REVIEW ARTICLE

Efficacy of Chlorhexidine in Preventing Ventilator-Associated Pneumonia: A Systematic Review of Randomized Controlled Trials

Wajan Alqathanin[1]*, Yara A. Alharthi[2], Sara Alqahtani[3], Renad Albalawi[4], Nouf Al Saad[5], Shahad Alamri[4], Wedad Alotaibi[6], Badriah Alqahtani[7], Noura Almotrib[8], Fatima Al-otaibi[8], Noura Al-amro[8], Sahar Alshehri[9], Refal Abusllam[9], Mohammed Alotaibi[10], Waad Alqaedi[11]

[1]Department of Doctor of Pharmacy, College of Pharmacy, King Khalid University, Abha, Saudi Arabia, [2]Department of Pharmacy, College of Pharmacy, Taif University, Taif, Saudi Arabia, [3]Department of Pharmacy, Abha International Private Hospital, Abha, Saudi Arabia, [4]PharmD Program, Faculty of Pharmacy, University of Tabuk, Tabuk, Saudi Arabia, [5]Department of Pharmaceutical Care, Ministry of National Guard-Health Affairs, Dammam, Saudi Arabia, [6]PharmD, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, [7]PharmaD Program, Faculty of Pharmacy, Shaqra University, Al-Dawadmi, Saudi Arabia, [8]Department of Doctor of Pharmacy, College of PharmaD, Buraydah Private Colleges, Buraydah, Saudi Arabia, [9]Department of Doctor of Pharmacy, College of PharmaD, King Khalid University, Abha, Saudi Arabia, [10]Department of Pharmacy, Medical Services at the Ministry of Interior, Riyadh, Saudi Arabia, [11]Department of Pharmacy, King Khalid University, Abha, Saudi Arabia

Abstract

Ventilator-associated pneumonia (VAP) is a common complication in intensive care units (ICUs) that leads to increased morbidity, mortality, and healthcare costs. Chlorhexidine (CHX), a broad-spectrum antiseptic, is widely used for oral care in intubated patients to prevent the development of VAP. This systematic review aimed to evaluate the efficacy of CHX in preventing VAP in adult patients in the ICU. A comprehensive search was conducted in PubMed for randomized controlled trials (RCTs) published between January 1, 2018, and October 30, 2024. Five RCTs met the inclusion criteria and were included in this review. The primary outcomes were overall mortality and VAP episodes, and the secondary outcomes were ICU stay duration and mechanical ventilation time. The results showed that CHX did not significantly reduce mortality rates, VAP incidence, ICU stay duration, or mechanical ventilation time compared to the control group. However, the risk of bias assessment revealed significant variability in the study quality, with concerns about selection, performance, and detection biases. Despite the lack of significant impact on the outcomes assessed, CHX may offer additional benefits in the ICU setting, such as reducing catheter-related bloodstream infections and improving oral health. The decision to use CHX should be based on a comprehensive assessment of its benefits and risks, considering patient characteristics and clinical settings. Further high-quality RCTs are needed to establish the effectiveness of CHX in preventing VAP and improving patient outcomes in the ICU setting.

Key words: Antibiotic resistance, chlorhexidine, efficacy, intensive care units, randomized controlled trials, Ventilator-associated pneumonia

INTRODUCTION

Oropharyngeal bacterial colonization leads to tracheal colonization, often resulting in ventilator-associated pneumonia (VAP) in intensive care units (ICUs). VAP affects 9–27% of ICU patients, increasing mortality and morbidity.[1] VAP-related mortality rates range from 24% to 50%, reaching 76% in severe cases. Main microorganisms

Address for correspondence:
Wajan Alqathanin, Department of Doctor of Pharmacy, College of Pharmacy, King Khalid University, Abha, Saudi Arabia. Phone: ???.
E-mail: wajankh0@gmail.com

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associated with death rates include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*, varying based on patient factors and hospital conditions.[2]

The factors predisposing patients to VAP include prior condition, health status, concurrent infections, and treatment-related variables. Aspiration of secretions also contributes to VAP onset.[3] Four mechanisms facilitate the development of VAP: aspiration of oropharyngeal pathogens, inhalation of aerosolized bacteria, hematogenous spread, and bacterial translocation from the gastrointestinal tract. The primary route of pulmonary infection in VAP is aspiration of oropharyngeal secretions colonized by pathogens.

Various treatments have been developed for VAP prevention, with oral decontamination being the primary low-resource approach. Although oral pharyngeal cleaning with antibiotics is more effective than that with antiseptics, concerns about antibiotic resistance have limited its use. Consequently, chlorhexidine (CHX) has become prevalent in ICUs, and its effectiveness in reducing VAP has been examined in multiple studies.[4]

CHX is a biguanide consisting of two chlorguanide chains connected by a hexamethylene chain. It is diluted with gluconic or acetic acid to create water-soluble salts.[5] At bacteriostatic concentrations, CHX disrupts the bacterial cytoplasmic membrane, causing the efflux of cytoplasmic components.[6] At higher doses, it exerts a bactericidal effect by forming irreversible precipitates with intracellular ATP and nucleic acids.[7] CHX is effective against Gram-positive bacteria owing to its affinity for the cell walls of these organisms.[8] It also demonstrates efficacy against Gram-negative bacteria, anaerobes, fungi, and some enveloped viruses, and its bactericidal properties improve with exposure.[9]

Using a 0.12% CHX solution as a mouth rinse for 30 s reduces aerobic and anaerobic bacterial counts owing to its absorption by oropharyngeal tissues and gradual release. CHX acts as a chemical biosecurity agent in preventing VAP by affecting the oral microbial flora and contributing to oral/digestive decontamination, offering a slight survival benefit.[10]

Frost *et al*. conducted a systematic review on CHX bathing's effectiveness in reducing hospital-acquired infections among critically ill adult patients.[11] This review focused on bloodstream infections, central line-associated bloodstream infections, multidrug-resistant organisms, VAP, and catheter-associated urinary tract infections. An analysis of five randomized controlled trials (RCTs) (n = 10,564) concluded that CHX bathing had no impact on reducing VAP in ICUs.

Villar *et al*. evaluated intraoral CHX for VAP prevention. After analyzing 13 RCTs (n = 1640), they concluded that oral care with CHX is effective in reducing VAP in adults when administered at a 2% concentration or four times daily.[12] Zhang *et al*. assessed the effectiveness of CHX in preventing VAP and determined its optimal dosage by examining outcomes such as efficacy, dose effectiveness, costs, adverse effects, and resistance.[13]

Carvajal *et al*. reviewed the efficacy of CHX in preventing VAP and found that it reduced the likelihood of VAP compared with the control group (odds ratio [OR] 0.56, 95% confidence interval [CI] 0.44–0.73).[14] However, reductions in mortality, duration of mechanical ventilation, and length of hospital stay were not observed.

The effectiveness of CHX in this application has been debated, and further research is necessary to reach a definitive conclusion. This review aimed to assess the effectiveness of CHX in the prevention of VAP in adult ICU patients.

METHODS

This review followed the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[15] A comprehensive search was conducted in PubMed for studies published from January 1, 2018, to October 30, 2024. The search used keywords and Medical Subject Headings terms such as "Ventilator-associated pneumonia," "Intensive care units," "Chlorhexidine," and "Treatment" with Boolean operators.

A search was conducted in PubMed, with no date limit until November 25, 2024. Abstracts of RCTs that evaluated the efficacy of CHX in preventing VAP in the adult ICU were selected, where the primary intervention was oral CHX at 0.12%, 0.2%, and 2% compared to other concentrations, placebo, or other solutions. There was no limit to the search in time and language. Case reports, editorials, narrative reviews, and meta-analyses were excluded.

Three authors (SD, SV, and KK) independently reviewed titles and abstract content against inclusion and exclusion criteria. Relevant studies were selected, and full texts were searched for further assessment. Discrepancies in selections were discussed together, and a consensus was reached. Selected articles were stored in EndNote X20 software.

Primary outcomes were overall mortality and VAP episodes, assessed by event frequency, whereas secondary outcomes were time in ICU and duration of mechanical ventilation (assessed as mean and standard deviation in days).

Two authors (JJB and JCA) independently extracted data using predefined forms. Disagreements were resolved by consensus, and a third author (EMR) was consulted if necessary. Data extracted were: first author, year, study

design, country(ies), number of participants, clinical characteristics (types of patients and treatment used), type of intervention, type of control, outcomes assessed, and results.

The risk of bias (RoB) for each study was evaluated using the Cochrane RoB Tool (RoB 2.0). Five domains were assessed: selection, performance, detection, attrition, and reporting biases. Two reviewers independently rated each study as having low, unclear, or high RoB. Disagreements were resolved through consensus. A graphical overview summarizes the RoB assessment.

This is a systematic review of published and open data that did not involve human subjects. Approval from an ethics committee was not required. This study is based on Council for International Organizations of Medical Sciences guidelines, such as justice based on fair distribution of the benefits and burdens of research, as well as scientific and ethical evaluation.

RESULTS

Through structured searches, the authors identified 139 studies from PubMed. The initial screening process involved the application of predetermined eligibility criteria. After excluding 36 studies owing to unavailable full-text data, 103 were screened. Of these, 81 studies were excluded. The remaining 22 studies underwent an eligibility assessment, resulting in 17 studies being excluded due to inadequate data and conclusions. Ultimately, five papers satisfied the inclusion criteria and were included in this systematic review.[16-20] Figure 1 illustrates the selection process, and Table 1 lists the five studies included.

This systematic review assessed the impact of different oral hygiene methods, focusing on CHX with and without toothbrushing, on preventing VAP in critically ill patients undergoing mechanical ventilation.

Meinberg *et al*. conducted a randomized placebo-controlled trial using 2% CHX gel with tooth brushing and observed no significant decrease in VAP incidence.[16] The VAP rate was higher in the intervention group (64.3%) than in the placebo group (45.8%), with a relative risk of 1.4 (95% CI: 0.83–2.34; P = 0.29), leading to early termination. Özçaka *et al*. found a significant reduction in VAP incidence with 0.2% CHX oral swabbing (41.4%) compared to saline swabbing (68.8%) (P = 0.03; OR = 3.12, 95% CI: 1.09–8.91).[17]

De Lacerda Vidal *et al*. observed a non-significant trend toward reduced VAP incidence in the group using toothbrushing plus 0.12% CHX gel (P = 0.084), but noted a significantly shorter duration of mechanical ventilation (P = 0.018).[18] Hanifi *et al*. compared 0.2% CHX with ozonated water and found a lower VAP incidence in the ozonated water group on day 4 of ICU stay (14.6% vs. 30.6%, P = 0.02).[19] Zand *et al*. demonstrated a significant reduction in VAP (P = 0.007) and oropharyngeal colonization (P = 0.007) with 2% CHX compared to 0.2% CHX, without increased adverse effects (P = 0.361).[20]

The RoB for the five RCTs was evaluated using the Cochrane RoB 2.0 tool, which examined selection, performance, detection, attrition, and reporting bias. Each area was classified as low, unclear, or high risk based on the agreement between the two independent reviewers. Meinberg *et al*. showed a high risk of selection and performance, with an unclear risk of detection, attrition, and reporting due to insufficient randomization reporting and the absence of

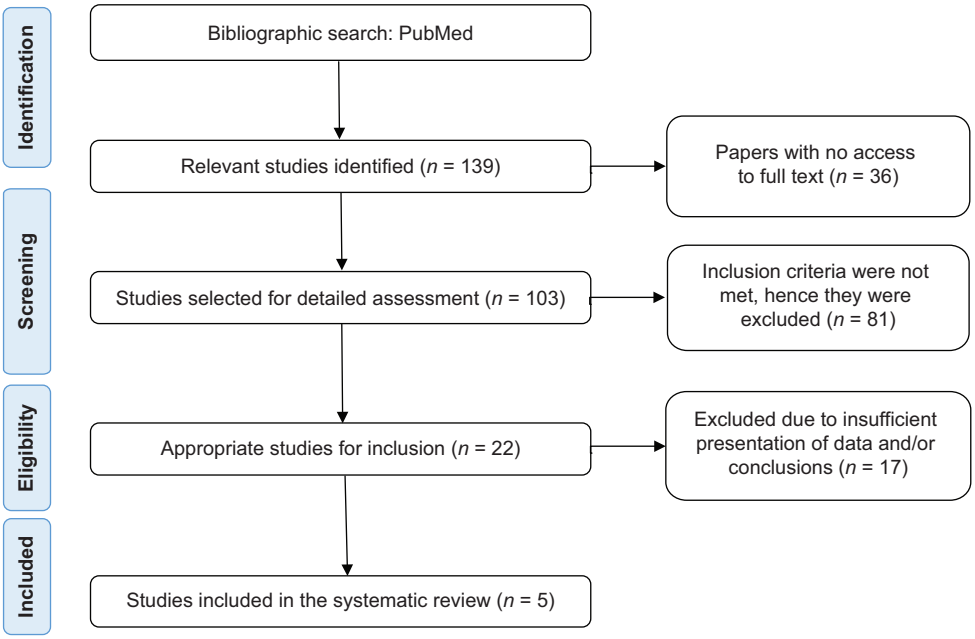
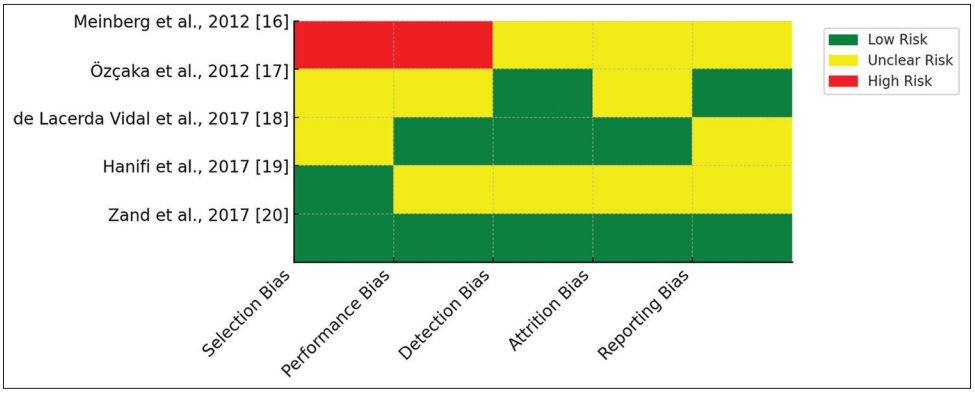


Figure 1: Preferred reporting items for systematic reviews and meta-analyses flowchart depicting the literature search and study selection process for the systematic review

Table 1: Characteristics of included RCTs evaluating CHX for the prevention of VAP

Study details	Intervention	Sample Size (n)	VAP Incidence (%)	Main findings
Meinberg *et al.* (2012)[16]	2% CHX gel+toothbrushing vs. placebo+toothbrushing	52 (28 CHX, 24 placebo)	64.3% (CHX) vs. 45.8% (placebo), *P*=0.29	Study terminated early due to futility.
Özçaka *et al.* (2012)[17]	0.2% CHX swabbing vs. saline swabbing	61 (29 CHX, 32 saline)	41.4% (CHX) vs. 68.8% (saline), *P*=0.03	OR=3.12 (95% CI: 1.09–8.91)
de Lacerda Vidal *et al.* (2017)[18]	0.12% CHX gel+toothbrushing vs. 0.12% CHX solution alone	213 (105 intervention, 108 control)	Lower in the CHX group, *P*=0.084	Significant reduction in ventilation time (*P*=0.018)
Hanifi *et al.*(2017)[19]	Ozonated water vs. 0.2% CHX	75 (39 ozonated, 35 CHX)	14.6% (ozonated) vs. 30.6% (CHX), *P*=0.02	Effect observed from day 4 onward
Zand *et al.* (2017)[20]	2% CHX vs. 0.2% CHX	114 (57/group)	Significantly lower in 2% CHX, *P*=0.007	No difference in adverse effects (*P*=0.361)

CHX: Chlorhexidine, VAP: Ventilator-associated pneumonia, OR: Odds ratio, CI: Confidence interval, RCTs: Randomized controlled trials, vs.: Versus



AQ3 **Figure 2:** Risk of bias (RoB) assessment of included studies based on the Cochrane RoB 2.0 tool

blinding.[16] Özçaka *et al*. had unclear risk in selection and performance bias but low risk in detection and reporting, with concerns about attrition bias due to incomplete data addressing.[17] De Lacerda Vidal *et al*. were generally low risk, except for unclear selection and reporting due to a lack of detail in randomization and outcome protocols.[18] Hanifi *et al*. showed a low risk of selection bias but an unclear risk in other areas, lacking a thorough description of outcome assessment and data completeness despite a double-blind design.[19] Zand *et al*. had a low risk across all areas, with well-documented randomization, blinding, and outcome assessment, and were considered the most methodologically sound.[20]

DISCUSSION

This systematic review evaluated the efficacy of CHX against VAP in adult critical care settings. The results showed that CHX did not significantly reduce mortality rates, VAP incidence, ICU stay duration, or mechanical ventilation time compared with the control group, impacting ICU clinical practices and decision-making.

VAP is a serious complication in mechanically ventilated patients and is associated with increased morbidity, mortality, and health care costs.[21] CHX, a broad-spectrum antiseptic, is used for oral care in intubated patients to prevent VAP.[22] However, this study's data suggested that CHX did not significantly lower VAP occurrence, consistent with other studies.[23,24]

Many studies found no significant reduction in mortality rates with CHX use compared to the control group, consistent with previous studies.[25,26] Mortality is influenced by factors such as disease severity, comorbidities, and quality of care. The lack of an impact of CHX on mortality does not imply its ineffectiveness in preventing VAP or improving other ICU patient outcomes.

CHX did not significantly shorten the ICU stay or mechanical ventilation duration compared to the control group, which is consistent with other studies.[27,28] These results may be influenced by factors such as condition severity, comorbidities, and quality of care.

Despite these findings, CHX may offer additional ICU benefits, which were not evaluated in this study. Research has shown CHX is effective in decreasing catheter-related bloodstream infections and surgical site infections, common ICU complications.[29,30] Furthermore, CHX may improve

oral hygiene and patient comfort, which is essential for the well-being of ICU patients.[31]

Although CHX did not significantly reduce VAP, mortality rates, ICU stay duration, or mechanical ventilation time, it should not be eliminated from ICU practice. The decision to use CHX should be based on a comprehensive assessment of its benefits and risks, considering the patient characteristics and clinical settings. For patients at a higher risk of developing VAP or catheter-related bloodstream infections, the potential advantages of CHX may outweigh possible risks.

Bias risk analysis revealed significant variability in study quality. Zand *et al*. consistently showed a low risk, boosting confidence in their results.[20] Meinberg *et al*. and Hanifi *et al*. raised concerns about the study design and methodological reporting transparency.[16,19] High or uncertain risks of selection and performance bias were common, often due to inadequate reporting of randomization techniques and lack of allocation concealment, potentially causing systematic group differences and impacting internal validity. Several studies have shown unclear detection bias, highlighting the need for stringent blinding, especially when assessing outcomes such as VAP, which may be diagnosed subjectively. Attrition and reporting biases were inconsistently addressed, with some studies lacking complete data on patient follow-up or fully prespecified outcomes, possibly leading to selective reporting and underestimation of adverse events and secondary outcomes. The bias risk assessment underscores the importance of methodological rigor and transparent reporting in clinical trials evaluating oral care interventions in the ICU settings. Variability in study quality should be considered when interpreting the overall results and generalizability of this systematic review's findings.

CONCLUSION

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REFERENCES

1. Safdar N, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: A systematic review. Crit Care Med 2005;33:2184-93.
2. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165:867-903.
3. Kollef MH. Prevention of hospital-associated pneumonia and ventilator-associated pneumonia. Crit Care Med 2004;32:1396-405.
4. Lewis SR, Schofield-Robinson OJ, Rhodes S, Smith AF. Chlorhexidine bathing of the critically ill for the prevention of hospital-acquired infection. Cochrane Database Syst Rev 2019;8:CD012248.
5. Bouadma L, Karpanen T, Elliott T. Chlorhexidine use in adult patients on ICU. Intensive Care Med 2018;44:2232-4.
6. Marshall AP, Weisbrodt L, Rose L, Duncan E, Prior M, Todd L, *et al.* Implementing selective digestive tract decontamination in the intensive care unit: A qualitative analysis of nurse-identified considerations. Heart Lung 2014;43:13-8.
7. Keykha A, Ramezani M, Amini S, Karimi Moonaghi H. Oropharyngeal decontamination for prevention of vap in patients admitted to intensive care units: A systematic review. J Caring Sci 2022;11:178-87.
8. Veitz-Keenan A, Ferraiolo DM. Oral care with chlorhexidine seems effective for reducing the incidence of ventilator-associated pneumonia. Evid Based Dent 2017;18:113-4.
9. Seguin P, Laviolle B, Dahyot-Fizelier C, Dumont R, Veber B, Gergaud S, *et al.* Effect of oropharyngeal povidone-iodine preventive oral care on ventilator-associated pneumonia in severely brain-injured or cerebral hemorrhage patients: A multicenter, randomized controlled trial. Crit Care Med 2014;42:1-8.
10. Keyt H, Faverio P, Restrepo MI. Prevention of ventilator-associated pneumonia in the intensive care unit: A review of the clinically relevant recent advancements. Indian J Med Res 2014;139:814-21.
11. Frost SA, Hou YC, Lombardo L, Metcalfe L, Lynch JM, Hunt L, *et al.* Evidence for the effectiveness of chlorhexidine bathing and health care-associated infections among adult intensive care patients: A trial sequential meta-analysis. BMC Infect Dis 2018;18:679.
12. Villar CC, Pannuti CM, Nery DM, Morillo CM, Carmona MJ, Romito GA. Effectiveness of intraoral chlorhexidine protocols in the prevention of ventilator-associated pneumonia: Meta-analysis and systematic review. Respir Care 2016;61:1245-59.
13. Zhang TT, Tang SS, Fu LJ. The effectiveness of different concentrations of chlorhexidine for prevention of ventilator-associated pneumonia: A meta-analysis. J Clin Nurs 2014;23:1461-75.
14. Carvajal C, Pobo A, Díaz E, Lisboa T, Llauradó M, Rello J. Oral hygiene with chlorhexidine on the prevention of ventilator-associated pneumonia in intubated patients: A systematic review of randomized clinical trials. Med Clin (Barc) 2010;135:491-7.
15. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
16. Meinberg MC, Cheade MF, Miranda AL, Fachini MM, Lobo SM. The use of 2% chlorhexidine gel and toothbrushing for oral hygiene of patients receiving

mechanical ventilation: Effects on ventilator-associated pneumonia. Rev Bras Ter Intensiva 2012;24:369-74.
17. Özçaka Ö, Başoğlu OK, Buduneli N, Taşbakan MS, Bacakoğlu F, Kinane DF. Chlorhexidine decreases the risk of ventilator-associated pneumonia in intensive care unit patients: A randomized clinical trial. J Periodontal Res 2012;47:584-92.
18. de Lacerda Vidal CF, Vidal AK, Monteiro JG Jr., Cavalcanti A, Henriques AP, Oliveira M, *et al.* Impact of oral hygiene involving toothbrushing versus chlorhexidine in the prevention of ventilator-associated pneumonia: A randomized study. BMC Infect Dis 2017;17:112.
19. Hanifi N, Masoumi M, Jamshidi MR, Faghihzadeh S. The effect of ozonated water and chlorhexidine gluconate on prevention of ventilator- associated pneumonia: A double-blind, randomized, clinical trial. Iran Red Crescent Med J 2017;19:e60576.
20. Zand F, Zahed L, Mansouri P, Dehghanrad F, Bahrani M, Ghorbani M. The effects of oral rinse with 0.2% and 2% chlorhexidine on oropharyngeal colonization and ventilator associated pneumonia in adults' intensive care units. J Crit Care 2017;40:318-22.
21. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, *et al.* International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). Eur Respir J 2017;50:1700582.
22. Labeau SO, Van de Vyver K, Brusselaers N, Vogelaers D, Blot SI. Prevention of ventilator-associated pneumonia with oral antiseptics: A systematic review and meta-analysis. Lancet Infect Dis 2011;11:845-54.
23. Klompas M, Speck K, Howell MD, Greene LR, Berenholtz SM. Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: Systematic review and meta-analysis. JAMA Intern Med 2014;174:751-61.
24. Price R, MacLennan G, Glen J, SuDDICU Collaboration. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. BMJ 2014;348:g2197.
25. Tantipong H, Morkchareonpong C, Jaiyindee S, Thamlikitkul V. Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia. Infect Control Hosp Epidemiol 2008;29:131-6.
26. Deschepper M, Waegeman W, Eeckloo K, Vogelaers D, Blot S. Effects of chlorhexidine gluconate oral care on hospital mortality: A hospital-wide, observational cohort study. Intensive Care Med 2018;44:1017-26.
27. Chan EY, Ruest A, Meade MO, Cook DJ. Oral decontamination for prevention of pneumonia in mechanically ventilated adults: Systematic review and meta-analysis. BMJ 2007;334:889.
28. Silvestri L, van Saene HK, Milanese M, Gregori D, Gullo A. Selective decontamination of the digestive tract reduces bacterial bloodstream infection and mortality in critically ill patients. Systematic review of randomized, controlled trials. J Hosp Infect 2007;65:187-203.
29. Darouiche RO, Wall MJ Jr., Itani KM, Otterson MF, Webb AL, Carrick MM, *et al.* Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. N Engl J Med 2010;362:18-26.
30. Mimoz O, Lucet JC, Kerforne T, Pascal J, Souweine B, Goudet V, *et al.* Skin antisepsis with chlorhexidine-alcohol versus povidone iodine-alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): An open-label, multicentre, randomised, controlled, two-by-two factorial trial. Lancet 2015;386:2069-77.
31. Terezakis E, Needleman I, Kumar N, Moles D, Agudo E. The impact of hospitalization on oral health: A systematic review. J Clin Periodontol 2011;38:628-36.

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