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The efficacy of chlorhexidine gluconate in reducing ventilator-associated pneumonia

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Thesis

THE EFFICACY OF CHLORHEXIDINE GLUCONATE IN REDUCING VENTILATOR-ASSOCIATED PNEUMONIA

by

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I would like to dedicate this work to my family and friends who have assisted, inspired me and devoted time to see me fulfill my goals.
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THE EFFICACY OF CHLORHEXIDINE GLUCONATE IN REDUCING VENTILATOR-ASSOCIATED PNEUMONIA

FELICIA A.E. SMITH

ABSTRACT

Respiratory assistance devices bypass essential host defenses and allow these pathogens direct access to the lower respiratory tract and hinder these defense systems to effectively clear respiratory pathogens (1). Mechanical ventilation in the presence of dental plaque with respiratory pathogens has the potential to lead to ventilator-associated pneumonia (VAP). Ventilator-associated pneumonia is the leading cause of morbidity and mortality in intensive care units. VAP influences increasing need for medical treatment and hospital length of stay (LOS) (2-4). Lower respiratory tract infections (LRTI) have been found to be the most expensive site per infection with 13% of all infections accounting for 29% of the total recorded cost (5).

The purpose of this systematic review is to perform a comprehensive literature search to identify published randomized clinical trials relating to the efficacy of chlorhexidine gluconate (CHX) oral rinse in preventing VAP. CHX has been identified as the “gold standard” to reduce the number of microorganisms. This review also addresses the importance of oral health and the increased risk of respiratory infections from colonization by harmful pathogens within the oral mucosa. Clinical trials relating to the hypothesis in question were evaluated using Consolidated Standards of Reporting Trials (CONSORT) checklist for validity. Quality and strength of each randomized clinical trial
were evaluated based on the requirements of the Agency for Healthcare Research and Quality (AHRQ). Nine bibliographic databases, from 1965-2012 were used to conduct the literature inquiry. Ten studies included populations greater than or equal to 18 years of age and admitted to the intensive care unit receiving mechanical ventilation. The patients were, ventilated due to either trauma, undergoing elective cardiothoracic surgery, or from some other form of surgery, at risk for VAP.

In one study, CHX oral rinse decreased microbial colonization of the respiratory tract and hospital-acquired pneumonia (HAP) in patients who underwent open-heart surgery and were intubated less than 24 hours. Yet the difference was not significant in patients intubated more than 24 hours who had a higher amount of bacterial colonization (6). Modulation of oropharyngeal colonization by the use of oral chlorhexidine has reduced the number of ICU-acquired HAP in selected patient populations such as those undergoing coronary bypass grafting, but its routine use is not recommended until more data become available (7). Findings from several studies suggest a significant decrease in the incidence of total nosocomial respiratory infections and systemic antibiotic use in patients who underwent open heart and used a CHX oral rinse as compared with ventilator patients who did not use the rinse; there was also a 65% decrease (13% vs. 4%) in the overall nosocomial infection rate in the chlorhexidine group (7,8,9). Using 2% chlorhexidine solution presents the strongest evidence for decreasing VAP (10,11). From Scannapieco and colleagues’ study we can conclude that twice daily is not necessarily better than once daily, but maybe a four times daily regimen with 2% instead of 0.12% CHX does make a difference in reducing the incidence of VAP (12).
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LIST OF ABBREVIATIONS

BAL.................................................................Bronchoalveolar Lavage
BUMC.......................................................Boston University Medical Campus
CAP...............................................................Community-Acquired Pneumonia
CDC............................................................Centers for Disease Control and Prevention
CHX.............................................................Chlorhexidine Gluconate
CPIS.............................................................Clinical Pulmonary Infection Score
EOP...............................................................Early-Onset Pneumonia
GNB.............................................................Gram-Negative Bacilli
HAI.............................................................Healthcare-Associated Infections
HAP...............................................................Hospital-Acquired Pneumonia
HCAP.........................................................Health Care–Associated Pneumonia
ICU.............................................................Intensive Care Unit
LOP.............................................................Late-Onset Pneumonia
LOS.............................................................Length of Stay
LRTI.............................................................Lower Respiratory Tract Infections
MESH..........................................................Medical Subject Headings
MDR..........................................................Multidrug-Resistant
MRSA.........................................................Methicillin-Resistant \textit{Staphylococcus aureus}
MSSA.........................................................Methicillin-Sensitive \textit{Staphylococcus aureus}
MV.............................................................Mechanical Ventilation
NHAP.........................................................Nosocomial-Hospital Acquired Pneumonia
NP…………………………………………………………………………. Nosocomial Pneumonia
OCPs……………………………………………………………………………… Oral Care Pathogens
PRP……………………………………………………………………………… Potential Respiratory Pathogen
PSB……………………………………………………………………………… Protected Specimen Brush
RCT……………………………………………………………………………… Randomized Control Trial
RR……………………………………………………………………………….. Relative-Risk
VAP……………………………………………………………………………… Ventilator-Associated Pneumonia
INTRODUCTION

Epidemiology

The number of years of life lost annually in the United States because of nosocomial infections is estimated at 350,000 (13). The impact of infectious diseases on the nation’s health is evaluated on an estimated number of infections treated annually in United States hospitals (14). Despite the availability of antimicrobial agents, infections of the urinary tract, lower respiratory tract, and surgical wounds account for the bulk of infectious diseases treated in hospitals and the burden of hospital costs (14). Lower respiratory tract infections (LRTI) have been found to be the most expensive site per infection with 13% of all infections accounting for 29% of the total recorded cost (5). Eliminating healthcare-associated infections (HAI) has been identified as an essential priority in many hospitals especially with a decrease in government funding (15-17).

Healthcare-associated infections are associated with healthcare treatment facilities in any setting (e.g. hospitals, long-term care facilities, ambulatory settings, and home care) where a patient may become exposed and colonized with pathogens associated with the healthcare treatment (18,19). Hospital-acquired pneumonia (HAP) affects at least 250,000 patients in U.S. acute care institutions each year and is associated with crude mortality of approximately 30% (20). Nosocomial infections are HAI that have a direct burden on the economy and are an important cause of mortality and morbidity in hospitals (14,21). Nosocomial infections are related to mortality; 9% of the infections reportedly caused death, 38% contributed to it, and 37% were not related to death; in
15% of these infections, the relationship of the infection to death could not be determined (22). A study of nosocomial infections in 42 hospitals in 1986 showed that 50% of all nosocomial infections lead to death (22). If 35 million patients are admitted each year to approximately 7,000 acute-case institutions in the United States, the number of nosocomial infections, assuming overall attack rates of 2.5%, 5%, or 10%, would be 875,000, 1.75 million, and 3.5 million, respectively (23). During the mid-1990’s, researchers noticed a steady rate of nosocomial infections with approximately five to six hospital-acquired infections per 100 admissions; nosocomial infections contributed $4.5 billion in hospital costs, and more than 88,000 deaths with approximately 1 death every 6 minutes (23). The average cost of these infections was $1,255, ranging from $866 for surgical wound infections and $203 for urinary tract infections (5). The rate of nosocomial infections per 1,000 patient days increased 36%, from 7.2% in 1975 to 9.8% in 1995 because of a dynamic shift of the healthcare system translating to shorter inpatient hospitalization with a dramatic increase in the number of patients (14).

Pneumonia is an infection of the pulmonary parenchyma classified as an acute lung injury, and is a cause of morbidity and mortality in the United States and developing countries (24). Necrotizing pneumonia may progress to other complications such as bronchiectasis and parenchymal scarring leading to recurrent pneumonias (24). In a study conducted by Langer et al., 23.2% of the 724 patients who received mechanical ventilation actually developed pneumonia (25). Healthcare-associated infections like bacterial pneumonia have accounted for the most frequent cause associated with healthcare infections with treatable clinical manifestations.
In the past, pneumonia was typically classified as community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), or ventilator-associated pneumonia (VAP) (24). The prevalence rate of community-acquired pneumonia ranges from 8 to 15 per 1000 persons per year, with infants and the elderly having the greatest risk for infection but not the highest rates (26). Higher rates of pneumonia have been found in men than in women and in African Americans versus Caucasians (26). The potential involvement of more virulent pathogens has led to a revised classification system in which infection is categorized as either CAP or healthcare–associated pneumonia (HCAP), with subcategories of HCAP including hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) (24). Even though CAP affects individuals in noninstitutionalized settings, whereas HCAP more often occurs in patients in a healthcare setting, more than 600,000 hospitalizations and 45,000 deaths annually are associated with CAP (9,19,24,27). In the United States, ~80% of the 4 million annual CAP cases are treated on an outpatient basis, and approximately 20% are treated in the hospital (24,26). Hospitalizations because of CAP cost $9-10 billion U.S. dollars annually (24,26).

Healthcare-associated pneumonia comprises the 15% of all HAI’s acquired in the medical intensive-care unit (ICU) (18,22,24,26). Nosocomial-hospital-acquired pneumonia (NHAP) is a subcategory of HCAP, and is among the most common infections in United States hospitals, with NHAP as the second most common infection worldwide (19,24). NHAP is an infection of the lung that a patient acquires in the hospital not related to the original admittance diagnosis (28). The crude mortality rate for
HAP may actually be as high as 30 to 70%, but many of these critically ill patients with HAP die of their underlying disease rather than pneumonia (18,29). Patients defined as having HAP have usually received some form of treatment such as antimicrobial agents, chemotherapy, or renal replacement therapy within 30 days before the onset of infection (19). HAP also includes patients who need emergency treatment and are hospitalized for 2 or more days within the 90-day National Healthcare Safety Network surveillance protocol (9,19).

Nationwide statistics collected from U. S. hospitals between 1975-1976 reported a nosocomial infection rate among the 6,449 acute-care U.S. hospitals of 5.7 infections per 100 admissions and the number of nosocomial infections of all types was just over 2.1 million per year in the mid-1970s (24). An analysis was conducted on 200 consecutive hospitalizations in Columbia-Presbyterian Medical Center and Hackensack Hospital (30). When nosocomial infections were causally related or contributed to death, infection of the lower respiratory tract contributed to 60% of the fatal infections and was the leading cause of death from hospital-acquired infections (30).

According to the 1997 Centers for Disease Control and Prevention (CDC) Guidelines, NHAP, such as ventilator-associated pneumonia, is the sixth leading cause of morbidity and mortality in healthcare facilities across the nation despite hospital efforts to provide excellent quality care (22,26,27). The primary risk factor for the development of hospital-associated bacterial pneumonia is mechanical ventilation (MV) following intubation (with its requisite endotracheal intubation) (18). Patients receiving ventilatory support increase their risk of VAP by 1% per day of ventilation and account for 86% of
the cases of nosocomial pneumonia (31). VAP is defined as pneumonia occurring more than 48 hours after endotracheal intubation and initiation of MV, and the crude mortality rate ranging from 24 to 50% can reach 76% in some specific settings or when lung infection is caused by high-risk pathogens (3,25,32).

Ventilator-associated pneumonia is the leading cause of morbidity and mortality in intensive care units, influences up to 30% of hospital mortality hospital charges, and is a determinant of the increasing need for medical treatment and hospital length of stay (LOS) (2-4). Hospital length of stay may average around 7-9 days per patient with a median length of stay in the ICU averaging around 21 days (3,33,34). VAP produces a 2-10 times greater probability of mortality for intensive care patients receiving ventilation compared to those patients who do not require mechanical ventilation (2,35,36). Prevalence estimates vary between 6 and 52 cases per 100 patients, with VAP, and an incidence of around 22.8% in patients receiving mechanical ventilation (24,37). This estimate may vary with certain population groups and microorganisms responsible for VAP, and do not reflect the reoccurrence of VAP in the same patient (24,32). Once a ventilated patient is transferred to a chronic care facility or home, the incidence of pneumonia drops significantly, especially in the absence of other risk factors for pneumonia (24). A large prospective cohort study conducted by Cook et al. focused on 16 Canadian intensive care units and observed a higher risk of VAP in the subset of patients treated with MV. Of the 16 ICUs, 177 patients out of 1014 mechanically-ventilated patients developed VAP (38). Patients treated with continuous ventilation had 21 times
greater risk of acquiring VAP than patients who had been previously treated with continuous ventilatory support (39).

VAP is a common nosocomial infection that is associated with poor clinical and economic outcomes. Apart from death, the major complication of VAP is prolongation of mechanical ventilation, with corresponding increases in length of stay in the ICU. The muscle loss and general debilitation from an episode of VAP often require prolonged rehabilitation, and are associated with higher incidence of pulmonary infection. Sometimes elderly patients are unable to return to independent function and need nursing home care which adds a considerable financial burden (24,25). Regardless of the causal relationship between pneumonia and mechanical ventilation, the increased length of hospital stay as a result of VAP in the US has averaged an excess cost over the years. In 1982, the excess cost was approximately $1,255. A similar study in 1985 reported an average extra cost of $2,863 per patient with nosocomial pneumonia (NP) (5). By 1996, mean hospital admission and charges per patient have been estimated to be an additional $40,000 including out billed charges (18,40-42). For example, if hospital costs averaged only $500/day and excess stay due to pneumonia were limited to seven days, the direct cost of NP would be $1.1 billion annually (20). Comparative cost analysis is dependent on a wide variety of factors that differ from one country to another, including healthcare system, organization of the hospital and the ICU, and the possibility of patients being treated by private practitioners (42).
**Etiology**

Time of onset is the most important variable risk factor in determining the prognosis of VAP. Other risk factors include duration of exposure to the healthcare environment, the causative microbial agents, a number of host factors, and treatment-related factors (4,7,24,32). The two classifications identifying time of onset for VAP is either early-onset pneumonia (EOP) or late-onset pneumonia (LOP) (18). These categories are based on the time frame from intubation to the development of pneumonia (18,31,43). Early-onset VAP, usually less severe with a more favorable outcome and associated with antibiotic-sensitive organisms, occurs 48 to 96 hours after intubation and initiation of mechanical ventilation (31,32,43,44). If pneumonia develops 96 hours after the patient’s admission to an ICU or more than 48 hours after intubation and initiation of mechanical ventilation, it is suggested that the patient has acquired LOP (18,44).

Differences between early and late onset VAP are due to the different distribution of etiologic agents and the frequent administration of prior antimicrobial therapy (32). The pathogens responsible for causing the highest incidence of hospital-acquired fatality are aerobic, Gram-negative bacilli (GNB) (45). These pathogens are historically associated with an increased prevalence of nosocomial pneumonia in studies of critically ill and/or mechanically ventilated patients in intensive-care units (46). The most commonly encountered and potentially antibiotic-resistant Gram-negative bacteria associated with VAP are *Pseudomonas aeruginosa*, *Acinetobacter* species, *Enterobacteriaceae* (*Proteus* spp., *Escherichia coli*, *Klebsiella* spp.,), and *Haemophilus influenzae* (7,18,47,48). Twenty-four bacteriologic studies conducted on VAP patients,
analyzed by Chastre et al. confirmed that 58% of aerobic GNB were recovered from the controlled uncontaminated specimens (32). Due to prior hospitalization and use of antibiotics in many patients developing early-onset VAP prior to their transfer to the ICU, the most common pathogens associated with early-onset VAP, according to Ibrahim et al., were *Pseudomonas aeruginosa* (25.1%), *Staphylococcus aureus* (17.9%), and *Enterobacter species* (10.2%) (48). Late-onset VAP (5 days or more) more commonly involve antibiotic-resistant bacteria and multidrug-resistant (MDR) pathogens, and are associated with increased patient mortality and morbidity (7,18). Patients with high-risk pathogens (*Pseudomonas aeruginosa, Acinetobacter* spp., and *Stenotrophomonas maltophilia*) had a significantly higher hospital mortality rate (65%) in comparison with patients who developed late-onset VAP due to other microbes (31%) or patients without late-onset pneumonia (37%) (49). These pathogens were usually not present alone, so that VAP is considered a polymicrobial infection. Over the last decade or two, however, patients presenting to the hospital as outpatients with onset of pneumonia are now more commonly infected with multidrug-resistant (MDR) pathogens that have previously associated with hospital-acquired pneumonia (50). MDR pathogens are a matter of concern since they are associated with significantly greater attributable mortality than non-MDR pathogens (24). It is important to keep a low frequency of MDR pathogens among healthy people in order to prevent the likelihood of them developing VAP from these organisms, if hospitalized and ventilated (24). More recently, however, some investigators have reported that Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-sensitive *S. aureus* (MSSA), have become
increasingly more common in hospital settings (32). When a study compared Gram-positive pneumonias, the VAP mortality due to MRSA was found in 86% of the cases with pneumonia with a relative risk of death equal to 20.7. However, mortality due to MSSA was found in 12% of the pneumonia cases (51,52). Hospital patients acquiring pneumonias due to other organisms, have a documented mortality rate of (55%), compared to the 87% mortality rate studied in patients with Pseudomonas aeruginosa and Acinetobacter spp. (32). Studies reporting on Pseudomonas pneumonia indicate that this organism accounts for 8.5% of all nosocomial infections, death rates of more than 80%, and an attack rate of 36 infections per 10,000 hospital discharges (32,53,54).

Clinicians must clearly be aware of the different distribution patterns of etiologic agents associated with early-and late-onset VAP and consider them when administering prophylactic antimicrobial therapy to avoid inadequate therapy (32,48). In a prospective study that included 129 episodes of nosocomial pneumonia, responsible pathogens were compared according to whether the patients had received antimicrobial therapy before pneumonia. The onset rate of pneumonia caused by Gram-positive cocci or H.influenzae was significantly lower in patients who had received antibiotics, whereas the rate of pneumonia caused by P. aeruginosa was significantly higher (55). Potentially drug-resistant bacteria are the most significant risk factor for VAP. For example, after prior use of broad-spectrum drugs such as the third generation cephalosporin, fluoroquinolone, and/or imipenem and 7 days of mechanical ventilation, MRSA, P. aeruginosa, A. baumannii, and/or S. maltophilia were found in 135 consecutive episodes of VAP (56).
Numerous fluctuations in the oral environment can influence many aspects of the initial colonization, maturation, and survival of microorganisms within oral plaque (57). It has been well established that Gram-negative bacilli play a major role in the relationship that exists between oropharyngeal colonization with GNB and nosocomial infections of the lower airways (58,59). Aerobic Gram-negative bacilli in pharyngeal cultures may be found infrequently in a healthy population that have or have not had a hospital exposure (18,58). The oropharynx is a non-sterile cavity, continuously colonized with facultative anaerobes and Gram-positive cocci; however, these organisms are considered part of the normal oropharyngeal flora (19,60). Actually all of the microorganisms, which comprise the microbiota in the human body, are naturally acquired from the environment and are considered part of our "normal" flora (19,57,61).

Endogenous and exogenous factors influence the general environment and microenvironments in the oral cavity (62). Endogenous factors in the oral cavity are derived from the host, and they include: salivary proteins, glycoproteins, enzymes, teeth, pellicle, shedding mucous membrane, barrier functions of oral mucous membranes, humoral immune factors (salivary and serum antibody), cellular immune factors (e.g., lymphocytes, neutrophils, and cytokines), and protective factors (62). Exogenous infections resulting from transient bacteria are virulent and less well adapted to the human host (62). Pathogens causing exogenous infections typically do not require predisposing host conditions or unusual environmental alterations to exert pathogenic potential (62). Native bacteria in the oral cavity play an integral part in preventing colonization by, emergence of, exogenous pathogens (62).
Dental plaque consists of different species of bacteria that are not uniformly distributed, because different species colonize the tooth surface at different times and under different circumstances; this explains the versatility of plaque to proliferate in different environments (9,57,63,64). Dental surfaces provide the perfect opportunity for bacteria attach to surfaces of the host and form colonies on oral soft tissues such as the gingiva, tongue, cheeks, and alimentary tract (57). The oral cavity of the host contains several types of surfaces, including keratinized and non-keratinized epithelium, and those of the teeth, which bacteria may colonize (61). Some bacteria may specifically require the presence of, or exhibit preferred attachment to, particular surfaces of the mouth. The development of bacterial plaque has been shown to involve the attachment of Streptococcus sanguis to the teeth, followed by Streptococcus mutans (S. mutans) (57). Other bacteria that may colonize the teeth include Streptococcus mitis, Actinomyces viscous, and Bacteroides gingivalis (24,57,61). Streptococcus mitis are usually found in high proportions on both buccal and tooth surfaces (61). The dorsal posterior aspect of the tongue harbors millions of organisms such as Streptococcus salivarius (57,61,65,66).

Mechanical ventilation in the presence of dental plaque containing respiratory pathogens has the potential to lead to ventilator-associated pneumonia (VAP). Biofilm formation in many cases precedes the development of VAP, and perhaps more importantly, represents a persistent source of organisms causing recurrent infections (67). A clean enamel surface is covered in a few seconds by an adsorbed layer of molecules comprising mainly glycoprotein from saliva, forming the acquired pellicle to which microorganisms initially adhere (19). A single bacterial species, or more than one
species, may aggregate on solid surfaces to form a biofilm composed of a slimy coat within a polysaccharide matrix (19). Alteration of the mucosal surface, destruction of the salivary film, and production of cytokines by the host defense system in response to bacterial invasion are the initial physiochemical and biochemical steps involved in the attachment of bacteria to solid surfaces and colonization by respiratory pathogens (19). Adhesion to the surfaces in the mouth is essential for the existence and proliferation of bacterial organisms (61). The primary colonizers, adhering directly to the acquired pellicle, such as streptococci and Actinomyces, are encased in an exopolysaccharide matrix (19,57,68). These undisturbed primary colonizers are eventually joined by secondary colonizers (57). Secondary colonizers synthesize protein adhesins that recognize receptors on primary colonizers (68). As bacteria proliferate, they synthesize extracellular matrix polymers to which other bacteria may bind, rather than to the pellicle, resulting in a complex biofilm of spatially arranged species eventually forming dental plaque (19,57,65). The polysaccharide layer serves as a nutrient to aid in the growth of bacteria, and is important for protection of the bacterial cells from the osmotic effects of sucrose, the inhibitory effect of toxic metabolic end products, antimicrobials, and the host’s immune mechanisms (19,57,69,70).

Pathogenesis

One factor contributing to mechanically ventilated patients acquiring VAP is the inability of their compromised host defenses to protect against endogenous and exogenous infections (4,32). When these patients are overwhelmed with a high inoculum of organisms, the impaired defense system is unable to clear or inactivate the organisms
which can then colonize and lead to the development of pneumonia (32). The normal human respiratory tract possesses a variety of defense mechanisms that protect the lung from infection (32). Anatomic barriers include the glottis and larynx, cough reflexes; tracheobronchial secretions, mucociliary lining, cell-mediated and humoral immunity; and a dual phagocytic system that involves both alveolar macrophages and neutrophils (32). Mechanical ventilation contributes to a break in the defense system with increased frequency of colonization among patients with respiratory disease, sputum production, or endotracheal intubation; this suggests that conditions that impair lung clearance may also promote colonization (59). Major host determinants interfering with the mucosa-associated defense system includes disease-induced changes of the upper respiratory tract resulting from severity of an underlying illness, or advanced age which may also increase oropharyngeal colonization by GNB (46,58,71,72).

Respiratory assistance devices bypass essential host defenses and allow pathogens direct access to the lower respiratory tract and hinder the ability of these defense systems to effectively clear respiratory pathogens (1). The response of the body’s defense system results in modifications of the respiratory epithelium that favor colonization by respiratory pathogens (19). With mechanical ventilation patients will have an automatic breakdown of host defenses by bypassing the host natural defense system with an artificial airway that compromises the natural barrier between the oropharynx and trachea (32). Starting as early as 12 hours after intubation, biofilm formation occurs with many patients undergoing mechanical ventilation (31,67,73). Bacterial biofilms may cause inflammation around the vocal cords and upper airway from leakage of oropharyngeal
secretions from above and below the endotracheal tube cuff (19,74,75). Biofilm particles on the inner surface of the endotracheal tube can detach and inoculate the lower respiratory tract from ventilatory-induced breaths, endotracheal suctioning, and bronchoscopy (19,24,31,76).

Endotracheal tubes, contaminated respiratory equipment, position of the patient, parenteral nutrition support, and insufficient head elevation in bed provide a route for colonizing pathogens to translocate from the oral cavity to the oropharynx and colonize the upper airway during mechanical ventilation (19,31,77). Respiratory equipment associated with mechanical ventilators, such as humidifying cascades and contaminated reservoir nebulizers, serve as reservoirs for condensate and deliver the contaminated condensate to the patient (74). Usually the extrinsic contamination of the patient’s ventilator circuit results from inoculation of large amounts of fluid with high bacterial concentrations produced from warm humidified air (74). Aspiration of contaminated secretions by the patient is facilitated by manipulation of ventilator tubing, patient transport, delivery of aerosolized medication, or placing the patient in a supine position (33,78,79). Ventilator tubing has been found as the primary factor for colonized bacteria; the highest levels of colonization (>1,000 CFU) have been found to occur at parts nearest to the patient (74,80). It has thus been hypothesized that the enteric microorganisms that colonize the stomach migrate to the oropharynx, and eventually reach the lungs of mechanically-ventilated patients via aspiration (60). When factoring other devices such as a nasogastric or orogastric tube, patients have a greater chance of developing
nosocomial pneumonia from aspirating gastric contents or stagnant oropharyngeal secretions into the lower airways while in the supine position (33,79,81).

Even with an artificial airway, a patient is also still susceptible to VAP with microaspiration (19,82). Mechanical ventilation causes changes in the cuff pressures, deforming it and allowing the secretions to be transported around it by capillary action thereby increasing the risk for microaspiration (19,83). Local trauma and inflammation caused by an endotracheal tube and possible leakage of contaminated secretions around the cuff and into the upper trachea increase lower airway colonization and the risk of tracheobronchitis and VAP (74,75). Reintubation magnifies the risk of aspiration of colonized oropharyngeal and gastric secretions into the lower airways (32).

Colonization of the upper respiratory tract (i.e., the oropharynx and trachea) by potentially pathogenic microorganisms is common in critically ill, mechanically-ventilated patients (60). Patients with chronic illnesses have more difficulty maintaining optimal oral hygiene, often because of a reduction in the natural cleansing of the mouth and/or reduced saliva from certain medications (19,46,58). If oral hygiene is neglected the accumulation of plaque can lead to gingivitis and a shift to aerobic Gram-negative bacilli (57). An ICU patient with an increased length of stay (more than five days) will more than likely see a dramatic decrease in oral hygiene and an increase in colonizing GNB and S. aureus in the upper airway (24,32,84). Oral flora can be affected by macroenvironmental changes associated with routine hospital care and respiratory equipment that exposes the patient to Gram-negative bacilli (43,74,85). Therefore,
tracheal colonization and other multifactorial risk factors are very important in the emergence of VAP (77).

Diagnosis

Evidence from Fàbregas et al., indicates that clinical diagnosis of VAP is associated with about 30 to 35% false-negative and 20 to 25% false-positive results (86). A major diagnostic dilemma for VAP is that no one specific criterion is available to give a definitive diagnosis. Yet, an accurate and specific diagnosis is critical for pneumonia treatment and prevention. With patients in the ICU comprising up to 10% of total cases of pneumonia, rapid identification of infection is important for appropriate antimicrobial treatment to prevent emergence of MDR pathogens (32,53). With the misdiagnosis of VAP, inappropriate clinical treatment often leads to a substantial source for morbidity and mortality (24). The inability to identify patients with VAP, treating those with VAP, treating those with VAP inappropriately may also potentially put them at risk for developing superinfections (24,31). For example, if a patient is treated empirically, but does not have an infection, the organisms that subsequently infect the patient may be either multidrug-resistant Gram-negative bacteria or MRSA, and the mortality risk will be increased (87).

Diagnosis relies heavily on clinical signs. However, these clinical signs can inflate incidence rates, which can impact the reportable impact of VAP mortality. In fact, clinical signs such as pulmonary infiltrates or tracheobronchial colonization do not necessarily mean that the patient has VAP (24,31,32,88). Radiographic infiltrates, other sources of fever, results of Gram staining and culture of tracheal aspirates can lead to
misdiagnosis and poor choices for the antibiotics (24,32). The differential diagnosis of VAP may include chemical pneumonitis, cardiogenic and noncardiogenic pulmonary edema, pulmonary thromboembolism, or persistent atelectasis, aspiration, pulmonary embolism, or acute respiratory distress syndrome (31,32,53,75).

The traditional criteria for diagnosing VAP are generally non-specific systemic symptoms that are typically found in all forms of pneumonia. The traditional criteria for clinical signs include new or worsening infiltrates seen on the chest radiograph, and bacteriologic evidence of pulmonary parenchymal infection (18,19,32,88). Some traditional nonspecific clinical symptoms include fever, leukocytosis, increase in respiratory secretions, purulent sputum, and pulmonary consolidation on physical examination, along with a new or changing radiographic infiltrate (19,24,26,32,89,90). Non-specific clinical findings may have alternative causes, including antibiotic-associated diarrhea, sinusitis, urinary tract infection, pancreatitis, and fever (24,80). Clinical signs that are more specific for diagnosing VAP include fever higher than 100.9°F, leukocytosis (25% increase and value greater than 10,000 mm$^3$), leukopenia (25% decrease and value less than 5,000 mm$^3$), or purulent tracheal secretions (58,63).

The evaluation of these signs, using the Clinical Pulmonary Infection Score (CPIS) recommended by the CDC, provides a numerical value for diagnosing VAP. The CPIS score usually sets precedence in identifying the need for more invasive diagnostic tests, such as obtaining tracheal aspirates, and in helping identify low-risk patients in need of short-course antibiotic therapy (24,83). The most important component and backbone for clinical diagnosis in evaluating hospitalized patients with suspected pneumonia, is a chest
Chest x-rays provide detection of progressive infiltrates such as a bronchopneumonia pattern, common in nosocomial pneumonias, whereas a lobar pattern is more common in bacterial CAP (24,31,89). If a new or persistent infiltrate is seen on a chest x-ray, the next step is to isolate an organism from sputum or pleural fluid, or a positive culture from a bronchoalveolar lavage, must be present (63). The drawbacks of chest x-rays are that they are not reproducible and lack specificity for differentiating among pulmonary processes that radiographically mimic pneumonia (24,31,32,53,75). As a result of the inaccuracies associated with the clinical approaches to VAP, many investigators have developed specialized diagnostic methods. Some methods include quantitative cultures of endotracheal aspirates obtained using bronchoscopic techniques such as bronchoalveolar lavage (BAL) and/or a protected specimen brush (PSB) (32).

In diagnosing pneumonia in intensive care unit patients, current practice is to rely heavily on analysis of sputum Gram stain (53). According to Salata et al., analysis of sputum using Gram stain provides a semi-quantitative estimate of bacteria (53). The absence of bacteria in Gram-stained endotracheal aspirates makes pneumonia an unlikely cause of fever or pulmonary infiltrates (24). Carefully performed Gram staining of purulent sputum specimens with few squamous cells present have been helpful in establishing a rapid diagnosis of pneumonia caused by pneumococci, staphylococci, and Gram-negative bacilli (53).

A diagnostic challenge for the microbiology laboratory is the need to differentiate between organisms responsible for infection and colonizing flora (91). Invasive techniques are the best method for alleviating this problem by obtaining a specimen with
the least amount of oropharyngeal contaminants (31,32). It is also the best method for rapid diagnosis for pneumonia caused by pneumococci, staphylococci, and invasive Gram-negative bacilli (49). It is believed that the bronchoscopic quantitative cultures are most effective, decreasing mortality among VAP patients by preventing inappropriate selection of antibiotics, and identifying other potential sources of infection (24). Invasive testing which leads to more accurate diagnosis and treatment has the advantage of reducing the risk of antimicrobial resistance, producing fewer side effects from unnecessary antibiotics, and a decrease in cost (87). Culture and sensitivity tests are best done as early as possible from all patients without contraindications (92).

Quantitative endotracheal aspirate cultures may be an adequate tool for diagnosing pneumonia when no fiberoptic techniques are available (32). Quantitative cultures are critical and complement clinical data by identifying patients with true VAP, facilitating appropriate treatment, and discriminating between colonization and true infection (24). It must be kept in mind that this quantitative technique has several potential pitfalls such as using the cutoff value of 10⁶ CFU/ml (32). This cutoff value may contain contaminants since endotracheal aspirates obtained through bronchoscopic secretion samples have higher levels of organisms (32,92).

The role of quantitative invasive diagnostic techniques to evaluate patients with clinical evidence of nosocomial pneumonia remains controversial (88). The controversy centers around whether invasive techniques should be used on a routine basis or rather on a targeted basis to diagnose pneumonia (88). Bronchoscopic techniques, when performed before introduction of new antibiotics, enable physicians to identify most patients who
need immediate treatment and help to select optimal therapy in a manner that is safe and well tolerated (32). As soon as a lower threshold is used, specificity declines sharply and overtreatment becomes a problem (32). Contaminants found in bronchoscopic secretion samples are usually present at less than $10^4$ CFU/ml (93). Higher levels of infecting organisms causing nosocomial pneumonia are usually present in concentrations of $10^5$ to $10^6$ CFU/ml (51,93). With such narrow values of the aforementioned concentrations, the quantitative technique is designed to distinguish between contaminants and infecting organisms (51,93).

The results of microbiological tests of sputum specimens obtained by either invasive or noninvasive methods are not sufficient to determine if pneumonia has resolved or the success of antibacterial treatment and the host defense system but can provide a quantitative and qualitative assessment of burden present in the lung tissue. However, the culture and sensitivity results can help in choosing an antibiotic (24,32). Microbiologic test results from sputum specimens have a high sensitivity for nonspecific bacterial pathogens. Due to the high sensitivity of microbiologic tests to nonspecific bacterial pathogens, the test should not be the sole basis for diagnosing VAP (31).

The two techniques that are considered superior but still controversial are protected specimen brush (PSB) and bronchoalveolar lavage (BAL) (32). Diagnoses achieved with invasive tests have led to a change in antibiotic in up to 50% of cases (87). For those with clinical signs of pneumonia, it has been noted that test results from tracheal aspirates correlate well with those from PSB (87). Results from studies have indicated that the PSB technique offers a sensitive and specific approach to identifying the microorganisms
involved in pneumonia in critically ill patients, and to differentiate between colonization of the upper respiratory tract and distal lung infection. Kirtland et al. (1997) has shown that a PSB culture with $\geq 10^3$ CFU was 100% sensitive in association with histologic pneumonia in patients with or without antibiotics with a negative predictive value of 100% (94). In patients receiving antibiotics, the specificity was 42% and positive predictive value was 22% compared with 87% and 80%, respectively, in patients not receiving antibiotics (94). Bronchoalveolar lavage technique is safe, efficient, and practical by providing immediate examination of the cells and secretions obtained from the large area of lung (32).

The major dilemma with all bronchoscopic techniques is selecting the proper sampling area in the tracheobronchial tree. Sampling the distal airways of the respiratory system produces specimens that are more reliable for diagnosing pneumonia (24,32). As discussed previously, BAL is a safe and effective method of obtaining specimens. Nonetheless, BAL may also affect the validity of results depending on the sampling area from which the diluted material is retrieved. Diluted material from the bronchial area rather than from the alveolar level will often give rise to false-negative results (32). Contamination can occur despite using a fiberoptic bronchoscope (FOB) in combination with either BAL or PSB. Any type of bronchoscope passing through the endotracheal tube and proximal airways plus aspiration of distal secretions may become contaminated with organisms from the normal flora (32). Besides contamination of the specimens, a patient is at risk for health complications when performing this procedure. The risk appears slight, even for critically ill patients requiring MV, although the associated
occurrence of cardiac arrhythmias, hypoxemia, or bronchospasm is not unusual (32,95,96). Patients in the ICU are at risk of relative hypoxemia during fiberoptic bronchoscopy even when high-level oxygen is provided to the ventilator and gas leaks around the endoscope (95). BAL could be performed without significant risk to most of the patients in the ICU (96).

Multiple studies have shown that both bronchoscopic and nonbronchoscopic BAL are significantly more sensitive and specific than nonquantitative endotracheal aspirate cultures in microbiologic diagnosis of pneumonia in mechanically-ventilated patients (88). Nonbronchoscopic techniques have also been developed for the evaluation of VAP, but they have the same limitations as those noted above for the bronchoscopic methods (97). However, nonbronchoscopic approaches have been advocated as potentially better alternatives because of their minimal invasiveness, wide availability, and relative inexpensiveness compared with fiberoptic bronchoscopy (97).

Treatment

For an overall successful treatment of VAP, optimal antibiotic treatment must be provided in a strategic manner (24,98). A different strategy for management of VAP involves some form of clinical and microbiological assessment (98). For any given patient, clinical management of VAP may include knowledge about local patterns of antimicrobial resistance, particularly in the ICU setting, administration of antibiotics, and the patterns of resistance of the most likely pathogen (24,88). The upper respiratory tract of most ICU patients with pneumonia remains colonized with multiple potential
pathogens (32). One factor in managing VAP involves using Gram stains of endotracheal aspirates as a guide for antimicrobial therapy along with diagnosing pneumonia (98).

The mainstay of VAP treatment is systemic antibiotic therapy in addition to maintenance of adequate perfusion and hydration, prevention of atelectasis, provision of aggressive pulmonary toilet, and weaning from mechanical ventilation as quickly as possible (88). Prevalence of antimicrobial resistance among VAP pathogens is steadily increasing especially against broad-spectrum antimicrobial drugs (88). There is some controversy regarding the role of antimicrobial therapy in preventing, treating, or putting patients at risk for VAP (99). The absence of antimicrobial therapy as a risk factor for VAP has not been identified but it has been found that prior antibiotic use was a risk factor for VAP (100). Prophylactic short-course treatment has been shown to provide a major benefit in decreasing the incidence of early-onset VAP, which is caused by the less pathogenic microorganisms (24).

Yet, insufficient treatment is common in VAP, ranging from 20% to 70%, and is associated with increased resource utilization, including increased ventilator days and increased length of stay (88). Inadequate initial antimicrobial treatment may also affect the emergence of infections resulting from antibiotic-resistant bacteria, and subsequent increased mortality rates in patients by facilitating colonization and superinfection with multiresistant microorganisms (24,32,88,98). MRSA is an important cause of VAP associated with high rates of inadequate initial empiric antimicrobial therapy and poor clinical outcomes (98). Treating VAP becomes complicated with an inadequate initial antibiotic regimen. This inadequate initial treatment may also result in an increased
morbidity and mortality (98). In general, the likelihood of MDR pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter* species, *Stenotrophomonas maltophilia*, and MRSA causing VAP depends on the duration of hospitalization prior to the onset of VAP and other risk factors for MDR pathogens (98). Late-onset pneumonia that occurred without antibiotics during the 15 days preceding the onset of infection largely were caused by *Streptococci*, MSSA, or *Enterobacteriaceae* (29). Recently received antibiotics for late-onset pneumonias were the result of MDR pathogens such as *P. aeruginosa*, *A. baumannii*, or MRSA in more than 40% of cases (29).

Selection of antimicrobial therapy for VAP is complex and increases the cost of treatment due to antimicrobial-resistant pathogens (98). When selecting a highly recommended broad-spectrum empirical treatment for VAP, one should be aware of underlying diseases and specific risk factors that may predispose patients to infection with specific organisms, especially MDR pathogens (29). Other factors include the epidemiologic characteristics of the patient, clinical examination of pulmonary secretions, and how the drug will absorb, distribute, metabolize, and exit the body (29,98). Primarily a broad-spectrum antibiotic regimen is selected to cover all potential pathogens both Gram-negative and Gram-positive including MDR pathogens (88,98). Two of the most common organisms isolated in HAP and VAP are *Pseudomonas* and *S aureus* (88). Antibiotics that can be considered in VAP treatment include the semisynthetic penicillins, fluoroquinolones, fourth-generation cephalosporin, and carbapenems (88). Infection due to antimicrobial-resistant pathogens necessitates broad-spectrum initial empiric antimicrobial therapy, usually with a combination of drugs (98).
In patients with severe infection due to *P. aeruginosa* or other MDR bacteria, such as *Klebsiella spp.* or *Acinetobacter spp.*, combination therapy of antipseudomonal beta-lactam with an aminoglycoside or ciprofloxacin is likely to obtain a much better outcome than monotherapy (24,29). The standard recommendation requires two drugs directed at *P. aeruginosa* and one at MRSA (24). Still it is suggested to reduce the antibiotic regimen to a single agent in more than half of the cases and to a two-drug combination in more than one-quarter for those patients at risk for experiencing MDR pathogens (24).

Once sputum or BAL culture results are obtained and a confirmed etiologic diagnosis is reached, a broad-spectrum empiric therapy can be modified and/or tapered down to address the known pathogen specifically while avoiding prolonged use of broad spectrum drugs (24,29,88). This strategy is known as de-escalation. De-escalation modifies antimicrobial treatment from aggressive broad-spectrum initial empiric antimicrobial therapy to a more narrow spectrum, or discontinuation of antimicrobial drugs (98). Drugs with a narrow spectrum that target the known pathogens are substituted for drugs with an unnecessarily broad spectrum in order to minimize excessive antimicrobial exposure (98). Even if a de-escalating approach to antibiotic therapy does not benefit the individual patient, the modification of therapy can reduce the selection for resistant strains of bacteria to develop in the ICU (29). Prolonged courses of antibiotic treatment demonstrated a consistent increased risk for VAP due to the more lethal MDR pathogens (24). It is rare for patients to require a complete antibiotic regimen of three drugs and other trials subgroup analyses have not found an increase in benefit with such a regimen (24). Furthermore randomized controlled trials have demonstrated a concrete
benefit with just a two-combination therapy such as beta-lactam and aminoglycoside (24).

The recommended duration of antibiotics depends on the severity of disease, the time to clinical response, and the microorganism(s) responsible (29). The recommended duration of therapy for hospital-acquired pneumonia, including VAP, has traditionally been long: a minimum of 7–10 days for patients at risk for Haemophilus or Staphylococcus infections, and 14–21 days for more typical cases (98). The optimal duration of therapy remains unknown, but in the last several years a number of clinical studies have lent support to using shorter courses of treatment (98). The general strategy of limiting the duration of therapy has been fully endorsed by the new American Thoracic Society/Infectious Diseases Society of America guidelines for the management of VAP (98). Treatment of at least 14 to 21 days is prescribed for patients with multilobular involvement, malnutrition, cavitation, Gram-negative necrotizing pneumonia, and infections P. aeruginosa or Acinetobacter spp., which correspond to the majority of pulmonary infections occurring in patients requiring mechanical ventilation (29).

Effective antibiotic treatment depends on the adequate delivery of the antibacterial agent, i.e. optimal doses of the drug that can be safely achieved and maintained at the site of the infection, a route of administration with minimal side effects, the antimicrobial efficacy of the drug against each infectious agent, local patterns of antimicrobial resistance, and the patient’s prior antibiotic exposure (24,29,98,99). Clinical improvement, if it occurs, is usually evident within 48–72 h of initiation of antimicrobial treatment (24). Findings on chest radiography often worsen initially during treatment;
they are less helpful than clinical criteria as an indicator of clinical response in severe pneumonia (24). Clinical response to treatment is usually tracked by repeating quantitative cultures to show the microbiologic response (24).

Treatment failure, due to deficiencies in the antibiotic treatment, is common in VAP patients before obtaining a definitive diagnosis for the pathogens responsible for the pneumonia (29). Signs such as an elevated or rising clinical pulmonary infection score (CPIS) value by day three of ventilation, especially with declining or poor oxygenation, is a strong indicator of treatment failure (24). CPIS is a score used in diagnosing VAP. The score is calculated on the basis of points assigned for various signs and symptoms of pneumonia. A CPIS >6 usually suggests VAP (7,27,51). Treatment failure due to an inadequate differential diagnosis may result from a new super infection causing the pneumonia, the presence of extrapulmonary infection and drug toxicity (24).

**Prevention**

Understanding the development of VAP and learning to recognize patients at risk permit an opportunity to implement simple but effective preventive measures (101). Despite the introduction and use of broad-spectrum antimicrobial agents, management of ventilator-dependent patients, and routine use of disinfecting respiratory equipment, VAP remains a cause of mortality, morbidity, and increases in healthcare costs (33). Decreasing the exposure to potential pathogens involves a collaborative effort among all healthcare professionals. When developing a strategic prevention plan for VAP, one must take into consideration a general framework of preventing VAP by decreasing the exposure of oropharyngeal secretions drifting toward the lower respiratory tree,
modifying the virulence and/or quantities of the microorganisms present in the oropharynx, and improving host defenses (31,33,101).

The simplest way to prevent VAP is to avoid endotracheal intubation and use a less noninvasive method of ventilation. If an endotracheal tube is used, it is best to use a modified orotracheal tube that allows removal of secretions above the endotracheal tube cuff, and minimize the time a patient is required to have an endotracheal tube in place (24). Once a patient is intubated, patient care should focus on aspiration of bacteria in the patient airway. Protection of the airway with invasive procedures such as tracheal intubation sometimes cannot be avoided but other available preventive measures still exist as not to further contribute to the risk of VAP (31). Measures taken to prevent aspiration include maintaining an appropriate level of no less than 20 cm of H2O in the endotracheal tube cuff, elevating the head of the bed at least 30° to 45°, and adjusting the patient’s position every two hours (31,101,102). Potential weaning, extubation from mechanical ventilation, and the use of heavy sedation are also taken into consideration to decrease the risk of VAP (31). In 1981, the CDC published guidelines with a traditional approach through infection control to prevent and control the spread of nosocomial pneumonia (18,19). This approach limited person-to-person spread of infection by wearing protective equipment, hand washing, and improving care of invasive devices (101,103). Often these traditional measures fail because they have little effect on the patient’s endogenous flora, which is an important source of infection in intensive care units (103).
Tracheal colonization precedes VAP in most patients but only a minority develops VAP (77). Oral flora can be affected by macroenvironmental changes associated with routine hospital care and respiratory equipment that expose the patient to Gram-negative bacilli (43,74,85). Researchers agree that prevention methods should focus more on decreasing the ability of VAP-associated pathogens to colonize the oral cavity preceding infection of the lower respiratory system (104). The CDC addressed the need to impede pathogens from translocating to other parts of the body. In 2003, the CDC guidelines provided ways for decreasing the number of opportunistic pathogens in the normal flora, and improving a patient’s immune system in response to acquired pathogens (18,19,33,105). Adequate oral hygiene has shown to decrease elevated enzymes such as neuraminidases and proteases, which can modify bacterial colonization and attachment (61). These enzymes are derived from inflammatory cells associated with gingival inflammation and bacterial plaque accumulations (61). These enzymes generate hidden receptors for bacterial adhesions that promote colonization of certain Gram-negative bacteria (61). With oral hygiene neglected, the accumulation of plaque can lead to gingivitis and a shift to aerobic Gram-negative bacilli including those known to cause pneumonia (57).

The question that arises for many clinicians is how does one provide adequate oral healthcare with these devices overcrowding the mouth. An adult size toothbrush is not able to fit thus leaving healthcare providers discouraged and frustrated. Yet, if normal adult size oral healthcare products are used, there may be a risk of dislodging the protective airway equipment (65). Challenges arise when attempting to provide adequate
oral care to a ventilated patient. With devices such as endotracheal, oral gastric tubes, and occasionally a temperature probe crowding the mouth, healthcare providers become frustrated trying not to dislodge these important medical devices, compromising the patient’s airway (31,83,106). Mechanical obstacles, perceptions of importance, patient discomfort by the nurse and family members, patient perception and ineffective communication are key barriers to achieving optimal oral hygiene (65).

Prevention measures for nosocomial infections can enhance a patient’s quality of life and our nation’s economy. Oral care practices vary among healthcare institutions with university and private nonprofit hospitals providing the least amount of care (82). The most effective and correct method of providing oral hygiene to ventilator patients is still unclear and there is a substantiated need to standardize oral care (63,65). Three protocols developed specifically for mechanically-ventilated patients encompass an oral assessment, a pediatric toothbrush, toothpaste, mouth rinses, and petroleum jelly for the lips with a frequency ranging from every 2 to 12 hours, and routine suctioning of secretions above the endotracheal tube (82,101). There are numerous methods and mouth rinses that can be used to improve oral hygiene in ventilator patients, but the most effective method with respect to concentration, frequency, and application is still unclear (29). The medical community continues to search for an effective standard of oral care. Some researchers have identified a unique element of oral care such as chlorhexidine gluconate (CHX) oral rinse. This antimicrobial reducing agent has been recognized as the “gold standard” for oral care (7,32,107,108).
Chlorhexidine gluconate is a cationic antiseptic compound solution that binds to the negatively charged hydroxyapatite of tooth enamel, the extracellular polysaccharide of plaque, and mucous membranes within the oral cavity inhibiting bacterial colonization and pellicle formation (57,65,81,109). Chlorhexidine reduces microbial adherence to the tooth and mucosal surfaces by attaching to the bacterial cell wall structures and altering the cell osmotic equilibrium. As a result, potassium and phosphorous leak and damage the cell contents (65). Therapeutic benefits of chlorhexidine include a reduction in bacterial plaque, gingivitis, and dental caries (57).

The use of preventive oral washes with chlorhexidine therefore seems reasonable in selected high-risk patients, given the easy administration and the reasonable costs (81). The use of oral antiseptic and antimicrobial agents to prevent nosocomial pneumonia has been widely studied, and based on what has been reported, changing the oral environment can reduce nosocomial pneumonia (19). When antimicrobial mouthrinses are used daily along with brushing and flossing, they are most effective in reducing plaque and gingivitis (110). Yet there are conflicting studies on whether antimicrobial solutions, used alone or in combination with chlorhexidine, may significantly improve the oral health of mechanically-ventilated patients (82,111).

This systematic review will address the importance of oral health and the increased risk of respiratory infections from colonization with harmful pathogens within the oral cavity. Furthermore, this review will investigate the efficacy of chlorhexidine, excluding other prevention measures, in reducing VAP. Risk factors including bacterial mechanisms of oropharyngeal colonization that contribute to acquiring ventilator-
associated pneumonia will be examined and prevention measures needed to prevent VAP will be detailed. The methods and results presented were determined from conducting a comprehensive literature search. For organizational purposes, the databases and terms used for the searches are documented in a table format. Results from each database include the number of articles retrieved, duplicate citations, and studies of interest for review. Articles from the literature search were carefully reviewed for relevance and evaluated as background information for clinical trials relating to chlorhexidine oral rinse. Clinical trials relating to the hypothesis of this thesis were evaluated using the Consolidated Standards of Reporting Trials (CONSORT) checklist for validity. All studies meeting the CONSORT criteria were separated into specific categories for a critical review and analysis. Based on the designated categories in the results section, the results from analyzing all clinical trials studies reflect strengths, weakness, and limitations in the discussion. This summary of data provides the best method to administer CHX oral rinse for all VAP protocols and evaluates the effectiveness of CHX oral rinse in preventing VAP, excluding other prevention measures. A brief synopsis of all content presented in the systematic review provides a concise list of prevention measures to reduce the incidence of VAP rates and recommendations for further research.
PUBLISHED STUDIES

This systematic review identifies published randomized clinical trials relating to the effectiveness of CHX gluconate (oral rinse) in preventing VAP. These intervention studies assess the efficacy of CHX gluconate (oral rinse) and provide recommendations for more specific measures for future clinical trials. To assist with analyzing CHX gluconate (oral rinse), a literature search was conducted to identify published randomized clinical trials studies relating to the efficacy of CHX gluconate oral rinse in preventing VAP. The electronic databases provided by Boston University Medical Center (BUMC) Alumni Medical Library’s educational resources were accessed to identify relevant evidence evaluating chlorhexidine pertaining to VAP reduction. Nine bibliographic databases, from 1965-2012 were used to conduct the literature inquiry. The databases searched included PubMed, Ovid, Gale Group, Medline, JSTOR, SAGE, Springerlink, Wiley, Biomedcentral, WorldCat, Science Direct, and Cochrane Library-Wiley. Online electronic databases accessed from Boston University Medical Campus (BUMC) Alumni Medical Library’s bibliographic and knowledge databases included British Medical Journal, American Journal of Critical Care, American Journal of Respiratory Care, American Chest, Academic Onefile, BioMedCentral, Elsevier ScienceDirect, New England Journal of Medicine, Journal of American Medical Association (JAMA), and Annals of Internal Medicine. Medical Subject Headings (MeSH) keywords utilized for PubMed included ventilator-associated pneumonia, oral rinse, chlorhexidine, mouthwash, prevention, nosocomial pneumonia, oral rinse, chlorhexidine gluconate, and VAP. A combination of MESH terms included chlorhexidine, ventilator, pneumonia,
VAP, oral care, mouth care. The aforementioned MESH combination keywords were also used for bibliographic and knowledge databases. Language of the study was not excluded from the original literature search, but foreign language randomized trials were not included in the systematic review. The bibliographic software RefWorks was used to record and manage references and retrieve journals. All results from the literature search were imported to the RefWorks software and organized into folders corresponding to the database accessed to produce the entry title. As shown in Figure 1, the initial search titles and abstracts were reviewed and examined thoroughly for meeting the inclusion criteria. Studies included in this systematic review included randomized controlled trial or clinical trial conducted on adult humans who were mechanically ventilated or treated with chlorhexidine gluconate oral rinse. The study participants exposed to CHX oral rinse used as an intervention, must also have had a clearly defined outcome such as decreasing potential respiratory pathogens located in the oral cavity and/or a declining VAP rate. Exclusion criteria were *in situ*, *in vitro* or of split-mouth design, if the chlorhexidine gluconate intervention could not be ascertained, or if outcomes were not clear. Entries also excluded for further evaluation included duplicate citations, those focusing on mechanically-ventilated patient groups under the age of 18, studies not available in full-text or the English language, product reports or abstracts, dissertations, and non-clinical trials focused on exposure other than the supplemental chlorhexidine use. The excluded studies were organized in the RefWorks software according to whether or not they met or the inclusion criteria and the reason(s) why the citation was not included in the systematic review.
Figure 1: Flow chart of systematic review process
The full text articles were retrieved for all titles and abstracts indicating that a citation was relevant for review, and then each full text article was reviewed. For studies that appeared to meet the inclusion criteria but a definite decision could not be made based on title and/or abstract, the full text article was retrieved for detailed assessment. Rejected citations were those that were evidently not related to the research question. A manual search in the library was also conducted on titles that seemed vague and did not have an abstract to determine if the article should be included or excluded. A manual search was executed for applicable references cited in the publications included in this literature review. The remaining articles included clinical trials, foreign language and English language abstracts.

Studies were read and data extracted for each of the included studies in the final review document. For the full text articles included, the author’s definition of VAP for each trial was accepted and then further evaluated based on the CDC guidelines. Studies were analyzed for quality and consistency of results from randomized control trials. The quality and strength of each randomized clinical trial was evaluated based on the requirements of the Agency for Healthcare Research and Quality (AHRQ). The quality and evaluation of studies that were included in this review were rated based on the domains and the associated elements shown in Table 1. The elements provided for each domain are in bold and were given a maximum score of 1.0; nonessential elements were given a maximum score of 0.25. Each article was scored from 0 to 13. For each study, data were extracted to develop Evidence Table 2 identifying population description, risk
assessment, statistical findings, and outcomes related to VAP prevention or decrease in pathogens related to the VAP intervention.

Table 1: Domain and Elements

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Table 1 (Cont’d): Domain and Elements

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Elements appearing in bold are considered Essential elements
Bolded items= 1pt, non bolded= 0.25 points; maximum total = 13pts
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<tr>
<th>Study (yr)(ref)</th>
<th>Subjects Risk status</th>
<th>Study Design</th>
<th>Duration</th>
<th>Experimental group (n)</th>
<th>Comparative group (n)</th>
<th>Outcome (exp versus control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeRiso et al. (1996)(108)</td>
<td>Population at risk: undergoing coronary artery bypass grafting, valve, or other open heart surgical procedures</td>
<td>Prospective, randomized, double-blind, placebo-controlled</td>
<td>10 months</td>
<td>0.5 fl oz of 0.12% CHX solution for 30s 2x/daily (173)</td>
<td>0.5 fl oz of placebo solution for 30s 2x/daily (180)</td>
<td>Incidence of total respiratory tract infections in the CHX-treated group/Control: (17/180 vs. 5/173; p&lt;0.05)</td>
</tr>
<tr>
<td>Genuit et al. (2001)(109)</td>
<td>Population at risk: Surgical ICU pts. requiring MV ≥ 48 hours</td>
<td>Prospective nonrandomized interventional trial</td>
<td>15 months</td>
<td>CHX protocol (WP+CHX): CHX oral rinse applied 2x daily with swab (56)</td>
<td>Oropharyngeal suctioning every 4hrs (39)</td>
<td>VAP rate 21.0 vs. 31.3, p&lt;0.025</td>
</tr>
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</table>
Table 2: Studies Included in Systematic Review (Con’t)

<table>
<thead>
<tr>
<th>Study (yr)(ref)</th>
<th>Subjects Risk status</th>
<th>Study Design</th>
<th>Duration</th>
<th>Experimental group (n)</th>
<th>Comparative group (n)</th>
<th>Outcome (exp versus control)</th>
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</thead>
<tbody>
<tr>
<td>Houston et al. (2002)(6)</td>
<td>Population at risk: undergoing aortoconary bypass or valve surgery requiring cardiopulmonary bypass</td>
<td>Prospective, randomized, case-controlled clinical trial</td>
<td>10 days or until extubation</td>
<td>15mL of PeriMixin, gargle in mouth for 30 secs pre-op and 2x daily for 10 days post-op (270)</td>
<td>15mL of Listerine, gargle in mouth for 30 secs pre-op and 2x daily for 10 days post-op (291)</td>
<td>Pna rate reduced by 58% (4/19 vs. 9/18; P = .06 Pts. highest risk for pna. 71% lower in PeriMixin group (intubated &gt;24 hrs) (2/10 vs. 7/10; P = .02)</td>
</tr>
<tr>
<td>Bellissimo-Rodrigues et al (2009) (110)</td>
<td>Population at risk: admitted to the ICU with length of stay ≥ 48 hours Individual risk: Mechanically ventilated pts.</td>
<td>Double-blind, randomized, placebo-controlled trial</td>
<td>1 year and 11 months</td>
<td>15mL of CHX oral rinse, 3x a day (once every 8 hours) for 1 minute (98)</td>
<td>15 mL of placebo, 3x a day (once every 8 hours) for 1 minute (96)</td>
<td>Incidence and VAP per 1,000 ventilator days (22.6 vs 22.3; P=.95); after adjustment for sex, age and length of stay RR= 1.0 [95% confidence interval [CII], 0.63-1.60]</td>
</tr>
<tr>
<td>Study (yr)</td>
<td>Subjects Risk status</td>
<td>Study Design</td>
<td>Duration</td>
<td>Experimental group (n)</td>
<td>Comparative group (n)</td>
<td>Outcome (exp versus control)</td>
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<tr>
<td>Scannapieco et al. (2009)(44)</td>
<td>Population at risk: admitted to ICU mechanically ventilated</td>
<td>Randomized, double-blind, placebo-controlled clinical trial</td>
<td>3 yrs 8 months</td>
<td>1st Experimental arm: 1x a day with 0.12% CHX and 1x a day oral with vehicle control (47) 2nd experimental arm: 2x daily with 0.12% CHX gluconate (about 8AM and about 8PM) (50)</td>
<td>2x a day oral topical applications of vehicle control (AM and PM) (42)</td>
<td>41% of reduction in the rate of pneumonia/placebo (odds ratio (OR) = 0.54, 95% CI): 0.23 to 1.25, P=0.1439</td>
</tr>
<tr>
<td>Segers et al. (2010)(111)</td>
<td>Population at risk: scheduled to undergo sternotomy for cardiothoracic surgery</td>
<td>Prospective, randomized, double-blind, placebo-controlled clinical trial</td>
<td>25 months</td>
<td>10mL chlorhexidine gluconate and nasal ointment for 30 secs 4x’s daily (485)</td>
<td>10mL placebo and nasal ointment for 30 secs 4x’s daily (469)</td>
<td>Incidence of LRTE (ARR of 6.5%, 95% CI, 2.3%-10.7%; P = .002; and 3.2%; 95% CI, 0.9%-5.5%; P = .002)</td>
</tr>
<tr>
<td>Study (yr)(ref)</td>
<td>Subjects Risk status</td>
<td>Study Design</td>
<td>Duration</td>
<td>Experimental group (n)</td>
<td>Comparative group (n)</td>
<td>Outcome (exp versus control)</td>
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<tr>
<td>0.12% Chlorhexidine solution</td>
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<tr>
<td>Grap et al. (2011)(112)</td>
<td>Population at risk: Trauma pts. requiring endotracheal intubation</td>
<td>Randomized intervention and control clinical trial</td>
<td>72 hours or until extubation</td>
<td>One 5 mL dose of CHX solution (.12%) applied w/swab (21)</td>
<td>Standard oral care that did not include CHX (18)</td>
<td>VAP after 48 hours or 72 hours Intervention/control: 33.3% (7/21) vs. 55.6% (10/18) CPIS at 72 hours Intervention/Control 1.49 +/- 1.11 (&gt;11% difference in CPIS) P = 0.27</td>
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<tr>
<td>2% Chlorhexidine gluconate Oral rinse</td>
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<tr>
<td>Tantipong et al. (2008)(113)</td>
<td>Adult pts. mechanically ventilated in ICUs</td>
<td>Randomized controlled trial and meta-analysis</td>
<td>15 months</td>
<td>Oral care 4x a day and rubbing the oropharyngeal mucosa with 15 mL of a 2% chlorhexidine solution (102)</td>
<td>Same oral care as CHX except 15mL of normal saline was used instead of 2% CHX solution (105)</td>
<td>Incidence of VAP: 4.9% (5 of 102) vs. 11.4% (12 of 105) (RR 0.43 [95% CI 0.16-1.17], P = .08)</td>
</tr>
<tr>
<td>Study (yr)(ref)</td>
<td>Subjects Risk status</td>
<td>Study Design</td>
<td>Duration</td>
<td>Experimental group (n)</td>
<td>Comparative group (n)</td>
<td>Outcome (exp versus control)</td>
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<tr>
<td>Ozeaka et al. (2012)(114)</td>
<td>Population at risk: Dentate pts. admitted to respiratory ICU and ventilated at ≥48hrs</td>
<td>Randomized, double-blind, controlled clinical trial</td>
<td>2 years</td>
<td>30 mL 0.2% CHX 1 min applications, 4x a day (at 6am, 12am, 6pm and 12pm) (29)</td>
<td>30mL saline applications, for 1min each, 4x a day (at 6am, 12am, 6pm and 12pm) (32)</td>
<td>VAP rate: 41% vs. 68.8%; (p = 0.03) with odds ratio 3.12 (95% confidence interval = 1.09 – 8.91)</td>
</tr>
<tr>
<td>Panchabhai et al. (2009)(115)</td>
<td>Population at risk: All pts admitted to the ICU</td>
<td>Concealed simple randomization</td>
<td>8 month study trial</td>
<td>10mL 0.2% chlorhexidine gluconate solution 2x daily (88)</td>
<td>10mL 0.01% potassium permanganate solution 2x daily using standard ICU protocol (83)</td>
<td>Nosocomial pna. 7.1% (16/224) vs. 7.7% (p = 0.82; relative risk, 0.93; 95% confidence interval, 0.49 to 1.76)</td>
</tr>
</tbody>
</table>
RESULTS

The total number of articles retrieved for the systematic review was 991. The number of duplicate citations was 95 which included both English and foreign articles. Out of the number retrieved, 946 entries were in the English language; 45 were foreign language entries with 31 retained for further review (See Figure 1). Pubmed produced the most entries when using a combination of key words totaling 538 entries; in which 127 of which met the qualifications for further review. From the entries accessed using OvidMedline and ScienceDirect databases, similar results were obtained. Out of the 94 articles produced by OvidMedline, 55 articles met the requirements for full text retrieval and review. Science Direct produced 104 articles for full text review. The Gale Group database produced 67 entries of which 57 were retrieved. Wiley produced 24 entries, 16 from Springerlink, and 11 from Sage. Many articles were not included due to being published in another language without available translation. Of the 39 foreign language titles, 10 warranted further evaluation. All 10 titles included English language abstracts but none were appropriate for inclusion in the final evaluation of articles. Other entries were from BU libraries and physical holdings. From the original literature search, 120 references were manually searched in the library. After reviewing or scanning the references from the initial search, 462 entries were accessed. From screening the abstracts, 330 journal entries were excluded. If the abstract was not available then the full text article was retrieved. Out of the 462 articles, 419 full text articles were assessed as meeting all the inclusion criteria. The remaining 122 full text articles that were excluded resulted in 10 studies meeting the inclusion criteria for this review. Of the ten studies
included in the final systematic review of chlorhexidine gluconate, information was gathered from each study, organized for further review and analysis.

A synopsis of the ten studies included in the final systematic review of chlorhexidine gluconate is presented in Table 2. These ten studies had populations ≥ 18 years of age, admitted to the intensive care unit receiving mechanical ventilation. The patients were at risk for VAP either from trauma, undergoing elective cardiothoracic surgery, or some other form of surgery. Results from this review were categorized by the various strengths of chlorhexidine used: 0.12% CHX oral solution [7 studies (6,47,112-116)], 2% CHX solution (117) and 0.2% CHX oral rinse [2 studies (118,119)].

Table 3 presents the overall quality score for each trial rated good in bold. The table also assesses the internal and external validity of the ten studies. The majority of the studies were of good quality in all domains. Internal validity includes the domain elements of randomization, blinding, clearly detailed interventions, and appropriate statistical analysis, all of which are valuable in strengthening the validity of the study. Four of the ten studies had quality scores rated as good, with representation in 0.12% and 0.2% categories of chlorhexidine gluconate but not for the category of 2% chlorhexidine gluconate oral rinse. When analyzing the ten studies with respect to at least three of the domains comprising internal validity, they were considered overall good quality studies. The independent study domains were evaluated as good in the following order: interventions, statistical analysis, blinding, and randomization. Three of the ten studies were of good quality (randomization, blinding, and statistical analysis) with all different strengths of chlorhexidine represented. For most of the studies, a quality rating of good
was noted in at least one domain. When assessing the internal validity of all of the quality domains, the well-detailed interventions had the highest value for strengthening the overall quality of each of the ten studies.

External validity or generalizability also predicts how applicable these findings may be to a larger community receiving mechanical ventilation than the study group. Subject characteristics taken into consideration included age, gender, and preexisting health conditions. Other factors taken into consideration when analyzing the findings included treatment regimen, and delivery of treatment. Five of the ten studies were rated as high quality overall with respect to external validity. However, three of the five studies with high quality scores and overall good internal validity also had good generalizability. This included two studies which evaluated 0.12% CHX solutions [Bellissimo-Rodrigues et al. (114) and Scannapieco et al. (47)] and one study evaluating 0.2% chlorhexidine gluconate [(Ozcaka et al (118)].
<table>
<thead>
<tr>
<th>Study</th>
<th>Overall Quality</th>
<th>Quality Domains Affecting Internal Validity</th>
<th>Generalizability (External Validity)</th>
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<td><strong>0.12% Chlorhexidine solution</strong></td>
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</tr>
<tr>
<td>DeRiso et al. (1998)</td>
<td>Fair</td>
<td>Randomization Good</td>
<td>Fair</td>
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<td></td>
<td></td>
<td>Blinding Poor</td>
<td>Consecutive patients undergoing CABG or other open heart surgical procedures</td>
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<td></td>
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<td>Interventions Good</td>
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<td>Stat. Analysis Poor</td>
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<tr>
<td><strong>Gemmiri et al. (2001)</strong></td>
<td>Fair</td>
<td>Randomization Poor</td>
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<tr>
<td></td>
<td></td>
<td>Blinding Poor</td>
<td>Surgical ICU patients, high risk, mean age &gt; 60</td>
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<td></td>
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<td>Interventions Fair</td>
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<td><strong>Houston et al. (2002)</strong></td>
<td>Poor</td>
<td>Randomization Good</td>
<td>Poor</td>
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<td></td>
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<td>Blinding Good</td>
<td>Patients underwent aorto-coronary bypass graft and/or valve surgery requiring cardiopulmonary bypass</td>
</tr>
<tr>
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<td></td>
<td>Interventions Poor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stat. Analysis Good</td>
<td></td>
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<tr>
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</tr>
<tr>
<td><strong>Bellissimo-Rodrigues et al. (2009)</strong></td>
<td>Good</td>
<td>Randomization Fair</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blinding Good</td>
<td>Mechanically ventilated ICU patients with chronic underlying disease and previous endotracheal intubations</td>
</tr>
<tr>
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<td></td>
<td>Interventions Good</td>
<td></td>
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<tr>
<td></td>
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<td>Stat. Analysis Good</td>
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<tr>
<td><strong>Scannapieco et al. (2009)</strong></td>
<td>Good</td>
<td>Randomization Good</td>
<td>Good</td>
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<td></td>
<td></td>
<td>Blinding Good</td>
<td>Trauma ICU with edentulous patients included</td>
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<td>Interventions Good</td>
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<tr>
<td><strong>Segars et al. (2010)</strong></td>
<td>Fair</td>
<td>Randomization Poor</td>
<td>Fair</td>
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<td></td>
<td>Blinding Poor</td>
<td>Patients scheduled for sternotomy for cardiothoracic surgery receiving preoperative selective decontamination of the digestive tract after</td>
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<td></td>
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<td></td>
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<tr>
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<td>Stat. Analysis Good</td>
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<tr>
<td><strong>Grap et al. (2011)</strong></td>
<td>Good</td>
<td>Randomization Poor</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blinding Poor</td>
<td>Trauma patients primarily male with a mean age of 43 years old</td>
</tr>
<tr>
<td></td>
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<td>Interventions Good</td>
<td></td>
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<tr>
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<td><strong>2% Chlorhexidine gluconate Oral rinse</strong></td>
<td></td>
<td>Randomization Fair</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Tantipong et al. (2008)</strong></td>
<td>Fair</td>
<td>Blinding Poor</td>
<td>Hospitalized ICU patients at a Tertiary care university hospital</td>
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<td></td>
<td></td>
<td>Interventions Good</td>
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<td></td>
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<td>Stat. Analysis Fair</td>
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<tr>
<td><strong>0.2% Chlorhexidine gluconate oral rinse</strong></td>
<td></td>
<td>Randomization Good</td>
<td>Good</td>
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<tr>
<td><strong>Ozazka et al. (2012)</strong></td>
<td>Good</td>
<td>Blinding Good</td>
<td>Study conducted in respiratory ICU</td>
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<td>Interventions Good</td>
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<td>Stat. Analysis Good</td>
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<tr>
<td><strong>Panchabhai et al. (2009)</strong></td>
<td>Fair</td>
<td>Randomization Poor</td>
<td>Good</td>
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<td></td>
<td></td>
<td>Blinding Fair</td>
<td>All patients admitted in tertiary care teaching hospital</td>
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<td></td>
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<td>Interventions Good</td>
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<td>Stat. Analysis Good</td>
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The category of 0.12% chlorhexidine solution presents the strongest evidence in Table 2. Seven of the studies included in this review used 0.12% chlorhexidine and, focused on patients 18 years of age and older admitted to the ICU with a prospective length of stay and who were at low to high risk for VAP. Each study had a specification on the number of times throughout a 24 hour period in which 0.12% chlorhexidine was applied to each subject. Three studies in this category focused on a low-risk population of cardiovascular surgery patients. These studies seemed to show conflicting results with respect to whether or not 0.12% CHX was significant in reducing the development of VAP. The most significant reduction in VAP, especially for patients undergoing cardiac surgery, was seen in DeRiso et al. with 69% reduction in total respiratory tract infections (112). In this study, 353 cardiac surgery subjects, who were admitted to a surgical ICU, were divided into two groups. A test group of 173 people who received a 0.12% chlorhexidine oral rinse twice a day and a control group of 180 subjects who received a placebo rinse. This study demonstrated that the use of the oral antiseptic chlorhexidine significantly reduced rates of nosocomial infection and VAP in a low-risk population of patients undergoing coronary artery bypass surgery (7,120). A prospective, randomized, case-controlled clinical trial conducted by Houston et al. tested the effectiveness of 0.12% CHX gluconate oral rinse on 561 patients undergoing aortocoronary bypass or valve surgery patients, (experimental =270 and control = 291). The intervention involved oral care with 15mL of Peridex or Listerine™ preoperatively and postoperatively. Unlike Peridex, Listerine™ is a nonsubstantive agent that has properties similar to Peridex (0.12% CHX gluconate) in that it kills bacteria immediately upon application but does
not persist in tissues (6). Overall, use of chlorhexidine oral rinse reduced the total nosocomial respiratory infection rate and the use of nonprophylactic systemic antibiotics in patients who had heart surgery. Peridex oral rinse decreased microbial colonization of the respiratory tract and hospital-acquired pneumonia in patients undergoing open-heart surgery. However, the difference was not significant in patients intubated more than 24 hours who had the highest degree of bacterial colonization (6). The results showed that the overall rate of hospital-acquired pneumonia was reduced by 52% but the reduction was not significant (4/270 vs. 9/291; P = (0.21) in patients treated with Peridex chlorhexidine gluconate when compared to patients treated with Listerine™ (8,26). Houston et al. compared chlorhexidine rinse to Listerine® and found no statistically significant difference in the pneumonia rate between the 2 groups (43). The final study that focused on cardiovascular patients was by Segers and coworkers. They focused on the efficacy of 0.12% CHX solution and 0.12% nasal ointment for patients preoperatively and postoperatively. The study included 991 patients who received CHX and nasopharynx decontamination (n = 500) or placebo (n = 491). All patients were older than 18 years of age and were scheduled to undergo sternotomy for cardiothoracic surgery. The treatment group received 10ml of oropharyngeal 0.12% CHX rinse and 0.12% CHX nasal ointment 4 times a day until the nasogastric tube was removed. Usually the nasogastric tube was removed the day after surgery. The control group received 10ml of oropharyngeal rinse and nasal ointment placebos. Any lower respiratory tract infection (LRTI), such as pneumonia, occurring during a hospital stay or within 48 hours after discharge was considered an infection related to a surgical procedure. They
found lower respiratory tract infections were less common in the chlorhexidine gluconate group, 9.3% compared to the placebo group, which was 15.8% (ARR, 6.5%; 95% CI, 2.3%-10.7%; P = .002). An incidence of LRTI was found in 119 patients (12.5%), which achieved a relative risk reduction of more than 60% in patients decontaminated with chlorhexidine gluconate. Decontamination of the nasopharynx with chlorhexidine gluconate resulted in a clinically important reduction in LRTI. Significant reductions were found in nosocomial infections in patients undergoing cardiac surgery and treated with chlorhexidine gluconate. It is effective in decontamination of the nasopharynx and oropharynx, resulting in less LRTI.

The other group of subjects evaluated in two other studies also using 0.12% CHX rinse focused on a particular population of surgical patients. However, these studies included a population of postoperative patients, whose clinical baseline characteristics and risks of nosocomial infections very different from those of a general medical ICU population. Genuit et al. implemented a weaning protocol (WP) along with the 0.12% CHX solution administered to 95 surgical subjects twice daily (113). Patients in the WP + CH group showed both a decreased incidence of pneumonia as well as a delay in the occurrence of VAP compared with the control group (113). Genuit et al. compared the early VAP phase WP group and control group and found that the risk of developing VAP increased significantly from 12.5% to > 45%. When CHX was added to the WP, there was only a moderate increased risk in VAP from 3.5% to 18%. A significant decrease was shown in the VAP rate for the WP + CHX group (21.0) with a 33% reduction compared with the control, p < 0.025) (113). The addition of oral care to a protocol of
weaning from mechanical ventilation led to a significant reduction of late-onset VAP (8). Grap utilized a block randomization scheme for 145 trauma patients requiring endotracheal intubation randomly assigned to the intervention or control group (116). Seventy percent of the patients were male, and 60% were white; their mean age was 42.4 years (±18.2). The 74 patients in the control group received standard endotracheal intubation and oral care that did not include CHX. The 71 patients in the intervention group received one 5mL dose of 0.12% CHX solution applied with a swab to all areas of the oral cavity. The VAP Clinical Pulmonary Infection Score was used to measure the VAP development rate on study admission and at 48 and 72 hours after intubation. Subjects without pneumonia where classified as having a baseline of CPIS <6. After 48 to 72 hours the intervention group had only 33% of their subjects with VAP whereas the control had 55.6%. A significant treatment effect was found on CPIS both from admission to 48 hours (P = 0.020) and to 72 hours (P = 0.027). An early, single application of CHX to the oral cavity significantly reduced CPIS and thus VAP in trauma patients. Since it is difficult to distinguish the pulmonary inflammation of sepsis from VAP, it may also be difficult to attribute all the differences in CPIS to the development of VAP alone.

Scannapieco et al. is the only study out of the seven studies using 0.12% CHX oral rinse that compared two different CHX protocols with the control group and observed a 41% reduction in VAP between the experimental and placebo group. The study included a control group (49 patients) and two intervention groups receiving CHX 0.12% either once (47 patients) or twice daily (50 patients). There was no statistically
significant difference when the two groups, one versus two applications of 0.12% CHX oral rinse were compared to each other with regard to the reduction of VAP development (47,118,121,122). Estimated reductions in colonization were 25% and 30% in the ‘twice-daily’ and ‘once-daily’ groups, respectively. The number of *Staphylococcus aureus* colony-forming units, a well-known colonizing potential respiratory pathogen (PRP), in dental plaque was reduced in both intervention groups, but no significant reductions were observed in the total number of respiratory pathogens or incidence of VAP (47,118,121,122). Scannapieco et al. postulated that the standardized oral-care regime for this particular study used in the ICU was effective in reducing the number of organisms in dental plaque to a level where additional reductions by CHX were not detectable, or other factors such as suctioning could have reduced the effect of the CHX oral rinse (118). Scannapieco et al. reported that there were no significant differences between one or two applications of 0.12% CHX rinse with regard to the reduction of VAP development (47,118,121,122). Oral application of a 0.12% solution of chlorhexidine was effective in reducing the number of PRPs in dental plaque, but not superior to the placebo in preventing respiratory tract infection among ICU patients.

A study by Bellissimo-Rodrigues et al. used a double-blind, randomized, placebo-controlled trial comprising 194 participants admitted to the ICU with a prospective length of stay greater than 48 hours. The patients were divided into two randomized groups: those who received 15ml of 0.12% chlorhexidine (n=98) and those who received 15ml of placebo (n=96) three times a day throughout the duration of the patient’s stay in the ICU. Rates of ventilator-associated pneumonia per 1,000 ventilator-days were similar between
both experimental and control groups (22.6 vs. 22.3; P = .95). There was no report in improvement in the incidence of pneumonia, mortality or the overall incidence of respiratory tract infections between the two groups (114). The 0.12% CHX solution showed the preventive measure’s relative risk (RR) =1.00 (95% confidence interval [CI], 0.63-1.60) after adjustment for sex, age, and LOS in the ICU. When analyzing the secondary endpoints, there was no significant difference in respiratory tract infection-free survival time, duration of mechanical ventilation, antimicrobial use either for respiratory infections or for any purpose, or LOS in the ICU. The data clearly indicated that oral application of a 0.12% solution of chlorhexidine was not superior to a placebo for the prevention of respiratory tract infection among ICU patients. Yet, for ICU patients, 0.12% CHX oral solution would be enough to minimize oral and tracheal microbial proliferation. The results suggest that oral application of a 0.12% solution of chlorhexidine does not prevent respiratory tract infections in ICU patients, although it may retard their onset.

Tantipong et al. used a stronger solution of CHX on patients in the ICU and medical wards. They used 2% chlorhexidine and measured the development of VAP and oropharyngeal colonization with Gram-negative bacilli (117). The study was conducted at Siriraj Hospital in Bangkok, Thailand. This study included all patients who underwent mechanical ventilation for more than 48 hours (117). The mean duration of mechanical ventilation was approximately 5 days, but only 43% of patients in the test group and 50% of patients in the control group received ventilation for more than 48 hours (117). Patients were randomized by sex into two groups: the chlorhexidine group (n=102) and
the normal saline group (n=105) (117). Each group received either 15ml of 2% chlorhexidine solution or 15ml of normal solution four times a day until the endotracheal tube was removed (117). The authors were unable to perform a double-blind study because the odor of chlorhexidine is very distinctive and could not be imitated (117,123). In order to avoid biases, the observer was unaware of how patients were assigned to each group. Many of the patients in the general medical ward were more stable than patients in the ICU, although they normally would have been kept in the ICU (117). Patients ended up in the general medical ward as a result of limited capacity in the ICU, which is sometimes the norm in developing counties (123). However the care of a patient who receives ventilation in the medical ward or ICU could not be compared with respect to regular protocols, parenteral antibiotic policy, and patient positioning (117). Approximately 60% of patients admitted to their study were adults who received ventilation in intensive care units (ICUs) (mainly surgical ICUs), whereas 40% received ventilation in general medical wards (117). Although use of chlorhexidine reduced the risk of VAP by approximately 55% in the overall population and among patients who received mechanical ventilation for more than 2 days, this reduction was not statistically significant, because both relative-risk (RR) calculations had large 95% confidence intervals (CIs) (RR, 0.43 [95% CI, 0.16–1.17] for study patients who received mechanical ventilation and oral decontamination (117). The Tantipong et al. study was not generalizable because it included patients who were mechanically ventilated ≤ 48 hours (117). Efficacy was demonstrated by the incidence of VAP, 4.9% (5 of 102) and 11.4% (12 of 105) for the CHX group and the normal saline group, respectively (117).
The study showed a significant (P = 0.04) reduction for the intervention group in the number of episodes of pneumonia per 1,000 ventilator-days, but this reduction was not statistically significant (P=0.06) when the authors evaluated only patients who received mechanical ventilation for more than 48 hours, which is an acceptable period for the diagnosis of VAP (11). They also showed that the nosocomial infection rate was decreased by as much as 65% in patients treated with chlorhexidine when compared with patients who received placebo (19). Along with the reduction in the incidence of VAP, 2% CHX also decreased or delayed the rate of oropharyngeal colonization with potential respiratory pathogens (PRPs) such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* (117). These PRPs have the ability to cause upper and lower respiratory tract infections such as VAP. Irritation of the oral mucosa was observed in ten (9.8%) of the patients in the chlorhexidine group and in one (0.9%) of the patients in the normal saline group (P=0.001) (117). Oropharyngeal colonization with Gram-negative bacilli, which are PRPs, was either reduced or delayed in the chlorhexidine group (117).

Two studies focused on 0.2 % chlorhexidine which is not as strong as the 2% used in Tantipong et al. study (117-119). Panchabhai and colleagues reported the results of a randomized trial of oropharyngeal cleansing with a 0.2% chlorhexidine solution twice daily vs. a 0.01% potassium permanganate solution as a control in patients who had been admitted to a combined medical-neurologic ICU in a 1,800-bed tertiary care teaching hospital in Mumbai, India, during the 8-month study period. There were 512 patients introduced to concealed randomization with an open label design. The 512 were
randomized to either the chlorhexidine group (n=250) or the control group (n=262). Out of the large randomized group only approximately one third of patients enrolled in the trial were actually intubated and receiving mechanical ventilation. The CHX group received oropharyngeal cleansing with a 0.2% chlorhexidine solution twice daily vs. a 0.01% potassium permanganate solution twice daily tested for the control group. Out of 471 subjects who completed the study protocol, oropharyngeal disinfection with a 0.2% CHX solution in critically ill patients did not decrease the incidence of pneumonia. The incidence of nosocomial pneumonia was found in 16 of 224 subjects (7.1%) in the chlorhexidine group and 19 of 247 subjects (7.7%) in the control group (p = 0.82; relative risk, 0.93; 95% confidence interval, 0.49 to 1.76). As expected, among mechanically-ventilated patients, the rates of pneumonia were considerably higher (chlorhexidine group, 15.9%; potassium permanganate group, 18.1%), but the sample sizes may not have been large enough to detect a significant difference in VAP rates between these groups, given the relatively low number of intubated patients (10). The incidence of VAP in patients in the study during the 6-month period, including three months of patients before the start of the study and three months after the study, was significantly higher. During this non-study period, nosocomial pneumonia developed in 21.7% subjects, which was significantly higher than the 7.4% incidence of nosocomial pneumonia observed during the study period (p< 0.001; relative risk, 0.34; 95% confidence interval 0.24 to 0.49). Panchabai et al. showed a decrease in the incidence of nosocomial pneumonia for both study groups when oral hygiene was implemented, however oropharyngeal cleansing with 0.2% chlorhexidine solution was not superior to oral
cleansing with the control solution (119). Nosocomial pneumonia also developed in fewer subjects (35 of 471 subjects [7.4%]) than in the three months preceding and following the study (98 of 452 subjects [21.7%]; p < 0.001; relative risk, 0.34; 95% confidence interval, 0.24 to 0.49). Oropharyngeal cleansing with 0.2% chlorhexidine solution was not superior to oral cleansing with the control solution. However, the decreased incidence of nosocomial pneumonia during the study period suggests a possible benefit of meticulous oral hygiene in ICU patients.

Özçaka et al. studied 61 dentate patients in a respiratory ICU, scheduled for mechanical ventilation for at least 48 hours. The randomized double-blind, controlled study provided oral care to these 61 patients randomized to a control group or a treatment group receiving oral swabs of 30ml of normal saline or 30ml of 0.2% CHX, respectively. In order to quantitatively determine whether or not patients developed VAP or PRPs, specimens were obtained from the lower respiratory tract. Specimens were obtained at each sampling timepoint, e.g. on admission and on day seven of intubation, or when suspected VAP occurred using a minibronchoalveolar lavage (mini-BAL). A microbiological analysis was conducted on the lower respiratory tract specimens during admission and when VAP was suspected. Colonies were quantified using standard culture techniques to identify pathogens. The samples from the mini-BAL included potential respiratory pathogens (S. aureus, P. aeruginosa, Acinetobacter species, and the enteric species Klebsiella pneumoniae, Serratia marcescens, Escherichia species, Proteus mirabilis and Escherichia coli). Acinetobacter baumannii was the most common pathogen (64.7%) of all species identified. The results from the specimens identified
ventilator-associated pneumonia development in 34/61 patients (55.7%) within 6.8 days. VAP development rate was significantly higher in the control group than in the CHX group (68.8% vs. 41.4%, respectively; p = 0.03). The rate of VAP occurrence in the control group was significantly higher than in the CHX group with an odds ratio of 3.12 (95% confidence interval = 1.09-8.91, p = 0.03). Twenty-two patients (68.8%) in the control group and 12 patients (41.4%) in the CHX group were diagnosed with VAP. There were no significant differences with regards to duration of VAP development between the CHX and control groups.

In conclusion, within the limits of the present study, it is suggested that oral care in ICU patients which includes application of 0.2% CHX four times a day, reduces the risk of VAP development. This means that the association between nosocomial pneumonia may be related to oral hygiene and not related to periodontal systemic disease interactions. Swabbing four times daily with 0.2% CHX reduced significantly the number of patients with VAP compared with the control. Findings of this systematic review strongly support its use in ICUs and indeed the importance of adequate oral hygiene in preventing medical complications.
DISCUSSION

Modulation of oropharyngeal colonization by the use of oral chlorhexidine has prevented ICU-acquired HAP in selected patient populations such as those undergoing coronary bypass grafting, but its routine use is not recommended until more data become available (7). Oral care is supported by previous studies and believed to reduce the risk of VAP development in mechanically-ventilated patients (118). This review looked at the best intervention performed in hospital environments to evaluate the efficacy of chlorhexidine in reducing the incidence of VAP.

This systematic review of clinical trials presents a mixture of evidence for effectiveness of chlorhexidine gluconate oral rinse use on high-risk adult mechanical ventilator patients. All authors have substantiated the need to standardize oral care for a variety of reasons, the most compelling of which is to prevent or lower VAP rates in mechanically-ventilated patients (63). As identified in Table 4, three types of CHX oral rinse were identified. For the various modes of CHX, there were studies that supported CHX oral rinse and were well executed and reported. The studies in this review revealed conflicting findings for the use of CHX oral rinse in preventing VAP.
<table>
<thead>
<tr>
<th></th>
<th>Author</th>
<th>% of CHX</th>
<th>Total Subjects</th>
<th>Experimental</th>
<th>Control/Placebo</th>
<th>ARR</th>
<th>RRR</th>
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<tr>
<td>1.</td>
<td>DeRiso et al. (1996)</td>
<td>0.12% CHX Oral Rinse</td>
<td>N = 353</td>
<td>n = 173</td>
<td>Lower resp. NI n = 3</td>
<td>0.03</td>
<td>0.65</td>
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<td>Lower resp. NI n = 9</td>
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<td>2.</td>
<td>Houston et al. (2002)</td>
<td>0.12% CHX Oral Rinse</td>
<td>N = 561</td>
<td>n = 270</td>
<td>Nosocomial Pna: n = 4</td>
<td>0.02</td>
<td>0.52</td>
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<td>Nosocomial Pna: n = 9</td>
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<td>3.</td>
<td>Tantipong et al. (2008)</td>
<td>2% CHX Oral Rinse</td>
<td>N = 207</td>
<td>n = 102</td>
<td>VAP: n = 5</td>
<td>0.07</td>
<td>0.57</td>
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<td>Rate per episodes: n = 7</td>
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<td>VAP: n = 12</td>
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<td>Rate per episodes: n = 22</td>
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<td>4.</td>
<td>Bellivismo-Rodrigues et al (2009)</td>
<td>0.12% CHX Oral Rinse</td>
<td>N = 194</td>
<td>n = 98</td>
<td>Cases of VAP: n = 16</td>
<td>0.014</td>
<td>0.08</td>
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<td>Cases of VAP: n = 17</td>
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<td>5.</td>
<td>Pauchabhai et al. (2009)</td>
<td>0.2% CHX Oral Rinse</td>
<td>N = 171</td>
<td>n = 88</td>
<td>nosocomial Pna: n = 14</td>
<td>0.02</td>
<td>.11</td>
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<td>nosocomial Pna: n = 15</td>
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<td>6.</td>
<td>Scannapieco et al. (2009)</td>
<td>0.12% CHX oral rinse</td>
<td>N = 146</td>
<td>CHX once a day: n = 47</td>
<td>Pna = 7</td>
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<td>n = 42</td>
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<td></td>
<td>Pna = 12</td>
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<td>7.</td>
<td>Segars et al. (2010)</td>
<td>0.12% solution oral rinse</td>
<td>N = 954</td>
<td>n = 485</td>
<td>Lower resp. infection: n = 45</td>
<td>0.06</td>
<td>0.412</td>
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<td>Lower resp. infection: n = 74</td>
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<td>8.</td>
<td>Genuit et al. (2011)-prospective study</td>
<td>0.12% oral rinse</td>
<td>N = 95</td>
<td>n = 56 (WP=CHX) VAP rate reported per 1,000 ventilator days: VAP n = 12</td>
<td>0.09</td>
<td>0.303</td>
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<td>31.3 Vaps reported per 1,000 ventilator days: VAP: n=12</td>
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<td>9.</td>
<td>Grap et al. (2011)</td>
<td>12% Oral Rinse</td>
<td>N = 39</td>
<td>n = 21</td>
<td>VAP: n = 7</td>
<td>0.22</td>
<td>0.40</td>
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<td>VAP= 10</td>
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<td>10.</td>
<td>Ozcaka et al. (2012)</td>
<td>0.2% CHX oral rinse</td>
<td>N = 61</td>
<td>n = 29</td>
<td>VAP: n = 12</td>
<td>0.27</td>
<td>0.40</td>
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<td>VAP= 22</td>
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Table 4: Risk Ratio
Studies included in the final review both supported and did not support the use of CHX oral rinse. Four out of ten studies evaluating CHX rinses had an overall quality rating of good. Two studies focused on 0.2 % chlorhexidine which is not as strong as the 2% used in Tantipong et al. study (117-119). Ozcaka et al. and Panchabhai et al, applied the 0.2 % chlorhexidine from two to four times daily (118,119). Ozcaka et al, demonstrated a rate of VAP occurrence in the control group that was significantly higher than in the CHX group (118). From Scannapieco and colleagues’ study we can conclude that twice daily is not necessarily better than once daily, but maybe a four times daily regimen with 2% instead of 0.12% CHX does make a difference (12). In a study (24) of patients undergoing cardiac surgery, use of chlorhexidine decreased the incidence of VAP by decreasing colonization of VAP by bacteria that can cause VAP (31). Bellissimo-Rodrigues et al. showed that 0.12% CHX was not superior to the placebo and did not prevent respiratory tract infections. Three other studies showed a reduction in VAP but were not significant enough to predict that CHX oral rinse will prevent VAP. Recently, the antiseptic chlorhexidine gluconate (0.12%) was used successfully as a perioperative oral rinse to decrease the overall incidence and demonstrated prevention of nosocomial respiratory tract infections in patients who underwent cardiac surgery (18). However, its use for preventing healthcare associated pneumonia in other groups of patients at high risk for this infection has not been evaluated (43). Three out of the four studies found the CHX oral rinse to be effective in preventing VAP. Chlorhexidine at 0.1-0.2 is recommended as the most effective antiplaque agent (65).
Adult mechanically-intubated patients considered to be at high-risk for VAP were subcategorized as low to high-risk patients based on the reason for mechanical ventilation. For instance, a patient intubated for a surgical procedure would be considered low risk for developing VAP whereas a patient intubated due to respiratory failure is considered a high-risk patient for VAP. Surgical procedure patients are less likely to stay on the ventilator for more than a day, which reduces their chances for developing VAP. In studies of cardiovascular, surgical, and trauma patients who were mechanically ventilated, a reduction in VAP was observed when CHX was used. Selected studies supporting the use of CHX in reducing VAP did not always produce statistically significant results. Some studies did produce results in reduction of oral colonization of PRPs and incidence of VAP. However other studies also showed a reduction of PRPs when using CHX yet VAP rates were still high. Then there are investigators in other selected studies reporting oral care with CHX to be effective in combating PRPs but without influence on VAP rates (124). These trials have yielded conflicting results.

Three of the ten studies included subjects who were receiving some type of cardiothoracic surgery, whether it was coronary artery bypass grafting (CABG) and/or valve replacement (6,112,115). Considering the specific patient population with low risks, CHX oral rinse as a preventive measure for VAP has been evaluated before in two trials among cardiac-surgical patients (21,120,125). There are, however, important differences between elective surgery and the emergency surgery populations that influence oral care strategies. Elective surgery subjects are likely to have different comorbidities and better physiologic status at the time of intubation than emergently
intubated patients. However, cardiac surgery patients who have elective surgery most likely have different comorbidity conditions and better physiological status at the time of intubation than do patients in the general adult ICU population. Studies in patients having elective cardiac surgery focused broadly on nosocomial infection (including surgical infection and tracheobronchitis) rather than on VAP (126).

Current evidence does not conclusively support the routine use of chlorhexidine in mechanically-ventilated patients other than those patients who have just undergone cardiac surgery. Some studies are not generalizable and included subjects who were at high-risk and could not be extubated within 24 hours. As patients are receiving mechanical ventilation for an extended period of time i.e., longer than 24 hours, this allows for opportunistic pathogens to multiply and colonize. Some of these studies included those subjects undergoing cardiothoracic surgery (6,47,112,114). The oral care recommendations are general, and evidence available when the guidelines were updated was insufficient for making a recommendation for use of chlorhexidine in the general ICU population (126). Oral decontamination with chlorhexidine in different concentrations is also considered a strategy for reducing the incidence of VAP (118). The meta-analysis by Pineda et al. included only four randomized control trials (RCTs) and was unable to demonstrate a significant reduction by using chlorhexidine solution in various concentrations for oral care (127). The efficacy of CHX is difficult to discriminate between control and experimental groups when other prophylactic measures are used in addition to CHX. The question that arises is how reliable are these studies that state that CHX reduces VAP. For instance, along with 0.12% CHX solution, the subjects
in the Segers et al. study used 0.12% CHX nose ointment in both nostrils. Patients in the control group received more nonprophylactic antimicrobials. Therefore it is not possible to determine if there is a difference in the mouth or the nose decontamination in reducing VAP. In De Riso et al., all patients received standard oral care. It is difficult to distinguish the role of the chlorhexidine in reducing VAP when the surgical patients have perioperative prophylaxis with parenteral antibiotics. It is not possible to discern if the reduction in VAP is due to the CHX or the other prophylactic measures.

No recommendation can be made for the routine use of an oral chlorhexidine rinse for the prevention of healthcare-associated pneumonia in all postoperative or critically ill patients or other patients at high risk for pneumonia (43). However, these studies included a population of postoperative patients, whose clinical baseline characteristics and risks of nosocomial infections were very different from those of a medical ICU population (8). Recommendations for patients having elective cardiac surgery include the use of chlorhexidine during the perioperative period and are based on the results of several studies in which patients began using chlorhexidine before hospital admission for elective cardiac surgery and chlorhexidine use was continued throughout the hospital stay. Not only are these studies not generalizable, but they also have demonstrated inconsistency of CHX effectiveness among mechanically-ventilated patients. Studies like Tantipong et al. are more generalizable since they included patients who were intubated more than 48 hours (117). The Scannapieco et al. study was of good quality but not generalizable because it included only white male subjects.
From this review, oral care performed regularly with an antiseptic solution is of high importance regardless of the optimal frequency and concentration of the solution (15). Regimens and concentrations, and dosing frequencies varied among the studies evaluated in this review and sometimes were not carefully described (12). For example, one study used 0.12% CHX twice daily to 2% CHX four times a day (12). In addition, patient populations varied widely from mixed ICU populations [9,12] to surgical ICU patients [10] and patients undergoing cardiac surgery [8,11,13] (12).

This safe and inexpensive disinfectant is effective in decontaminating the nasopharynx and oropharynx, resulting in less LRTI, and should be considered in the preoperative preparation of a patient undergoing cardiac surgery. Any of the at-risk patients excluded from this study, would be of interest for further research to compare chlorhexidine gluconate with a more selective decontamination of the digestive tract protocol, which uses antibiotics and has an increased risk of promoting microbial resistance. What we need now are well-designed and adequately powered studies to evaluate the effects of CHX on length of ICU stay and survival. If these effects were demonstrated, chlorhexidine selective oropharyngeal decontamination would offer a very cheap and (ecologically) safe infection prevention measure in patient populations increasingly suffering from lower respiratory tract infections (12).
References


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PERSONAL

Year of Birth: 1979
Place of Birth: David Grant USAF Medical Center
Travis Air Force Base, Fairfield, CA

EDUCATION

2008 – 2015 Master of Science Concentration Oral Health Candidate
Boston University Graduate School of Medical Sciences,
Boston, MA
Thesis: The effectiveness of Chlorhexidine Gluconate (mouth rinse) in Preventing Ventilator-Associated Pneumonia

2003 – 2005 Master of Public Health-
Environmental and Occupational Health
Florida A&M University College of Pharmacy and Pharmaceutical Sciences Institute of Public Health, Tallahassee, FL
Special Project: A Modified Risk Assessment on the Wet Removal Methods of Asbestos Containing Materials Prior to Demolition

1997 – 2003 Bachelors of Science in Cardiopulmonary Sciences
Florida A&M University
School of Allied Health Sciences, Tallahassee, FL
**WORK EXPERIENCE**

2013 – 2015  **Wellstar- Kennestone Regional Medical Center**- Marietta, GA  
*Registered Respiratory Therapist*

**Duties:** Implement respiratory care based on expanded knowledge, knowledgeable on ventilatory protocols, proficient in intensive care and emergency department patient care areas, served as an agency therapist  
**Respiratory Care Director:** Mr. Scott Cochran

2013  **Peregrine's Landing at Peachtree Creek** - Smyrna, GA  
*Supervisor of Memory Community Care Facility*

**Duties:** Evaluate medical records, progress notes, and incident reports, regulate distribution of medication and resident care supplies, reconcile daily concerns of staff, resident, and family members, liaison between management and physicians  
**Executive Director:** Ms. Kimberlee Kelly

2010  **Boston Medical Center**- Boston, MA  
*Registered Respiratory Therapist*

**Duties:** Evaluate appropriateness and implement care plan for a team approach, managed ventilator and analyze reports for future recommendations, elicit patient cooperation with accurate explanation and instructions, provide adequate resources by serving as charge/lead therapist  
**Director:** Mr. Charlie O’ Donnell

2008  **Florida A&M University** - Tallahassee, FL  
*Adjunct Clinical Instructor*

**Duties:** Assign, monitor, evaluate, and assess cardiopulmonary students in various clinical settings, appraise students clinical performance, faculty liaison between healthcare facilities and students  
**Director:** Mr. Patrick. L. Johnson, Jr., PhD, RRT, FAARC

2006 - 2008  **Tallahassee Memorial Hospital** - Tallahassee, FL  
*Registered Respiratory Therapist*

**Duties:** Demonstrate and modify respiratory care plans utilizing assessment skills to evaluate patient’s response to plan of care, execute advance/basic life support  
**Director:** Ms. Mary Lesher, MBA, RRT
2002 - 2008  **Capital Regional Medical Center** - Tallahassee, FL  
*Respiratory Therapist/ Hyperbaric Chamber Technician*

**Duties:** Facilitate in monitoring patients’ cardiac changes during therapeutic procedures, operate and monitor hyperbaric treatments for proper safety measures, perform quality control measures for ventilators and blood gas machines  
**Director:** Mr. Curt Varner, RRT

**LICENSURES/ CERTIFICATIONS**

- **2014 - 2016**  
  American Heart Association  
  Basic Life Support for Healthcare Providers  
  (CPR and AED) Program

- **2014 - 2016**  
  Advanced Cardiac Life Support Provider (ACLS)  
  American Heart Association for the Advanced Life Support

- **2015 - 2017**  
  State of South Carolina  
  Dept. of Labor, Licensing and Regulation  
  Board of Medical Examiners  
  **Licensure:** Respiratory Care Practitioner  
  **License No:** TL5625

- **2012 - 2017**  
  State of Georgia  
  Georgia Composite Medical Board  
  Respiratory Care Professional  
  **Licensure:** Registered Respiratory Therapist  
  **License No:** 8865

- **2009 - 2014**  
  Commonwealth of Massachusetts  
  Board of Registration in Respiratory Care  
  **Licensure:** Registered Respiratory Therapist  
  **License No:** RT9706

- **2007 - 2011**  
  Florida Department of Health  
  Board of Respiratory Care  
  **Licensure:** Registered Respiratory Therapist  
  **License No:** RT8805

- **2007 - Present**  
  Credentialed by National Board of Respiratory Care as a Registered Respiratory Therapist (RRT)
RESEARCH

2008
A Modified Risk Assessment on the Wet Removal Method of Asbestos Containing Materials Prior to Demolition
Florida A&M University, College of Pharmacy and Pharmaceutical Sciences Institute of Public Health, Tallahassee, FL
Duties: Collect and analyze the air-sampling data from Florida High School demolition sites, quantitatively estimate the hazard potential of asbestos, integrate risk assessment results for protecting construction worker safety
Special Project Advisor: Adrienne Hollis, PhD Toxicologist

2005
Occupational Health Intern- Capital Regional Medical Center (CRMC)
Graduate Internship - Tallahassee, FL
Duties: Research protocols for Bacille Calmette-Guérin (BCG) vaccines and Purified Protein Derivative (PPD) testing in Hospital Corporation (HCA) facilities, propose recommendations for treating health care workers with BCG vaccination, assist in developing new policy for CRMC
Supervision: Department of Human Resources and Occupational Health

2004
Tallahassee/Immokalee, Florida Research Assistant
Florida A&M University College of Pharmacy and Pharmaceutical Sciences, Tallahassee, FL
Co-PI: Cynthia, Harris, PhD, DABT and Linda S. Forst, MD, Ms, MPH
Duties: Assist with developing culturally appropriate training for farm workers, Camp Health Aides (CHAs), to educate their peers on occupational eye injuries, assemble data and results for model program (Promotores de Salud peer education program) for Collier County, Florida

GRANTS, AWARDS, DISTINCTIONS

2010 - 2011 Delta Dental Scholarship Recipient

2010 In Touch with Biomedical Science Careers Program, 2010 Conference Students Speak
April 2010, Vol. 15 No. 2
2009 Boston University School of Medicine Graduate Medical Sciences Scholarship

2003 - 2004 Outstanding Role as Co-Advisor
Kappa Psi Psi Professional Healthcare Sorority, Inc.

LEADERSHIP POSITIONS

2009 Graduate Representative- Boston University Student Advisory Council for Immunology and Microbiology


2005 Committee Planner for Northwest and Big Bend Region – American Lung Association Asthma Walk

2003 - 2005 Community Chairperson- Future Public Health Professionals of FAMU Institute of Public Health

AFFILIATIONS, ACTIVITIES, SKILLS

Professional

2010 - 2012 Young Professionals Network Urban League of Eastern Massachusetts

2009 - Present Biomedical Science Careers Program- Harvard Medical School

2008 - 2010 Boston University Chapter of Student National Dental Association (SNDA) -Graduate Medical Sciences Representative

2007- Present PresentAlpha Kappa Alpha Sorority, Incorporated

2004 - 2006 Clinical Observation Coordinator
FAMU Chapter of Undergraduate Student National Dental Association (USNDA)

2004 - 2005 The Florida Environmental Health Association, Incorporated

2004 - Present National Board of Respiratory Care