]. Based on an intent-to-treat analysis, the incidence of VAP was non-significantly lower in each of the CHG cohorts than in the vehicle-treated group, and a survival analysis showed trends of VAP delay in the CHG groups compared to the control cohort. The frequency of CHG administration did not affect outcomes, and CHG did not affect patient mortality. Consistent with these findings, in an RCT, Grap et al. (2011) showed that the use of a single dose of CHG (0.12%) early in the intubation period reduced VAP among 145 patients (mean age = 42 years) [41]. Among patients who did not have pneumonia at the initiation of MV, 55.6% (10/18) of such patients who received oral care without CHG

developed VAP by 48 or 72 hours compared to 33.3% (7/21) of these patients who received oral care with 0.12% CHG. Özçaka et al. (2012; RCT) indicated that oral swabbing with 0.2% CHG reduced the risk of VAP development in M-V patients (N = 66; mean age = 58 years), with VAP incidence being significantly higher in the control (68.8%) group than in the CHG group (41.4%) [42].

Bellissimo-Rodrigues et al. and respective colleagues discovered contrasting outcomes as a result of running two independent RCTs separated by 5 years that were intended to examine the prevention of RTIs among critically ill patients who were expected to stay at least 48 hours in the ICU. In 2009, patients (N = 194; median age = 59 years) received mechanical cleaning of the oral cavity plus 0.12% CHG or placebo [43]. The incidences of RTIs and of VAP did not significantly differ between study cohorts. In 2014, study groups (N = 254; mean age = 57 years) received 1) dental care provided by a dental surgeon 4-5 times a week, teeth brushing, tongue scraping, removal of calculus, atraumatic restorative treatment of caries, and tooth extraction, or 2) routine oral hygiene only, which included use of a CHG mouth rinse [44]. Both LRTI and VAP rates were significantly lower in the CHG-treated cohort. The disparate findings between these studies suggest that the relatively more aggressive physical maneuvers to treat caries and remove teeth in the 2014 investigation may have eliminated plaque and colonizing microorganisms that could not be otherwise removed by the CHG treatment, thus lessening oral microbial loads to an extent that may have also elicited a difference in VAP rates between the two study groups.

Haydari et al. (2017) compared the ability of three different commercial products containing various concentrations of CHG, 0.2%, 0.12% containing 910 parts per million (ppm) sodium fluoride (NaF), and 0.06% with 250 ppm NaF to inhibit dental plaque and gingivitis among 3 groups of healthy volunteers (N = 60; mean age = 21 years) [45]. The maxillary right quadrant of each individual received mouthwash only, whereas the maxillary left quadrant was subject to both rinsing and mechanical (teeth brushing and flossing) oral hygiene. After 21 days of mouth rinsing only treatment, the CHG-only cohort had significantly less plaque than that in either of the other test groups. In contrast, all subjects in the investigation showed an insignificant difference in plaque burden when mechanical oral hygiene was added to mouth rinsing with the respective test solutions. There were no differences in the extent of gingivitis across study groups, regardless of mechanical oral hygiene integration. Adverse effects equally associated with the use of each of the test solutions included poor taste, soreness of oral mucosa/tongue/gingiva, and feeling of dryness. Statistically significant differences were observed, where respectively 65%-60%, 55%-40%, and 21%-26% of subjects complained about "loss of taste" - "numb feeling" in the 0.2%, 0.12% and 0.06% CHG groups. Insignificant teeth discoloration was noted in every study cohort. Khaky et al. (2018; RCT) compared the effects of a commercially-available nano-silver antiseptic spray to 0.12% CHG on VAP incidence among 80 patients (mean age = 43 years) [46]. The CHG mouthwash was administered 3 times/day for 5 days and was accompanied by brushing of the teeth, suctioning of oral secretions, and rubbing of the oropharyngeal mucosa. The provision of the commercially-available antiseptic solution was included in the same protocol. Both treatments continued for 5 days or until an event (e.g., death, extubation) that would have discontinued a patient from the study. On day 5 following the initiation of the oral care interventions, the VAP rate was significantly lower in the cohort of patients that used the commercially-available antiseptic mouth rinse.

Ventilator-Associated Pneumonia Bundles

In their prospective observational investigation (N = 331) of ventilated trauma patients, Lansford et al. (2007) observed that a VAP prevention (VAPP) protocol including elevation of the head of the bed more than 30 degrees, twice-daily 0.12% CHG oral cleansing, a once-daily respiratory therapy-driven weaning attempt, and conversion from a nasogastric to an orogastric tube whenever possible reduced the incidence of VAP from 6.9 (no VAPP protocol) to 2.8 cases/1000 days of ventilation [47]. The difference in the mean Injury Severity Score between study groups was not significant and thus could not account for the differences in VAP rates between groups. Caserta et al. (2012) reported that their quasi-experimental study over a 2-year period (N = 5422; mean age = 67 years; 21,984 patient-days; 6,052 ventilator-days) in a medical-surgical ICU revealed that a VAPP protocol that included oral decontamination by administration of 0.12% CHG added to a VAP bundle (elevation of the head of the bed 30-45 degrees, daily "sedation vacations" and assessment of readiness to extubate, peptic ulcer disease prophylaxis, and deep venous thrombosis/pulmonary thromboembolism prophylaxis for all ICU patients requiring MV) could eliminate VAP from occurring for one or several months at a time, if such practices were performed with >95% compliance [48]. The VAP bundle/CHG combination regimen significantly reduced VAP incidence

compared to bundle use alone, but the addition of continuous aspiration of subglottic secretions (CASS) to the VAP bundle/CHG protocol did not decrease the VAP rate further. Eom et al. (2014) assessed the preventive efficacy of a VAP bundle in a prospective observational study involving patients distributed among 6 ICUs [49]. Of the individual bundle elements, which included head of the bed elevation, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis, oral decontamination with CHG 0.12%, and optional CASS, compliance with oral decontamination with CHG 0.12% had the greatest impact on VAP reduction.

Interestingly, CHG oral care is the only common feature among the bundles described above. Hence, as suggested by Eom et al. [49], CHG oral care may be the most important feature of a VAP bundle. However, as conveyed by Klompas et al. (2016), who assessed various outcomes associated with use of individual VAP bundle components, including head-of-bed elevation, sedative infusion interruptions, spontaneous breathing trials, thromboprophylaxis, stress ulcer prophylaxis, and oral care with CHG, CHG may promote mortality among ventilated individuals [50]. The details of this report by Klompas et al. are described in Table 1, and a discussion about the association of CHG oral care with patient mortality is provided below.

Concentration-Dependent Outcomes

Zand et al. (2017; RCT; N = 114 ICU patients; mean age = 45 years) reported that oral decontamination with 2% compared to 0.2% CHG is a more effective method in the prevention of VAP [51]. These researchers observed that two patients developed tooth discoloration and one patient developed oral mucosal irritation as a consequence of 2% CHG treatment. Despite the fact that the concentrations and frequencies of application of CHG oral care differed widely within the studies included in their systematic review, Kocaçal Güler and Türk (2018) concluded that 0.2% CHG may be more effective for reducing VAP incidence compared to 2% CHG [52].

Prophylactic Administration

As indicated by Mohr et al. (2015; prospective interventional concurrent-control study; N = 67), pre-hospital oral CHG administered to intubated trauma patients failed to decrease the Clinical Pulmonary Infection Score (CPIS) during the first 2 days of hospitalization [53]. Although all patients were transported by air to the hospital, a fraction of them received oral 0.12% CHG by swabbing of oral surfaces for 15 seconds, while others did not. Despite the CHG intervention, no difference in CPIS score changes, tracheal colonization, or clinical pneumonia was noted between cohorts.

Enwere et al. (2016) investigated the effect of pre- and post-surgical use of CHG mouthwash on the rate of pneumonia [54]. In this retrospective cohort study that included patients who were M-V for ≥2 days and had a positive bacterial quantitative bronchoalveolar lavage culture within 2 days of the onset of worsening oxygenation (N = 158; median age = 57 years), participants either did not receive CHG prophylaxis or did receive this treatment twice daily prior to surgery. The CHG implementation significantly reduced the incidence of probable VAP.

Systematic Reviews/Meta-Analyses

In their meta-analysis that considered data from their own RCT and that by Koeman et al. (2006) [55], Tantipong et al. (2008) determined that oral care with 2% CHG significantly reduced the VAP rate [56]. By a meta-analysis of 18 studies, Zhang et al. (2014) evaluated the effectiveness of CHG to prevent VAP and explored the preferred concentration of CHG [57]. Seventeen investigations involved adults (> 18 years old), and one included children. All patients were M-V in ICUs of various specialties. Chlorhexidine was administered at various concentrations: 0.12% (9 studies), 0.2% (5), 2% (3), and 0.5% (1), and was compared against placebo (6), standard oral care (3), a phenolic mixture (1), Vaseline (1), potassium permanganate (1), sterile water (1), or normal saline (5). The evaluations demonstrated that both 0.12% and 2% CHG significantly decreased VAP incidence compared to its respective control agent comparator, while 0.2% CHG had no such effect, and 0.5% CHG could not be analyzed because only one study of its kind was considered in the meta-analysis. Adverse events attributable to CHG were teeth staining and taste abnormality (2 studies), transient discoloration of the teeth (1 study), a higher incidence or oral mucosa irritation (difference = ~ 10%; 1 study), and unpleasant taste of the CHG solution (1 study). The resistance of microorganisms to CHG was not reported in any of the studies. While 9 studies showed 0.12% CHG had a significant effect, and 3 studies proved the effect of 2% CHG on the prevention of VAP, it was determined that 0.12% CHG had the best effect on the prevention of VAP according to the meta-analysis, cost analysis, adverse reactions, and drug resistance analysis.

Cochrane Database systematic reviews and meta-analyses published by Shi et al. (2013; 17 RCTs (2402 participants)) [58] and Hua et al. (2016; 18 RCTs (2451 participants)) [59], reported that oral healthcare that includes either CHG mouthwash or gel is associated with a 40% odds reduction [58] and 6% risk reduction [59], respectively, versus placebo or usual care (not specified) of developing VAP

in critically ill adults. Normalizing the results of each study to a common outcome, these investigations concluded that for every 15 [58] or 17 [59] people, respectively, on ventilators in intensive care, CHG oral care will prevent one person from developing VAP.

Villar et al. (2016) conducted a systematic review and meta-analysis, with intention-to-treat analysis, of RCTs that assessed the effectiveness of different intraoral CHG protocols for the prevention of VAP [60]. The included RCTs mandated CHG oral care versus placebo or no treatment in intubated patients who were MV. From the 13 studies (1640 patients) included as a result of these selection criteria, the main results indicated that overall CHG use did not significantly reduce VAP incidence. The overall analyses were confounded by the multiple concentrations and forms of CHG that were used and the failure of effectiveness in pediatric populations. Specified examinations of the data that focused on adult populations only revealed that 2% CHG, but not 0.12% or 0.2%, and CHG administration 4 times/day, but not 1-3 times/day, each significantly reduced VAP incidence. One study reported that mild irritation of the oral mucosa was associated with CHG oral care use more often than that with saline.

Effectiveness to Prevent Nosocomial Pneumonia in Children

In contrast to its demonstrated ability to significantly decrease NP incidence among adults, CHG has not shown such an effect in children. In three RCTs performed by Jácomo et al. (2011; N = 160; mean age = 12 months) [61], Kusahara et al. (2012; N = 96; mean age = 23 months) [62], and Sebastian et al. (2012; N = 86; age range = 3 months-15 years) [63], respectively, CHG at 0.12% [61,62] or 1% [63] failed to significantly attenuate NV-HAP [61] or VAP [61-63] incidence in children. Jácomo et al. studied CHG in cardiac surgery patients who were post-operatively admitted to an ICU, while those in the latter two studies were critically ill patients treated in ICUs. Chlorhexidine did not influence the need for reintubation [61], time interval between hospitalization and NP diagnosis [61], time interval between surgery and NP diagnosis [61], time on antibiotics and vasoactive drugs [61], mortality rates [61-63], length of hospital stay [61-63], or length of ICU stay [61-63]. These results are perplexing, considering that CHG significantly attenuated NP in various studies discussed above, and especially so because CHG reduced NV-HAP incidence in adults who had cardiac surgery, but not in children who had this procedure. Perhaps differences in immune system competencies between adults and children permit proliferation of putative CHG-resistant microbial oral pathogens in children that are inhibited in adults. It appears that more work is warranted to determine why NP can be reduced by CHG in adults, but not in children.

Effects in Cardiac Surgery Patients

In the absence of M-V, DeRiso et al. (1996; RCT; N = 353; mean age = 64 years) concluded that inexpensive and easily applied oropharyngeal decontamination with 0.12% CHG oral rinse reduces the total nosocomial respiratory infection rate and the use of non-prophylactic systemic antibiotics in patients undergoing heart surgery [21]. This results in significant cost savings for those patients who can thus avoid additional antibiotic treatment. Three hundred fifty-three consecutive patients undergoing coronary artery bypass grafting (CABG), valve surgery, septal surgery, cardiac tumor excision, or combined CABG valve surgery requiring cardiopulmonary bypass were enrolled and received either 0.12% CHG oral rinse or a matching placebo that contained 3.2% alcohol compared to 11.6% alcohol in the base CHG solution. The nosocomial infection rate, the incidence of total RTIs, the involvement of Gram-negative organisms in nosocomial and total RTIs, the use of nonprophylactic IV antibiotics, and mortality were significantly lower in the CHG group. In an RCT, Houston et al. (2002) compared oral care with 0.12% CHG vs. that with a phenolic mixture in patients (N = 561) who underwent aortocoronary bypass graft and/or valve surgery requiring cardiopulmonary bypass [22]. Oral care with CHG reduced the overall rate of NP by 52%. In patients at the highest risk for pneumonia (intubated >24 hours, with cultures showing the most growth), the VAP rate was 71% lower in the CHG group than in the phenolic mixture group. The significant effect of CHG to reduce the VAP rate compared to the phenolic mixture group occurred only among those patients who were at the highest risk of VAP, as defined by intubation >24 hours, with cultures showing the most growth. Segers et al. (2006) illustrated in an RCT that decontamination of the nasopharynx and oropharynx with 0.12% CHG appeared to be an effective method to reduce nosocomial infection in patients (N = 954; mean age = 65 years) after cardiac surgery [64]. The incidence of nosocomial infection in the CHG and placebo groups was significantly different (19.8% vs. 26.2%, respectively). The nasal Staphylococcus aureus burden was significantly reduced by CHG compared to the placebo (57.5% vs. 18.1%). Nicolosi et al. (2014; quasi-experimental study; N = 300) compared cardiac surgery patients who engaged in toothbrushing and oral rinses with 0.12% CHG every 12 hours for 3 days to those who previously received regular oral hygiene care, which

included intranasal 2% mupirocin ointment twice daily for 3 days before surgery and a third-generation cephalosporin administered 30 minutes before surgery until 24 hours after surgery (the CHG/toothbrushing group also experienced this protocol) [65]. The regular oral hygiene cohort was asso ciated with a higher incidence of VAP and a 3-fold higher risk of developing pneumonia after surgery. In accordance with these findings, Lin et al. (2015; RCT; N = 94; age range = 18-65 years) indicated a reduced occurrence of VAP after cardiac surgery when pre-operative 0.2% CHG oral rinse was administered to patients [66]. Ventilator-associated pneumonia occurred in 8.5% of the CHG group and in 23.4% of the control (normal saline) cohort.

Systematic Reviews/ Meta-Analyses - Cardiac Surgery Patients

Labeau et al. (2011) performed a systematic review and random effects meta-analysis of randomized trials to assess the effect of oral care with CHG or povidone-iodine on the prevalence of VAP versus oral care without these antiseptics in adults [24]. The authors published the results of fourteen studies that included 2481 patients, 12 investigating the effect of CHG (2341 patients; 0.12% = 6 studies, 0.2% = 4, 2% = 2). The patient pools among the studies included in the meta-analysis consisted of those in various ICUs and individuals who underwent cardiac surgery. While the effects of povidone-iodine were nebulous due to a relative paucity of studies/data, CHG was determined to be significantly effective, with favorable effects more pronounced related to use of 2% CHG, and in cardiosurgical studies. Klompas et al. (2014) produced a systematic review and meta-analysis about the impact of routine oral care with CHG in patients receiving MV [67]. Of 171 unique citations, 16 studies, including 3630 patients, met inclusion criteria. There were fewer LRTIs in cardiac surgery patients randomized to CHG, but no significant difference in VAP risk in double-blind studies of non-cardiac surgery patients. There was no significant mortality difference between CHG and placebo in cardiac surgery studies and non-significantly increased mortality in non-cardiac surgery studies. The study concluded that routine oral care with CHG prevents VAP in cardiac surgery patients, but may not decrease VAP risk in non-cardiac surgery patients. In a meta-analysis involving seventeen RCT investigations (N = 4249 patients), Li et al. (2015) noted that CHG (N = 14 studies) significantly prevented the occurrence of VAP in M-V ICU patients, but povidone-iodine (N = 3) did not [68]. As observed earlier by Labeau et al. [24], the inhibitory effect of CHG on VAP was most marked in cardiac surgery patients. Neither antiseptic significantly reduced ICU mortality, length of ICU stay, or duration of MV. Spreadborough et al. (2016) considered 3 RCTs and 1 quasi-experimental study in their systematic review and meta-analysis (N = 2205) [69]. The investigations included only patients having elective cardiac surgery who were treated before and after (3 studies) or pre-treated only (1) with CHG oral care. The longest pre-treatment occurred for 3 days, while CHG administration after surgery lasted for at least 10 days in some patients. Compared to control oral agents (see Table 2 for details), peri-operative CHG oral care significantly reduced the risk of postoperative pneumonia and nosocomial infections.

Oral Chlorhexidine Use and its Association with Patient Mortality

Table 1 lists studies in which CHG oral care was tested and mortality was included as an outcome of such practice. Eighteen of the 25 analyses (24 studies) shown in Table 1 indicate that mortality incidence associated with CHG was not significantly different than that compared to counterpart control agents, while in 5 of the studies, CHG oral care was associated with less mortality compared to control treatments. These findings were made in the context of a variety of patient populations (e.g., surgical, non-surgical, M-V, non-M-V), CHG concentrations (0.12%, 0.2%, or 2%), and oral care agent administration protocols. It is important to note, however, that mortality was tested as a primary outcome, and thus statistically powered to determine the effect of CHG on mortality, in just 4 (DeRiso et al. (1996) [21], Özçaka et al. (2012) [42], Klompas et al. (2016) [50], Deschepper et al. (2018) [70]) of the 24 studies listed (Table 1). The primary objectives of most examinations were to evaluate the effectiveness of CHG on the development of NP and on reducing oral microbial colonization. A retrospective analysis by Klompas et al. (2016) divulged that CHG oral care may be associated with mortality (Hazard Ratio, 1.63; 95% confidence interval, 1.15-2.31; p = 0.006 (statistically significant)) [50]. Due to a possible correlation between CHG oral care use and mortality, the combined European and Latin American guidelines (2017) chose not to issue a recommendation on CHG use for VAP prevention until further efficacy data became available [71]. The mechanism by which CHG might increase mortality is uncertain, though it may be due to the development of acute respiratory distress syndrome (ARDS) that is secondary to aspiration of CHG, as suggested by Klompas (2017) [2]. Support for this hypothesis can be traced back to a report made available by Hirata and Kurokawa in 2002, in which they conveyed that an 80-year-old woman died of ARDS 12 hours after

accidentally ingesting approximately 200 ml of a 5% CHG solution [72]. Although this amount and concentration of CHG exceed that routinely used for single oral decontamination, the principle of CHG causing ARDS applies, and so warrants caution when CHG is used for oral care.

Evidence for exercising vigilance when using CHG as an oral care substance emerged further from Deschepper et al. (2018) who primarily investigated the effect of CHG oral care on mortality in a general hospitalized population [70]. This single-center, retrospective, hospital-wide, observational cohort study included 82,274 adult hospitalized patients of which 11,133 (14%) received CHG oral care. Low-level exposure to CHG oral care (≤300 milligrams (mg)) was associated with an increased risk of death. This association was stronger among patients with a lower risk of death compared to those with an extreme risk of mortality. Similar observations were made for high-level exposure to CHG (>300 mg). Increased risk of death was observed in patients who did not receive MV and was not admitted to ICUs. The authors concluded that the data argue against the indiscriminate widespread use of CHG oral care in hospitalized patients, in the absence of proven benefit in specific populations.

Indications that CHG-associated mortality may be patient population-dependent also came from a systematic review and meta-analysis by Klompas et al. (2014) when these investigators found that there was no significant mortality difference between CHG and placebo in cardiac surgery studies (relative risk (RR), 0.88 [95%CI, 0.25-2.14]) and non-significantly increased mortality in non-cardiac surgery studies (RR, 1.13 [95%CI, 0.99-1.29]) [67]. These findings are consistent with those of Deschepper et al. [70] in that patients at a lesser risk of mortality to begin with appear to be most vulnerable to the risk of mortality resulting from CHG oral care. While the systematic review and meta-analysis by Price et al. (2014) also found a positive correlation between CHG and patient mortality [73], the other 6 reports of this methodological design listed in Table 2 did not, with the most recent being published in 2019 by Lee at al. [74]. None of the systematic reviews and meta-analyses listed in Table 2 included the following original literature contributions in which mortality was included as an outcome of CHG oral care: Pobo et al. (2009) [39], Bellissimo-Rodrigues et al. (2014) [44], Lev et al. (2015) [75], Chen et al. (2016) [36], Klompas et al. (2016) [50], Deschepper et al. (2018) [70], and Khaky et al. (2018) [46], with those by Klompas et al. (2016) [50] and Deschepper et al. (2018) [70] reporting that CHG was associated with patient mortality (Table 1). In addition, the reports by Silvestri [35], Shi [58], and Hua [59] and their respective colleagues included mortality outcomes in children following CHG oral care. In each of these pediatric populations [60-62], the mortality incidence linked to CHG use was not significantly different than those observed to be associated with the control treatments in each study.

Comparisons Between Chlorhexidine and Other Oral Care Agents, and Other Comparisons

Based on the volume of literature observed to produce this article, CHG is the most-studied oral care medication and has shown evidence of its usefulness to reduce pathogenic microbial colonization, NV-HAP, and VAP. However, these benefits must be balanced with emerging evidence that CHG oral care may be associated with patient mortality [50,67,70,73]. Thus, it may make sense to consider the use of other oral care agents as substitutes for CHG. As such, we provide a summary of studies that directly compared CHG to other agents with respect to examining various oral and respiratory health parameters (Table 3).

Pizzo et al. demonstrated that plaque burden was limited best by 0.12% or 0.2% CHG when compared to 0.05% CPC or 0.03% triclosan (TRN) [76]. Further, CHG and EOs seemed equally effective as anti-plaque/anti-gingivitis agents, with CPC lagging behind in both aspects [77]. Compared to CHG, NaHCO3 may be superior [78,79] or equivalent [80] for controlling oral mucositis, but the relative ability of NaHCO3 to prevent oral bacterial contamination [78,81,82] is nebulous. Multiple investigations showed that CO is as effective as CHG in reducing the number of Streptococcus mutans in the oral cavity [84-87], and one illustrated that the Lactobacillus burden is equally decreased by CO and CHG [84]. Other examinations determined that Camellia sinensis [88] and alcohol+EOs [89] are each as good as CHG to control dental plaque, while TRN+NaF [90], normal saline [89], and other chemicals in combination with CHG [90] may not have equivalent anti-plaque/anti-gingivitis properties compared to CHG alone.

Inspection of Table 3 reveals that investigations aimed at comparing CHG to other oral care agents regarding NV-HAP or VAP as an outcome are lacking. Senol et al. (2007) reported that the in vitro antibacterial effects of H2O2 and CHG tested against 32 different strains of VAP-causing pathogens were equivalent, and both were better than a commercial product containing glucose oxidase, lactoperox idase, lysozyme, and lactoferrin [91]. However, in clinical testing, H2O2 did not achieve anti-VAP activity equal to that of CHG [92]. Other than 2 other

studies, which showed that the incidence of VAP in patient groups treated with NaHCO3 [81] or CPC [93] was higher compared to cohorts that used CHG oral care, and 1 investigation demonstrating that the VAP rate associated with a combination of NaHCO3 and H2O2 oral care was significantly lower than that when 0.2% CHG was used [75], we could find no other study that considered NV-HAP or VAP as an outcome between CHG and other major oral care agents discussed in this review article. Ironically, despite the relative paucity of studies describing the effects of CPC on NV-HAP or VAP, CPC oral care was used in the majority (16/25; 64%) of hospital ICUs in Brazil evaluated by e Silva et al. (2015), followed by CHG (32%) and NaHCO3 (4%) [94]. Based on responses to a questionnaire distributed by Saddki et al. (2014), 91%, 13%, and 11% of ICU nurses in a Malaysian hospital used CHG, NaHCO3, and sterile water or normal saline as oral care mouthwash in the ICU, respectively, while 4% and 3% used tap water or H2O2 [95]. Although CO reduced Streptococcus mutants [84-87] and Lactobacillus [84] equally as well as CHG, these bacterial species are primarily associated with tooth decay [96] rather than pneumonia. It is unclear, however, if observations made to suggest that other agents such as alcohol+EOs, which demonstrated anti-plaque properties equivalent to those of CHG [89], can be manifested to inhibit NV-HAP or VAP as CHG can. Taken together, it is clear that more examinations are necessary to address whether substances other than CHG, such as CO or novelties, as examples, can significantly eliminate pneumonia-causing oral pathogens and reduce NV-HAP and/or VAP.

Cetylpyridinium Chloride

Cetylpyridium chloride is a cationic quaternary ammonium compound commonly used as an active ingredient in various mouthwashes, toothpaste, lozenges, throat sprays, breath sprays, and nasal sprays [101]. It is indicated as an antiseptic to aid in the prevention and reduction of plaque and gingivitis and to freshen breath [102]. As an active ingredient in oral antiseptics, it has been noted to have broad-spectrum anti-microbial activity with a rapid bactericidal effect on gram-positive pathogens and a fungicide effect on yeasts in particular [101].

Cetylpyridinium chloride binds to both tooth structure and dental plaque biofilm [103]. Application of CPC at a concentration of 0.05% as a mouth rinse results in an immediate reduction in bacterial counts [101]. It is cleared from the mouth more rapidly than CHG, which explains its lower efficacy [104]. However, CPC has less prominent side effects than CHG, such as staining of the teeth and lower substantivity (i.e., the persistence of effect determined by the degree of physical and chemical bonding to a surface, and resistance to removal or inactivation, among other factors) [104].

Based on the 2003 recommendations of the Dental Plaque Subcommittee of the Nonprescription Drugs Advisory Committee (NDAC), which is part of the US Food and Drug Administration's (FDA) ongoing review of over-the-counter (OTC) drugs, it was concluded in a Federal Monograph that CPC at concentrations of 0.045% to 0.1%, with at least 72% to 77% chemically available CPC, is safe and effective for use in mouth rinse formulations as an OTC anti-plaque/anti-gingivitis agent. [105]. Because the positively charged hydrophilic region is critical to anti-microbial activity, any formulation that diminishes the activity of this cationic group or that competes with this group [106], such as when preceded by dentifrice (a paste or powder used to clean teeth) ingredients sodium monofluorophosphate or sodium lauryl sulphate (SLS) [104], may inactivate the product. Rinsing with water helps to eliminate the SLS residual in the oral cavity and to enhance CPC activity [104]. It is essential to establish that the CPC in products is sufficiently biologically active to justify an anti-gingivitis claim [105]. Oral liquid CPC formulations in the US include 0.07% [106] and 0.075% [107] in an alcohol-free formulation, and 0.05% with alcohol [102].

Cetylpyridinium Chloride Effects in Oral Care

Effects on Dental Plaque and Gingivitis

In an RCT that included 120 healthy adults (age range = 18-57 years), Allen et al. (1998) evaluated the effectiveness of a newly developed after-brushing mouth rinse containing 0.05% CPC compared to a rinse without CPC to control supragingival dental plaque and gingivitis [108]. At both the 3- and 6-month study follow-up time-points, significantly less supragingival plaque and gingivitis were observed in the CPC mouth rinse group than in the control cohort. The extent of these CPC effects supported a claim of efficacy, in accordance with the criteria provided by the published guidelines of the American Dental Association (ADA). Mankodi et al. (2005; RCT; N = 139; age range = 18-65 years) also assessed the effects of a novel mouth rinse containing CPC (0.07%) on the development of gingivitis and plaque versus a placebo control rinse (alcohol-free) absent of CPC in healthy adults over a period of 6 months [109]. When used twice daily after toothbrushing, assessments at both 3 and 6 months showed that reductions in gingival inflammation, gingival bleeding, and plaque were significantly greater in the CPC group than in the placebo group.

Angular cheilitis was the lone AE linked to CPC used in this study. In an RCT, Stookey et al. (2005) evaluated the effects of two experimental CPC mouth rinses containing 0.075% or 0.10% CPC against a placebo on the development of gingivitis and plaque in healthy subjects (N = 366; age range = 18-66 years) over a period of 6 months [110]. At 3 and 6 months post-initiation of the study, subjects who used either CPC solution had significantly less gingivitis, gingival bleeding, and plaque than those using a placebo, with no difference observed between each CPC solution on these end-points. As a result of a systematic review that included 8 RCTs (N = 867 subjects) with follow-up periods ranging between 4 weeks to 6 months, Haps et al. (2008) concluded that CPC (0.01%-0.1%; 1-2 times/day)-containing mouth rinses provide a small, but significant, additional benefit when compared with toothbrushing only or toothbrushing followed by a placebo rinse, with respect to dental plaque accumulation and gingival inflammation [104].

Versus other Agents

Two studies assessed whether CPC plus NaF or NaF alone afforded an advantage in oral care. Ayad et al. (2011) performed a RCT to evaluate the clinical efficacy of an anti-plaque, alcohol-free mouthwash containing 0.075% CPC and 0.05% NaF, compared to a control mouthwash containing only 0.05% NaF in healthy adult individuals (N = 110; age, ≥18 years), to control established dental plaque and gingivitis after 3 and 6 months of product use [111]. The authors indicated that 1) an alcohol-free mouthwash containing a combination of 0.075% CPC and 0.05% NaF produced statistically significant reductions in dental plaque and gingivitis after 3 and 6 months compared to baseline, and 2) the alcohol-free CPC mouthwash provided a statistically significantly greater level of efficacy in controlling established dental plaque and gingivitis after 3 and 6 months of product use compared to the control mouthwash containing only NaF. In healthy adult subjects (N = 188; age range = 23-69 years) of a RCT, He et al. (2011) compared the anti-microbial efficacy of two mouthwashes: 1) 0.075% CPC + 0.05% NaF in an alcohol-free base and 2) 0.075% CPC + 0.05% NaF in a 6% alcohol base, and 3) a negative control mouthwash containing 0.05% NaF in an alcohol-free base [112]. After both 12 hours and 14 days of using the washes, supragingival anaerobic plaque bacteria were significantly decreased in subjects who used either of the CPC treatments compared to the control wash. The effects of the CPC washes were not different.

In other examinations, CPC was compared to EO-containing mouth rinses. Albert-Kiszely et al. (2007; RCT) compared the effects of an experimental mouth rinse containing 0.07% CPC to those provided by a commercially-available mouth rinse containing EOs on dental plaque accumulation and prevention of gingivitis in healthy subjects (N = 151; mean age = 40 years) [113]. The data indicated that there was no significant difference in the anti-plaque/anti-gingivitis benefits between the experimental CPC mouth rinse and EO mouth rinse over a 6-month period. In contrast to these findings, Charles et al. (2011; RCT; N = 147; mean age = 39 years) observed that an EO-containing mouth rinse had superior anti-plaque/anti-gingivitis effectiveness compared to a 0.07% CPC-containing mouth rinse 2-weeks following initiation of the interventions [114]. The CPC rinse produced anti-plaque/anti-gingivitis outcomes that were significantly better than those of a 5% hydroalcohol control rinse, however. While the age groups (ranges = approximately 18-65 years-old), treatment application cadence (twice daily), and commercial forms of the CPC and EO solutions were the same in this study as that by Albert-Kiszely et al. [112], the follow-up periods were different, being at 2-weeks in this study, and 3 and 6 months in that by Albert-Kiszeley et al. [113]. Thus, these conflicting findings suggest that EO has faster anti-plaque/anti-gingivitis properties than CPC. A subsequent RCT by Cortelli et al. (2014) compared the anti-plaque/anti-gingivitis potential of an EO- vs. a 0.07% CPC-containing mouth rinse among 354 healthy volunteers (age range = 18-71 years) [115]. Although there were statistically significant reductions in gingivitis, bleeding, and dental plaque observed for both EO and CPC at 1, 3, and 6 months post-treatment initiation compared to the control, at all study follow-up time-points, EO more favorably affected gingivitis and plaque than CPC. In agreement with these findings, Charles et al. (2015) later determined that EO significantly reduced gingival inflammation and dental plaque compared to both 0.075% CPC and a 5% hydroalcohol negative control 1 month following implementation of the oral interventions [116]. Extrinsic tooth stain was cited as an AE that occurred as a result of CPC use. Taken together, these studies implicate EOs as working faster as an antiplaque/anti-gingivitis agent than CPC, with results in favor of EOs for up to 1 month consistently being observed.

Ayad et al. (2015) evaluated, in an RCT, the efficacy of different regimens to reduce and control established dental plaque and gingivitis among hea-

lthy subjects (N = 120; age range = 18-70 years) after 4 weeks of implementation [117]. The test regimen (TR) consisted of 1) use of commercially-available triclosan (TRN)-, polyvinyl methyl ether/maleic acid copolymers, and NaF- containing toothpaste, 2) a manual toothbrush with cheek and tongue cleaner, and 3) an alcohol-free, fluoride-free 0.075% CPC mouthwash. The negative control regimen (NCR) was comprised of 1) a commercially-available 0.76% sodium monofluorophosphate toothpaste, 2) a manual toothbrush, and 3) a fluoride-free and alcohol-free non-anti-bacterial mouthwash. Subjects using the TR exhibited statistically significant reductions in mean plaque burden and gingivitis severity compared to subjects using the NCR. Because of the multiple variables, including different kinds of toothpaste, toothbrushes, and mouthwashes used between study cohorts, the relatively greater beneficial effects of the TR cannot be specifically attributed to CPC use. That same year, Latimer et al. (2015) showed that a fluoride-free, alcohol-free 0.075% CPC-containing mouth rinse displayed significant bactericidal activity in vitro toward Fusobacterium nucleatum, an oral bacterium associated with the gingival disease, and significantly inactivated plaque biofilm compared to a CPC-free control mouth rinse [118]. In an RCT, Schmidt and Jentsch (2015) compared mechanical cleaning with interdental brushes combined with 0.3% CPC gel to mechanical cleaning with interdental brushes alone for plaque control among patients (N = 40; age range = 30-70 years) with periodontitis [119]. The authors concluded that mechanical interdental plaque control using interdental brushes combined with the use of CPC gel significantly improved 6-month gingival and periodontal outcomes compared with mechanical cleaning with interdental brushes alone. Later, Teng et al. (2016; RCT; N = 91; age range = 18-53 years) investigated the influence of CPC-containing oral rinses on the supragingival plaque in experimental gingivitis [120]. Compared to healthy subjects who used water only-rinse in oral care, a CPC rinse resulted in slower development of gingival inflammation due to the inhibition of 17 gingivitis-enriched bacterial genera. Cetylpyridinium chloride prevented the acquisition of new taxa that would otherwise accumulate but maintained the original biodiversity of healthy plaques. Furthermore, CPC rinses reduced the size, local connectivity, and microbiota-wide connectivity of the bacterial correlation network, particularly for nodes representing gingivitis enriched taxa.

Sodium Bicarbonate

Mechanical disruption, as through tooth brush ing, of dental biofilm, is critical to maintaining periodontal health [121]. Sodium bicarbonate (otherwise known as baking soda) has been used as an ingredient in toothpastes and mouthrinses to be potential aids to improve gingival health and maintain dental biofilm control. Per the US FDA Federal Register in 2003, $NaHCO_3$ is safe, has low abrasivity, and has been generally regarded as a bactericidal agent [105]. Sodium bicarbonate is classified with the category of dentifrice abrasives and is naturally compatible with NaF [122]. In addition to the mechanical mechanism of plaque removal, research has shown that $NaHCO_3$ induces a biological reaction that can aid in caries prevention due to having a buffering capability that will allow the plaque pH to return to normal, thus decreasing the risk for caries [123].

Sodium bicarbonate can neutralize acid and prevent dental erosion [124] caused by episodes of prolonged exposure to weak acids (for example, wine tasting) or short-term exposure to strong acids (for example, reflux or vomiting) [125], increase salivary pH and buffer capacity, and thus facilitate mineralization in patients with caries or dental erosion [125], suppress the growth of aciduric microorganisms such as Streptococcus mutans [124,125], improve or normalize taste function in patients with xerostomia-related taste dysfunction [124,125], and help to control halitosis [126].

Sodium bicarbonate is bland and thus unlikely to irritate the oral mucosa in patients with xerostomia or oral ulcerative disease [124]. For chemotherapy patients with established mucositis, Negrin et al. (2019) suggest routine mouth care, including oral rinses with a weak solution of salt and $NaHCO_3$ (one-half teaspoon of salt and one teaspoon of $NaHCO_3$ in a quart of water), be performed every four hours [127]. Although data are insufficient to make a recommendation of an optimal specific oral care therapy for patients with head and neck cancer, Galloway et al. (2018) suggest rinsing and gargling at least several times a day with a solution of warm salt water or $NaHCO_3$ solution [128].

Sodium Bicarbonate Properties and Effects in Oral Care

Anti-Infection

Zambon et al. (1996) conveyed the results of a prospective study (N = 101;) that examined the clinical and microbiological changes associated with regular use of $NaHCO_3$ dentifrices in healthy individuals [129]. One dentifrice contained 52% $NaHCO_3$ and 3% sodium percarbonate, while the other dentifrice contained 65% $NaHCO_3$. Both dentifrices resulted in statistically significant reductions in dental plaque, gingival inflammation, and stain

compared to baseline at 3 and 6 months post-implementation of the oral interventions and 3 months after the treatments were halted. Microbiological assays confirmed the safety of both formulations, and each significantly reduced the burden of the Actinomyces species dental plaque bacterium. The authors concluded that dentifrices containing high levels of NaHCO3 are clinically-effective and microbiologically safe. In another prospective investigation, Chandel et al. (2017) considered the influence of NaHCO3 oral rinse on salivary pH and oral microflora in healthy subjects (N = 25) [130]. The NaHCO3 oral rinse significantly elevated salivary pH and moderately decreased oral bacterial load, especially Viridans Streptococci and Moraxella. Although a direct comparison to CHG was not made in this investigation, the authors concluded that NaHCO3 oral rinse may be considered as a cheap and effective alternative to CHG- and alcohol-based mouthwash, especially where long duration usage is required.

Effects on Dental Plaque

In their combined meta-analysis and graphical depictions of plaque index reductions, Thong et al. (2011) examined 6 randomized controlled, blinded clinical trials constituting 14 comparisons of NaHCO3 to non-NaHCO3 toothpaste with respect to plaque removal from various dentition areas, including the anterior-facial/mid-surface sites, the posterior-lingual/mid-surface sites, and the posterior-lingual/proximal sites, among others [131]. The toothpaste contained 20%-65% NaHCO3. The NaHCO3-containing toothpaste removed significantly more plaque than toothpaste that did not contain NaHCO3. In light of these findings, the authors indicated that limited accessibility by toothbrushes to difficult-to-reach dentition sites may account for differences in plaque removal observed between toothpaste that did or did not contain NaHCO3. However, in a review article published 6 years following the report above by Thong and colleagues, Myneni et al. (2017) [122] indicated that multiple studies cited NaHCO3-containing toothpastes as being more effective at removing plaque than toothpastes having formulations without NaHCO3, including those that contained hydrated silica [132], dicalcium phosphate [132], triclosan and copolymer [133], stannous fluoride and silica [133], NaF and silica [133], and calcium carbonate [134]. Putt et al. (2008) hypothesized that the relatively advantageous plaque removal ability of NaHCO3 toothpaste may be attributable to inherent characteristics NaHCO3, specifically 1) having larger crystals than other abrasive agents, 2) dissolving NaHCO3 may physically disrupt the bacterial polysaccharide matrix of plaque, making it easier to remove with the toothbrush and 3) the bicarbonate ions may disrupt bacterial attachment and sequester the calcium as calcium carbonate, leading to easier plaque biofilm removal [133]. Thus, the plaque-removal effectiveness of a dentifrice may be determined not only by accessibility to dentition sites by a toothbrush, as suggested above by Thong et al. [131], but also by physical phenomena afforded by its chemical structure. Sabharwal and Scannapieco (2017) indicated their doubts about pooling data in reference to the study by Thong et al. [131] regarding 1) production of a meta-analysis from clinical studies resulting from a variety of dentifrice formulations, 2) use of different indexes to measure similar outcomes, 3) the lack of standardization of oral hygiene methods, and 4) variable length of follow-up [121]. Despite having cited investigations that showed comparatively favorable results of NaHCO3-containing dentifrices on periodontal health, including plaque control, for up to 6 months following treatment initiation in their own review article [121], these investigators suggested that additional well-powered, randomized trials are required to determine the efficacy of NaHCO3 dentifrices for the prevention of periodontal disease progression.

Effects on Gingival Health

In order to assess the effects of a NaHCO3/xylitol spray associated with non-surgical periodontal therapy in participants with primary Sjogren's syndrome, Gambino et al. (2017) randomized patients (N = 24; mean age = 65 years) with this disorder into three groups, including those treated: A) once with non-surgical periodontal therapy, education and motivation to oral hygiene, associated with the use of NaHCO3/xylitol (a sugar alcohol that is used as a sugar substitute) spray; B) only with a NaHCO3/xylitol spray; C) only with non-surgical periodontal therapy, and education and motivation to practice oral hygiene [135]. The use of the NaHCO3/xylitol spray in Groups A and B produced significant enhancements in unstimulated salivary flow rates, while Group A only was associated with reduced signs of periodontal disease and xerostomia-induced oral pain. A significant decrease in periodontal disease symptoms and an increase in salivary pH followed the Group C treatment regimen. These phenomena may not be correlated, since only the former effect, but not the latter was observed following the Group A regimen. Curiously, salivary pH was not significantly affected in either NaHCO3/xylitol group but was in Group C, which did not include NaHCO3 in its paradigm. Whereas unopposed NaHCO3 can significantly increase salivary pH [129], it is possible that combining NaHCO3 with xylitol compromised the ability of NaHCO3 to do so this study,

given that carbohydrate (glucose) can reduce pH of tooth surfaces [136].

Effects as a Prophylactic

Sodium bicarbonate has been tested for its ability to prevent oral mucositis (OM). By conducting an RCT, Piredda et al. (2017) sought to investigate the utility of a treatment to prevent chemotherapy (doxorubicin and cyclophosphamide)-induced oral mucositis in breast cancer patients (N = 60; mean age = 52 years) [137]. As such, these investigators compared two different treatments concurrently with chemotherapy, one consisting of a tablet of a dry extract of propolis (i.e., bee glue: a resinous mixture that honey bees produce by mixing saliva and beeswax with exudate gathered from tree buds) with 8%-12% of galangin (a flavonoid naturally found in propolis) plus mouth rinsing with NaHCO3 (experimental arm), and the other mouth rinsing with NaHCO3 (control arm). Up to 15 days following the first cycle of chemotherapy, mild OM developed in the experimental cohort, while patients in the NaHCO3-only group experienced more severe OM. The propolis/NaHCO3 combination was safe and relatively more effective than NaHCO3 alone in preventing OM caused by chemotherapy. Adverse events associated with NaHCO3 use were poor taste, nausea, and mild OM. In a related study, Chitapanarux et al. (2018; RCT; N = 60; age range = 18-70 years) compared benzydamine HCl to NaHCO3 to prevent concurrent chemoradiation-induced OM among patients with non-metastatic head and neck cancer [138]. The authors concluded that prophylaxis oral rinsing with benzydamine HCl for patients undergoing high-dose radiotherapy concurrently with platinum-based chemotherapy was superior to NaHCO3 mouthwash to mitigate the severity of OM and encouraging a trend for reducing the need of oral anti-fungal agents use.

Yang et al. (2017; RCT; N = 104; age range = 18-75 years) investigated the effect of NaHCO3 on the incidence of candidiasis occurring after free flap surgery for reconstruction of oral and maxillofacial tissue defects [139]. The control group of patients underwent standard oral care: twice daily rinses with 3% H2O2 and 0.9% NaCl, and then gargled with CHG 3 times/day. Patients in the experimental arm also received standard oral care, and two phases of additional care: 1) a 3% NaHCO3 saline oral rinse twice daily, and 2) gargling with a NaHCO3 saline solution 3 times/day. Each treatment scheme reduced salivary pH values below normal, with those in the NaHCO3 being significantly higher than in the group that did not use NaHCO3. Moreover, oral candidiasis incidence was significantly lower in the cohort that included the application of NaHCO3.

Effects in Mechanically-Ventilated Patients

Berry (2013) conducted an RCT (N = 398; mean age = 58 years) to test the relative effectiveness of oral rinses with EOs, NaHCO3, or sterile water on dental plaque colonization with respiratory pathogens and subsequent development of VAP [140]. Four days following the start of the test regimens, no effectiveness differences were noted among the treatments. Because the VAP rate in the study population as a whole was low (N = 18 patients affected), the investigator reasoned that the common factor of a small, soft toothbrush as part of an oral hygiene regimen suggested possible benefit in M-V patients. Given the remarkable outcome of sterile water performing as well as the other treatment agents, which includes this intervention being associated with the lowest proportion of VAP incidence (albeit insignificantly so compared to the other treatments; EOs, 4.7%; NaHCO3, 4.5%; sterile water, 4.3%) the author-indicated study limitations are provided here for perspective 1) a lack of accurate and specific criteria for the diagnosis of VAP without employing invasive methods of microbial assessment [141]. The diagnostic criteria used in this study of new or worsening radiographic infiltrates together with one of the clinical features of fever, leukocytosis, purulent sputum or increased oxygen need, is reported to have high sensitivity but low specificity for VAP [142], and 2) since this study is a single-center study with a relatively small sample of 398 participants, it may not be possible to generalize the findings to the broader ICU community.

Hydrogen Peroxide

Hydrogen peroxide is classified as an oral debriding agent and oral wound cleanser with anti-microbial properties It is an antiseptic oxidant that slowly releases oxygen and water upon contact with serum or tissue catalase [143]. The release of oxygen causes foaming, which removes mucus, provides mechanical cleansing to remove mouth debris and treats oral irritations [144]. The duration of H2O2 action occurs while it forms bubbles [144]. Hydrogen peroxide has been used orally as an antiseptic to prevent mouth infection [144], a mouthwash or gargle for removal of phlegm, mucus, or other oral secretions associated with occasional sore mouth [143], an oral rinse (alcohol-free) and gel for mouth, gum, or dental irritation, and a tooth whitener (bleaching) when used in the form of carbamide peroxide [145].

Hydrogen peroxide can be absorbed through the oral mucosa and epidermis, but the exposure of the oral cavity to H2O2 is generally limited since it

undergoes rapid decomposition [105]. After one minute of brushing, less than 20% of the H2O2 introduced into the oral cavity can be recovered [105]. Hydrogen peroxide (diluted 1:1 with saline or water) may be used for gentle debridement [127]. The duration of the use of H2O2 should be limited, as chronic therapy may delay healing [127]. The US FDA Federal Register Subcommittee of May 29, 2003, concluded that H2O2 is safe at concentrations of up to 3%, but there were insufficient data available to permit final classification of its effectiveness at 1.5% to 3% concentrations for long-term OTC use as an antiplaque/anti-gingivitis agent [105].

Hydrogen Peroxide Properties and Effects in Oral Care

Therapeutic Effects

In their double-blind crossover investigation, Wennström and Lindhe (1979) demonstrated the anti-microbial, -plaque, and -gingivitis properties of a mouth rinse that released H2O2 into the oral cavity of healthy dental students (N = 14) [146]. The rinses occurred during a no-toothbrushing period after breakfast, lunch, and dinner for 14 days. The H2O2-releasing rinse prevented the colonization of filaments, fusiform, motile, and curved rods as well as spirochetes in developing plaque, reduced plaque accumulation, and mitigated development of gingivitis. In their literature review concerning the use of H2O2 in dentistry, Marshall et al. (1995) [147] indicated that there is sufficient evidence that H2O2 can damage DNA through the intermediate formation of reactive oxygen species, particularly the hydroxyl radical when metals are present. The ability to damage DNA is one factor in the anti-bacterial activity associated with the use of H2O2 as a disinfectant. When combined with NaHCO3, H2O2 decomposition is thought to be accelerated, and thus decrease levels of H2O2 necessary to achieve anti-bacterial effects. Dunlap et al. (2011) conducted a laboratory-based proof of concept investigation to determine the efficacy of a custom-fabricated tray in placing anti-microbial and debriding agents in the periodontal pockets of persons with active gingival infections [143]. The debriding effect of 1.7% H2O2 gel was illustrated by its ability to disrupt exopolysaccharide slime and cell walls of Streptococcus mutans. Further analyses showed that H2O2 could penetrate into the deeper pockets (9 millimeters (mm)), but also its concentration in these deep pockets could increase over wearing time in the absence of degradation by peroxidases and catalase. Delivery of 1.7% H2O2 and Vibramycin Syrup (10 mg/ml) by a tray reduced subgingival bacterial loads and improved pre-treatment pocket depths of up to 8 mm.

Effects on Oral Structural Components and Materials

Tombes and Gallucci (1993; prospective controlled study) found that daily rinsing with 0.75% or 1.5% H2O2 mouth rinses 4-times each day caused significant mucosal abnormalities, including elongation and/or discoloration of the filiform papillae of the tongue and a diffusely increased whiteness of the mucosal surfaces, among normal volunteer study subjects (N = 35; age range = 25-40 years) [148]. In addition, 60% of subjects who used the H2O2 rinses complained that their mouths did not feel "normal" due to an unpleasant initial taste, burning, and stinging and tingling sensations. Bacterial adherence was significantly reduced in the 0.75% H2O2 group, but not in the 1.5% H2O2 group. Despite reports of dry mouth, salivary flow rates were not altered significantly. The authors concluded that, since H2O2 rinses were associated with mucosal abnormalities and elicit overwhelmingly negative subjective reactions in normal individuals, they should not be recommended for oral care. Pelino et al. (2018) evaluated the in vitro effects, including surface morphological characteristics and chemical elemental properties, of different mouthwash formulations on enamel and dental restorative materials, simulating up to 6 months of daily use [149]. Human enamel samples, hydroxyapatite, composite resin, and ceramic surfaces were exposed to three different types of mouthwash, as defined by their respective active components: 1) EOs, 2) EOs + fluoride + zinc chloride (EOFZC), and 3) 2% H2O2. Scanning electron microscopy did not reveal damage to dental enamel, hydroxyapatite, or composite resin surfaces by EO or EOFCZ mouthwashes. The H2O2 mouthwash caused a transient, superficial change to the enamel surface, which resolved after 3 months. Energy-dispersive X-ray showed no demineralization of tested surfaces, as there were no changes in the relative concentrations of calcium and phosphorus in enamel, silicon, and barium in composite resin, and silicon and aluminum in the ceramic material before and after treatment. Fourier transform infrared microscopy produced spectra characteristic of those for enamel, ceramic, and composite resin surfaces. No change was detected in the color properties of any specimen, except for the H2O2 rinse, which had a whitening effect on the enamel surface.

Mouth Moisturizers: Lemon-Glycerin and Glycerin

Xerostomia, also termed dry mouth or hyposalivation, affects 30% of the population and manifests as a side effect of medications, systemic diseases, or

cancer therapy [150]. Oral moisturizers can provide significant comfort to patients suffering from dry mouth and prevent dental erosion and caries. However, it is imperative that the moisturizers themselves do not have pH values below the critical pH of enamel or root dentin [150]. Recent studies have concluded that there is a large variation in the pH values among the most common oral moisturizers on the market and that there is a strong correl ation between the pH values and the erosive potential of these products [151,152].

Manufacturers recommend using oral moisturizers as needed throughout the day, and some products are intended for swishing or being held in the mouth for as long as possible for the maximum effect. Care should be taken to formulate and use products with safe pH values for both enamel and root dentin which, based on specific formulation, should be around 6.7 or higher [150]. There is a substantial evidence base indicating that glycerin products, including glycerin and lemon swabs, are detrimental to oral care [153]. Detrimental effects include increased alkalinity; decalcification of teeth; adverse effects to oral mucosa and microorganisms; and the loss of saliva due to over-stimulation by glycerin and lemon mix [154]. Puntillo et al. (2014) referred to the fact that protocols for mouth care in ICU patients, including those for VAP prevention, have eliminated the use of lemon-glycerin swabs because they produce an acid pH, dry oral tissues, cause irreversible softening and erosion of tooth enamel, exhaust salivary mechanisms, and worsen xerostomia [155]. The American Association of Critical-Care Nurses (AACN) 2017 Practice Alert for treating patients who are at high risk for ventilator-associated complications, including VAP, and non-intubated patients, recommend providing oral moisturizers to the oral mucosa and lips every 2-4 hours [26].

Lemon-Glycerin and Glycerin Effects in Oral Care

Comparisons to Other Agents

By an RCT, Van Drimmelen and Rollins (1969; N = 172; age range = 40-95 years) evaluated the effectiveness of lemon juice and glycerin as an oral hygiene agent in a 1:1 proportion [156]. Compared to normal saline exposure, the extent of drying of the oral cavity was greater with lemon juice and glycerin compared to exposure to normal saline. In their RCT, Little et al. (1981) compared a saliva substitute to a glycerin (placebo) mouthwash in patients (N = 148; mean age = 58 years) with Sjögren's syndrome [157], which involves salivary gland dysfunction [158], and thus can primarily manifest as xerostomia, and secondarily, as dysphagia, dysarthria, halitosis, rampant dental caries, mucosal ulceration, hypogeusia, hyposmia, and other complications [159]. Sixty percent of the patient pool was graded as having moderate xerostomia, while 30% and 10% of the remainder had mild and severe forms, respectively. Compared to the glycerin placebo, the saliva substitute was associated with significant relief of nocturnal oral discomfort, and more patients reported "excellent" improvement. An unequivocal advantage of the saliva substitute vs. glycerin was not conveyed, as the frequency of use of each product did not differ between patient groups. Furthermore, there were no significant differences between treatment groups regarding Sjögren's symptoms due to xerostomia, such as the occurrence of halitosis occurrence.

In order to explore best practices to manage xerostomia, Poland et al. (1987) performed an RCT to compare swabs pre-moistened with an aqueous solution of sorbitol, sodium carboxymethylcellulose, and electrolytes (Na, K, Cl) to traditionally used lemon-glycerin swabs [160]. With each patient (N = 20) who had received chemotherapy, oxygen therapy, radiation in the head/neck area, and mouth suctioning, serving as her/his own control, the use of each intervention was separated by one day. Whether treatment with the aqueous solution preceded or followed lemon-glycerin, oral symptoms of discomfort, such as lip and tongue dryness, and mucous membrane conditions, were improved by exposure to the aqueous solution but tended to worsen with lemon-glycerin exposure. Overall, treatment with the aqueous solution, but not lemon-glycerin, significantly improved patients' dentition and gingival scores, which could not be attributed to a mechanical effect, given that the swab sticks used in each study group were similarly designed. Ten years later, Foss-Durant and McAfee (1997; N = 21; mean age = 67 years) published the results of their RCT that compared the same aqueous solution as that tested by Poland et al. [160], lemon-glycerin swabs, and toothpaste (pink sponge applicators) and water [161]. Consistent with observations made by Poland et al. [160], the aqueous solution performed better than either lemon-glycerin or toothettes and water regarding various oral assessments, including oral moisture and texture. In their review article, Miller and Kearney (2001) indicated that, although lemon and glycerine swabs may initially stimulate salivary flow, they may exhaust this mechanism when they are used excessively, thereby causing xerostomia [162].

Effects on Tooth Enamel

Meurman et al. (1996) performed an in vitro study to investigate the erosive effects of three

commercially-available swab-sticks on bovine dental enamel: 1) two citric acid-based lemon-glycerin products, and 2) a malic acid-based product [163]. A malic acid-based saliva-stimulant chewing tablet was also assessed. After 4 hours of exposure to each of the test products, significant enamel softening caused by the two lemon-glycerin products was noted, but relatively little softening was observed following incubation in the two malic acid-based solutions. Consistent with this, stereomicroscopy and scanning electron microscopy demonstrated erosion only by the citric acid-based lemon-glycerin products.

Coconut Oil

Coconut oil is an edible oil extracted from the meat of coconuts and is used in a process called oil pulling. Oil pulling, or oil swishing therapy, is a traditional procedure in which practitioners rinse or swish oil in their mouth. Oil pulling with CO is an effective method to reduce plaque formation and plaque-induced gingivitis [84-86,164]. The fatty acid composition of CO is different from that of other dietary oils [165]. Indeed, CO is mostly composed of a medium chain fatty acid, and it contains 92% saturated acids, approximately 50% of which is lauric acid [165]. Lauric acid has proven anti-inflammatory and anti-microbial effects [166,167], and thus are likely largely responsible for the favorable effects of CO in oral care, which are discussed below.

Coconut Oil Properties and Effects in Oral Care

Anti-Microbial Properties

Ogbolu et al. (2007) aimed to determine the effectiveness of CO as an anti-fungal agent on Candida species in vitro [168]. With exposure to 100% CO, Candida albicans had the highest susceptibility, and Candida krusei showed the highest resistance. By comparison, Candida albicans was completely susceptible to 64 micrograms (μg)/ml fluconazole, while Candida krusei, displayed the highest resistance to this drug at a dose >128 μg/ml. The authors recommended that CO should be used in the treatment of fungal infections, given the emergence of drug-resistant Candida species in orally-related clinical conditions. Thaweboon et al. (2011) reported that CO had anti-microbial activity against Streptococcus mutans and Candida albicans, while Lactobacillus casei was resistant to CO in vitro [169]. Other oils such as corn oil, palm oil, rice bran oil, and soybean oil showed no anti-microbial activity. In a randomized controlled concurrent parallel triple blinded clinical trial, Pavithran et al. (2017) compared pure CO to sesame oil (SO) and to saline regarding Streptococcus mutants count in saliva among 30 subjects who were 20-23 years-old [170]. The participants were instructed to swish and pull 10 ml of oil on empty stomach in the early morning for 10-15 minutes. Coconut oil significantly reduced the Streptococcus mutans count, but there was no remarkable difference between SO and CO. The effect of CO was significantly larger than that of saline.

Effects on Dental Plaque and Gingivitis

Peedikayil et al. (2015) evaluated the effect of CO pulling/swishing on plaque formation and plaque-induced gingivitis in a prospective study (N = 60; age range = 16-18 years) [86]. A statistically significant decrease in the plaque and gingival indices (measures of dental plaque and gingival (gum) inflammation, respectively, with increasing numbers on each scale indicating worsening conditions) was noticed from day 7, and the scores continued to decrease during the period of study (up to 30 days). Kaushik et al. (2016) [85] and Peedikayil et al. (2015) [86] independently concluded that CO pulling is an easily usable, safe, and cost-effective procedure with minimal to no side effects, which can be used as an effective adjuvant procedure to decrease plaque formation and plaque-induced gingivitis [85,86], and may be investigated as an alternative to CHG for oral care [84]. Nagilla et al. (2017) performed an RCT involving 40 dental students (mean age = 21 years) to compare and evaluate the anti-plaque efficacy of CO pulling to a placebo (mineral water) [171]. Greater plaque reduction was observed in the CO cohort on the third and seventh days following treatment initiation, with statistical significance achieved on day 7. Kaliamoorthy et al. (2018) conducted a prospective interventional comparative study to compare the effects of CO, SO or toothbrushing on plaque-induced gingivitis [172]. Both CO and SO induced significant reductions in gingivitis up to 21 days following treatment initiation, with CO being significantly more effective than either of the other study regimens. The authors concluded that oil pulling with CO is more effective in reducing the severity of gingivitis than that with SO.

Alcohol-Free Mouthrinse/Mouthwash/Agent

Antiseptic mouth rinses such as CHG, EOs, and CPC have been found to be safe, and are widely recommended as a supplement to mechanical plaque removal to improve oral health, with varying effectiveness in controlling plaque and gingivitis. Formulations are available as alcohol-containing or alcohol-free. Kulkarni et al (2017) noted that, in some patients, alcohol-containing mouthwash can cause an initial burning sensation, unpleasant taste, and dryness of mouth [89].

Alcohol-Free Mouthrinse/Mouthwash/ Agent Properties and Effects in Oral Care Anti-Infection Properties

Hildebrandt et al. (2010; RCT; N = 105; mean age = 34) observed that xylitol rinse (4.4 g/day) and xylitol chewing gum (4.3 g/day) each caused a similar, but statistically insignificant, reduction in Streptococcus mutans levels in the mouth 3 months following test regimen initiation [173]. Differences between groups were not significant. Chalhoub et al. (2016) noted that reduction of dental plaque and oral pathogen levels by an alcohol-free EO mouthwash (AF-EOMW) in 18 institutionalized elderly participants (age range = 65-85 years) was not superior to use of tap water [174]. In a randomized, double-blind clinical study, Rezaei et al. (2016) investigated a natural herbal mouthwash containing Salvadora persica ethanol extract (10 mg/ml) and aloe vera gel (940 mg/ml) vs. 0.2% mouthwash CHG on the gingival index of 76 M-V ICU patients (age range = 18-64 years) [175]. Use of CHG rinse or herbal extract mouthwash along with mechanical methods, which involved brushing internal and external dental surfaces, gums and tongue, reduced the GI in intubated patients, but the reduction in GI in the herbal mouthwash group was significantly greater than in the CHG cohort. Houttuynia cordata (HC) (Saururaceae) has been used internally and externally as traditional medicine and as an herbal tea for healthcare in Japan. Sekita et al. reported that water solution of HC poultice ethanol extract (wHCP; 1%, 5%, or 10%) significantly inhibited biofilm formation by several oral pathogens, including Fusobacterium nucleatum, Streptococcus mutans, and Candida albicans, following in vitro incubation of these microorganisms in wHCP for up to 24 hours [176]. Up to 10% wHCP was not toxic toward keratinocytes, while 0.1% of this extract inhibited interleukin-8 and CCL20 productions by Porphyromonas gingivalis lipopolysaccharide-stimulated human oral keratinocytes. The authors concluded that the study's outcomes suggested that wHCP may be clinically useful as a mouthwash to prevent oral infectious challenges such as periodontal disease.

Treatment of Xerostomia

Mouly et al. (2007) performed a RCT that enlisted institutionalized elderly patients (N = 41; mean age = 84 years old) to use an oxygenated glycerol triester (OGT) oral spray (N = 22) or a commercially-available saliva substitute (N = 19) to treat xerostomia [177]. The OGT intervention was significantly better than the saliva substitute with respect to multiple endpoints, including mouth dryness, swallowing difficulty, speech difficulty, general relief of symptoms, mucositis relief, and resolution of tongue thickening. In a double-blind, RCT involving elderly participants (age range = 68-89 years), Gómez-Moreno et al. (2014) treated 21 subjects with a topical sialogogue spray containing 1% malic acid, 10% xylitol, and 0.05% fluoride or 20 subjects with a placebo composed of the same ingredients, but without malic acid [178]. The malic acid formulation significantly reduced xerostomia and increased unstimulated and stimulated salivary flow rates.

Exposure-Associated Physical Changes to Teeth and Dental Materials

Moreira et al. (2013) assessed, in vitro, the color of teeth exposed to different mouthrinses for a prolonged period [179]. Bovine teeth were distributed among four treatment groups: control (artificial saliva), alcohol-containing (21.6%) mouth rinse, alcohol-free mouth rinse (CPC), and CHG (0.06 grams) mouth rinse. While incubated in their respective test solutions, teeth were submitted to two cycles of staining and artificial aging by exposing the teeth to ultraviolet light, heat, and humidity for 24 hours. The teeth exposed to the alcohol-containing mouthwash displayed a clinically-perceptible color change, but the other test solutions did not cause this effect.

Other Topics

In order to determine if use of a CPC mouth rinse affects the incidence of pre-term birth (PTB; < 35 weeks), Jeffcoat et al. (2011) conducted a prospective single-blind clinical trial that included pregnant women (N = 226; 6-20 weeks' gestation) with periodontal disease who refused dental care [180]. The CPC rinse group had significantly fewer episodes of PTB, and gestational age and birth weight were significantly higher in the CPC cohort. In addition, while the CPC group showed signs of reduced periodontal disease at 6 months, the no-rinse subjects had exacerbations of periodontal disease.

In a prospective investigation, Eliot et al. (2013) examined associations between oral hygiene, including a history of periodontal disease and mouthwash use, and risk of head and neck squamous cell carcinoma (HNSCC) [181]. The authors measured the history of oral hygiene and dental care in 513 HNSCC cases and 567 controls from a population-based study of HNSCC (mean age of study subjects = 58 years). Periodontal disease was associated with a significant risk of HNSCC, and using mouthwash at least once per day, compared to never using mouthwash, was associated with an 11% increase in the risk of HNSCC. Relatively frequent use of low or non-alcoholic mouthwash was significantly more associated with HNSCC risk than less frequent use of these mouthwashes. The authors did not observe a difference between the effects of alcohol-contain

ing and non-alcohol mouthwashes on HNSCC risk.

Conclusions

The agents discussed in this report are purposeful components of oral care protocols that are intended to reduce the likelihood that patients will develop oral and respiratory infections. Indeed, CHG, CPC, NaHCO3, H2O2, CO, and alcohol-free formulations have each demonstrated anti-microbial properties and abilities to reduce dental plaque and/or mitigate gingivitis. While the emphasis of this review article is on oral care agent performance, it is critical to also consider any AEs that may be associated with the use of these agents. Such events include those that occur during real-world medical treatment experiences as well as those reported in clinical studies. Other than a potential for CHG to be linked to mortality, the AEs associated with oral care agent use in studies discussed in this review article are few and minor in nature, and so suggest an acceptable risk-benefit ratio to incentivize the continued use of these agents in the clinic to reduce the incidence of orally-derived healthcare complications. Three critical lessons have emerged from studies that examined the utility of CHG in oral care, including 1) CHG appears to be most effective for inhibiting VAP in adult cardiac surgery patients, 2) CHG may be unable to significantly mitigate NP development in children, and 3) CHG oral care may be associated with mortality in some patient populations, including those who, ironically, are at relatively less risk of dying prior to CHG oral care. Thus, an alternate treatment paradigm may be warranted to prevent NP in hospitalized children, which may require identification of a different oral care agent having effectiveness in adults as well, but without the putative mortality complication. Until the results of studies become available to address these important healthcare issues, CHG oral care should be practiced cautiously, with current clinical study findings in mind.

Table 1: Original studies assessing patient mortality incidence during chlorhexidine oral care.

Reference	Study Methodology and Population	Study Agents and Administration Protocols	Mortality Results
DeRiso et al., 1996[21]	RCT/Consecutive eligible patients who underwent CABG, valve surgery, septal surgery, cardiac tumor excision, or combined CABG valve surgery requiring cardiopulmonary bypass (N = 353; mean age = 64 years).	• Mouthrinses: CHG (11.6% alcohol) vs placebo (3.2% alcohol). • Doses of each mouthrinse were 0.5 fluid ounces of solution to be used as an oropharyngeal rinse or rigorously applied to the buccal, pharyngeal, gingival, tongue, and tooth surfaces for 30 seconds twice-daily.	In-hospital mortality was significantly less in the CHG group (1.16%) than in the placebo group (5.56%).
Fourrier et al., 2000[27]	RCT/Patients consecutively admitted in the ICU with a medical condition suggesting an ICU stay of 5 days and requiring MV (N = 60; mean age = 51 years).	During patients' ICU stays: • 0.2% CHG gel was applied after mouthrinsing and oropharyngeal aspiration by a sterile glove-protected finger 3 times/day • Control: mouthrinsing with bicarbonate isotonic serum, and then oropharyngeal aspiration 4 times/day.	The mortality rate was less in the CHG group (10%) than in the control group (23%).
Houston et al., 2002[22]	RCT/patients undergoing aortocoronary bypass or valve surgery requiring cardiopulmonary bypass (N = 561).	• 0.12% CHG- oral rinse (15 ml) pre-operatively and twice-daily for 10 days post-operatively or until extubation, tracheostomy, death, or diagnosis of pneumonia. Post-operatively, 15 ml of oral rinse was administered to intubated patients twice a day by thoroughly swabbing the surfaces in the patient's oral cavity. • Phenolic mixture mouthrinse - same protocol as for CHG.	In-hospital mortality rates were not different: CHG, 2.4; phenolic mixture, 1.1.

MacNaughton et al., 2004[37]	RCT/Patients who were predicted to require more than 48 hours of MV (N = 179; age = > 18 years).	• 0.2% CHG - twice-daily oropharyngeal suction to remove secretions, followed by 15 ml of mouthrinse using a sponge applicator to the roof of the mouth, inside of cheeks, tooth surfaces, gums, tongue, and buccal cavity. • Placebo - 50% peppermint water, 50% sorbitol mouthrinse- same protocol as for CHG mouthrinse.	The cardiac care unit mortality rate did not significantly differ: CHG, 18%; Placebo, 13%.
Fourrier et al., 2005[28]	RCT/Non-edentulous patients requiring endotracheal intubation and MV, with an anticipated length of stay >5 days (N = 228; mean age = 61 years).	During patients' ICU stays (until day 28): • 0.2% CHG gel applied after mouthrinsing and oropharyngeal aspiration over the dental and gingival surfaces of the patient, with a sterile glove–protected finger 3 times/day. • Placebo gel applied as for CHG gel.	The ICU mortality rate up to 28 days was not significantly differently between groups: CHG, 27.1%; Placebo, 21%.
Koeman et al., 2006[55]	RCT/Patients needing MV for 48 hours (N = 385; mean age = 62 years).	• 2% CHG - administered 4 times/day, after removing remnants of the previous dose with a gauze moistened with saline. Approximately 2 centimeters of paste, approximately 0.5 grams, was put on a gloved fingertip and administered to each side of the buccal cavity. • 2% CHG + 2% colistin - same protocol as for CHG. • Placebo - same protocol as for CHG.	ICU mortality rates did not differ among study groups.
Segers et al., 2006[64]	RCT/Patients older than 18 years undergoing elective cardiothoracic surgery (N = 991; mean age = 66 years).	• 0.12% CHG oropharyngeal rinse and a nasal ointment. The oropharyngeal solution (10 ml) was used as a mouthrinse and applied to buccal, pharyngeal, gingival, and tooth surfaces for 30 seconds 4 times/day. The nose ointment was applied 4 times/day in both nostrils. The protocol was continued until the nasogastric tube was removed, usually the day after surgery. • Placebo oropharyngeal rinse and a nasal ointment - same protocol as for CHG.	The in-hospital mortality rate did not significantly differ: CHG, 1.7%; Regular care, 1.3%.
Tantipong et al., 2008[56]	RCT/Patients who were hospitalized in ICUs or general medical wards, and who received MV (N = 207; mean age = 59 years).	• 2% CHG was administered 4 times/day by rubbing the oropharyngeal mucosa, after brushing the teeth, and suctioning any oral secretions. • Normal saline was administered as described in the 2% CHG group. • CHG or normal saline were provided until the endotracheal tube was removed. • Selective decontamination of the digestive tract or continuous aspiration of subglottic secretions was not performed.	The mortality rate was not significantly differently between groups: CHG, 32.3%; Saline, 35.2%.
Bellissimo-Rodrigues et al., 2009[43]	RCT/Patients admitted to the ICU with a prospective length of stay greater than 48 hours (N = 194; median age = 59 years).	• Placebo vs. 0.12% CHG. • Oral rinses with placebo or CHG were performed 3 times/day throughout the duration of the patient's stay in the ICU.	The mortality rates were not significantly different: Placebo, 34%; CHG, 36%.
Munro et al., 2009[13]	RCT/Critically ill adults in 3 ICUs (medical respiratory, neurosurgical, and surgical trauma) who were enrolled in the study within 24 hours of intubation (N = 547; mean age = 48 years).	• 0.12% CHG (5 ml by oral swab twice-daily). • toothbrushing 3 times/day. • combination care (toothbrushing 3 times a day and CHG every 12 hours). • control (usual care).	The in-hospital mortality rate in the CHG group 3 days post-initiation of interventions was not significantly different than that of the other study cohorts: toothbrush, 20%; CHG, 30%; toothbrush+CHG, 25%.
Panchabhai et al., 2009[34]	RCT/ICU patients (N = 512; mean age = 36 years).	• 0.2% CHG: twice-daily oropharyngeal cleansing - obtunded and tracheostomy patients - swabbed; non-intubated pts - rinsed. • 0.01% potassium permanganate solution: oropharyngeal cleansing with 0.01% potassium permanganate solution twice-daily - same protocol as for CHG.	The in-hospital mortality rates did not significantly differ between study groups: CHG, 34.8%; potassium permanganate, 28.3%.

Pobo et al. 2009[39]	RCT/Consecutive adult patients who were intubated without evidence of pulmonary infection were randomized within 12 hours of intubation if they were expected to remain on MV for > 48 hours (N = 147; mean age = 55 years).	Standard Group • Aspiration of oropharyngeal secretions and adjustment of endotracheal cuff pressure. • A gauze containing 20 ml of 0.12% CHG was applied to all dental pieces, tongue, and the mucosal surface, and 10 ml of 0.12% CHG was injected into the oral cavity, being aspirated after 30 seconds. • This protocol occurred every 8 hours, maintaining head elevation at 30°. Toothbrush Group • Toothbrushing was added to the protocol described for use of CHG. • Brushing was administered tooth by tooth, on anterior and posterior surfaces, and along the gum line, and the tongue was brushed.	The ICU mortality rate was not significantly different between groups: Standard/CHG, 31.5%; Toothbrush, 21.6%.
Scannapieco et al., 2009[40]	RCT/ICU patients who were expected to be MV within 48 hours of admission (N = 175; age range = 18-88 years).	• Control: twice-daily oral topical applications with the CHG vehicle control. • CHG 1: once-daily oral topical treatment with 0.12% CHG and once-daily oral topical treatment with vehicle control. • CHG 2: patients received twice-daily oral topical treatments with 0.12% CHG.	The ICU mortality rates were not significantly different: Control, 17%; CHG 1, 17%, CHG 2, 16%.
Ćabov, et al., 2010[29]	RCT/Non-edentulous M-V and non-M-V patients consecutively admitted to the surgical ICU and requiring a minimum stay of three days (N = 60; mean age = 55 years).	Mouthrinsing with bicarbonate isotonic serum followed by gentle oropharyngeal sterile aspiration plus: • 0.2% CHG dental gel applied directly by nurses over the dental, gingival, and oral surfaces with a sterile glove-protected finger three times daily. The gel was left in place and the oral cavity was not rinsed after application. or • placebo dental gel.	The mortality rate in the CHG group (3.3%) was lower than that in the placebo group (10%).
Berry et al., 2011[81]	RCT/Patients with an expected duration of MV more than 48 hours (N = 225; mean age = 58 years).	• Sterile water - oral rinsing second hourly. • $NaHCO_3$ mouthwash - oral rinsing second hourly. • CHG - twice-daily irrigation with 0.2% aqueous oral rinse with second hourly irrigation with sterile water. • Mouthrinses were applied using a curved tip dental syringe. All treatment options included a comprehensive cleaning of the mouth using a soft pediatric toothbrush 3 times/day.	ICU mortality rates less than 96 hours after treatment initiation: • Sterile water, 5%. • $NaHCO_3$, 17%. • CHG, 7%.
Meinberg et al., 2012[83]	RCT/Patients who were receiving MV, admitted less than 24 hours prior, and anticipated to require MV for more than 72 hours (N = 87; mean age = 41 years).	• 2% CHG gel + toothbrushing - manual cleaning of oral cavity with a toothbrush and application of the gel to the entire oral cavity 4 times/day until patient was released from the ICU. • Placebo - same protocol as for CHG.	The ICU mortality rate did not significantly differ: CHG, 46.5%; Placebo, 37.5%.
Özçaka et al., 2012[42]	RCT/Dentate patients in respiratory ICU scheduled for MV for at least 48 hours (N = 61; mean age = 59 years).	• 0.2% CHG - swabbing of the oral mucosa 4 times/day). Applications (30 ml) lasted for 1 minute. • Saline - same protocol as for CHG.	The mortality rates in each study group were not significantly different: CHG, 59%; saline, 59%.
Bellissimo-Rodrigues et al., 2014[44]	RCT/ICU patients who were in the ICU for at least 48 hours (N = 294; mean age = 57 years)	• Dental care 4-5 times a week: vigorous teeth brushing with a child toothbrush, tongue scraping, removal of calculus, atraumatic restorative treatment of caries, teeth extraction, and oral topical application of CHG (2.0% gel - unconscious patients; 0.12% - conscious patients, preferable due to taste). • Routine oral hygiene 3 times/day: mechanical cleansing of the oral cavity with a spatula wrapped in gauze, followed by topical application of CHG 0.12% or 2.0%, according to consciousness level.	The mortality rates in each study group were not significantly different: CHG, 31.5%; saline, 29.1%.

Nicolosi et al., 2014[65]	Quasi-experimental/ Patients scheduled for cardiovascular surgery requiring sternotomy (N = 300; mean age = 63 years).	• 0.12% CHG + toothbrushing - mouthrinsing with CHG every 12 hours for 3 days before surgery. • regular oral hygiene care - pre- and post-surgical antibiotic administration.	The in-hospital mortality rate did not significantly differ: CHG, 5.3%; Regular care, 4.7%.
Lev et al., 2015[75]	Prospective, controlled/ adult M-V ICU patients (N = 90; mean age = 71 years).	• Study group o tooth brushing, NaHCO3 on the suction toothbrush, rinsing with an antiseptic solution containing 1.5% H2O2, and a mouth moisturizer. • Control group o cleaning with a sponge and atraumatic clamp, and rinsing with a 0.2% solution of CHG.	The in-hospital mortality rates in each study group were not significantly different: CHG, 28.9%; Study group, 26.7%.
Chen et al., 2016[36]	Prospective/Emergency ICU patients (N = 873; mean age = 63).	• 0.08% MDE - swabbing of the oral mucosa, teeth, and tongue with sponge pellets impregnated with 20 ml 2 times/day until discharge from ICU or death (1 year). • 0.2% CHG - same protocol as for MDE (next 3 consecutive years).	• ICU mortality of non-intubated patients was significantly greater in the MDE group: o MDE, 16.3%; CHG (2 different CHG periods, both = 7%). • ICU mortality of VAP patients was not significantly different: o MDE (27.5%); CHG (21.4%, 22.5%, 15.6%).
Klompas et al, 2016[50]	Retrospective analysis of prospectively collected data/Patients who underwent M-V for at least 3 days (N = 5539; mean age = 61 years).	Ventilator bundle: head-of-bed elevation, sedative infusion interruptions, spontaneous breathing trials, thromboprophylaxis, stress ulcer prophylaxis, and oral care with CHG.	Oral care with CHG was associated with an increased risk for ventilator-associated mortality.
Deschepper et al., 2018[70]	Retrospective observational cohort/Patients (≥ 16 years) hospitalized and discharged over a 3-year period. Hospitalized patients allocated to an All Patient Refined-Diagnosis Related Groups category without risk of mortality were not considered: all patients admitted to psychiatric or rehabilitation wards were excluded. (N = 82, 274; age ranges: survivors, 42-69 years; non-survivors, 60-80 years).	• CHG oral care is covered by a protocol prescribing a rinse and-spit approach for autonomous patients and cleaning of the oral cavity by the nurse with CHG soaked sterile gauze in dependent patients. • CHG oral care is applied twice-daily in general wards and thrice-daily in ICUs.	• 11,133 (14%) patients received CHG oral care (0.05% (N = 1175) or 0.12% (N = 9963)). Low-level exposure to CHG oral care (≤ 300 mg) was associated with increased risk of death. This association was stronger among patients with a lower risk of death. Similar observations were made for high-level exposure (> 300 mg). • CHG oral care had no significant effect on in-hospital mortality in cardiothoracic and vascular surgery patients. • CHG oral care was associated with increased risk of death in patients who did not receive MV and were not admitted to the ICU during their hospitalization. • CHG oral care had no effect on in-hospital mortality among non-ventilated ICU patients. • Among patients with an extreme risk of mortality CHG oral care is not associated with increased mortality. Among patients with a major risk of mortality CHG oral care is significantly associated with mortality, as in patients with a minor or moderate risk of mortality.
Khaky et al., 2018[46]	RCT/ICU patients (N = 80; mean age = 43 years).	• 2% CHG: 15 ml 3 times/ day for 5 days, with brushing the teeth, suctioning oral secretions, and rubbing the oropharyngeal mucosa. • H2O2 and silver ions solution: same protocol as for CHG.	Mortality rate: First day of study: No significant difference between study groups. Fifth day of study: Significantly less compared to day 1 within each group, but no significant difference between groups.

RCT, randomized controlled trial; CABG, coronary artery by-pass grafting; N, number of study patients/ subjects; CHG, chlorhexidine gluconate (chlorhexidine); ICU, intensive care unit; ml, milliliters; MV, mechanical ventilation; M-V, mechanically-ventilated; NaHCO3, sodium bicarbonate; MDE, metronidazole; mg, milligrams; H2O2, hydrogen peroxide.

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Table 2: Systematic reviews and meta-analyses evaluating patient mortality incidence during chlorhexidine oral care.

Reference	Inclusion Criteria of Analysis	Details of CHG/Mortality-Centered Analysis	Results of Analysis on Mortality
Shi et al., 2013[58]	• Focus on oral healthcare effects in critically ill patients receiving MV for at least 48 hours.	• Number of Studies: 15 • Number of Patients: 3511 • Study Methodologies: RCT • Number of studies in which mortality was a primary outcome: 2	The data did not show that there is a difference between the incidence of patient mortality associated with CHG oral care compared to that associated with placebo/usual care.
Klompas et al., 2014[67]	• CHG: any preparation, daily oral care. • Control: inert comparators for routine care. • Adult patients receiving MV. • All dates and languages. • Outcome(s) for comparison of interest: pneumonia, mortality, duration of MV, ICU LOS, hospital LOS, and antibiotic dispensing. • Trials that provided outcome data ≥ 80% of randomized patients.	• Number of Studies: 12 • Number of Patients: 3263 • Study Methodologies: RCT • Number of studies in which mortality was a primary outcome: 2	The difference in mortality rates between CHG and placebo in cardiac surgery patients (3 studies) was not significant, but among non-cardiac surgery patients (9 studies), CHG demonstrated a trend toward increased mortality.
Price et al., 2014[73]	• Adult patients in general intensive care units. • No placebo control or blinding requirement. • CHG must have been applied at any concentration in any formulation to the oropharynx. • Control group must have received only standard care or placebo.	• Number of Studies: 11 • Number of Patients: 2772 • Study Methodologies: RCT • Number of studies in which mortality was a primary outcome: 0	CHG oral care was associated with increased mortality.
Silvestri et al., 2014[35]	• CHG: critically ill patients • Control: placebo or another product for oral care	• Number of Studies: 16 • Number of Patients: 4026 • Study Methodologies: RCT • Number of studies in which mortality was a primary outcome: 2	CHG oral care had no significant effect on patient mortality.
Li et al., 2015[68]	• All languages o Adults patients receiving MV o VAP-focused outcome o Sample size > 50	• Number of Studies: 9 • Number of Patients: 2452 • Study Methodologies: RCT • Number of studies in which mortality was a primary outcome: 2	CHG oral care had no effect on patient mortality.

Hua et al., 2016[59]	• Focus on oral healthcare effects in critically ill patients receiving MV for at least 48 hours.	• Number of Studies: 14 • Number of Patients: 2043 • Study Methodologies: RCT • Number of studies in which mortality was a primary outcome: 2	The data did not show that there is a difference between the incidence of patient mortality associated with CHG oral compared to that associated with placebo/usual care.
Spreadborough et al., 2016[69]	• Meta-analysis - followed PRISMA guidelines. • Systematic Review sources: MEDLINE, EMBASE, and Cochrane databases. o Limited to a 20-year period. o English language. o All trial designs and interventions. o Patients ≥ 18 years.	• Number of Studies: 4 • Number of Patients: 2205 • Study Methodologies: RCT (3) and Quasi-Experimental (1) • Number of studies in which mortality was a primary outcome: 1	• All patients underwent elective cardiac surgery. • The mortality rates associated with the CHG and control oral care treatments did not differ significantly.
Lee et al., 2019[74]	• Literature Search - followed PRISMA guidelines o Population: -ventilated adult subjects in ICU settings of high-income countries (i.e., gross national income per capita $12,236). -adult subjects on ventilation and in ICU settings of low- and middle-income countries. -no previous intubation, no baseline clinical pneumonia, and MV need for at least 48 hours. o Intervention: -CHG - multiple concentrations and formulations. -Control: placebo or standard ICU care without CHG application as a preventive therapy for VAP in the ICU. o Outcomes: -mortality (defined as ICU mortality (directly and indirectly attributable) -VAP incidence (defined as pneumonia that developed after at least 48 hours of endotracheal intubation and MV in the ICU)	• Number of Studies: 11 • Number of Patients: 1914 • Study Methodologies: RCT • Number of studies in which mortality was a primary outcome: 2	No evidence of a significant effect of CHG on mortality was found, regardless of CHG concentration (0.12%, 0.2%, and 2%) or application method (gel or rinse).

RCT, randomized controlled trial; MV, mechanical ventilation; CHG, chlorhexidine gluconate (chlorhexidine); ICU, intensive care unit; LOS, length of stay; VAP, ventilator-associated pneumonia; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 3: Original studies comparing chlorhexidine to other oral care agents, and other comparisons of oral care agents.

Reference	Study Objective	Study Design and Participants	Comparators	Author-Indicated Study Results/Conclusions
Chlorhexidine Gluconate vs. Cetylpyridinium Chloride				
Pizzo et al., 2006[76]	To investigate the plaque inhibitory effects of CHG, CPC, and TRN delivered by sprays and mouthrinses.	Randomized controlled trial (RCT)/healthy volunteers (N = 15; age range = 22-27 years).	Mouthrinses: • 0.12% CHG • 0.2% CHG • 0.05% CPC • 0.03% TRN	CHG sprays were the most effective sprays in preventing plaque regrowth, without significant differences between the two concentrations tested. TRN spray showed a significant inhibition of plaque regrowth in comparison to the negative control. CPC spray did not differ from saline spray. A similar trend of efficacy was detected for rinses. Although the effect on plaque regrowth observed with CHG rinses was superior to that of CHG sprays, the latter did not cause side effects.
Hutchins et al., 2009[93]	Though a performance improvement project, to address an unacceptable VAP rate and determine the effectiveness of combining an oral care protocol with a ventilator bundle to prevent VAP in intubated/M-V ICU patients.	Quality improvement project (QIP) (no control group or randomization)/M-V ICU patients.	Ventilator bundle + Oral care protocol: • Brush teeth using suction toothbrush with: • CPC (2005 and 2006) • 0.12% CHG (2007)	VAP Rate (number of incidents/1000 ventilator days) • For 2004 (prior to QIP): 12.6 • For 2005: May (start of QIP) to December: 4.12 • For 2006: 3.57 • For 2007: 1.3 • The VAP rate decreased by 89.7% from 2004 to 2007.
Osso and Kanani, 2013[77]	To summarize current studies on the comparative effectiveness of selected anti-septic mouthrinses in controlling plaque and gingivitis, and risks associated with daily exposure, including salivary flow rate, oral cancer and wear of composite restorations.	Narrative Literature Review	Mouthrinses: • 0.12% CHG • EOs (menthol, thymol and eucalyptol) and methyl salicylate • 0.7% CPC • 20% aloe vera gel	The majority of studies showed that mouthrinses containing CHG or EOs and methyl salicylate provide clinically significant anti-gingivitis and anti-plaque benefits. Cetylpyridinium chloride provides only limited clinical benefits compared to inactive control mouthrinse. Inadequate evidence is available to evaluate the clinical effectiveness of aloe vera gel. Chlorhexidine, EOs, and CPC have been found to be safe. However, limited data are available on the effects of the mouthrinse on wear patterns of dental restorations. Studies reviewed reported no significant difference in salivary flow rate related to alcohol-based mouthrinse.
Chlorhexidine Gluconate vs. Sodium Bicarbonate				
Berry et al., 2011[81]	To test oral hygiene mouthrinse	RCT/M-V ICU patients (N = 109; mean age = 58 years).	Mouthrinses:	NaHCO3 showed a greater trend to reduction in bacterial colonization;

	strategies on the effects of microbial colonization of dental plaque with respiratory pathogens (primary outcome) and incidence of VAP (secondary outcome).		• 0.2% CHG + sterile water • NaHCO3 • sterile water	no significant differences among groups could be demonstrated at day 4 of admission. The incidence of VAP (N = 9 cases at study day 8) was not different between the NaHCO3 and CHG/sterile water groups (5%), and it was less in the sterile water group (1%).
Choi and Kim, 2012[78]	To compare the effectiveness of NaHCO3 mouthwash with CHG mouthwash in oral care of acute leukemia patients under induction chemotherapy.	RCT/acute myelogenous leukemia or acute lymphoblastic leukemia patients under induction chemotherapy (N = 48; mean age = 39 years).	Mouthwashes: • 0.1% CHG • NaHCO3	Of all the patients in the NaHCO3 group, 25.0% developed ulcerative oral mucositis, whereas 62.5% in the CHG group did. The onset of oral mucositis was later in the NaHCO3 group than the CHG group. The oral bacterial colonization in the NaHCO3 group was significantly higher than that in the CHG group, but clinical signs associated with infection did not differ in both groups.
Özden et al., 2014[80]	To determine the influence of three different oral care solutions on oral mucous membrane integrity in critically ill patients.	RCT/critically-ill patients (N = 60).	• 0.2% CHG • 5% NaHCO3 • saline	There was no difference between patient groups receiving saline solution, NaHCO3, or 0.2% CHG in terms of oral mucous membrane integrity; the oral mucosa of all patients was found to be mildly dysfunctioning.
Cabrera-Jaime et al., 2018[79]	To compare the efficacy of various mouthrinses: Plantago major extract versus 0.12% CHG versus 5% NaHCO3 in the symptomatic treatment of chemotherapy-induced oral mucositis in solid tumor cancer patients.	RCT/patients with solid tumors and undergoing chemotherapy (N = 50; mean age = 60 years).	Mouthrinses: • 5% NaHCO3 + 5% NaHCO3 • 5% NaHCO3 + 5% Plantago major extract • 5% NaHCO3 + 0.12% CHG	Healing time was shorter with the double NaHCO3 solution compared to the other two rinses, but the differences were not significant. It may be time to reconsider the use of Plantago major extract in the management of oral mucositis.
Shin and Nam, 2018[82]	To emphasize the necessity of gargling for a pleasant oral environment, to examine the changes in the oral environment through the saliva before and after the use of optimal mouthwashes for the most effective and continuous oral care among various mouthwashes, and to improve the oral environment.	Prospective/ healthy female university students (N = 20)	Mouthwashes: • 0.2% CHG • 7.5% PVI • NaHCO3-normal saline • sterile distilled water	Salivary pH significantly increased in the CHG and PVI groups, and there was a significant decrease in dental plaque burden in the CHG, PVI, and NaHCO3-normal saline groups. In addition, there was a statistically significant reduction in salivary Streptococcus mutans in the PVI and CHG groups. All treatments reduced susceptibility to dental caries.
Chlorhexidne Gluconate vs. Hydrogen Peroxide				
Dahiya et al., 2012[92]	To assess the effect of oral decontamination with 0.2% CHG mouthrinse and H2O2 mouthrinse on the incidence of VAP and oropharyngal colonization.	RCT/adult M-V ICU patients (N = 70; age = >18 years)	Mouthrinses: • 0.2% CHG • H2O2 diluted 1:8 in normal saline	The incidence of VAP was approximately 3.5-times higher in the H2O2 group. CHG more effectively reduced oropharyngeal colonization.
Chlorhexidne Gluconate vs. Sodium Hydroxide+Hydrogen Peroxide				
Lev et al., 2015[75]	To compare the incidence of VAP among patients treated with oral care combined with	Prospective, controlled/ adult M-V ICU patients	• Study group o tooth brushing, NaHCO3	• The VAP rate was significantly lower in the Study Group: 8.9% vs. 33.3%.

	the brushing of teeth to those treated with conventional methods of oral care.	(N = 90; mean age = 71 years).	on the suction toothbrush, rinsing with an antiseptic solution containing 1.5% H2O2, and a mouth moisturizer. • Control group o cleaning with a sponge and atraumatic clamp, and rinsing with a 0.2% solution of CHG.	• The development of VAP per 1,000 ventilation days was significantly lower in the Study Group: 10.2 vs. 29.5.
Chlorhexidine Gluconate vs. Coconut Oil				
Singla et al., 2014[84]	• To assess reduction in Streptococcus mutans and Lactobacillus species count in saliva sample after ten minutes of oil gum massage therapy (massage of gingival tissues) per day for three weeks with sesame oil, olive oil, and CO in three different groups of subjects. • To compare the efficacy between three different oils and the "gold standard" CHG gel. • To assess reduction in gingival scores and plaque scores of study subjects.	RCT/housekeeping personnel at a hospital (N = 32; age range = 18-55 years).	Massage solutions: • sesame oil • olive oil • CO • CHG gel	There was a significant reduction in mean Streptococcus mutans count, Lactobacillus count, plaque scores, and gingival scores in all four groups after the study. However, there was no significant difference found in percentage reduction of these variables among the 4 groups.
Kaushik et al., 2016[85]	To evaluate the effect of CO pulling on the count of Streptococcus mutans in saliva and to compare its efficacy with that of CHG mouthwash in vivo.	RCT/healthy volunteers (N = 60).	Mouthwashes: • CHG • CO • distilled water	Both CHG and CO significantly reduced Streptococcus mutans load in saliva. Oil pulling can be explored as a safe and effective alternative to CHG.
Peedikayil et al., 2016[97]	To determine the anti-bacterial efficacy of CO mouthrinse and compare it with CHG mouthrinse.	RCT/children (N = 50; age range = 8-12 years).	Mouthrinses: • 2% CHG • CO	The results showed that there is a statistically significant decrease in Streptococcus mutans in both the CO and CHG groups from baseline to 30 days. There was no significant difference in anti-bacterial efficacy between CO and CHG. CO is as effective as CHG in the reduction of Streptococcus mutans.
Shino et al., 2016[98]	To isolate Candida species in children with early childhood caries and study the anti-fungal effect of CO, probiotics, Lactobacillus, and 0.2% CHG on Candida albicans in comparison with ketoconazole.	Susceptibility analysis of oral samples (Candida albicans) to various oral care agents/children with early childhood caries (N = 80; age range = 3-6 years).	Mouthrinses: • 2% Ketoconazole • 0.2% CHG • Probiotics (lactic acid Bacillus) • CO	CHG and CO showed significant anti-fungal activity that was comparable to ketoconazole. The anti-fungal effects among the study groups were not significantly different.
Owittayakul et al., 2018[87]	To investigate the effect of CO in reducing the levels of total bacteria and Streptococcus mutans in saliva, and to compare its efficacy with that of 0.12% CHG mouthrinse.	RCT/healthy undergraduate dental students (N = 40; age range = 18-25 years).	Mouthrinses: • 0.12% CHG • CO	Two weeks of CO pulling showed a similar percentage reduction in total bacterial and Streptococcus mutans count to that produced by 0.12% CHG mouthrinse. Thus, coconut oil can be an alternative mouthrinse in preventive therapy to maintain oral hygiene.

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Other Comparisons Made Among Oral Care Agents				
Miyasaki et al., 1986[99]	To examine both minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) of NaHCO3 and H2O2 individually and in combination against selected facultative, Gram-negative oral bacteria in a microtiter dilution assay.	Laboratory examination	• NaHCO3 • H2O2	At sub-lethal concentrations toward various bacteria, NaHCO3 antagonized the ability of H2O2 to inhibit bacterial growth, but sub-lethal concentrations of H2O2 had no effect on NaHCO3. Lethal concentrations of H2O2 and NaHCO3 exhibited synergistic anti-microbial activity in combination in one-hour bactericidal assays. Since the bactericidal properties of these anti-microbial agents are synergistic, we conclude that it may be rational to use them in combination to treat certain forms of periodontal disease. Also, lower and perhaps safer concentrations of H2O2 can be used in combination with NaHCO3 when oxidative anti-microbial chemotherapy is indicated.
Shibly et al., 1997[100]	To evaluate the effects of a 20% NaHCO3 dentifrice, a 1.5% H2O2 solution, and a mouth moisturizer on oral tissues and microflora.	Prospective/ healthy volunteers (N = 150; age range 18-70 years).	• Brush with a 20% NaHCO3 dentifrice or a 2) brush with a dentifrice lacking NaHCO3, followed by use of a toothette saturated with NaHCO3 dipped in 1.5% H2O2 solution, and then use of a mouth moisturizer. • Brush with a dentifrice lacking NaHCO3, followed by 1) use of a toothette saturated with NaHCO3 with a mint-flavored solution with no application of a mouth moisturizer, 2) use of a toothette without NaHCO3 and colored saline as the liquid with no application of a mouth moisturizer, or 3) use of a toothette without NaHCO3, and colored, flavored 1.5% H2O2 as the liquid with no application of a mouth moisturizer.	Clinical parameters showed a statistically significant reduction in gingivitis, with no significant differences among the groups, while dental plaque differences were not statistically significant from each other or baseline. There were insignificant increases in tooth staining in all groups, with no differences among the groups.
Kumar et al., 2013[90]	To assess the effectiveness of three different mouthrinses: CHG, TRN + NaF, and CHG + TRN + NaF + ZnCl2, on plaque, calculus, gingivitis and stains, and to evaluate the occurrence of adverse effects with these three treatments.	RCT/healthy subjects (N = 48; mean age = 21 years)	Mouthrinses: • 0.2% CHG • 0.03% TRN + 0.025% NaF + 12% ethyl alcohol • 0.2% CHG + 0.3% triclosan + 0.3% NaF + 0.09% ZnCl2	CHG mouthrinse was most effective in controlling plaque and gingivitis, but caused greatest deposition of extrinsic stains. Supragingival calculus deposition was least in the TRN + NaF group, followed by CHG + TRN + NaF + ZnCl2, and then CHG. Most of the adverse events occurred in the TRN + NaF group: oral itching and aphthous ulcers; CHG group: oral soreness; CHG/TRN/NaF/ZnCl2: dryness of the mouth.

Hambire et al, 2015[88]	To compare the anti-plaque efficacy of 0.5% Camellia sinensis extract, 0.05% NaF, and 0.2% CHG mouthwash in children.	RCT/healthy children (N = 60; of age range = 9-14 years).	Mouthwashes: • 0.2% CHG • 0.05% NaF • 0.5% Camellia sinensis extract	The anti-plaque effectiveness of 0.5% Camellia sinensis extract was greater than that of 0.05% NaF or 0.2% CHG mouthrinses. Camellia sinensis should be explored as a cost-effective and safe long-term adjunct to oral self-care of patients as it has prophylactic benefits with minimum side effects.
Kulkarni et al., 2017[89]	To compare the anti-plaque efficacy of alcohol-based mouthwash with EOs and non-alcohol-based CHG mouthrinse in 4 days plaque re-formation study.	RCT/healthy dental students (N = 90; age range = 20-24 years).	• alcohol-based mouthwash with EOs • non-alcohol-based CHG mouthwash • saline mouthwash	The alcohol-based mouthwash with EOs and 0.2% CHG alcohol-free mouthrinse compared to normal saline showed significant reductions in gingival index and plaque index scores. The anti-plaque efficacy of both alcohol-based mouthwash with EOs and non-alcohol-based CHG mouthwash were equally effective in 4 days of plaque re-formation.

CHG, chlorhexidine gluconate (chlorhexidine); CPC, cetylpyridinium chloride; TRN, triclosan; RCT, randomized controlled trial; N, number of study patients/subjects; EO, essential oils; M-V, mechanically-ventilated; ICU, intensive care unit; NaHCO3, sodium bicarbonate; PVI, povidone iodine; H2O2, hydrogen peroxide; VAP, ventilator-associated pneumonia; CO, coconut oil; ZnCl2, zinc chloride; NaF, sodium fluoride.

Declarations of Interest

The authors are employed as a part-time consultant (PSL (RPh)) and a full-time Senior Clinical Scientist (MCL) by Avanos Medical, Inc., a manufacturer of oral care kits. Mark Lavigne has several patent applications sponsored by Avanos Medical, Inc. on file. These patent applications do not involve oral care agents or oral care devices of any kind.

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