Original Article
Can routine oral care with antiseptics prevent ventilator-associated pneumonia in patients receiving mechanical ventilation? An update meta-analysis from 17 randomized controlled trials

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Abstract: Background: Whether oral antiseptics could reduce the risk of ventilator associated pneumonia (VAP) in patients receiving mechanical ventilation remains controversial. We performed a meta-analysis to assess the effect of oral care with antiseptics on the prevalence of ventilator associated pneumonia in adult critically ill patients. Methods: A comprehensive search of PubMed, Embase and Web of Science were performed to identity relevant studies. Eligible studies were randomized controlled trials of mechanically ventilated adult patients receiving oral care with antiseptics. The quality of included studies was assessed by the Jadad score. Relative risks (RRs), weighted mean differences (WMDs), and 95% confidence intervals (CIs) were calculated and pooled using a fixed-effects model or random-effects model. Heterogeneity among the studies was assessed with I^2 test. Results: 17 studies with a total number of 4249 met the inclusion criteria. Of the 17 studies, 14 assessed the effect of chlorhexidine, and 3 investigated the effect of povidone-iodine. Overall, oral care with antiseptics significantly reduced the prevalence of VAP (RR=0.72, 95% CI: 0.57, 0.92; P=0.008). The use of chlorhexidine was shown to be effective (RR=0.73, 95% CI: 0.57, 0.93; P=0.012), whereas this effect was not observed in povidone-iodine (RR=0.51, 95% CI: 0.09, 2.82; P=0.438). Subgroup analyses showed that oral antiseptics were most marked in cardiac surgery patients (RR=0.54, 95% CI: 0.39, 0.74; P=0.00). Patients with oral antiseptics did not have a reduction in intensive care unit (ICU) mortality (RR=1.11, 95% CI: 0.95, 1.29; P=0.201), length of ICU stay (WMD=-0.10 days, 95% CI: -0.25, 0.05; P=0.188), or duration of mechanical ventilation (WMD=-0.05 days, 95% CI: -0.14, 0.04; P=0.260). Conclusion: Oral care with antiseptics significantly reduced the prevalence of VAP. Chlorhexidine application prevented the occurrence of VAP in mechanically ventilated patients but povidone-iodine did not. Further large-scale, well-designed randomized controlled trials are needed to identify the findings and determine the effect of povidone-iodine application.

Keywords: Oral care, antiseptics, ventilator associated pneumonia, meta-analysis

Introduction

Ventilator associated pneumonia (VAP) is defined as the occurrence of pneumonia in patients receiving mechanical ventilation for more than 48 hours after endotracheal intubation [1]. VAP remains the leading cause for nosocomial infection in intensive care units (ICU), affecting 10-30% patients receiving mechanical ventilation [2, 3]. Moreover, VAP is associated with prolonged hospital stay [4-6], longer duration of mechanical ventilation [3], higher health-care cost [3, 4, 7], and a two-fold risk of mortality [3]. Thus, considering the consequences attributable to VAP, prevention of VAP is a priority in ICU care [8, 9], and many new efforts have been taken to assess the various preventive measures [10-12].

The most important mechanism of the development of VAP is aspiration of oropharyngeal organisms into the lower respiratory tract, fol-

lowed by bacterial proliferation and parenchymal invasion [13-15]. The oropharynx and upper gastrointestinal tract are the potential reservoirs for bacteria associated with VAP [16, 17], so the reduction of oral bacteria might have a potential for prevention of VAP [27].

Oral care with antiseptics, such as chlorhexidine and povidone-iodine, has been proven to be effect in the prevention of VAP. However, potential factors, including type of antiseptics, frequency of use and targeted patients, still have remained inconclusive. Thus, we conducted this meta-analysis to assess the effects of oral care with antiseptics on the prevalence of VAP and other clinical outcomes in critically ill patients undergoing mechanical ventilation.

Material and methods

Literature search

A comprehensive literature search was conducted to search for relevant randomized controlled trials. PubMed, Embase and Web of Science were searched before 6 April 2014, using the searching terms: ("mouth" [MeSH Terms] OR "mouth" [All Fields] OR "oral" [All Fields]) AND care [All Fields] AND ("pneumonia, ventilator-associated" [MeSH Terms] OR ("pneumonia" [All Fields] AND "ventilator-associated" [All Fields]) OR "ventilator-associated pneumonia" [All Fields] OR ("ventilator" [All Fields] AND "associated" [All Fields] AND "pneumonia" [All Fields]) OR "ventilator associated pneumonia" [All Fields]). Other websites, including Cochrane Central Register of Controlled Trials, Google Scholar, and hettp://ClinicalTrials.gov, were also searched. No language restriction was limited. We also manually screened the reference lists of the retrieved articles to find the potentially eligible trials. This process was performed iteratively until no potential articles could be identified. For studies without complete data, we contacted the authors for detail information if needed.

Review strategy and data extraction

Endnote bibliographic software was used to establish an electronic library of citations identified in the literature searches. PubMed, Embase and Web of Science were performed, and duplicate records were deleted. Two authors (LONGTI LI and ZHIBING AI) indepen-

dently trained to screen the abstract review and then the full text review. Disagreements were resolved by consensus and discussion between the authors.

A structured questionnaire was used for data extraction. The following data were extracted independently by the two authors (LONGTI LI and ZHIBING AI): first author, year of publication, baseline characteristics of the population (age, gender), sample size, inclusion and exclusion criteria, definitions and diagnosis of VAP, intervention group (oral care with antiseptics), control group (oral care without antiseptics), the prevalence of VAP, and other important clinical outcome data.

Study inclusion and exclusion criteria

We include studies in all languages when they met the following criteria: (1) randomized controlled trials; (2) adults patients receiving mechanical ventilation; (3) randomized allocation to intervention group (oral care with antiseptics) or control group (standard oral care without antiseptics); (4) reporting data on the prevalence of VAP; (5) sample size more than 50.

Quality assessment

The quality of the included studies was assessed by using the Jada scale [18]. The scale consists of the following three items to define the quality of a randomized controlled trial: (1) randomization (0-2 points); (2) masking (0-2 points); (3) dropouts and withdrawals (0-1 points). A score of 1 is given for each of the item described. A further point is obtained when the method of randomization or double-blinding is given. The scale ranges from 0 to 5 points. The RCTs are considered to be of high quality if the Jadad score is ≥ 3 [18].

Statistical analysis

We assessed the effect of the oral antiseptics on the prevention of VAP based on the data from 17 randomized trials. The prevalence of VAP and ICU mortality were treated as dichotomous variables and were expressed as relative risk (RR) with 95% confidence intervals (CI). Length of ICU and duration of mechanical ventilation were treated as continuous variables, thus they were expressed as mean difference
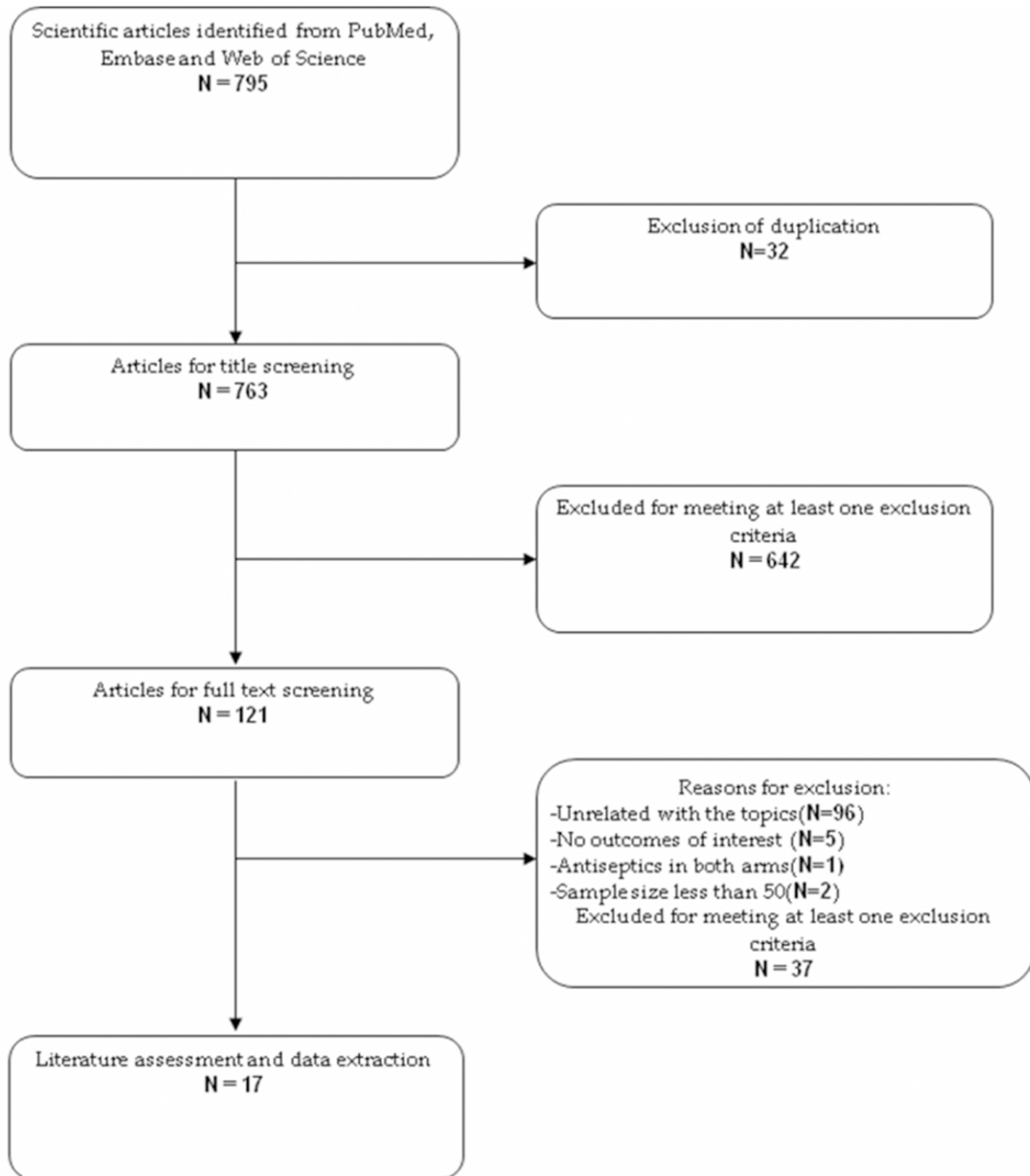
Figure 1. Search strategy and flow diagram for this meta-analysis.

(WMD) with 95% CI. Heterogeneity among the studies was tested using the I^2 statistic, a quantitative method measuring inconsistency across the studies. Studies with an I^2 of 25% to 50%, 50% to 75%, and greater than 75% are considered to have low, moderate and high heterogeneity, respectively [19]. Pooled estimates were calculated using fixed-effects model (Mantel-Haenszel method) [20] or randomized-effects model (DerSimonian-Laird method) [21]. A randomized-effects model was used to summarize the pool data if substantial heterogeneity was found ($I^2 > 10\%$). A subgroup analysis was performed based on type of antiseptics and type of surgery patients. Publication bias was evaluated using the Begg tests [22]. $P < 0.05$ was considered statistical significant. All analyses were performed using STATA version

Table 1. Baseline characteristics of the trials included in the meta-analysis

Study	Number of patients (I/C)	Setting	Diagnosis VAP	Intervention group	Control group	Jadad score
F.Fourrier [26]	60 (30/30)	Medical surgical ICU	Temperature > 38°C or < 36°C, presence of infiltrates on chest radiography, leukocytosis or leuko-penia, positive culture from tracheal aspirate (106 CFU/mL) and/or BAL (104 CFU/mL)	CHX 0.2% gel TID	Bicarbonate isotonic serum, gentle oro-pharyngeal sterile aspiration, QID	3
Philippe Seguin [27]	67 (36/31)	Surgical ICU	New clinical findings, with new pulmonary infiltrates plus two of the following items: 1) fever of > 38°3C or hypothermia of < 36°C, 2) purulent endotracheal aspi-rate; and 3) a peripheral white blood cell count of > 10,000 cells/mm³ or < 5,000 cells/mm³	CHX 2% paste QID	placebo	5
Anthony J [28]	353 (173/180)	Cardiac surgery ICU	New or progressing pulmonary infiltrate, fever, leucocytosis, and purulent tracheobronchial secre-tions	CHX 0.12% oral rinse BID	placebo	4
Francois Four-rier [29]	228 (114/114)	Medical-surgi-cal ICU	Temperature > 38°C or < 36°C, new infiltrates on chest radiographs, leucocytosis (> 10,000 cells per µL)or leucopenia (< 3,000 cells per µL),positive quantitative culture from tracheal aspirate or BAL, or both	CHX 0.2% gel TID, without toothbrushing	placebo	4
Susan Houston [30]	561 (270/291)	Cardiac surgery ICU	New or progressing pulmonary infiltrate, fever, leucocytosis, positive microbial culture results	CHX 0.12% oral rinse BID,	Listerine 15 ml oral rinse BID	3
Mirelle Koe-man [31]	385 (128/130)	Mixed and surgical ICUs	New, persistent or progressive infiltrate on chest radiograph and at least three of four criteria: fever > 38°C or < 35.5°C, leucocytosis (> 10,000 cells per µL) or leucopenia (< 3,000 cells per µL), puru-lent aspect of tracheal aspirate, positive semiquantitative culture from tracheal aspirate	CHX 2% paste QID	placebo	5
Macnaughton P D [32]	179 (91/88)	Mixed surgical ICU	Leukocytosis, fever > 38°C, deterioration in oxygenation or chest signs, new consolidation on chest radiograph, substantial bacterial growth on BAL, CPIS > 6	CHX 0.2% BID	placebo	3
Hutsaya Tanti-pong [33]	207 (102/105)	Mixed surgical ICU	New, persistant, or progressive infiltrate on chest radiograph and at least three of four criteria: fever > 38°C or < 35.5°C, leucocytosis (> 10×10³ cells per µL) or leucopenia (< 3×10³ cells per µL), purulent tracheal aspirate, positive semiquantitative culture from tracheal aspirate	CHX 2% 15 ml solution QID with toothbrushing	Saline	2
Bellissimo-Ro-drigues [34]	194(98/96)	Mixed ICU	Defined based on CDC criteria[b]	CHX 0.12% 15 ml TID	Placebo 15 ml TID	4
Tanmay S [35]	471(250/262)	Mixed surgical ICU	development of new persistent alveolar infiltrates on chest radiograph; > 38°C; leucocytosis (> 12×10³ WBCs per µL), and purulent sputum developing > 48 h after ICU admission with worsening of hypoxaemia obtained by arterial blood gas analysis; semiquantitative cultures obtained by the protected non-bronchoscopic mini-BAL technique were considered positive with > 10³ CFU per mL.	CHX 0.2% 10 ml BID	potassium permanganate 10 mL 0.01% BID	3
Frank A Scan-napieco [36]	99(50/49)	Trauma ICU	Upon suspicion of pneumonia, lung secretions analysis by bqBAL by use of a mini-BAL technique with > 10⁴ CFU/mL of a target PRP in bqBAL fluid or a positive pleuralfluid culture in the absence of previous pleural instrumentation regarded as positive evidence for diagnosis of pneumonia	CHX 0.12% BID	Placebo BID	4
Suzana M L [37]	52 (28/24)	Mixed surgical ICU	the presence of a new radiological pulmonary infiltrate on chest X-rays after 48 hours in the ICU, plus 2 or more of the following clinical or laboratory signs: axillary temperature ≥ 38°C or ≤ 36°C, leuko-cytes > 11×10³/mm³ or leucopenia < 4×10³/mm³, or the presence of purulent tracheal secretions.	CHX gel 2%	Placebo	4
Patrique Segers [38]	954 (485/469)	Cardiac surgery ICU	Defined based on CDC criteria[c,d]	CHX gluconate solution 0.12%	Placebo	4
A.M. Berry [40]	148 (71/77)	Mixed surgical ICU	Not described	CHX 0.2% solu-tion BID	Sterile water	4
Oz,caka [41]	61 (29/32)	Respiratory ICU	Using a mini-BAL technique collecting sample; The presence of ≥ 10⁴ colony-forming units/mL of a target PRP in mini-BAL fluid, or a positive pleural fluid culture in the absence of previous pleural instrumentation	CHX 0.2% QID	Saline QID	4
Jafari S[a] [39]	80 (40/40)	Mixed surgical ICU	Not described	CHX 0.2% solu-tion BID	Normal saline	None

Philippe Seguin [42]	150 (78/72)	Brain-Injured or Cerebral Hemorrhage ICU	new and persistent pulmonary infiltrates on chest radiograph, occurring after 48 hours of mechanical ventilation, combined with at least two of the following criteria: purulent tracheal secretions and/or body core temperature > 38°C and/or leukocytosis > 10,000/mm^3 or leukopenia < 3,000/mm^3 and microbiological confirmation with quantitative culture from bronchoalveolar lavage or endotracheal aspirate, growing ≥ 10^4 cfu/mL or ≥ 10^6 cfu/mL, respectively	Povidone-iodine 10% 20 ml	Placebo (sterile water)	4

Abbreviations: CHX, chlorhexidine; BID, twice daily; MRN, medical record number; QID, 4 times daily; TID, 3 times daily. [a]only abstracts were available for review; [b]Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008; 36: 309-332. [c]Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Infect Control Hosp Epidemiol. 1999; 20: 250-278. [d]Kluytmans JA, Wertheim HF. Nasal carriage of Staphylococcus aureus and prevention of nosocomial infections. Infection. 2005; 33: 3-8.
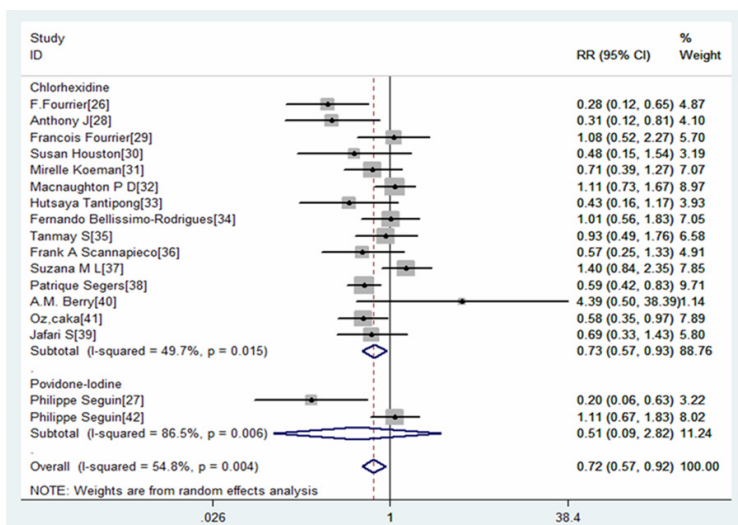
Figure 2. Forest plot showing the effect of oral care with chlorhexidine or povidone-iodine on the prevalence of ventilator associated pneumonia (VAP).

12.0 (Stata Corporation, College Station, TX, USA).

Results

Study identification and selection

The initial search yielded 795 relevant publications, of which 32 were excluded for duplicate studies and 642 were excluded based on the title and abstracts screening (**Figure 1**). The remaining 121 were then retrieved for the full text review, and five were excluded because they did not report the outcomes of interest, one was excluded because antiseptics were used in both groups [23], and two were excluded because the sample size was less than 50 [24, 25]. Thus, 17 RCTs included in the meta-analysis [26-42].

Description of the included studies

The main characteristics of the 17 RCTs included in the meta-analysis are presented in **Table 1**. These studies were published from 1996 to 2014. The sample size ranged from 52 to 954. All the 17 studies were randomized trials, including a total number of 4249 patients. Of the 4249 patients, 2161 were randomized allocation to the intervention group (oral care with antiseptics), and 2088 were allocated to the control group (standard oral care, or use of placebo). 15 studies including 4032 patients assessed the effect of chlorhexidine [26,

28-41], whereas 2 studies involving 217 patients evaluated the effect of povidone-iodine [27, 42]. Most of the studies included patients in non-cardiac surgery ICU, comprising surgical, medical-surgical or mixed (medical, surgical/trauma) ICU [26, 27, 29, 31-37, 39-42]. However, 3 studies [28, 30, 38], exclusively included cardiac surgical patients, accounting for 51.3% of all the patients forming the total population for this meta-analysis.

With respect to interventions, Seguin et al [27] randomly assigned the patients into three arms: povidone-iodine group, saline group and control group. In this meta-analysis, we set the povidone-iodine group as the intervention group, and compared it with the control group. In another RCT [31], there were two intervention groups: 2% chlorhexidine with colistin, and 2% chlorhexidine. We preferred the former as the experimental group. In another study conducted by Scannapieco et al [36], patients were randomly allocated to three arms: (1) a control arm with oral placebo application twice daily; (2) an experimental arm with 0.12% chlorhexidine once daily plus placebo oral application once daily; (3) an additional experimental arm with 0.12% chlorhexidine twice daily. For this meta-analysis, we chose the third group as intervention group. The median Jadad score of the included studies was 4 (range from 3 to 5).

Prevalence of ventilator-associated pneumonia

All 17 RCTs reported the VAP in patients. Meta-analysis from the included studies showed that oral care with antiseptics significantly reduced the prevalence of VAP (RR=0.72, 95% CI: 0.57, 0.92; *P*=0.008) (**Figure 2**). This analysis showed a moderate statistical heterogeneity (I^2=54.8%, *P*=0.004). To explore the reasons for the heterogeneity, we performed subgroup analysis based on type of antiseptics. The pooled results showed that the use of chlorhexidine was associated with a relative risk of 0.73 (95CI: 0.57, 0.93; *P*=0.012), indicating a 27% relative risk reduction for VAP for that patient population. In contrast, the use of povidone-iodine did not show any effect (RR=0.51, 95% CI: 0.09, 2.82;
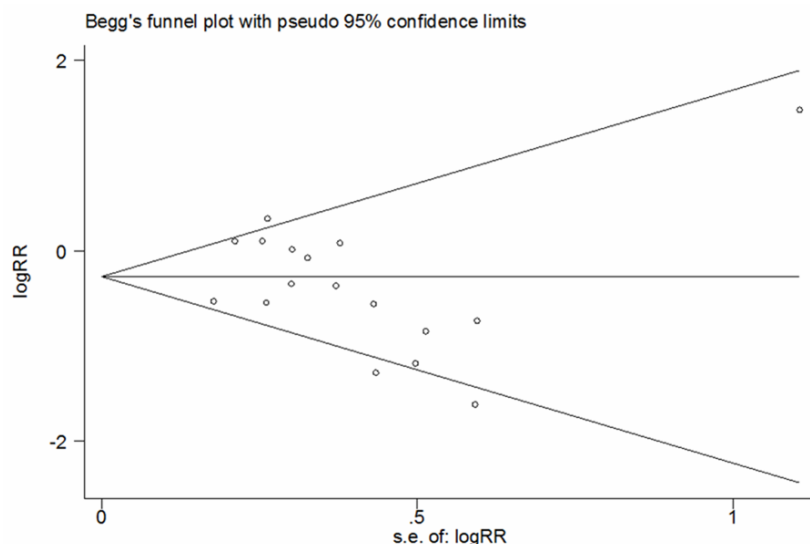
Figure 3. Forest plot assessing publication bias for ventilator associated pneumonia.

P=0.438) (**Figure 2**). The Begg's test (P=0.296) revealed no publication bias (**Figure 3**).

Subgroup analysis was performed on different type of surgery patients: cardiac surgery patients and non-cardiac surgery patients. The results revealed that the use of oral care with antiseptics significantly reduced the prevalence of VAP in the cardiac surgery patients (RR=0.54, 95% CI: 0.39, 0.74; P=0.00), but not in non-cardiac surgery patients (RR=0.78, 95% CI: 0.60, 1.02; P=0.072) (**Figure 4**).

ICU mortality

Eleven RCTs reported the data of ICU mortality [26-28, 32, 34-38, 41, 42]. The pooled results of these studies suggested that oral antiseptics did not decrease the ICU mortality (RR=1.11, 95% CI: 0.95, 1.29; P=0.201) (**Figure 5**). No heterogeneity was observed among the studies (I²=0.0%, P=0.540).

Subgroup analysis based on type of antiseptics showed that, neither oral care with chlorhexidine or povidone-iodine would significantly reduce the ICU mortality (for chlorhexidine, RR=1.10, 95% CI: 0.93, 1.30; P=0.26; for povidone-iodine, RR=1.15, 95% CI: 0.75, 1.75; P=0.528).

Subgroup analysis base on different type of surgery patients resulted in similar results: oral antiseptic did not decrease the ICU mortality for cardiac surgery patients (RR=1.00, 95% CI:

0.79, 1.28; P=0.968) or non-cardiac surgery patients (RR=1.17, 95% CI: 0.96, 1.44; P=0.117) (**Figure 6**).

Length of ICU stay

Eight RCTs reported the data of length of ICU stay [26, 27, 29, 31, 36, 38, 41, 42]. The pooled results revealed that oral antiseptics were not associated with a decrease in the length of ICU stay (WMD=-0.10 days, 95% CI: -0.25, 0.05; P=0.188). No heterogeneity was found among the studies (I²=0.0%, P=0.692). Among six of the eight studies, chlorhexidine was used in the intervention group, while the remaining two were povidone-iodine. Base on the type of antiseptics, subgroup analysis was performed. The results showed that these two types of oral care regimens could not reduce the length of ICU stay (for chlorhexidine, WMD=-0.10 days, 95% CI: -0.25, 0.05; P=0.202; for povidone-iodine, WMD=-1.83 days, 95% CI: -5.52, 1.85; P=0.329) (**Figure 7**). Due to the inadequate data, we did not perform the subgroup analysis to explore the effect of antiseptic on different surgery patients.

Duration of mechanical

Seven RCTs provided the data of duration of mechanical ventilation [26, 27, 29, 31, 36, 38, 41]. The aggregated results of these studies suggest that oral care with antiseptic was not associated with a significantly decrease in the duration of mechanical ventilation (WMD=-0.05 days, 95% CI: -0.14, 0.04; P=0.260) (**Figure 8**). The test for heterogeneity was not significant (I²=33.4%, P=0.173). Owing to the limited number of studies included in this analysis, the subgroup analysis based on type of antiseptics, or different survey patients were not performed.

Discussion

The major purpose of this meta-analysis was to update and evaluate the effect of antiseptics on the prevention of VAP in adult critically ill
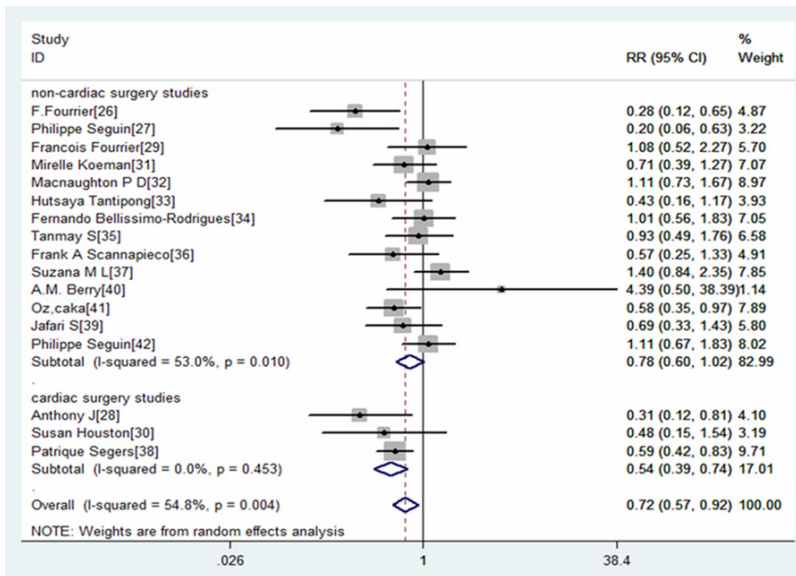
Figure 4. Forest plot showing the effect of oral care with antiseptics on the prevalence of VAP in different surgery patients.

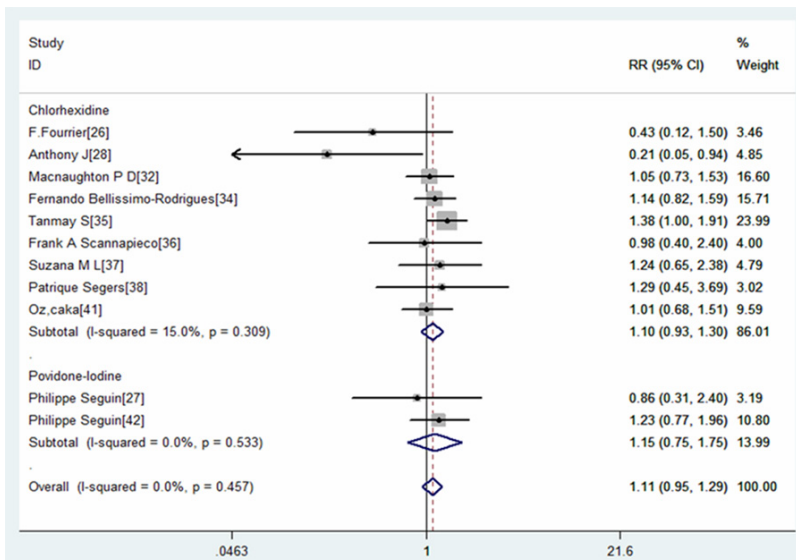**Figure 5.** Forest plot showing the effect of oral care with chlorhexidine or povidone-iodine on intensive care unit (ICU) mortality.

remarkable in cardiac surgery patients, and no significant benefit is found in non-cardiac surgery patients. Possible explanations for these discrepant findings between the two categories of patients include the different characteristics of the populations and oral care protocols. Moreover, cardiac surgery is an elective procedure, and cardiac surgery patients usually have better physical condition than those admitted to the intensive care units. Also, for cardiac surgery patients, the intubation is performed under optimum and controlled conditions, whereas the intubation is more often emergently performed under less optimum condition for the critically ill patients. Thirdly, the cardiac surgery patients usually have a shorter period of mechanical ventilation (less than 1 day), whereas the non-cardiac surgery patients are usually required prolonged period of ventilation (1 to 2 weeks). Considering these differences above, it is not surprising that oral care with antiseptics show beneficial effect in cardiac surgery patients rather than non-cardiac surgery patients in the terms of prevalence of VAP.

patients undergoing mechanical ventilation. Our results indicate that oral care with antiseptics significantly reduces the prevalence of VAP. However, oral care with antiseptics is not effective at reducing ICU mortality, length of ICU stay or duration of mechanical ventilation.

According to this meta-analysis, oral antiseptic is associated with a 28% relative reduction in the risk of VAP. This beneficial effect is more

Additionally, it is assumed that oral care with antiseptic would be more effective for the prevention of early onset rather than later onset VAP. However, in the two studies included in this meta-analysis [26, 29], this difference was not observed between the oral antiseptics and control group in the time to develop VAP. In other words, the beneficial effect from oral care with antiseptics on preventing the development of VAP is limited to the patients who received
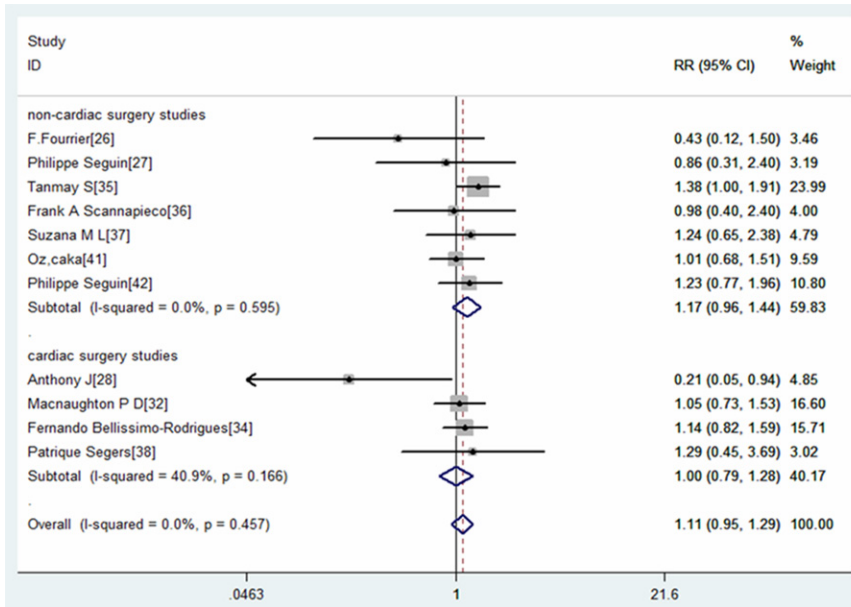
Figure 6. Forest plot showing the effect of oral care with antiseptics on intensive care unit (ICU) mortality in different surgery patients.
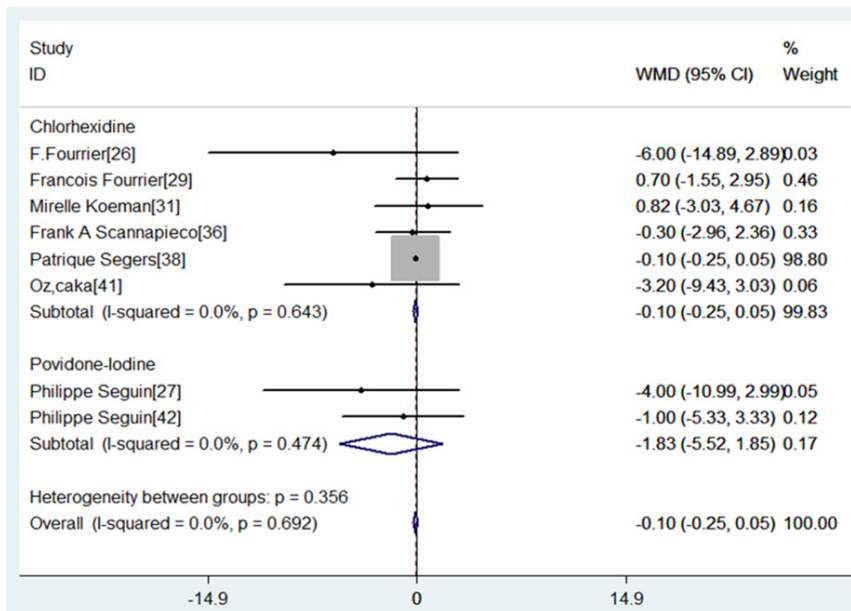

Figure 7. Forest plot showing the effect of oral care with chlorhexidine or povidone-iodine on length of intensive unit stay (ICU).

tion, this benefit may not be observed. Owning to a lack of available data, we did not address this issue in this meta-analysis.

The subgroup analyses based on type of antiseptics showed that oral care with chlorhexidine significantly reduced the prevalent of VAP, whereas the povidone-iodine did not. Notably, the subgroup analyses for povidone-iodine application was based on only two RCTs with high statistically heterogeneity. Of the two studies, one [27] found a beneficial effect of povidone-iodine for prevention of VAP, whereas the other not. However, in the study with positive outcomes, the baseline characteristics of the patients were significantly different between the two groups. Thus, based on the current evidence, it is difficult to tell whether povidone-iodine is effective for prevention of VAP. Much more prospective RCTs are needed to verify the effect of povidone-iodine in oral care.

cardiac surgery and who required shorted period of ventilation. It is possible that oral antiseptics just delays rather than prevents the occurrence of VAP. Thus, for patients intubated a short period of ventilation, oral antiseptic would reduce the risk of VAP, whereas for critically ill patients requiring prolonged period of ventila-

Another factor that may affect the results of the trials is the concentration of chlorhexidine solutions. Chlorhexidine 0.12%, which is the recommended dosage by the CDC for cardiac surgery patients [43], significantly reduced the rate of VAP in cardiac surgery patients [28, 30]. However, among the non-cardiac surgery
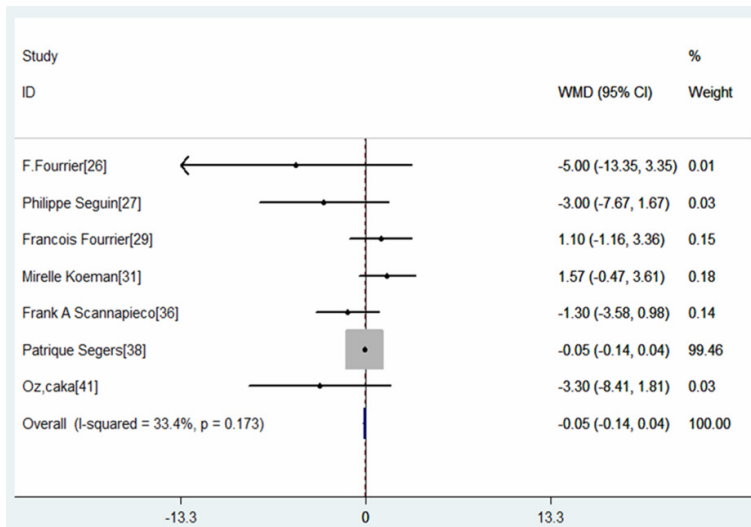
Figure 8. Forest plot showing the effect of oral care with antiseptics on duration of mechanical ventilation.

addresses the effects of oral care with antiseptics on different type of surgery patients: cardiac and non-cardiac surgery patients; it provides a quantitative assessment of different type of antiseptics on the prevalence of VAP; it includes recently published studies [37, 40-42] that had not been included in the prior meta-analysis; it excludes studies with sample size less than 50 [24, 25]; it systematically assesses the effect of oral care with antiseptics in terms of clinical endpoints, including ICU mortality, duration of mechanical ventilation, and length of ICU stay.

patients, a higher concentration may be necessary. In the trial conducted by Koeman et al. [31], a 2% chlorhexidine solution was used for mixed ICU patients, which is a higher concentration than that (0.12%, or 0.2%) in other studies. This may partially explain why the use of chlorhexidine significantly reduced the prevalence of VAP in this trial.

Our meta-analysis showed that oral care with antiseptic was not associated with a reduced ICU mortality. One possible explanation is that some patients aspirate small amounts of oral antiseptic, leading to acute respiratory lung injury [44-46]. This association was observed in one of RCTs included in our study [42]. Seguin and colleagues [42] found that, among the patients with oral povidone-iodine solution, a 6% rate of respiratory distress syndrome occurred, whereas 0% occurred in those with placebo. Another possible explanation is that the use of antiseptic may interfere with VAP diagnosis by inhibiting pathogen culture in the laboratory. The false-negative diagnoses would lead to withholding antibiotics. Moreover, some researchers have found that patients with culture-negative VAP have a higher mortality rates than those with culture-positive VAP [47].

This meta-analysis involving 4249 patients provides a comprehensive and updated assessment of the benefit profile of oral care with antiseptics in the prevention of ventilator-associated pneumonia. It differs from previous meta-analysis [48-51] in several ways: it specifically

Although this meta-analysis is based on high quality RCTs, there are some limitations of our study. First, although studies with small size were excluded in this meta-analysis, some of the included studies had a modest sample size, which would overestimate the treatment effect when compared with larger trials. In addition, some of the subgroup analyses are based only on 2 to 3 studies; thus caution should be taken when applying these conclusions into the clinical practice. Second, there was considerable heterogeneity among the studies, including different patient population, the definition of VAP, concentrations of antiseptic (0.12%, 0.2%, 2%), forms of agent (oral rinse, gel), the frequencies of administration. These factors would have a potential impact on the results. Finally, it is possible that the existence of some unpublished studies could lead to bias in effect size. In general, considering the limitations mentioned above, we should interpret our results with adequate caution.

In conclusion, this meta-analysis suggests that oral care with antiseptics significantly reduces the prevalence of VAP, especially in cardiac surgery patients, but does not have effect on other important clinical outcomes, such as ICU mortality, length of ICU stay, duration of mechanical ventilation. However, given the relatively small studies and heterogeneity among studies, further large-scale, well-designed RCTs are needed to indentify the current findings and investigate the effects of povidone-iodine in patients with mechanical ventilation.

Disclosure of conflict of interest

None.

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