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Review Article

The Efficacy of Oral Chlorhexidine as an Oral Hygiene Measure in Reducing the Incidence of Ventilator-Associated Pneumonia: Integrative Review

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Abstract: Implementation of standardised oral hygiene protocols could potentially minimise the occurrence of ventilator-associated pneumonia (VAP) among critically ill patients. However, inclusion of the topical application of oral chlorhexidine as an effective oral antiseptic in such protocols and VAP guidelines remains controversial and questionable, due to inconstancy in the current evidential findings. The aim is to investigate the efficacy of oral chlorhexidine in reducing the incidence of VAP among mechanically ventilated patients in different critical care settings. A comprehensive electronic and manual literature search was conducted utilising different databases, including Cinahl, Medline, PubMed, Google Scholar and Scopus, and using related keywords to identify the relevant primary research sources published in English since 2005. Data were extracted and summarised in tables and then were critically appraised using validated tools. When the relevant studies were analysed, they were grouped based on two main themes and varied subthemes. One of these is the patient population, including those admitted to mixed or general ICU and those who had undergone cardiac surgery. The second theme is the chlorhexidine type, in which solution and gel were investigated at varied concentration using different frequencies. Topical application of chlorhexidine may have the potential benefit of reducing VAP incidence; however, no recommendation can be made regarding the best type or optimal concentration that can be used. Thus, a large-scale randomised control trial to investigate further the effectiveness of its routine use among mixed ICU patients and to demonstrate the optimal form, as well as concentration and frequency, is required.

Keywords: Ventilator associated pneumonia, hospital acquired infection, pneumonia, oral chlorhexidine, oral hygiene, critical care

INTRODUCTION

Hospital acquired infection (HAI), which is also known as nosocomial infection (NI), poses a great threat to hospitalised patients' safety, as well as health professionals and institutions worldwide [1-3]. The critically ill are among the most vulnerable patients and are susceptible to nosocomial infections, due to their comorbidities and compromised immunity [4, 5]. It has been widely argued that estimating NI-associated harms could be difficult due to the potentially increased risk of biases in the statistics due to ignorance of the infection occurrence time [6]. Nevertheless, based on the CDC report, 722,000 HAIs in US acute care hospitals were reported in 2011 and hospital acquired pneumonia was estimated to be the most common infection, with 157,000 incidences in the same year [7]. One of the most common HAIs that could affect such a patient population is pneumonia, which is widely defined as an inflammatory condition that affects the lungs and is caused by either bacterial or viral infections and, rarely, fungal infection [8]. Among critically ill patients who are vulnerable due to either their compromised immunity or comorbidities, the risk of acquiring infection is significantly higher [5]. In intensive care unit (ICU) settings, around 30% of patients have acquired at least one type of HAI during their stays [9].

Critically ill patients often require admission to critical care units, due to their need to receive mechanical ventilation support following the placement of an artificial airway. These procedures, that is, artificial airway and mechanical ventilation, could result in comprising the airway defence, leading to translocation of respiratory pathogens from the oral cavity to the lungs and to ventilator-associated pneumonia (VAP) development [10]. Microorganisms, which normally reside in the oral cavity and gut, were found to be the leading cause of VAP development. This was greatly linked to the aspiration of colonised secretions with such pathogens from the oral cavity following the placement of an artificial airway in the respiratory tract and, subsequently, the lungs. Despite the fact that intubation and connecting critically ill patients to MV are considered lifesaving interventions [11], they can be associated with varied complications ranging from infection to causing lung injury and death in some cases. In critical care settings, VAP is believed to be one of the most challenging issues, and can result in huge harm, not only to patients but also to their families, as well as health organisations.

VAP, which is known as pneumonia that develops after 48 hours of intubation and mechanical ventilation [3], is considered to be the second most common HAI in healthcare settings and the most common acquired infection in intensive care units (ICUs) [12]. Its occurrence poses a great challenge, not only to healthcare organisations but also to health professionals, due to difficulties that might be encountered during the diagnosis process, as well as the VAP-associated negative consequence. The prevalence of VAP is reaching alarming rates in developing and developed countries, despite the implementation of widely proven preventative strategies (World Health Organization, 2012). VAP is still considered the second most common type of HAI following the urinary tract infection, and is believed to be the most common one in the ICU environment around the globe, with an incidence rate ranging from 8 to 28% [12]. This variation in statistical data could be due to a number of factors, including the diagnostic criteria used and the patient population and their characteristics [13]. Although a significant decline in VAP incidence has been noted over the last two decades in developed countries [2], a number of leading health organisations have reported that VAP incidence remains alarming [14]. Mean VAP rate has declined in both medical and surgical ICUs from 4.9 to 1.4 and 9.3 to 3.8, respectively, per 1000 ventilator days between 2002 and 2009 in varied US health facilities [15]. Casemix differences as well as discrepancies in patients' characteristics and comorbidities could hugely affect the reliability and applicability of such statistical data in other countries' health contexts [16]. In a recent systematic review, it was reported that VAP among adult critically ill patients continues to be a major issue in developing countries' hospitals, including Middle East healthcare facilities, as its incidence remains significantly higher than The National Healthcare Safety Network (NHSN) benchmark rates and ranges from 10 to 41.7 per 1000 ventilator days [14].

Until today there is no gold standard in diagnosing VAP [3]; however, some organisations, including Centres for Disease Prevention and Control (CDC) advocate using clinical signs criteria in conjunction with radiologic criteria and microbiologic findings [17]. Nevertheless, early diagnosis and identification of VAP occurrence, and hence, implementing prompt and appropriate treatment is crucial as it could be lifesaving in some situations [17]. The onset of VAP can be early or late based on its occurrence time. Early onset VAP, which is characterised by low to medium severity, can be defined as the pneumonia developing within 2-4 days [18, 19]. It is often attributed to pathogens that are generally sensitive to antibiotics. Late onset VAP, which is more severe and is usually caused by multidrug resistant pathogens, is pneumonia that develops after 96 hours of mechanical ventilation with prior exposure to antimicrobial agents [19].

It is well established in the literature that VAP development is a major cause of avoidable mortality and morbidity, increased hospital and ICU length of stay, and prolonged mechanical ventilation (MV) for patients who are already critically ill [12]. It was also postulated that VAP is associated with potential economic implications, not only for health organisations with high VAP rates but also for patients affected [3, 20]. In the US, attributable deaths related to VAP occurrence is estimated to be 9% [21]. VAP has been reported to be associated with significant figures of crude mortality and attributable death that ranges from 25-40% and 0-15%, respectively [22]. Among those who acquired VAP during their ICU admission, the median hospital length of stay was estimated to increase by almost 7-8 days. Nevertheless, whether the extended length of stay is a cause or an effect of VAP development remains widely controversial [23]. VAP is believed to have a substantial economic impact that is associated with increased resources utilisation, such as ICU beds and antibiotics. In the US, incremental healthcare spending as a result of VAP was estimated to be $20,000-$40,000 [24].

VAP treatment remains complicated and in some situations, insufficient. Prior to medical interventions, performing various investigations, including microbiological, obtaining sputum for culture and sensitivity, and radiological studies are often required [17]. Systematic antibiotics based on microbiological findings, in combination with adequate

hydration and atelectasis prevention, as well as early extubation are the most common treatment strategies [10, 24]. Despite the effectiveness of this approach, it is still associated with increased resources utilisation and prolonged length of stay and MV duration [24]. Therefore, the urging need to implement strategies that are associated with lower cost and higher effectiveness has emerged in recent years. A considerable interest in VAP prevention has emerged widely and much literature has provided interesting evidence supporting the implementation of number of cost effective preventative strategies that work efficiently towards combating VAP development [2, 25, 26]. These measures include, but are not limited to, oral hygiene using oral antiseptics, suctioning the colonised secretions and elevating the head of the bed. These measures were then incorporated in various care bundles that aim to prevent VAP occurrence. Although Recommendation around making all the efforts to prevent VAP development in critical care settings through implementation of various VAP prevention strategies has been widely reported in the literature and health organisations guidelines [10, 24], yet, there is no gold standard bundle that was investigated and identified in the recent literature or guidelines search.

Various modifiable factors are considered to be potential causes of VAP. This includes but is not limited to transmission of pathogens from ventilator circuits and aspiration of colonised secretions [23]. Of all the factors that can contribute to VAP occurrence, oropharyngeal colonisation has a pivotal role in VAP pathogenesis [5, 27]. Due to the significant role of aspirating colonised secretions in VAP development, evidence supporting implementing strategies that incorporate interventions to prevent such issues is targeted [28]. These strategies include but are not limited to elevation of the head of bed, use of subglottic secretion drainage, performing efficient oral hygiene, and decontaminating the oral cavity and dental plaque [26]. For the purpose of minimising VAP incidence, a number of leading health organisations, including the CDC and the Infectious Disease Society of America (IDSA) have developed bundles of care, in which a number of strategies are incorporated to comprehensively combat VAP development in mechanically-ventilated patients. In spite of the availability of these guidelines and the proven effectiveness of most of the intervention, a zero VAP has not yet been reached [29].

The efficacy of oral chlorhexidine towards mitigating oropharyngeal colonisation and reducing VAP occurrence rate has been widely reported in the literature[24, 30].; however, its role in reducing hospital and ICU associated mortality or shortening hospital stay and MV duration has not yet been widely proven [31]. Although Houston, Hougland [32] and DeRiso, Ladowski [33] reported the effectiveness of CHX as VAP prevention measure when used preoperatively in patients undergoing heart surgery, there is no consistency in the studies' findings in regards to the effect of routine application of CHX on VAP incidence reduction. Therefore, its wider use remains controversial, and its routine use and inclusion in VAP bundles in a number of health organisations remains controversial and questionable, due to the inconsistency around its efficacy in the published literature [21, 31]. The Infectious Disease Society of America (IDSA), for example, did not include the routine application of CHX in its 2005 VAP guidelines update until further evidence might become available [21, 34].

Ventilator acquired-pneumonia is a global issue that is associated with a substantial financial burden as well as various negative impacts on critically ill patients' overall health status [35]. Thus, there has been wide agreement towards developing effective approaches in which VAP occurrence among ICU patients could be minimised [36]. Of all these approaches, oral hygiene using oral antiseptics was proposed as one of the most important strategies due to its favourable effect in inhibiting oral colonisation; therefore, the risk of aspirating colonised secretions, which are considered crucial for VAP development, is lessened. Despite the fact that many clinical studies showed the superiority of CHX in reducing VAP rate, comparable incidence of VAP between the control group and CHX has been shown in other trials [21]. This could be the reason behind not introducing such product as a routine practice in critical care settings by numbers of VAP guidelines. 2004 CDC guidelines did not recommend the inclusion of CHX in their VAP bundle, although it advocated its application for cardiac surgery patients [8]; however, this was changed as in their last review of VAP guidelines in 2010, the use of 0.12% CHX solution was included in the CDC VAP bundle [37]. Nevertheless, IDSA did not recommend the use of oral chlorhexidine in its last VAP guidelines update in 2005 in the ICU settings, and it requires the availability of more data in regards to its efficacy in combating VAP. IDSA argued that available evidence in 2005 about this product and its relation to improvements in VAP management was limited [21]. This valuable information highlights the importance of reviewing the evidence published since 2005 regarding the beneficial use of CHX as VAP prevention. To the point of my knowledge, no review focusing at analysing and synthesising the evidence around this topic and aimed at including only studies that are published from 2005 onwards with different designs, was identified. Therefore, it is of value to review the literature for evidence updates with regard to the use of CHX as the method of choice in minimising VAP incidence, and hence, this integrative review has been developed. Nevertheless, evidence from primary research papers

that are published from 2005 onwards will be reviewed and their findings will be synthesised.

METHODOLOGY

In order to conduct this study and for the purpose of addressing its proposed clinical question, and to generate a better understanding about the proposed issue, an integrative review method was utilised. In the integrative literature review framework described by Whittemore and Knafl [38], summarising and synthesising the results of the previously undertaken studies and then establishing a conclusion in regards to examined themes based on the findings analysis is permitted, and a more structured and rigorous search is facilitated. It is considered to be the method of choice as it allows the researcher to widen the research to include varied studies with different designs, including quantitative and qualitative studies [39]. To achieve this aim of this review, the following clinical question, using a PICO framework, was framed:

In mechanically ventilated adult patients, is the use of oral chlorhexidine effective in terms of reducing the incidence of ventilator-associated pneumonia?

SEARCH STRATEGY

For the purpose of this integrative review and to identify the available literature that has investigated the efficacy of oral chlorhexidine as a measure to reduce VAP rates among critically ill patients, a comprehensive, systematic, and standardised search strategy was used. A computerised search was conducted in five electronic databases, including Cinahl, Embase, Medline, PubMed, and Scopus to satisfy the urgent need to find relevant evidence surrounding this issue. While searching these databases, the types of research methodology and study designs accessed and reviewed were not restricted. Nevertheless, some other limiters were set and utilised at the beginning of each search in order to help locate the most relevant sources that could be potentially useful in this type of review. The previously mentioned databases were limited to include only peer-reviewed primary studies that were conducted on adult human populations and published in the English language. A manual search was also undertaken to identify further relevant sources through citing some articles in the reference lists of some of the identified studies or reviews, or in some cases conference reports and scientific meeting papers.

A number of search terms and keywords were utilised to identify sources related to the review core concept and the targeted clinical question. Certain search terms, including "ventilator-associated pneumonia", "oral chlorhexidine", and "critical care" were recognised when the preliminary literature survey was conducted. Each search term was comprised of different keywords, as shown in Table 1. Searching the databases consisted of performing different combinations using "or" and "and" in order to help find the most suitable research papers that could help in addressing the framed clinical question. In Cinahl and Medline, mapping terms to subject headings was not utilised for the benefit of wide exploration of the chosen topic and to minimise the risk of missing some important studies. Nonetheless, in PubMed database search terms were sometimes utilised as medical subject heading (Mesh) keywords.

Table 1: Keywords and search terms

Primary Search Term	Keywords
Ventilator associated pneumonia	Ventilator associated pneumonia,, Hospital-acquired pneumonia, Vent*, pneumonia, nosocomial, infection, respiratory infection, hospital acquired, VAP, HAI, intub*
Oral chlorhexidine	Oral, care, hygiene, antiseptic, chlorhexidine, decontamination, colonization, chlorhexidine gluconate, mouthwashes
Critical care	Critic*, intensive care, ICU, critically ill.

While it was difficult to retrieve a good range of articles relevant to the review purpose, which is gathering and synthesising the findings from the available literature, and then, drawing a conclusion based on this synthesis, a number of inclusion and exclusion criteria were set. These criteria helped the author not only to recognise the appropriate search terms, but also to effectively screen the identified sources. These included the following:

Inclusion criteria

- Studies that examined oral chlorhexidine as the main intervention.
- Studies on adult mechanically-ventilated patients.
- Studies that investigated the CHX as intervention, with VAP as the primary endpoint or outcome.

Exclusion criteria

- Studies that examined the application of oral chlorhexidine in conjunction with antibiotics.
- The VAP incidence as an outcome is not clearly calculated, stated, or identified.

Search outcomes

The outcome of search is illustrated in the below PRISMA flow diagram (Figure 1). The cited

studies were carefully reviewed and numbers of them were then excluded due to a range of reasons as shown in the PRISMA flow chart. After this step, 19 primary research articles, of which 16 studies are randomised controlled trials, 2 cohort studies and 1 quasi-experimental study, relevant to this review question were included.

Quality appraisal

The quality of the selected studies was investigated and critically appraised to evaluate their validity and reliability using a standardised critical appraisal checklist based on the Critical Appraisal Skills Programme (CASP) guidelines prior to including them in this review. As the research designs of the retrieved studies for this review differed, consisting of 16 RCTs, 2 cohort studies and a quasi-experimental study, three checklists design applicable guidelines were used. All of these studies has examined the relationship between VAP incidence as an outcome of interest and the CHX as intervention among critically ill patients. VAP incidence was clearly calculated and reported in all of the examined studies. When the checklist for appraising the randomised control trials was used, the quality judgment was based on three perspectives including the results' validity of the examined studies, reporting results and examining its applicability. Although the included RCTs demonstrated varied ranges of similarities in regards to patients characteristic, intervention methods, and diagnosing VAP and calculating its incidence, they had some differences in their methodology in terms of randomisation, blinding and allocation methods. Most of the included RCTs has used double blinding technique; this has added additional strength and validity to these included RCTs.

Similarly, the CASP cohort studies checklist, which examined the same three perspectives with different questions, was utilised to evaluate the included cohort studies. Overall, all of the examined studies have showed a methodological rigour and were of good quality.

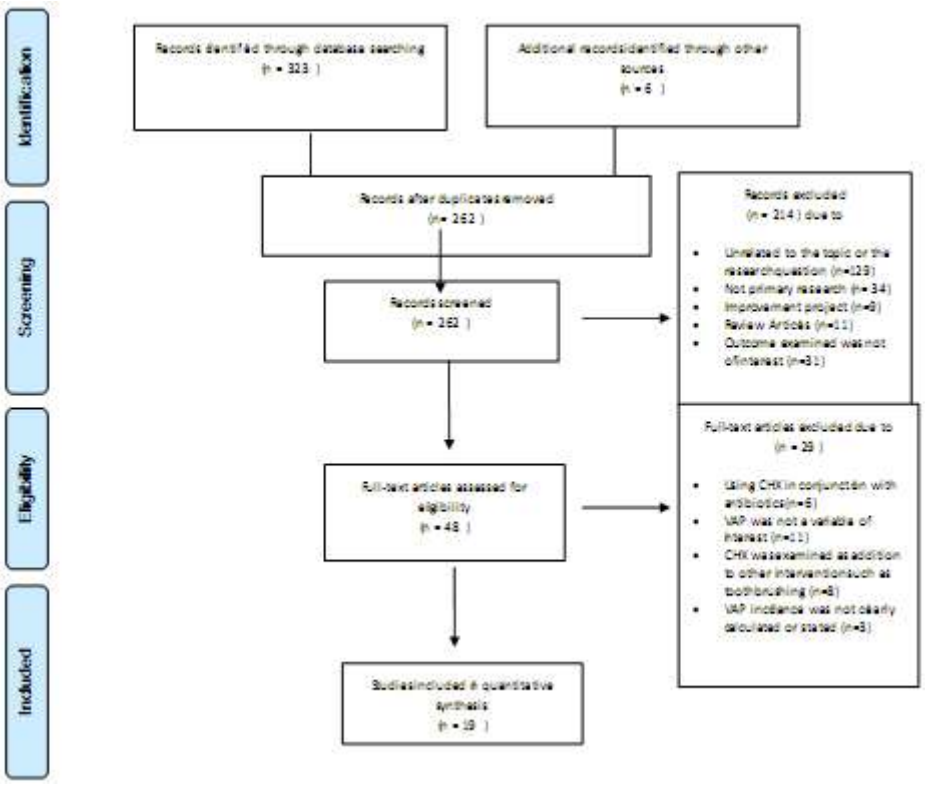

Fig-1: PRISMA 2009 Flow Diagram

Table 2: Descriptive and analytical table

No.	Author/Year	Study Design	Setting	CHX presentation	Sample	Intervention vs control	Findings	Themes
1	[20]	Double blinded RCT	ICU	2% CHX solution	N= 385 (130 in CHX, 127 Placebo, 128 CHX/Colistin)	• Intervention: CHX, CHX/col 4x/a day. • Control: NSS 4x a day.	• The daily risk of VAP was reduced in both treatment groups compared with placebo: CHX by 65% & CHX/Col by 55% • No differences in duration of mechanical ventilation, intensive care unit stay, or intensive care unit survival could be demonstrated.	• Clinical setting: ICU • CHX presentation: Solution; 2%
2	[35] [35]	Double blinded RCT and meta-analysis	ICU	2% CHX solution	N= 207 (102 vs. 105)	• Intervention: oral care & oropharyngeal rubbing with 15 ml 2% CHX 4x a day • Control: oral care & oropharyngeal rubbing with 15 ml NSS 4x a day	• Incidence of VAP was 4.9% (5 in 102) in the CHX group vs. 11.4 (12 of 105) in the control group (p .08) • Adverse events: mucosal irritation in 10 patients (9.8%) in CHX group • Secondary outcome: No significant difference in mortality was observed in both groups.	• Clinical setting: ICU • CHX presentation: Solution; 2% • adverse events
3	[12]	Double blinded RCT	ICU	0.2% CHX gel	N=60 (30 vs 30)	• Intervention: 0.2% CHX gel • Control: was treated with placebo gel.	• VAP was higher in control group than intervention (26.7%vs6.7%) • Secondary outcomes: Mortality was also lower in the treatment group (3.3% *vs*. 10%) • Oral colonization was reduced by the CHX gel	• Clinical setting: ICU • CHX presentation: gel; 0.2% • adverse events
4	[40]	Double blinded RCT	ICU	0.12% CHX solution	N= 145 (71 vs 74)	• Intervention: 0.12% CHX 5ml by swab within 12 hour of intubation 1x/day • Control: standard oral care that did not include CHX, 1x/day	• Among participants without pneumonia at baseline (CPIS < 6), only 33.3% of the intervention patients (7/21) had developed VAP by 48 or 72 hours versus 55.6% of the control patients (10/18). • No secondary outcomes were	• Clinical setting: ICU • CHX presentation: Solution; 0.12%

							reported.	
5	[25]	Double blinded RCT	ICU	0. 2% CHX solution	N= 61 (29 vs 32)	• Intervention: 0. 2% CHX by swab 4x a day • Control: NSS by swab 4x a day.	• VAP rate was significantly higher in the control (68.8% vs. 41.4%, respectively; p = 0.03) • Secondary outcomes: No difference between both groups in VAP development time, LOS, and mortality.	• Clinical setting: ICU • CHX presentation: Solution; 0.2% • adverse events
6	[23]	Double blinded RCT	ICU	0.12% CHX solution	N=260 (130 vs. 130)	• Intervention: 0.12% CHX oral rinse 2x daily • Control: placebo which did not contain CHX and substituted with NSS 2x daily	• VAP incidence was significantly lower in the treatment group (5.7% vs 35.4%) Adverse events: mucosal irritation in 2 subjects in CHX group; not significant (P<0.05) .	• Clinical setting: ICU • CHX presentation: Solution; 012% • adverse event
7	[21]	Retrospective cohort study	ICU	0.12 CHX solution	N= 547	• VAP was assessed prior to & following implementation of CHX mouth wash(3x daily)	• The probable VAP rate was reduced from 1.85% to .81% after the use of CHX. • secondary outcomes: No significant reduction in the duration of MV, hospital LOS & mortality rate.	• Clinical setting: ICU • CHX presentation: Solution; 0.12%
8	[41]	Double blinded RCT	ICU	0.2% CHX gel	N=228 (114 vs. 114)	• Intervention: 0.2% CHX gel TID • Control: Placebo gel TID •	• Incidence of VAP was less in CHX group compared to placebo (17.8% vs 18.4%) but not statistically significant • On day 10, the number of positive dental plaque cultures was significantly lower in the treated group (29% vs. 66%; $p < .05$). • Secondary outcomes: no difference in MV duration, LOS, and mortality in both groups	• Clinical setting: ICU • CHX presentation: gel; 0.2%
9	[36] [36]	Single blinded RCT	ICU	0.2% CHX solution	N= 512 (250 vs 262)	• Intervention: 0.2% CHX solution 2x daily • Control: 0.01% potassium	• No significant difference between groups in VAP occurrence. VAP occurred in 7.1% of the CHX group and	• Clinical setting: ICU • CHX presentation:

						permanganate solution 2x daily	7.8% potassium group (p 0.82; relative risk, 0.93; 95% confidence interval, 0.49 to 1.76). • Secondary outcomes: No difference between both groups in the median day to VAP development (5.0 days: interquartile range IQR, 3.0 to 7.7 vs 5.0 days: IQR, 3.0 to 6.0, respectively), mortality rate (34.8% vs 28.3%)	Solution; 0.2%
10	[42]	Double blinded RCT.	ICU	0.12% CHX solution	N=226.	• Intervention: 0.12% CHX oral rinse 5ml was applied for 1 min. • Control: placebo oral rinse 5ml was applied for 1 min.	• No significant reduction in VAP incidence was found in CHX group compared to the placebo (OR = 0.54, 95% CI: 0.23 to 1.25, *P* = 0.15) • CHX reduces the number of staphylococcus aurous pathogens. • No adverse events were observed from the use of CHX	• Clinical setting: ICU • CHX presentation: Solution; 0.12% • adverse events
11	[31]	Double blinded RCT	ICU	0.12% CHX solution	N=194 (98 vs 96)	• Intervention: Oral rinses with CHX 15 ml performed 3x a day for 1 min. • Control: Placebo solution 15ml 3X a day for min.	• VAP rate/1,000 ventilator-days was similar in both groups (22.6 vs 22.3; *P* p .95) • RTI survival time, MV duration, mortality, ICU and hospital LOS did not differ in both groups. • Adverse events: 3 patients complained from unpleasant taste and one discontinued the use of CHX.	• Clinical setting: ICU • CHX presentation: Solution; 0.12% • adverse events
12	[43]	Single blinded RCT	ICU	0.2% CHX solution	N=194 (98 vs 96)	• Intervention: 0.2% CHX oral rinse 2x daily • control: NSS oral rinse 2x	• VAP was developed in 9 (22.9%) participants in the intervention group & 13 (32.5) patients in the control. • Incidence of late onset of VAP was significantly lower in the treatment group (5 VS 25% in experimental and control groups,	• Clinical setting: ICU • CHX presentation: Solution; 0.2%

							respectively • No secondary outcomes was reported.	
13	[44]	Single blinded RCT	ICU	0.2% CHX solution	N=70 (35 vs 35)	• Intervention: 0.2% CHX oral rinse 15ml 2x daily • Control: H2o with NSS 16ml 2x daily	• VAP incidence was lower in the treatment group (5.7% vs 20%) • Secondary outcomes: Oral colonization was reduced by using 0.2% CHX (20% vs 80.0%; p=0.0001)	• Clinical setting: ICU • CHX presentation: Solution; 0.2%
14	[27]	Retrospective cohort study	ICU	.2% CHX solution	N= 104 56 & 48 in standard care group and CHX cohorts, respectively.	• CHX cohort: 2% CHX by swab 4x daily • Standard oral care: NSS 4x daily	• CHX oral decontamination showed a significant effect on respiratory colonization during MV (102 [55%] vs 173 [62%]) and hence VAP incidence reduction; however, not statistically significant.	• Clinical setting: ICU • CHX presentation: Solution; 2%
15	[26]	Single blinded RCT	ICU	0.12% CHX solution	N=314 (157 vs 157)	• Intervention: 0.12% CHX mouth rinse 5ml before intubation • Control: no CHX before intubation • All subjects received CHX bid after intubation.	• Applying CHX prior to intubation didn't provide benefit over the intervention period compared to the use of daily CHX after intubation. • No statistical difference in CPISs scores between both groups; however, CPIS remains <6 in both groups. NO difference in VAP incidence.	• Clinical setting: ICU • CHX presentation: Solution; 0.12%
16	[30]	Double blinded RCT	Cardiothoracic	0.12% CHX solution	N=954	• Intervention: 0.12% oral rinse 2x a day • Control: placebo 2x a day	• Incidence of lower respiratory infection and hence VAP after cardiac surgery was lower in the CHX group (19.8 vs 26.2%, respectively. • Secondary outcomes: no significant difference was found between groups in mortality and LOS.	• Clinical setting: ICU • CHX presentation: Solution; 0.12%
17	[28]	Quasi-experimental study	Cardiothoracic	0.12% CHX solution	N= 300 (150 vs. 150)	• Intervention: oral rinses with 0.12% CHX • historical control group (patient who had cardiac surgery between	• CHX group showed lower incidence of VAP (2.7% [95% CI 0.7–7.8] vs 8.7% [95% CI 4.9–14.7], P .04) • Risk for pneumonia	• Clinical setting: ICU • CHX presentation: Solution; 0.12%

						2009 & 2010) and received standard oral care with no CHX	development was higher in the group 2 by 3-fold. • Secondary outcomes: shorter LOS (P .01) in the CHX group; no difference in mortality	
18	[5]	A single arm prospective intervention study	Cardiothoracic	0.12% CHX solution	N=226	• Chlorhexidine gluconate (CXG) 0.12 % oral rinse twice a day was used until cardiac surgery.	• The mean pneumonia rate in ICU in the 6 months before the study protocol was 32 per 1,000 ventilator-days, 24 during the 6-month intervention period, and 10 during the next 6 months following the study. • Secondary outcomes: Mortality in patients without pneumonia was 9/208 (4.32 %) vs. 6/19 (33.3 %) in those with pneumonia.	• Clinical setting: ICU • CHX presentation: Solution; 0.12%
19	[45]	Single blinded RCT	Cardiothoracic	0.2% CHX solution	N=194 (98 vs 96)	On the day before surgery • Intervention: Oral rinses with 0.2% CHX performed 2x a day. • Control: NSS 2x a day	• Incidence of VAP was significantly lower in CHX group as it occurred in only 8.5% compared to 23.4% in control • No adverse reaction developed with the use of 0.2% CHX • CPIS score was significantly lower in CHX group on the 3rd (P 1⁄4 0.024) and 5th (P 1⁄4 0.005) day post-surgery compared to control • Secondary outcomes:	• Clinical setting: ICU • CHX presentation: Solution; 0.2%

FINDINGS

The 19 studies identified are described in Table 2. In order to address the aim of this review and after analysing the identified evidence, studies were grouped based on the studied patient populations – either ICU or cardiothoracic – and CHX presentations, including its form and concentrations. These groups will be utilised to inform the structure of the findings section in this review. Most of the studies (15 of 19) examined the effectiveness of CHX in general ICU settings, whilst the rest were conducted on cardiothoracic ICU patients only. A possible distinction between these two groups is that while there is heterogeneity among the patients in the ICU settings, the groups in the cardiac setting are often homogenous. Additionally, it is worthy to note that in the ICU settings, CHX was administered periodically; however, in the studies that evaluated the efficacy of CHX in subjects undergoing heart surgery, it was also administered preoperatively. In regards to CHX presentation, 17 studies (89%) have examined the solution form, of which nine were concerned about 0.12%, five examined the 2% concentration and only three used the 2% as the intervention. The gel form of CHX was investigated in only two (11%) of the studies evaluated in this review. Despite the perceived importance of knowing the potential side effect of the topical application of CHX, only six studies have reported the adverse events that are associated with it. Therefore, to address the aim of this review, these themes and sub-themes form the structure of the following section and will be discussed more thoroughly.

Clinical Settings

General ICU

This section aims to synthesise the evidence from studies that examined the efficacy of CHX in reducing VAP risk for intubated and mechanically ventilated patients in ICU, regardless of the type of ICU.

Özçaka et al., [25], and Sharma and Kaur [23] concluded in their double-blinded RCTs' findings, using the same CHX concentration, that the use of such antiseptic twice and four times a day was effective in minimising the incidence of VAP in ICU settings, without any significant side effects. While Özçaka et al., [25], on a relatively small sample size, noted that VAP incidence was higher in the control group in relation to that found in the intervention group (68.8% v 41.4%, respectively; p = .03), Sharma and Kaur [23], who included 260 patients in their RCT, found that 35.4% of the control group manifested VAP, compared to only 5.7% of the chlorhexidine group ($p < 0.05$). Although both studies used a similar design to a great extent, the control groups received different products (Table 2). Scannapieco, Yu [42] found that, despite the fact that the total number of respiratory pathogens was not reduced by using 0.12% chlorhexidine twice a day, it was efficient in reducing colonisation with *Staphylococcus aureus* and, hence, the VAP' rate. The reason behind this could be the fact that the gram-negative bacteria is less sensitive to CHX. It is worth noting that when the probable VAP was examined in a retrospective study conducted in a multicentre, Enwere, Elofson [21] found that there was a significant decrease in the probable VAP rate from pre-CHX to post-CHX use (1.85% pre v 0.81% post, $P = 0.0082$). However, Postma, Sankatsing [27], in a study on a smaller sample (n=104) with almost similar design, failed to reveal any statistical relationship between the use of CHX and the VAP rate, although there was a trend towards a lower number of positive cultures in the CHX group. Nevertheless, the results from both studies need to be cautiously interpreted, due to the use of a retrospective data collection method, as this will place it at greater risk of selection bias.

When CHX was utilised with a higher concentration as the intervention, three of the examined studies have highlighted its efficacy in decreasing VAP incidence. A statistically significant reduction in VAP occurrence in the treatment group compared to the control group was reported by [20]. Despite the fact that VAP incidence in this study could be overestimated, due to the use of a VAP diagnosis criterion that is characterised by high validity but relatively low specificity, the authors argued that both groups are equally affected by this because of the use of a double-blind and randomisation design. This diagnosis criterion incorporated a combination of clinical, microbiological and radiographic criteria. Nonetheless, their findings were replicated by Tantipong, Morkchareonpong [35], in an RCT and meta-analysis which included their study and that of [20]. They found that VAP incidence were reduced in a statistically significant way with the application of CHX among intubated mechanically ventilated patients. Both studies reported no significant differences in the compared group characteristics. Although the authors in both studies did not to perform a double-blind design, due to the distinctive smell of CHX compared to the normal saline in the control, they argued that the investigators were unaware of the solution used in each group; this, in turn, could have minimised the risk of bias. Ćabov, Macan [12], using a lower concentration (0.2%) to assess the effect of CHX on VAP development through decontaminating oral mucosa and dental plaque, reported some consistent findings in which CHX use has resulted in a statistically significant decrease in plaque formation and, subsequently, a reduction in VAP incidence among the 60 patients analysed in the ICU setting (6.7 v 26.7%, p = 0.0418 with relative risk of nosocomial infection of 0.25).

In contrast to those studies in which a significant relationship between CHX application and VAP incidence reduction among patients in the ICU setting was identified, three RCTs using the same concentration of CHX reported no benefits of adding it to the oral hygiene practices in terms of reducing VAP incidence among critically ill mechanically ventilated patients. Fourrier, Dubois [41], in a double-blind study that was conducted on a total of 228 patients in six ICUs, found that although the oropharyngeal colonisation was reduced with CHX use, no significant difference in VAP incidence was observed (17.5% – 13.2 per 1,000 ICU days – v 18.4% – 13.3 per 1,000 ICU days – respectively). Although the patients analysed were homogenous in terms of demographic characteristics, a more in-depth analysis, such as illness severity as a variable, was not considered. Ranjbar, Jafari [43], using a like concentration (0.2%), reached similar findings in which VAP incidence was not significantly reduced using CHX twice daily. However, a significant difference between the two groups, in terms of reducing the late VAP incidence, was reported (5% v 25% in experimental and control groups, respectively, $p<0.05$). Dahiya [44] supported this conclusion in a study with a similar design and in which an almost adequate number of patients were comparable with regard to demographic characteristics.

Despite the fact that four of the analysed RCTs (Table 2: studies 4, 9, 11, 15) also reported no significant reductions in VAP incidence among the patient population studied using CHX as an intervention, contradictory findings regarding the effect of such interventions on VAP onset were reported across these studies. In a double-blind RCT with a relatively large sample (n=194), [31] highlighted the efficacy of CHX incorporation among mechanically ventilated patients in delaying the onset of VAP occurrence, as the CHX group exhibited a larger interval between intubation and VAP development (11.3 v 7.6 days; p =. 05), although they failed to report any statistical difference between the CHX group and control group in terms of reduction of VAP incidence per 1,000 ventilator-days (22.6 v 22.3; p = .95). Grap, Munro [40] found, in their RCT on traumatic and surgical patients, supported this finding and showed that early application of oral chlorhexidine immediately after intubation, as early as within 12 hours, resulted in mitigating or delaying the onset of VAP development and reducing its occurrence in some cases. However, Munro, Grap [26], in a double blind RCT that used the same CHX concentration with a larger sample, reached contradictory findings and showed that immediately application of CHX prior to intubation did not result in further decrease in or mitigation of VAP incidence in relation to routine use of CHX among ICU patients. Koeman et al., [20] also reported that oropharyngeal decontamination through utilisation of CHX is an effective measure in terms of delaying the onset of VAP. A reduction in the daily risk of VAP was achieved by 65% through utilisation of CHX [20]. In an open-labelled randomised trial on 512 patients, however, no difference was reported between the two groups in terms of delaying VAP onset, as the median day to VAP development in the experimental and the control group was 5.0 days: interquartile range (IQR), 3.0 to 7.7 v 5.0 days: IQR, 3.0 to 6.0, respectively [36]. Nevertheless, both studies relied on CPIS, which is widely criticised due to its varied limitation, as the VAP diagnosis criteria.

Cardiothoracic ICU

Of the 19 studies identified, only four have been found to have been performed on cardiothoracic participants (Table 2: studies 16-19). Unlike patients who are admitted to the ICU and receive CHX periodically, the group of patients in all four studies had also received the intervention in the perioperative period of cardiac surgery, in addition to using such intervention routinely after surgery until extubating takes place. Although the design of three of the studies evaluated in this section was similar (RCTs), they have incorporated varied methodologies (Table 2: studies 16, 18, 19).

A significant relationship between using CHX preoperatively, prior to intubation, and postoperatively, during the period in which the participants remained intubated and ventilated, has been shown in the all four studies. When 954 patients were analysed between 2003 and 2005, in a prospective and double-blind RCT, the incidence of VAP was reduced significantly in the chlorhexidine group (9.3% and 15.8%, respectively) [30]. The findings from this study were replicated in a more recent study with a relatively small sample size (n=194), in which the authors concluded that lower VAP incidence was associated with the use of CHX among patients undergoing heart surgery, compared to those that had received a placebo (8.5% v 23.4%, P= .04) [45]. They also reported that VAP incidence in the CHX group was of late onset, unlike the control group in which VAP incidence developed early (P = 0.027). Bergan, Tura [5], who used a lesser concentration (0.12%) of CHX in a single-blind and a single-arm intervention study on a homogenous patient population, achieved similar findings in which the VAP rate was significantly reduced from 32 per 1000 ventilator-days prior to undertaking this study to ten during the six months after the study. Scannapieco, Yu [42] also observed a significant decrease in VAP incidence following the perioperative use of CHX as oral hygiene measure in patients undergoing heart surgery, compared to the historical control group of patients who had cardiac surgery between 2009 and 2010 and received usual oral hygiene.

Chlorhexidine types

As regards CHX presentation, all 19 studies evaluated have reported the examined CHX form and concentration; however, only a few of them have identified the frequency used and method of application. By contrast, 17 studies tested the CHX solution with varied concentration as the intervention utilised to reduce VAP incidence, only two studies focused on using the CHX gel (Table 2: studies 3, 8). These studies have reported findings that range from CHX being effective in reducing the incidence of pneumonia among mechanically ventilated patients to not having a significant effect or not differing from the control group in terms of decreasing the VAP rate.

Solution

Seventeen studies, 14 RCTs, 2 retrospectives in design and one quasi-experimental, have evaluated the relationship between CHX in the solution form and the VAP rate in different settings, including ICU and cardiothoracic. Although the CHX form was similar across all of these studies, the concentration of such antiseptics varied, with 0.12% CHX being the most examined strength in the studies (9). Five tested the CHX oral rinse in the concentration of 0.2% and only three used the 2% CHX as an intervention. Therefore, each CHX strength that uses the solution form and is discussed in the body of evidence presented will structure the following section and the evidence will be analysed and synthesised accordingly.

0.12% solution

Despite the fact that this concentration is the most commonly examined strength in the studies assessed, inconsistent findings were reported in terms of its potential effect on VAP reduction.

The beneficial effect of adding 0.12% CHX to oral hygiene practices in the care of mechanically ventilated patients was reported in three of the investigated RCTs [23, 30, 40]. Although these studies used the 0.12% CHX at varying times and intervals throughout the study periods (four times, two times and once a day), all demonstrated a more substantial decrease in the risk of VAP development among the intervention groups. These findings were substantiated in a RCT by Bergan, Tura [5], in which 0.12% CHX was used twice daily preoperatively prior to the cardiac surgery and postoperatively in critical care settings. Sharma and Kaur [23], however, added suctioning as a measure to remove the pooled secretions; this might, in turn, affect the study findings. The latter were also replicated in two studies with different designs [21, 28]. Although Enwere, Elofson [21] reached a consistent finding, their results remain questionable, due to the use of retrospective data collection.

Interestingly, contradictory findings were revealed when the same strength of CHX at varied frequency of application was used in another RCT [31]. The authors reported that CHX was not superior to the placebo in reducing VAP incidence among subjects, although it showed a beneficial effect in retarding VAP occurrence. Scannapieco, Yu [42] also failed to show any association between application of 0.12% once daily and a reduced number of respiratory pathogens among intubated patients, although CHX was effective in reducing staphylococcus colonisation in the subjects examined. Application of 0.12% CHX to the subjects in the intervention group of the RCT of Munro, Grap [26], immediately prior to intubation and then at a twice daily frequency during the period when patients were kept on mechanical ventilation, revealed no association between the application of CHX using this particular technique and VAP incidence. However, the utilisation of CHX in both groups with the same frequency after intubation in both groups made it difficult to disentangle the efficacious impact of CHX on VAP incidence, regardless of the timing of application.

0.2% solution

Five studies, all of which were RCTs, examined this strength in terms of its effect in reducing the risk of VAP development (Table 2: studies 5, 9, 12, 13, 19). When the results were analysed carefully, it was noted that in three of the identified RCTs, the topical application of 0.2% chlorhexidine at varied frequency as an oral hygiene practice among mechanically ventilated patients is effective in reducing VAP incidence, with statistically significant results [25, 44, 45]. After performing the sub-group analysis in an RCT that uses similar concentration twice daily, no difference was noted between the treatment group and the control group in terms of VAP incidence in subjects receiving MV or tracheal intubation [36]. Although the authors considered their sample to be relatively large (n= 512), the results could be underestimated, due to the incorporation of 0.1% potassium permanganate as control rather than placebo. Nevertheless, when Ranjbar, Jafari [43] used 0.2% CHX, they failed to report any significant effect on the VAP rate of CHX at this particular strength, although its potential effect in terms of delaying the onset of VAP was reported. However, it is worth mentioning that the sample size in this study is considered small; this, in turn, could affect the applicability of such findings in wider contexts.

2% solution

Using a stronger solution of CHX, both Koeman et al., [20] and Tantipong, Morkchareonpong [35] found a strong relationship between the topical use of 2% CHX four times daily and reduced incidence of VAP among patients receiving mechanical ventilation. However, generalisability of Tantipong, Morkchareonpong [35] to a wider population could be

impaired, due to the inclusion of patients ventilated <48 hours, which is contradicted by widely acceptable VAP definition. Nevertheless, Tantipong, Morkchareonpong [35] also reported that the 2% CHX is cost effective compared to the use of antibiotics to treat one episode of VAP ten times. The findings from these two RCTs were supported by a retrospective study that concluded that 2% chlorhexidine is an effective oral care measure in terms of minimising risk of VAP development in highly vulnerable mechanically ventilated patients [27]. However, not only was the sample size relatively small in each cohort, but also the subjects' characteristics were different in each cohort and the authors failed to correct these differences. In turn, this might make their findings unreliable and questionable.

Gel

Among all studies examined, only two, which investigated the efficacy of CHX gel in mitigating or reducing VAP occurrence, were identified. Although both studies had similar designs (Table 2: studies 3, 8), contradictory findings were achieved concerning the benefit of using CHX gel at a 2% concentration on VAP incidence in the treatment groups. In a multicentre and double-blind RCT, Fourrier, Dubois [41] found no difference in the incidence of VAP between the patients in the treatment group and the control, as the rate of VAP per 1,000 days was similar. However, Ćabov, Macan [12], revealed that the use of this concentration resulted in a statistically significant reduction in VAP incidence. The efficacy of such concentration was demonstrated by having only 6.7% of patients in the intervention group develop VAP during the study period, compared to 26.3% in the control group. Nevertheless, the generalisability of this study's results and its applicability in clinical practice are limited on account of a small sample size. Thus, future research to examine the efficacy of such form (gel) is required, due to the limitation of the identified studies, including small sample size as in [12].

Side effects of CHX application for the purpose of reducing VAP incidence in patients receiving mechanical ventilation and intubation were not commonly reported in clinical trials [23]. Not all of the studies analysed in this review reported adverse events that are associated with the topical application of CHX at its different concentrations and forms. Side effects relating to 0.12% CHX were not reported to be significant in three RCTs (Table 2: 6, 10, 11). While Bellissimo-Rodrigues, Bellissimo-Rodrigues [31] observed that only three participants in the intervention group had complained of the unpleasant taste of CHX and that one had discontinued the use of the CHX solution, Sharma and Kaur [23] found that adverse effects of 0.12% solution were minimal, as only two subjects had demonstrated mucosal irritation following the application of such antiseptic. However, [12] argued that no side effect of CHX gel at concentration of 0.2% was observed in terms of tooth staining or mucosal irritation among subjects in the treatment group. Interestingly, when the same concentration was used, but at liquid form, similar observations were reported [25].

It is important to mention that fungal growth, including yeast, was observed with high prevalence in the CHX cohort in a retrospective study [27]. The authors also highlighted the negative consequences, including prolongation of hospital stay and duration of MV, that were observed in those who developed fungal colonisation in the CHX cohort. Interestingly, Tantipong, Morkchareonpong [35] reported that about 9.8% in the treatment group, patients who receive 2% CHX, developed mucosal irritation, compared to 0.9% in the control group, although the authors considered this adverse event mild and reversible.

DISCUSSION

Given that a myriad of evidence considered VAP the most common hospital-acquired infection to develop in the critical care settings, and that it is associated with avoidable negative consequences, including but not limited to raised morbidity and mortality rates, prolonged length of stay and increased financial burden, Oliveira, Zagalo [19] asserted that the potential to minimise its occurrence needs to be well investigated and explored. Developing and implementing a multifaceted approach that could effectively contribute to minimising the risk of VAP across critical care areas has been identified by a number of leading health organisations (including CDC, IDSA) as a top priority [8, 21]. A considerable interest has emerged in the recent evidence to prevent VAP incidence through treating and eliminating its causative pathogens, which normally reside in and colonise the oropharyngeal cavity and the gut [3]. The relationship between the oropharyngeal colonisation with respiratory pathogens and the development of pneumonia among the mechanically ventilated patients with artificial airways has been well demonstrated in the literature over the last two decades [24, 37]. Despite this evidence, advancements in developing a standardised oral care protocol remain poor. Although some guidelines recommend using comprehensive oral hygiene as an effective measure to prevent VAP development in acute care settings, there remains uncertainty around the best techniques (including the type of oral antiseptics) that can be used to achieve proper oral hygiene [21].

Using oral chlorhexidine as oral antiseptics to modulate oropharyngeal colonisation and, subsequently, reduce VAP risk has been widely recommended in selected patient populations, including those undergoing some types of cardiac surgery [9, 16]. However, until

solid evidence becomes available and sensible, in its last VAP guidelines update in 2005, IDSA did not recommend routine use of CHX as the oral antiseptic of choice [21, 34]. Moreover, the author of this integrative review could not cite any reviews that analysed and synthesised the results of studies published since 2005 that focused on both cardiothoracic and general ICU patient population, as well as highlighting the efficacy of different CHX types. Therefore, this integrative review investigated the efficacy of CHX at different types and concentrations in reducing the incidence of VAP among selected patient populations, including cardiothoracic and general ICU patients. This was achieved through analysing and synthesising the results of the 19 studies identified, which varied in design and methodology to some extent, as shown in Chapters 2 and 3. Nevertheless, it is worth mentioning that the studies in which CHX was used in conjunction with prophylactic topical antibiotics as the intervention were not included in this review. The reason behind this is that the effectiveness of antibiotics in reducing the colonisation is well established in the literature. Thus, using it with CHX at the same time might result in overestimating the treatment effect of CHX in reducing the oropharyngeal colonisation and, hence, potentially minimise the risk of VAP development.

Although most of the studies evaluated (Table 2: studies 1-15) in this review have been conducted in ICU settings, in which heterogeneous population are cared for, inconsistencies in the results have been revealed when the efficacy of CHX in reducing VAP incidence was examined among this patient population. In other words, the use of CHX in this specified category of patients was both supported and not supported; however, the limitations of some of the body of evidence mandate interpreting the results with caution. Of the 15 studies conducted in the ICU, 6 RCTs (Table 2: studies 1-6) favoured the use of CHX as the oral antiseptic of choice in reducing VAP incidence. Although these studies have the same design, they demonstrated some differences in the sample size (ranges from n=60 to n=385), as well as the method of randomisation and blindness. Nevertheless, oropharyngeal decontamination through routine use of CHX was reported as effective in all of these studies in terms of reducing the risk of VAP development in patients who receive mechanical ventilation for > 48 hours. These findings were consistent with a meta-analysis by Kola and Gastmeier [34], in which CHX application was demonstrated to be an effective measure in preventing VAP among ICU patient populations. Additionally, in a retrospective study, similar findings were reached [21]; however, the use of retrospective data collection in this study could increase the risk of selection bias and, subsequently, compromise the reliability of the findings.

Conversely, eight of the evaluated studies (Table 2: studies 8-15) revealed contradictory findings. They all failed to show any significant effect of routine application of CHX as an oral antiseptic in minimising the incidence of VAP, although four argued that the use of this antiseptic could be beneficial in mitigating or delaying VAP incidence in such patient populations. These findings were consistent with Pineda, Saliba [46], whereby the researchers were unable to indicate whether the routine application of CHX to decontaminate the oral cavity of mechanically ventilated patients with endotracheal intubation can significantly lessen the incidence of VAP. Yet, Koeman et al. [20] reported that CHX application is significantly effective in terms of both reducing VAP incidence and delaying its onset. Despite the fact that VAP incidence in this study could be overestimated, due to the use of a VAP diagnosis criterion that is characterised by high validity but relatively low specificity, the authors argued that both groups are equally affected by this because of the use of a double-blind and randomisation design. Thus, the results could be considered unaffected by such variables.

In contrast to the results from these studies conducted in general ICU, an intriguing finding of this integrative review is that those studies which were conducted on patients undergoing heart surgery reported a significant relationship between the topical application of CHX at different concentration, prior to surgery and postoperatively in critical care settings, and VAP incidence. Although the CHX form and concentration varied across these studies, having such consistency in the findings could further indicate the efficacy of CHX in reducing the risk of nosocomial pneumonia in this patient category. Additionally, the findings from these studies are similar to those presented in the RCTs of DeRiso, Ladowski [33] and Houston, Hougland [32], in which CHX was reported to have a beneficial effect in reducing the risk of VAP development and antibiotic use in this selected patient population. Moreover, the CDC has recommended the use of CHX (0.12%) as a VAP-prevention strategy preoperatively for patients undergoing heart surgery [8].

Overall, as a result of the inconsistencies observed in the findings across those studies conducted on ICU patient category, it appears that the application of CHX demonstrated a remarkably beneficial effect on the cardiac surgery patient population in terms of reducing VAP rate and the use of systematic antibiotics. Having these discrepancies in the findings between these two groups of patient populations could be due to several explanations that could greatly influence oral care strategies. One of these could be differences in the oral hygiene protocols used, in which, unlike ICU patients, cardiac surgery patients often receive CHX prophylactically prior to surgery. Moreover, differences

in patient characteristics, in which cardiac surgery patients show more homogeneity, could be another confounding variable. It is often assumed that since intubation during elective procedures like heart surgery is performed under controlled conditions, this will place patients at a lower risk of acquiring nosocomial infection. Another explanation could be that although cardiac surgery patients often have several comorbidities at the time of intubation, due to the cardiac surgery work-up they usually demonstrate better physiological status than those admitted to ICU as emergency cases. Finally, patients who undergo heart surgery usually have a shorter time on mechanical ventilation, rarely exceeding 24-48 hours, compared to those admitted to ICU for other reasons; this will eventually minimise their risk of acquiring VAP, as CHX is reported to be effective in delaying VAP onset, as discussed earlier in this chapter. When these reasons are considered, it would not be surprising that the use of CHX as a VAP-prevention measure has a more positive effect on cardiosurgery patients in terms of VAP prevention and that the benefits to this patient population would be more significant and impressive. In contrast, patients in mixed ICU often have underlying comorbidities and their mechanical ventilation is often prolonged, usually exceeding 48-72 hours, making them more susceptible to VAP development [42]. Nevertheless, what is paramount is a well-designed multi-centre RCT with a large sample that compares the effectiveness of CHX application in both categories of patient, in order to discover whether the settings, the method of intubation and length of ventilation are the confounding variables.

CHX presentation varied across the studies and is used at different concentration, as well as timing and intervals. As for the solution, the studies assessed and included in this review investigated three concentrations – 0.12%, 0.2% and 2% – with the majority examining CHX (0.12%). Although inconsistent findings were reported when these concentrations were used at different frequencies (once, twice, three times and four times a day), most of the studies favoured the use of CHX as the antiseptic of choice to reduce the risk of VAP, despite the identified limitations that could hinder the applicability of this evidence. The effectiveness of 0.12% CHX was highlighted in three of the analysed RCTs (Table 2: studies 4, 6, 16); however, three more recent RCTs have reported contradictory results. Enwere et al. (2016), in a retrospective study, also reported the beneficial effect this particular concentration has on lessening the VAP rate. However, the results from such study design could be compromised, due to an increased risk of selection bias. Despite the fact that 0.12% CHX is reported to be the safest and most economic dosage, and is the recommended concentration for cardiosurgical patients in the CDC guidelines [8], this review presented inconsistent findings with regard to its efficacy. Nevertheless, when a higher concentration (2%) was examined in two RCTs, each reported that this concentration could be more effective in reducing VAP incidence among mixed ICU patients; however, this concentration could be associated with minor adverse events, including mucosal irritation [20, 35]. Therefore, and due to the limited evidence supporting this high concentration, a more rigorous RCT examining the effectiveness of such concentration is required.

The gel form of CHX at the concentration of 0.2% was the least examined in the studies examined in this review (Table 2: studies 3, 8). Although the latter had similar design, agreement was not achieved in terms of the efficacy of such forms in reducing the VAP rate. Although Cabov et al. [12] highlighted the effectiveness of CHX gel in reducing VAP incidence, they claimed that their sample was relatively small. Compared to larger trials, this limitation might result in overestimation of the treatment effect; thus, their validity could be questionable. As far as this author knows, no study anywhere has compared the different CHX types to show the superiority of one in terms of VAP prevention. Therefore, further investigation to distinguish the most appropriate form of presentation, as well as the ideal concentration and frequency, would be required.

While investigating the efficacy of CHX in reducing VAP rate, this integrative review has identified some gaps in current research. One of these is that as the usefulness of CHX application among mechanically ventilated patients in the general ICU setting was not conclusively supported by an analysis of the evidence, further studies with RCT design would be required, in order to demonstrate CHX efficacy in this patient population. Second, a large-scale multicentre RCT could be needed to compare the efficacy of CHX in different patient populations, including mixed ICU patients and cardiothoracic patients. No studies that compare the effectiveness of different CHX type at different concentration and frequencies were identified; thus, further research to identify the superiority of one CHX type or one concentration is warranted.

One of the strengths of this integrative review is that it includes studies with different designs (RCT, cohort and quasi experimental studies). The considerable heterogeneity among the studies evaluated, in terms of patient population, CHX type, concentration and frequency of application, could be another strength in this review. These factors could help in building a better and broader understanding of the treatment effect of such an oral antiseptic among patients with an endotracheal tube and receiving mechanical ventilation. This review did not examine the role of CHX application in reducing the consequences of VAP,

including mortality, length of stay and MV duration, and developing a more comprehensive understanding of CHX efficacy from varied perspectives. However, this could be justified, as it is not known if either of these consequences are VAP causes or effect of VAP. Although a comprehensive search was utilised to identify relevant literature for potential inclusion in this review, there is a possibility that some trials were missed. This could pose a limitation to this review and its findings.

As mentioned earlier, this integrative review has included varied and diverse studies in terms of methodological quality. As shown and described in Table 2, some of the studies analysed demonstrate various limitations, which in turn could have impeded the analysis of their results. For example, two studies (Table 2: studies 7, 14) had a retrospective design, placing them at greater risk of selection bias and subsequently compromising their reliability. Additionally, Postma, Sankatsing [27] acknowledge that their retrospective study has different patient characteristics in each cohort; however, this was not corrected because of a relatively small sample (n=104) in each cohort. This, in turn, could affect the reliability of the results from a study of this nature. The authors in three of the studies (Table 2: studies 3, 5, 13) report their study sample size as small and some others were conducted in a single centre. These factors could hinder the generalisability of those studies and, in some cases, lead to overestimation or underestimation of the treatment effect of the intervention (CHX).

Although Fourrier et al.'s (2005) multi-centre RCT included a relatively large sample (n=228), in which participants were homogenous in terms of demographic characteristics, a more in-depth analysis, such as illness severity as a variable, was not considered. This could be a limitation to such a study, as heterogeneity among the group via illness severity might be a variable that could contribute significantly to having varied VAP incidence among the study groups. Results from some studies could have overestimated the occurrence of VAP on account of the use of a VAP diagnosis criterion (CPIS) that is characterised by high validity but relatively low specificity. However, the authors in one RCT argued that both groups are equally affected by this variable, due to the use of a double-binding and randomisation design [20]. Nevertheless, results from studies in which limitations in design or methodology were reported have been replicated in several studies that are considered of higher quality.

CONCLUSION

This integrative review aimed to investigate the effectiveness of different CHX types in reducing VAP incidence and to develop a better understanding of its applicability in the mixed ICU and cardiothoracic ICU patient populations. Seven of the 15 studies conducted on patients admitted to general ICU settings reported the effectiveness of topical CHX application in reducing VAP incidence. Of the eight studies that did not support routine CHX application in this patient population, four have highlighted its efficacy in mitigating the onset of VAP. On the other hand, CHX use was favoured as an effective VAP-prevention strategy in all of the studies investigated, which included participants from cardiothoracic ICU. As for adverse events in CHX, these were reported to be minimal and reversible. Therefore, based on the synthesised results from the studies analysed in this review, implementing standardised oral hygiene with the inclusion of topical use of chlorhexidine seems to be an effective, safe and quite tolerable strategy for preventing dental plaque formation and oropharyngeal colonisation, thereby reducing the incidence of VAP. However, further well-designed studies to establish the most appropriate form of presentation and administration technique, as well as optimal concentration and frequency, are warranted.

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