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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Chlorhexidine for Oral Care: A Review of Clinical Effectiveness and Guidelines

Service Line: Rapid Response Service
Version: 1.0
Publication Date: January 25, 2019
Report Length: 45 Pages

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Cite As: Chlorhexidine for Oral Care: A Review of Clinical Effectiveness and Guidelines. Ottawa: CADTH; 2019 Jan. (CADTH rapid response report: summary with critical appraisal).

Acknowledgments:

ISSN: 1922-8147 (online)

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Abbreviations

AHA	American Hospital Association
ALAT	Asociación Latinoamericana del Tórax
AGREE II	Appraisal of Guidelines for Research and Evaluation II
APIC	Association for Professionals in Infection Control and Epidemiology
CHX	Chlorhexidine
CI	Confidence interval
ERS	European Respiratory Society
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESICM	European Society of Intensive Care Medicine
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GI	Gingival index
GSC	Glasgow Coma Scale
HAP	Hospital-acquired pneumonia
HTA	Health technology assessment
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
MCPIS	Modified clinical pulmonary score
MA	Meta-analysis
MCPIS	Modified clinical pulmonary score
MDRGNB	Multi-drug resistant gram negative-bacteria
MV	Mechanical ventilation
NP	Nosocomial pneumonia
NR	Not reported
OHI-S	Oral Hygiene Index Simplified score
OR	Odds ratio
PICO	Population, intervention, comparator and outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
SD	Standard deviation
SDD	Selective digestive tract decontamination
SHEA	Society for Healthcare Epidemiology of America
SOD	Selective oropharyngeal decontamination
SOFA	Sequential organ failure assessment
SR	Systematic review
VAP	Ventilator-associated pneumonia

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Context and Policy Issues

Nosocomial pneumonia (NP) is a lower respiratory tract infection acquired during hospital stay in non-intubated patients that occurs after two or more days of hospitalization.[1] Ventilator-associated pneumonia (VAP) is hospital-acquired pneumonia that presents in patients receiving mechanical ventilation through an endotracheal tube at time of admission for at least 48 hours.[1] The main mechanism in the development of VAP is the continuous aspiration of pathogenic microorganisms that colonize the upper respiratory tract or respiratory support equipment into the lower respiratory tract.[1] NP and VAP are the most common cause of death among hospital-acquired infections, with mortality rates of up to 33%.[1] In Canada, VAP is responsible for approximately 230 deaths per year, and the cost for treatment of VAP to the healthcare system is estimated to be $46 million per year and approximately $11,500 per case.[2]

Chlorhexidine gluconate is an antiseptic agent with a broad spectrum (gram-positive bacteria, gram-negative bacteria, and yeast) that has been widely included in different hospitals' protocols for oral hygiene care in intubated patients to reduce the incidence of VAP.[3,4] Previous practice guidelines published in the US, Canada and Europe in 2008 and 2010 have recommended that daily oral care with chlorhexidine should be considered for all patients receiving mechanical ventilation.[5-8] However, recent re-examination of the evidence on the effectiveness and safety of chlorhexidine has questioned the indiscriminate use of chlorhexidine oral care in all hospitalized patients.[9]

The aim of this report is to review the clinical effectiveness and evidence-based guidelines on the use of chlorhexidine for oral care in hospitalized patients.

Research Questions

1. What is the clinical effectiveness of Chlorhexidine for oral care in hospitalized adults?
2. What are the evidence-based guidelines regarding the use of Chlorhexidine for oral care in hospitalized adults?

Key Findings

Chlorhexidine oral care was effective for the prevention of nosocomial pneumonia (NP), ventilator-associated pneumonia (VAP) and bloodstream infection among adult populations in cardiothoracic intensive care units (ICUs), but evidence is unclear in the medical or non-cardiac surgery ICUs. Chlorhexidine was associated with a high risk of mortality in non-cardiac surgery patients. The effectiveness of chlorhexidine of different strengths, preparation or frequency of use for the prevention of NP and VAP was inconclusive. There was no evidence for an association between chlorhexidine and the reductions in duration of ventilation, duration of ICU stay, antibiotic exposures or oral health indices. Oral mucosal lesions were common adverse events associated with chlorhexidine. Current guidelines provided no formal recommendations due to the uncertainty in the risk-benefit balance of chlorhexidine oral care.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized control trials and guidelines. An additional focused search on the patient population was also conducted. No filters were applied to the focused search to limit the retrieval by study type. Both searches were limited to English language documents published between January 1, 2013 and December 21, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1&Q2: Hospitalized adults
Intervention	Q1&Q2: Chlorhexidine oral swabs or oral mouth rinse
Comparator	Q1: Any comparator Q2: N/A
Outcomes	Q1: Clinical effectiveness (benefit, Harms, safety, mortality, morbidity) Q2: Guidelines
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), non-randomized studies, and evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1 and if they were published prior to 2014. Systematic reviews, in which their included studies were overlapped with another SR published at a later date, were excluded. Primary studies were also excluded if they had been included in the identified SRs. Non-evidence based guidelines were excluded.

Critical Appraisal of Individual Studies

The AMSTAR-2 checklist was used to assess the quality of SRs.[10] The SIGN checklist was used to assess the quality of the included randomized controlled trials (RCTs).[11] The quality of the evidence-based guidelines was assessed using AGREE II instrument.[12] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 408 citations were identified in the literature search. Following screening of titles and abstracts, 372 citations were excluded and 36 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search. Of the 39 potentially relevant articles, 21 publications were excluded for various reasons, while 18 publications including one overview of SRs, nine SRs, five additional primary studies (RCTs), and three guidelines met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The characteristics of the identified overview of SRs[13] (Table 2), SRs[14-22] (Table 3), and primary studies[23-27] (Table 4) are presented in Appendix 2.

Study Design

The overview of SRs [13] performed an electronic search in major databases from inception to September 2016 for relevant SRs. A hand search and grey literature search were also performed.

Eight of the identified SRs[14-16,18-22] included RCTs and one identified SR[17] included RCTs and quasi-experimental studies. Search periods of the SRs varied.

All additional primary studies were RCTs. Three RCTs[23,25,27] were single-center, and two RCTs[24,26] were multicenter. Four RCTs[23-26] were open-label, and one RCT[27] was single-blinded. Four RCTs[23-25,27] included a parallel design, and one RCT[26] was cross-over design.

Country of Origin

The overview of SRs [13] was conducted in Brazil and was published in 2018.

The identified SRs were conducted by authors from Turkey,[14] Italy,[15,21] China,[16,22] Denmark,[17] Brazil,[18] USA,[28] and UK.[20]

The additional primary studies were conducted in Iran,[23,25] Sweden,[24] the Netherlands[26] and China,[27] and were published in 2018[23-25] and 2015.[27]

Population and Setting

Of the 16 SRs included in the overview of SRs, 15 involved ventilated and non-ventilated adult patients and one had a mixed population of adults and children, but mostly adults.[13] The overview of SRs included different types of ICU settings (e.g., surgical, medical, trauma, neuroscience, etc.).[13]

Five of the identified SRs included studies involving adult patients only,[14,15,17,19,20] two SRs included studies with mixed populations,[16,21] and two SRs included studies with patients greater than 15 years of age.[18,22] However, patients were mostly adults in studies involving mixed populations or patients greater than 15 years of age. All patients required intubation or mechanical ventilation, and were admitted to ICUs of different settings including, medical, cardiac surgery, thoracic surgery, trauma, respiratory or neuroscience surgery.

In the additional primary studies, participants were adult patients receiving mechanical ventilation and/or orotracheal intubation in ICUs of trauma,[23] medical,[24-26] and cardiac surgery.[27] Mean age ranged from 41 to 65 years. Percentage of male was higher than female (ranging from 51% to 74%).

Interventions and Comparators

In the overview of SRs, the interventions were chlorhexidine at 0.12% to 2.0% in the form of solution or gel used for oral healthcare in association with manual or electric toothbrushing and standard care of the ICUs.[13] Various controls were identified including placebo, solution of phenolic mixture, isotonic bicarbonate solution, hydrogen peroxide, Vaseline, normal saline, 0.01% potassium permanganate, and sterile water, associated with manual or electronic brushing.[13]

In the identified SRs, all assessed the effectiveness and/or safety of chlorhexidine for oral hygiene care in patients admitted in ICUs. The chlorhexidine, formulated as solution, gel, Vaseline petroleum jelly or foam, varied in concentrations, from 0.1% to 2.0%. It was applied as mouth rinse or swab with varying frequencies, ranging from one to four times per day. In eight SRs,[14-19,21,22] chlorhexidine was compared with placebo or usual care with or without tooth brushing. In one SR which conducted a network meta-analysis,[20] chlorhexidine was compared with "selective digestive decontamination" (SDD) and "selective oropharyngeal decontamination" (SOD).

In the additional primary studies, one RCT[25] compared 0.2% chlorhexidine and 0.01% sodium permanganate mouthwash solutions (3 times daily) with placebo. One RCT[27] compared 0.2% chlorhexidine mouthwash solution (4 times daily) with normal saline. One RCT[23] compared 2% nanosil solution with 2% chlorhexidine solution (3 times daily). One RCT[24] compared swabbing of probiotic bacterium Lactobacillus plantarum 299 (Lp299) with swabbing with 0.1% chlorhexidine solution (2 times daily). One cross-over RCT[26] compared 2% chlorhexidine mouthwash solution, SDD and SOD with baseline. After reporting of oral mucosal adverse effects in 29 of 295 (9.8%) patients, 1% chlorhexidine oral gel was used instead.[26] The frequency of application was 4 times daily.[26]

Outcomes

In the overview of SRs, the outcomes investigated in this study were incidence of NP or lower tract infections, and incidence of VAP.[13] VAP was diagnosed based on the clinical pulmonary infection score (CPIS), criteria of the Center for Disease Control and Prevention and reference of American Thoracic Society / Infectious Disease Society of America.[13]

The reported outcomes varied among identified SRs, including NP, VAP, bloodstream infection, deep surgical site infection, urinary tract infection, mortality, oral health indices, ICU length of stay, hospital length of stay, duration of ventilation, antibiotic exposures, and adverse events.

The outcomes investigated in the additional primary studies included VAP, mortality, ICU stay, ventilator day, ICU-acquired bloodstream infection with antibiotic-resistant bacteria, and adverse events.

Treatment Duration

Treatment duration was not reported in the overview of SRs.[13]

In the identified SRs and additional primary studies, treatment duration continued until extubation, ICU discharge or death.

Quality Appraisal

The authors of the overview of SRs used the AMSTAR checklist to assess the methodological quality of the SRs, and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system to evaluate the quality of evidence and strength of recommendation.[13]

The authors in six SRs used the Cochrane risk of bias tool was used to assess the methodological quality of included studies.[14-16,18,20,22] The authors of one SR[21] used Jadad scores and one SR[17] used the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (MAStARI) to assess the methodological quality of included studies. The authors of another SR[17] used GRADE to assess the quality of evidence.

Data Analysis and Synthesis

One SR analyzed the data using narrative synthesis approach,[14] while eight SRs[15-22] synthesized the data using pairwise meta-analysis. One SR[20] used network meta-analysis in addition to pairwise meta-analysis. Subgroup analysis was performed based on concentration of chlorhexidine, formulation of chlorhexidine, frequency of chlorhexidine application, type of ICU, type of populations, and type of microorganisms.

In the additional primary studies, all RCTs used various statistical methods for comparisons of observations between treatments. None of the RCTs used an intention-to-treat approach in their analyses. Two RCTs[26,27] reported sample size calculations.

Guidelines

The characteristics of the identified guidelines[29-31] are presented in Table 5 in Appendix 2

Country of Origin

Three identified evidence-based guidelines (European Respiratory Society/European Society of Intensive Care Medicine/European Society of Clinical Microbiology and Infectious Diseases/ Asociación Latinoamericana del Tórax [ERS/ESICM/ESCMID/ALAT],[29] Society for Healthcare Epidemiology of America/Infectious Disease Society of America/Association for Professionals in Infection Control [SHEA/IDSA/APIC],[30] "Zero-VAP"[31]) were from Europe,[29] USA,[30] and Spain,[31] and were published in 2017[29] and 2014.[30,31]

Objectives

The overall objectives of the guidelines[29-31] were to provide recommendations related to effective treatments, implementation and strategies to prevent VAP and other hospital-associated infections in mechanical ventilated patients.

Target Users of the Guidelines

The guidelines[29-31] were targeted to healthcare workers (e.g., specialists in respiratory medicine and critical care managing adults with hospital-associated pneumonia or VAP, general internists, specialists in infectious diseases, pharmacists, microbiologists) and policy makers.

Methods Used to Formulate Recommendations

Systematic methods used to search for evidence was not provided in two guidelines.[30,31] The level of evidence and grade of recommendations were assessed using GRADE in the guidelines.[29-31]

Summary of Critical Appraisal

The quality assessment of the included overview of SRs[13] and SRs[14-22] is presented in Table 6 and Table 7 in Appendix 3. The quality assessment of the included primary studies is presented in Table 8 in Appendix 3. The quality assessment of the included guidelines is presented in Table 9 in Appendix 3.

All SRs, including the overview of SRs,[13] provided appropriate research questions, explanations for selection of the study designs for the inclusion, used comprehensive literature search strategies, performed study selection and data extraction in duplicate, described the included studies in adequate detail and used appropriate methods for statistical combination of results in meta-analyses. None of the SRs provided lists of excluded studies, reported the sources of funding of the included studies, and accounted for risk of bias in individual studies when interpreting or discussing the results. All SRs, except two,[19,20] did not carry out investigation of publication bias. All SRs, except two,[17,20] provided a satisfactory explanation for, discussion of, any heterogeneity observed in the results of the review. Three SRs[15,20,21] did not report potential sources of conflict of interest.

All of the additional primary studies provided appropriate research questions, conducted randomization, indicated similarities in patient characteristics between groups, and used valid and reliable methods to measure relevant outcomes. Four RCTs[23-26] were open-label and one was patient-blinded.[27] There were no dropout patients in all RCTs. For multicentre RCTs,[24,26] it was unclear if the results were comparable for all sites.

The included guidelines[29-31] were explicit in terms of scope and purpose, and clarity of presentation, but not completely clear for other components such as stakeholder involvement, rigour of development, applicability and editorial independence. For stakeholder involvement, the guidelines[29-31] did not report if the views and preferences of the target population were sought. For rigor of development, two guidelines[30,31] did not report the use of systematic methods to search for evidence, and all guidelines[29-31] did not describe the methods of formulating the recommendations, and were not explicit in terms of external peer-review prior to publication. In terms of applicability, the guidelines[29-31] did not provide advice or tools on how to implement recommendations, and did not state if costs were considered in their recommendations. For editorial independence, it was unclear if the view of the funding body had any influence in the content of the guidelines. [29-31]

Summary of Findings

The main findings and conclusions of the included studies are presented in Table 10, Table 11 and Table 12 in Appendix 4.

Clinical Effectiveness

Comparison 1: Chlorhexidine versus placebo or usual care

Incidence of NP or lower respiratory tract infections

Three SRs in the overview[13] and one identified SR[17] reported a significant difference in favor of chlorhexidine in the reduction of overall NP incidence, while one SR in the overview[13] found no significant difference between groups.

- Subgroup analysis by patient population revealed that the use of oral chlorhexidine was associated with a significant reduction in the incidence of NP in patients who underwent heart surgery (two SRs in the overview[13] and one identified SR[17]), but not in non-cardiac surgery patients regardless of chlorhexidine concentrations (0.1%, 0.2% or 2%) (one SR in the overview[13]).

Incidence of VAP

Eight SRs in the overview,[13] three identified SRs[14,16,22] and one identified RCT[25] reported a significant difference in favor of chlorhexidine in the reduction of overall VAP incidence, while one SR in the overview[13] and one identified SR[18] fond no significant difference between groups. One identified RCT[27] showed that preoperative mouthwash with chlorhexidine significantly reduced incidence of postoperative VAP compared to normal saline in cardiac surgery patients.

- In subgroup analysis based on patient population, the results significantly favored the use of chlorhexidine in cardiac surgery patients (five SRs in the overview[13]), but not in non-cardiac surgery patients (one SR in the overview[13]). One SR in the overview[13] showed that chlorhexidine was associated with significant reduction of VAP in cardiac surgery patients as well as in non-cardiac surgery patients.
- In subgroup analysis based on chlorhexidine concentration, seven SRs in the overview[13] and one identified SR[14] found that chlorhexidine was associated with significant reduction of VAP incidence at any concentrations (i.e., 0.12% to 2.0%), while four SRs in the overview[13] found no significant results with chlorhexidine concentrations of 0.12% or 1.2%. One identified SR,[18] through its subgroup analysis, showed that chlorhexidine at 2%, but not at 0.12% and 0.2%, promoted a significant reduction in VAP incidence. One identified SR[22] showed that significant reduction in VAP incidence was associated with chlorhexidine at 0.12% or 2%, but not at 0.2%.
- In subgroup analysis based on formulation (solution or gel), the results of one of the identified SRs were significantly in favor of chlorhexidine solution compared to control (placebo or usual care) when used without tooth brushing in either group.[16] With toothbrushing, chlorhexidine either formulated as solution or gel did not show any significant difference in the incidence of VAP compared to control.[16]
- In subgroup analysis based on frequency of treatment, one identified SR[18] showed that only the use of four times daily resulted in a significant difference in favor of chlorhexidine. Another identified SR[14] reported that the use of chlorhexidine two or four times per day was effective in reducing VAP incidence.
- Subgroup analysis in one identified SR[18] investigated chlorhexidine used as monotherapy or in combination with mechanical cleansing of the oral cavity showed that chlorhexidine used either way failed to reduce VAP incidence.

Mortality

The results from four identified SRs[15,16,19,21] and one identified RCT[25] showed that chlorhexidine did not significantly reduce overall mortality among critically ill patients admitted in ICUs compared to placebo or usual care. One identified crossover RCT[26] also found that chlorhexidine was not associated with reduction in mortality compared to baseline.

- In subgroup analysis, chlorhexidine did not significantly reduce mortality irrespective to the type of population (surgical or medical),[15,21] chlorhexidine concentration (0.12%

to 2%),[15,19,21] and chlorhexidine formulation (solution or gel, with or without toothbrushing).[16,19]

- One identified SR[19] found that mortality risk was higher, although not statistically significant, across non-cardiac surgery studies. The effect estimates for mortality increased with increasing concentrations of chlorhexidine.[19] One identified SR[20] showed that chlorhexidine was associated with significant increased mortality (OR 1.25; 95% CI 1.05 to 1.50; 11 RCTs) in non-cardiac surgery patients compared with control (placebo or usual care).

Bloodstream infection

The results from one identified SR[15] showed that chlorhexidine did not significantly reduce bloodstream infection among critically ill patients admitted in ICUs. One identified crossover RCT[26] found that chlorhexidine was not associated with reductions in ICU-acquired bloodstream infection with multidrug-resistant gram-negative bacteria compared to baseline.

- Subgroup analysis based on type of population showed that chlorhexidine was associated with significant reduction of bloodstream infection in surgical patients, but not in medical or mixed populations.[15]
- Subgroup analysis based on chlorhexidine concentration showed that chlorhexidine at 0.12%, but not at 0.2%, was associated with significant reduction of bloodstream infection.[15]
- Chlorhexidine did not significantly reduce bloodstream infection when analyzed by type of microorganisms.[15]

Other types of infection

One identified SR[17] reported that among patients admitted to elective thoracic surgery, chlorhexidine significantly reduced deep surgical site infection compared to usual care. There was evidence of difference in urinary tract infection between groups.

Duration of ventilation (days)

Meta-analysis from two identified SRs[16,19] showed no evidence of a difference in the duration of ventilation between chlorhexidine and placebo/usual care groups. There was also no difference in duration of ventilation in subgroups based on formulation (solution or gel), and with or without toothbrushing.[16]

Duration of ICU stay (days)

Meta-analysis from two identified SRs[16,19] showed no evidence of a difference in the duration of ICU stay between chlorhexidine and placebo/usual care groups. There was also no difference in duration of ICU stay in subgroups based on formulation (solution or gel), and with or without toothbrushing.[16]

Antibiotic exposures

Two identified SRs[16,19] found no evidence of a difference in the duration of systemic antibiotic therapy between chlorhexidine and placebo or usual care groups.

Oral health indices: Plaque index

There was no difference in plaque indices between chlorhexidine and placebo or usual care groups.[16]

Adverse events

Two identified SRs reported adverse events.[16,22] Common adverse event associated with chlorhexidine was irritation of oral mucosa (10% in chlorhexidine and 1% in control),[16] especially with chlorhexidine 2% mouthwash.[26,32] Other transient and reversible adverse events included staining and discoloration of teeth, unpleasant taste and dysgeusia.[22]

Comparison 2: Chlorhexidine versus "Selective digestive decontamination (SDD)" versus "Selective oropharyngeal decontamination (SOD)"

Direct evidence (pairwise meta-analysis) from one identified SR[20] showed that chlorhexidine was associated with increased mortality (OR 1.25; 95% CI 1.05 to 1.50; 11 RCTs), while SDD (OR 0.73; 95% CI 0.64 to 0.84; 15 RCTs) and SOD (OR 0.85; 95% CI 0.74 to 0.97; 4 RCTs) reduced mortality in non-cardiac surgery patients. When the interventions were compared with each other using direct and indirect evidence in a network meta-analysis, SDD and SOD were superior to chlorhexidine in the prevention of mortality.[20]

Comparison 3: Chlorhexidine versus probiotic bacterium Lactobacillus plantarum 299 (Lp299)

In patients receiving mechanical ventilation in ICUs, one identified RCT[24] did not find any difference between chlorhexidine and Lp229 in the incidence of VAP, ICU mortality, additional in-hospital mortality, duration of ICU stay, duration of ventilation, and total number of bacteria or fungi. However, fewer patients in the Lp229 group had fungi compared to those in the chlorhexidine group (RR 0.53; 95% CI 0.30 to 0.95).

Guidelines

The Spanish guideline ("Zero-VAP" bundle)[31] for the prevention of VAP recommended that chlorhexidine solution (0.12% to 2%) should be used every 8 hours for oral hygiene in ventilated patients admitted in ICU. The SHEA/IDSA guideline,[30] in its special approaches category, downgraded oral care with chlorhexidine from basic practices to special approaches due to possible risks. It stated that oral care with chlorhexidine may reduce incidence of VAP, but there were insufficient data of its impact on duration of ventilation, ICU length of stay and mortality. Both of these guidelines were published in 2014. A recent European guideline (ERS/ESICM/ESCMID/ALAT),[29] published in 2017, provided no formal recommendation on the use of chlorhexidine for oral care in patients required mechanical ventilation due to lack of safety data and unclear balance between potential reduction in VAP and potential increase in mortality.

Limitations

For clinical effectiveness, important identified limitations included the heterogeneity of the ICU populations, types of included studies in the meta-analysis (blinded and non-blinded studies), variability in diagnostic criteria of VAP, variability in nursing care protocols among ICUs, variability in the interventions (chlorhexidine preparation and strength) and control groups, and variability in time point at which mortality was measured. To overcome some of these limitations, subgroup analyses were performed in most SRs. Few studies reported the adverse events associated with oral care with chlorhexidine.

For guideline recommendations, two of three identified guidelines were not explicit in their recommendations on the use of chlorhexidine for oral care in patients admitted in ICU, due to limited, mixed or insufficient evidence.

Conclusions and Implications for Decision or Policy Making

Evidence suggests that chlorhexidine is effective in oral care for the prevention of NP and VAP in adult patients admitted in ICUs. However, subgroup analysis showed that effect of chlorhexidine for the prevention of NP and VAP was significant among adult populations in cardiothoracic ICUs, but unclear in the medical or non-cardiac surgery ICUs. This may be due to shorter intubation period in cardiothoracic ICUs, usually 12 to 24 hours, compared to the intubation period in other types of ICUs, where patients are intubated at least 48 hours after admission that provided higher chance for the development of VAP.[9] The effectiveness of chlorhexidine of different strengths, preparation or frequency of use for the prevention of NP and VAP was inconclusive. Oral care with chlorhexidine may increase mortality risk, especially in non-cardiac surgery patients. The increased mortality risk by chlorhexidine was further supported by a network meta-analysis, in which direct and indirect evidence showed that oral care with chlorhexidine was associated with increased mortality in non-cardiac surgery patients. The network meta-analysis also showed that chlorhexidine was inferior to SDD and SOD in the prevention of mortality. It was speculated that acute respiratory distress syndrome (ARDS) may develop in some patients who aspire chlorhexidine into the lung, thus increasing in mortality risk.[9] However, aspiration of chlorhexidine leading to fatal ARDS has not been empirically proven.[9] There was no evidence that chlorhexidine was associated with significant reductions in duration of ventilation, duration of ICU stay, antibiotic exposures or oral health indices. Chlorhexidine appeared to reduce ICU-acquired bloodstream infection in surgical patients, but not in medical or mixed populations. Oral care using probiotics Lp299 was found as effective as chlorhexidine in mechanically ventilated patients. Oral mucosal lesions were common adverse events associated with chlorhexidine. Given the uncertainty in the risk-benefit balance of oral care with chlorhexidine, current guidelines were hesitant to give formal recommendations. Further studies are needed to provide new insight on the risk-benefit balance of chlorhexidine, or to explore alternative interventions, such as SDD, SOD or probiotics, with clearer evidence of benefit and risk.

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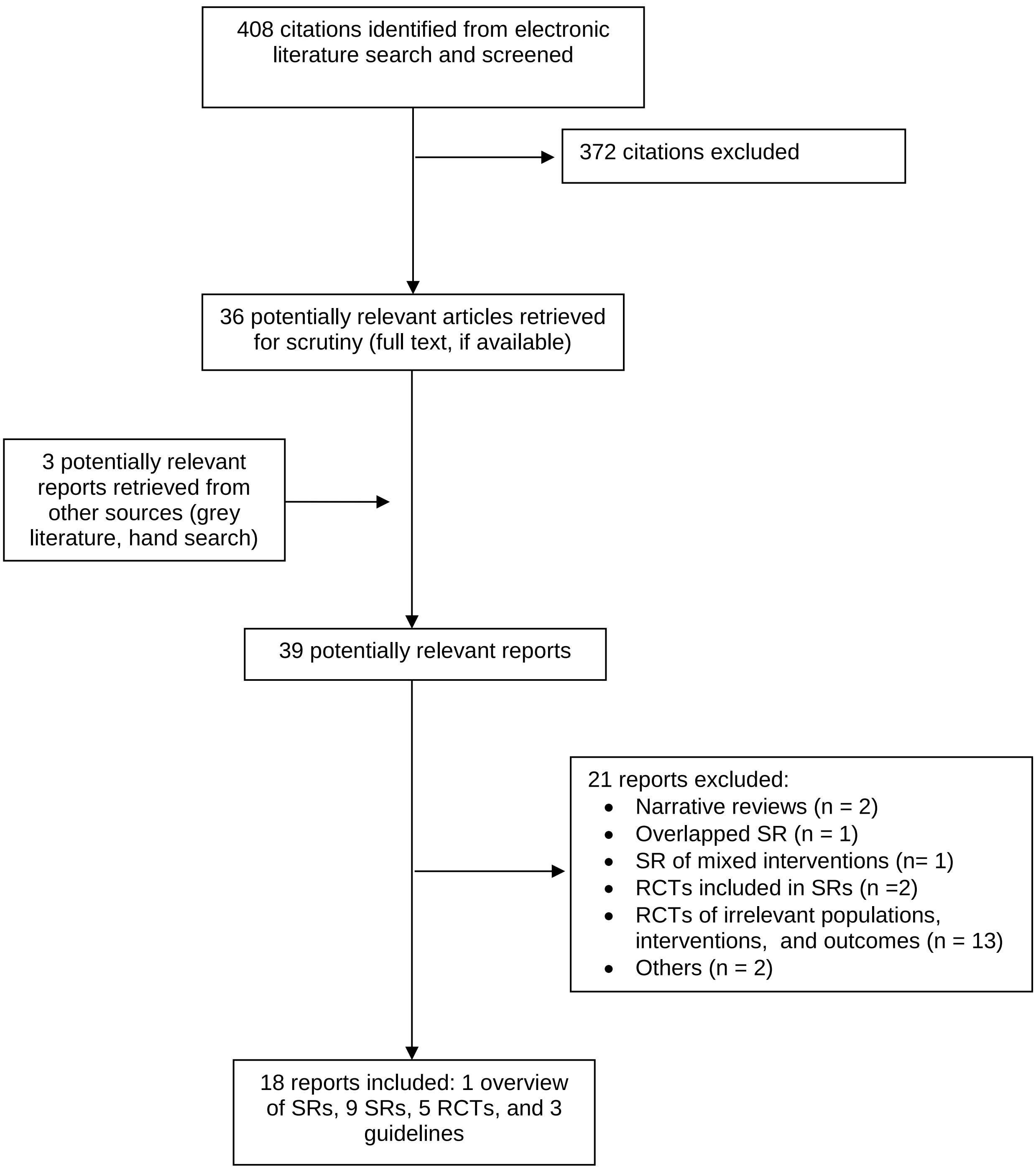
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Overview of Systematic Reviews

First Author, Publication Year, Country, Funding	Numbers of Systematic Reviews Included, Quality Appraisal, Databases and Search Date	Treatment Setting	Interventions and Control	Outcomes
Rabello et al., 2018[13] Brazil Funding: No specific grant from any funding agency	16 SRs, including 14 meta-analysis AMSTAR checklist, GRADE PUBMED, Cochrane Library, LILACS, CRD, CINHAL, manual search and grey literature Since inception to September 2016	ICUs	Interventions: Chlorhexidine (0.12% to 2% solution or gel) for oral healthcare, associated with manual or electric toothbrushing and standard care of the institutions. Control: varies (placebo, solution of phenolic mixture, isotonic bicarbonate solution, hydrogen peroxide, Vaseline, normal saline, 0.01% potassium permanganate, sterile water, manual or electronic brushing Volume: 2 to 20 ml Application: Spray, oropharyngeal lavage, with swap or sponge Frequency: 1 to 4 times per day	– Nosocomial pneumonia (NP) or lower respiratory tract infections – Ventilator-assisted pneumonia (VAP), reported after 48 hours of ventilation (Diagnostic methods of VAP: Clinical pulmonary infection score (CPIS), criteria of the Center for Disease Control and Prevention and reference of American Thoracic Society / Infectious Disease Society of America)

ICU = intensive care unit; NP = nosocomial pneumonia; SR = systematic review; VAP = ventilator-associated pneumonia

Table 3: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Types of Comparisons, Treatment Setting, Dose, Duration of Treatment	Outcomes
Guler and Turk, 2018[14] Turkey Funding: No financial support	Objectives: To determine the effect of chlorhexidine at different concentration and frequency on VAP and microbial colonization in mechanically ventilated patients 10 RCTs (single-blinded, double-blinded) published from 2010 to 2017 Cochrane risk of bias PubMed, EMBASE, Cochrane Library, CINAHL, Web of Science, and MEDLINE databases. Google Scholar and Ulakbilim National Search Engine. Search date: NR	Intubated patients (intubation for ≥ 12 hours or ≥ 72 hours) Age: ≥ 18 years, except ≥ 15 years in two SRs Total 877 patients	Interventions: Chlorhexidine (0.12% to 2% solution or gel) Control: Placebo, sterile water, standard oral care without chlorhexidine, herbal mouth wash, normal saline Frequency: 1 to 4 times per day Setting: Surgical, medical, respiratory, trauma, neuroscience ICU ICU stay: > 3 days MV duration: within 12 hours to 4 days of intubation Duration of treatment: varied	– Development of VAP – Incidence of VAP – Bacterial colonization of dental plaque
Silvestri et al., 2017[15] Italy Funding: NR	Objectives: To determine the effect of oral chlorhexidine on the incidence of blood stream infection, the causative microorganism, and on all-cause mortality in critically ill patients 5 RCTs (double-blinded in 4 RCTs) Cochrane risk of bias PUBMED, CENTRAL Since inception to December 2015	Critically ill adult patients receiving mechanical ventilation in hospital ICUs Age: NR Total 1,655 patients	Interventions: Chlorhexidine (0.12% to 0.2% solution or gel) Control: Placebo, usual care Application: Mouthrinse or swap Frequency: 2 to 4 times per day Setting: medical, surgical, cardiac surgery ICUs Duration of treatment: varied	– Bloodstream infection – Mortality – Microorganisms Subgroup analysis
Hua et al., 2018[16] China Funding: Internal and external sources (Academic)	Objectives: To assess the effects of oral hygiene care on incidence of VAP in critically ill patients receiving mechanical ventilation in hospital ICUs 18 RCTs for chlorhexidine versus	Critically ill patients receiving mechanical ventilation in hospital ICUs, required assistance from nursing staff for oral hygiene care Age: Adults in 15 RCTs and	Interventions: Chlorhexidine (0.12% to 2% solution or gel) Control: Placebo or usual care, with or without toothbrushing	– Incidence of VAP – Mortality – Duration of ventilation – Duration of ICU stay – Use of systemic antibiotics – Oral health indices: plaque

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Types of Comparisons, Treatment Setting, Dose, Duration of Treatment	Outcomes
	placebo / usual care (with or without toothbrushing). Three RCTs involved pediatrics. Cochrane risk of bias Cochrane Oral Health's Trials Register, CENTRAL, MEDLINE, EMBASE, CINAHL, LILACS, Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure, Wan Fang Database, VIP Database. Search date: Varied	children in 3 RCTs Total 2,451 patients	Application: Spray, mouthrinse or swap Frequency: 1 to 4 times per day Setting: Surgical, medical, trauma ICUs Duration of treatment: varied	index – Adverse effects Subgroup analysis Sensitivity analysis
Pedersen et al., 2016[17] Denmark Funding: NR	Objectives: To assess the evidence on the effectiveness of systemic perioperative oral hygiene in the reduction of postoperative respiratory airway infections in adult patients undergoing elective thoracic surgery 6 studies (3 RCTs and 3 quasi-experimental studies); 4 used in meta-analysis JBI Meta-Analysis of Statistics Assessment and Review Instrument (MAStARI), GRADE PUBMED, CINAHL, EMBASE, Scopus, Swemed+, Health Technology Assessment Database, Turning Research Into Practice (TRIP) database Since inception to December 2014	Adults (> 60 years) admitted to elective thoracic surgery Type of surgery: Included, but not limited to, elective or acute Coronary Artery By-pass Grafting (CABG), coronary valve surgery, any type of lung surgery, or surgery for oesophageal cancer. Total 2,470 patients	Interventions: Chlorhexidine (0.12% solution) with toothbrushing in 3 RCTs and 2 quasi-experimental studies. One study used only toothbrushing 5 times per day. Control: Usual care Application: Mouthrinse Frequency: 2 to 4 times per day Setting: Surgical ICUs Duration of treatment: at least one day before surgery and continued until one day after surgery or discharge from ICU	– Nosocomial infections – Lower respiratory tract infections – Surgical site infections – Urinary tract infections
Villar et al., 2016[18] Brazil Funding: NR	Objectives: To assess the evidence of effectiveness of different intraoral chlorhexidine protocols for the prevention of VAP 13 RCTs (three involved children) Cochrane risk of bias	Patients requiring orotracheal or nasotracheal intubation and mechanical ventilation in hospital ICUs Age: >15 years in one RCT, ≥ 18 years in 9 RCTs, and	Interventions: Chlorhexidine (0.12% to 2% solution, gel or foam) Control: Placebo or usual care Application: Mouthrinse, gel,	– Incidence of VAP – Subgroups (chlorhexidine concentration, chlorhexidine frequency of use, chlorhexidine used as monotherapy or in combination with

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Types of Comparisons, Treatment Setting, Dose, Duration of Treatment	Outcomes
	MEDLINE, EMBASE, LILACS Since inception to January 2016	children in 3 RCTs Total 1,640 patients	Vaseline petroleum jelly, foam Frequency: 1 to 4 times per day Setting: Surgical, medical, trauma, neuroscience ICUs; emergency department, general medical wards Duration of treatment: varied or until ICU discharge or death	mechanical means) – Safety
Klompas et al., 2014[19] USA Funding: NR	Objectives: To evaluate the impact of routine oral care with chlorhexidine on patient-centered outcomes in patients receiving mechanical ventilation 16 RCTs Quality assessment based on basis of randomization strategy, allocation concealment, blinding, and completeness of follow-up. PUBMED, EMBASE, Web of Science, and CINAHL Since inception to July 2013	Adult patients receiving mechanical ventilation in ICUs Total 3,630 patients	Interventions: Chlorhexidine (0.12% to 2% solution, or gel) Control: Placebo or usual care Application: Mouthrinse or gel Frequency: 1 to 4 times per day Setting: Cardiac surgery and non-cardiac surgery (surgery, trauma, respiratory, neuroscience) Ventilation duration: 48 hours to 5 days	– Incidence of VAP – Mortality – Duration of mechanical ventilation – ICU length of stay – Hospital length of stay – Antibiotic exposures Subgroup analysis
Price et al., 2014[20] UK Funding: No specific grants from any funding agency in the public, commercial, or not-for-profit sectors	Objectives: To determine the effect on mortality of selective digestive decontamination, selective oropharyngeal decontamination, and topical oropharyngeal chlorhexidine in adult patients in general ICUs, and to compare these interventions with each other in a network meta-analysis 29 RCTs Cochrane risk of bias MEDLINE, EMBASE, CENTRAL	Ventilated and non-ventilated adult patients admitted to ICUs Total patients: NR	Interventions: – “Selective digestive decontamination” = application of a combination of poorly absorbable antibiotics to the oropharynx and the stomach combined with empirical intravenous antibiotics – “Selective oropharyngeal decontamination” = application of a	Mortality

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Types of Comparisons, Treatment Setting, Dose, Duration of Treatment	Outcomes
	Starting date: varied Ending date: December 2012		combination of poorly absorbable antibiotics only to the oropharynx – "Topical oropharyngeal chlorhexidine" = application of any concentration of chlorhexidine in any formulation to the oropharynx Control: placebo or standard care Setting: ICUs Duration of treatment: varied	
Silvestri et al., 2014[21] Italy Funding: NR	Objectives: To determine the evidence of effectiveness of oral chlorhexidine on NP, causative bacteria, and mortality 22 RCTs Jadad scores PUBMRD, EMBASE, CENTRAL Since inception to July 2012	Critically ill patients in ICUs Age: mixed (adults and children) Total 4,277 patients	Interventions: Chlorhexidine (0.12% to 2% solution or gel) Control: Placebo or usual care, with or without toothbrushing Application: mouthrinse, mouth cleansing, toothbrushing, gingival brushing, use of a gloved finger or swab, etc. Frequency: 1 to 4 times per day Setting: Surgical, medical, trauma ICUs Duration of treatment: varied	– Incidence of VAP – Incidence of NP (Gram-positive bacteria, Gram negative bacteria, "normal" and "abnormal" bacteria, type of microorganism) – Mortality Subgroup analysis (randomization, blinded, study quality, chlorhexidine concentration, surgical/medical, adult/children)
Zhang et al., 2014[22] China Funding: NR	Objectives: to evaluate the evidence of effectiveness of chlorhexidine for the prevention of VAP and explore the preferred concentration of chlorhexidine 18 RCTs	Critically ill patients receiving mechanical ventilation in ICUs Age: > 15 years in one RCT, > 18 years in 17 RCTs Total 3,812 patients	Interventions: Chlorhexidine (0.12% to 2% solution or gel) Control: Placebo or usual care, with or without toothbrushing Application: mouthrinse,	Incidence of VAP Adverse effects Subgroup analysis (chlorhexidine concentration)

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Types of Comparisons, Treatment Setting, Dose, Duration of Treatment	Outcomes
	Cochrane risk of bias Cochrane Library, PUBMED, EMBASE, CINAL, CMB disc, CNNKI and Google Scholar Search date: NR		mouth cleansing, toothbrushing, gingival brushing, use of a gloved finger or swab, etc. Frequency: 1 to 4 times per day Setting: Surgical, medical, trauma ICUs Duration of treatment: varied	

ICU = intensive care unit; MV = mechanical ventilation; NP = nosocomial pneumonia; NR = not reported; RCT = randomized controlled trial; VAP = ventilator-associated pneumonia; UK = United Kingdom

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Table 4: Characteristics of Included Primary Studies

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
Khaky et al., 2018[23] Iran Funding: NR	Single-center, open-label, two arms, 1:1 ratio, parallel RCT Analysis: Chi-square test, Fisher's exact test, Mann-Whitney and Wilcoxon test, per protocol Sample size calculation: No	Adult patients receiving mechanical ventilation in ICU Mean age (years): – Intervention: 41.6 – Control: 44.1 Sex (% male): – Intervention: 72.5 – Control: 67.5 Clinical characteristics: Similar in both groups in underlying disease, smoking, and primary mean scores of Glasgow Coma Scale (GCS), modified clinical pulmonary score (MCPIS), and sequential organ failure assessment (SOFA)	15 ml of 2% Nanosil solution with toothbrushing, suctioning of oral secretion, and rubbing the oropharyngeal mucosa (n = 37) Treatment duration: 5 days after intubation of treatment until death, extubation, transfer to other wards, or performing any diagnostic and therapeutic procedures in the oral and throat areas Frequency: 3 times a day	15 ml of 2% chlorhexidine solution, with toothbrushing, suctioning of oral secretion, and rubbing the oropharyngeal mucosa (n = 38) Treatment duration: Same Frequency: 3 times a day	– Mean scores of: GCS, MCPIS, and SOFA – Incidence of VAP – Mortality GSC: a measure to determine the severity of alertness in people over the age of 5 years (3 parts: opening the eyes, verbal answer, and movement response) MCPIS: calculated by evaluation of tracheal secretions, chest x-ray infiltrates, temperature, leukocyte count, PAO2/FIO2, and microbiology SOFA: evaluate the function of six vital organs including respiratory systems, cardiovascular systems, coagulation system, liver function
Klarin et al., 2018[24] Sweden Funding: Private and public sources	Multicenter, open-label, two arms, 1:1, parallel ratio RCT Analysis: Student's *t* test, Fisher's exact test, per protocol Sample size calculation: No	Adult patients receiving mechanical ventilation of at least 24 hours in ICUs Mean age (years): – Intervention: 66 – Control: 65.5 Sex (% male): – Intervention: 58 – Control: 53 Clinical characteristics: Similar between groups in sepsis, bacteremia, septic shock, meningitis, cardiac arrest and cardiac failure,	Mechanical steps were the same as oral care in the control, but swabbing instead with carbonated water, after probiotic bacterium *Lactobacillus plantarum* 299 (Lp299) was applied (n = 69) Frequency: 2 times a day	Oral care: Suctioning of mucosa secretions, toothbrushing with toothpaste, swabbing all mucosal surfaces with 0.1% chlorhexidine solution (n = 68) Frequency: 2 times a day	– Incidence of VAP – ICU stay – Ventilator day – Mortality (ICU, in-hospital) – Microbiology tests

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
		respiratory insufficiency, abdominal condition, vascular condition, trauma,…			
Meidani et al., 2018[25] Iran Funding: Public	Single-center, open-label, three arms, 1:1:1 ratio, parallel RCT Analysis: Chi-square test, Student's *t* test, per protocol Sample size calculation: No	Adult patients receiving mechanical ventilation of at least 48 hours in ICU Mean age (years): – Chlorhexidine: 50.6 – Potassium permanganate: 49.8 – Control: 51.7 Sex (% male): – Chlorhexidine: 74 – Potassium permanganate: 74 – Control: 66	– 0.2% chlorhexidine solution (n = 50) – 0.01% sodium permanganate (n = 50) Mouth washing with 10 ml solution, 3 times a day, 5 minutes each times, done by trained nurses	Placebo (n = 50)	– Incidence of VAP – Mortality – ICU stay – Ventilator day
Wittekamp et al., 2018[26] The Netherlands Funding: Public	Multicenter, open-label, four arms, cross-over RCT Analysis: Adjustment for differences in patient characteristics (propensity scores using generalized boosted methods), balancing the distribution of confounders (inverse probability weighting), Cox-proportional hazard analysis, mixed-effect logistic regression model, sensitivity analysis Sample size calculation: Yes	Adult patients with mechanical ventilation of at least 24 hours in ICUs Mean age (years): – Chlorhexidine: 61.4 – Selective oropharyngeal decontamination (SOD): 61.6 – Selective digestive tract decontamination (SDD): 62.8 Sex (% male): – Chlorhexidine: 64.4 – SOD: 64.7 – SDD: 64.6	– 2% chlorhexidine[a] (mouthwash solution) (n = 2,108) – SOD[b] (n = 2,224) – SDD[b] (n = 2,082) [a] After reporting of oral mucosal adverse effects in 29 of 295 patients (9.8%) treated in two hospitals, 1% chlorhexidine oral gel was used instead [b] SOD and SDD consist of topical antimicrobial agents targeting aerobic gram-negative pathogens, Staphylococcus aureus, and yeasts in the gastrointestinal tract (SDD) and oropharynx (SDD, SOD)	Baseline: at least 6 months, which included daily chlorhexidine-digluconate 2% body washing for all ICU patients until ICU discharge (n = 2,251). Chlorhexidine mouthwash (0.12% or 0.20%) was included. Interventions were compared with baseline Washout period: one month	– Incidence of ICU-acquired bloodstream infection with MDRGNB – Mortality – Adverse events

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
			Frequency: 4 times per day after regular oral care until mechanical ventilation was stopped		
Lin et al., 2015[27] China Funding: Public	Single-center, single-blinded, two arms, 1:1 ratio, parallel RCT Analysis: Student's *t* test, Fisher's exact test, per protocol Sample size calculation: Yes	Adult patients with mechanical ventilation and orotracheal intubation in ICU after cardiac surgery Age: 18 to 65 years, similar between groups Sex (% male): – Intervention: 53.2 – Control: 51.1 Clinical characteristics: Similar between both groups in education level, smoking history, primary disease, surgical treatment, cardiopulmonary bypass time, duration of mechanical ventilation, APACHE II score, operation duration, and blood loss	Preoperative mouthwash with 0.2% chlorhexidine (n = 47) Frequency: 4 times per day (30 minutes after all meals, and 5 minutes after brushing teeth at bedtime). CHX mouthwash was gargled for 30 seconds, repeated 3 times at 1-minute intervals During intubation and mechanical ventilation, both groups received oral rinse with 50 ml chlorhexidine 0.2%, four times per day provided by trained healthcare professionals. After extubation, all patients gargled once after each meal with 50 ml chlorhexidine 0.2% for 3 days.	Preoperative mouthwash with normal saline (n = 47) Frequency: Same	– Incidence of VAP – Safety

GCS = Glasgow Coma Scale; ICU = intensive care unit; MCPIS = modified clinical pulmonary score; MDRGNB = multi-drug resistant gram negative-bacteria; MV = mechanical ventilation; NP = nosocomial pneumonia; NR = not reported; RCT = randomized controlled trial; SDD = selective digestive tract decontamination; SOD = selective oropharyngeal decontamination; SOFA = sequential organ failure assessment; VAP = ventilator-associated pneumonia

Table 5: Characteristics of Included Guidelines

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users/ Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
ERS / ESICM/ ESCMID / ALAT, Torres et al., 2017[29] Europe Funding: NR	Intended users: specialists in respiratory medicine and critical care managing adults with HAP or VAP, general internists, specialists in infectious diseases, pharmacists, microbiologists and policy makers Target population: Adult patients with HAP or VAP	Effective treatments and management strategies	Prevention of – HAP, VAP – Mortality	Systematic methods used to search for evidence were reported The level of evidence and grade of recommendations were assessed using GRADE	A panel of experts and methodologists appointed by the ERS, ESICM, ESCMID and ALAT for the guidelines development process and clinical recommendations. On seven PICO questions regarding diagnosis, empirical and definitive antibiotic therapy, and prevention of HAP and VAP	Published by the European Respiratory Society (ERS) No guideline validation was reported
SHEA / IDSA / AHA / APIC, Klompas et al., 2014[30] USA Funding: NR	Intended users: Healthcare workers in acute care hospitals Target population: Mechanically ventilated adults, children and neonates	Implementing and preventing strategies to prevent VAP and other ventilator-associated events	Prevention of – VAP and other complications – Mortality	Systematic methods used to search for evidence were not reported Quality of evidence was assessed using GRADE Strength of recommendations was classified as basic practices, special approaches, generally not recommended, and no recommendation	Collaborative effort led by SHEA, IDSA, AHA, APIC, and the Joint Commission No guideline development process was reported	Sponsored by SHEA, and published in a peer-reviewed journal (Infection Control and Hospital Epidemiology) No guideline validation was reported
“Zero-VAP”, Alvarez Lerma et al., 2014[31]	Intended users: Healthcare workers in acute care hospitals	Implementation of a simultaneous multimodal intervention in	Reduction of VAP	Systematic methods used to search for evidence were not reported	A national task force of experts involved in the project	Supported by the Spanish Ministry of Health, and published in a

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users/ Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
Spain Funding: Spanish Ministry of Health	Target population: Mechanically ventilated patients	Spanish ICUs consisting of a bundle of VAP prevention measures		The level of evidence and grade of recommendations were assessed using GRADE		peer-reviewed journal (Medicina Intensiva). The project incorporates an integral patient safety program and continuous online validation of the application of the bundle.

AHA = American Hospital Association; ALAT = Asociación Latinoamericana del Tórax; APIC = Association for Professionals in Infection Control and Epidemiology; ERS = European Respiratory Society; ESICM = European Society of Intensive Care Medicine; ESCMID = European Society of Clinical Microbiology and Infectious Diseases; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; HAP = hospital-acquired pneumonia; IDSA = Infectious Diseases Society of America; PICO = population, intervention, comparator and outcome; SHEA = Society for Healthcare Epidemiology of America; VAP = ventilator-associated pneumonia

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Appendix 3: Quality Assessment of Included Studies

Table 6: Quality Assessment of Systematic Reviews

AMSTAR 2 Checklist[10]	Rabello et al., 2018[13]	Guller et al., 2018 [14]	Silvestri et al., 2017[15]	Hua et al., 2016[16]	Pedersen et al., 2016[17]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No	No	Yes	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Partial Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No	No	No
8. Did the review authors describe the included studies in adequate detail?	Partial Yes	Yes	Yes	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	Yes	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Not applicable	No meta-analysis	Yes	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Not applicable	No meta-analysis	Yes	Yes	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No	No	No	No	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	Yes	No

AMSTAR 2 Checklist[10]	Rabello et al., 2018[13]	Guller et al., 2018 [14]	Silvestri et al., 2017[15]	Hua et al., 2016[16]	Pedersen et al., 2016[17]
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Not applicable	No meta-analysis	No	No	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	No	Yes	Yes

Table 7: Quality Assessment of Systematic Reviews (continued)

AMSTAR 2 Checklist[10]	Villar et al., 2016[18]	Klompas et al., 2014[19]	Price et al., 2014[20]	Silvestri et al. 2014[21]	Zhang et al., 2014[22]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No	No	No	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Yes	NA	Yes	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No	No	NA	No	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	NA	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Yes	NA	No	No
16. Did the review authors report any potential sources of conflict of	Yes	Yes	No	No	Yes

AMSTAR 2 Checklist[10]	Villar et al., 2016[18]	Klompas et al., 2014[19]	Price et al., 2014[20]	Silvestri et al. 2014[21]	Zhang et al., 2014[22]
interest, including any funding they received for conducting the review?					

Table 8: Quality Assessment of Primary Studies

SIGN Checklist for Randomized Controlled Trials: Internal Validity[11]	Khaky et al., 2018[23]	Klarin et al., 2018[24]	Meidani et al., 2018[25]	Wittekamp et al., 2018[26]	Lin et al., 2015[27]
1. The study addresses an appropriate and clearly focused question.	Yes	Yes	Yes	Yes	Yes
2. The assignment of subjects to treatment groups is randomized.	Yes	Yes	Yes	Yes	Yes
3. An adequate concealment method is used.	Can't say	Yes	Can't say	Can't say	Yes
4. The design keeps subjects and investigators 'blind' about treatment allocation.	No	No	No	No	Patient-blinded
5. The treatment and control groups are similar at the start of the trial.	Yes	Yes	Yes	Yes	Yes
6. The only difference between groups is the treatment under investigation.	Yes	Yes	Yes	Yes	Yes
7. All relevant outcomes are measured in a standard, valid and reliable way.	Yes	Yes	Yes	Yes	Yes
8. What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	0%	0%	0%	0%	0%
9. All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	No	No	No	No	No
10. Where the study is carried out at more than one site, results are comparable for all sites.	Does not apply	Can't say	Does not apply	Can't say	Does not apply

Table 9: Quality Assessment of Guidelines

AGREE II checklist[12]	ERS / ESICM/ ESCMID / ALAT, Torres et al., 2017[29]	SHEA / IDSA / AHA / APIC, Klompas et al., 2014[30]	“Zero-VAP”, Alvarez Lerma et al., 2014[31]
Scope and purpose			
1. Objectives and target patients population were explicit	Yes	Yes	Yes
2. The health question covered by the guidelines is specifically described	Yes	Yes	Yes
3. The population to whom the guidelines is meant to apply is specifically described	Yes	Yes	Yes
Stakeholder involvement			
4. The guideline development group includes individuals from all relevant professional groups	Yes	Yes	Yes
5. The views and preferences of the target population have been sought	Not clear	Not clear	Not clear
6. The target users of the guideline are clearly defined	Yes	Yes	Yes
Rigour of development			
7. Systematic methods were used to search for evidence	Yes	Not clear	Not clear
8. The criteria for selecting the evidence are clearly described	Yes	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described	Yes	Yes	Yes
10. The methods of formulating the recommendations are clearly described	Not clear	Not clear	Not clear
11. The health benefits, side effects, and risks have been considered in formulating the recommendations	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication	Not clear	Not clear	Not clear
14. A procedure for updating the guideline is provided	Yes	Yes	Yes
Clarity of presentation			
15. The recommendations are specific and unambiguous	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented	Yes	Yes	Yes
17. Key recommendations are easily identified	Yes	Yes	Yes
Applicability			
18. The guideline describes facilitators and barriers to its application	Yes	Yes	Yes
19. The guidelines provides advice and/or tools on how the recommendations can be put into practice	Not clear	Not clear	Not clear

AGREE II checklist[12]	ERS / ESICM/ ESCMID / ALAT, Torres et al., 2017[29]	SHEA / IDSA / AHA / APIC, Klompas et al., 2014[30]	"Zero-VAP", Alvarez Lerma et al., 2014[31]
20. The potential resource (cost) implications of applying the recommendations have been considered	No	No	No
21. The guideline presents monitoring and/or auditing criteria	Yes	Yes	Yes
Editorial independence			
22. The views of the funding body have not influenced the content of the guideline	Not clear	Not clear	Not clear
23. Competing interests of guideline development group members have been recorded and addressed	Yes	Yes	Yes

AHA = American Hospital Association; ALAT = Asociación Latinoamericana del Tórax; APIC = Association for Professionals in Infection Control and Epidemiology; ERS = European Respiratory Society; ESICM = European Society of Intensive Care Medicine; ESCMID = European Society of Clinical Microbiology and Infectious Diseases; IDSA = Infectious Diseases Society of America; SHEA = Society for Healthcare Epidemiology of America

Appendix 4: Main Study Findings and Author's Conclusions

Table 10: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusions
Rabello et al., 2018[13]	
Overview of SRs: Chlorhexidine versus placebo or usual care in patients in ICUs **Methodological quality of SRs (based on AMSTAR)** – High: 14 SRs – Moderate: 2 SRs **Quality of evidence (based on GRADE)** – High: 12 SRs – Moderate: 4 SRs **Strength of recommendation on the use of chlorhexidine for prevention of NP and VAP in ICUs** – Strong in favor: 14 SRs – Weak in favor: 2 SRs **Nosocomial pneumonia or lower respiratory tract infections (4 SRs)** • Non-significant reduction – Overall (1 SR) OR (95% CI) = 0.42 (0.16 to 1.06); *P* = 0.07 – Non-cardiac surgery ICU (1 SR) RR (95% CI) = 0.78 (0.60 to 1.02); *P* = 0.06 ✓ By chlorhexidine concentration (1 SR) 0.12%: RR (95% CI) = 0.80 (0.51 to 1.25) 0.2%: RR (95% CI) = 0.76 (0.47 to 1.20) 2%: RR (95% CI) = 0.75 (0.35 to 1.63) • Significant reduction (3 SRs) – Overall (2 SRs) RR (95% CI) = 0.58 (0.45 to 0.74); *P* < 0.05 OR (95% CI) = 0.66 (0.51 to 0.85); *P* < 0.001 – Cardiac surgery ICU (2 SRs) RR (95% CI) = 0.56 (0.41 to 0.77); *P* < 0.001 OR (95% CI) = 0.52 (0.33 to 0.82); *P* < 0.001 **Ventilator-associated pneumonia (13 SRs)** • Non-significant reduction – Overall (1 SR) RR (95% CI) = 0.70 (0.48 to 1.04); *P* = 0.08 – Type of ICU (1 SR) Medical: OR (95% CI) = 0.53 (0.26 to 1.09); *P* = 0.08 Mixed: OR (95% CI) = 0.82 (0.60 to 1.12); *P* = 0.22 – By chlorhexidine concentration (4 SRs) 0.12%: RR (95% CI) = 0.73 (0.51 to 1.05); *P* = 0.09 0.12%: RR (95% CI) = 0.70 (0.39 to 1.24); *P* = 0.19 0.12% TID: RR (95% CI) = 1.06 (0.68 to 1.64); *P* = 0.53 0.2%: RR (95% CI) = 0.72 (0.45 to 1.27); *P* > 0.05 0.2%: RR (95% CI) = 0.79 (0.46 to 1.36); *P* = 0.39 0.2%: RR (95% CI) = 0.62 (0.19 to 1.95); *P* = 0.62 – Non-cardiac surgery ICU (1 SR) RR (95% CI) = 0.68 (0.45 to 1.02); *P* = 0.06	*"Chlorhexidine has proven to be effective for the prevention of NP among adult populations in cardiothoracic ICU. In ICUs with patients who had varied clinical-surgical conditions, the effectiveness of chlorhexidine for the prevention of NP and VAP was inconclusive."*[13] p.441

Main Study Findings	Author’s Conclusions
• Significant reduction – Overall (8 SRs) RR (95% CI) = 0.56 (0.39 to 0.81); *P* = 0.002 OR (95% CI) = 0.56 (0.44 to 0.73); *P* < 0.05 RR (95% CI) = 0.72 (0.55 to 0.94); *P* = 0.02 RR (95% CI) = 0.64 (0.44 to 0.91); *P* = 0.012 RR (95% CI) = 0.70 (0.55 to 0.89) RR (95% CI) = 0.60 (0.47 to 0.76); *P* < 0.01 RR (95% CI) = 0.59 (0.47 to 0.73); *P* < 0.001 OR (95% CI) = 0.60 (0.47 to 0.77); *P* < 0.001 RR (95% CI) = 0.71 (0.54 to 0.94); *P* = 0.02 – Cardiac surgery ICU (5 SRs) RR (95% CI) = 0.41 (0.17 to 0.98); *P* = 0.04 RR (95% CI) = 0.41 (0.17 to 0.98); *P* = 0.05 RR (95% CI) = 0.28 (0.12 to 0.64) RR (95% CI) = 0.47 (0.33 to 0.65); *P* < 0.001 Patients in cardiothoracic ICU can benefit from the use of chlorhexidine – Non-cardiac surgery ICU (1 SR) RR (95% CI) = 0.59 (0.40 to 0.86); *P* = 0.006 – By chlorhexidine concentration (7 SRs) 0.12%: RR (95% CI) = 0.52 (0.37 to 0.72); *P* < 0.05 0.12% BID: RR (95% CI) = 0.69 (0.53 to 0.91) 0.12% to 0.2%: OR (95% CI) = 0.60 (0.47 to 0.76); *P* < 0.001 0.12% to 0.2%: OR (95% CI) = 0.70 (0.52 to 0.94); *P* = 0.02 0.2% TID: RR (95% CI) = 0.66 (0.13 to 0.80); *P* = 0.044 1% to 2%: OR (95% CI) = 0.59 (0.35 to 0.97); *P* = 0.04 2%: RR (95% CI) = 0.48 (0.26 to 0.88); *P* < 0.05 2%: RR (95% CI) = 0.53 (0.31 to 0.91); *P* = 0.04 2% QID: RR (95% CI) = 0.53 (0.31 to 0.90); *P* = 0.02 The use of chlorhexidine 2% for oral hygiene favored the prevention of VAP	
Guler and Turk 2018[14]	
Chlorhexidine versus placebo or usual care in intubated patients **Study quality (risk of bias):** Only two RCTs had overall low risk of bias <u>High</u>: other sources of bias (40%), blinding of outcome assessment (30%), selective reporting (30%) <u>Low</u>: random sequence generation (100%), allocation concealment (80%), incomplete income data (80%), blinding of outcome assessment (70%) <u>Unclear</u>: blinding pf participants and personnel (30%), selective reporting (30%) **Development of VAP** – 0.12% and 0.2% chlorhexidine was more effective in preventing VAP development compared to placebo or normal saline (4 RCTs) – Four patients developed VAP in 2% chlorhexidine group, two patients developed VAP in normal saline (1 RCT) – Chlorhexidine two or four times per day was effective in the prevention of VAP development (5 RCTs) **Incidence of VAP** – 0.2% chlorhexidine had fewer incidence of VAP compared to normal saline (1 RCT) – Lower VAP incidence in 2% chlorhexidine compared to placebo (2 RCTs) – No significant difference in VAP incidence between 2% chlorhexidine and placebo (1RCT)	*“Chlorhexidine is an effective intervention in oral care for ventilator-associated pneumonia and microbial colonization.”*[14] p.1

Main Study Findings	Author’s Conclusions
– Chlorhexidine two or four times per day was effective in minimizing VAP incidence (8 RCTs). One RCT showed no significant difference between groups **Bacterial colonization of dental plaque** – 0.2% and 2% chlorhexidine was more effective than placebo or normal saline (5 RCTs) – No significant difference between 0.2% chlorhexidine and sterile water (1 RCT) – Chlorhexidine 2 to 3 times a day was effective (3 RCTs). One RCT showed no difference between chlorhexidine 2 times per day and control	
Silvestri et al., 2017[15]	
Chlorhexidine versus placebo or usual care in critically ill patients **Study quality (risk of bias):** High: at allocation procedure (1 RCT) Unclear: at completeness of outcome data (4 RCTs) **Bloodstream infection** • Overall OR (95% CI) = 0.74 (0.37 to 1.50); *P* = 0.40 (5 RCTs) • Chlorhexidine concentration 0.12%: OR (95% CI) = 0.46 (0.22 to 0.99); *P* = 0.049 (2 RCTs) 0.2%: OR (95% CI) = 0.35 (0.53 to 3.45); *P* = 0.53 (3 RCTs) • Type of population Surgical: OR (95% CI) = 0.47 (0.22 to 0.97); *P* = 0.04 (3 RCTs) Medical: OR (95% CI) = 1 (0.23 to 4.43); *P* = 1 (1 RCT) Mixed: OR (95% CI) = 2.4 (0.61 to 9.61); *P* = 0.21 (1 RCT) • Type of microorganisms Gram-positive bacteria: OR (95% CI) = 0.72 (0.23 to 2.22); *P* = 0.57 (3 RCTs) Gram-negative bacteria: OR (95% CI) = 0.83 (0.16 to 4.41); *P* = 0.83 (3 RCTs) “Normal” flora: OR (95% CI) = 0.63 (0.21 to 1.88); *P* = 0.49 (3 RCTs) “Abnormal” flora: OR (95% CI) = 1.12 (0.14 to 8.66); *P* = 0.36 (3 RCTs) **Mortality** • Overall OR (95% CI) = 0.69 (0.31 to 1.53); *P* = 0.43 (5 RCTs) • Chlorhexidine concentration 0.12%: OR (95% CI) = 0.55 (0.09 to 3.44); *P* = 0.52 (2 RCTs) 0.2%: OR (95% CI) = 0.74 (0.25 to 2.16); *P* = 0.58 (3 RCTs) • Type of population Surgical: OR (95% CI) = 0.50 (0.14 to 1.89); *P* = 0.31 (3 RCTs) Medical: OR (95% CI) = 0.37 (0.09 to 1.58); *P* = 0.18 (1 RCT) Mixed: OR (95% CI) = 1.4 (0.76 to 2.58); *P* = 0.28 (1 RCT)	*“In critically ill patients, oropharyngeal chlorhexidine did not reduce bloodstream infection and mortality significantly and did not affect any microorganism involved. The presence of a high risk of bias in 1 study and unclear risk of bias in others may have affected the robustness of these findings.”*[15] p.2236
Hua et al., 2017[16]	
Chlorhexidine versus placebo or usual care in patients receiving mechanical ventilation **Study quality (overall risk of bias):** High (9 RCTs) Low (4 RCTs) Unclear (5 RCTs) **Incidence of VAP** • Overall: RR (95% CI) = 0.75 (0.62 to 0.91); *P* = 0.004 (18 RCTs)	*“Oral hygiene care including chlorhexidine mouthwash or gel reduces the risk of developing ventilator-associated pneumonia in critically ill patients from 24% to about 18%. However, there is no evidence of a difference in the outcomes of mortality, duration of mechanical ventilation or duration*

Main Study Findings	Author's Conclusions
• By formulation Without toothbrushing in either groups Chlorhexidine solution: RR (95% CI) = 0.71 (0.53 to 0.94); *P* = 0.016 (7 RCTs) Chlorhexidine gel: RR (95% CI) = 0.66 (0.41 to 1.05); *P* = 0.17 (5 RCTs) With toothbrushing in both groups Chlorhexidine solution: RR (95% CI) = 0.69 (0.29 to 1.36); *P* = 0.40 (3 RCTs) Chlorhexidine gel: RR (95% CI) = 1.22 (0.83 to 1.79); *P* = 0.32 (2 RCTs) **Mortality** • Overall: RR (95% CI) = 1.09 (0.96 to 1.23); *P* = 0.20 (14 RCTs) • By formulation Without toothbrushing in either groups Chlorhexidine solution: RR (95% CI) = 1.11 (0.88 to 1.39); *P* = 0.38 (6 RCTs) Chlorhexidine gel: RR (95% CI) = 0.94 (0.59 to 1.50); *P* = 0.80 (3 RCTs) With toothbrushing in both groups Chlorhexidine solution: RR (95% CI) = 1.04 (0.77 to 1.41); *P* = 0.81 (3 RCTs) Chlorhexidine gel: RR (95% CI) = 1.00 (0.59 to 1.68); *P* = 0.99 (2 RCTs) **Duration of ventilation (days)** • Overall: MD (95% CI) = -0.09 (-1.73 to 1.55); *P* = 0.91 (6 RCTs) • By formulation Without toothbrushing in either groups Chlorhexidine solution: MD (95% CI) = -1.34 (-3.70 to 1.03); *P* = 0.27 (2 RCTs) Chlorhexidine gel: MD (95% CI) = 1.26 (-0.78 to 3.30); *P* = 0.23 (3 RCTs) With toothbrushing in both groups Chlorhexidine solution: MD (95% CI) = -1.30 (-4.20 to 1.60); *P* = 0.38 (1 RCT) **Duration of ICU stay (days)** • Overall: MD (95% CI) = 0.21 (-1.48 to 1.89); *P* = 0.81 (6 RCTs) • By formulation Without toothbrushing in either groups Chlorhexidine solution: MD (95% CI) = -1.22 (-4.07 to 1.62); *P* = 0.40 (2 RCTs) Chlorhexidine gel: MD (95% CI) = 0.53 (-1.56 to 2.61); *P* = 0.62 (3 RCTs) With toothbrushing in both groups Chlorhexidine solution: MD (95% CI) = 5.00 (-2.20 to 12.20); *P* = 0.17 (1 RCT) **Duration of systemic antibiotic therapy (days)** • Overall: MD (95% CI) = 0.23 (-0.85 to 1.30); *P* = 0.68 (2 RCTs) • By formulation Without toothbrushing in either groups Chlorhexidine gel: MD (95% CI) = -1.18 (-3.41 to 1.05); *P* = 0.30 (1 RCT) With toothbrushing in both groups Chlorhexidine solution: MD (95% CI) = 0.65 (-0.58 to 1.88); *P* = 0.30 (1 RCT) **Plaque index** MD (95% CI) = 1.90 (-8.42 to 12.22) (1 RCT) **Adverse effects (reversible mild irritation of oral mucosa)** RR (95% CI) = 10.29 (1.34 to 78.97) (1 RCT); favor placebo	*of ICU stay."*[16]
Pedersen et al., 2016[17]	
Chlorhexidine versus usual care in patients admitted to elective thoracic surgery **Study quality:**	*"Systematic perioperative oral hygiene reduces postoperative*

Main Study Findings	Author's Conclusions
"Two studies fulfilled all criteria of the critical appraisal checklist and four studies met six to nine criteria. Overall, all studies were well designed and carried out." p.150 **Nosocomial infection:** RR (95% CI) = 0.65 (0.55 to 0.78); *P* < 0.0001 (3 RCTs) **Lower respiratory tract infection:** RR (95% CI) = 0.48 (0.36 to 0.65); *P* < 0.0001 (4 RCTs) **Deep surgical site infection:** RR (95% CI) = 0.48 (0.27 to 0.84); *P* < 0.0001 (3 RCTs) **Urinary tract infection:** RR (95% CI) = 0.79 (0.51 to 1.21) (3 RCTs)	*nosocomial, lower respiratory tract infections and surgical site infection but not urinary tract infections. The effect is statistically, clinically and practically significant."*[17] p.141
Villar et al., 2016[18]	
Chlorhexidine versus placebo or usual care in patients requiring orotracheal or nasotracheal intubation and mechanical ventilation **Study quality (overall risk of bias):** High (8 RCTs) Low (1 RCT) Unclear (4 RCTs) **Incidence of VAP** • Overall (adults) RR (95% CI) = 0.70 (0.48 to 1.00); *P* = 0.05 (10 RCTs) • By Chlorhexidine concentrations 0.12%: RR (95% CI) = 1.00 (0.51 to 1.99); *P* = 0.99 (3 RCTs) 0.2%: RR (95% CI) = 0.63 (0.32 to 1.12); *P* = 0.17 (5 RCTs) 2%: RR (95% CI) = 0.56 (0.39 to 0.81); *P* = 0.02 (2 RCTs) • By frequency Single dose: RR (95% CI) = 2.79 (0.75 to 10.37); *P* = 0.13 (1 RCT) One time per day: RR (95% CI) = 0.59 (0.25 to 1.40); *P* = 0.23 (1 RCT) Two times per day: RR (95% CI) = 1.25 (0.19 to 8.31); *P* = 0.82 (2 RCTs) Three times per day: RR (95% CI) = 0.64 (0.31 to 1.31); *P* = 0.22 (4 RCTs) Four times per day: RR (95% CI) = 0.56 (0.38 to 0.81); *P* = 0.002 (3 RCTs) • Mechanical means Without: RR (95% CI) = 0.65 (0.39 to 1.09); *P* = 0.1 (6 RCTs) With: RR (95% CI) = 0.77 (0.43 to 1.39); *P* = 0.39 (4 RCTs)	*"We found that oral care with chlorhexidine is effective in reducing VAP incidence in adult population if administered at 2% concentration or 4 times/d."*[18] p.1245
Klompas et al., 2014[19]	
Chlorhexidine versus placebo or usual care in patients receiving mechanical ventilation **Study quality (overall risk of bias):** Presented in the form of summary table **Incidence of NP** • Overall RR (95% CI) = 0.73 (0.58 to 0.82) (16 RCTs) • Type of population Cardiac surgery RR (95% CI) = 0.56 (0.41 to 0.77) (3 RCTs) Non-cardiac surgery RR (95% CI) = 0.78 (0.60 to 1.02) (13 RCTs) **Mortality** • Overall RR (95% CI) = 1.13 (0.99 to 1.28) (12 RCTs) • By population Cardiac surgery patients RR (95% CI) = 0.88 (0.25 to 3.14) (3 RCTs)	*"Routine oral with chlorhexidine prevents nosocomial pneumonia in cardiac surgery patients but may not decrease ventilator-associated pneumonia risk in non-cardiac surgery patients. Chlorhexidine use does not affect patient-centered outcomes in either population. Policies encouraging routine oral care with chlorhexidine for non-cardiac surgery patients merit re-evaluation."*[19] p.751

Main Study Findings	Author's Conclusions
Non-cardiac surgery patients RR (95% CI) = 1.13 (0.99 to 1.29) (9 RCTs) • By chlorhexidine concentration among non-cardiac surgery patients 0.12%: RR (95% CI) = 1.01 (0.46 to 2.20) 0.2%: RR (95% CI) = 1.13 (0.96 to 1.32) 2%: RR (95% CI) = 1.16 (0.92 to 1.46) • By formulation Gel: RR (95% CI) = 1.23 (0.96 to 1.57) Solution: RR (95% CI) = 1.10 (0.95 to 1.28) **Duration of mechanical ventilation (days)** • Overall MD (95% CI) = 0.01 (-1.12 to 1.14 (6 RCTs) • Type of population Cardiac surgery MD (95% CI) = -0.05 (-0.14 to 0.04) (1 RCT) Non-cardiac surgery MD (95% CI) = -0.15 (-2.18 to 1.89) (5 RCTs) **ICU length of stay (days)** • Overall MD (95% CI) = -0.10 (-0.25 to 0.05 (6 RCTs) • Type of population Cardiac surgery MD (95% CI) = -0.10 (-0.25 to 0.05) (1 RCT) Non-cardiac surgery MD (95% CI) = 0.08 (-1.41 to 1.57) (5 RCTs) **Hospital length of stay (days)** No significant difference (2 RCTs of non-cardiac surgery and 1 RCT of cardiac surgery). Data not shown. **Antibiotic exposures** No significant difference (2 RCTs of non-cardiac surgery). Data not shown.	
Price et al., 2014[20]	
"Selective digestive decontamination (SDD)" versus "Selective oropharyngeal decontamination (SOD)" versus oropharyngeal chlorhexidine (CHX) **Study quality (overall risk of bias):** Present in table form the components of Cochrane risk of bias tool for each intervention without summary of study quality **Mortality** • Pairwise meta-analysis (Direct evidence) SDD versus control: OR (95% CI) = 0.73 (0.64 to 0.84); *P* < 0.001 (15 RCTs) SOD versus control: OR (95% CI) = 0.85 (0.74 to 0.97); *P* = 0.02 (4 RCTs) CHX versus control: OR (95% CI) = 1.25 (1.05 to 1.50); *P* =0.01 (11 RCTs) SDD versus SOD: OR (95% CI) = 0.97 (0.79 to 1.18) (1 RCT) • Network meta-analysis (Direct and indirect evidence) SDD versus control: OR (95% CI) = 0.74 (0.63 to 0.86) SOD versus control: OR (95% CI) = 0.82 (0.62 to 1.02) CHX versus control: OR (95% CI) = 1.23 (0.99 to 1.47) SDD versus CHX: OR (95% CI) = 0.61 (0.47 to 0.78) SOD versus CHX: OR (95% CI) = 0.67 (0.48 to 0.91) SDD versus SOD: OR (95% CI) = 0.91 (0.70 to 1.19) • Probabilistic ranking of interventions	*"Selective digestive decontamination has a favorable effect on mortality in adult patients in general intensive care units. In these patients, the effect of selective oropharyngeal decontamination is less certain. Both selective digestive decontamination and selective oropharyngeal decontamination are superior to chlorhexidine, and there is a possibility that chlorhexidine is associated with increase mortality"*[20] p.1

Main Study Findings	Author's Conclusions
SDD (1); SOD (2); control (3); CHX (4) • Estimated probability of death SDD (0.213); SOD (0.228); control (0.266); CHX (0.305)	
Silvestry et al., 2014[21]	
Chlorhexidine versus placebo or usual care in ICU patients **Study quality (overall risk of bias):** Jadad scores not reported **Incidence of NP** • Overall OR (95% CI) = 0.66 (0.51 to 0.85); *P* < 0.001 (22 RCTs) • By chlorhexidine concentration 0.12% to 0.2%: OR (95% CI) = 0.70 (0.52 to 0.94); *P* = 0.02 (18 RCTs) 1% to 2%: OR (95% CI) = 0.59 (0.35 to 0.97); *P* = 0.04 (3 RCTs) • Type of population Surgical: OR (95% CI) = 0.52 (0.33 to 0.82); *P* < 0.01 (6 RCTs) Medical: OR (95% CI) = 0.53 (0.26 to 1.09); *P* = 0.08 (4 RCTs) Mixed: OR (95% CI) = 0.82 (0.60 to 1.12); *P* = 0.22 (12 RCTs) Adult: OR (95% CI) = 0.59 (0.45 to 0.79); *P* < 0.001 (19 RCTs) Children: OR (95% CI) = 1.07 (0.65 to 1.77); *P* =0.79 (3 RCTs) • Type of microorganisms Gram-positive bacteria: OR (95% CI) = 0.41 (0.19 to 0.85); *P* = 0.02 (9 RCTs) Gram-negative bacteria: OR (95% CI) = 0.68 (0.51 to 0.90); *P* < 0.01 (9 RCTs) "Normal" flora: OR (95% CI) = 0.51 (0.33 to 0.80); *P* < 0.01 (7 RCTs) "Abnormal" flora: OR (95% CI) = 0.78 (0.54 to 1.21); *P* = 0.16 (7 RCTs) **Incidence of VAP** • Overall OR (95% CI) = 0.68 (0.53 to 0.87); *P* < 0.01 (21 RCTs) **Mortality** • Overall OR (95% CI) = 1.11 (0.92 to 1.33); *P* =0.28 (162 RCTs) • By chlorhexidine concentration 0.12% to 0.2%: OR (95% CI) = 1.10 (0.88 to 1.37); *P* = 0.412 (13 RCTs) 1% to 2%: OR (95% CI) = 1.13 (0.785 to 1.62); *P* = 0.52 (3 RCTs) • Type of population Surgical: OR (95% CI) = 0.80 (0.35 to 1.81); *P* = 0.59 (5 RCTs) Medical: OR (95% CI) = 0.99 (0.62 to 1.58); *P* = 0.98 (4 RCTs) Mixed: OR (95% CI) = 1.15 (0.90 to 1.46); *P* = 0.27 (7 RCTs) Adult: OR (95% CI) = 1.16 (0.96 to 1.41); *P* = 0.13 (13 RCTs) Children: OR (95% CI) = 0.73 (0.41 to 1.30); *P* =0.28 (3 RCTs)	
Zhang et al., 2014[22]	
Chlorhexidine versus placebo or usual care in ICU patients receiving mechanical ventilation **Study quality (overall risk of bias):** High (3 RCTs) Low (10 RCTs) Unclear (5 RCTs) **Incidence of VAP** • Overall RR (95% CI) = 0.59 (0.50 to 0.69); *P* < 0.00001 (18 RCTs) • By Chlorhexidine concentrations 0.12%: RR (95% CI) = 0.53 (0.43 to 0.67); *P* < 0.00001 (9 RCTs)	*"Chlorhexidine can prevent and reduce the incidence of ventilator-associated pneumonia. Chlorhexidine of 0.12% has the best effect on the prevention of ventilator-associated pneumonia according to the meta-analysis, cost analysis, adverse reactions and drug resistance analysis"*[22] p.1461

Main Study Findings	Author's Conclusions
0.2%: RR (95% CI) = 0.72 (0.42 to 1.24); *P* = 0.23 (5 RCTs) 2%: RR (95% CI) = 0.55 (0.37 to 0.81); *P* = 0.002 (3 RCTs) Adverse effects Staining of teeth and transient abnormality of taste (1 RCT) Temporarily minor discoloration of teeth (1 RCT) Irritation of oral mucosa (9.8% in CHX and 0.9% in control) (1 RCT) Unpleasant taste of the solution and dysgeusia (1 RCT)	

AMSTAR = Assessing the Methodological Quality of Systematic Reviews; BID = twice daily; CHX = chlorhexidine; CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; ICU = intensive care unit; MD = mean difference; MV = mechanical ventilation; NP = nosocomial pneumonia; NR = not reported; OR = odds ratio; QID = four times daily; RCT = randomized controlled trial; RR = relative risk; SDD = selective digestive tract decontamination; SOD = selective oropharyngeal decontamination; TID = three times daily; VAP = ventilator-associated pneumonia;

Table 11: Summary of Findings of Included Primary Studies

Main Study Findings	Author's Conclusions
Khaky et al., 2018[23]	
Chlorhexidine (CHX 2%) verus Nanosil in adults patients receiving mechanical ventilation in ICU • Mean score (SD) of SOFA on fifth day of intubation: 6.8 (2.8) versus 6.7 (2.5), *P* = 0.50 • Mean score (SD) of GSC on fifth day of intubation: 6.8 (2.3) versus 7.0 (2.1), *P* = 0.70 • Mean score (SD) of MCPIS on fifth day of intubation: 3.5 (0.3) versus 1.2 (0.1), *P* < 0.001 • Incidence of VAP on fifth day of intubation: 9 (23.7%) versus 1 (2.7%); *P* = 0.008 • Mortality rate on first and fifth day of intubation: no significant difference between groups (*P* > 0.05)	*"The use of oral care program with Nanosil mouthwash is better than Chlorhexidine for the prevention of VAP in patient who admitted in ICU."*[23] p.206
Klarin et al., 2018[24]	

Chlorhexidine (CHX 0.1%) versus probiotic bacterium *Lactobacillus plantarum* 299 (Lp299) in adults patients receiving mechanical ventilation in ICUs
• Incidence of VAP; n (%): 10 (14.7) versus 7 (10); *P* = 0.45
• ICU mortality; n (%): 11 (16.2) versus 10 (14.5)
• Additional in-hospital mortality; n (%): 12 (17.6) versus 14 (20.3)
• Mean ICU stay (days): 6.59 versus 7.67
• Mean ventilator days: 4.23 versus 4.79
• Microorganisms
  – No significant differences between groups in new emerging bacteria for oropharyngeal cultures or tracheal cultures
  – For oropharyngeal cultures, fewer patients in the Lp299 group had fungi compared to those in the CHX group (RR [95% CI] = 0.53 (0.30 to 0.95])
	"In this multicentre study, we could not demonstrate any difference between LP299 and CHX used in oral care procedures regarding their impact on colonization with emerging potentially pathogenic enteric bacteria in the oropharynx and trachea."[24] p.1

Meidani et al., 2018[25]	
Chlorhexidine (CHX 0.2%) versus potassium permanganate versus placebo in adults patients receiving mechanical ventilation in ICU • Incidence of VAP; n (%): 6 (12) versus 7 (14) versus 15 (30). Compared to placebo, incidence of VAP in the CHX group and the permanganate group differed significantly (*P* = 0.041) • ICU mortality; n (%): 4 (8) versus 7 (14) versus 5 (10) • Mean (SD) ICU stay (days): 22.2 (13.4) versus 20.9 (11.9) versus 21.1 (14) • Mean (SD) ventilator days: 16.6 (9.6) versus 16.2 (10.1) versus 16.5 (11.7)	*"The use of common mouthwashes, especially chlorhexidine solution, for washing oropharynx of ICU patients, can decrease pneumonia incidence, especially in patients under ventilation. Thus, washing and sterilizing mouth of patients with mouthwashes is recommended due to the high risk of hospital-acquired pneumonia in these patients"*[25] p.2
Wittekamp et al., 2018[26]	

Chlorhexidine (CHX 2%, 1%), SOD, SDD versus baseline
• ICU-acquired bloodstream infection with MDRGNB
  – Crude
    Baseline: 2.1%; CHX: 1.8%; SOD: 1.5%; SDD: 1.2%
  – Absolute risk reductions (95% CI) compared with baseline
    CHX: 0.3% (-0.6 to 1.1); SOD: 0.6% (-0.2 to 1.4); SDD: 0.8% (0.1 to 1.6)
  – Adjusted hazard ratios (95% CI) compared with baseline
	"Among patients receiving mechanical ventilation in ICUs with moderate to high antibiotic resistance prevalence, use of CHX mouthwash, SOD, or SDD was not associated with reductions in ICU-acquired bloodstream

Main Study Findings	Author's Conclusions
CHX: 1.13 (0.68 to 1.88); SOD: 0.89 (0.55 to 1.45); SDD: 0.70 (0.43 to 1.14) • Mortality on day 28 – Crude Baseline: 31.9%; CHX: 32.9%; SOD: 32.4%; SDD: 34.12% – Adjusted OR (95% CI) compared to baseline CHX: 1.07 (0.86 to 1.32); SOD: 1.05 (0.85 to 1.29); SDD: 1.03 (0.80 to 1.32) • Adverse events – Oromucosal lesions recorded in 29 (9.8%) of 295 patients treated with CHX 2% – No serious adverse events reported for CHX 1%, SOD or SDD	*infections caused by MDRGNB compared with standard care"*[26] p.2087
Lin et al., 2015[27]	
Preoperative mouthwash with chlorhexidine (CHX 0.2%) versus normal saline in patients with mechanical ventilation and orotracheal intubation after cardiac surgery • Incidence of VAP; n (%): 4 (8.5%) versus 11 (23.4%); P = 0.049 • Safety: No adverse reactions associated with CHX administration	*"Preoperative chlorhexidine mouthwash reduced the incidence of postoperative VAP significantly."*[27] p.362

CHX = chlorhexidine; CI = confidence interval; GCS = Glasgow Coma Scale; GI = gingival index; ICU = intensive care unit; MCPIS = modified clinical pulmonary score; MDRGNB = multidrug-resistant gram-negative bacteria; OHI-S = Oral Hygiene Index Simplified score; OR = odds ratio; SD = standard deviation; SDD = selective digestive tract decontamination; SOD = selective oropharyngeal decontamination; SOFA: sequential organ failure assessment; VAP = ventilated-associated pneumonia

Table 12: Summary of Findings of Included Guidelines

Recommendations
ERS / ESICM/ ESCMID / ALAT, Torres et al., 2017[29]
"The guideline panel decided not to issue a recommendation on the use of chlorhexidine to perform selective oral decontamination (SOD) in patients requiring mechanical ventilation until more safety data become available, due to the unclear balance between a potential reduction in pneumonia rate and a potential increase in mortality. (No formal recommendation)"[29] p.8
SHEA / IDSA / AHA / APIC, Klompas et al., 2014[30]
"(Perform oral care with chlorhexidine) may lower VAP rates but for which there are insufficient data at present to determine their impact on duration of mechanical ventilation, length of stay, and mortality. (Quality of evidence: Moderate[a]; Recommendation: Special approaches)[30] p.S137
Alvarez Lerma et al., 2014[31]
"Oral hygiene with aqueous chlorhexidine solutions (0.12 – 2%) should be performed every 8 h. Before its application, cuff pressure should be above 20 cmH2O. Formal training of nurse's aides, responsible for this procedure in most ICUs, will be done. (quality of evidence: Moderate[b])"[31] p.231

AHA = American Hospital Association; ALAT = Asociación Latinoamericana del Tórax; APIC = Association for Professionals in Infection Control and Epidemiology; ERS = European Respiratory Society; ESICM = European Society of Intensive Care Medicine; ESCMID = European Society of Clinical Microbiology and Infectious Diseases; IDSA = Infectious Diseases Society of America; SHEA = Society for Healthcare Epidemiology of America

[a] The true effect is likely to be close to the estimated size and direction of the effect, but there is a possibility that it is substantially different. Evidence is rated as moderate quality when there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide.

[b] Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.