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# Effect of 0.12% Chlorhexidine Use for Oral Care on Ventilator-Associated Respiratory Infections: A Randomized Controlled Trial

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## ABSTRACT

**Background:** Evidence suggests that the effect of 0.12% chlorhexidine (CHX) use for oral care on the development of ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis (VAT) is lacking. Evidence-based approaches to the prevention of VAP and VAT are of paramount importance for improving patients' outcomes.

**Objectives:** This study aimed to (1) compare the effect of 0.12% CHX use for oral care on preventing VAP and VAT with the placebo group, as well as (2) compare its effect on oral health and prevention of oral microbial colonization with the placebo group.

**Methods:** Prospective, single-blinded, randomized controlled trial performed in 2 intensive care units at a hospital. The sample comprised 57 mechanically ventilated adults randomly allocated to the 0.12% CHX group and the placebo group. Barnason's oral assessment guide was used to evaluate the oral health of both groups before oral care during the first 24 hr of tracheal intubation (Day 0) and at Day 2 and Day 3. Oropharyngeal secretion, endotracheal tube aspirate, and nonbronchoscopic bronchoalveolar lavage samples were collected on Day 0 and Day 3.

**Results:** The rate of VAT development was not statistically different between the groups ($p = .318$). However, a significant difference existed in the rate of VAP development ($p = .043$). The frequency of oropharyngeal colonization significantly decreased in the 0.12% CHX group compared with the placebo group at Day 3 ($p = .001$).

**Conclusion:** The use of 0.12% CHX for oral care could be effective for VAP prevention and reducing microbial colonization in mechanically ventilated patients.

## Key Words

Chlorhexidine, Oral care, Oral hygiene, Ventilator-associated pneumonia, Ventilator-associated tracheobronchitis

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Ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis (VAT) are defined as infections that occur more than 48 hr after intubation in an intensive care unit (ICU) (Craven, Hudcova, & Lei, 2011, Torres et al., 2017). These infections are a crucial cause of prolonged hospital stay, increased need for antimicrobial therapy, and increased health costs, morbidity, and mortality in the ICU (Agrafiotis, Siempos, & Falagas, 2010; Craven et al., 2011; Craven, Lei, Ruthazer, Sarwar, & Hudcova, 2013; Martin-Loeches et al., 2015). Therefore, prevention of VAP and VAT is important to reduce complications and increase the quality of life in mechanically ventilated patients.

Oropharyngeal flora and microorganisms change within 24 hr after admission to the ICU (Drakulovic et al., 2001). The mechanical process of intubation breaks the natural barrier and could facilitate bacterial colonization. Microorganisms enter the lower respiratory tract from the oropharynx, leakage around the endotracheal tube cuff, or the biofilm in the endotracheal tube (Craven et al., 2011). In addition, dental plaque pathogens are linked to microaspiration of bacteria

into the lower respiratory tract (Kocacal Guler & Turk, 2018). As a result, VAP, VAT, or both may occur in patients receiving mechanical ventilation (Craven et al., 2011). Effective oral care can play an important role in preventing VAP or VAT (Kocacal Guler & Turk, 2018; Zhang, Tang, & Fu, 2014).

Chlorhexidine (CHX) is a broad-spectrum antiseptic solution used widely in oral care that reduces microbial accumulation in the oral cavity (Tran & Butcher, 2019). Several recent studies have used CHX at different concentrations (2%, 0.2%, 0.12%), and clinical applications of CHX for oral care have varied from one to four times a day in patients receiving mechanical ventilation (Kocacal Guler & Turk, 2018; Tran & Butcher, 2019; Zhang et al., 2014). However, there is insufficient evidence of the superiority of one solution over another in the prevention of VAP or VAT (Kocacal Guler & Turk, 2018; Tran & Butcher, 2019; Zhang et al., 2014). This suggests that additional studies are needed to determine which concentration is more appropriate for clinical practice. A meta-analysis reported that 0.12% CHX has the best effect on the prevention of VAP. However, the studies included in the meta-analysis had a moderate to high degree of bias (Zhang et al., 2014). Furthermore, guidance of outcomes regarding the effect of 0.12% CHX for oral care on the development of VAT is lacking. For this reason, this study contributes to the literature by providing information about the development of VAT in oral care using 0.12% CHX.

## OBJECTIVE

This study aimed to (1) compare the effect of 0.12% CHX gluconate use for oral care on preventing VAP and VAT with the placebo group, as well as (2) compare its effect on oral health and prevention of oral microbial colonization with the placebo group.

## METHODS

### Design, Setting, and Sample

This study was conducted from April 15, 2019, to March 3, 2020, as a prospective, single-blinded, randomized controlled trial. Subjects were adult patients who were mechanically ventilated in the 18-bed anesthesiology and surgical ICU of an urban training and research hospital in northwest Turkey. The inclusion criteria were as follows: age 18 years or more, admission to a critical care unit within 24 hr, and having an endotracheal tube. The exclusion criteria were as follows: duration of mechanical ventilation less than 48 hr, confirmed diagnosis of pneumonitis before admission to the ICU, a history of CHX allergy, transfer from another ICU, receiving chemotherapy or radiotherapy, having immunodeficiency or tracheostomy, requiring specific oral hygiene procedures, having maxillofacial or dental trauma or surgery, and being pregnant.

The sample size and power analysis were calculated with G*Power Version 3.1.2 and based on DeRiso et al.'s study (DeRiso, Ladowski, Dillon, Justice, & Peterson, 1996; Faul, Erdfelder, Buchner, & Lang, 2009). DeRiso et al. (1996) reported that respiratory tract infections were reduced in the intervention group by 69% compared with those in the control group. According to the calculated difference between two independent proportion analyses with a two-sided α of 5%, statistical power of 90%, and an anticipated dropout rate of 10%, at least 38 patients were required for each group.

A total of 436 patients were admitted to the ICU over 17 months. A total of 360 participants were excluded because of not meeting inclusion criteria. After obtaining their informed consent, the remaining 76 participants were divided randomly into two groups (CHX group: $n = 38$; placebo group: $n = 38$). A total of 57 patients remained at the end of the study (see Figure, Supplemental Digital Content, available at: http://links.lww.com/JTN/A27).

Computer-generated randomization was used to assign patients to one of the two groups. Information concerning allocation was available only to the researcher (the fourth coauthor). The pharmacy department stored all the study solutions. All study solution packs were prepared identically in outward appearance by the fourth coauthor. Patients were assigned a sequential number placed in an opaque, sealed envelope by the fourth coauthor. When the patient was intubated, the fourth coauthor opened the envelope and then the critical care nurses performed oral care. The critical care nurses and other researchers were blinded to the random assignments throughout the study period.

### Data Collection and Intervention

Before study implementation, the researchers (the principal, second, and sixth researchers) developed an oral care protocol and obtained advice from experts (ICU nurses, an infectious disease specialist, and an infection control nurse) (Barnason et al. 1998; Berry et al., 2011; Booker, Murff, Kitko, & Jablonski, 2013; Cuccio et al., 2012; Feider, Mitchell, & Bridges, 2010; Hillier, Wilson, Chamberlain, & King, 2013; Hua et al., 2016; Prendergast, Jakobsson, Renvert, & Hallberg, 2012; Vollman, Sole, & Quinn, 2016). The protocol was modified according to the expert opinions (see Table, Supplemental Digital Content, available at: http://links.lww.com/JTN/A28) and then the nurses were trained on the oral care protocol by the principal and second researchers. The oral care in the CHX group was performed three times a day with 0.12% CHX gluconate by the nurses. In the placebo group, oral care was performed three times a day with sodium bicarbonate. The same oral protocol was applied to the patients of both groups. Barnason's oral assessment guide (BOAG)

was used to evaluate the oral health of both groups before oral care by the nurses during the first 24 hr of tracheal intubation (Day 0) and at Day 2 and Day 3. The tool has six items that assess teeth, lips, oral mucosa, saliva, and gums. Scores range from 6 to 18, with higher scores indicating worse oral health (Barnason et al., 1998).

Oropharyngeal secretion, endotracheal tube aspirate (ETA), and mini-bronchoalveolar lavage (mini-BAL) samples were collected on Day 0 and Day 3 by the nurses and the ICU physicians. The nurses and ICU physicians applied standardized oropharyngeal secretion, ETA, and nonbronchoscopic bronchoalveolar lavage (mini-BAL) sample collection techniques. The first samples were collected before the oral care. The last samples were collected approximately 8–10 hr after the last oral care. The nurses transported the samples to the microbiological laboratory. The nurses applied a standard protocol for storage, labeling, and transport to the microbiological laboratory. The samples were analyzed using semiquantitative methods by the third researcher, who was blinded to the treatment allocation code. The automated system performed bacterial species identification.

Clinical criteria for VAP consisted of worsening or new infiltrate on chest radiographs correlated with at least two of the following: body temperature less than 35 °C or 38.5 °C or more; leukocyte count less than 4,000/$mm^3$ or more than 11,000/$mm^3$; sputum or purulent tracheal aspirate; and positive end-expiratory pressure requirement by more than 20% to maintain oxygen saturation above 92% or increase in the fraction of inspired oxygen. In addition, a microbiological confirmation was required for all patients (cutoffs of $\geq 10^5$ CFU/ml for ETA and $\geq 10^4$ CFU/ml for mini-BAL were defined as positive airway colonization). Ventilator-associated tracheobronchitis was defined using the same criteria as for VAP, except for the presence of progressive or new pulmonary infiltrate. Ventilator-associated tracheobronchitis was defined with the same criteria with no radiographical signs of new pneumonia (Pugin, Auckenthaler, Lew, & Suter, 1991). The fifth researcher used Clinical Pulmonary Infection Score (CPIS) to determine the diagnosis of VAP or VAT. CPIS consists of temperature, chest radiographs, leukocyte count, arterial oxygenation, volume of tracheal secretions, and secretion culture results. The scores range from 0 to 12, with a score of 6 or more indicating the presence of VAP or VAT (Pugin, Auckenthaler, Mili, et al., 1991). Clinical differentiation between VAT and VAP was confirmed with a chest radiograph by the fifth researcher, ICU physicians, and a radiologist blinded to the treatment allocation code.

## Data Analysis

All statistical analyses were conducted using SPSS Version 25.0 (IBM, Armonk, NY). The skewness and kurtosis were used for testing normality. All statistical tests were one-tailed, and statistical significance was considered as $p < .05$. Differences between groups were assessed using Fisher's exact test or the chi-square test for nominal data. Numerical variables were evaluated using the Mann–Whitney *U* test or Student's *t* test. A two-way repeated-measures analysis of variance was used to compare the BOAG values based on the groups and time, whereas Duncan's test was used in multiple comparisons. Bonferroni correction was utilized to compare the main effects.

## Ethical Consideration

Ethical approval was obtained from the ethical committee (No. 77192459-050.99-E.30983) and the institution (No. 98024045-604.01.02). Written informed consent for patients who were unconscious or intubated was obtained from their guardians or first-degree relatives.

# RESULTS

As shown in Table 1, the mean (*SD*) age of patients in the placebo and 0.12% CHX groups was 77.37 (10.1) and 72.79 (12.0) years, respectively. No significant differences existed between groups for gender, duration of mechanical ventilation, or length of ICU admission.

Fisher's exact test showed that the rate of VAT development was not statistically different between the groups. However, a significant difference existed in the rate of VAP development. In the 0.12% CHX group, *Acinetobacter baumannii* and *Klebsiella pneumonia* predominated in patients with VAP. In the placebo group, in addition to the species identified in the 0.12% CHX group, there was a higher frequency of *Pseudomonas aeruginosa* and *Escherichia coli* isolated from mini-BAL cultures of patients with VAP. Similar to the results found for the ETA samples, *Acinetobacter baumannii* and *Klebsiella pneumoniae* were observed in patients with VAT in the 0.12% CHX group (see Table 2).

As shown in Table 3, no significant difference was found between the two groups in the frequency of oropharyngeal colonization at Day 0. However, the frequency of oropharyngeal colonization significantly decreased in the 0.12% CHX group compared with the placebo group at Day 3 ($p = .001$). The presence of *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* decreased in the 0.12% CHX group, whereas that of *Klebsiella pneumoniae* decreased in the placebo group.

The group effect on the BOAG values was found to be statistically significant ($p = .025$). The mean (*SD*) value of the CHX group was 10.18 (2.82), whereas that of the placebo group was 11.00 (2.36). The effect of time on the BOAG values was found to be significant ($p < .001$). The mean (*SD*) value at Day 0 was 11.63 (2.70), the mean (*SD*) value at Day 2 was 10.67 (2.52), and the mean (*SD*) value at Day 3 was 9.46 (2.63). The highest mean value

**TABLE 1 Characteristics of Patients ($N = 57$)**

| | CHXG ($n = 29$) | PG ($n = 28$) | $p$ |
|---|---|---|---|
| Age, mean (*SD*), years | 72.79 (12.0) | 77.37 (10.1) | .132[a] |
| Length of ICU stay, median, days | 28.05 | 29.98 | .660[b] |
| Duration of MV, median, days | 26.55 | 31.54 | .255[b] |
| APACHE II, mean (*SD*) | 16.1 (6.4) | 16.6 (6.1) | .700[a] |
| Reason for ICU admission, *n* (%) | | | |
| Cardiovascular cause | 3 (10.3) | 4 (14.3) | |
| Neurological cause | 5 (17.2) | 3 (10.7) | .974[c] |
| Respiratory cause | 1 (3.4) | 2 (7.1) | |
| Multiple-organ failure | 1 (3.4) | 2 (7.1) | |
| Renal cause | 1 (3.4) | 1 (3.6) | |
| Major surgery/ postoperative | 6 (20.7) | 5 (17.9) | |
| Trauma | 12 (41.4) | 11 (39.3) | |
| Antibiotics before admission, *n* (%) | | | |
| Yes | 13 (44.8) | 15 (53.6) | .600[d] |
| No | 16 (55.2) | 13 (46.4) | |
| Gender, *n* (%) | | | |
| Male | 18 (62.1) | 16 (57.1) | .705[d] |
| Female | 11 (37.9) | 12 (42.9) | |

*Note. CHXG = 0.12% chlorhexidine group; ICU = intensive care unit; MV = mechanical ventilation; PG = placebo group.*

[a]*Student's t test.*

[b]*Mann–Whitney U test.*

[c]*Fisher–Freeman–Halton exact test.*

[d]*Chi-square test.*

was obtained on Day 0, whereas the lowest value was obtained on Day 3. The effect of the interaction of groups and time on the BOAG values was determined to be significant ($p < .001$). The highest mean (*SD*) value was obtained as 12.28 (2.83) on Day 0 in the CHX group, whereas the lowest value was 8.48 (1.96) on Day 3 in the CHX group. The time-related change within the CHX group was statistically significant, and the mean BOAG value tended to decrease until Day 3 compared with the baseline value. In the placebo group, the time-related decrease was not significant. The main effect of time on the BOAG values was more significant than those of the groups and the interaction of groups and time. The partial eta-squared value of the main effect of time was determined to be .126 (see Tables 4 and 5).

**TABLE 2 A Comparison of the Rates of VAP and VAT Development Between the Two Groups**

| | CHXG, *n* (%) | PG, *n* (%) | $p$ |
|---|---|---|---|
| VAP ($n = 27$) | 10 (34.5) | 17 (60.7) | .043 |
| Bacterial species | | | |
| *Acinetobacter baumannii* | 4 | 3 | |
| *Escherichia coli* | – | 3 | |
| *Klebsiella pneumoniae* | 4 | 5 | |
| *Klebsiella oxytoca* | – | 1 | |
| *Pseudomonas aeruginosa* | – | 4 | |
| *Candida albicans* | 2 | 1 | |
| VAT ($n = 6$) | 2 (6.9) | 4 (14.3) | .318 |
| *Escherichia coli* | – | 1 | |
| *Klebsiella pneumoniae* | 1 | – | |
| *Acinetobacter baumannii* | 1 | 1 | |
| *Pseudomonas aeruginosa* | – | 2 | |

*Note. CHXG = 0.12% chlorhexidine group; PG = placebo group; VAP = ventilator-associated pneumonia; VAT = ventilator-associated tracheobronchitis.*

## DISCUSSION

The first aim of this study was to assess the effect of 0.12% CHX gluconate use for oral care on the development of VAP. This study revealed a beneficial effect on VAP prevention in mechanically ventilated patients. The meta-analysis by Zhang et al. (2014), including nine randomized controlled trials, showed that 0.12% CHX gluconate could prevent VAP effectively, which coincided with the findings of this study. Similarly, Nicolosi, del Carmen Rubio, Martinez, Gonzalez, and Cruz. (2013) and Sharma and Kaur (2012) demonstrated that using 0.12% CHX twice a day could significantly reduce the incidence of VAP. Galhardo et al. (2020) also found that 0.12% CHX use significantly reduced the risk of early development of VAP. These results indicated that nurses might use 0.12% CHX for oral care three times a day in the ICU.

The second aim of this study was to assess the effect of 0.12% CHX gluconate use for oral care on the development of VAT. Only a few previous studies have examined the effect of 0.12% CHX on the development of VAT (Bellissimo-Rodrigues et al., 2009; Muszynski et al., 2013; Peña-López et al., 2016). Bellissimo-Rodrigues et al. (2009) reported no significant differences in the incidence of VAT between the two groups, which was consistent with the findings of this study. Other studies have been limited by their use of 0.12% CHX combined with care bundle implementations in the pediatric population,

**TABLE 3 A Comparison of Oropharyngeal Colonization Between Two Groups on Day 0 and Day 3**

| | Day 0 | | Day 3 | |
|---|---|---|---|---|
| | CHXG (*n* = 29) | PG (*n* = 28) | CHXG (*n* = 29) | PG (*n* = 28) |
| Number of patients colonized | 16 (55.2) | 15 (53.6) | 8 (27.6) | 20 (71.4) |
| Differences between groups (*p* value) | .557 | | .001 | |
| Bacterial species | | | | |
| *Acinetobacter baumannii* | 4 | 5 | 3 | 5 |
| Pseudomonas aeruginosa | 2 | 1 | – | 5 |
| *Klebsiella pneumoniae* | 5 | 1 | 4 | 2 |
| *Klebsiella oxytoca* | – | 1 | – | – |
| *Enterobacter cloacae* | 2 | – | – | – |
| *Enterobacter aerogenes* | – | – | – | 1 |
| *Staphylococcus aureus* | 1 | – | – | – |
| *Escherichia coli* | – | 5 | – | 4 |
| *Enterococcus faecalis* | – | – | – | 1 |
| *Candida albicans* | 2 | 2 | 1 | 2 |

*Note. CHXG = 0.12% chlorhexidine group; PG = placebo group.*

which does not allow assessing effects in the adult population (Muszynski et al., 2013; Peña-López et al., 2016). Therefore, more evidence is needed to understand whether CHX use for oral care is beneficial in VAT prevention. Future studies should examine the effect of 0.12% CHX use for oral care on preventing VAT in the adult population, where clinical characteristics are more diverse.

This study observed that in the CHX group, strains of *Acinetobacter baumannii* and *Klebsiella pneumoniae* were isolated from the tracheal cultures in the patients with VAT. These oropharyngeal pathogens were similar to the tracheal pathogens in patients with VAT. Therefore, 0.12% CHX use for oral care could be less effective in *Acinetobacter baumannii* and *Klebsiella pneumoniae*. Previous studies regarding the effect of 0.12% CHX for oral care on the development of VAT are lacking. Therefore, the relevant literature regarding observational study outcomes for pathogen microorganisms is discussed in a limited scope in this section (Craven et al., 2013; Dallas, Skrupky, Abebe, Boyle, & Kollef, 2011; Karvouniaris et al., 2013; Martin-Loeches et al., 2015). The results of this study support the results reported by Agrafiotis et al. (2010). In contrast, most observational studies have stated that multidrug-resistant pathogens were isolated from tracheal cultures at higher frequencies (Craven et al., 2013; Dallas et al., 2011; Karvouniaris et al., 2013; Martin-Loeches et al., 2015). Differences in the types of pathogens isolated from cultures in these studies could have resulted from different types of antibiotics that were used.

The third aim of this study was to evaluate the effect of 0.12% CHX gluconate use for oral care on preventing oral microbial colonization. Based on the baseline, the results found for oropharyngeal colonization on Day 3 indicated that 0.12% CHX gluconate could effectively reduce the frequency of bacterial colonization in the oropharynx. The results of this study were in agreement with those reported by DeRiso et al. (1996) and Nicolosi et al. (2013). However, Scannapieco et al. (2009) and La Combe et al. (2018) showed that the use of 0.12% CHX did not reduce oropharyngeal bacterial colonization. One possible

**TABLE 4 Comparison of BOAG Values Based on Groups and Time**

| | Sum of Square | *df* | Mean Square | *F* | *p* | Partial Eta Squared |
|---|---|---|---|---|---|---|
| Group | 28.463 | 1 | 28.463 | 5.135 | .025 | .030 |
| Time | 131.976 | 2 | 65.988 | 11.905 | <.001 | .126 |
| Time × Group | 97.028 | 2 | 48.514 | 8.752 | <.001 | .096 |

*Note. BOAG = Barnason's oral assessment guide. $R^2$ = .222; adjusted $R^2$ = .222.*

**TABLE 5 Descriptive Statistics on BOAG Values Based on Groups and Time**

| | CHXG ($n$ = 29) | PG ($n$ = 28) | Total Score |
|---|---|---|---|
| Day 0 | 12.28 (2.83)$^{D}$ | 10.96 (2.43)$^{BC}$ | 11.63 (2.70)$^{a}$ |
| Day 2 | 9.79 (2.21)$^{B}$ | 11.57 (2.53)$^{CD}$ | 10.67 (2.52)$^{b}$ |
| Day 3 | 8.48 (1.96)$^{A}$ | 10.46 (2.06)$^{BC}$ | 9.46 (2.23)$^{c}$ |
| Total score | 10.18 (2.82) | 11.00 (2.36) | 10.58 (2.63) |

*Note. BOAG = Barnason's oral assessment guide; CHXG = 0.12% chlorhexidine group; PG = placebo group. a–c: There is no significant difference between time points with the same letter. A–D: There is no significant difference between interactions with the same letter.*

explanation for this might be that the frequency and application of CHX were different in the interventions. In addition, this study observed that 0.12% CHX use for oral care could reduce the colonization of pathogens such as *Staphylococcus*, Enterobacteriaceae, and *Pseudomonas aeruginosa*, which cause VAP and VAT; this finding was consistent with the finding of previous studies (La Combe et al., 2018; Scannapieco et al., 2009).

The pathogenesis of ventilator-associated respiratory infections is multifactorial, with pathogen colonization of poor oral hygiene being a significant factor (Craven et al., 2011). The fourth study aim was to evaluate the effect of 0.12% CHX gluconate use for oral care on oral health. This study demonstrated that the BOAG score in the CHX group significantly decreased compared with the control group over time, indicating that using 0.12% CHX gluconate for oral care could improve oral hygiene. The findings of this study were consistent with those reported in the study by Park and Sohng (2010). Similarly, Ames et al. (2011) found that the 0.12% CHX group had significantly reduced BOAG scores between Day 1 and Day 5 compared with the control group.

## Strengths and Limitations of the Study

One of the strengths of our study is that VAT and VAP were diagnosed both clinically and microbiologically. Second, another strength is a randomized, single-blinded, placebo group design. However, the present study has certain limitations. First, it was conducted within two ICUs in a single hospital, so its generalizability is limited. Future research should involve a prospective, multicenter, larger-population study. Second, we assessed the effect of 0.12% CHX gluconate on early-onset VAP development. We suggest that nurses should assess the effect of 0.12% CHX gluconate on late-onset VAP development in the future.

# CONCLUSION

This study demonstrated that 0.12% CHX gluconate use for oral care three times a day is an effective intervention for VAP prevention and reducing microbial colonization in mechanically ventilated patients. In addition, 0.12% CHX gluconate could improve oral health. We suggest that nurses should integrate 0.12% CHX gluconate use three times a day into oral care protocols in the ICU. However, 0.12% CHX gluconate use did not significantly influence VAT prevention.


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## KEY POINTS

- Little is known about the effectiveness 0.12% CHX gluconate use for oral care.
- The use of 0.12% CHX gluconate for oral care three times a day may be an effective intervention for VAP prevention and reducing microbial colonization in mechanically ventilated patients.
- This study results showed that oral care with 0.12% CHX gluconate did not prevent VAT.

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