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# Effects of Daily Oral Care with 0.12% Chlorhexidine Gluconate and a Standard Oral Care Protocol on the Development of Nosocomial Pneumonia in Intubated Patients: A Pilot Study

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Purpose. The purpose of this pilot study was to determine if a difference existed between nosocomial pneumonia rates for intubated critical care unit (CCU) patients who received twice-daily oral hygiene care with 0.12% chlorhexidine gluconate and those who received the standard oral care.

Methods. Over seven months (February to August), CCU patients were identified through screening and informed consent procedures, and randomized into1 of 2 groups. Over the 7 months, due to the critically ill nature of the patients, only 5 subjects were enrolled. While in the study, twice-daily oral hygiene care consisted of brushing the cheeks, teeth, and endotracheal tube with a suctioning toothbrush using an FDA-approved 0.12% chlorhexidine gluconate antimicrobial agent with the experimental group (2 intubated patients in the CCU). The control group (3 intubated patients in the CCU) received the standard oral care 6 times per day utilizing a soft foam swab and half strength hydrogen peroxide. All oral care was performed by the nursing staff. The number of persons developing nosocomial pneumonia was monitored until hospital discharge.

Results. Results revealed that 1 person out of 3 in the control group was discharged from the hospital with a diagnosis of nosocomial (aspiration) pneumonia. Neither of the 2 subjects in the experimental group was diagnosed with nosocomial pneumonia. Preliminary findings suggest that twice-daily oral hygiene care with 0.12% chlorhexidine gluconate may reduce the risk of nosocomial pneumonia in intubated patients more than the 6-times daily standard oral care protocol. The standard oral care protocol does not include the use of an FDA-approved antimicrobial solution. However, the small size of the sample makes this finding inconclusive.

Conclusion. Twice-daily oral hygiene care with 0.12% chlorhexidine gluconate may hold promise as a nosocomial pneumonia reduction strategy within hospital CCUs; however, its application requires further testing.

**Keywords:** nosocomial pneumonia, hospital-based dental hygiene, oral-systemic disease links, respiratory disease, oral disease

## Introduction

A systematic review of articles on risk factors for nosocomial bacterial pneumonia suggests the oral cavity as a reservoir for nosocomial respiratory pathogens.<sup>1,2</sup> The incidence of nosocomial pneumonia greatly increases morbidity and mortality and the length and expense of hospitalizations among critical care unit (CCU) patients. Currently, nosocomial pneumonia is the second most common nosocomial infection in the United States.<sup>3</sup> At particular risk for hospital-acquired pneumonia are CCU patients undergoing intubation for airway management (See Figure 1). This disease occurs in 20% to 25% of patients treated with mechanical ventilation and is associated with a mortality rate of 50% to 80%.<sup>4</sup>



Current theories explaining this incidence center on sources of normal flora bacteria or nosocomial bacteria from the hospital environment that colonize the patient and are then aspirated into the lungs.<sup>5,6</sup> Although theories about these mechanisms present strong cases for both nasopharyngeal and gastric colonization, this pilot study focused on the oral environment as the source of bacterial inoculation.

Patients in CCU settings are predisposed to develop colonies of more virulent pathogens than found in the normal oral environment of healthy people. Data supports an association between nosocomial pneumonia and poor oral health for persons with chronic obstructive pulmonary disease (COPD), congestive heart failure, diabetes mellitus, age greater than 70, mechanical ventilations, history of smoking, previous antibiotic treatment, immunosupression, depressed consciousness, cross-infections, internal tube feeding, gastroesophazeal reflux, a long preoperative stay, and/or prolonged surgical procedures.<sup>1,2,7,8</sup> Predisposing conditions such as mucosal desiccation, xerostomia, reduced immunoglobin, poor nutrition, severe stress, intubation mechanical injury from nasogastricandeneo tracheal tubes, and a compromised immune system allow respiratory bacteria to establish a population in the oral cavity. Rapid bacterial growth and mucosal adhesion occurs on pharyngeal mucosa.<sup>5</sup> These bacteria are then aspirated leading to life-threatening respiratory infection. Various methods

of selective decontamination of the digestive tract using systemic and topical antibiotics have been studied with varying success;<sup>9</sup> however, broad use of antibiotic therapy increases patient risk of developing resistant bacterial strains.<sup>9</sup> Hospitals have implemented other strategies to reduce nosocomial pneumonia rates, such as meticulous handwashing by hospital staff, early extubation, frequent suctioning of patients, and semi-Fowler's positioning of patients. Since current research suggests that colonization of the oral cavity with respiratory pathogens precedes pulmonary colonization, the use of effective oral hygiene protocols and antimicrobial products might provide a noninvasive, cost-effective method to decrease the incidence of nosocomial pneumonia in the CCU environment.<sup>2,9</sup>

The original purpose of this study was to collect preliminary data on a protocol for oral decontamination of intubated patients. The specific question addressed was: Does twice-daily oral hygiene care of intubated patients with 0.12% chlorhexidine gluconate reduce the nosocomial pneumonia rate within a hospital CCU to a greater degree than the standard oral care administered 6 times per day by the nursing staff? The exploratory hypothesis was:

Intubated patients who receive the twice-daily oral hygiene care with 0.12% chlorhexidine gluconate will experience a lower incidence of nosocomial pneumonia compared to those who received the standard oral hygiene care 6 times per day, as measured by overall nosocomial pneumonia rates. However, because of the small number of subjects enrolled, the hypothesis could not be tested and the results are reported as a pilot study. See Table I for terms associated with this topic.

#### Table I

#### Terms used in this study

Intubation	The insertion of a tube via the oral or nasal cavity, into the larynx. The purpose of intubation varies with the location and type of tube inserted; generally the procedure is done to allow for drainage, to maintain an open airway, or for the administration of anesthetics or oxygen. For the purposes of this study, intubation was used to ensure a patent airway for the delivery of oxygen. Intubation was determined by the physical presence of an oral endotracheal tube in critical care patients for 48-hours or longer.	
Nosocomial Pneumonia	An infection and inflammation of the lung with consolidation and exudation that is pertaining to or originating in a hospital. The development of nosocomial pneumonia was diagnosed by the attending physician and recorded in the patient's chart.	
Nosocomial Pneumonia Morbidity	Assessing the condition of acquiring pneumonia within the hospital critical care setting. Nosocomial pneumonia morbidity was measured by the frequency at which intubated subjects developed pneumonia while in the study. This was the original outcome variable measure of the study.	
Ventilator- Associated Pneumonia	The development of pneumonia due to or resulting from the presence of an endotracheal tube. The infection can be classified as primary, secondary, or aspiration pneumonia.	
Mechanical Ventilation	The placement of an endotracheal tube, through the oropharynx, that is attached to a ventilator in order to assist a patient to breathe.	
Oral Hygiene Protocol with 0.12% Chlorhexidine Gluconate	The twice-daily brushing of the oropharynx, including the cheeks, teeth, endotracheal tube with an FDA approved 0.12% chlorhexidine gluconate solution and a suctioning toothbrush. This was the protocol used with subjects in the experimental group.	
Standard Oral Care	This is the oral care provided to critical care patients at the site hospital. It included the brushing of the mouth with a soft foam swab dipped in half strength hydrogen peroxide or Listerine every four hours. This was the protocol used with subjects in the control group.	

#### **Review of the Literature**

Nosocomial pneumonia affects up to 40% of all critically ill or immunocompromised patients with fatality rates reported ranging from 13% to 55%.<sup>10</sup> Patients receiving mechanically-assisted ventilation have higher mortality rates than do patients not receiving ventilation support;<sup>4</sup> however, other factors such as the patient's underlying disease and organ failure are stronger predictors of death in patients who have pneumonia.<sup>11</sup> In addition, nosocomial pneumonia increases the time required for hospitalization by 5 days to 7 days, resulting in increased hospital charges of approximately \$1.3 billion per year.<sup>3,12</sup> Nosocomial pneumonia is a major infection control issue because of its reported frequency, high fatality rate, and associated costs.<sup>7</sup>

The majority of nosocomial pneumonia cases are associated with extremes of age, underlying medical and respiratory conditions, compromised immune systems, and trauma.<sup>13, 14</sup> Intubation increases the risk of nosocomial infection because it interferes with the body's initial reflexes to dispel aspirated bacteria.<sup>15</sup> Intubation interferes with the body's cough reflex and its mucociliary clearance; intubation also stimulates excess mucous secretions.<sup>3,13,15</sup> Placement of an endotracheal tube impairs the gag and cough reflexes that normally act to prevent organisms from entering the lower respiratory tract.<sup>13</sup> In addition, inspired air is no longer heated and humidified by the upper respiratory tract, but instead is artificially heated and humidified by the ventilator. As a result, mucociliary clearance is impeded.<sup>10</sup> In hospital settings, ventilator-associated pneumonia usually occurs as a result of the colonization of microorganisms in the patient's oropharynx or gastrointestinal tract at the time of admission or within a short time of admission.<sup>4</sup>

Numerous factors contribute to an unhealthy oral environment for an intubated patient: the patient's inability to perform oral care; medications that cause xerostomia alter the body's host-response to infection or modify the normal bacterial flora; presence of nasogastric and endotracheal tubing; trauma from the insertion of the endotracheal tube; lack of time for oral care; and ineffective hand washing techniques by hospital staff.<sup>16-20</sup> Such opportunities for contamination by the oropharyngeal flora along with the microbial colonization of this compromised environment by more virulent pathogens increases the probability for aspiration and subsequent infection in the lower respiratory tract.

Current evidence-based measures to control nosocomial pneumonia include disinfection of the hospital environment, sterilization of critical care unit (CCU) equipment, pneumococcal vaccines, and education of all health care workers on handwashing to further prevent cross-contamination of patients.<sup>21</sup> Attention has also focused on decreasing the intubation time, the continuous aspiration of subglottic secretions (CASS), and semi-Fowler's patient positioning. No clearly defined, constantly used, evidence-based protocol has been developed for oral decontamination of intubated patients.<sup>19-20</sup>

Studies have looked at interventions to reduce the levels of oropharyngeal and gastrointestinal microorganisms, but most methods utilize topical and systemic antibiotics termed selective decontamination of the digestive tract (SDD).<sup>22</sup> The goal of SDD is to reduce the number of microorganisms in the oropharynx and gastrointestinal tract; however, it may contribute to antibiotic-resistant microorganisms and superinfections.<sup>23</sup> One study could be found that tested the use of a topical antimicrobial, such as 0.12% chlorhexidine gluconate, for oral decontamination of intubated patients.<sup>24</sup> Twice-daily rinsing with 0.12% chlorhexidine has been used successfully for many years in healthy patients to control dental plaque and gingival inflammation.<sup>25</sup> Chlorhexidine gluconate mouthrinse has been shown to be beneficial in reducing oral infections and severe mucositis during cancer therapy,<sup>26</sup> and to control oral soft tissue inflammation in patients with AIDS.<sup>27</sup>

Pneumonia may be caused by bacteria that are not normally residents of the oropharynx, but enter from the CCU environment.<sup>1,9,24,28</sup> The colonization of these microorganisms first takes place in the oropharynx with subsequent aspiration into the lungs.<sup>1,12,21,24</sup> If the oropharyngeal microorganisms are the primary contributors, then utilizing effective oral antimicrobial decontamination twice-daily may decrease the risk of nosocomial pneumonia and decrease pneumonia rates in CCU patients.<sup>24</sup> Development of an effective oral hygiene protocol for intubated patients without the use of SDD could feasibly provide a safe, efficient, and cost-effective way to diminish the morbidity, mortality, and expense of

ventilator-associated pneumonia and nosocomial pneumonia in intensive care unit (ICU) patients.<sup>19,20,29</sup> The oral care protocol may also have implications for reducing respiratory infections in the elderly and in nursing home residents.<sup>13,14,30,31</sup>

# **Methods and Materials**

Each orally and nasally intubated patient who entered the critical care unit (CCU) during the 7-month study had an opportunity to participate, pending informed consent from the patient or legally authorized representative/ medical decision maker. Many patients admitted to the CCU were unable to provide informed consent to participate. Upon admission, potential subjects were screened to determine if it was possible for the subject to make the decision to participate, or if a legally authorized representative or health care decision maker would make the decision. To minimize risks, approximately 20 potential subjects with the following characteristics were excluded from enrolling: currently taking metronidizole; a history of allergy to chlorhexidine gluconate; sensitivity to alcohol; moderate or high risk for infective endocarditis; congenital heart disease; a history of rheumatic fever or previous endocarditis; a surgically constructed pulmonary shunt; hypertrophic cardiomyopathy; history of joint replacement and immunosuppressed by medications taken for rheumatoid arthritis; systemic lupus erythematosis; hemophilia; insulin dependent diabetes; uncontrolled diabetes; sickle cell anemia; a ventriculoatrial shunt; and /or were admitted to the hospital with pneumonia and were subsequently intubated.

The original desired minimum sample size was 30 to 60, but this number depended on the number of intubated patients who entered the CCU, met the inclusion criteria, and agreed to participate during the study period. At the completion of the study in August 2002, only 5 patients had completed the study (N=5), although approximately 10 other patients met enrollment criteria but declined to participate.

Subjects ranged in age from 28 years of age to 81 years of age. Four of 5 subjects were 50 years of age or older. One hundred percent of the subjects were Caucasian. Two of the subjects were male and 3 of the subjects were female. These 5 patients were randomly assigned to either the control or experimental treatment by using the flip of a coin. A coin flipped that landed on "heads" indicated that the patient be placed in the experimental group; "tails" indicated that the patients be placed in the control group. Patients in the experimental group (n=2) received the twice-daily oral hygiene care with 0.12% chlorhexidine gluconate during their intubation period. The patients in the control group (n=3) received the standard oral care (Table II).

	EXPERIMENTAL GROUP (n=2)	CONTROL GROUP (n=3)
GENDER	FEMALE	FEMALE MALE MALE
MEAN AGE	40 YEARS	73.7 YEARS
AGE RANGE	28 TO 52	62 TO 81
RACE	CAUCASIAN	CAUCASIAN
MEAN LENGTH OF TIME INTUBATED	5.5 DAYS	5 DAYS
RANGE	2 TO 9	4 TO 7
MEAN LENGTH OF TIME IN CRITICAL CARE UNIT	18 DAYS	10.3 DAYS
RANGE	3 TO 33	7 TO 17

Table II Characteristics of Intubated Subjects in the Study (N=5)

The original plan was to utilize a randomized, 2 groups, post-test only experimental design. The 2 independent variables included the twice-daily oral hygiene care with 0.12% chlorhexidine gluconate that the experimental group would receive and the standard oral care that the control group would receive 6 times daily from the critical care nursing staff during their entire intubation time. Twice daily administration of the experimental protocol was used because of the substantivity of chlorhexidine, because dental patients are likely to clean their mouths morning and night, and to accommodate nursing staff efficiencies. The outcome variable was the nosocomial pneumonia rate as determined by the attending physician and recorded in patients' charts.

Although the structure of the study design remained intact, the investigation was modified to a case study due to the final small sample size. Upon discharge, the nursing staff and principal investigator completed a demographic data sheet for each of the 5 subjects enrolled in the study. This information was compiled to analyze the characteristics of the participants in the sample descriptively.

The CCU nursing staff attended an educational session conducted by the 2 dental hygiene researchers on the twice-daily oral hygiene protocol, recruited case study participants at the time of admittance to the critical care unit, provided the twice-daily oral hygiene care protocol with chlorhexidine gluconate to the experimental group or the standard oral care protocol that the hospital already followed to the control group, and kept a record of the oral hygiene administration and adverse effects to the subjects.

The principal investigator visited the CCU every 3 days to 4 days to monitor record keeping and to note adverse effects. No adverse effects were noted. The record of oral hygiene administration was kept with each patient's hospital chart. The equipment and materials utilized for the twice-daily oral hygiene protocol in this study included the Plak-Vac<sup>TM</sup> Oral Evacuator Brush distributed by Trademark Corporation (Figures 2 & 3) and 0.12% chlorhexidine gluconate distributed by the Discus Dental Company. The materials utilized for the standard oral care protocol included a suctioning foam swab, hydrogen peroxide, and oral lubricant (Figure 4).



Figure 3 Participant Receiving the Experimental Treatment, The Twice-Daily Oral Hygiene Care with Plak-Vac™ and 0.12% Chlorhexidine Gluconate, From A CCU Nurse.



Photo taken by Michelle Bopp



Nothing was requested of the eligible subjects except for their informed consent to receive a twice-daily oral hygiene care regimen with chlorhexidine gluconate or the standard oral care protocol. No modifications were made in the nursing care routine, other than the twice-daily oral hygiene care provided to the 2 intubated patients in the experimental group. Both oral hygiene protocols were conducted for as long as the 5 intubated patients remained in the CCU. These intubated subjects were a transient population to the CCU; none remained for the entire 7-month study period. The CCU nursing staff monitored each subject for nosocomial pneumonia with a diagnosis made by a physician.

The small sample size prohibited the use of parametric statistical analysis and hypothesis testing; therefore, descriptive statistics, in the form of frequencies, percentages, and measures of central tendency were used. Demographic data were reported to thoroughly describe the patients in the study, to verify group equivalency, and to identify possible external factors that might have influenced the development of nosocomial pneumonia.

### Results

Upon discharge from the critical care unit (CCU), the nursing staff and principal investigator completed a demographic data sheet for each of the 5 subjects enrolled in the study. Interestingly, one control group subject was diagnosed with aspiration pneumonia. Males comprised 40% (n=2) of the sample, while women represented 60% (n=3) of the overall sample population (Figure 5). Males comprised 67% (n=2) of the control group, while females comprised 33% (n=1) of the control group and 100% (n=2) of the experimental group. Subjects ranged in age from 28 years of age to 81 year of age (Figure 6). Four of the 5 subjects were 50+ years of age or older. The overall mean age of the subjects was 60.2 years. The mean age of the experimental group was 40 years and the mean age of the control group was 73.7 years. The ethnic/racial background of the subjects was 100 % Caucasian (N=5).



The sizes of the endotracheal tubes for all subjects ranged from 7mm to 8 mm. One hundred percent (N=5) of the subjects were orally intubated; 80% (n=4) had nasogastric tubes. The number of days spent at the hospital ranged from 9 days to 99 days, with a mean of 39.2 days from admission to discharge. The number of days spent in the CCU ranged from 3 days to 33 days, with a mean of 13.4 days. The length of intubation time for the subject who developed nosocomial pneumonia was 7 days. The number of days the control group (n=3) received the standard oral care ranged from 4 days to 7 days, with a mean of 5 days (Figure 7). The number of days the experimental group (n=2) received the oral hygiene protocol with 0.12% chlorhexidine gluconate ranged from 2 days to 9 days, with a mean of 5.5 days (<sup>Figure 8</sup>).



#### Discussion

The exploratory hypothesis that intubated patients who receive the twice-daily oral hygiene care with 0.12% chlorhexidine gluconate will experience less nosocomial pneumonia compared to those who received the standard oral care protocol, as measured by overall nosocomial pneumonia rates could neither be rejected nor retained because no inferential statistical analysis could be performed on data from only 5 subjects. However, the fact that one member of the control group developed pneumonia deserves some explanation. Perhaps a contributing factor is that the subject was taking steroids, which can mask the signs of infection, decrease the body's resistance to infection, and undermine the host-defense mechanism.<sup>32</sup> The subject was also taking an antibiotic, which can change the normal flora leading to a superinfection.<sup>3</sup> Length of intubation (7 days) may have played a role in the subject acquiring nosocomial pneumonia. According to Hixson et al<sup>33</sup> the risk of nosocomial pneumonia increased from 6.5% in those ventilated 10 days, to 28% in those ventilated 30 days. The longer

to the hospital was respiratory failure, which is also a risk factor for the development of nosocomial pneumonia.<sup>29</sup> The patient was in the control group, which did not receive the 0.12% chlorhexidine gluconate with the Plak-Vac<sup>TM</sup> Oral Evacuation Brush. The control group received oral hygiene care with a foam swab and hydrogen peroxide. However, a toothbrush is a superior dental aid to a foam swab.<sup>34,35</sup>

a patient is intubated, the greater the risk of a nosocomial pneumonia infection. The subject's diagnosis upon admission

The use of a 0.12% chlorhexidine gluconate mouthwash has been shown to greatly reduce the bacterial load in dental plaque.<sup>24,25</sup> DeRiso et al<sup>22</sup> found that chlorhexidine gluconate reduced nosocomial pneumonia infection rates by 69%. Overall, respiratory infection incidence of gram-negative bacteria was reduced by 67%.<sup>22</sup> Perhaps not having the chlorhexidine protocol further contributed to an already high-risk situation for the subject who developed nosocomial pneumonia.

In hindsight, the stringent exclusionary criteria kept too many patients from qualifying for the study, impeding the achievement of a large sample size. As reported by the critical care nursing staff, the patients admitted to the hospital CCU have multiple and complex medical conditions. The primary exclusionary criteria that kept critical care unit patients from qualifying for the study was a diagnosis of uncontrolled diabetes, closely followed by admission with pneumonia and subsequent intubation. Also, given this high degree of medically complicated patients, family members and medical decision-makers often were reluctant to consent to participation in the study. Many felt that their loved ones had been through enough and viewed the study as an unnecessary intrusion.

Demographically, the study sample comprised only Caucasian subjects. This lack of diversity does not favor the generalization of the results to diverse cultural backgrounds. The sample was comprised of a larger proportion of females

(n=3). The majority of the subjects were over the age of 50 (n=4). Craven and Steger<sup>36</sup> reported that host factors, such as advanced age and underlying diseases, significantly increase the risk of pneumonia and colonization of the upper respiratory tract, but are often not effective targets for prevention. Subjects in the control group were far older than the subjects in the experimental group, which could also explain why one person in the control group developed nosocomial pneumonia.

Craven and Steger<sup>36</sup> also suggest the placement of oral gastric tubes in place of nasogastric tubes to decrease the incidence of nosocomial pneumonia. The subject in the control group who was discharged with a diagnosis of aspiration pneumonia did have a nasogastric tube in place. This apparatus may have increased the subject's risk of acquiring the infection. The serendipitous inclusion of the use of continuous suction endotracheal tubes for continuous aspiration of subglottic secretions (CASS) in the CCU may have confounded the study and reduced nosocomial pneumonia rates. CASS has been shown

through previous research to be an effective component in the fight again nosocomial pneumonia.<sup>37,38</sup> Fortunately, this new procedure was used in all the subjects in the case study and therefore its effects were balanced across both experimental and control groups.

Serendipitously, the nurses provided some feedback on their views of the experimental protocol. They noted that the gingival tissues of the experimental group subjects appeared healthier, with less redness and reduced mouth debris. They also felt the Plak-Vac<sup>TM</sup> Oral Evacuator Brush and chlorhexidine gluconate were easier and less time consuming to use than the standard oral care protocol they currently utilize.

The nursing staff also expressed that the complex medical conditions of the patient population at the hospital CCU were not conducive to subject enrollment. The exclusionary criterion, diabetes, should not have been used because most critically ill patients experience changes in their blood glucose levels temporarily while in the hospital. A reported nursing staff shortage interfered with having a clinical nurse specialist on site who could focus on subject screening, informed consent procedures, and oral hygiene administration. These limitations may also have negatively affected the sample size.

### **Conclusions and Recommendations**

The most important finding of the case study was that no subjects receiving the experimental treatment were diagnosed with nosocomial pneumonia; however, one subject receiving the standard oral care did have an affirmative diagnosis of nosocomial pneumonia upon discharge from the hospital. Results, although inconclusive because of the small sample size and case study format, suggest that the twice-daily oral hygiene care of intubated patients with 0.12% chlorhexidine gluconate may hold promise as a nosocomial pneumonia reduction strategy within a hospital critical care unit (CCU); however, its application requires further testing.

Recommendations for future studies include the use of 0.12% chlorhexidine gluconate at multiple hospital-based sites so that the sample size and diversity can be increased and the findings can be generalized. Furthermore, instead of recruiting patients from the CCU, patients could be recruited in the step down unit or a department where patients have less complex medical conditions. Utilizing a patient population with less complex medical conditions would increase the number of eligible subjects and hence, the number of subjects enrolled, making the study more valid and reliable. Also, a hospital-based person specifically paid to recruit patients on a daily basis is needed for future research in this area. The utilization of a pre-procedural rinse with 0.12% chlorhexidine gluconate before endotracheal tube placement to reduce nosocomial pneumonia risk needs further study. Future research would also need to address the question of whether the reduction in nosocomial pneumonia rates came primarily from the 0.12% chlorhexidine gluconate mouthrinse or from the suctioning of oral secretions and mouth debris by the Plak-Vac<sup>TM</sup> Oral Evacuator Brush. Preliminary data warrant further investigation. Given the nursing shortage, if mouthcare by nurses can be reduced from 6 times per day to twice daily, then the hospital is likely to accrue savings in personnel time and mouth care supplies.

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#### Notes

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