DOES ORAL CHLORHEXIDINE MOUTH CARE PRIOR TO INTUBATION IMPACT VENTILATOR-ASSOCIATED PNEUMONIA? A SYSTEMATIC REVIEW

by

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Abstract

Background: Chlorhexidine gluconate (CHG) is a broad-spectrum antiseptic agent that has become widely used for mouth care in intubated patients. Many studies have found it to be effective in the prevention of ventilator-associated pneumonia (VAP) when used after intubation; however, there is very limited research exploring the proper time to initiate CHG. *Purpose:* The purpose of this systematic review was to determine if the use of oral care with CHG prior to intubation impacts the incidence of VAP. *Methods:* The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) was used to guide the selection process of articles and the Critical Appraisal Skills Programme (CASP) was used to critically appraise the randomized control trials (RCTs) selected for this systematic review. Four randomized RCTs met inclusion criteria. *Results:* Three of the four RCTs which met inclusion criteria, Houston et al. (2002), DeRiso et al. (1996), and Lin et al. (2015), showed an improvement in VAP rates with the use of preintubation CHG in cardiac surgery patients. Only one RCT, the Munro et al. (2015) study, showed no benefit; this was the only study that included non-cardiac surgery patients. *Conclusion:* Based on the results of this systematic review, it can only be recommended that cardiac surgery patients receive CHG prior to or after intubation; however, more research needs to be done to determine the most effective dosing, frequency, and CHG application procedure. In addition, further study exploring the safety of administering CHG prior to intubation in noncardiac surgery patients is needed.

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Does Oral Chlorhexidine Mouth Care Prior to Intubation Impact Ventilator-Associated Pneumonia?

A Systematic Review

Background/Statement of the Problem

Hospital-acquired infections (HAIs) have a significant impact on mortality and health care costs. The five HAIs identified by the Centers for Disease Control and Prevention (CDC) include central line-associated bloodstream infections (CLABSI), catheter-associated urinary tract infection (CAUTI), surgical site infection (SSI), clostridium difficile-associated diarrhea (CDAD), and ventilator-associated pneumonia (VAP) (CDC, 2010). According to the National Nosocomial Infection Surveillance System VAP is the second most common nosocomial infection after urinary tract infections. Ventilator-associated pneumonia occurs in 9–27% of all intubated patients (American Thoracic Society; Infectious Diseases Society of America, 2005) leading to prolonged intubation and hospitalizations. A diagnosis of VAP can have a huge impact on mortality with an estimated cost upwards of $40,000 per patient and a mortality rate estimated between 27-76% (Klompas, Speck, Howell, et al., 2014).

The Centers for Medicare and Medicaid Services listed VAP as one of the most reasonably preventable diseases. Sedwick et al. (2012) explain that since the centers view VAP as preventable, insurance companies may not reimburse hospitals for the diagnosis of VAP leading to a huge economic burden. With such a large mortality and financial burden, many hospitals utilize “VAP Bundles” which provide strategies to prevent the occurrence of VAP. Components of the VAP bundle may include: elevation of the head of the bed to 30º to 45º; prophylaxis for peptic ulcer disease; prophylaxis for deep-vein

thrombosis; daily interruption of sedation (sedation holiday); daily assessment of readiness for extubation; and daily oral care with chlorhexidine.

Chlorhexidine gluconate (CHG) is a broad-spectrum antiseptic agent that has become widely used for mouth care in intubated patients. Many studies have found it to be effective in the prevention of VAP when used after intubation. There is very limited research exploring the proper time to initiate chlorhexidine. The purpose of this paper was to determine if the use of oral care with chlorhexidine prior to intubation impacts the incidence of ventilator-associated pneumonia.

Literature Review

A literature search was performed using CINHAL, Google Scholar, Cochrane, and Medscape combining the key terms: ventilator-associated pneumonia; chlorhexidine; and oral care. The additional term prior to intubation was also included later in the literature search. Literature was searched from 2005 to 2020. Searches were limited to the English language and articles that included adults 18 years and older.

The Body's Natural Defense Mechanisms for Prevention of Respiratory Infection

A healthy person has multiple host defense mechanisms that hinder the development of pneumonia. The major defense mechanisms include airway barriers such as the epiglottis, cough reflexes, mucus, and mucociliary clearance (Safder et al., 2005). Mucosal ciliary move bacteria up and out of the bronchioles and a cough reflex assists this process. Additionally, the cellular and humoral immune systems help to eradicate potential pathogens on a cellular and extracellular level, respectively. In the mechanically ventilated patients, however, multiple factors compromise the body's natural defenses such as critical illness, comorbidities, and malnutrition thereby impairing the immune system. Furthermore, endotracheal intubation blocks the cough reflex and mucociliary clearance, injures the tracheal epithelial surface, and provides a direct passage of bacteria into the lower respiratory tract (Safder et al., 2005).

Pathophysiology of VAP

Normally, the lower respiratory tract is sterile whereas pneumonia is an infection in the lungs that causes the air sacs, or alveoli, to fill up with fluid or pus. The major routes of VAP are from oropharyngeal colonization, from the stomach related to secondary colonization, or from endotracheal-tube (ETT) biofilms (Safder et al., 2005). A

biofilm is a collection of microbes that form an extracellular matrix or "slime" that traps bacteria or fungus and can lead to an infection (Bonez et al., 2013). The mechanical process of intubation alone facilitates microbial entry into the lungs by disrupting the body's natural defense between the oropharynx and trachea allowing micro-aspiration. Critically ill patients may have a depressed level of consciousness further compounding the decreased gag reflex and pooling of secretions. Intubated patients are also at increased risk for the buildup of dental plaque and biofilms, which can harbor respiratory pathogens. This plaque accumulation may create an environment that allows for the adherence of organisms such as pseudomonas aeruginosa (Berry et al., 2011). The positive pressure from the ventilator then propels oral contaminants forward into the lungs.

Diagnosis of VAP

One of the significant challenges in diagnosing VAP is that there is no recognized diagnostic gold standard, leading to both under and over diagnosis. Many conditions in an intubated patient such as congestive heart failure or sepsis can mimic signs and symptoms of VAP as well as how they appear on imaging. As a result, this may interfere with correct and timely diagnosis (Kollef, 2018).

Ventilator-associated pneumonia is currently a clinical diagnosis made with a new or progressive lung infiltrate on imaging that coincides with clinical signs and symptoms of infection (i.e. leukocytosis, purulent secretions, and fever) as well as a positive pathogen from a respiratory sample (Kollef, 2018). Pneumonia is considered a VAP when it occurs more than 48-72 hours post endotracheal intubation. With the presence of

radiologic infiltrates and two clinical criteria, the sensitivity of diagnosing VAP is 69% and the specificity is 75% (Amanullah, 2015).

Healthcare providers rely upon radiographic, clinical, and laboratory indicators to diagnose VAP and initiate empiric antibiotics. Some of these have been combined into clinical diagnostic models, the most popular of which is the Clinical Pulmonary Infection Score (CPIS). This tool was developed to facilitate the diagnosis of VAP based on points assigned for each of the following signs and symptoms of pneumonia: tracheal secretions, temperature, white blood cell (WBC) count, oxygenation, chest radiograph, and tracheal aspirate culture. A score of > 6 indicates a VAP is more likely.

A systematic review and meta-analysis by Fernando et al., 2020 sought to characterize and compare the accuracy of physical examination, chest radiography, endotracheal aspirate (ETA), bronchoscopic sampling cultures, and CPIS > 6 to diagnose VAP. Researchers included 25 studies totaling 1639 patients. Inclusion criteria included: English-language articles through 2019, retrospective and prospective observational studies, RCTs, adult intensive care unit (ICU) patients ≥ 16 years, and invasive mechanical ventilation ≥ 48 hours. Additionally, the studies must have evaluated one or more of the following characteristics: fever (defined as body temperature ≥ 38 degrees Celsius), purulent secretions, leukocytosis (any threshold), chest radiography, gram stain and/or culture from the lungs, or CPIS for diagnosis of VAP. Histopathological analysis from lung biopsy and bronchoalveolar lavage (BAL) were the primary and secondary reference standards, respectively. The two researchers independently extracted data and assessed study quality.

Fernando et al. (2020) found that none of the clinical diagnostic methods used to diagnose VAP were very accurate. The pooled sensitivity and specificity of physical examination findings for VAP were poor: fever (66.4% [95% CI: 40.7–85.0], 53.9% [95% CI 34.5–72.2]) and purulent secretions (77.0% [95% CI 64.7–85.9], 39.0% [95% CI 25.8–54.0]). An infiltrate on chest radiography had a sensitivity of 88.9% (95% CI 73.9–95.8) and specificity of 26.1% (95% CI 15.1–41.4). ETA had a sensitivity of 75.7% (95% CI 51.5–90.1) and specificity of 67.9% (95% CI 40.5–86.8). Protected specimen brush bronchoscopy (PSB) had a sensitivity of 61.4% [95% CI 43.7–76.5] and specificity of 76.5% [95% CI 64.2–85.6]; while BAL had a sensitivity of 71.1% [95% CI 49.9–85.9] and specificity of 79.6% [95% CI 66.2–85.9]. CPIS > 6 had a sensitivity of 73.8% (95% CI 50.6–88.5) and specificity of 66.4% (95% CI 43.9–83.3). The findings were consistent when using either reference standard.

The presence of infiltrate on chest radiography had the highest sensitivity of 88.9% but had poor specificity. The CPIS was deemed inaccurate by researchers regardless of the reference standard used. This meta-analysis suggests that the methods clinicians routinely use to diagnose VAP and initiate antibiotics in the ICU are neither sensitive nor specific.

The study has some limitations; it does not include the sensitivity and specificity of histopathology from lung biopsy and this was the reference standard utilized suggesting it is most accurate. They did state it was impractical for routine diagnosis, and that results may be influenced by the area of the lung that is biopsied. The study used published data so not all details of subjects included may have been known as well as if

patients were on antibiotics prior to bronchoscopic sampling, both of which may confound the results.

Consequences of VAP

Ventilator-associated pneumonia is correlated with increases in mortality, length of stay, and exponential increases in health care costs. A patient with VAP remains in the ICU 4 to 19 days longer than patients who were intubated and did not acquire a VAP. This longer stay is associated with higher costs. The cost of care for a patient with VAP is approximately $40,000 to $57,000 higher than the cost for a patient on mechanical ventilation without VAP (Sedwick et al., 2012). The mortality rate for VAP ranges from 27-76% (Amanullah, 2015).

VAP Bundles

The 100,000 Lives Campaign was a nationwide initiative launched by the Institute for Healthcare Improvement (IHI) in 2006 with a goal to reduce morbidity and mortality in health care in the United States. The campaign focused on six key areas for improvement including: initiating rapid response teams; acute myocardial infarction interventions; preventing adverse drug reactions; preventing central line infections; preventing surgical site infections; and preventing VAP (IHI, n.d.).

The IHI recommends VAP bundles, which are evidenced-based interventions, to improve patient outcomes. The VAP bundle originally included: elevation of the head of bed between 30 and 45 degrees, daily sedation interruptions, daily assessment of readiness to extubate, stress ulcer prophylaxis, and deep vein thrombosis prophylaxis. In the spring of 2010, after new clinical trials were examined, oral care with chlorhexidine 0.12% was added to the bundle.

Recent evidence has challenged the VAP bundle and added further up to date recommendations on interventions. “Strategies to Prevent Ventilator-Associated Pneumonia in Acute Care Hospitals: 2014 Update” was published to update the 2008 guidelines to include the new recommendations of the use of subglottic secretion drainage ports for patients likely to require intubation >48 hours and only changing the ventilator circuit as needed rather than on a fixed schedule. The subglottic suction drains potential pathogens that pool above the ETT. The humidified gas in the ventilator circuit is at increased risk for contamination with frequent manipulation and would have direct entry through the ETT into the lungs. The new guidelines also do not recommend the use of stress ulcer prophylaxis as it did not have an impact on VAP rates (Klompas, Branson, Eichenwald, et al., 2014). The Intensive Care Society (ICS) and the National Institute for Health and Care Excellence (NICE) recently withdrew its recommendation for the use of oral chlorhexidine in non-cardiac surgery patients in 2016 after a new meta-analysis suggested its association with an increase in mortality (Hellyer et al., 2016). The exact mechanism resulting in higher mortality rates remains unclear, but it may be that some patients aspirate chlorhexidine and develop acute respiratory distress syndrome (ARDS) (Price et al., 2014).

Although many medical experts believe that the campaign has been a success, the IHI has not been able to accurately calculate and quantify the data (IHI, n.d.). A systematic review by Lawrence and Fulbrook (2011) examined the impact of VAP bundles on the incidence of VAP. Inclusion criteria included English language experimental studies between 2004-2009, clinical outcomes measured, and studies that included head of the bed minimum of 30 degrees, daily sedation holiday, gastric ulcer

prevention, and DVT prophylaxis. Ten studies were included in the review. Three of the studies had chlorhexidine mouth care as a bundle component. The studies included were observational with no control group because the researchers deemed it unethical to not implement the IHI's recommendation for the bundle. Therefore, the researchers could not definitively conclude a causal relationship between the bundle implementation and incidence of VAP; however, there was a positive association.

Chlorhexidine and Oral Care

Oral CHG is a prescribed antiseptic that reduces microbial colonization in the oral cavity. It covers a broad spectrum of microorganisms including gram-positive bacteria, gram-negative bacteria, and yeast. A 0.12% concentration is currently the only oral formulation approved by the Food and Drug Administration (FDA) for use in the United States (Grap et al., 2017). This germicidal rinse is typically used to treat gum disease such as gingivitis and periodontitis in adults. It has been adopted into oral care protocols up to twice daily for mechanically ventilated patients to decrease the pathogen load in oral plaque and the risk of VAP.

The technique of applying CHG during oral care is done by rinsing the mouth with a CHG solution using a sponge or toothbrush followed by oral suction; generally, a suction catheter kit that has a toothbrush or sponge is used. Some manufacturers sell commercially packaged "24-hour systems" which include all-inclusive kits with individually packaged products to use every two to four hours for mouth care. The kits may include mouth moisturizer for every two to four hours and chlorhexidine solution for twice daily oral care (Q•CareOral Cleansing & Suctioning Systems, 2018). Many

hospitals are utilizing these kits; however, there are no universal protocols for continuity between hospitals on exact mouth care procedures and products used.

A prospective, randomized, double-blind, placebo-controlled clinical trial by Ćabov et al. (2010) included a total of 60 intubated patients in a surgical ICU in Croatia assessed whether oral CHG mouth care impacted dental plaque, colonization of the oral cavity, and nosocomial infections. The control group received standard oral care, which consisted of rinsing the mouth with bicarbonate isotonic solution and gentle oropharyngeal sterile suctioning followed by the application of a placebo gel. The experimental group received the same standard care with the addition of a 0.2% chlorhexidine gel rubbed on the teeth by a gloved finger of a nurse three times daily. Dental status, plaque samples, nasal and tracheal aspirates, and urine samples were obtained 24 hours after admission and then every three days until discharge. Dental status was assessed using the caries-absent-occluded (CAO) dental index which is calculated as the sum of decayed, missing, and filled teeth and ranges from 0 (normal dental status) to 28 (all teeth absent or decayed). The study found that 63% of patients had preexisting colonized dental plaque and oral mucosa with multiple aerobic organisms on admission. Moreover, they found a positive correlation between colonized dental plaque and the development of numerous nosocomial infections such as bacteremia, UTI, or VAP. The rate of these nosocomial infections was four times lower in the group receiving the chlorhexidine oral care. The most frequently acquired nosocomial infection was pneumonia, with a statistically higher rate of occurrence in the placebo group. More specifically, the number of cases of pneumonia was significantly higher in the placebo group (6/30) than the chlorhexidine group (1/30) (p=0.039) (Ćabov et al., 2010). The

number of patients being admitted colonized with pathogens that cause VAP paired with the positive correlation of chlorhexidine reducing infection rates, supports the theory that chlorhexidine oral care prior to intubation may impact and potentially reduce VAP rates.

The study had some notable limitations. The sample size was small, having only 60 patients, which decreases the power of the study's results. The study also did not compare the differences in infection rates between the patients that came in with colonization versus those that did not. Patients were first randomized into a group by computer generation then swabbed for colonization on admission after being assigned a group. However, the researchers stated there was no statistical differences in bacterial colonization of dental plaque ($P = 0.21$) or buccal mucosa ($P = 0.42$) between the groups on day 0.

CHG and the Prevention of VAP in Mechanically Ventilated Patients

Saliva acts as a lubricant to the oral cavity and provides antibacterial and buffering properties in healthy patients. Mechanically ventilated patients may lack saliva related to side effects from the multiple medications they are receiving and prolonged mouth opening related to the ETT (Hua et al., 2016). Regularly scheduled oral care is intended to mimic the function of the saliva by moistening the mouth as well as removing debris and plaque (Hua et al., 2016). Using an antiseptic such as CHG, may further reduce the bacterial burden or delay a subsequent increase in bacterial burden (Hua et al., 2016). Decreasing the bacterial burden from the oral cavity would reduce the opportunity of bacteria being aspirated into the respiratory tract and causing a VAP plaque (Hua et al., 2016).

A systematic review by Hua et al. (2016) analyzed 38 randomized controls trials comparing four main groups of interventions (CHG mouth rinse vs. placebo, toothbrushing vs. no toothbrushing, powered toothbrush vs. oral care with manual toothbrush, oral care with other solutions) in the oral hygiene care of critically ill patients receiving mechanical ventilation for at least 48 hours in intensive care units. The 18 RCTs that compared CHG versus placebo used concentrations 0.12%, 0.2%, 1%, and 2%. The study found the use of chlorhexidine reduced the risk of VAP compared to placebo from 24% to 18% (P = 0.004). There was no evidence that use of CHG was associated with a difference in mortality, duration of mechanical ventilation or duration of ICU stay.

There were some limitations in this systematic review including the potential bias in the variation and subjective nature of criteria used for VAP diagnosis per each study. This makes it difficult to compare VAP results when different diagnostic tools were used to define VAP. Also, the specific details of what was involved in the oral hygiene care intervention were poorly described in some of the studies.

Klompas, Speck, Howell, et al. (2014) conducted a systematic review and meta-analysis of 16 RCTs examining the use of CHG versus placebo on the incidence of VAP. Researchers sought to reappraise the evidence after noting bias in previous systematic reviews. Previous reviews included studies with a majority of cardiac surgery patients that were primarily extubated within 24 hours and that little distinction was made between open-label versus double-blind investigations leading to bias in favor of CHG use. Due to the lack of gold standard for the diagnosis of VAP the researchers chose to compare duration of mechanical ventilation, length of stay, and mortality as more objective patient-centered outcomes. Inclusion criterion was RCTs evaluating daily oral

care with CHG (any preparation) versus a placebo in adult patients receiving mechanical ventilation. Data bases were searched without date restrictions and previously published meta-analyses and the reference lists of all suggestive articles were reviewed for inclusion. Cardiac surgery studies accounted for 51% of patients and non–cardiac surgery investigations included 49% of patients in this review.

The results indicated there were fewer lower respiratory tract infections in cardiac surgery patients receiving chlorhexidine (relative risk (RR), 0.56; 95% confidence interval (CI), 0.41-0.77) but no significant difference in VAP in noncardiac surgery patients (RR, 0.88; 95% CI, 0.66-1.16). There was no significant difference in mean duration of mechanical ventilation or intensive care length of stay in either groups. There was a nonsignificant result of increased mortality with chlorhexidine use among non–cardiac surgery studies. Limitations included the pulmonary outcomes in the cardiac surgery studies were specified as "nosocomial pneumonia," "upper respiratory tract infections," "lower respiratory tract infections," or "total respiratory tract infections" (Klompas, Speck, Howell, et al. 2014), but in all non–cardiac surgery studies the outcomes were defined as VAP. No further definitions were given as to what criteria were used to diagnose these.

Deschepper et. al. (2018) conducted a retrospective, observational cohort study including 82,274 patients hospitalized in various settings in Belgium with the objective of assessing the effect of CHG oral care on mortality. Oral care with 15 mL 0.05% or 0.12% CHG was given twice daily on general wards and three times daily to ICU patients. A proxy measure for CHG exposure was defined as low ≤ 300 mg or high > 300 mg, respectively. Independent patients were given instructions to swish and spit and

dependent patients had oral swabbing provided by nurses. This two-year study included patients 16 years or more with adjustment for risk of mortality and severity of illness based on the All Patient Refined-Diagnosis Related Groups (APR-DRG). Patients without APR-DRG risk of mortality were excluded as well as childbirth related admissions.

A total of 14% of patients hospitalized and discharged between 1 January 2012 and 31 December 2014 that met inclusion criteria received CHG oral care during their hospitalization, either in a solution of 0.05% (n = 1175) or 0.12% (n = 9963). The study found no association between CHG oral care and increased mortality in postoperative cardiothoracic and vascular surgery patients or patients receiving mechanical ventilation. In cardiothoracic and vascular surgery patients the relationship between CHG oral care and mortality did not reach statistical significance (CHG exposure ≤ 300 mg odds ratio (OR) 0.96; 95% CI 0.60–1.55; P = 0.874, CHG exposure > 300 mg OR 1.43; 95% CI 0.88–2.32; P = 0.146). CHG oral care was associated with increased risk of death in patients who were not admitted to the ICU and those that did not receive mechanical ventilation. Overall, the patient's with better prognosis on risk assessment for mortality was associated with a greater chance for adverse effects related to CHG oral care.

The study has several limitations including its observational design which is prone to bias. Also, it is unclear why there were two different doses (0.05% and 0.12%) of CHG, why one was indicated over the other, and why only 14% of patients included in the study received CHG oral care during their hospitalization. This is a small percentage of their sample size and is the purpose of the study. Perhaps more strict inclusion criteria were required to yield a higher percentage. The lack of a tangible pathogenic mechanism

leading to increased risk of mortality leaves the data difficult to interpret. The study proposes micro-aspiration of CHG leading to ARDS or anaphylactic reactions as potential links to increased mortality but states further research is indicated with these outcome criteria.

Varying evidence supports the use of chlorhexidine in select populations and it is being utilized in ICUs throughout the United States, but little research has been done to study when chlorhexidine should be initiated. Given that there is some evidence that CHG use decreases VAP rates and that intubation is a risk for infection, it could be hypothesized that the use of oral chlorhexidine prior to intubation would decrease VAP rates.

Chlorhexidine Prior to Intubation and VAP Prevention

As previously discussed, the process of intubation is a risk factor for VAP as the ETT passes through the microbe rich oropharynx and down into the lungs. In most other invasive clinical procedures where a tube is inserted, decontamination procedures are done at the insertion site to reduce the risk of colonization or infection. For example, prior to a urinary catheter insertion the meatus is scrubbed with an antiseptic. Endotracheal intubation usually proceeds without any preparation of the mouth other than the removal of dentures and potentially suctioning of oral secretions. The use of oral chlorhexidine prior to intubation could potentially eliminate the risk of introducing microbes from the oral cavity into the lungs during the intubation procedure (Munro et al., 2015).

Nicolosi et al. (2014) conducted a quasi-experimental study to test this hypothesis. The study took place in a large hospital in Argentina and included patients

undergoing cardiothoracic surgery. The control and experimental group each included 123 patients. The control group received the hospital's standard preoperative protocol of mupirocin antibiotic nasally for three days prior to surgery, administration of a third-generation cephalosporin 30 minutes before and after surgery, and continuation of the patient's normal oral routine prior to admission. The experimental group received the same treatment with the addition of 0.12% CHG every 12 hours for three days preoperatively with education on proper tooth brushing techniques by a dentist. The measurable outcome was the development of VAP. The group that received oral decontamination preoperatively with chlorhexidine had a VAP rate of 2.7% while the control group had a rate of 8.7% demonstrating the risk of developing VAP after surgery was more than 3 times greater in patients who did not receive oral decontamination with chlorhexidine. Study limitations include its small sample size and its quasi-experimental design.

A similar prospective intervention study by Bergan et al. (2013) tested the same hypothesis including 226 patients undergoing cardiothoracic surgery at a federal public hospital in Brazil. Patients received education from a dentist on proper tooth brushing techniques and were instructed to rinse their mouth and gargle with CHG 0.12 % twice a day for 2 minutes and just prior to the operating room. Postoperatively, the nurses performed the toothbrushing and CHG oral care. The measurable outcome was diagnosis of VAP. All patients received two grams of cefazolin 30 minutes before cardiac surgery as standard preoperative prophylaxis. Prior to the implementation of the CHG, the VAP rate was 32 per 1,000 (3.2) ventilator-days; the rate declined to 10 per 1,000 (1) ventilator-days within one year of the start of the new protocol. The hospital had a 69%

reduction in the incidence of VAP by 12 months. This is significant since the study also found the presence of pneumonia increased the chances of death by 11 times, $P < 0.0001$. Mortality in patients with pneumonia was 6/19 (33.3 %) versus 9/208 (4.32 %) in those without pneumonia. Limitations include small sample size and being a single center study in the setting of a developing country. The study does speculate that cardiac surgery patients at their institution have lower postoperative pneumonia rates related to their regular referrals for dental care preoperatively to prevent endocarditis.

There are limited randomized control trials investigating the use of oral chlorhexidine prior to intubation and the impact on the incidence of VAP. Four published studies meet inclusion criteria of this systematic review.

Theoretical Framework

Louis Pasteur proposed the germ theory in 1858 theorizing that specific organisms are capable of causing infectious diseases. This simple cause and effect theory has been critical to the development of modern medical care and its impact has helped to drastically decrease the number of deaths from infection (Mcewen & Wills, 2011). Pasteur's theory is predominantly utilized in disease prevention and epidemiological studies. The theory seeks to identify, understand, and manage infectious diseases leading to the development of ways to prevent and treat disease.

This systematic review utilizes the principles of Pasteur's germ theory. During the literature review, the problem of VAP was identified and explored. Causative mechanisms were further investigated with intubation and biofilms identified as leading factors. Methods to prevent VAP were explored specifically focusing on chlorhexidine mouth care prior to intubation.

Methods

A systematic review was conducted to determine if the use of oral care with chlorhexidine prior to intubation impacts the incidence of ventilator-associated pneumonia. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) was used to guide the selection process of articles and the Critical Appraisal Skills Programme (CASP) was used to critically appraise the randomized control trials selected for this systematic review. The ethical considerations for this systematic review are that PRISMA, as well as the inclusion and exclusion criteria, were strictly followed.

Using the PRISMA checklist (Appendix A) and the flow diagram (Appendix B), a comprehensive literature search for RCTs was performed using the databases CINHAL, Google Scholar, and Medscape and combining the key terms: ventilator-associated pneumonia; chlorhexidine; oral care; and prior to intubation. The inclusion criteria included randomized control trials, age greater than 18 years, and receiving oral chlorhexidine prior to being intubated. The study had to compare the use of chlorhexidine mouth care prior to intubation versus not using chlorhexidine prior to intubation and the incidence of VAP had to be the measurable outcome. Only articles published in English were reviewed. Exclusion criteria were randomized control trials that did not use chlorhexidine prior to intubation, participants less than 18 years old, non-English language articles, studies that were not randomized control trials, and studies that did not have VAP as the measurable outcome. Literature was searched initially from 2006 to 2020 and then with no date restriction using the above-mentioned inclusion and exclusion criteria related to the limited number of RCTs available on this topic.

PRISMA consists of a 27-item checklist (Appendix A) and a four-phase flow diagram (Appendix B) that dictates the steps of the evaluation of each study and in turn allows for presentation of the information in a precise and consistent manner. The checklist includes the major sections of a systematic review and what is to be included in each section. These sections include the major categories of title, abstract, introduction, methods, results, and funding (Moher et al., 2009). There are also several subcategories within each section. The PRISMA checklist was utilized to ensure data extracted from each of the included randomized control trials was complete and consistent.

The four-phase flow diagram (Appendix B), including identification, screening, eligibility, and inclusion, was used to select the articles appraised for the systematic review (Moher et al., 2009). Identification involves identifying records through databases and other sources. Screening involves refining the search to only pertinent studies related to the specific research question at hand and eliminating any duplicates that occur. The eligibility phase uses inclusion and exclusion criteria to omit any studies that do not meet criteria and includes an explanation of why. Lastly, the inclusion phase is the final number of studies that will be used in the systematic review. Using this four-phase process, studies were identified, screened for duplicates, and assessed for eligibility, which resulted in a select number of studies to be used in this systematic review.

Once the randomized control trials were selected, each article was analyzed and pertinent data was presented in an organized table (Appendix C1-4) allowing for comparison of the studies' purposes, designs, sites and samples, methods, results, and limitations. Each randomized control trial was then critically appraised using the CASP checklist for RCTs to determine the studies' scientific integrity (Appendix D1-4).

The CASP is part of the Oxford Centre for Triple Value Healthcare and strives to systematically assess the trustworthiness, relevance, and results of published papers. The CASP checklist for randomized control trials is an 11-question standardized checklist to methodically determine the quality, validity, and integrity of a study (CASP, 2018).

Lastly, a cross study analysis (Appendix E1-4) was performed to compare the placebo used in each study, the CHG dose selected, and the effect on incidence of VAP. The similarities and differences between the studies were compared.

Results

Search Results

The search terms yielded 236 results; 62 duplicates were eliminated leaving 174 remaining for review. The abstracts were then reviewed to determine if they met inclusion and exclusion criteria; 16 articles remained. The full texts of the remaining articles were read and assessed for the inclusion/exclusion criteria, leaving a total of 4 articles that were used in this systematic review. Pertinent data from each article was organized into data a table (Appendix C). Next, each study was summarized as follows and the studies were critically appraised using the CASP checklist (Appendix D).

Study Characteristics

A randomized control trial by Munro et al. (2015) (Appendix C1) evaluated the benefit of adding a preintubation CHG dose to the hospital's standard postintubation CHG to reduce the risk of VAP. Prior to intubation, study personnel swabbed the oral cavity with 5 mL of a 0.12% CHG. Postintubation, the same dose and concentration of CHG was administered by the responsible nurse on a twice daily schedule until extubation. A secondary aim was to test the effect of a preintubation oral application of CHG on early endotracheal tube (ETT) colonization. The RCT included 314 subjects from two large Southern urban teaching hospitals in the United States. Immediately prior to intubation, subjects were recruited from multiple clinical areas, including critical care units, emergency departments, preoperative areas, procedural areas, and medical surgical units during rapid response or code calls. The CHG group was 58% male with a mean age of 58.1 years and a mean Acute Physiology and Chronic Health Evaluation (APACHE) score of 69.1. The control group consisted of 62% males with a mean age of

58.2 years and a mean APACHE score of 65.1. Patients with a clinical diagnosis of pneumonia at the time of intubation were excluded.

Subjects were randomly assigned to the intervention group that received oral application of 5 mL 0.12% CHG by oral swab or the control group that received no preintubation intervention. All subjects received CHG twice a day after intubation as standard of care. The Clinical Pulmonary Infection Score (CPIS) was used to evaluate the risk of VAP with a VAP threshold score of > 6. Any score > 6 signified an increased risk for VAP. Researchers chose the CPIS to evaluate the risk of early-onset VAP because it permitted serial prospective evaluation of VAP risk without substantially increasing risks to human subjects. A swab was taken of the distal ETT after extubation to assess the secondary aim of ET colonization.

The results of this study (Appendix E1) demonstrated no statistically significant improvement in CPIS scores from the CHG group over the control group. The mean CPIS scores from both groups remained below the VAP threshold of 6 signifying a VAP was not likely. Regarding the study's secondary aim of ETT colonization occurrence, the majority of ETTs in both study groups were not colonized at the time of extubation (81.4% in the CHG group and 82.5% in the control group). There was no statistically significant difference in ETT colonization between the groups (P = 0.8656).

Critical analysis of the Munro et al. (2015) study using the CASP checklist (Appendix D-1) revealed both groups were statistically similar. Although the sample size was small, a priori power analysis was used to determine the sample size required to detect a difference in CPIS of 1 between the two groups. The clinical providers were blinded to study group assignment, as well as the clinical laboratory personnel who

performed microbial analyses and the coinvestigator who evaluated the chest x-rays. This study had several limitations. Nine subjects in the CHG group did not receive the intervention and the study does not explain why. Furthermore, there were four subjects listed as "other" that did not remain in the intervention group and eight that did not remain in the control group without rationale as to why. The study reported most subjects were extubated prior to the full 5-day intervention period leading to unavoidable attrition over the course of the study. There was no mention of a standard mouth care swabbing technique or training to ensure continuity and it was being performed by hospital nurses not study personnel. The possibility of data entry error exists due to the possibility that CHG administration was recorded but not actually performed. The CPIS score used as a diagnostic tool for VAP in the study only had a sensitivity of 73.8% and specificity of 66.4% (Fernando et al., 2020). Lastly, it is not made clear how randomization was achieved or what additional inclusion criteria was used besides prior to intubation without an existing diagnosis of pneumonia.

Houston et al. (2002) tested the effectiveness of 0.12% CHG oral rinse compared to the standard control of phenolic mixture (Listerine) in decreasing microbial colonization of the respiratory tract and hospital-acquired pneumonia in patients undergoing open heart surgery. A total of 561 patients undergoing aortocoronary bypass or valve surgery requiring cardiopulmonary bypass were randomized to an experimental (n = 270) or a control (n = 291) group. The CHG group was 73% male, and the Listerine group was 79% male. Patients were excluded from the study if they died during surgery, were pregnant, or had a documented or patient reported preoperative respiratory infection. Patients were randomized by medical record numbers. Preoperatively, both

groups received 15 mL of their respective oral rinse to swish and spit and postoperatively received the same by mouth swab twice daily until extubation, tracheostomy, death, or diagnosis of pneumonia. Both groups received preoperative and perioperative prophylactic antibiotics as part of the routine cardiac surgery protocol. Sputum samples were collected every 48 hours until extubation. VAP was diagnosed using criteria established by the Centers for Disease Control and Prevention.

Results of this study (Appendix E-2) revealed that VAP rates did not differ significantly (4/270 vs. 9/291; P=0.21) in the CHG group compared to the Listerine group. The study also found that only patients intubated for more than 24 hours developed pneumonia (0/486 vs. 13/75; P = 0.01). The pneumonia rate was reduced by 58% (4/19 vs. 9/18; P = 0.06) overall in patients treated with CHG who were intubated for more than 24 hours and had sputum cultures that showed positive microbial growth. In patients at highest risk for pneumonia (intubated > 24 hours, with sputum cultures showing the most growth), the rate was 71% lower in the CHG group than in the Listerine group (2/10 vs. 7/10; P =.02).

Critical analysis of the Houston et al. (2015) study using the CASP checklist (Appendix D-2) showed the two groups did not differ significantly in characteristics. None of the patients extubated within hours of surgery developed pneumonia. Most patients included in this study were extubated within hours of surgery, therefore, a limitation may be the relatively small sample size. However, the sample size of 600 was projected based on the hospital's historical rate of VAP and was deemed sufficient to detect a 0.20 effect size with 99% power. Perhaps the biggest limitation of the study is that the researchers did not disclose whether the participants or providers were blinded.

Age ranges of participants were not included. The study does not state how many doses of oral rinse patients received in total preoperatively. There also could be error in self-reporting of the preoperative doses that patients did independently at home. Some doses may have been skipped and not reported. The study refers to attrition resulting from death and tracheostomy. However, it is not disclosed how many patients were properly accounted for at the conclusion of the study.

DeRiso et al. (1996) examined whether twice daily preoperative use of 0.12% CHG oral rinse reduced hospital-acquired infection rates in patients undergoing open heart surgery in a prospective, randomized, double-blind, and placebo-controlled study. Of the 353 patients who were included, 173 patients were randomized to the CHG group and 180 to the placebo group. The CHG group was 69% male with the mean age of 64.1 years and the control group was 68% male with the mean age of 63.5 years. The chemical make-up of the base solution of both the intervention and placebo oral rinses was similar; the placebo had no antimicrobial properties. Each group received their respective oral rinse twice daily preoperatively with an unspecified number of doses and postoperatively twice daily until discharge from the ICU or death. Prophylactic antibiotics and intravenous ranitidine were given as standard postoperative care. Exclusion criteria were intraoperative death, preoperative infection or intubation, pregnancy, heart and lung transplant recipients, and known hypersensitivity to CHG. The patients who failed early extubation received tracheal aspirate culture at 48 hours and then every two days until discharge from the ICU or death. This study also used the CDC's diagnostic infection criteria for VAP. Outcomes measured were overall rates of nosocomial infections, upper and lower respiratory tract infections, urinary tract infections, fungemias, central line

infection rates, wound infections, blood infections, other infections, nonprophylactic IV antibiotic use, length of stay (LOS) in the hospital, duration of intubation, need for reintubation, and in-hospital mortality.

Study results pertinent to this review (Appendix E-3) demonstrated an overall decrease in all hospital-acquired infection rates in the CHG treated patients by 65% ($P < 0.01$). Total respiratory tract infections were 69% less common in the CHG treated group ($P<0.05$) and the use of nonprophylactic IV antibiotics was lowered by 43% ($P<0.05$). Although they found no statistical differences between the two groups regarding average duration of mechanical ventilation, reintubation rate, or length of stay in the hospital, there was a reduction in mortality in the CHG group versus control group (1.16% vs. 5.56% respectively).

Critical appraisal (Appendix D-3) of the DeRiso et al. (1996) study using CASP revealed it was unclear whether all patients that entered the study were accounted for at the end of the study. Researchers also did not state why they chose the sample size they selected; however, the sample that was selected did not statistically differ in characteristics. The trial did clearly address the focus issue and the randomized double-blind placebo-controlled design gives the study further validity.

Lin et al. (2015) investigated the effect of preoperative 0.2% CHG on postoperative VAP rates. Patients that met inclusion criteria were selected prior to cardiac surgery at a medical university hospital in China. Inclusion criteria were consciousness; age >18 years; ability to independently gargle in the oropharynx; and requiring orotracheal intubation and mechanical ventilation. The exclusion criteria were pneumonia before intubation; history of previous heart surgery and intubation; or severe brain, liver,

or kidney disease. Of the 94 patients that met the inclusion criteria, 47 were randomized to the CHG group and 47 to the control group. All patients were blinded to their grouping.

The day prior to surgery the CHG group gargled with 50 mL 0.2% CHG 30 minutes after all meals and 5 minutes after brushing teeth at bedtime. CHG was gargled for 30 seconds and was repeated three times at one-minute intervals while the control group gargled with normal saline adhering to the same schedule. Postoperatively, as part of standard care while on mechanical ventilation, both groups had oral rinses with 50 mL of 0.2% CHG, four times a day. After extubation, they were each required to gargle once with 50 mL of 0.2% CHG then once after each meal for three days. The oral care of all patients was performed by the same two trained healthcare professionals who were blinded to the patients grouping. The outcome of VAP was diagnosed using the simplified Clinical Pulmonary Infection Score (CPIS) and was assessed on days 1, 3, 5, and 7 after intubation with a threshold of ≥ 6. Patients with CPIS ≥ 6 and < 6 were classified as those with and without VAP, respectively.

Results of the study (Appendix E-4) revealed that preoperative CHG mouthwash reduced the incidence of postoperative VAP significantly; VAP occurred in 8.5% of the chlorhexidine group and 23.4% in the control group ($P = 0.049$). CPIS scores were not different between the two groups on postoperative day one; however, they were significantly lower in the CHG group on the third ($P = 0.024$) and fifth ($P = 0.005$) day when compared to the controls.

Critical analysis of the Lin et al. (2015) study using the CASP checklist (Appendix D-4) revealed the study clearly addressed the focus of this review and met all

criteria other than the small sample size of only 47 in each group. To achieve a power of 80% with a risk ratio of 0.36 over 90 patients would have been required in each group. The ideal power of 80% means the study would have a high chance of detecting a difference between the two groups. Since the study fell short of this goal without explanation, caution should be used when drawing conclusions as to whether there was a true difference between the two groups. The researchers had used a prior study to estimate the group sizing, which was 98 in each group, so they still fell short based on their initial needs assessment. This known small sample size is a limitation of the study. Additionally, the preoperative rinse was to be used the day before surgery after meals and before bed. This may lead to some patients receiving a different number of doses based on how many meals were eaten that day. The total mL of preoperative CHG and saline was not disclosed. Furthermore, self-reporting the correct use of four times a day preoperative CHG oral rinse may have led to error related to inaccurate reporting from patients. The study design is unclear with researchers stating 1:1 randomization by computer generator followed by statements that the treating physician assigned the groups the day before surgery. Lastly, the study does not make clear if the two trained and blinded nurses performing oral care, data collection, and diagnosis of VAP were from the researchers' team or the hospital's.

Cross Analysis

A cross study analysis table (Appendix E) was created to compare the RCTs used for this systematic review. The table includes which placebo was utilized, the CHG dose and frequency of administration and the effect on incidence of VAP.

A different placebo and CHG dose were used in each of the four RCTs. Munro et al. (2015) were the only researchers to investigate noncardiac surgery patients. They included patients from multiple clinical areas of the hospital including those prior to emergent intubations. The intervention group received 5 mL 0.12% CHG prior to intubation while the control group received no CHG prior to intubation. The intervention group received 5 mL 0.12% CHG by swab to the oral cavity administered by study personnel prior to intubation while the control group received none. After intubation both groups received 5 mL 0.12% CHG administered by the responsible nurse twice daily until extubation. Houston et al. (2002) used 15 mL of Listerine brand phenolic mouth rinse as the placebo. Each group received 15 mL of either the Listerine mixture or 0.12% CHG preoperatively (30 sec swish & spit) and twice daily postoperatively (30 sec swab) for 10 days postoperatively or until extubation, tracheostomy, death, or diagnosis of pneumonia. DeRiso et al. (1996) used a placebo with similar chemical makeup without CHG or antimicrobial properties that had identical packing. Either the placebo or the 0.12% CHG was given twice daily preoperatively, however, the study failed to disclose for how many days. Postoperatively 15 mL of either solution as an oropharyngeal rinse or rigorously applied to the buccal, pharyngeal, gingival, tongue, and tooth surfaces for 30 seconds twice daily until discharge from the ICU or death. Lastly, Lin et al., 2015 used 0.9% saline solution as a placebo in the control group but did not specify the amount. The

day prior to surgery, patients gargled three times with 50 mL 0.2% CHG or the saline placebo 30 minutes after all meals and 5 minutes after brushing teeth at bedtime. Either solution was gargled for 30 seconds and was repeated three times at one-minute intervals. Once intubated both groups had oral rinse with 50 mL of 0.2% CHG four times a day.

Three of the four RCTs, Houston et al. (2002), DeRiso et al. (1996), and Lin et al. (2015), showed an improvement in VAP rates with the use of preintubation CHG. Only one RCT, the Munro et al. (2015) study, showed no benefit. There was no statistically significant improvement in the CPISs from the CHG group over the control group and both groups CPS scores remained less than the VAP threshold of 6. In regard to the study's secondary aim of evaluating preintubations impact on ETT colonization, both groups were < 20% colonized with no significant difference (P = 0.8656).

There were some variances in the amount of total risk reduction among the other three studies that found a reduction in VAP with the use of preintubation CHG. Houston et al. (2002) found the overall rate of nosocomial pneumonia was reduced by 52% (4/270 vs 9/291; P =.21) in the CHG-treated patients. DeRiso et al. (1996) found VAP 69% less common in the CHG-treated group compared to the placebo group (5/173 vs 17/180; $p < 0.05$). Lin et al. (2015) found an absolute risk reduction of VAP with the CHG group of 14.9% (23.4%/8.5%).

Discussion

The previously discussed differences in the dosages and application techniques may have influenced these varying results as well as many other factors that will be discussed in the summary and conclusions section.

Ventilator-associated pneumonia is a major concern in hospitals that is correlated with increases in mortality, length of stay, and exponential increases in health care costs (Sedwick et al., 2012). In response to this, the IHI developed VAP bundles in 2006, which are evidenced-based interventions to improve patient outcomes. The inclusion of oral care with chlorhexidine 0.12% was made in the spring of 2010 after new clinical trials suggested an improvement in VAP rates. There have been multiple changes to the bundle over the years related to updated recommendations following new clinical trial. The ICS and NICE withdrew its recommendation for the use of oral chlorhexidine in non-cardiac surgery patients in 2016 after a new meta-analysis suggested its association with an increase in mortality (Hellyer et al., 2016). There is limited research exploring the proper time to initiate chlorhexidine. The purpose of this paper is to determine if the use of oral care with chlorhexidine prior to intubation impacts the incidence of ventilator-associated pneumonia.

A comprehensive literature search for RCTs was performed using the databases CINHAL, Google Scholar, and Medscape. The PRISMA 27-item checklist and four-phase diagram (Moher et al., 2009) were utilized in the search process to ensure a thorough selection of studies. This search strategy resulted in four RCTs meeting inclusion criteria for this systematic review. Pertinent data from these studies were then organized into a data collection table (Appendices C1-4) allowing for comparison of the studies' purposes, designs, sites and samples, methods, results, and limitations. The CASP checklist for RCTs

was used for critically appraisal to determine the scientific integrity of each of the four studies (Appendix D1-4). Lastly, a cross study analysis (Appendix E1-4) was performed to compare the placebo used in each study, the CHG dose selected, and the effects of the intervention variables on the incidence of VAP.

Three of the four RCTs, Houston et al. (2002), DeRiso et al. (1996), and Lin et al., (2015), showed an improvement in VAP rates with the use of preintubation CHG. Only one RCT, the Munro et al., 2015 study, showed no benefit. This was the only study that included non-cardiac surgery patients. Researchers did not perform any analysis on the varying types of patients and the incidence on VAP. It is recommended that a secondary analysis be done specific to cardiac surgery patients to see the impact of CHG application on the incidence of VAP in this population. The Society of Thoracic Surgeons (STS) promotes the practice of extubating patients within 6 hours after cardiac surgery as a quality of care benchmark (Goeddel, Hollander & Evans, 2018) while other patient populations requiring mechanical ventilation tend to remain intubated longer. The inclusion of other patient populations in the Monroe et al. (2015) study may have negatively impacted results.

One of the significant challenges in diagnosing VAP is that there is no recognized diagnostic gold standard or definition (Kollef, 2018) and the definition has evolved over time. VAP is currently a clinical diagnosis therefore subjective to some extent varying from provider to provider based on his or her interpretation. Fernando et al. (2020) found that none of the clinical diagnostic methods used to diagnose VAP were very accurate. Some of the radiographic, clinical, and laboratory indicators were combined into clinical diagnostic models, the most popular of which is the Clinical Pulmonary Infection Score (CPIS). This scale was also deemed unreliable by Fernando et al. (2020) with a sensitivity

of 73.8% (95% CI 50.6–88.5) and specificity of 66.4% (95% CI 43.9–83.3). There were differences in the four studies in the criteria used to diagnose VAP. The CPIS score was utilized in the Lin et al. (2015) and Munro et al. (2015) while the CDC criteria was used to diagnose VAP in the older RCTs DeRiso et al. (1996) and Houstan et. al (2002). Since none of the clinical diagnostic methods used to diagnose VAP were reliable perhaps more concrete primary outcomes such as mortality, duration of intubation, and antibiotic utilization should be used.

Limitations

There were several limitations in this systematic review. Only four studies met the inclusion and exclusion criteria which may affect generalizability. Also, all the RCTs were relatively small with each including between 94-561 participants. Practice differences related to ever changing standards of care plays a large factor in difficulties comparing the RCTs. Some of the trials date back prior to the initiation of the bundles; DeRiso et al. was published in 1996 and Houstan et. al in 2002, both well before the initiation of the IHI bundle in 2006. Therefore only Lin et al., (2015) and Munro et al., (2015) included all updates to the bundles to include elevation of the head of the bed to 30º to 45º; prophylaxis for peptic ulcer disease; prophylaxis for deep-vein thrombosis; daily interruption of sedation (sedation holiday); daily assessment of readiness for extubation; the use of subglottic secretion drainage ports for patients likely to require intubation > 48 hours and only changing the ventilator circuit as needed rather than on a fixed schedule as well as daily oral care with chlorhexidine. Therefore, the bundle itself is a cofounder in the newer studies since it may be responsible for some of the positive effects and CHG alone cannot be held solely accountable.

Another limitation with comparing studies is the differing concentrations of CHG used. A 0.12% concentration is currently the only oral formulation approved by the Food and Drug Administration (FDA) for use in the United States (Oral Care for Acutely and Critically Ill Patients, 2017). Lin et al. (2015) was the only study to use a strength other than 0.12%; researchers used 0.2% as the study was done in China where this concentration is available. All other studies were performed in the United States.

Lastly, there is no worldwide standardized mouth care protocol. Each study had a different method, duration, length of time and process for the administration of either the placebo or the CHG. This may have further influenced the ability to fairly compare the results.

Summary and Conclusions

The results of this systematic review demonstrate the use of CHG prior to intubation was effective in reducing the VAP rates in post-cardiac surgery patients in three of the four studies included in this review. These findings are not generalizable, however, related to the lack of large, randomized control trials including both cardiac and noncardiac patients. It remains unclear as to most effective dosing, frequency, and application procedure of CHG. The majority of patients in the studies were intubated for less than one week, however, some studies did not disclose an exact number of days. There is no evidence demonstrating a definitive time frame of CHG use related to length of intubation post cardiac surgery. Also, now that oral CHG is not being utilized in non-cardiac ICU patients, further studies of its use prior to intubation could be more accurate as they will not be receiving the CHG after intubation. More research is needed to determine effective dosing, frequency, and application procedures of CHG as well as exploring if it is safe to administer CHG prior to intubation in noncardiac surgery patients.

Although there were several limitations in the RCTs and some differences made them difficult to compare, the achievement of the primary aim in this systematic review results in recommendations and implications that can be made for the advanced practice nurse in the clinical setting.

Recommendations and Implications for Advanced Nursing Practice

The role of the advanced practice nurse (APN) has evolved to meet the challenge of access to health care across the United States. APNs have become an integral part of healthcare teams in both the inpatient and outpatient setting. APNs utilize evidence-based practice (EBP) methods to provide safe and efficient care to their patients. This systematic review presents evidence-based findings that may guide APNs in making informed decisions in future practice.

Based on this systematic review, it can only be recommended that cardiac surgery patients receive CHG prior to and after intubation; however, more research needs to be done to determine the effective dosing, frequency, and application procedures as well as exploring if it is safe to administer CHG prior to intubation in noncardiac surgery patients.

The results of this systematic review demonstrate the use of CHG prior to intubation was effective in reducing the VAP rates in three of the four studies included in this review; however, the three studies that did show an improvement only included cardiac surgery patients. Munro et al., (2015) was the only study to include non-cardiac surgery patients including emergent intubations and the results yielded no benefit with the use of CHG and VAP. The ICS and the NICE withdrew its recommendation for the use of oral CHG in non-cardiac surgery patients in 2016 after a new meta-analysis suggested its association with an increase in mortality (Hellyer et al., 2016). Now that oral CHG is not being utilized in non-cardiac ICU patients, further studies of its use prior to intubation could be more accurate as they will not be receiving the CHG after intubation. APNs are in a position to lead research projects and develop new EBP

standards and implementation in clinical practice. In addition, they can develop safe policies and educate staff on safe practices.

Further research is recommended. The next RCT trials to explore CHG prior to intubation should have larger sample sizes and the controls should be double blind. Utilizing different primary outcomes in these studies such as mortality, duration of intubation, and antibiotic usage may be more effective in quantifying VAP occurrences than the previously used ineffective CPIS scores. These outcomes may be more sensitive regarding the impact of VAP since there remains no gold standard for diagnosing it.

The lack of a standardized approach to mouth care in the ICU setting was also evident throughout this review. The APN has the ability to work closely with interdisciplinary teams, including dentistry, to create one evidence-based, standard approach to oral care in intubated patients. Creating such a procedure with a stepwise approach would create continuity across ICUs worldwide.

The current healthcare environment focus is on delivering superior patient care for less cost. Low expenditure preventative interventions such as oral care with CHG could help reduce VAP rates and decrease mortality, length of stay, and costs. Ventilator-associated pneumonia has a detrimental cost effect on the healthcare system and more research should be executed focused on prevention including trials of CHG application prior to intubation in noncardiac surgery patients. The APN can then use this knowledge to train bedside nurses who provide oral care to ensure it is performed appropriately. As research for VAP prevention advances, the diagnosis for this complex condition will be more universally understood and more interventions put into practice to improve patient outcomes.

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Appendix A

Check List for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al., 2009)

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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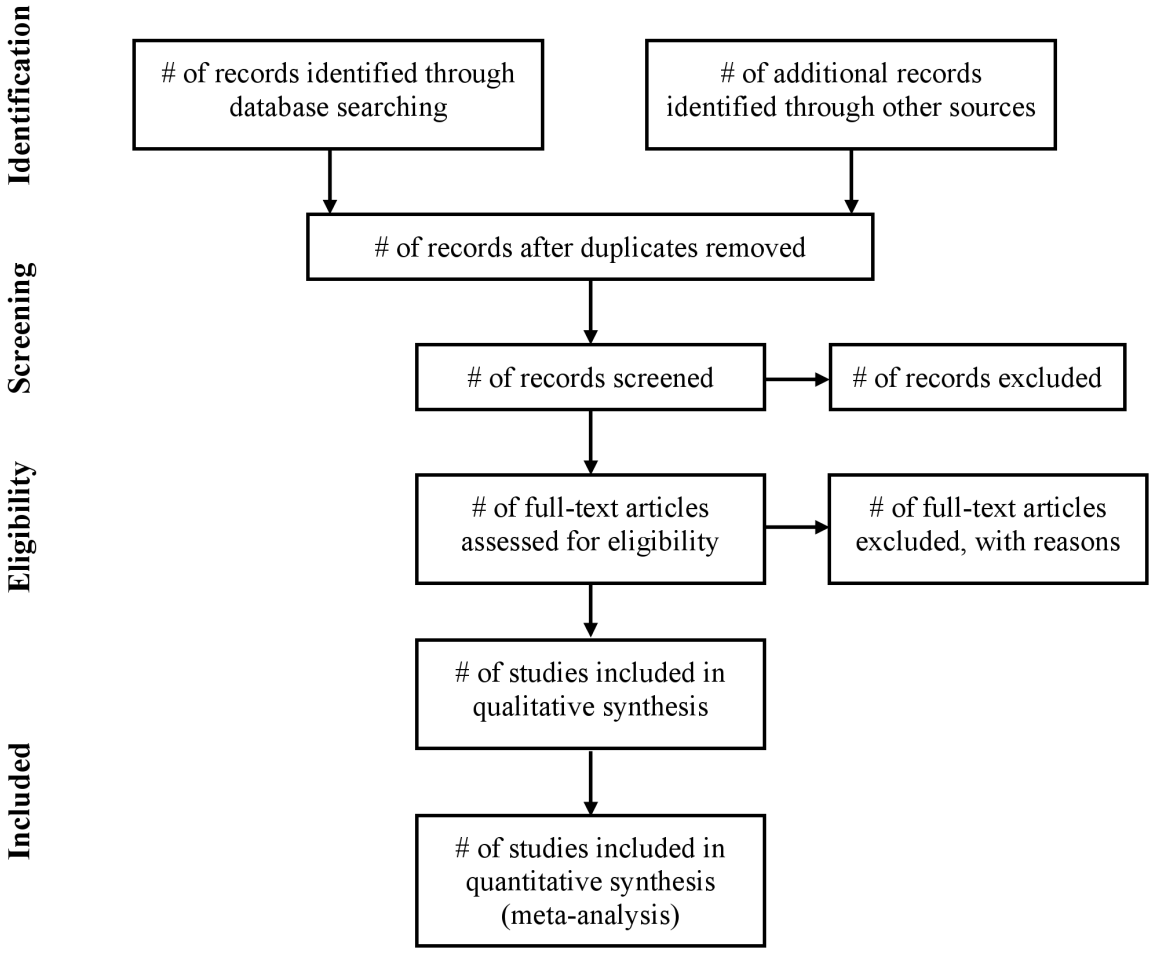
Appendix B

Flow diagram for preferred reporting items for systematic reviews and meta-analyses (Moher et al., 2009)



Appendix C-1

Descriptive Data Tables

Munro, C. L., Grap, M. J., Sessler, C. N., Elswick, R. K., Mangar, D., Karlnoski-Everall, R., & Cairns, P. (2015). Preintubation Application of Oral Chlorhexidine Does Not Provide Additional Benefit in Prevention of Early-Onset Ventilator-Associated Pneumonia. *Chest,* 147(2), 328–334. doi: 10.1378/chest.14-0692					
Purpose	Design	Site/Sample	Methods	Results	Limitations
Primary aim to test the effect of preintubation 0.12% CHG in reducing VAP risk. Secondary aim to test the effect of preintubation 0.12% CHG on early ET colonization.	Clinical randomized control trial	314 subjects from multiple clinical areas (just prior to intubation, including critical care units, EDs, preoperative areas, procedural areas, and medical surgical units during rapid response or code calls) were recruited by meeting inclusion criteria and being just prior to intubation at 2 large urban teaching hospitals in Virginia. Intervention group with CHG prior to intubation = 157, control group = 157. IRB approved a waiver of prospective consent but required written documentation of consent (including information about voluntary withdrawal) from the subjects' legally authorized representatives at the earliest opportunity following study enrollment. Mean age (SD): intervention group = 59.5 (11.5), control group = 56.4 (16.5) Gender: male/female in intervention group = 55/45, control group= 60/40 Mean APACHE score (SD): intervention group = 81.2 (25.2) control group = 73.3 (26.3) Exclusion criteria: Clinical diagnosis of pneumonia at time of intubation.	Subjects randomly assigned to intervention group who received oral application of 5 mL CHG 0.12% solution before intubation or to a control group who received no CHG before intubation. All subjects received CHG twice a day after intubation. Preop: oral application of 5 mL 0.12% CHG solution by swab to the oral cavity administered by study personnel Postop: 5 mL 0.12% CHG administered by the responsible nurse on a twice daily schedule until extubation. Subjects remained in the study for a max of 6 days. If extubated prior to 6 days, the participation ended on the day of extubation. Groups were compared using a repeated-measures model with Clinical Pulmonary Infection Score (CPIS) as the response measure. ETTs were cultured at extubation. Clinical providers, laboratory personnel, and radiologists were all blinded to study groups.	Application of a preintubation dose of CHG did not provide benefit. The P values from comparing each group's change from baseline with study days 2, 3, 4, and 5 were 0.4217, 0.9930, 0.1484, and 0.1763, respectively. ETT colonization at extubation was 20% in both groups; no statistically significant difference (P = 0.8656). Mean CPIS remained below 6 (VAP threshold score) in both groups.	Relatively small sample size but priori power analysis utilized to determine sample size required. May have been variations in the procedure of swabbing the oral cavities postintubation since this was done by staff at the hospital not the study personnel. Most subjects were extubated prior to the full 5-day intervention period. No standard noted for the procedure of swabbing to ensure continuity. Medical records were audited to ensure postintubation administration of CHG was given so there may be a chance it was scanned but not given. Does not state how randomization was achieved or what inclusion criteria was besides being prior to intubation without an existing diagnosis of pneumonia.

Appendix C-2

Houston, S., Hougland, P., Anderson, J. J., LaRocco, M., Kennedy, V., & Gentry, L. O. (2002). Effectiveness of 0.12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery. *American journal of critical care: an official publication, American Association of Critical-Care Nurses, 11(6),* 567–570.					
Purpose	Design	Site/Sample	Methods	Results	Limitations
To test the effectiveness of 0.12% CHG oral rinse in decreasing microbial colonization of the respiratory tract and nosocomial pneumonia in patients undergoing open heart surgery.	Prospective, randomized, case-controlled clinical trial	St. Luke's Episcopal Hospital in Houston, Tx; a tertiary care center. All eligible patients who underwent aortocoronary bypass graft and/or valve surgery requiring cardiopulmonary bypass were invited to participate. Exclusion criteria: death during surgery, pregnant, or had a preoperative respiratory infection that had been documented in the medical record or reported by the patient. 561 patients included in the final data analysis, 270 were randomized to the CHG (experimental) group and 291 to the Listerine (control) group. Gender: male in intervention group = 73%, control group = 79%	Randomized by medical record numbers. Intervention group was 0.12% CHG, Listerine brand phenolic mouth rinse was the standard agent for routine oral care (control group). Participants received 15 mL of either CHG or Listerine oral rinse preoperatively (30 sec swish & spit) and twice daily postoperatively (30 sec swab) for 10 days postoperatively or until extubation, tracheostomy, death, or diagnosis of pneumonia. Oral rinses dispensed by pharmacists and administered by nurses. Both groups received perioperative prophylactic antibiotics per cardiac surgery protocol. Sputum samples were collected at the time of extubation. For intubation > 24 hours of surgery, sputum samples were obtained routinely every 48 hours until extubation. Infections were diagnosed by using a tool based on the CDC criteria for nosocomial pneumonia	Rates of nosocomial pneumonia were lower in patients treated with CHG than in patients treated with Listerine, but the difference was significant only in those patients intubated >24 hours who had the highest degree of bacterial colonization. The overall rate of nosocomial pneumonia was reduced by 52% (4/270 vs. 9/291; P =.21) in the CHG-treated patients. Among patients intubated for > 24 hours who had cultures that showed microbial growth (all pneumonias occurred in this group); the pneumonia rate was reduced by 58% (4/19 vs. 9/18; P = .06) in patients treated with CHG. In patients at highest risk for pneumonia (intubated >24 hours, with cultures showing the most growth), the rate was 71% lower in the CHG group than in the Listerine group (2/10 vs. 7/10; P =.02).	Because of the low overall pneumonia rate, a large sample size would be required to detect a significant difference in infection rate between the CHG and the Listerine groups. There was no blinding in this study. Does not include age ranges of participants. Does not state how many doses of oral rinse patients received in total preoperatively. There could be error in self-reporting of the preoperative doses that patients did at home. Some doses may have been skipped and not reported.

Appendix C-3

DeRiso, A. J., 2nd, Ladowski, J. S., Dillon, T. A., Justice, J. W., & Peterson, A. C. (1996). Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. *Chest*, 109(6), 1556–1561. https://doi.org/10.1378/chest.109.6.1556

Purpose	Design	Site/Sample	Methods	Results	Limitations
Primary aim was to test the hypothesis that the preoperative use of twice-daily 0.12% CHG oral rinse can reduce nosocomial infection rates in patients undergoing open heart surgery. Additional outcome measures • Overall nosocomial infection rates • Upper and lower respiratory tract infection rates • Urinary tract infection rates • Fungemias • Line infection rates • Wound infection rates • Blood infection rates • Other infections • Nonprophylactic IV antibiotic use • Length of stay (LOS) in the hospital • Duration of intubation • Need for reintubation • In-hospital mortality	Prospective, randomized, double-blind, placebo-controlled clinical trial	Cardiovascular ICU at Lutheran Hospital of Indiana, a tertiary care hospital 353 consecutive patients undergoing coronary artery bypass grafting, valve, or other open-heart surgical procedures chosen & randomized. Exclusion criteria: intraoperative death, preoperative infection or intubation, pregnancy, heart and lung transplant recipients, and known hypersensitivity to CHG. Consecutive eligible patients over a 10-month period prior to cardiac surgery were invited to participate. Gender: male/female in intervention group = 119/54, control group = 123/57 Mean ages intervention group = 64.1, control group = 63.5.	Participants were randomized by computer-driven random number generator into either the CHG 0.12% or placebo solutions that were liquids of comparable color, taste, and smell were dispensed. Oral rinse given preoperatively and twice daily postoperatively until discharge from the ICU or death. Doses were 0.5 fl oz (15 mL) as an oropharyngeal rinse or rigorously applied to the buccal, pharyngeal, gingival, tongue, and tooth surfaces for 30 seconds twice daily. Both groups received perioperative prophylactic antibiotics per cardiac surgery protocol. Patients who failed early extubation (within 24 hours) received tracheal aspirate culture analysis at 48 hours and then every 2 days until discharged from the ICU or death. Infections were diagnosed by CDC criteria for nosocomial pneumonia.	The overall nosocomial infection rate was decreased in the CHG-treated patients compared to the placebo group by 65% (8/173 vs. 24/180; $p < 0.0l$) respectively. Respiratory tract infections were 69% less common in the CHG-treated group compared to the placebo group (5/ 173 vs. 17/180; $p < 0.05$). A reduction in mortality in the CHG-treated group was also noted (1.16% vs. 5.56%).	Does not specify how long preoperatively patients used CHG. There could be error in self-reporting of the preoperative doses that patients did at home. Some doses may have been skipped and not reported.

Appendix C-4

Lin, Y. J., Xu, L., Huang, X. Z., Jiang, F., Li, S. L., Lin, F., Ye, Q. Y., Chen, M. L., & Lin, J. L. (2015). Reduced occurrence of ventilator-associated pneumonia after cardiac surgery using preoperative 0.2% chlorhexidine oral rinse: results from a single-centre single-blinded randomized trial. The Journal of hospital infection, 91(4), 362–366. https://doi.org/10.1016/j.jhin.2015.08.018					
Purpose	Design	Site/Sample	Methods	Results	Limitations
To investigate the effect of preoperative 0.2% CHG on postoperative incidence of VAP.	Single-center single-blinded randomized trial	Patients who met inclusion and exclusion criteria from those scheduled for cardiac surgery between August 2013 and April 2014 at the Fujian Medical University Union Hospital, China. The inclusion criteria were conscious; age >18 years; able to gargle in the oropharynx by themselves; and required orotracheal intubation and mechanical ventilation. The exclusion criteria were pneumonia before intubation; history of previous heart surgery and intubation; or severe brain, liver, or kidney disease. Of the 94 patients who met the inclusion criteria, 47 were randomized to the CHG group and 47 to the control group.	1:1 Randomization was by a computer-generated random number table and sealed envelopes prepared by a statistician. The treating physician assigned the patient to a group the day before surgery. All patients were blinded to their grouping. In the CHG group, patients gargled with 50 mL 0.2% CHG 30 minutes after all meals and 5 minutes after brushing teeth at bedtime. CHG was gargled for 30 seconds and was repeated three times at one-minute intervals while the control group gargled with normal saline adhering to the same schedule. All oral care and data collection were done by same two trained and blinded nurses to avoid bias. The outcome of VAP was diagnosed using the simplified Clinical Pulmonary Infection Score (CPIS) and was assessed on days 1, 3, 5, and 7 after intubation. A CPIS score > 6 is suggestive of pneumonia.	VAP occurred in 4 patients (8.5%) in the CHG group and in 11 patients (23.4%) in the control group (P=0.049). VAP within 5 days was defined as early onset and VAP after five days was late onset. In the CHG group, there was 1 case of early onset VAP (25.0%) and 3 cases of late onset VAP (75.0), whereas in the control group, there were 9 cases of early onset VAP (81.8%) and 2 cases of late onset VAP (18.2%) (P = 0.027). The relative risk for VAP in the CHG group was 0.36 8.5% versus 23.4% in the control group The absolute risk reduction was 14.9% in the CHG group and (23.4%/8.5%). The number needed to treat was 6.7 (1/0.149). CPIS scores were not different between the two groups on postoperative day 1; however, they were significantly lower in the CHG group on the 3rd (P = 0.024) and 5th (P = 0.005) days when compared to the controls. Since only 2 and 3 cases completed data collection on the 7th day in the CHG and control groups, respectively, because they were extubated no analysis could be performed.	The preoperative rinse was used the day before surgery after meals and before bed; some patients may have used different amounts of doses based on how many meals eaten that day. Total mL of preoperative CHG and saline was not disclosed. Risk for self-reporting error by patients about how often they performed the preoperative rinse The sample size was small and to achieve a power of 80% at a risk ratio of 0.36 over 90 patients would have been required in each arm. The presence of VAP was only analyzed for the first seven postoperative days. Unclear study design stating 1:1 randomization by computer generator but then states physician assigned the groups. Study does not make clear if the two trained and blinded nurses performing oral care, data collection, and diagnosis of VAP were from their team or the hospitals.

Appendix D-1

CASP Checklist

Munro, C. L., Grap, M. J., Sessler, C. N., Elswick, R. K., Mangar, D., Karlnoski-Everall, R., & Cairns, P. (2015). Preintubation Application of Oral Chlorhexidine Does Not Provide Additional Benefit in Prevention of Early-Onset Ventilator-Associated Pneumonia. Chest, 147(2), 328–334. doi: 10.1378/chest.14-0692				
1	Did the trial address a clearly focused issue?	**Yes**	Can't tell	No
2	Was the assignment of patients to treatments randomized?	**Yes**	Can't tell	No
3	Were all the patients who entered the trial properly accounted for at its conclusion?	**Yes**	Can't tell	No
4	Were patients, health workers and study personnel 'blind' to treatment?	**Yes**	Can't tell	No
5	Were the groups similar at the start of the trial?	**Yes**	Can't tell	No
6	Aside from the experimental intervention, were the groups treated equally?	**Yes**	Can't tell	No
7	How large was the treatment effect? ETT colonization at extubation was, 20% in both groups (no statistically significant difference P =0.8656).	Yes	Can't tell	No
8	How precise was the estimate of the treatment effect? A logistic regression analysis was performed using the binary response variable of colonization or no colonization and dependent variables for group, length of intubation, and group-by-length-of-intubation interaction. The probability of a type 1 error (alpha) was set to 0.05.	Yes	Can't tell	No
9	Can the results be applied in your context? (or to the local population?)	**Yes**	Can't tell	No
10	Were all clinically important outcomes considered?	**Yes**	Can't tell	No
11	Are the benefits worth the harms and costs?	**Yes**	Can't tell	No

Appendix D-2

Houston, S., Hougland, P., Anderson, J. J., LaRocco, M., Kennedy, V., & Gentry, L. O. (2002). Effectiveness of 0.12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery. American journal of critical care: an official publication, American Association of Critical-Care Nurses, 11(6), 567–570.				
1	Did the trial address a clearly focused issue?	**Yes**	Can't tell	No
2	Was the assignment of patients to treatments randomized?	**Yes**	Can't tell	No
3	Were all the patients who entered the trial properly accounted for at its conclusion?	Yes	**Can't tell**	No
4	Were patients, health workers and study personnel 'blind' to treatment?	Yes	Can't tell	**No**
5	Were the groups similar at the start of the trial?	**Yes**	Can't tell	No
6	Aside from the experimental intervention, were the groups treated equally?	**Yes**	Can't tell	No
7	How large was the treatment effect? The overall rate of nosocomial pneumonia was reduced by 52% (4/270 vs. 9/291; P=.21) in the CHX patients.	Yes	Can't tell	No
8	How precise was the estimate of the treatment effect? This sample size was sufficient to detect a 0.20 effect size with 99% power.	Yes	Can't tell	No
9	Can the results be applied in your context? (or to the local population?)	**Yes**	Can't tell	No
10	Were all clinically important outcomes considered?	**Yes**	Can't tell	No
11	Are the benefits worth the harms and costs?	**Yes**	Can't tell	No

Appendix D-3

DeRiso, A. J., 2nd, Ladowski, J. S., Dillon, T. A., Justice, J. W., & Peterson, A. C. (1996). Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. Chest, 109(6), 1556–1561. https://doi.org/0.1378/chest.109.6.1556				
1	Did the trial address a clearly focused issue?	**Yes**	Can't tell	No
2	Was the assignment of patients to treatments randomized?	**Yes**	Can't tell	No
3	Were all the patients who entered the trial properly accounted for at its conclusion?	Yes	**Can't tell**	No
4	Were patients, health workers and study personnel 'blind' to treatment?	**Yes**	Can't tell	No
5	Were the groups similar at the start of the trial?	**Yes**	Can't tell	No
6	Aside from the experimental intervention, were the groups treated equally?	**Yes**	Can't tell	No
7	How large was the treatment effect? 69% reduction in the incidence of total respiratory tract infections in the CHX-treated group (17/180 vs. 5/173; $p<0.05$). A reduction in mortality in the CHX-treated group was also noted (1.16% vs. 5.56%).	Yes	Can't tell	No
8	How precise was the estimate of the treatment effect? Statistical analysis was carried out via computer using software (Systat Statistical). Analysis of variance was used to compare numeric data, while the x2 test with Yates' correction or the Fisher's Exact Test was used for categorical data depending on the sample size. In all cases, significance was defined as $p<0.05$.	Yes	Can't tell	No
9	Can the results be applied in your context? (or to the local population?)	**Yes**	Can't tell	No
10	Were all clinically important outcomes considered?	**Yes**	Can't tell	No
11	Are the benefits worth the harms and costs?	**Yes**	Can't tell	No

Appendix D-4

Lin, Y. J., Xu, L., Huang, X. Z., Jiang, F., Li, S. L., Lin, F., Ye, Q. Y., Chen, M. L., & Lin, J. L. (2015). Reduced occurrence of ventilator-associated pneumonia after cardiac surgery using preoperative 0.2% chlorhexidine oral rinse: results from a single-centre single-blinded randomized trial. The Journal of hospital infection, 91(4), 362–366. https://doi.org/10.1016/j.jhin.2015.08.018				
1	Did the trial address a clearly focused issue?	**Yes**	Can't tell	No
2	Was the assignment of patients to treatments randomized?	**Yes**	Can't tell	No
3	Were all the patients who entered the trial properly accounted for at its conclusion?	**Yes**	Can't tell	No
4	Were patients, health workers and study personnel 'blind' to treatment?	**Yes**	Can't tell	No
5	Were the groups similar at the start of the trial?	**Yes**	Can't tell	No
6	Aside from the experimental intervention, were the groups treated equally?	**Yes**	Can't tell	No
7	How large was the treatment effect? VAP occurred in four patients (8.5%) in the chlorhexidine group and in 11 patients (23.4%) in the control group (P ¼ 0.049).	Yes	Can't tell	No
8	How precise was the estimate of the treatment effect? Based on a previous study, the estimated incidence of VAP was 30% in the placebo group and 15% in the study group, resulting in an estimated sample size of 98 patients in each arm, for a power of 80% and alpha =0.05.	Yes	Can't tell	No
9	Can the results be applied in your context? (or to the local population?)	**Yes**	Can't tell	No
10	Were all clinically important outcomes considered?	**Yes**	Can't tell	No
11	Are the benefits worth the harms and costs?	**Yes**	Can't tell	No

Appendix E

Cross Study Analysis

Study/Year	Identified Placebo	CHG Dose/ Frequency	Effect on Incidence of VAP (Results)
Munro et al., 2015	No preintubation CHG	Preintubation: 5 mL 0.12% CHG by swab to the oral cavity administered by study personnel Postop: 5 mL 0.12% CHG administered by the responsible nurse twice daily until extubation	Application of a preintubation dose of CHG did not provide benefit in reducing incidence of VAP Mean CPIS < 6 (VAP threshold score) in both groups. Secondary aim of evaluating preintubations impact on ETT colonization: both groups were < 20% colonized with no significant difference (P = 0.8656).
Houston et al., 2002	15 mL Listerine brand phenolic mouth rinse (Given on same schedule as CHG administration)	15 mL 0.12% preoperatively (30 second swish & spit) and twice daily postoperatively (30 second swab) for 10 days postoperatively or until extubation, tracheostomy, death, or diagnosis of pneumonia.	The overall rate of nosocomial pneumonia was reduced by 52% (4/270 vs. 9/291; P = .21) in the CHG-treated patients. Among patients intubated for > 24 hours who had cultures that showed microbial growth (all pneumonias occurred in this group); the pneumonia rate was reduced by 58% (4/19 vs. 9/18; P = .06) in patients treated with CHG. In patients at highest risk for pneumonia (intubated >24 hours, with cultures showing the most growth), the rate was 71% lower in the CHG group than in the Listerine group (2/10 vs. 7/10; P =.02).

Study/Year	Identified Placebo	CHG Dose/ Frequency	Effect on Incidence of VAP (Results)
DeRiso et al., 1996	Similar chemical makeup without CHG or antimicrobial properties. Identical packaging. (Given on same schedule as CHG administration)	Twice daily preoperative 0.12% CHG (unspecified for how many days preoperatively). Then postoperatively 15 mL 0.12% as an oropharyngeal rinse or rigorously applied to the buccal, pharyngeal, gingival, tongue, and tooth surfaces for 30 seconds twice daily until discharge from the ICU or death.	Respiratory tract infections were 69% less common in the CHG-treated group compared to the placebo group (5/173 vs. 17/180; $p < 0.05$).
Lin et al., 2015	0.9% NS (unspecified amount) (Given on same schedule as CHG administration)	50 mL 0.2% CHG 30 minutes after all meals and 5 minutes after brushing teeth at bedtime. Either solution was gargled for 30 seconds and was repeated three times at one-minute intervals. Once intubated both groups had oral rinse with 50 mL of 0.2% CHG four times a day.	VAP occurred in 4 patients (8.5%) in the CHG group and in 11 patients (23.4%) in the control group ($P = 0.049$). Absolute risk reduction was 14.9% (23.4%/8.5%).